THE CAPOTEN REVOLUTION

More and more Canadian physicians are turning to Capoten...

for efficacy with minimal effect on lifestyle in newly diagnosed hypertensive patients, if traditional therapy is unacceptable*

Parameter	CAPOTEN (captopril) (N = 181)	Methyldopa (N = 143)	Propranolol (N = 162)
AT WORK			
Work Performance	●	●	●
Cognitive Skills	●	●	●
AT PLAY			
Physical Symptoms	●	●	●
Life Satisfaction	●	●	●
Social Participation	●	●	●
IN GENERAL			
Well-being	●	●	●
Sexual Function	●	●	●
Sleep Disturbance	●	●	●

● Improved**
● Stable
● Worsened**

**Statistically significant change, compared to pre-treatment

Changes in patient lifestyle during active therapy with Capoten, methyldopa and propranolol (30-centre, randomized, double-blind, 24-week study)[1]

SQUIBB
Innovators in cardiovascular medicine

(captopril)
The World's #1 ACE Inhibitor†

b.i.d.

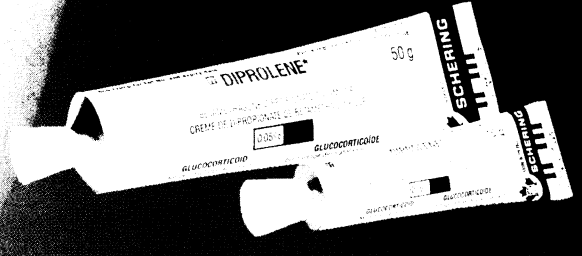
For prescribing information see page 1936

Bad news for difficult dermatoses!

For those stubborn skin conditions that need a more potent topical steroid, **Diprolene**'s 'dissolved-state' formulations have been shown to produce significantly greater improvement in crusting, scaling and excoriation than clobetasol propionate ointment.[1]

Good news for patients!

And just as important for you and your patients "Notably, the [**Diprolene**] preparation was well tolerated by patients."[1] No major adverse reactions were reported. **Diprolene** glycol cream and ointment go on smoothly and don't stain clothes or leave greasy residues. **Diprolene** promotes high patient acceptance and compliance, an important consideration in topical steroid therapy.



Dissolved-state

Diprolene®

GLYCOL CREAM AND OINTMENT

betamethasone dipropionate glycol 0.05%)

Patient-friendly steroid therapy

[1] [illegible] et al.: Acta Therapeutica 1983; 9:197-207.

PAAB

[illegible] see page 1748

BENEATH YOUR HYPERTENSIVE'S CALM EXTERIOR

COULD BE PRESSURE SURGES CAUSED BY STRESS...

UNLESS...

HER ANTIHYPERTENSIVE PROTECTS LIKE β_1-β_2 BLOCKADE

Many of your hypertensive patients may have above normal catecholamine levels and experience surges of blood pressure during regular daily stress.[2] Agents that affect mainly β_1 receptors – or no beta receptors at all – may leave your patients more vulnerable to this excessive stimulation.[1,2]

NONSELECTIVE (β_1-β_2) INDERAL*-LA CAN PROTECT YOUR PATIENTS... AND MAY TAKE THE STRESS OUT OF CONTROLLING HYPERTENSION

Maintaining β_1-β_2 blockade can protect hypertensives from such significant pressure spikes on a 24-hour basis.[2] Therapy with once-daily INDERAL-LA is an excellent choice. In fact, when it comes to acceptability and patient compliance, INDERAL-LA has been proven superior to propranolol tablets.[3,4]

THE ONE YOU KNOW BEST KEEPS LOOKING BETTER

ONCE-DAILY

INDERAL*-LA

(PROPRANOLOL HYDROCHLORIDE)

CONTROLLED-RELEASE CAPSULES

80 mg 120 mg 160 mg

†

FOR MAINTENANCE THERAPY IN HYPERTENSION

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Ayerst*

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*Reg'd TM 1324

For prescribing information see page 1780

sweating
chest pains
numbness of extremities
insomnia
lack of concentration
palpitations
feeling blue
crying

The message is clear.
When a patient presents with mixed messages of anxiety, call for 'Lectopam'.

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bromazepam

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D4289

A First Line Asthma Therapy with a proven track record.

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For over 15 years Alupent® Syrup has enjoyed the trust of doctors and patients alike.

Safety

Alupent® Syrup is associated with minimal adverse G.I. side effects.[1,2,3,4] The adverse effects, behavioral difficulties and continuous blood level monitoring associated with theophylline may be avoided.[1,2,5,6,7]

Efficacy

Alupent® Syrup provides more immediate relief from bronchoconstriction than theophylline.[1,4]

Compliance

Simple dosage and pleasant taste for convenience of therapy.[2] Ages 4-12 years: 10 mg (1 teaspoon) t.i.d. above 12 years: 20 mg (two teaspoons) t.i.d. - q.i.d.

... made just for kids

Pr **Alupent® Syrup**

(orciprenaline sulphate)

No Sugar
No Alcohol
No Sedatives
No Tranquilizers

Boehringer Ingelheim

PAAB CCPP

For prescribing information see page 1792

Boehringer Ingelheim (Canada) Ltd./Ltée
977 Century Drive, Burlington, Ontario L7L 5J8

PCE*

particle coated erythromycin tablets
Dispertab* Tablets 333 mg — Antibiotic

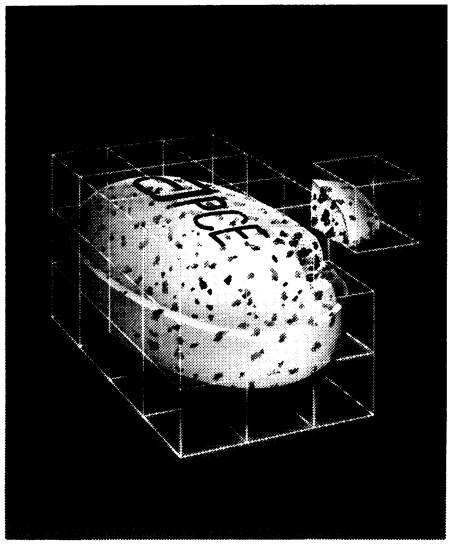
DESCRIPTION
PCE* contains polymer-coated erythromycin base particles.

ACTIONS, CLINICAL PHARMACOLOGY
Erythromycin exerts its antibacterial action by binding to the 50 S ribosomal subunit of susceptible bacteria and suppressing protein synthesis. Erythromycin is usually bacteriostatic but may be bactericidal in high concentrations or against highly susceptible organisms.
Orally administered erythromycin base is absorbed in the microbiologically active form. Significant interindividual variations in the absorption of erythromycin were observed and some patients do not achieve maximal serum levels.
Erythromycin is largely bound to plasma proteins (over 70%).
In the presence of normal hepatic function, erythromycin is concentrated in the liver and is excreted in the bile; the effect of hepatic dysfunction on biliary excretion of erythromycin is not known.
From 12 to 15 percent of intravenously administered erythromycin is excreted in the active form in the urine. After oral administration, less than 5% of the administered dose can be recovered in the active form in the urine.

INDICATIONS AND CLINICAL USES
Erythromycin may be indicated for the treatment of infections caused by susceptible strains of the designated microorganisms in the diseases listed below:
Upper respiratory tract infections of mild to moderate severity caused by *S. pyogenes* (group A beta-hemolytic streptococci), *S. pneumoniae* and *H. influenzae*. Not all strains of *H. influenzae* are susceptible to erythromycin at the concentrations of the antibiotic achieved with usual therapeutic doses.
Lower respiratory tract infections of mild to moderate severity caused by *S. pyogenes* (group A beta-hemolytic streptococci), *S. pneumoniae* and *M. pneumoniae*.
Skin and soft tissue infections of mild to moderate severity caused by *S. pyogenes* and *S. aureus* (resistance of staphylococci may emerge during treatment).
Primary syphilis caused by *T. pallidum*. Erythromycin may be an alternate choice of treatment for primary syphilis in patients allergic to penicillins. Spinal fluid examinations should be performed before treatment and as part of the post-therapy follow-up.
Diphtheria caused by *C. diphtheriae*. As an adjunct to antitoxin, to prevent the establishment of carriers, and to eradicate the organisms in carriers.
Erythrasma caused by *C. minutissimum*.
Pertussis caused by *B. pertussis*. Erythromycin is effective in eliminating the organism from the nasopharynx of infected individuals, rendering them non-infectious. Some clinical studies suggest that erythromycin may be helpful in the prophylaxis of pertussis in exposed susceptible individuals.
Legionnaires' disease caused by *L. pneumophila*. Although no controlled clinical efficacy studies have been conducted, *in vitro* and limited preliminary clinical data suggest that erythromycin may be effective in treating Legionnaires' disease.
Specimens for bacteriologic culture should be obtained prior to therapy in order to isolate and identify the causative organisms and to determine their susceptibility to erythromycin. Therapy may be instituted before results of susceptibility studies are known; however, antibiotic treatment should be re-evaluated when the results become available or if the clinical response is not adequate.

CONTRAINDICATIONS
Erythromycin is contraindicated in patients with known hypersensitivity to this antibiotic.

WARNINGS
Erythromycin should be administered with caution to any patient who has demonstrated some form of allergy to drugs.
If an allergic reaction to erythromycin occurs, administration of the drug should be discontinued. Serious hypersensitivity reactions may require epinephrine, antihistamines, or corticosteroids.
There have been reports of hepatic dysfunction, with or without



jaundice, occurring in patients receiving erythromycin products. If findings suggestive of significant hepatic dysfunction occur, therapy with erythromycin products should be discontinued.
Pseudomembranous colitis has been occasionally reported to occur in association with erythromycin therapy. Therefore, it is important to consider its diagnosis in patients administered erythromycin who develop diarrhea. Mild cases of colitis may respond to drug discontinuation alone. Moderate to severe cases should be managed with fluid, electrolyte and protein supplementation as indicated. If the colitis is not relieved by discontinuation of erythromycin administration or when it is severe, consideration should be given to the administration of vancomycin or other suitable therapy. Other possible causes of the colitis should also be considered.

PRECAUTIONS
Prolonged or repeated use of erythromycin may result in an overgrowth of non-susceptible bacteria or fungi and organisms initially sensitive to erythromycin. If superinfection occurs, erythromycin should be discontinued and appropriate therapy instituted.
Since erythromycin is principally excreted by the liver, caution should be exercised when erythromycin is administered to patients with impaired hepatic function.

Drug Interactions
Recent data from studies of erythromycin in patients reveal that its use in patients who are receiving high doses of theophylline may be associated with an increase in serum theophylline levels and potential theophylline toxicity. In case of theophylline toxicity and/or elevated serum theophylline levels, the dose of theophylline should be reduced while the patient is receiving concomitant erythromycin therapy.
Erythromycin should be used with caution if administered concomitantly with the following drugs:
Lincomycin, Clindamycin, Chloramphenicol: *In vitro* experiments have demonstrated that binding sites for erythromycin, lincomycin, clindamycin and chloramphenicol overlap and competitive inhibition may occur.
Carbamazepine, Digoxin: Concomitant administration of erythromycin with carbamazepine or digoxin have been reported to result in elevated plasma levels of these agents, leading to toxicity in some patients.
Oral anticoagulants: Published reports indicate that caution should be observed when some antibiotics, including erythromycin, and oral anticoagulants are used concurrently since prolonged prothrombin time may occur.
Ergotamine: There are reports that ischemic reactions may occur when erythromycin is given concurrently with ergotamine-containing drugs.
Cyclosporin: There have been reports that there is a rise in plasma cyclosporin levels during concomitant administration of erythromycin.

Pregnancy
The safety of erythromycin for use during pregnancy has not been established. Erythromycin crosses the placental barrier.

Nursing mothers
The safety of erythromycin for use during breast feeding has not been established. Erythromycin is excreted in breast milk.

Neonates
The safety of erythromycin for use in neonates has not been established.

ADVERSE REACTIONS
Gastrointestinal: abdominal cramping, discomfort. Nausea, vomiting and diarrhea are also observed but less frequently. Pseudomembranous colitis has been occasionally reported to occur in association with erythromycin therapy. (see WARNINGS).
Allergic reactions: Urticaria, mild skin eruptions and anaphylaxis.
Miscellaneous: During prolonged or repeated therapy, there is a possibility of overgrowth of nonsusceptible bacteria or fungi and organisms initially sensitive to erythromycin (e.g. *Staphylococcus aureus, Hemophilus influenzae*). If such infections occur, erythromycin should be discontinued and appropriate therapy instituted.
Occasionally there have been reports of reversible hearing loss occurring chiefly in patients with renal insufficiency and in patients receiving high doses of erythromycin.

SYMPTOMS AND TREATMENT OF OVERDOSAGE
Symptoms: In oral doses of over 2 g/day, abdominal discomfort, nausea or diarrhea may occur.
Treatment: There is no specific treatment for overdosage. Erythromycin should be discontinued and gastric lavage should be considered; otherwise, the treatment should be symptomatic. Erythromycin is not removed by peritoneal dialysis or hemodialysis.

DOSAGE AND ADMINISTRATION
Dosage (for all erythromycin preparations)
Adults:
Upper and lower respiratory tract and skin and soft tissue infections: A therapeutic dosage of oral erythromycin should be administered for at least 10 days. The recommended dosage is 1 g per day given two, three or four times a day, depending on the erythromycin preparation chosen. Depending on the severity of infection, larger doses may be considered; however, a single dose should not exceed 1 g.
Primary syphilis: 2 g per day given in divided doses either twice a day, three times a day or four times a day depending on the erythromycin preparation chosen, over a period of 10 to 15 days.
Pertussis: Although optimum dosage and duration of therapy have not been established, doses of erythromycin utilized in reported clinical studies were 40 to 50 mg/kg/day, given in divided doses for 5 to 14 days.
Legionnaires' disease: Although optimal dosages have not been established, doses utilized in reported clinical data were 1 to 4 g daily in divided doses.
Prophylaxis: For prophylaxis against bacterial endocarditis due to alpha-hemolytic streptococci in penicillin-allergic patients with valvular heart disease when undergoing dental procedures or surgical procedures of the upper respiratory tract, the adult dose is 1 g orally 1 hour prior to the procedure, and then 500 mg orally 6 hours later. For continuous prophylaxis against recurrences of streptococcal infections in persons with a history of rheumatic heart disease, the dose is 250 mg twice a day.

Administration
Adults: PCE* 333 mg tablets should be administered for at least 10 days given three times a day. Maximum blood levels are obtained when PCE* is given in the fasting state (1/2 hr and preferably 2 hours before meals).

AVAILABILITY
PCE* (particle coated erythromycin tablets) is supplied in bottles of 100 and 250 ovaloid pink-speckled white Dispertab* tablets containing 333 mg of erythromycin base.
Product monograph available upon request.

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MONTRÉAL, CANADA

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Actions speak louder than words.

Feldene has been helping arthritic patients worldwide for 10 years.

Feldene – the original and only clinically-tested piroxicam in Canada.

Start once-a-day

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for full anti-arthritic action.

Available as 10 mg and 20 mg capsules or suppositories.
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Low-dose

Catapres®

(clonidine HCl)

PRESCRIBING INFORMATION

Composition 2-(2,6-dichlorophenylamino)-2-imidazoline hydrochloride.

Indications Catapres has been used successfully to treat hypertension of all grades of severity.

Contraindications There are no known absolute contraindications to the use of Catapres.

Warnings If Catapres therapy is discontinued for any reason, withdrawal should be done gradually over several days rather than abruptly. There have been rare instances of rebound hypertensive crises following sudden discontinuation of high doses of the drug. This can be effectively controlled by reinstituting Catapres at the previous dosage level; however if more rapid control is necessary, intravenous infusions of alpha adrenergic blocking agents, such as intravenous phentolamine (5-10 mg doses at 5 minute intervals up to a total of 30 mg) are effective in reducing the blood pressure.

Precautions Patients with a known history of depression should be carefully supervised while under treatment with Catapres, as there have been occasional reports of further depressive episodes occurring in such patients. As an abrupt withdrawal of Catapres is followed in rare instances by an excess of circulating catecholamines, caution should be exercised in the concomitant use of drugs which affect the metabolism or the tissue uptake of these amines (MAO inhibitors and tricyclic anti-depressants respectively.)
A few instances of a condition resembling Raynaud's phenomenon have been reported. Caution should therefore be observed if patients with Raynaud's disease or thromboangiitis obliterans are to be treated with Catapres. Catapres has a mucous membrane drying effect on the eyes. On rare occasions this has led to corneal ulceration.
As with any drug excreted primarily in the urine, smaller doses of Catapres are often effective in treating patients with a degree of renal failure.
The use of Catapres during the first trimester of pregnancy is subject to the normal precautions surrounding the use of any drug. Animal tests have shown no evidence of foetal abnormality, though there was some decreased fertility.

Adverse effects The most commonly encountered side effects are initial sedation and dry mouth. However, these effects are seldom severe and tend to be dose related and transient.
There are occasional reports of fluid retention and weight gain during the initial stages of treatment with Catapres. This side effect is usually transient but the addition of a diuretic will correct any tendency to fluid retention in these cases.
Other occasional drug-related side effects which have been noted in literature include dizziness, headache, dryness, itching or burning of the eyes, rarely corneal ulceration, nocturnal unrest, nausea, euphoria, constipation, impotence (rarely) and agitation on withdrawal of therapy. Facial pallor has occasionally been noted at high dosage levels.
No toxic reactions have been observed on investigating blood status, renal function and liver function. Long-term treatment has shown no adverse effect on blood urea nitrogen levels, and in patients with pre-existing renal damage there is no suggestion of further impairment of the renal blood flow despite a fall in arterial blood pressure.

Dosage Initially 0.05-0.1 mg four times daily. This dosage may be increased every few days until satisfactory control is achieved. ***When used alone*** the final dosage usually ranges between 0.2 and 1.2 mg daily. The last dose of the day should be given immediately before retiring to ensure blood pressure control during sleep.

Catapres used with a diuretic. Catapres has been used successfully together with chlorthalidone, furosemide and the thiazide diuretics. Lower doses of Catapres or the diuretic may be used to achieve the same degree of blood pressure control whenever a diuretic is added to the Catapres regimen or vice-versa. In these circumstances, most ***mild-to-moderate hypertensives*** can be controlled using only 0.3-0.6 mg of Catapres daily in divided doses.

Availability
1. ***0.1 mg Tablet:*** A white, single-scored tablet, impressed with the motif on one side and the Boehringer Ingelheim symbol on the reverse. Bottles of 100 and 500 tablets.
2. ***0.2 mg Tablets:*** An orange, single-scored tablet, impressed with the motif on one side and the Boehringer Ingelheim symbol on the reverse. Bottles of 100 and 500 tablets.
Combipres is available as a pink oval, biconvex tablet containing 0.1 mg Catapres and 15 mg chlorthalidone. Supplied in bottles of 100 tablets.
For further prescribing information, consult the Catapres Product Monograph or your Boehringer Ingelheim representative.

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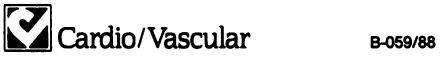

B-059/88

skill, patient characteristics, and practice circumstance do indeed produce variations in referral rate, how much variation is acceptable? Would it be desirable to describe ideal patterns of referral and, even if that were possible, what sort of training programs could be structured to produce them, and how would such programs be mounted and results monitored?

The difficulty is that the research efforts to date seem to have concentrated on counting the rate of a process that is, to put it charitably, poorly understood. In this field, researchers have done things backward, and quantitative research that counts numbers of events seems less likely to lead to understanding than qualitative methods that look at events one at a time. Dowie[5] in the United Kingdom has produced some useful work in this area, as have Wilkin and Smith,[3] while in Canada, Grant[6] and Muzzin[7] have done pioneering qualitative studies.

Concerns about the costs of health care may lead to changes in referral systems based more on politics than on a real understanding of the situation. If this happens, we will have only ourselves to blame for neglecting a subject in which we continue to profess expertise, and yet are unable to explain what we do and why. ■

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Effective allergy relief. Day in, day out.

HISMANAL* astemizole
TABLETS AND SUSPENSION

INDICATIONS HISMANAL* astemizole is indicated for the treatment of seasonal allergic rhinitis, allergic conjunctivitis, chronic urticaria and other allergic conditions. **CONTRAINDICATIONS** HISMANAL is contraindicated in patients with known hypersensitivity to the drug. **WARNINGS Use in Pregnancy:** Experience with HISMANAL in pregnant women is inadequate to determine whether there exists a potential for harm to the fetus. Therefore, HISMANAL should be used in pregnant women only when, in the opinion of the physician, the potential benefits outweigh the possible hazards. **PRECAUTIONS Use with C.N.S. Depressants:** HISMANAL had no potentiating effects with alcohol or other C.N.S.depressants in clinical and laboratory studies. **Drug Interaction:** No drug interaction has been found between astemizole and bronchodilators, other systemic antihistamines, antibiotics, sulfonamides, corticosteroids, estrogens, progestogens, oral contraceptives, diuretics, antihypertensive agents, analgesics and anti-inflammatory agents, tranquillizers and antidepressants. **ADVERSE REACTIONS** The incidence of adverse experiences during astemizole treatment was comparable to that during placebo control treatment. During chronic treatment, body weight tended to increase. This is probably due to an increase in appetite. Astemizole had no effect on laboratory parameters. **SYMPTOMS AND TREATMENT OF OVERDOSAGE** In cases reported to date, involving oral ingestions of up to 300 mg of HISMANAL astemizole, no untoward effects have been noted. **DOSAGE AND ADMINISTRATION** Adults and children older than 12 years of age: 1 tablet (10 mg) once a day. HISMANAL is not recommended for use in children under the age of 12 years in the absence of professional guidance. The following dosage may guide the physician when prescribing HISMANAL for children under 12 years of age: Children between 6 and 12 years of age: ½ tablet (5 mg) once a day. Children under 6 years of age: 2 mg (1 mL suspension) per 10 kg/day. To achieve optimal absorption, astemizole should be taken on an empty stomach. Patients should be instructed that peak symptomatic relief may not be achieved for up to 3 days. It is therefore important that daily therapy be continued for at least this long in order to obtain and maintain this relief. Clinical effects of the medication may be seen for several days following discontinuation of therapy. **AVAILABILITY Tablets:** Each white, round scored compressed tablet contains 10 mg astemizole. Available in blister packs of 6, 12 and 18 tablets and HDPE bottles of 100. **Suspension:** Each mL contains 2 mg astemizole. Available in bottles 30 mL. Product Monograph available on request.

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JANSSEN PHARMACEUTICA

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la capacité statistique de démontrer ces différences. On peut démontrer cette difficulté en utilisant des intervalles de confiance de 95% dans les taux de consultations observés. Wilkin et Smith [3] ont démontré que, même si un taux observé de six demandes de consultation par 100 patients pour un médecin donné, sur un total de 654 visites, s'avère une bonne estimation de l'intervalle (4.2 à 7.8), un taux de 8.7 demandes de consultation basées sur seulement 138 visites au bureau révèle des intervalles de confiance beaucoup plus larges (4.0 à 13.4) et, donc, la nécessité d'être beaucoup plus prudent lorsqu'on interprète de telles données. Malheureusement, la plupart des études sur les demandes de consultation ne se sont pas suffisamment attardées à ce problème de précision dans les estimations du taux de demandes.

Même si nous pouvions obtenir des données significatives sur le plan statistique démontrant effectivement des variations dans les taux de demandes de consultation, nous serions toujours confrontés à ce problème d'interprétation. Peut-on s'attendre à ce que tous les praticiens aient le même taux de demandes de consultation ? Quel serait donc le taux idéal ? Le taux idéal risque-t-il de varier si l'on mesure aussi les composantes économique et de soins au patient ? Généralistes et spécialistes peuvent-ils réalistement s'entendre sur le taux idéal et, s'il faut trancher, les opinions de quel groupe faudrait-il choisir ? Si les différences au niveau des connaissances, des habiletés, des caractéristiques des patients et du type de pratique produisent effectivement des variations dans le taux de demandes de consultation, quel pourcentage de variation serait acceptable ? Serait-il souhaitable de définir des protocoles idéals et, si c'était possible, quelle sorte de programmes de formation pourrait-on structurer pour pouvoir les appliquer, comment pourrait-on les organiser et comment pourrait-on en évaluer les résultats ?

Les efforts de recherche, à ce jour, semblent s'être attardés à procéder au décompte du taux d'un processus qui, il faut bien le dire, n'est que très mal compris. Dans ce domaine, les chercheurs ont commencé par la fin, et la recherche quantitative qui dénombre les événements a moins de chances de contribuer à la compréhension que les méthodes qualitatives qui observent un à un les événements. Au Royaume-Uni, Dowie[5] a produit une recherche utile dans ce domaine, tout comme Wilkin et Smith[3] alors qu'au Canada, Grant[6] et Muzzin[7] ont innové au niveau des études qualitatives.

Les préoccupations quant au coût des soins de santé risquent d'altérer les modes de consultation qui deviendront davantage axés sur des questions d'ordre politique que sur la compréhension de la situation. Dans une telle éventualité, nous serons les seuls à blâmer pour avoir négligé un sujet dont nous continuons de professer l'expertise, tout en étant incapable d'expliquer ce que nous faisons et pourquoi.

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Uniphyl® Tablets

theophylline sustained release tablets 400 mg and 600 mg

THERAPEUTIC CLASSIFICATION: Bronchodilator

INDICATIONS: The symptomatic treatment of reversible bronchoconstriction associated with bronchial asthma, chronic obstructive pulmonary emphysema, chronic bronchitis and related bronchospastic disorders.

CONTRAINDICATIONS: Uniphyl tablets (theophylline sustained release tablets) should not be administered to patients with hypersensitivity to xanthines, to patients with coronary artery disease where cardiac stimulation might prove harmful, or to patients with active peptic ulcer.

WARNINGS: In clinical situations where immediate bronchodilation is required, such as status asthmaticus, Uniphyl tablets (a sustained release preparation) are not appropriate.

Theophylline has a narrow therapeutic index, the margin of safety above therapeutic doses is small.

Whenever signs of intolerance to theophylline develop, the therapy should be reassessed.

Theophylline clearance can be affected by various disease states, the age of the patient, concomitant use of other medication and lifestyle habits (See Precautions).

A dosage schedule in the pediatric population has not been established. Use of Uniphyl tablets in children under 12 years of age is not recommended.

PRECAUTIONS: General: There is a marked variation in serum levels achieved in different patients given the same dose of theophylline. Therefore, high serum levels may occur in some patients receiving doses considered to be conventional. The possibility of theophylline overdose should always be considered. Overdoses of theophylline may cause serious side effects such as tachycardia, arrhythmias, seizures, vascular collapse and even death. These may occur without warning and may not be preceded by less severe side effects such as nausea or restlessness.

The variability in serum levels is primarily due to differences in the rate of metabolism. Therefore, it is advisable to individualize the dosage regimen. Ideally, all patients should have serum theophylline levels measured which would enable doses and dosing regimens to be tailored for each patient in order to maintain therapeutic levels, ensure optimal clinical response and avoid toxicity. The incidence of adverse reactions increases at theophylline levels greater than 15 mg/L (82.5 μ mol/L) and levels above 20 mg/L (110 μ mol/L) are usually quite toxic in most adults.

Although Uniphyl tablets have pharmacokinetic properties similar to other sustained release theophylline formulations, it is not possible to ensure interchangeability between different formulations. Careful clinical monitoring is required when changing from one formulation to another. The equivalent content of anhydrous theophylline is the active ingredient that determines the blood concentration and clinical response. If a change in theophylline product is made and it involves a change in anhydrous theophylline equivalence, the dose should be adjusted accordingly.

Patients with Special Diseases and Conditions: Theophylline clearance is decreased, which may result in increased serum levels and resultant toxicity in patients:

- with impaired liver or kidney function
- over 55 years of age, particularly males and those with chronic lung disease
- with cardiac failure from any cause
- with active influenza or other viral disease or after influenza immunization
- with a high carbohydrate, low protein diet
- patients taking certain drugs such as cimetidine, erythromycin and troleandomycin

Laboratory monitoring of serum theophylline levels is especially appropriate in the above individuals in order to maintain the appropriate theophylline dosage.

Patients who are rapid metabolizers of theophylline, such as the young, smokers and some non-smoking adults may not be suitable candidates for once-daily dosing. In rapid metabolizers, peak to trough fluctuations in theophylline levels may be greater than desirable or result in side-effects at the time of maximum levels and/or the recurrence of symptoms toward the end of the 24 hour dose interval when levels are lowest. In such patients, dividing the total daily theophylline dose into two equal doses may be indicated.

Theophylline is known to stimulate gastric acid secretion and may also act as a local G.I. irritant. Therefore, the drug should only be used with caution in patients with a history of peptic ulcer disease.

Theophylline may cause arrhythmia and/or worsen pre-existing arrhythmia. Any significant change in rate and/or rhythm warrants monitoring and further investigation.

Many patients who require theophylline may exhibit tachycardia due to their underlying disease process so that the cause/effect relationship to elevated serum theophylline concentrations may not be appreciated.

Use with caution in patients with severe cardiac disease, severe hypoxemia, hypertension, hyperthyroidism, acute myocardial injury, cor pulmonale, congestive heart failure, liver disease, in the elderly (especially males).

Drug Interactions:

A. **Theophylline pharmacokinetics are altered by the concurrent use of various drugs as listed below:**

Drug	Effect on theophylline clearance and elimination half-life	
Cimetidine, propranolol, allopurinol, macrolide antibiotics (erythromycin, troleandomycin), oral contraceptives.	↑ T1/2,	↓ clearance
Alkalinizing agents	↑ T1/2,	↓ clearance
Influenza vaccine	↑ T1/2,	clearance reported to be decreased or no change
Phenytoin, barbiturates, carbmazepine, isoproterenol, rifampin	↓ T1/2,	↑ clearance
Tobacco	↓ T1/2,	↑ clearance
Acidifying agents	↓ T1/2,	↑ clearance

B. **Concurrent use of theophylline influences the actions of certain drugs:**

Drug	Influence of theophylline
Digitalis glycosides	↑ cardiac effect
Thiazides	↑ diuresis
Nephrotoxic drugs	↑ nephrotoxicity
Lithium	↑ ratio of lithium/creatinine clearance, thus a decrease in serum lithium levels
Sympathomimetic amines	↑ toxicity, ↑ CNS stimulation
Coumarin anticoagulants	↓ anticoagulant activity ↑ prothrombin and fibrinogen blood concentrations ↓ prothrombin time
Allopurinol	↓ antihyperuricemic action
Probenicid and pyrazolon derivatives	↓ uricosuric action

Use in Pregnancy and Lactation: Theophylline crosses the placental barrier and also passes freely into breast milk, where concentrations are similar to plasma levels. Safe use in pregnancy has not been established relative to possible adverse effects on fetal development, but neither have adverse effects on fetal development been established. Therefore, use of theophylline in pregnant women and nursing mothers should be balanced against the risk of uncontrolled asthma.

Laboratory Test Interactions: When plasma levels are measured by spectrophotometric methods, coffee, tea, cola beverages, chocolate and acetaminophen contribute to falsely high values.

When high pressure liquid chromatography (HPLC) method is used, plasma theophylline concentration may be falsely increased by caffeine, some cephalosporines and sulfa medications.

Theophylline may cause elevation of urine catecholamines, plasma uric acid and free fatty acids.

Food Interaction: When immediate release theophylline formulations are administered with food, the rate of absorption is reduced but absorption remains complete. Various sustained release formulations, because of differences in their release mechanisms, may be affected in different ways by concomitant food intake.

Studies have shown that Uniphyl tablets are more completely absorbed when taken with food as opposed to under fasting conditions (See Bioavailability and Clinical Data).

ADVERSE REACTIONS: The most common adverse reactions are gastric irritation, nausea, vomiting, epigastric pain, and tremor. These are usually early signs of toxicity, however, with high doses ventricular arrhythmias or seizures may be the first signs to appear.

Adverse reactions include:

Gastrointestinal: nausea, vomiting, epigastric pain, hematemesis, diarrhea, anorexia, intestinal bleeding and reactivation of peptic ulcer.

Central Nervous System: headache, irritability, restlessness, insomnia, twitching, convulsions and reflex hyperexcitability.

Cardiovascular: palpitations, tachycardia, hypotension, circulatory failure, ventricular arrhythmias, extrasystoles and flushing.

Renal: albuminuria, diuresis and hematuria.

Others: hyperglycemia, tachypnea and inappropriate ADH syndrome.

DOSAGE AND ADMINISTRATION: Administration and dosing of theophylline should be individualized in respect of the patient's clinical response and serum theophylline levels. There is considerable patient-to-patient variation in the daily theophylline dose required to achieve therapeutic and safe levels. Ideally, all patients should have serum theophylline levels measured which would enable doses and dosing regimens to be tailored in order to maintain therapeutic levels, ensure optimal clinical response and avoid toxicity. Therapeutic serum levels are generally considered to be between 10 and 20 mg/L (55-110 μ mol/L). Dosage calculations should be based on lean body mass (ideal body weight). A serum level of 20 mg/L (110 μ mol/L) is an important reference point in terms of toxicity (See Precautions).

Initial Adult Dose: For patients not currently receiving oral theophylline, the recommended initial dose is 400-600 mg once-daily.

In patients currently controlled on oral theophylline, Uniphyl therapy should start at the same daily theophylline dosage (mg for mg basis) provided by the previous formulation. For example, a patient receiving 400 mg twice-daily (800 mg daily dosage) would be given two 400 mg Uniphyl tablets once-daily. A minimum of 12 hours should elapse between a patient's last dose of the previous oral theophylline formulation and the first dose of Uniphyl.

It is recommended that once-daily Uniphyl be taken in the evening. Studies have demonstrated that while the bioavailability and pharmacokinetics of Uniphyl tablets were not significantly different between morning and evening dosing, a better clinical response was obtained with evening dosing. Subsequent studies indicate that the clinical advantages of evening dosing are likely a result of the maximum theophylline levels occurring in the early morning hours, a time of greatest bronchoconstriction and symptoms for many asthmatics.

It is advisable that Uniphyl be taken with food, or within 1-2 hours of mealtime, as studies have suggested that absorption may be incomplete if taken under conditions of prolonged fasting.

Overall, therefore, it is recommended that most patients should take once-daily Uniphyl with, or shortly following, the evening meal.

Dose Titration: Dosage adjustments should be based on the patient's clinical response and/or serum theophylline levels, with increases of 1/2 tablet per day at 3 to 4 day intervals. Individual requirements vary considerably, therefore, the physician should be prepared to adjust each patient's dose. Do not attempt to maintain any dosage that is poorly tolerated.

Monitoring serum theophylline levels is important, especially during initiation of therapy and dosage adjustment. For serum levels to be most useful, it is important that the patient not have missed or added any doses during the previous 3 days and that the dose intervals remained relatively constant. At steady-state, Uniphyl tablets produce peak theophylline levels between 8 and 12 hours post-dose, and trough levels almost always occur at the time of dosing. During once-daily dosing, the mean fluctuation between peak and trough theophylline levels is 130%.

The generally accepted optimal therapeutic range is 10-20 mg/L (55-110 μ mol/L), although some patients obtain a very good bronchodilator effect from serum levels less than 10 mg/L (55 μ mol/L). In cases where it is not possible to monitor theophylline levels, patients should be closely observed for signs of toxicity and dosages greater than 13 mg/kg/day (or 900 mg/day, whichever is less) should not be given.

Uniphyl tablets should not be chewed or crushed, they may be halved.

AVAILABILITY: Uniphyl (theophylline sustained release tablets) is available in 400 mg and 600 mg strengths.

The 400 mg Uniphyl tablets are round, flat-faced, white and scored. They are engraved U/400 on one side and PF on the reverse.

The 600 mg Uniphyl tablets are capsule shaped, concave-faced, white and scored. They are engraved U 600 on one side and PF on the reverse.

Supplied in opaque, plastic bottles of 50 tablets.

Dispense in amber or opaque containers.

Store below 30°C (86°F).

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Product Monograph available on request.

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MEMBER PMAC PAAB CCPP

WE'VE CUT OUT THE ONE THING WE KNEW YOU WOULDN'T MISS FROM VOLTAREN® T.I.D.

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We've cut out the midday dosage from Voltaren® 50 mg enteric coated.

Because it's the one thing we knew you wouldn't miss.

And neither will your OA patients.

When we looked for a way to improve Voltaren 50 mg enteric coated, there weren't a lot of options.

Voltaren® is one of the best-tolerated antiarthritics available. Worldwide data indicates that the incidence of gastric or duodenal ulceration and bleeding in patients on Voltaren is rare.[1]

In fact, there was one way to make Voltaren even more convenient.

Since many patients forget to take it, the midday dosage is one thing that can get in the way of long term maintenance OA therapy.

So we simply cut it out.

Now you can prescribe Voltaren® SR 75 mg Twice Daily, offering improved convenience and improved compliance for improved OA control.

New VOLTAREN® SR 75 mg Twice Daily

Sustained release diclofenac sodium.

PROVEN TOLERABILITY AT MAXIMUM DOSAGE.[2]

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For prescribing information see page 1942

Geigy
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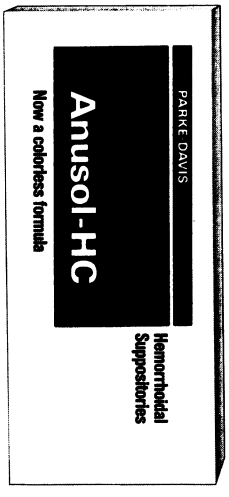
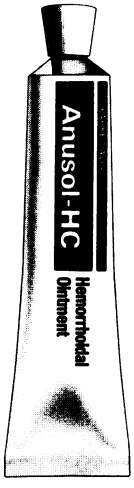
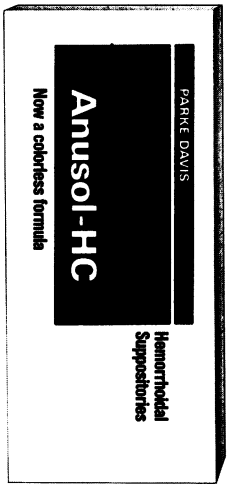
L5N 2W5

Hurts.

Helps.







For relief of the pain, swelling
and inflammation of hemorrhoids.

Pr Anusol*-HC

hydrocortisone – zinc sulfate

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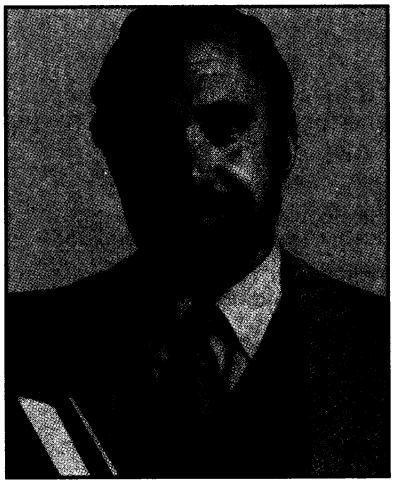
Full prescribing information available on request.

Who's
TAKING MEVACOR®?
(lovastatin)



Patient profile*:

Male, age 44

College professor

Elevated total cholesterol – 9.1 mmol/L (352 mg/dL) after attempts to lower cholesterol through diet and exercise

Total cholesterol after 4 months on MEVACOR® (40 mg b.i.d.) plus continued diet, is 6.0 mmol/L (232 mg/dL)

*Hypothetical case. It should be determined that patients for whom treatment with MEVACOR® is being considered have an elevated LDL-cholesterol as the cause for an elevated serum cholesterol.

Effectively lowers elevated cholesterol in many patients

- MEVACOR® has a beneficial effect on all three key lipid parameters

TOTAL CHOLESTEROL	LDL-CHOLESTEROL	HDL-CHOLESTEROL
–18% to –34%	–19% to –39%	+3% to +13%

Mean changes in two dose-ranging clinical studies[1] after six weeks. Doses ranged from 20 mg once daily to 40 mg b.i.d.

- **MEVACOR® lowered triglycerides:** In these studies MEVACOR®, given once-a-day, also produced a reduction in median triglyceride values from baseline, ranging from –7% to –22%.
- **Response is usually rapid and consistent.** In clinical studies, substantial response was usually seen at 2 weeks, with maximum response at 4 to 6 weeks.
- **Response was maintained** during therapy.

For many patients with primary hypercholesterolemia (Types IIa and IIb)

Mevacor®

(lovastatin) 20 mg tablets

when diet and other measures alone are inadequate

PLEASE SEE ENCLOSED PRESCRIBING INFORMATION, INCLUDING SIDE EFFECTS, CONTRAINDICATIONS AND PRECAUTIONS ON LIVER, MUSCLE, AND EYE

[1] Data on file, Merck Sharp & Dohme Research Laboratories

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MSD
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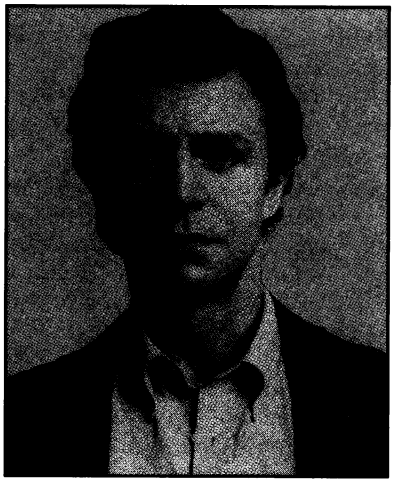
who's TAKING MEVACOR®?
(lovastatin)



Patient profile*:

Male, age 42, asymptomatic for cardiac disease

Father and paternal uncle died prematurely of coronary heart disease

Elevated total cholesterol of 7.3 mmol/L (280 mg/dL) on a cholesterol-lowering diet

After 7 weeks on MEVACOR® (20 mg at suppertime) plus continued diet, total cholesterol is 5.9 mmol/L (230 mg/dL)

*Hypothetical case. It should be determined that patients for whom treatment with MEVACOR® is being considered have an elevated LDL-cholesterol as the cause for an elevated serum cholesterol.

Very good tolerability for many patients

- In clinical studies, side effects were usually mild and transient
- About 2% of patients were discontinued from all studies (controlled and uncontrolled) due to drug-related adverse events.

For many patients with primary hypercholesterolemia (Types IIa and IIb)

Mevacor®

(lovastatin) 20 mg tablets

when diet and other measures alone are inadequate

PLEASE SEE ENCLOSED PRESCRIBING INFORMATION, INCLUDING SIDE EFFECTS, CONTRAINDICATIONS AND PRECAUTIONS ON LIVER, MUSCLE, AND EYE

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MVC-89-CDN-2498-JA

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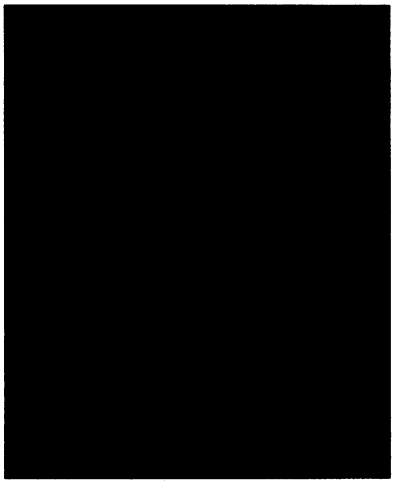
who's TAKING MEVACOR®?
(lovastatin)



Patient profile*:

- Female, age 61
- Smokes more than a pack of cigarettes daily; repeatedly advised to stop
- Younger brother suffered MI 5 years ago
- Elevated total cholesterol – 7.4 mmol/L (285 mg/dL) on a cholesterol-lowering diet
- Total cholesterol after 3 months on MEVACOR® (20 mg b.i.d.) plus continued diet, is 5.5 mmol/L (212 mg/dL)

*Hypothetical case. It should be determined that patients for whom treatment with MEVACOR® is being considered have an elevated LDL-cholesterol as the cause for an elevated serum cholesterol.

Helps improve patient acceptance

Recommended Starting Dose:
20 mg ONCE-A-DAY with Evening Meal

- Continue a cholesterol-lowering diet
- Wait four weeks between dosage adjustments
- Titrate dose schedule and dosage (to a maximum of 80 mg/day) for desired therapeutic response
- Maximum therapeutic response achieved in 4 to 6 weeks

For many patients with primary hypercholesterolemia (Types IIa and IIb)

Mevacor®

(lovastatin) 20 mg tablets

when diet and other measures alone are inadequate

PLEASE SEE ENCLOSED PRESCRIBING INFORMATION, INCLUDING SIDE EFFECTS, CONTRAINDICATIONS AND PRECAUTIONS ON LIVER, MUSCLE, AND EYE

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CANADA

For prescribing information see page 1938

IBUPROFEN*
PRODUCT MONOGRAPH

Actiprofen* (TABLETS U.S.P.)
200 mg

PHARMACOLOGICAL CLASSIFICATION
Analgesic/antipyretic

Indications For the temporary relief of mild to moderate pain associated with headache, dysmenorrhea, aches and pains in muscles, bones and joints (arthritic pain), dental pain and fever. Also, for the symptomatic treatment of colds.

† Reg. Trade Mark, The Upjohn Company of Canada

Contraindications Ibuprofen should not be used in patients who have exhibited hypersensitivity to it, to ASA or to any other nonsteroidal antiinflammatory drugs. Hypersensitivity reactions to these agents include urticaria, angioedema, laryngeal edema, bronchospasm, hypertension; Stevens-Johnson syndrome (a severe form of erythema multiforme) and toxic epidermal necrolysis have been reported, but only rarely.

Ibuprofen should not be used in patients with active peptic ulcer or G.I. bleeding, in pediatric patients, pregnant women or nursing mothers because its safety in such patients has not been established. Ibuprofen has been shown to inhibit prostaglandin synthesis and release, an action which has been associated with an increased incidence of dystocia and delayed parturition in pregnant animals, when nonsteroidal anti-inflammatory drugs were administered late in pregnancy. Ibuprofen is also contraindicated in patients with systemic lupus erythematosus: anaphylactic-like reactions with fever may occur, particularly when ibuprofen has been used previously; aseptic meningitis has also been reported in such patients.

Warnings Anaphylactoid reactions have occurred in patients with known ASA hypersensitivity (see Contraindications).

Although ibuprofen is generally safer than other non-steroidal anti-inflammatory agents, including ASA, peptic ulceration and gastrointestinal bleeding, sometimes severe, have nevertheless been reported in patients receiving ibuprofen. Peptic ulceration, perforation, or severe gastrointestinal bleeding can have a fatal outcome and although a few such reports have been received with ibuprofen, a cause and effect relationship has not been established. Ibuprofen should be given under close supervision to patients with a history of upper gastrointestinal tract disease.

Precautions Blurred and/or diminished vision, scotomata, and changes in color vision have been reported. Medication should be discontinued if there is any evidence of abnormal ocular manifestation. Patients presenting these changes should be followed up by an ophthalmologist.

Mild impairment of renal function (decreased renal blood flow and glomerular filtration rate) can occur at maximal prescription doses. One case of renal papillary necrosis of uncertain etiology has been reported.

Fluid retention and edema have been reported in association with ibuprofen and the drug should be used cautiously in patients with a history of cardiac decompensation or renal disease.

Advanced age, hypertension, use of diuretics, diabetes, atherosclerotic cardiovascular disease, chronic renal failure, cirrhosis and conditions which may be associated with dehydration appear to increase the risk of renal toxicity. Therefore ibuprofen should be used with caution when these risk factors are present.

Ibuprofen, like other nonsteroidal anti-inflammatory agents, can inhibit platelet aggregation but the effect is quantitatively less than that seen with ASA.

Ibuprofen has been shown to prolong bleeding time (but within normal range) in normal subjects. Because this prolonged bleeding effect may be exaggerated in patients with underlying hemostatic defects, ibuprofen should be used with caution in patients with intrinsic coagulation defects and those on anticoagulant therapy.

When ibuprofen is added to the treatment program of patients who have been on prolonged corticosteroid therapy and a decision is made to reduce or discontinue this treatment, corticosteroids should be withdrawn gradually to avoid exacerbation of disease or adrenal insufficiency.

Patients receiving ibuprofen should be instructed to report to their physicians any gastrointestinal manifestations, ocular symptoms, skin rash, tinnitus, dizziness, weight gain, edema or respiratory difficulties.

Particular caution should be observed in elderly patients taking ibuprofen, as they are more likely to be taking other medications or have pre-existing disease states which can increase the likelihood of the complications that have been associated with ibuprofen. Elderly patients appear to be more susceptible to the central nervous system adverse reactions; cognitive dysfunction (forgetfulness, inability to concentrate, a feeling of separation from the surroundings), has been reported in such patients.

Drug Interactions:
Coumarin Type Anticoagulants: Several short-term controlled studies failed to show that ibuprofen significantly affected prothrombin time or a variety of other clotting factors when administered to patients on coumarin-type anticoagulants. However, bleeding has been reported when ibuprofen and other nonsteroidal anti-inflammatory agents have been administered to patients on coumarin-type anticoagulants and therefore, ibuprofen should be used cautiously in such cases. ***ASA:*** Animal studies indicated that ASA administered with nonsteroidal anti-inflammatory drugs, including ibuprofen, produced a net decrease in anti-inflammatory activity with lowered blood levels of the non-ASA drug. Single dose bioavailability studies in normal volunteers have failed to show an effect of ASA on ibuprofen blood levels. Correlative clinical studies have not been performed. ***Other anti-inflammatory agents (NSAIDS):*** The addition of ibuprofen to a pre-existent prescribed NSAID regimen in patients with a condition such as rheumatoid arthritis may result in increased risk of adverse effects. ***Diuretics:*** Ibuprofen, because of its fluid retention properties, can decrease the diuretic and antihypertensive effects of diuretics, and increased diuretic dosage may be needed. Patients with impaired renal function taking potassium sparing diuretics who develop ibuprofen-induced renal insufficiency might be in serious danger of fatal hyperkalemia. ***Acetaminophen:*** Although interactions have not been reported, concurrent use with ibuprofen is not advisable. ***Other drugs:*** Although ibuprofen binds to a significant extent to plasma proteins, interactions with other protein-bound drugs occur uncommonly. Nevertheless, caution should be observed when other drugs also having a high affinity for protein binding sites are used concurrently. Some observations have suggested a potential for ibuprofen to interact with digoxin, phenytoin and lithium salts. However the mechanisms and clinical significance of these observations are presently not known.

Adverse Effects THE FREQUENCY AND SEVERITY OF IBUPROFEN-RELATED ADVERSE EFFECTS, ESPECIALLY THOSE AFFECTING THE GASTROINTESTINAL SYSTEM, ARE DOSE-RELATED. THE FREQUENCIES OF THE ADVERSE EFFECTS REPORTED IN THIS SECTION ARE INCLUSIVE OF IBUPROFEN DOSAGES IN EXCESS OF THOSE APPROVED FOR SELF-ADMINISTRATION BY THE GENERAL PUBLIC. WHEN USED IN THE OTC DOSAGE RANGE AS INDICATED BELOW, IBUPROFEN IS LESS LIKELY THAN ASA OR OTHER NSAIDS TO CAUSE SIDE-EFFECTS SUCH AS STOMACH UPSET.

Gastrointestinal: The most frequently encountered adverse reactions following ibuprofen administration involve the gastrointestinal tract. Nausea, heartburn, epigastric pain (3 to 9%); vomiting, diarrhea, constipation, abdominal cramps or pain, dyspepsia, bloating or flatulence (1 to 3%); gastric or duodenal ulcer with bleeding and/or perforation, gastrointestinal hemorrhage, melena, hepatitis, jaundice, abnormal liver function (SGOT, serum bilirubin and alkaline phosphatase) (less than 1%). The generally modest elevations of serum transaminase activity that have been observed are usually without clinical sequellae but severe, potentially fatal, toxic hepatitis can occur. ***CNS:*** Dizziness (3 to 9%); headache, nervousness (1 to 3%); depression, insomnia (less than 1%). Paresthesias, hallucinations and dream abnormalities have been reported in conjunction with ibuprofen treatment, although a causal relationship has not definitely been established. Aseptic meningitis has been reported in patients with systemic lupus erythematosus. ***Special Senses:*** Tinnitus (1 to 3%); amblyopia (blurred and/or diminished vision, scotomata and/or change in color vision) (less than 1%). Any patient with eye complaints during ibuprofen therapy should have an ophthalmological examination (see Precautions). Conjunctivitis, diplopia and optic neuritis have been reported but causal relationship with ibuprofen administration has not been established. ***Skin:*** Rash (including maculopapular type) (3 to 9%); pruritus (1 to 3%); vesiculobullous eruptions, urticaria, erythema multiforme (less than 1%). Alopecia and Stevens-Johnson syndrome have been reported but causal relationship with ibuprofen administration has not been established. ***Hematologic:*** Leukopenia and decreases in hemoglobin and hematocrit (less than 1%). Rare cases of hemolytic anemia, thrombocytopenia, granulocytopenia and bleeding episodes (purpura, epistaxis, hematuria, menorrhagia) have been reported in conjunction with ibuprofen administration. Autoimmune hemolytic anemia occurred in one patient taking 400 mg ibuprofen t.i.d. for eight months and was fatal in one patient after 400 mg t.i.d. for 10 days. Fatal aplastic anemia was reported in one patient who took 600 mg/day for eight months. ***Metabolic:*** Edema, fluid retention (1 to 3%). Fluid retention generally responds promptly to drug discontinuation (see Precautions). ***Cardiovascular:*** Congestive heart failure in patients with marginal cardiac function, elevated blood pressure (less than 1%). Rare cases of arrhythmias (sinus tachycardia, sinus bradycardia, palpitations) have been reported. Conditions such as congestive heart failure and hypertension may be aggravated by the sodium retention and edema caused by ibuprofen in some patients. ***Renal:*** Rare cases of decreased creatinine clearance, polyuria and azotemia have been reported in conjunction with ibuprofen treatment, as well as a case of renal papillary necrosis of uncertain etiology. Like other non steroidal antiinflammatory drugs, ibuprofen inhibits renal prostaglandin synthesis, which may decrease renal function and cause sodium retention. Renal blood flow and glomerular filtration rate decreased in patients with mild impairment of renal function who took 1200 mg/day of ibuprofen for one week. A number of factors appear to increase the risk of toxicity (see Precautions). ***Endocrine:*** Rare cases of gynecomastia and hypoglycemic reactions have been reported in conjunction with ibuprofen administration. ***Allergic:*** Anaphylaxis (see Contraindications) (less than 1%). Fever, serum sickness and lupus erythematosus have been rarely reported in connection with ibuprofen administration.

Overdose: Symptoms and Treatment The safety of ibuprofen extends even to overdosage conditions when compared to cases associated with the use of such common analgesics as ASA and acetaminophen.

Reports of overdosage indicate that drowsiness and lethargy (or unconsciousness) appear to be the main problem in most cases. Acidosis, apnea, and other symptoms have been seen.

The following cases of overdosage have been reported. A 19 month old child, 1.5 hours after the ingestion of 7-10 tablets of ibuprofen 400 mg, presented with apnea, cyanosis and responded only to painful stimuli. After treatment with oxygen, sodium bicarbonate, infusion of dextrose and normal saline, the child was responsive and 12 hours after ingestion appeared completely recovered. Blood levels of ibuprofen reached 102.9 μg/mL 8.5 hours after the incident.

Two other children, weighing approximately 10 kg, had taken an estimated 120 mg/kg. There were no signs of acute intoxication or late sequelae. In one child, the ibuprofen blood level at 90 minutes after ingestion was 700 μg/mL.

A 19 year old male who had taken 8,000 mg of ibuprofen over a period of a few hours complained of dizziness, and nystagmus was observed. After hospitalization, hydration and 3 days bed rest, he recovered without sequelae.

In cases of acute overdosage, the stomach should be emptied by vomiting or lavage. Because the drug is acidic and is excreted in the urine it is theoretically beneficial to administer alkali and induce diuresis.

Dosage For temporary relief of mild to moderate pain associated with headache, dysmenorrhea, aches and pains in muscles, bones and joints (arthritic pain), dental pain and fever: 200-400 mg repeated as required every 4 to 6 hours, while symptoms persist. The daily dosage should not exceed 1200 mg, except as directed by a physician.

Children: Due to lack of clinical experience, ibuprofen is not indicated in children under 12.

Availability Each white, oblong, film-coated ACTIPROFEN* (ibuprofen) caplet, imprinted with purple "A 200," contains 200 mg of ibuprofen USP. Available in blister packages of 8 and 24 caplets and bottles of 50 and 100 caplets.

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common problems tend to be common, and second, that the family physician is more than capable of attending fully to 75% to 90% of those problems in his or her office. The remaining 10% to 25% require specialist or sub-specialist care or sophisticated hospital facilities.

Although it is pleasant to have one's family physician involved in hospital care, the practice is confined primarily to North America, and especially to smaller centres in Canada. It is entirely possible that, in an effort to maintain the traditional role of the family physician, being all things to all people in an urban setting, we may in fact be an anachronism, if not an impediment, in the performance of highly technical in-hospital procedures.

It seems most unusual that family physicians would not only accept, but indeed promote, the premise that hospital privilege for family physicians makes them accept the ultimate responsibility and liability for patients in hospital, no matter what the complexity of the surgical or medical situation. Just such a protocol has been approved by the section of family practice at a hospital where I am a member of the hospital staff.

An observer might well applaud the family physician's attempt to be an intermediary, or an expediter, where highly specialized intervention is required. The same observer might have difficulty with the family physician's accept once of ultimate responsibility.

We must recognize that we do handle the vast majority of patient problems, and we do it skillfully. When we accept the onus for the remaining 10% to 25% of problems that fall well outside our area of expertise, we may well appear, act, and be perceived as intrusive amateurs.

Gerald M. Deyo, MD
Peterborough, Ont.

In the treatment of depression it's time to follow a new course.

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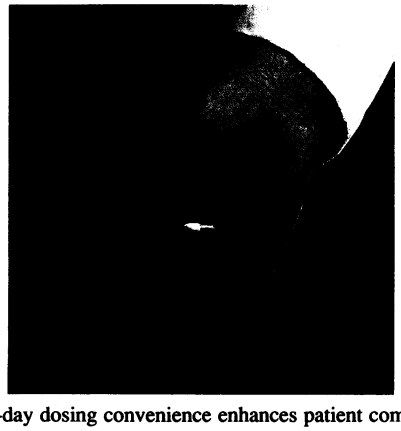

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Pr PROZAC® 20

Fluoxetine HCl

Once a day from day one

THERAPEUTIC CLASSIFICATION
Antidepressant

ACTION
The antidepressant action of fluoxetine is presumed to be linked to its ability to inhibit the neuronal reuptake of serotonin. Fluoxetine preferentially inhibited the reuptake of serotonin into brain synaptosomes and platelets in rats and humans respectively. In receptor binding studies, fluoxetine was shown to have only weak affinity for various receptor systems, namely opiate, serotonergic $5HT_1$, dopaminergic, ß-adrenergic, α_2-adrenergic, histaminergic, α_1-adrenergic, muscarinic, and serotonergic $5HT_2$ receptors. Unlike most clinically effective antidepressants, fluoxetine did not down-regulate ß-adrenergic receptors; however, like all tested antidepressants, it caused up-regulation of GABA-B receptors. Mixed effects have been observed on serotonergic receptor sensitivity.

Pharmacokinetics: Fluoxetine is well absorbed after oral administration. In man, following a single 40 mg dose, peak plasma concentrations of fluoxetine from 15 to 55 ng/mL were observed after 6 to 8 hours (range = 1.5 to 12 hours). Food appears to affect the rate but not the extent of absorption. Fluoxetine is extensively metabolized in the liver to a major active metabolite, norfluoxetine, and other, unidentified metabolites. Norfluoxetine, a desmethyl metabolite, is also a serotonin uptake inhibitor, contributing to the long duration of action of the drug. Elimination of metabolites occurs primarily in the urine with a smaller amount also being present in the feces.

Clinical Issues Related to Metabolism/Elimination: The complexity of fluoxetine's metabolism has several consequences which may potentially affect its clinical use. The half-life of fluoxetine after a single dose is 1 to 4 days (mean = 2 days) and after multiple dosing 2 to 7 days (mean = 4 days). The corresponding values for norfluoxetine are similar for single and multiple dosing, i.e. 4 to 15 days (means = 8.6 and 9.3 days). After 30 days of dosing at 40 mg/day, plasma concentrations of fluoxetine in the range of 91 to 302 ng/mL and norfluoxetine in the range of 72 to 258 ng/mL have been observed. Plasma concentrations of fluoxetine were higher than those predicted by single dose studies, presumably because fluoxetine's metabolism is not proportional to dose. Norfluoxetine, however, appears to have linear pharmacokinetics. Steady state plasma levels are attained after 4 to 5 weeks of continuous drug administration. Patients receiving fluoxetine at doses of 40 to 80 mg/day over periods as long as 3 years exhibited, on average, plasma concentrations similar to those seen among patients treated for 4 to 5 weeks. Similarly because of the long half-lives of fluoxetine and norfluoxetine, it may take up to 1 to 2 months for the active drug substance to disappear from the body. This is of potential consequence in withdrawal of fluoxetine. Approximately 94% of fluoxetine is protein bound. The interaction between fluoxetine and other highly protein bound drugs has not been fully evaluated, but may be important. As might be predicted from its primary site of metabolism, liver impairment can affect the elimination of fluoxetine. In patients with alcohol-induced cirrhosis, the half-lives of both fluoxetine and norfluoxetine were prolonged and plasma clearance was significantly reduced. This suggests that the use of fluoxetine in patients with liver disease must be approached with caution (see PRECAUTIONS and DOSAGE AND ADMINISTRATION).

Renal Disease: In single dose studies, the pharmacokinetics of fluoxetine and norfluoxetine were similar among subjects with all levels of impaired renal function including anephric patients on chronic hemodialysis. However, with chronic administration, additional accumulation of fluoxetine or its metabolites (possibly including some not yet identified) may occur in patients with severely impaired renal function and use of a lower or less frequent dose is advised (see PRECAUTIONS).

Age: The effects of age upon the metabolism of fluoxetine have not been fully explored. The disposition of single doses of fluoxetine in healthy elderly subjects (greater than 65 years of age) did not differ significantly from that in younger normal subjects. However, given the long half-life and nonlinear disposition of the drug, a single-dose study is not adequate to rule out the possibility of altered pharmacokinetics in the elderly, particularly if they have systemic illness or are receiving multiple drugs for concomitant diseases.

INDICATIONS
PROZAC (fluoxetine) may be indicated for the symptomatic relief of depressive illness. The antidepressant action of PROZAC in hospitalized depressed patients has not been adequately studied. The effectiveness of PROZAC in long-term use (ie. for more than 5 to 6 weeks) has not been systematically evaluated in controlled trials. Therefore, the physician who elects to use PROZAC for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient.

CONTRAINDICATIONS
PROZAC (fluoxetine) is contraindicated in patients with known hypersensitivity to the drug. Data on the effects of the combined use of fluoxetine and MAO inhibitors are limited. While a causal relationship to fluoxetine has not been established, death has been reported to occur following the initiation of MAOI therapy shortly after discontinuation of fluoxetine. Therefore their combined use should be avoided. Based on experience with the combined administration of MAOIs and tricyclics, at least 14 days should elapse between discontinuation of an MAO inhibitor and initiation of treatment with fluoxetine. Because of the long half-lives of fluoxetine and its active metabolite, at least 5 weeks (approximately 5 half-lives of norfluoxetine) should elapse between discontinuation of fluoxetine and initiation of therapy with an MAOI. Administration of an MAOI within 5 weeks of discontinuation of fluoxetine may increase the risk of serious events.

WARNINGS
Allergic Reactions (Rash and Accompanying Events): During premarketing testing of more than 5,600 patients given fluoxetine, approximately 4% developed a rash and/or urticaria. Among these cases, almost a third were withdrawn from treatment because of the rash and/or systemic signs or symptoms associated with the rash. Clinical findings reported in association with these allergic reactions include rash, fever, leukocytosis, arthralgias, edema, carpal tunnel syndrome, respiratory distress, lymphadenopathy, proteinuria, and mild transaminase elevation. Most patients improved promptly with discontinuation of fluoxetine and/or adjunctive treatment with antihistamines or steroids, and all patients experiencing these events were reported to recover completely. Two patients are known to have developed a serious cutaneous systemic illness. In neither patient was there an unequivocal diagnosis, but one was considered to have a leukocytoclastic vasculitis, and the other severe desquamation that was considered variously to be a vasculitis or erythema multiforme. Several other patients have had systemic manifestations suggestive of serum sickness. No patient is reported to have sustained lasting injury. Even though almost two-thirds of those developing a rash continued to take fluoxetine without any consequences, the physician should discontinue PROZAC (fluoxetine) upon appearance of rash. Particular caution should be exercised in patients with a history of allergic reactions.

Implications of the Long Elimination Half-Life of Fluoxetine: Because of the long elimination half-lives of the parent drug and its major active metabolite, changes in dose will not be fully reflected in plasma for several weeks, affecting both strategies for titration to final dose and withdrawal from treatment (see ACTIONS and DOSAGE AND ADMINISTRATION). Even when dosing is stopped, active drug substance will persist in the body for weeks due to the long elimination half-lives of fluoxetine and norfluoxetine. This is of potential consequence when drug discontinuation is required or when drugs are prescribed that might interact with fluoxetine and norfluoxetine following discontinuation of PROZAC. Since clearances of fluoxetine and norfluoxetine may be decreased in patients with impaired liver function including cirrhosis, a lower or less frequent dose should be used in such patients.

PRECAUTIONS
During premarketing clinical trials, anxiety, nervousness and insomnia were reported by 10 to 15% of patients treated with PROZAC (fluoxetine). These symptoms led to discontinuation of the drug in 5% of the patients. Significant weight loss, especially in underweight depressed patients, may be an undesirable result of treatment with PROZAC. During premarketing testing in a patient population comprised primarily of unipolar depressives, hypomania or mania occurred in approximately 1% of fluoxetine treated patients. The incidence in a general patient population which might also include bipolar depressives is unknown. The likelihood of hypomanic or manic episodes may be increased at the higher dosage levels. Such reactions require a reduction in dosage or discontinuation of the drug. PROZAC should be used with caution in patients with a history of convulsive disorders. The incidence of seizures associated with fluoxetine during clinical trials did not appear to differ from that reported with other marketed antidepressants; however, patients with a history of convulsive disorders were excluded from these trials. Concurrent administration with electroshock therapy should be avoided because of the absence of experience in this area. A single report of a prolonged seizure in a patient on fluoxetine has been reported. The possibility of a suicide attempt is inherent in depression and may persist until significant remission occurs. Therefore, high risk patients should be closely supervised throughout therapy and consideration should be given to the possible need for hospitalization. In order to minimize the opportunity for overdosage, prescriptions for fluoxetine should be written for the smallest quantity of drug consistent with good patient management. Clinical experience with PROZAC in patients with concomitant systemic illness is limited and it should be used cautiously in such patients, especially those with diseases or conditions that could affect metabolism or hemodynamic responses. PROZAC has not been evaluated or used to any appreciable extent in patients with a recent history of myocardial infarction or unstable heart disease. Patients with these diagnoses were systematically excluded from premarketing clinical studies. Retrospective evaluation of EKGs in some of these studies showed no conduction abnormalities that resulted in heart block. The mean heart rate was reduced by approximately 3 beats/minute. Patients should be cautioned against driving an automobile or performing hazardous tasks until they are reasonably certain that treatment with PROZAC does not affect them adversely. Since fluoxetine is extensively metabolized, excretion of unchanged drug in urine is a minor route of elimination. However, until adequate numbers of patients with severe renal impairment have been evaluated during chronic treatment with fluoxetine, it should be used with caution in such patients. Several cases of hyponatremia (some with serum sodium lower than 110 mmol/L) have been reported. The hyponatremia appeared to be reversible when PROZAC was discontinued. Although these cases were complex with varying possible etiologies, some were possibly due to the syndrome of inappropriate antidiuretic hormone secretion (SIADH). The majority of these occurrences have been in older patients and in patients taking diuretics or who were otherwise volume depleted.

Use in Pregnancy and Lactation: Safe use of fluoxetine during pregnancy and lactation has not been established. Therefore it should not be administered to women of childbearing potential or nursing mothers unless, in the opinion of the treating physician, the expected benefits to the patient outweigh the possible hazards to the child or fetus.

Use in Children: Safety and effectiveness in patients below the age of 18 have not been established.

Use in the Elderly: Elderly patients should initially receive fluoxetine in low dosage with slow progressive increases only if required and tolerated. Patients who have concomitant systemic illnesses or who are receiving other drugs concomitantly should be under careful observation at all dosage levels.

Drug Interactions: Combined use of PROZAC and MAO inhibitors is contraindicated, (see CONTRAINDICATIONS). The half-life of concurrently administered diazepam may be prolonged in some patients. Experience with the use of PROZAC in combination with other CNS-active drugs is limited and caution is advised if such concomitant medication is required (see WARNINGS). There have been greater than 2-fold increases of previously stable plasma levels of other antidepressants when PROZAC has been administered in combination with these agents. Five patients receiving PROZAC in combination with tryptophan experienced adverse reactions, including agitation, restlessness and gastrointestinal distress. Because fluoxetine is highly bound to plasma protein, the administration of fluoxetine to a patient taking another drug which is tightly bound to protein (eg, warfarin, digitoxin) may cause a shift in plasma concentrations potentially resulting in an adverse effect. Conversely, adverse effects may result from displacement of protein bound fluoxetine by other tightly bound drugs. Since nothing is known about the interaction between fluoxetine and general anesthetics, fluoxetine should be discontinued for as long as clinically possible prior to elective surgery.

Dependence Liability: PROZAC has not been systematically studied, in animals or humans, for its potential for abuse, tolerance, or physical dependence. While the premarketing clinical experience with PROZAC did not reveal any tendency for a withdrawal syndrome or any drug seeking behaviour, these observations were not systematic and it is not possible to predict on the basis of this limited experience the extent to which a CNS active drug will be misused, diverted, and/or abused once marketed. Consequently, physicians should carefully evaluate patients for history of drug abuse and follow such patients closely, observing them for signs of misuse or abuse of PROZAC (eg, development of tolerance, incrementation of dose, drug-seeking behaviour).

ADVERSE REACTIONS
In clinical trials, the most commonly observed adverse events associated with the use of PROZAC (fluoxetine) and not seen at an equivalent incidence among placebo treated patients were: central nervous system complaints, including headache, nervousness, insomnia, drowsiness, fatigue or asthenia, anxiety, tremor, and dizziness or lightheadedness; gastrointestinal complaints, including nausea, diarrhea, dry mouth and anorexia; and excessive sweating. Fifteen percent of approximately 4,000 patients who received PROZAC in North American clinical trials discontinued treatment due to an adverse event. The more common events causing discontinuation included: psychiatric (5.3%), primarily nervousness, anxiety, and insomnia; digestive (3.0%), primarily nausea; nervous system (2.4%), primarily dizziness, asthenia and headaches; skin (1.4%), primarily rash and pruritus. In countries where the drug has already been marketed, the following potentially serious adverse reactions have been reported: interactions with MAO inhibitors and possibly other drugs, allergic reactions, cardiovascular reactions, syndrome of inappropriate ADH secretion, and grand mal seizure. Death and life-threatening events have been associated with some of these reactions, although causal relationship to PROZAC has not necessarily been established. Postmarketing experience also confirms the profile of adverse reactions commonly reported during clinical trials with PROZAC, including allergic skin reactions. The following adverse reactions, arranged by body system, were reported on at least one occasion by patients during treatment with PROZAC either during clinical trials or after marketing. All reported events are included except those where a drug cause was remote or the event term so general as to be unhelpful. Multiple events may have been reported by a single patient and related to a single condition, which may have preexisted. Therefore, while the following events occurred during treatment with PROZAC, they were not necessarily caused by it.

Allergic or Toxic: rash, pruritus. Infrequent: chills and fever, urticaria, maculopapular rash. Rare: allergic reaction, erythema multiforme, vesiculobullous rash, serum sickness, contact dermatitis, erythema nodosum, purpuric rash, leukocytoclastic vasculitis, leukopenia, thrombocytopenia, arthralgia, angioedema, lung fibrosis, allergic alveolitis, larynx edema, respiratory distress.

Neurologic: headache, tremor, dizziness or lightheadedness, asthenia. Infrequent: abnormal gait, ataxia, akathisia, buccoglossal syndrome, hyperkinesia, hypertonia, incoordination, neck rigidity, extrapyramidal syndrome, convulsions, photophobia, myoclonus, vertigo, migraine, tinnitus, hypesthesia, neuralgia, neuropathy, acute brain syndrome. Rare: dysarthria, dystonia, torticollis, decreased reflexes, nystagmus, paralysis, paresthesia, carpal tunnel syndrome, stupor, coma, abnormal electroencephalogram, chronic brain syndrome.

Behavioural: insomnia, anxiety, nervousness, agitation, abnormal dreams, drowsiness and fatigue. Infrequent: confusion, delusions, hallucinations, manic reaction, paranoid reaction, psychosis, depersonalization, apathy, emotional lability, euphoria, hostility, amnesia, increased libido. Rare: antisocial reaction, hysteria.

Autonomic: excessive sweating. Infrequent: dry mouth, constipation, urinary retention, vision disturbance, diplopia, mydriasis, hot flushes.

Cardiovascular: Infrequent: chest pain, hypertension, syncope, hypotension (including postural hypotension), angina pectoris, arrhythmia, tachycardia. Rare: bradycardia, ventricular arrhythmia, first degree AV block, bundle branch block, myocardial infarct, cerebral ischemia, thrombophlebitis.

Gastrointestinal: nausea, disturbances of appetite, diarrhea. Infrequent: vomiting, stomatitis, dysphagia, eructation, esophagitis, gastritis, gingivitis, glossitis, melena, thirst, abnormal liver function tests.

Rare: bloody diarrhea, hematemesis, g.i. hemorrhage, duodenal ulcer, stomach ulcer, mouth ulceration, hyperchlorhydria, colitis, enteritis, cholecystitis, cholelithiasis, hepatitis, hepatomegaly, liver tenderness, jaundice, increased salivation, salivary gland enlargement, tongue discolouration, fecal incontinence.

Respiratory: bronchitis, rhinitis, yawn. Infrequent: asthma, dyspnea, hyperventilation, pneumonia, hiccups, epistaxis. Rare: apnea, lung edema, hypoxia, pleural effusion, hemoptysis.

Endocrine: weight loss. Infrequent: generalized edema, peripheral edema, face edema, tongue edema, hypoglycemia, hypothyroidism, weight gain. Rare: dehydration, gout, goitre, hyperthyroidism, hypercholesteremia, hyperglycemia, hyperlipemia, hyperprolactinemia, hypokalemia, hyponatremia, iron deficiency anemia, syndrome of inappropriate ADH secretion.

Hematologic: Infrequent: anemia, lymphadenopathy, hemorrhage. Rare: bleeding time increased, leukocytosis, lymphocytosis, thrombocythemia, retinal hemorrhage, petechia, purpura, sedimentation rate increased.

Dermatologic: Infrequent: acne, alopecia, dry skin, herpes simplex. Rare: excema, psoriasis, seborrhea, skin hypertrophy, skin discolouration, herpes zoster, fungal dermatitis, hirsutism.

Musculoskeletal: muscle pain, back pain, joint pain. Infrequent: arthritis, bone pain, bursitis, tenosynovitis, twitching. Rare: bone necrosis, osteoporosis, pathological fracture, chrondrodystrophy, myositis, rheumatoid arthritis, muscle hemorrhage.

Urogenital: painful menstruation, sexual dysfunction, urinary tract infection, frequent micturition. Infrequent: abnormal ejaculation, impotence, menopause, amenorrhea, menorrhagia, ovarian disorder, vaginitis, leukorrhea, fibrocystic breast, breast pain, cystitis, dysuria, urinary urgency, urinary incontinence. Rare: breast enlargement, galactorrhea, abortion, dyspareunia, uterine spasm, vaginal hemorrhage, metrorrhagia, hematuria, albuminuria, polyuria, pyuria, epididymitis, orchitis, pyelonephritis, salpingitis, urethritis, kidney calculus, urethral pain, urolithiasis.

Miscellaneous: chills. Infrequent: amblyopia, conjunctivitis, cyst, ear pain, eye pain, jaw pain, neck pain, pelvic pain, hangover effect, malaise. Rare: abdomen enlarged, blepharitis, cataract, corneal lesion, glaucoma, iritis, ptosis, strabismus, deafness, taste loss, moniliasis, hydorcephalus, LE syndrome.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

During clinical trials, there were two deaths among approximately 38 reports of acute overdose with fluoxetine, either alone or in combination with other drugs and/or alcohol. One death involved a combined overdose with approximately 1800 mg of fluoxetine and an undetermined amount of maprotiline. Plasma concentrations of fluoxetine and maprotiline were 4.57 mg/L and 4.18 mg/L, respectively. A second death involved 3 drugs yielding plasma concentrations as follows: fluoxetine, 1.93 mg/L; norfluoxetine, 1.10 mg/L; codeine, 1.80 mg/L; temazepam 3.80 mg/L. One other patient who reportedly took up to 3000 mg of fluoxetine experienced two grand mal seizures that remitted spontaneously without specific treatment. Since vomiting occurred, the amount of drug absorbed may have been less than that ingested. In the postmarketing phase, there have been 16 confirmed reports of overdose of PROZAC (fluoxetine) taken alone. The amount of drug ingested has varied from 80 mg to 2000 mg and the patients have ranged in age from 13 to 51 years. There have been no deaths in this group of patients, some of whom were treated vigorously with activated charcoal in the acute phase. Furthermore, patient recoveries were remarkable in the absence of serious adverse events with the exception of a 13 year old male who ingested 1880 mg and experienced two brief seizures but thereafter had an uneventful recovery. Symptoms: Nausea and vomiting were prominent in overdoses involving higher fluoxetine doses. Other prominent symptoms of overdose included agitation, restlessness, hypomania, and other signs of CNS excitation, including seizures. Treatment: Establish and maintain an airway; insure adequate oxygenation and ventilation. Activated charcoal, which may be used with sorbitol, may be as or more effective than emesis or lavage, and should be considered in treating overdose. Cardiac and vital signs monitoring is recommended, along with general symptomatic and supportive measures. Based on experience in animals, which may not be relevant to humans, fluoxetine-induced seizures which fail to remit spontaneously may respond to diazepam. There are no specific antidotes for PROZAC. Due to the large volume of distribution of PROZAC, forced diuresis, dialysis, hemoperfusion, and exchange transfusion are unlikely to be of benefit. In managing overdosage, consider the possibility of multiple drug involvement. The physician should consider contacting a poison control centre on the treatment of any overdosage.

DOSAGE AND ADMINISTRATION

Since it may take up to four or five weeks to reach steady-state plasma levels of PROZAC (fluoxetine), sufficient time should be allowed to elapse before dosage is gradually increased. Higher dosages are usually associated with an increased incidence of adverse reactions.

Initial Adult Dosage: The recommended initial dosage is 20 mg administered once daily in the morning. A gradual dose increase should be considered only after a trial period of several weeks if the expected clinical improvement does not occur. Dosage should not exceed a maximum of 80 mg per day since clinical experience with doses above 80 mg per day is very limited. During maintenance therapy, the dosage should be kept at the lowest effective level. A lower or less frequent dosage should be used in patients with renal and/or hepatic impairment and in those on multiple medications.

Use in the Elderly: A lower or less frequent dosage is also recommended in the elderly. The safety and effectiveness of PROZAC in the pediatric age group has not been established.

HOW SUPPLIED

PROZAC (fluoxetine hydrochloride) Pulvules 3105
20 mg, green and off-white. Bottles of 100.
PROZAC is a Schedule F drug and cannot be obtained without a written order from a licenced practitioner.

Product Monograph available upon request.
New Product, November, 1988

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Zantac®

(RANITIDINE HCl)

PRESCRIBING INFORMATION

ZANTAC TABLETS (ranitidine hydrochloride)

Pharmacological Classification

Histamine H_2 – receptor antagonist

Indications and Clinical use

Zantac Tablets are indicated for the treatment of all conditions where a controlled reduction of gastric secretion is required for the rapid relief of pain and/or ulcer healing. These include duodenal ulcer, benign gastric ulcer and reflux oesophagitis.

Contraindications – Zantac is contraindicated for patients known to have hypersensitivity to the drug.

Warnings – Gastric ulcer – Treatment with a histamine H_2 – antagonist may mask symptoms associated with carcinoma of the stomach and therefore may delay diagnosis of the condition. Accordingly, where gastric ulcer is suspected the possibility of malignancy should be excluded before therapy with Zantac is instituted.

Precautions – Use in pregnancy and nursing mothers – The safety of Zantac in the treatment of conditions where a controlled reduction of gastric secretion is required during pregnancy has not been established. Reproduction studies performed in rats and rabbits have revealed no evidence of impaired fertility or harm to the foetus due to Zantac. If the administration of Zantac is considered to be necessary, its use requires that the potential benefits be weighed against possible hazards to the patient and to the foetus. Ranitidine is secreted in breast milk in lactating mothers but the clinical significance of this has not been fully evaluated.

Use in impaired renal function – Ranitidine is excreted via the kidney and in the presence of severe renal impairment plasma levels of ranitidine are increased and prolonged. Accordingly, in the presence of severe renal impairment clinicians may wish to reduce the dose by one half.

Children – Experience with Zantac Tablets in children is limited and such use has not been fully evaluated in clinical studies. It has however been used successfully in children aged 8-18 years in doses up to 150 mg twice daily without adverse effect.

Interactions with other drugs – Although ranitidine has been reported to bind weakly to cytochrome P450 in vitro, recommended doses to the drug do not inhibit the action of the cytochrome P450-linked oxygenase in the liver. There are conflicting reports in the literature about possible interactions between ranitidine and several drugs, the clinical significance of these reports has not been substantiated. Amongst the drugs studied were warfarin, diazepam, metoprolol and nifedipine.
If high doses (2g) of sucralfate are co-administered with ranitidine the absorption of the latter may be reduced. This effect is not seen if sucralfate is taken after an interval of 2 hours.

Adverse Reactions – Headache, sometimes severe, rash, dizziness, constipation, diarrhoea and nausea have been reported in a very small proportion of drug-treated patients but these also occurred in patients receiving placebo. A few patients on re-challenge with Zantac have had a recurrence of skin rash, headache or dizziness. Rare reports of bradycardia have occurred. Rare cases of reversible mental confusion and hallucinations have been reported, predominantly in severely ill and elderly patients. There have been a few reports of reversible blurred vision suggestive of a change in accommodation.
Some increases in serum transaminases and gamma-glutamyl transpeptidase have been reported which have returned to normal either on continued treatment or on stopping Zantac. In placebo controlled studies involving nearly 2,500 patients, there was no difference between the incidence of elevations of SGOT and/or SGPT values in the Zantac treated or placebo treated groups. There have been occasional reports of reversible hepatitis (hepatocellular, hepatocanicular or mixed) with or without jaundice.
Hypersensitivity reactions (urticaria, angioneurotic oedema, bronchospasm, hypotension) have been seen rarely following the parenteral and oral administration of Zantac® These reactions have occasionally occurred after a single dose.
Reversible blood count changes (leucopaenia, thrombocytopaenia) have occurred in a few patients. Rare cases of agranulocytosis or of pancytopaenia sometimes with marrow hypoplasia have been reported.
Other haematological and renal laboratory tests have not revealed any drug related abnormalities.
No clinically significant interference with endocrine or gonadal function has been reported. There have been a few reports of breast symptoms (swelling and/or discomfort) in men taking ranitidine; some cases have resolved on continued treatment.

Symptoms and Treatment of Overdosage – No particular problems are expected following overdosage with Zantac. Symptomatic and supportive therapy should be given as appropriate. If need be, the drug may be removed from the plasma by haemodialysis.

Dosage and Administration – Adults: Duodenal ulceration, benign gastric ulceration, or reflux oesophagitis: 300 mg once daily at bedtime.
It is not necessary to time the dose in relation to meals. In most cases of duodenal ulcer and benign gastric ulcer, healing will occur in four weeks. In the small number of patients whose ulcers may not have fully healed, these are likely to respond to a further course of treatment.
Patients who have responded to this short term therapy, particularly those with a history of recurrent ulcer, may usefully have extended maintenance treatment at a reduced dosage of one 150 mg tablet at bedtime.
To help in the management of reflux oesophagitis, the recommended course of treatment is one 300 mg tablet once daily at bedtime or one 150 mg tablet twice daily for up to 8 weeks.

Children: Experience with Zantac in children is limited and it has not been fully evaluated in clinical studies – see **Precautions**.

Availability – Zantac Tablets are available as white film-coated tablets engraved ZANTAC 150 on one face and GLAXO on the other, containing 150 mg ranitidine (as the hydrochloride), in packs of 30 and 60 tablets.
Zantac Tablets are also available as white, capsule shaped, film-coated tablets engraved ZANTAC 300 on one face and GLAXO on the other, containing 300 mg ranitidine (as the hydrochloride), in packs of 30 tablets.
Zantac Injection is available as 2 mL ampoules each containing 50 mg ranitidine (as the hydrochloride) in 2 mL solution for intravenous or intramuscular administration. Packages of 10 ampoules.
Product Monograph available on request.

References

1. Ireland *et al:* The Lancet, August 4, 1984; 274-275. **2.** Barbara *et al:* International J. of Clinical Pharmacology, Therapy and Toxicology 1986; *24* (2): 104-107. **3.** Product Monograph. **4.** Silvis *et al:* J. of Clinical Gastroenterology 1985; 7 (6): 482-487. **5.** Gough *et al:* The Lancet, September 22, 1984; 659-662. **6.** Simon *et al:* J. of Clinical Gastroenterology 1986; *8* (3): 482-487. **7.** Jensen *et al:* New England Journal of Medicine 1983; 308: 883-887. **8.** Data on File. **9.** Smith *et al:* Br. J. of Clin Pharmacology 1987; (23): 311-315. **10.** Powell *et al:* Arch Internal Med 1984; (144): 484-486.
11. Sutherland *et al:* Eur J Clin Pharmacology 1987; 32: 159-164. **12.** Siepler *et al:* Clin Pharmacy 1986; 5: 129-142. **13.** Wormsley: Postgrad Med J 1988; 64 (Suppl 1): 47-53.

Glaxo
Glaxo Canada Inc.

PAAB CCPP

IDARAC

PRESCRIBING INFORMATION floctafenine 200 mg tablets. **THERAPEUTIC CLASSIFICATION:** Analgesic **ACTION:** IDARAC (floctafenine) is an anthranilic acid derivative which has analgesic and anti-inflammatory properties. Floctafenine has been shown to inhibit in vitro biosynthesis of prostaglandins PGE2 and PGF2*a*. Gastrointestinal bleeding determined by daily fecal blood loss was shown in one clinical trial to be approximately 1.2 mL after 1600 mg/day of floctafenine compared to 10.4 mL after 2400 mg/day of acetylsalicylic acid. In normal volunteers, IDARAC was well absorbed after oral administration and peak plasma levels were attained 1-2 hours after administration and declined in a biphasic manner with an initial (*a* phase) half-life of approximately 1 hour and a later (β phase) half-life of approximately 8 hours. Floctafenine and its metabolites do not accumulate following oral administration of multiple doses. After oral and intravenous administration of 14C labelled IDARAC, urinary excretion accounted for 40% and fecal and biliary excretion accounted for 60% of the recovered radioactivity. The main urinary metabolites are floctafenic acid and its conjugate with minimal amounts of free floctafenine. **INDICATIONS:** IDARAC (floctafenine) is indicated for short-term use in acute pain of mild and moderate severity. **CONTRAINDICATIONS:** IDARAC (floctafenine) is contraindicated in patients with peptic ulcer or any other active inflammatory disease of the gastrointestinal tract and in patients who have demonstrated a hypersensitivity to the drug. **WARNINGS:** USE IN PREGNANCY: The use of IDARAC (floctafenine) in women of childbearing potential requires that the likely benefit of the drug be weighed against the possible risk to the mother and fetus. Use of the drug in women who are nursing is not recommended. USE IN CHILDREN: The safety and efficacy of IDARAC in children have not been established and therefore is not recommended. The safety and efficacy of long-term use of IDARAC have not been established. **PRECAUTIONS:** IDARAC (floctafenine) should be used with caution in patients with impaired renal function. In clinical trials with IDARAC, dysuria without apparent changes in renal function was reported. The incidence of dysuria was greater in males than in females and occurred primarily in the first morning voiding. It has not been established whether dysuria is related to dose and or duration of drug administration. Patients taking anticoagulant medication may be given IDARAC with caution. Alterations in prothrombin time have been observed only in clinical trials where the administration of IDARAC was extended beyond two weeks. IDARAC should be used with caution in patients with a history of peptic ulcer or other gastrointestinal lesions. **ADVERSE REACTIONS:** The most commonly occuring side effects reported during IDARAC (floctafenine) therapy were: CENTRAL NERVOUS SYSTEM: Drowsiness, dizziness, headache, insomnia, nervousness, irritability. GASTROINTESTINAL SYSTEM: Nausea, diarrhea, abdominal pain or discomfort, heartburn, constipation, abnormal liver function, gastrointestinal bleeding. UROGENITAL SYSTEM: Dysuria, burning micturition, polyuria, strong smelling urine, urethritis and cystitis. ALLERGIC-TYPE REACTIONS: Maculopapular skin rash, pruritis, urticaria, redness and itching of the face and neck. Other less frequently occurring side effects were: tinnitus, blurred vision, dry mouth, thirst, bitter taste, anorexia, stomach cramps, flatulence, hot flushes and sweating, tachycardia, weakness and tiredness. **SYMPTOMS AND TREATMENT OF OVERDOSE:** In a case of overdose standard procedures to evacuate gastric contents, maintain urinary output and provide general supportive care should be employed. **DOSAGE AND ADMINISTRATION:** The usual adult dose of IDARAC (floctafenine) in 1 to 2 tablets (200 to 400 mg), every 6 to 8 hours as required. The maximum recommended daily dose is 1200 mg. IDARAC is recommended for short-term management of acute pain. The tablets should be taken with a glass of water. IDARAC is not recommended for use in children. **AVAILABILITY:** Each tablet of IDARAC contains 200 mg of floctafenine. Tablets are biconvex, round, creamy-white, with W on one side and $\frac{1}{200}$ on the other side. IDARAC is available in bottles of 100 tablets. Store at room temperature, protected from light. IDARAC is a Schedule F (prescription) drug. Product monograph is available upon request.

Winthrop

Winthrop Laboratories
Division of Sterling Drug Ltd.**
Aurora, Ontario L4G 3H6
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**Registered User

PAAB CCPP

Dermacase

Tom Enta, MD

Dr. Enta is a Professor of Medicine at the University of Calgary and a Consultant of the Skin Clinic at the Tom Baker Cancer Centre, Calgary, Alberta.

Can you identify this condition?

A shy young man of 27 noted these purple papules and soft nodules on his penis. The first ones appeared when he was about 17. They were asymptomatic. He was afraid that they would rupture with vigorous sexual activity.

Your diagnosis is:

1. Angiokeratoma of Fordyce
2. Blue rubber-bleb nevus
3. Kaposi's sarcoma
4. Hemorrhoids of the penis

Answer on page 1960.

Colour separations sponsored by Glaxo Canada Inc.

WITHOUT COMPLIANCE, TREATING CHLAMYDIA CAN BE AN EXERCISE IN INFERTILITY.

For as long as *Chlamydia* remains the most prevalent STD in Canada, it will be a primary cause of pelvic inflammatory disease[1] which, all too often, can lead to ectopic pregnancy and infertility.[1,2]

Only through early diagnosis and successful treatment can *Chlamydia* and its consequences be diminished.

Whenever *Chlamydia* is present, consider the Vibra-Tabs* C-Pak*, the only approved pre-packaged anti-chlamydial. Vibra-Tabs* C-Pak* can eradicate the infection *before* serious consequences develop.

Designed to minimize the risk of missed doses, the Vibra-Tabs* C-Pak*—1 tablet B.I.D. for 10 days—promotes the compliance required for successful treatment.

The Vibra-Tabs* C-Pak*. Because ending the spread of *Chlamydia* begins with compliance.

Vibra-Tabs* C-Pak*

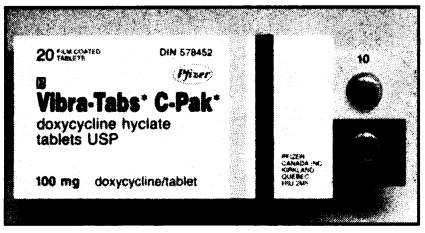
(doxycycline hyclate/pfizer)

THE 10-DAY ANTI-CHLAMYDIAL.

PAAB CCPP

Pfizer

Pfizer Canada Inc.
Kirkland, Quebec
H9J 2M5



PRODUCT INFORMATION

Broad-spectrum antibiotic

ACTION
VIBRA-TABS (doxycycline) is a broad-spectrum antibiotic, active against a wide range of Gram-negative and Gram-positive organisms. VIBRA-TABS (doxycycline) exerts its antimicrobial effect by inhibition of protein synthesis.

INDICATIONS AND CLINICAL USE
VIBRA-TABS (doxycycline) as VIBRA-TABS C-PAK is indicated for the treatment of:

Genitourinary Tract Infections:

In adult patients with urethritis, cervicitis and vaginitis with a positive test for *Chlamydia trachomatis* and/or *Ureaplasma urealyticum*, clinical resolution and absence of detectable organisms have been observed at completion of therapy with VIBRA-TABS (doxycycline). Relapses or reinfection can occur. In these cases, limited data suggest that some patients may derive clinical benefit from the administration of VIBRA-TABS (doxycycline) or an alternative therapy. The effect on long term morbidity has not been established.

CONTRAINDICATIONS
VIBRA-TABS (doxycycline) is contraindicated in individuals who have shown hypersensitivity to tetracyclines.

WARNINGS
As with other tetracyclines, VIBRA-TABS (doxycycline) may form a stable calcium complex in any bone-forming tissue, though *in vitro* it binds calcium less strongly than other tetracyclines. Though not observed in clinical studies to date, it should be anticipated that like other tetracyclines the use of VIBRA-TABS (doxycycline) during tooth development (last trimester of pregnancy, during lactation, neonatal period and early childhood) may cause discoloration of the teeth. Though more commonly associated with long term use of tetracyclines, this effect has also been known to occur after short courses.

PRECAUTIONS
In clinical studies to date, doxycycline administration did not lead to increased serum levels nor to an increase in the serum half-life of doxycycline in patients with impaired renal function. VIBRA-TABS (doxycycline) in normal dosage may be used to treat these patients. Although no evidence of increased toxicity has been observed in such patients, the potential for increased hepatic or other toxicity should be considered until further data on the metabolic fate of doxycycline under these conditions become available. Liver function tests should be carried out at regular intervals on patients receiving high doses for prolonged periods of time. Concurrent administration of VIBRA-TABS (doxycycline) and agents known to be hepatotoxic should be avoided if possible.

The use of antibiotics may occasionally result in overgrowth of non-susceptible organisms; thus, observation of the patient is essential. There is evidence to suggest that VIBRA-TABS (doxycycline) may have less effect on the gut flora than other tetracyclines.

Certain hypersensitive individuals may develop a photodynamic reaction to sunlight during treatment with VIBRA-TABS (doxycycline). If this or any other allergic reaction should occur, medication should be discontinued.

Increased intracranial pressure with bulging fontanelles has been observed in infants receiving therapeutic doses of tetracycline. Although the mechanism of this phenomenon is unknown, the signs and symptoms have disappeared rapidly upon cessation of treatment with no sequelae.

Esophageal injury consisting of esophagitis and esophageal ulceration have rarely been reported in patients receiving doxycycline orally. If this should occur, VIBRA-TABS (doxycycline) should be discontinued until healing occurs. Administration of antacids and/or cimetidine has provided relief in the treatment of such cases. To reduce the risk of esophageal injury, patients should be advised to take VIBRA-TABS (doxycycline) with an adequate amount of fluid while standing or sitting upright.

Use in Pregnancy and Lactation:
VIBRA-TABS (doxycycline) should not be administered to pregnant and lactating women or neonates until its safety in such cases has been established beyond all reasonable doubt, unless in the judgment of the physician the potential benefit to the patient outweighs the risk to the fetus or child.

ADVERSE REACTIONS
As with other broad spectrum antibiotics, gastrointestinal disturbances such as nausea, vomiting and diarrhoea, as well as glossitis, stomatitis and proctitis may occur, but have rarely been sufficiently troublesome to warrant discontinuation of therapy.

Rare instances of esophagitis and esophageal ulcerations in patients receiving the capsule form of doxycycline have been reported. (See PRECAUTIONS and DOSAGE AND ADMINISTRATION Sections.)

As with other tetracyclines, elevation of SGOT or SGPT values, anemia, neutropenia, eosinophilia, leukopenia or elevated BUN has been reported, the significance of which is not known.

SYMPTOMS AND TREATMENT OF OVERDOSAGE
Gastric lavage if necessary.

DOSAGE AND ADMINISTRATION OF VIBRA-TABS C-PAK
ADULTS:
For treatment of uncomplicated urethral, endocervical, or vaginal infections in adults associated with *Chlamydia trachomatis* and *Ureaplasma urealyticum:* 100 mg, by mouth, twice a day for at least 10 days.

As absorption is not significantly affected by food or milk VIBRA-TABS (doxycycline) should be given with or after a meal thus minimizing the possibility of gastric upset. Antacids and iron preparations impair absorption and should not be given concomitantly to patients taking VIBRA-TABS (doxycycline).

VIBRA-TABS (doxycycline) should be given to patients with adequate amounts of fluid while standing or sitting upright to reduce the risk of esophageal injury.

Therapy should be continued after symptoms and fever have subsided. It should be noted, however, that effective antibacterial levels are usually present 24 to 36 hours following discontinuance of VIBRA-TABS (doxycycline) therapy.

No alteration in recommended dosage schedule need be made when treating patients with impaired renal function.

AVAILABILITY
VIBRA-TABS C-PAK contains 20 orange film coated tablets, each tablet containing doxycycline hyclate equivalent to 100 mg of doxycycline.

Intended for adult use as a 10 day treatment for urethral, endocervical, or vaginal infections associated with *Chlamydia trachomatis* and *Ureaplasma urealyticum*.

Storage: VIBRA-TABS (doxycycline) 100 mg: Protect from light.

PRODUCT MONOGRAPH AVAILABLE ON REQUEST.

References
1. Sorbie J. *Chlamydia* infection: a common sexually transmitted disease. *Can Fam Physician* 1982;28:2185-90.
2. Centers for Disease Control (US Dept. Health and Human Services). *Chlamydia trachomatis* infections: policy guidelines for prevention and control. Atlanta, GA: CDC, 1985:19 p.

* Prepared by Pfizer Canada Inc. (R.U.)
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Pfizer
Pfizer Canada Inc.
Kirkland, Quebec
H9J 2M5

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Vibra-Tabs* C-Pak*
(doxycycline hyclate/pfizer)

THE 10-DAY ANTI-CHLAMYDIAL.

Diprolene*
GLYCOL

Betamethasone Dipropionate Glycol Ointment/Cream 0.05%.
Topical corticosteroid.

ACTIONS — Anti-inflammatory, antipruritic and vasoconstrictive.

INDICATIONS AND CLINICAL USES — DIPROLENE Glycol is indicated for the relief of the inflammatory manifestations of resistant or severe psoriasis and corticosteroid-responsive dermatoses.

CONTRAINDICATIONS: — DIPROLENE Glycol is contraindicated in viral diseases including vaccinia, varicella, herpes simplex, and fungal infections; also, tuberculosis of the skin. Hypersensitivity to any one of the components of DIPROLENE Glycol is a contraindication to its use.

WARNING — The safety of this product has not been established during pregnancy or lactation. The potential benefit, if used during pregnancy or lactation, should be weighed against possible hazards to the fetus or the nursing infant. This drug should not be used in or near the eyes since DIPROLENE Glycol is not formulated for ophthalmic use. This product should not be used under occlusive dressing.

PRECAUTIONS
1. Suitable precautions should be taken in using topical glucocorticoids in patients with stasis dermatitis and other skin diseases with impaired circulation; hypersensitive subjects and in patients with glaucoma.
2. Patients should be advised to inform subsequent physicians of the prior use of glucocorticoids.
3. If irritation, sensitization, excessive dryness develop with the use of DIPROLENE Glycol, treatment should be discontinued.
4. Application of corticosteroids over extensive lesions, or failure to follow dosage schedule may result in significant systemic absorption producing hypercortisonism manifesting itself by adrenal suppression, moon facies, striae and suppression of growth.
5. During the use of topical corticosteroids, infections may occur.
6. If an overt infection is present, appropriate antimicrobial treatment is indicated.
7. If symptomatic response is not noted within a few days to a week, the local application of corticosteroids should be discontinued and the patient re-evaluated.
8. Prolonged use of corticosteroid preparations may produce striae or atrophy of the skin or subcutaneous tissues. If this occurs, treatment should be discontinued.

ADVERSE REACTIONS: The following adverse reactions were reported with DIPROLENE Glycol: mild to moderate transient folliculitis, increased redness of lesions, increased erythema, itching, vesiculation, perilesional scaling, telangiectasia, dryness, stinging, burning, skin atrophy, local irritation, urticaria. Subnormal plasma cortisol levels were also reported.

The following adverse skin reactions have been reported with the use of topical steroids: striae, hypertrichosis, change in pigmentation, secondary infection, perioral dermatitis, allergic contact dermatitis, maceration of the skin, acneiform eruptions and miliaria. Adrenal suppression has also been reported following topical corticosteroid therapy. Posterior subcapsular cataracts have been reported following systemic use of corticosteroids.

SYMPTOMS AND TREATMENT — No specific antidote is available and treatment should be symptomatic.

Percutaneous absorption of corticosteroids can occur when large amounts of corticosteroids are applied. Toxic effects may include ecchymosis of skin, peptic ulceration, hypertension, aggravation of infection, hirsutism, acne edema and muscle weakness due to protein depletion. Treatment of a patient with systemic toxic manifestations consists of assuring and maintaning a patent airway and supporting ventilation using oxygen and assisted or controlled respiration as required. This usually will be sufficient in the management of most reactions. Should circulatory depression occur, vasopressors such as ephedrine or metaraminol and intravenous fluids may be used. Should a convulsion persist despite oxygen therapy, small increments of an ultra-short acting barbiturate (pentobarbital or secobarbital) may be given intravenously. Allergic reactions are characterized by cutaneous lesions, urticaria, edema or anaphylactoid reactions.

DOSAGE AND ADMINISTRATION — A thin film of DIPROLENE Glycol should be applied to cover completely the affected area once daily, in the morning. DIPROLENE Glycol may also be applied twice daily, in the morning and at nigh or as directed by the physician. Treatment should be discontinued when the dermatologic disorder is controlled. According to clinical response, duration of therapy may vary from a few days to a longer period of time. However, treatment should not be continued for more than four weeks without patient re-evaluation.

DIPROLENE Glycol should not be used under occlusive dressing.

AVAILABILITY — DIPROLENE Glycol Ointment: Each gram of ointment contains 0.5 mg betamethasone (as dipropionate USP, micronized), propylene glycol monostearate USP, propylene glycol USP, in a base of white wax and white petrolatum.

DIPROLENE Glycol Cream: Each gram of cream contains 0.5% mg betamethasone (as dipropionate USP, micronized), in a base of propylene glycol USP.

DIPROLENE Glycol Ointment/Cream is packaged in 15 and 50 gram aluminum tubes. Store at 15° to 25°C.

Complete monograph on request.

SCHERING CANADA INC.
Pointe Claire (Quebec) H9R 1B4

PMAC
PAAB

*Reg'd TM

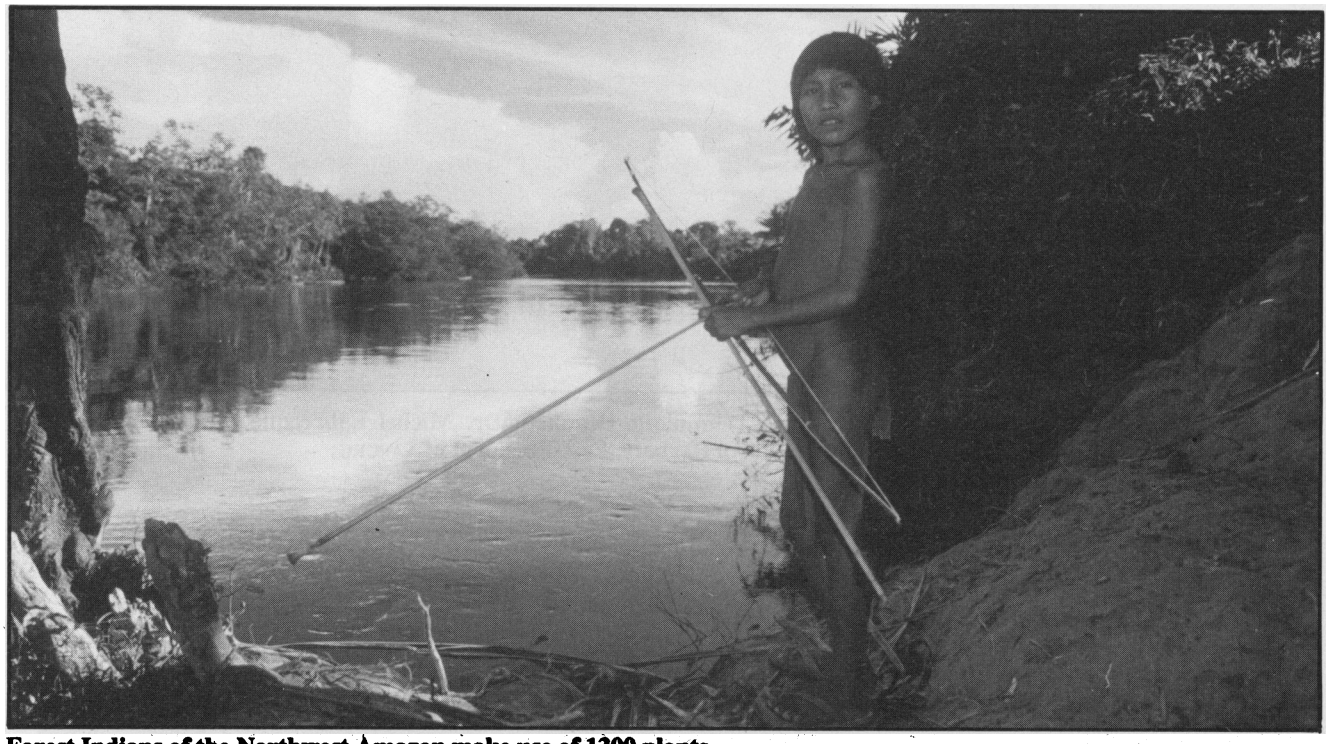
with Death of Amazonian Rainforests

meadowsweet had never been discovered? The rate at which species of plant are becoming extinct is soon going to be too fast for anyone to record: at the moment it is happening at 1000 times the natural rate. These lost species "take with them a pharmacopeia of unknown size and value to mankind," say the WWF's recent publication, *The Importance of Biological Diversity*.

As a warning of the need for "safeguarding our options for future use", WWF cites the example of diosgenin, a substance that is at the base of the contraceptive pill industry. "The best known source of diosgenin is *Dioscorea deltiodea*, which grows in the Himalayan foothills of Northern India," writes the WWF. "Industrial companies have ignored restrictions on collection, and the remaining small specimens yield less than 15% of the diosgenin found in the large old tumors, which have mostly been uprooted."

Aboriginal people from all around the world, including Canada, complain that they have to go further and further afield to find the plants that they need for their medicines. The WWF is working to preserve those "afields" against further exploitation. "Our objective," it states, "is health insurance for the people of the world."

WWF Canada is located at 60, St. Clair Ave. E., Suite 201, Toronto, Ontario M4T 1N5. Telephone (416) 923-6177.



Forest Indians of the Northwest Amazon make use of 1300 plants

It's precise.

Group Celebrates 17th Anniversary in Texas

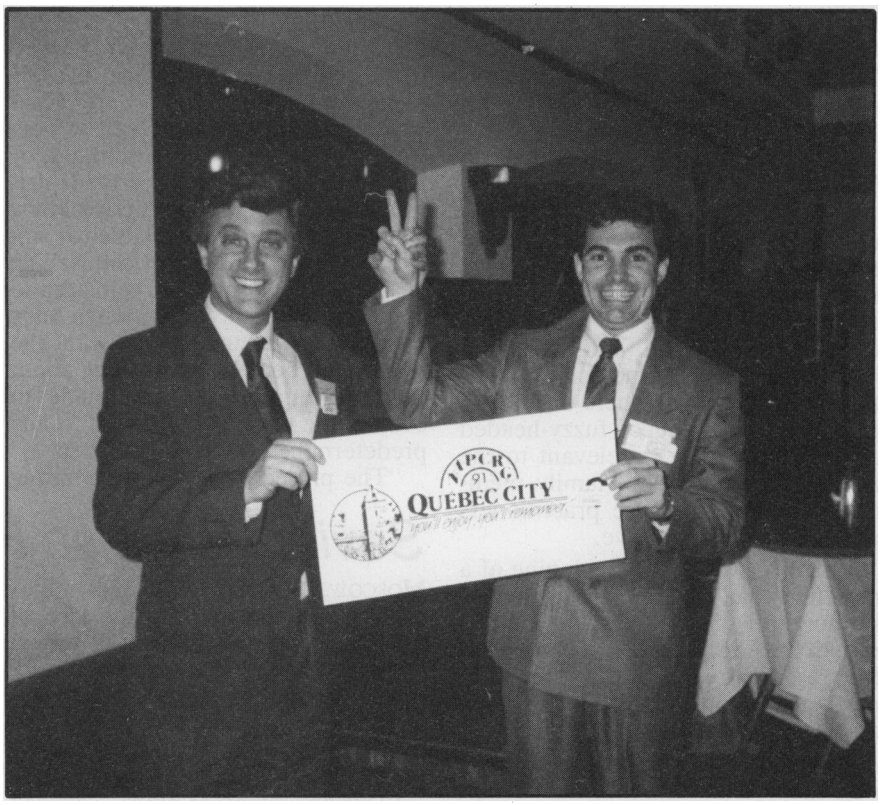
primary care and obstetrics. The groups give participants a chance to meet others with mutual interests.

NAPCRG is a supportive group and is very interested in helping all family physicians, including those in practice, to become involved in research. In order to help the beginner researcher, NAPCRG now has a list of consultants and mentors available.

Anyone needing information about these can contact Ms. Inese Grava-Gubins, Director of Research, the College of Family Physicians of Canada, 4000 Leslie Street, Willowdale, Ont. M2K 2R9.

Next year's meeting will be held in Denver, Colorado,and the following year it will be hosted by Laval University in Quebec City. The organizers in Quebec City are looking forward to a large Canadian contingent and hope to attract new researchers and residents. Now is the time to formulate your questions and plan for Quebec in 1991!

For further information, contact: Dr. Ann C. McCaulay, Canadian Representative to NAPCRG, Montreal General Hospital, 1650 Cedar Avenue, Montreal, Que. H3G 1A4



Dr. Louis Latulippe and Dr. Michel Labrecque (both from Quebec City) made a successful bid to host NAPCRG '91 in their home city.

Measuring the Present

MUNICH, F.D.R.G.—Have you ever wondered how long the present lasts? German perception physiologists of the *Max-Planck-Gesellschaft* (Max Plank Society) have found the answer: 2.9 seconds. To check it properly, the researchers studied rhythmic work processes involving instruments, and movements during which one hand comes into contact with either the person's skin or clothing.

The movements were divided into individual and repeated movements, the latter including activities such as scratching oneself or hammering. They studied the Himba people of Southern Africa, the Trobriand people of Papua New Guinea, and the Yanomani Indians of South America.

["What are you doing with my wife?", demands Trobriand Islander returning from a hunting trip to find German researcher making a video of his wife scratching herself.

"Don't get upset, good man, I am a perception physiologist, and I am just measuring the present," he replies.]

The evaluation of the study revealed that there are no cultural differences in the duration of these kinds of movements, and that the time intervals last an average of two seconds with repeated movements and 2.9 seconds with non-repeated movements.

Keats' famous "hour" of happiness must now be corrected: "I scarcely remember counting upon happiness —I look not for it if it be not in the present 2.9 seconds."

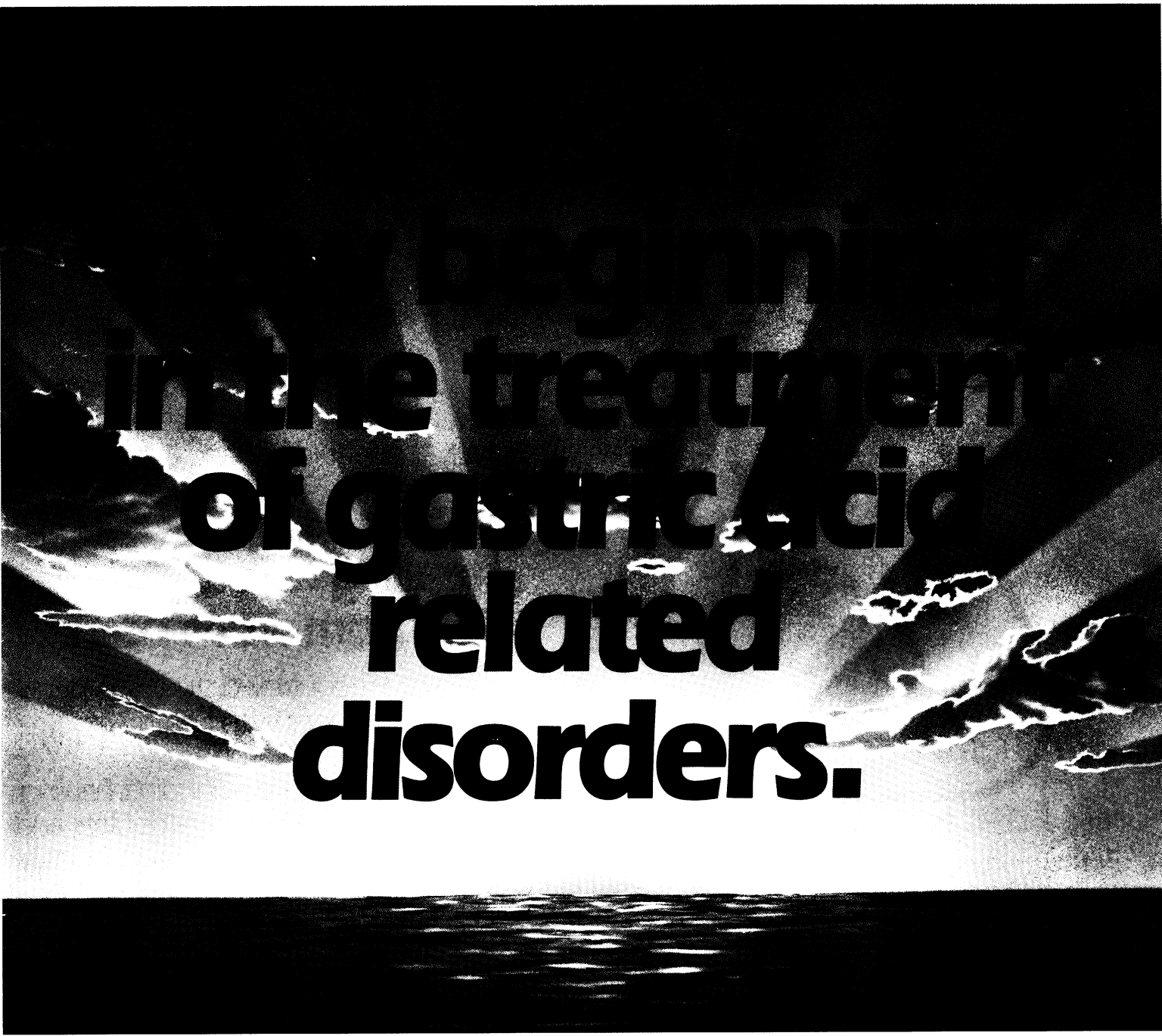
Off-Hours Clinics

Continued from page 1749

patients; that we hadn't served them properly and had basically handed them over to be someone else's responsibility.

"Patient's prefer to come to the clinic rather than to the ER. When they come here, children aren't going to be frightened out of their wits seeing six stretchers coming past with all the blood and broken bones, as they often do in emergency."

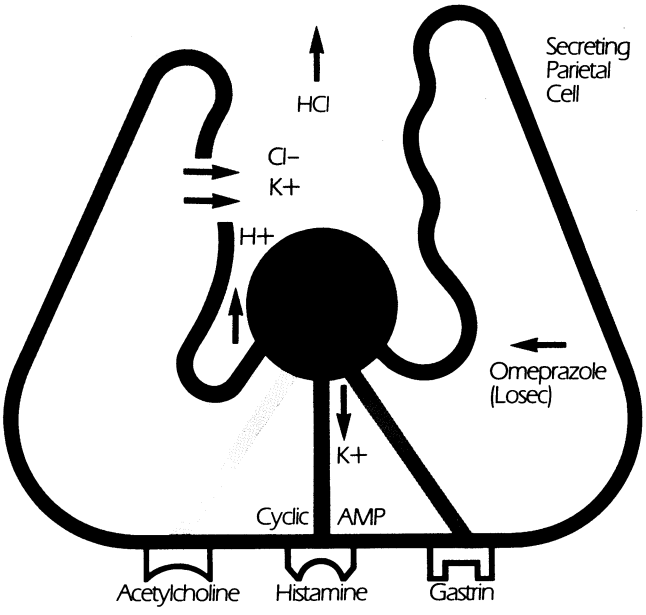
Family physicians involved in off-hours clinics are now forming the Ontario Association of Off-Hours Clinics and are hoping to become a subdivision of the OMA. There are now nearly 400 physicians involved across Ontario.



INTRODUC

The first acid

Precise action, consistent control of gastric acid.



Losec inhibits the final common pathway of acid production – the acid pump.[1]

It is now very well established that inhibiting gastric acid secretion effectively heals ulcers and reduces acid-related symptoms.

Losec® controls acid at its source, the acid pump of the parietal cell located in the oxyntic glands of the gastric mucosa.[1]

Since the acid pump is the final common pathway for gastric acid secretion, Losec inhibits acid more effectively than ranitidine and cimetidine.[2]

Significantly superior healing rates, faster freedom from pain.

In well-controlled studies, patients felt better sooner with Losec.

With good reason.

Compared with ranitidine, healing rates in duodenal ulcer, gastric ulcer, and reflux esophagitis were endoscopically proven to be significantly superior.[3,4,5,6]

ING LOSEC®

pump inhibitor.

(omeprazole)

Proven safety profile.

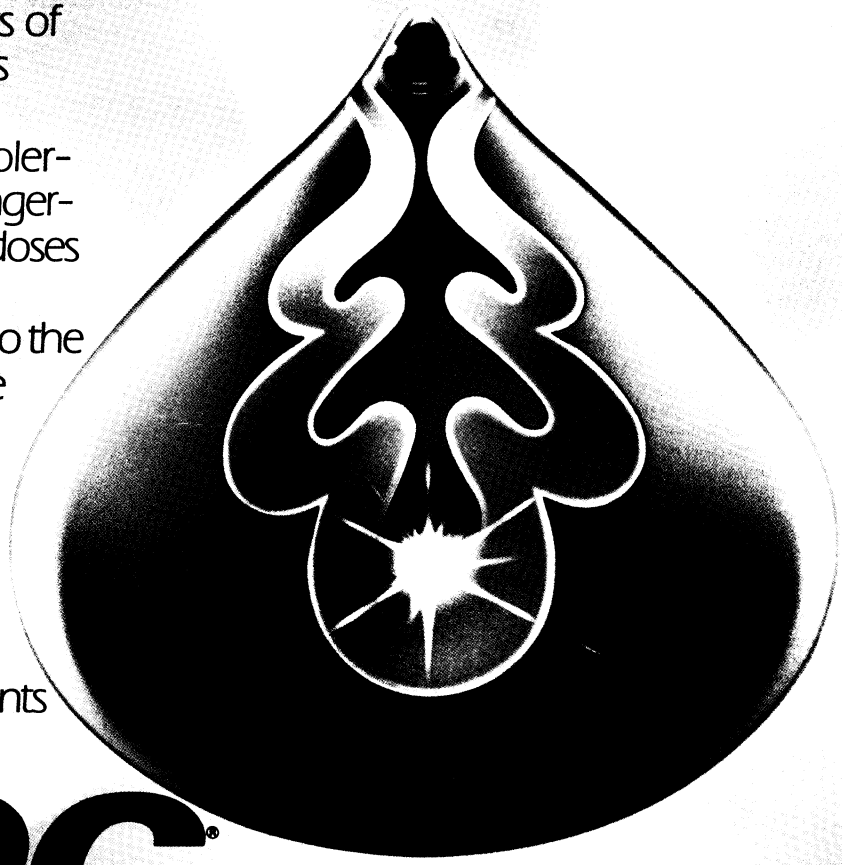
The safety profile of Losec has been established in seven years of studies involving 13,000 patients and healthy volunteers.[6]

Losec was generally well tolerated including patients with Zollinger-Ellison Syndrome receiving high doses for up to 5 years.[6]

Since Losec is highly specific to the acid pump and becomes active only in the high acidity of the parietal cell, its side effect profile is low.[6]

Losec is a new beginning in the treatment of gastric acid related disorders.

The time to start your patients on Losec is now.



LOSEC®

(omeprazole)

prescribing information see page 1[illegible]

Opticrom®

Sodium cromoglycate ophthalmic solution 2% w/v – Anti Allergic Agent

Indications: Treatment of seasonal allergic conjunctivitis and vernal keratoconjunctivitis.
Contraindications: Hypersensitivity to components of OPTICROM.
Warning: The number of drops to be instilled into the eye per day should be specified to the patient. Regular dosage is important.
Any remaining contents should be discarded four weeks after opening.
Precautions: Possible immunologic changes resulting in reactions such as polymyositis, pneumonitis and heart failure, urticaria and anaphylaxis, have been reported rarely with sodium cromoglycate preparations administered by inhalation.
Clinical experience in children under five (5) years of age is limited.
During clinical use there have been, to date, no reports of adverse effects on the mother or the fetus that could be ascribed to the use of sodium cromoglycate. Nevertheless, as with all medications, caution must be exercised during pregnancy.
During treatment with OPTICROM soft contact lenses should not be worn.
Adverse Reactions: Causes of erythema, urticaria or maculo-papular rash have been reported with other sodium cromoglycate preparations. These have cleared within a few days on withdrawal of the drug. Occasional headache, sneezing, cough and unpleasant taste in the mouth have been reported after nasal or inhalation therapy. Eosinophilic pneumonia has been reported rarely after administration by inhalation.
Symptoms and Treatment of Overdosage: There have been no reported cases in humans of overdosage of the drug. Symptomatic treatment is suggested should accidental ingestion occur.
Dosage and Administration: Note: In patients with seasonal allergic conjunctivitis, clinical response to OPTICROM may be expected within ten days, in those with vernal keratoconjunctivitis, within a few weeks.
Dose: One or two drops into each eye four times daily.
Each drop of 2% ophthalmic solution delivers approximately 0.04 mL of solution containing 0.8 mg sodium cromoglycate.
The maximum single dose (per eye) is 2 drops or 1.6 mg sodium cromoglycate. The maximum total daily dose is 16 drops or 12.8 mg sodium cromoglycate.
Availability: OPTICROM is supplied in a plastic dropper bottle containing 10 mL of a sterile 2% solution of sodium cromoglycate preserved with benzalkonium chloride.
Product Monograph available on request to health professionals.

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Fisons Corporation Limited registered user
©Fisons Corporation Limited 1988

FISONS Pharmaceuticals

Fisons Corporation Limited
70 Gough Road, Markham, Ontario L3R 8G9

Op-21E-2/88
Revised February 1989

PMAC PAAB

Radiology Rounds

T. R. Marotta, MD M. K. McLennan, MD

Drs. Marotta and McLennan are residents in the radiology program of the University of Toronto at the Toronto Hospital, Western Division.

Figure 1
Images from dynamic computed tomography at level of aortic arch. Figure 1A was "sliced" a few seconds before Figure 1B.

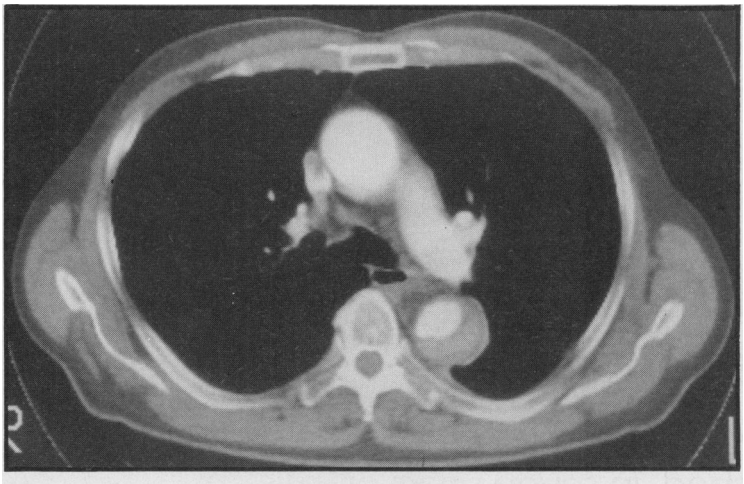

Figure 1A

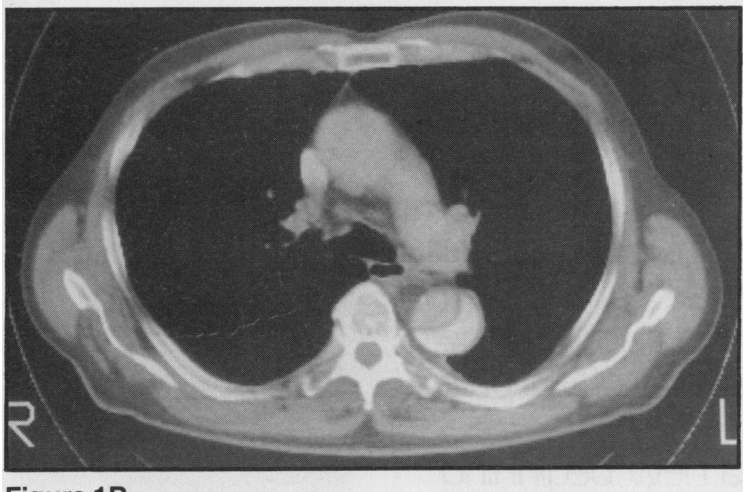

Figure 1B

Clinical History

The patient reported interscapular pain of acute onset.

What abnormality is demonstrated by the radiographs? What is the significance of this finding?

Answer on page 1963

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Prescribe Ceclor® (cefaclor)

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CECLOR: PRESCRIBING SUMMARY

INDICATIONS: The treatment of the following infections caused by *Strept. pyogenes, Strept. pneumoniae.* Staphylococci (including coagulase-positive, coagulase-negative, and penicillinase-producing strains), *E. Coli, Proteus mirabilis, Klebsiella pneumoniae, H. influenzae* (including ampicillin-resistant strains):
1. Otitis media,
2. Lower Respiratory Infections, including pneumonia, bronchitis, and pulmonary complications resulting from cystic fibrosis,
3. Upper Respiratory Infections, including pharyngitis and tonsillitis,
4. Skin and Soft-Tissue Infections,
5. Urinary Tract Infections.

CONTRAINDICATIONS: Persons who have shown hypersensitivity to the cephalosporin antibiotics.

WARNINGS: Cephalosporins should be given only with caution to penicillin-sensitive patients. There is some evidence of cross-allergenicity between penicillins and cephalosporins. Patients have been reported to have had severe reactions (including anaphylaxis) to both.

Administer with caution to any patient who has demonstrated some form of allergy, particularly to drugs. If an allergic reaction to Ceclor occurs, the drug should be discontinued and the patient treated with the usual agents. Pseudomembranous colitis has been reported with virtually all broad-spectrum antibiotics; therefore, it is important to consider its diagnosis in patients who develop diarrhea in association with the use of antibiotics.

PRECAUTIONS: Safety during pregnancy has not been established. Small amounts of Ceclor have been detected in mother's milk following administration of single 500 mg doses. The effect on nursing infants is not known. Caution should be exercised when Ceclor is administered to a nursing woman. Prolonged use may result in the over-growth of non-susceptible organisms. If superinfection occurs, administration of Ceclor should cease and appropriate measures taken. Positive direct Coombs' tests have been reported during treatment with cephalosporins and may be due to the drug. Administer with caution in the presence of markedly impaired renal function. The safe dosage is likely to be lower than that usually recommended. A false-positive reaction for glucose in the urine may occur with Benedict's or Fehling's solution or with Clinitest tablets but not with Tes-Tape® (Glucose Enzymatic Test Strip, USP).

ADVERSE REACTIONS: Of 1,493 patients treated with cefaclor, 87 (5.8%) had adverse reactions or abnormal laboratory values judged to be drug-related. These included: nausea and vomiting, dyspepsia, diarrhea, rash (including urticaria & morbilliform eruptions), positive Coombs', eosinophilia, genital moniliasis, vaginitis, elevated SGOT, and elevated SGPT. Other adverse reactions experienced less frequently include: pruritus, dizziness, headache, somnolence, abdominal pain, leg cramps, abnormal taste, and fever. Leukopenia, decreased hemoglobin and hematocrit, neutrophilia, elevated alkaline phosphatase, lymphocytosis, lymphocytopenia, thrombocytosis, elevated BUN and creatinine, hematuria and pyuria have also been reported. Cases of serum-sickness-like reactions (including skin manifestations, fever and arthralgia/arthritis), anaphylaxis, and pseudomembranous colitis have been reported.

SYMPTOMS AND TREATMENT OF OVERDOSAGE: There has been no experience of overdosage with Ceclor. If a large overdose has been recently consumed, the patient should be kept under observation and appropriate treatment undertaken as considered necessary.

DOSAGE AND ADMINISTRATION: Ceclor is administered orally. *Adults* — The usual adult dosage is 250 mg every 8 to 12 hours. The maximum recommended dosage is 2 g per day, although doses of 4 g per day have been administered safely for 28 days.
Children — The usual dosage for children is 20 mg/kg/day in divided doses every 8 to 12 hours. In more serious infections, otitis media, and those infections caused by less susceptible organisms, 40 mg/kg/day is recommended, up to 1 g per day.

For lower respiratory tract infections, the total daily dosage should be divided and administered 3 times daily. For B-hemolytic streptococcal infections administer for at least ten days.

DOSAGE FORMS:

Ceclor 250 mg Pulvules 3061. Each opaque purple and white capsule contains 250 mg cefaclor. Bottles of 100 capsules.

Ceclor 500 mg Pulvules 3062. Each opaque purple and grey capsule contains 500 mg cefaclor. Bottles of 30 and 100 capsules.

Ceclor 125 mg for Oral Suspension (M-5057). Strawberry flavored, 125 mg/5 mL.

Ceclor 250 mg for Oral Suspension (M-5058). Grape flavored, 250 mg/5 mL.

Reconstitute suspensions by adding 60 mL of water to each 100 mL bottle or 90 mL for each 150 mL bottle in two portions. Shake well after each addition. After mixing, store in a refrigerator. The mixture may be kept for 14 days without significant loss of potency. Shake well before using. Keep tightly closed.

Product Monograph available on request.

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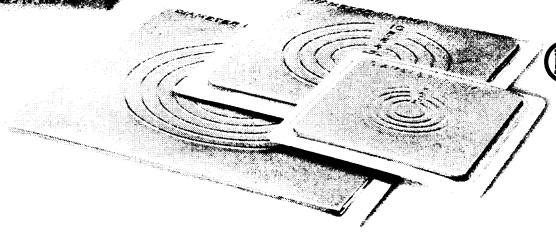

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PULMICORT®
Full Disclosure Document
Effective October 1988 - October 1990

PULMICORT® Inhaler
PULMICORT® SPACER® Inhaler
(budesonide)

THERAPEUTIC CLASSIFICATION
Glucocorticosteroid aerosol for the treatment of bronchial asthma.

ACTION
PULMICORT (budesonide) is a potent non-halogenated synthetic glucocorticosteroid with strong topical and weak systemic effects.

PULMICORT has a high topical anti-inflammatory potency and it is rapidly biotransformed in the liver. This favourable separation between topical anti-inflammatory activity and systemic effect is due to strong glucocorticosteroid receptor affinity and an effective first pass metabolism with a short half-life.

Pretreatment with inhaled budesonide inhibits the late bronchial reaction. The immediate reaction may also be reduced if PULMICORT is given at least 6 hours before a bronchial challenge.

It has also been shown that by using the Spacer® (tube extension device), the oral impaction of PULMICORT was reduced.

Pharmacokinetics:
Peak plasma levels occur immediately after inhalation with the Spacer® device. The plasma half-life of budesonide is 2.0 ± 0.2 hours and the systemic bioavailability after inhalation is calculated to be 72.8 ± 42.0% of the dose retained by the patient after mouth rinsing. The oral bioavailability is calculated to be 10.7 ± 4.3%. Plasma protein binding is estimated at 88.3 ± 1.5%. In human volunteers 31.8 ± 7.5% of an inhaled dose of budesonide was recovered in the urine and 15.1 ± 4.3% in the faeces.

INDICATIONS
Patients with bronchial asthma:
1. In patients who do not respond adequately to conventional therapy and require inhaled steroids,
2. In patients for whom a reduction of systemic glucocorticoids is desirable.

CONTRAINDICATIONS
1. Status asthmaticus; not to be used in primary treatment of acute episodes of asthma or in patients with moderate to severe bronchiectasis,
2. Known hypersensitivity to any of the aerosol's components,
3. Active or quiescent pulmonary tuberculosis,
4. Untreated fungal, bacterial or viral infections of the respiratory system.

WARNINGS
1. **Deaths due to adrenal insufficiency have occurred in asthmatic patients during and after transfer from systemic corticosteroids to inhaled corticosteroids;** therefore particular care is needed in patients who are transferred from systemically active corticosteroids to PULMICORT. After withdrawal from systemic corticosteroids, a number of months are required for recovery of hypothalamic-pituitary-adrenal (HPA) function. During this period of HPA suppression, patients may exhibit signs and symptoms of adrenal insufficiency when exposed to trauma, surgery or infections, particularly gastroenteritis. Although PULMICORT may provide control of asthmatic symptoms during these episodes, it does NOT provide the systemic steroid which is necessary for coping with these emergencies.
   During periods of stress or a severe asthmatic attack, patients who have been withdrawn from systemic corticosteroids should be instructed to resume systemic steroids (in large dosages) immediately and to contact their physicians for further instruction. These patients should also be instructed to carry a warning card indicating that they may need supplementary systemic steroids during periods of stress or a severe asthma attack. To assess the risk of adrenal insufficiency in emergency situations, routine tests of adrenal cortical function, including measurement of early morning and evening cortisol levels, should be performed periodically in all patients. An early morning resting cortisol level may be accepted as normal only if it falls at or near the normal mean level.
   Patients previously on high doses of systemic steroids may regain earlier symptoms such as rhinitis and eczema when transferred from oral therapy to PULMICORT. These symptoms are a result of the generally lower systemic steroid action which will be experienced. Patients may also suffer from tiredness, headache, pain in muscles and joints and, occasionally, nausea and vomiting. Temporary resumption of systemic steroids may be necessary to treat these conditions.
2. THE DEVELOPMENT OF PHARYNGEAL AND LARYNGEAL CANDIDIASIS IS CAUSE FOR CONCERN BECAUSE THE EXTENT OF ITS PENETRATION OF THE RESPIRATORY TRACT IS UNKNOWN. IF ORAL PHARYNGEAL CANDIDIASIS DEVELOPS, PULMICORT TREATMENT SHOULD BE SUSPENDED UNTIL APPROPRIATE ANTI-FUNGAL THERAPY ERADICATES THE INFECTION. The incidence of candidiasis can generally be held to a minimum by having patients rinse their mouths out with water after each inhalation (See DOSAGE AND ADMINISTRATION).
3. Glucocorticosteroids may mask some signs of infection and new infections may appear during its use.
4. PULMICORT is not to be regarded as a bronchodilator and is not indicated for rapid relief of bronchospasm. Patients should be instructed to contact their physicians immediately if episodes of asthma not responsive to bronchodilators occur.
5. There is no evidence that control of asthma can be achieved by administration of PULMICORT in doses higher than those recommended. During such episodes, patients may require therapy with systemic corticosteroids.

PRECAUTIONS
1. In transferring patients from a systemic steroid to PULMICORT, the reduction of the systemic steroid must be very gradual and carefully supervised by the physician since systemic withdrawal symptoms (e.g. joint and/or muscular pain, lassitude, depression), may occur in spite of maintenance or improvement of respiratory functions. (See DOSAGE AND ADMINISTRATION.)
2. It is essential that the patient be instructed that PULMICORT is a preventative agent which must be taken at regular intervals and is not to be used to relieve an acute asthmatic attack.
3. The long-term effects of budesonide in human subjects are still unknown. In particular, the local effects of the agent on developmental or immunologic processes in the mouth, pharynx, trachea, and lung are unknown. There is also no information about the possible long-term systemic effects of budesonide therapy.
4. Treatment with PULMICORT should not be stopped abruptly, but tapered off gradually.
5. Pulmonary infiltrates with eosinophilia may occur in patients on PULMICORT therapy. Although it is possible that in some patients inhalational steroids are administered, their causative role, or their vehicle, cannot be ruled out.
6. **Usage During Pregnancy**
   Administration of PULMICORT during pregnancy should be avoided unless there are compelling reasons. In experimental animal studies, budesonide was found to cross the blood-placenta barrier. Like other glucocorticosteroids, budesonide is teratogenic to rodent species. High doses of budesonide administered subcutaneously produced fetal malformations, primarily skeletal defects, in rabbits, rats, and in mice. The relevance of these findings to humans has not yet been established. In the absence of further studies in humans, budesonide should be used during pregnancy only if the potential benefits clearly outweigh the risk to the fetus. Infants born of mothers who have received substantial doses of corticosteroids during pregnancy should be carefully observed for hypoadrenalism.
7. **Lactation**
   Glucocorticoids are secreted in human milk. It is not known whether budesonide would be secreted in human milk, but it is suspected to be likely. The use of PULMICORT in nursing mothers, requires that the possible benefits of the drug be weighed against the potential hazards to the mother, or infant.
8. **Children under 6 years of age**
   PULMICORT is not presently recommended for children younger than 6 years of age due to limited clinical data in this age group.
9. Corticosteroids may mask some signs of infections and new infections may appear. A decreased resistance to localized infection has been observed during corticosteroid therapy. During long-term therapy, pituitary-adrenal function, hematological status and height (in children) should be periodically assessed.
10. Patients should be advised to inform subsequent physicians of the prior use of corticosteroids.
11. There may be enhanced effect of budesonide in patients with an advanced liver cirrhosis, and in those with hypothyroidism.
12. Acetylsalicylic acid should be used cautiously in conjunction with corticosteroids in hypoprothrombinemia.
13. Fluorocarbon propellants may be hazardous if they are deliberately abused. Inhalation of high concentrations of aerosol sprays has brought about cardiovascular toxic effects and even death, especially under conditions of hypoxia. Aerosols are safe when used properly and with adequate ventilation, but excessive use should be avoided.
14. To ensure the proper dosage and administration of the drug, the patient should be instructed by a physician or other health professional in the use of the Inhaler or Spacer®.
15. Adequate oral hygiene is of primary importance in minimizing overgrowth of micro-organisms such as **candida albicans** (see DOSAGE AND ADMINISTRATION).

ADVERSE REACTIONS
No major side effects attributable to the use of PULMICORT have been reported. During clinical trials, the frequency of subjectively reported side effects was low.

The most common side effects were cough, throat irritation, and hoarseness (2-4%). Bad taste, headache, nausea and dryness of the throat were reported less frequently. Other side effects reported on occasion during budesonide treatment were tiredness, thirst, and diarrhea. **Systemic effects and oropharyngeal complications caused by budesonide were found to be dose-dependent.** Candidiasis has been reported by some patients and may occur at therapeutic doses. Rarely, PULMICORT, may provoke bronchoconstriction in hyperreactive patients. The bronchospasms can be treated with a β_2-agonist for inhalation. In these patients the bronchospasm can be prevented by inhaling a β_2-agonist 5-10 minutes before inhalation of PULMICORT.

In patients in whom systemic steroids are reduced or stopped, withdrawal symptoms due to decreased systemic activity occur frequently (See DOSAGE AND ADMINISTRATION: CLINICAL MANAGEMENT).

SYMPTOMS AND TREATMENT OF OVERDOSAGE
Occasional overdosing will not give any obvious symptoms in most cases but it will decrease the plasma cortisol level and increase the number and percentage of circulating neutrophils. The number and percentage of eosinophils will decrease concurrently. Stopping the treatment or decreasing the dose will abolish the induced effects.

Habitual overdosing may cause hypercorticism and hypothalamic-pituitary-adrenal suppression. Decreasing the dose or stopping the therapy will abolish these effects, although the restitution of the HPA-axis may be a slow process and during periods with pronounced physical stress (severe infections, trauma, surgical operations, etc.) it may be advisable to supplement with systemic steroids.

DOSAGE AND ADMINISTRATION
Adults and Children over 12 Years of Age
The initial dose of PULMICORT is 400-1600 μg daily divided into 2-4 administrations. The maintenance dose is usually 200-400 μg twice daily but higher doses may be necessary for longer or shorter periods of time in some patients. The dose of PULMICORT should be individualized to the patient's need and should be the lowest possible dose that fills the therapeutic objective. Treatment with PULMICORT should not be stopped abruptly, but tapered off gradually.

Children 6 - 12 years
When starting therapy with budesonide in children, during periods of severe asthma and while reducing or discontinuing oral corticosteroids, the dosage should be 200-400 μg daily, given in divided doses twice daily at 100 to 200 micrograms per inhalation.

The maintenance dose is individual and should be the lowest dose which keeps the patient symptom-free. Administration twice daily is usually adequate in stable asthmatics.

Children under 6 years of age
Not recommended in children in this age group.

Patients receiving bronchodilators by inhalation should be advised to use the bronchodilator before PULMICORT in order to enhance its penetration into the bronchial tree. Several minutes should elapse between the use of the two inhalers to reduce the potential toxicity from the inhaled fluorocarbon propellants and to allow for some bronchodilation to occur.

Since the effect of PULMICORT depends on its regular use and on the proper technique of inhalation, patients must be instructed to use their PULMICORT Inhaler or Spacer® daily, as prescribed by their physician and not as with other aerosols, as they feel necessary. They must also be instructed in the correct method which is described in the PATIENT INSTRUCTIONS.

Spacer®
Use of the Spacer® during aerosol inhalation has been shown to result in decreased oral and increased airway deposition of the active substance and to decrease the need for co-ordination between release of the dose and inhalation. Thus the Spacer® can either be used to increase the effectiveness of a certain dose or to decrease the dose without loss in effect.

CLINICAL MANAGEMENT
1. **Patients – non-steroid dependent**
   Treatment with the recommended doses of PULMICORT usually gives a therapeutic effect within 10 days. However, certain patients might have an excessive collection of mucous secretion in the bronchi which reduces the penetration of the active substance in PULMICORT into the bronchial mucosa. In these cases, it is desirable to initially give a short (about 2 weeks) oral corticosteroid regimen in addition to PULMICORT aerosol. The oral treatment is started on a rather large dose which is then gradually reduced. Thereafter treatment with PULMICORT only is sufficient. Exacerbations of the asthma caused by bacterial infections are controlled by adequate antibiotic regimens and also by increasing the PULMICORT dosage.
2. **Patients – steroid dependent**
   Transferral of patients dependent upon oral steroids to treatment with PULMICORT demands special care mainly because of the slow restitution of the disturbed hypothalamic-pituitary-adrenal function caused by extended treatment with oral corticosteroids. When PULMICORT treatment is initiated, the patient should be in a relatively stable phase. PULMICORT is then given in combination with the previously used oral steroid dose for about 10 days. After this period of time, reduction of the oral corticoid dose may be started gradually. The oral dose is thus reduced to the lowest level which, in combination with PULMICORT, gives a stable respiratory capacity.

   In adults, the usual rate of withdrawal of the systemic corticosteroid is the equivalent of 2.5 mg of prednisone every four days if the patient is under dose observation. **If continuous supervision is not feasible, the withdrawal of the systemic steroid should be slower**, approximately 2.5 mg of prednisone (or equivalent) every ten days. A slow rate of withdrawal cannot be overemphasized. If withdrawal symptoms appear, the previous dosage of the systemic drug should be resumed for a week before further decrease is attempted. During withdrawal, some patients may experience symptoms of systemically active steroid withdrawal, e.g., joint and/or muscular pain, lassitude, and depression, despite maintenance or even improvement of respiratory function. Such patients should be encouraged to continue with the aerosol but should be watched carefully for objective signs of adrenal insufficiency such as hypotension and weight loss. If evidence of adrenal insufficiency occurs, the systemic steroid dosage should be boosted temporarily and thereafter further withdrawal should continue more slowly.

   In many cases it may be possible to completely replace the oral steroid with PULMICORT treatment. In other patients, a low oral steroid maintenance dosage may be required. The length of time needed for the body to regain its natural production of corticosteroid in sufficient quantity is often extended. **Thus, during severe asthma attacks or physically stressing situations such as severe infections, trauma, and surgical operations, it is necessary to resume systemic steroids (in large dosages) in order to avoid adrenocorticoid insufficiency.** Acute exacerbations, especially in connection with increased viscosity and mucous plugging, may require complementary treatment with a short course of oral corticosteroids which are gradually tapered as symptoms subside.

   During transfer from oral therapy to PULMICORT, a lower general steroid action is experienced. The patients might regain earlier symptoms (rhinitis, eczema) or suffer from tiredness, headache, pain in muscles and joints and, occasionally, nausea and vomiting. In these cases, further medical support may be required.

NOTE: Patients should be instructed to rinse their mouths with water after each inhalation. This will help prevent the occurrence of candidiasis. Cleansing dentures has the same effect.

AVAILABILITY
PULMICORT Inhaler is provided in a metered dose canister containing 200 doses of 50 μg/dose (1 mg/mL) or 100 doses of 200 μg/dose (4 mg/mL). A standard mouthpiece is provided with each canister. The mouthpiece should be discarded when the canister is empty.

PULMICORT Spacer® is also provided in a metered dose canister containing 200 doses of 50 μg/dose (1 mg/mL) or 100 doses of 200 μg/dose (4 mg/mL). The Spacer® extension mouthpiece is provided with this package and should also be discarded when the canister is empty. The Spacer® is designed to accommodate only Astra Pharma Inc., aerosol canisters.

Storage Recommendation:

CAUTION:
Container may explode if heated. Contents under pressure. Do not place in hot water or near radiators, stoves or other sources of heat. Do not puncture or incinerate container or store at temperatures over 25°C. Do not use in presence of open flame or spark. Keep out of the reach of children.

Product Monograph available on request.
Astra Pharma Inc., 1004 Middlegate Rd., Mississauga, Ontario L4Y 1M4
DATE OF PREPARATION: September 6, 1988

MEMBER PMAC PAAB CCPP

INDERAL*-LA

(propranolol hydrochloride)
Controlled-Release Capsules†

CONTROL, CONVENIENCE AND COMPLIANCE

Anti-anginal and antihypertensive agent

Actions

INDERAL-LA is a special formulation of propranolol hydrochloride consisting of capsules filled with spheroids of the active drug having a sustained-release coating.

INDERAL (propranolol hydrochloride) is a beta-adrenergic receptor blocking drug. It has no other autonomic nervous system activity. INDERAL is a competitive antagonist which specifically competes with beta-adrenergic receptor stimulating agents for available beta-receptor sites. When access to beta-adrenergic receptor sites is blocked by INDERAL, the chronotropic, inotropic, and vasodilator responses to beta-adrenergic stimulation are decreased proportionately. Beta-adrenergic blockade is useful in some clinical conditions in which sympathetic activity is excessive or inappropriate, and therefore detrimental to the patient. Sympathetic stimulation is, however, vital in some situations (eg. in patients with AV block or with a severely damaged heart), and should be preserved. The basic objective of beta-adrenergic blockade is to decrease adverse sympathetic stimulation but not to the degree that impairs necessary sympathetic support. Beta-blockade results in bronchial constriction by interfering with endogenously or exogenously induced bronchodilation. (See Contraindications and Warnings).

The mechanism of the antihypertensive effects of INDERAL has not been established. Among the factors that may be involved are (1) decreased cardiac output, (2) inhibition of renin release by the kidneys, and (3) diminution of tonic sympathetic nerve outflow from vasomotor centers in the brain. It has been suggested, but not established, that INDERAL may achieve a better antihypertensive effect in patients with normal or elevated plasma renin activity than those with low PRA.

INDERAL may reduce the oxygen requirement of the heart at any level of effort by blocking catecholamine-induced increases in the heart rate, systolic blood pressure, and the velocity and extent of myocardial contraction. On the other hand, INDERAL may increase oxygen requirements by increasing left ventricular fiber length, end diastolic pressure, and systolic ejection period. When the net effect is beneficial in anginal patients, it manifests itself during exercise or stress by delaying the onset of pain and reducing the incidence and severity of anginal attacks.

INDERAL is almost completely absorbed from the gastrointestinal tract and undergoes extensive presystemic (or "first pass") elimination due to its high hepatic clearance. Inter-individual variations in circulating drug concentrations due to this "first pass effect" have been documented and differ according to a number of factors including genetic make-up.

The INDERAL-LA 80 and 160 mg peak blood levels are comparable to those obtained with a single 20 or 40 mg propranolol tablet, respectively. The peak blood level with INDERAL-LA 120 is less than that obtained with a single 40 mg tablet. INDERAL-LA has an apparent half-life of approximately 12 hours. At "steady state", achieved after five to six days administration, blood levels of propranolol at the beginning and end of a 24-hour period are similar. The INDERAL-LA blood level profile has been shown to be reproducible under different conditions of diet and rest.

Indications

INDERAL-LA is indicated for maintenance therapy in the treatment of hypertension and the prophylaxis of angina pectoris. In hypertension, propranolol hydrochloride is usually used in combination with other drugs, particularly a thiazide diuretic. In certain patients, it can, however, be used alone or as an initial agent in those patients in whom, in the judgement of the physician, treatment should be started with a beta-blocker rather than a diuretic. The combination of INDERAL-LA with thiazide-like diuretics and/or peripheral vasodilators has been shown to be compatible and generally more effective than INDERAL-LA alone. Experience with most commonly used antihypertensive agents has not suggested evidence of incompatibility. Treatment must always be initiated and individual titration of dosage carried out using the regular tablets. The long-acting formulation may be used for maintenance provided the dosage requirement is suitable. INDERAL-LA is not indicated for the emergency treatment of hypertensive crises.

Contraindications

INDERAL-LA is contraindicated in:

1) bronchospasm including bronchial asthma
2) allergic rhinitis during the pollen season
3) sinus bradycardia and greater than first degree block
4) cardiogenic shock
5) right ventricular failure secondary to pulmonary hypertension
6) congestive heart failure (see Warnings)

Warnings

Cardiac Failure: Sympathetic stimulation is a vital component supporting circulatory function in congestive heart failure; therefore, inhibition by means of beta-adrenergic blockade is a potential hazard as it may further depress myocardial contractility and precipitate cardiac failure. INDERAL-LA acts selectively without abolishing the inotropic action of digitalis on the heart muscle (ie, that of supporting the strength of myocardial contractions). In patients already receiving digitalis, the positive inotropic action of digitalis may be reduced by INDERAL'S negative inotropic effect. The effects of INDERAL and digitalis are additive in depressing AV conduction.

In Patients Without a History of Cardiac Failure: continued depression of the myocardium over a period of time can, in some patients, lead to cardiac failure. In rare instances, this has been observed during INDERAL therapy. Therefore, at the first sign or symptom of impending cardiac failure, patients should be fully digitalized and/or given a diuretic, and the response observed closely: a) if cardiac failure continues, despite adequate digitalization and diuretic therapy, INDERAL-LA should be withdrawn immediately; b) if tachyarrhythmia is being controlled, patients should be maintained on combined therapy and closely followed until threat of cardiac failure is over. Abrupt Cessation of Inderal Therapy in Angina Pectoris: Severe exacerbation of angina and the occurrence of myocardial infarction have been reported in some patients with angina pectoris following abrupt discontinuation of INDERAL therapy. Therefore, when discontinuation of INDERAL-LA is planned in patients with angina pectoris, the dosage should be gradually reduced over a period of about two weeks and the patient should be carefully observed. This can be achieved by substituting INDERAL-LA with the equivalent dosage of conventional INDERAL 40 mg tablets spread throughout the day and then gradually reducing the dose. In situations of greater urgency, INDERAL-LA dosage should be similarly reduced stepwise, in four days, under close observation. If angina markedly worsens, or acute coronary insufficiency develops, it is recommended that treatment with conventional INDERAL tablets be reinstituted promptly, at least temporarily. In addition, patients with angina pectoris should be warned against abrupt discontinuation of INDERAL-LA.

Oculomucocutaneous Syndrome: Various skin rashes and conjunctival xerosis have been reported in patients treated with beta-blockers including INDERAL. A severe oculomucocutaneous syndrome, whose signs include conjunctivitis sicca and psoriasiform rashes, otitis, and sclerosing serositis has occurred with the long-term use of one beta-adrenergic blocking agent. This syndrome has not been observed with INDERAL, however, physicians should be alert to the possibility of such reactions and discontinue treatment if they occur.

In Patients with Thyrotoxicosis, possible deleterious effects from long-term use of INDERAL have not yet been adequately appraised. Special consideration should be given to INDERAL'S potential for aggravating congestive heart failure. INDERAL-LA may mask the clinical signs of developing or continuing hyperthyroidism or its complications, and give a false impression of improvement. Therefore, abrupt withdrawal of INDERAL-LA may be followed by an exacerbation of symptoms of hyperthyroidism, including thyroid storm. This may be another instance where INDERAL-LA should be withdrawn slowly by reducing dosage. INDERAL does not distort thyroid function tests. In Patients with Wolff-Parkinson-White Syndrome, INDERAL-LA should be used with caution since several cases have been reported in which, after INDERAL treatment, the tachycardia was replaced by a severe bradycardia requiring a demand pacemaker. In one patient, this occurred after an initial dose of 5 mg of INDERAL.

In Patients Undergoing Elective or Emergency Surgery: The management of patients with angina being treated with beta-blockers and undergoing elective or emergency surgery, is controversial because beta-adrenergic receptor blockade impairs the ability of the heart to respond to beta-adrenergically mediated reflex stimuli, but abrupt discontinuation of therapy with INDERAL may be followed by severe complications (see Warnings). Some patients receiving beta-adrenergic blocking agents have been subject to protracted severe hypotension during anesthesia. Difficulty in restarting and maintaining the heartbeat has also been reported. For these reasons, in patients with angina undergoing elective surgery, INDERAL-LA should be withdrawn gradually following the recommendation given under Abrupt Cessation of Therapy (see Warnings). According to available evidence, all clinical and physiologic effects of beta-blockade are no longer present 48 hours after cessation of medication.

In emergency surgery, since INDERAL-LA is a competitive inhibitor of beta-adrenergic receptor agonists, its effects may be reversed, if necessary, by sufficient doses of such agonists as isoproterenol or levarterenol. Anesthesia with agents which maintain cardiac contractility by virtue of their effect on catecholamine release (eg, ether) should be avoided in patients on INDERAL-LA therapy.

In Patients Prone to Nonallergic Bronchospasm (eg, Chronic Bronchitis, Emphysema, Bronchiectasis), INDERAL-LA should be administered with caution since it may block bronchodilation produced by endogenous and exogenous catecholamine stimulation of beta-adrenergic receptors.

In Patients with Diabetes and in Those Subject to Hypoglycemia, INDERAL-LA, because of its beta-adrenergic blocking activity, may block premonitory signs and symptoms (pulse rate and pressure changes) of acute hypoglycemia. This is especially important to keep in mind in patients with labile diabetes. Hypoglycemia attacks may be accompanied by a precipitous elevation of blood pressure.

Use in Pregnancy: The safe use of INDERAL-LA in pregnancy has not been established. Use of any drug in pregnancy or in women of child bearing potential requires that the possible risk to mother and/or fetus be weighed against the expected therapeutic benefit. Perinatal complications, such as small placenta and intrauterine growth retardation, have been reported in a few cases where the mother took INDERAL during pregnancy. Some infants born to mothers treated with INDERAL were reported to have hypoglycemia and/or bradycardia.

Use in Children: While experience with INDERAL in children under 12 is limited, the indications for which INDERAL-LA is recommended occur infrequently in childhood. Although reports fail to indicate that children respond in a manner different from the adult, physicians are advised to undertake treatment with caution.

Precautions

Some slowing of heart due to unopposed vagal activity is usual in patients receiving INDERAL-LA, however, occasionally severe bradycardia occurs and may lead to vertigo, syncopal attacks or orthostatic hypotension. Patients, especially those with limited cardiac reserve, should be monitored for signs of excessive bradycardia. Should the patient become symptomatic the dose of INDERAL should be decreased or, if necessary, the drug should be discontinued. If it is essential to correct the bradycardia, intravenous atropine or isoproterenol should be considered.

The combination of INDERAL with a thiazide-like diuretic and/or peripheral vasodilator produces a greater fall in blood pressure than either drug alone. This occurs regardless of which drug is administered first. The same degree of blood pressure control can be achieved by lower than usual dosages of each drug. Therefore, when using such combined therapy, careful monitoring of the dosages is required until the patient is stabilized.

Patients receiving catecholamine depleting drugs such as reserpine or guanethidine should be closely observed if INDERAL-LA is administered concomitantly. The added catecholamine blocking action of this drug may produce an excessive reduction of the resting sympathetic nervous activity.

In patients on long-term treatment with INDERAL-LA, laboratory determinations should be made at regular intervals. The drug should be used with caution in patients with impaired renal and hepatic functions.

Adverse Reactions

The most serious adverse reactions encountered with INDERAL are congestive heart failure and bronchospasm (see Contraindications, Warnings and Precautions). Gastrointestinal disturbances (anorexia, nausea, vomiting, diarrhea, abdominal pain) are the most common adverse reactions reported. Other less frequently reported adverse reactions are: (in descending order) cold extremities and exacerbation of Raynaud's phenomenon; congestive heart failure; sleep disturbances including vivid dreams; dizziness, fatigue and bronchospasm.

Reported adverse reactions, according to organ systems are recorded below:

Cardiovascular: Congestive heart failure (see Warnings); secondary effects of decreased cardiac output which could include: syncope, vertigo, lightheadedness, decreased renal perfusion and rarely, postural hypotension; intensification of A.V. block and hypotension; severe bradycardia; claudications and cold extremities, Raynaud's phenomenon; dyspnea; palpitations; precordial pain.

Central Nervous System: Dizziness; lethargy; weakness; drowsiness; headache; insomnia; fatigue; anorexia; anxiety; mental depression; poor concentration; reversible amnesia and catatonia; vivid dreams with or without insomnia; hallucinations; paresthesia; incoordination.

Gastrointestinal: Nausea; vomiting; epigastric distress; anorexia; bloating; mild diarrhea; constipation.

Respiratory: Bronchospasm; laryngospasm and respiratory distress. (See Contraindications and Warnings)

Dermatologic: A few cases of erythematous rashes and increase of facial acneiform lesions have been reported; urticaria; exfoliative psoriasiform eruption.

Others: Reduction or loss of libido; reversible alopecia and rarely; diminution and loss of hearing; tinnitus; visual disturbances; diminished vision; conjunctivitis; thrombocytopenic purpura; pharyngitis and agranulocytosis, fever combined with aching and sore throat; urinary retention associated with repeated bouts of paroxysmal tachycardia; flushing of the face.

Clinical Laboratory Test Findings: Elevated blood urea levels in patients with severe heart disease, elevated serum transaminase, alkaline phosphatase, and lactate dehydrogenase have been reported.

Symptoms and Treatment of Overdose:

See product monograph.

Dosage and Administration

INDERAL-LA controlled-release capsules are intended for maintenance therapy in those patients requiring doses within the range of 80 to 320 mg per day. Initiation of treatment and individual titration of dosage should be carried out using the conventional tablets. INDERAL-LA may be preferred for maintenance because of the convenience of once daily dosage. Patients with angina or hypertension on a maintenance regimen within the range of 80 and 320 mg per day regular tablets taken in divided doses may be changed to the appropriate number of INDERAL-LA capsules taken once daily in the morning or evening.

When propranolol is to be combined with another antihypertensive agent which is already being administered, therapy should be initiated with conventional INDERAL tablets following usual dosage recommendations. Once adequate blood pressure control has been obtained, INDERAL-LA capsules may be used for maintenance provided the dosage requirement is suitable.

In the treatment of hypertension, if required, further reduction of blood pressure may be attained by the addition of a diuretic and/or peripheral vasodilator. Addition of another antihypertensive agent should, however, be gradual, beginning with 50% of the usual recommended starting dose, to avoid excessive reduction of blood pressure.

Availability

No. 3417 Each capsule contains 80 mg propranolol hydrochloride, in bottles of 100 and 500.

No. 3473 Each capsule contains 120 mg propranolol hydrochloride, in bottles of 100.

No. 3472 Each capsule contains 160 mg propranolol hydrochloride, in bottles of 100 and 500.

Product Monograph available on request.

†The appearance of these capsules is a registered trademark of Ayerst Laboratories

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teurs ont pu influencé l'observance du spermogramme. Si les facteurs précités sont peu modifiables, une information insuffisante ou de mauvaise qualité entraînant l'inobservance pourrait être rectifiée. En fait, cette cause n'a jamais été citée de façon spontanée à la question ouverte. Une combinaison d'informations verbales et écrites insistant sur l'importance du spermogramme est donnée aux patients à la première visite ainsi que le jour de la chirurgie. L'inobservance notée ne provient probablement pas d'une lacune à ce niveau. Rappelons que le type d'informations ne semble pas jouer un rôle important dans l'observance du spermogramme.[9]

En conclusion, tout comme la prescription médicamenteuse, la prescription du spermogramme post-vasectomie n'est pas toujours respectée. De plus, il est probable que malgré tous les efforts du médecin pour contrer ce phénomène, peu de résultats seront obtenus. Il sera pourtant intéressant d'évaluer l'efficacité de la mise en place des techniques suggérées par les clients pour améliorer le taux d'observance. Parmi ces suggestions, nous retenons principalement la prescription d'une date précise, fixée lors de la vasectomie, une relance téléphonique ou par lettre, six mois après la vasectomie et l'assouplissement des heures d'ouverture du laboratoire. ■

Remerciements

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MAXENAL*
Pseudoephedrine HCl 240 mg.
CONTROLLED RELEASE CAPSULES

INDICATIONS:
Relief of nasal congestion associated with allergic rhinitis, acute coryza, vasomotor rhinitis, acute and subacute sinusitis, acute otitis media, asthma, postnasal drip, acute eustachian salpingitis. It may also be used as an adjunct to antibiotics, antihistamines, analgesics and antitussives in the treatment of the above conditions.

CONTRAINDICATIONS:
Patients receiving or having received MAO inhibitors in the preceding 3 weeks; known hypersensitivity to pressor amines.

PRECAUTIONS:
As pseudoephedrine is a sympathomimetic amine, it should be used with caution in hypertensive and diabetic patients, patients with latent or clinically recognized angle-closure glaucoma, coronary artery disease, congestive heart failure, prostatic hypertrophy, hyperthyroidism, urinary retention.

ADVERSE EFFECTS:
As with other sympathomimetic amines, headache, dizziness, insomnia, tremor, confusion, CNS stimulation, muscular weakness, dry mouth, nausea and vomiting.

OVERDOSE:
Symptoms: Increase in pulse and respiratory rate. CNS stimulation, disorientation, headache, dry mouth, nausea and vomiting.

OVERDOSE TREATMENT:
Gastric lavage, repeated if necessary. Acidify the urine and institute general supportive measures. If CNS excitement is prominent, a short-acting barbiturate may be used.

DOSAGE:
Adults and children 12 years and older: One capsule every 24 hours. Not recommended for children under 12 years of age.

SUPPLIED:
Each clear capsule filled with white pellets contains 240 mg controlled-release pseudoephedrine HCl. In recommendation packages of 6 push-through blisters or bottles of 100.

JANSSEN PHARMACEUTICA
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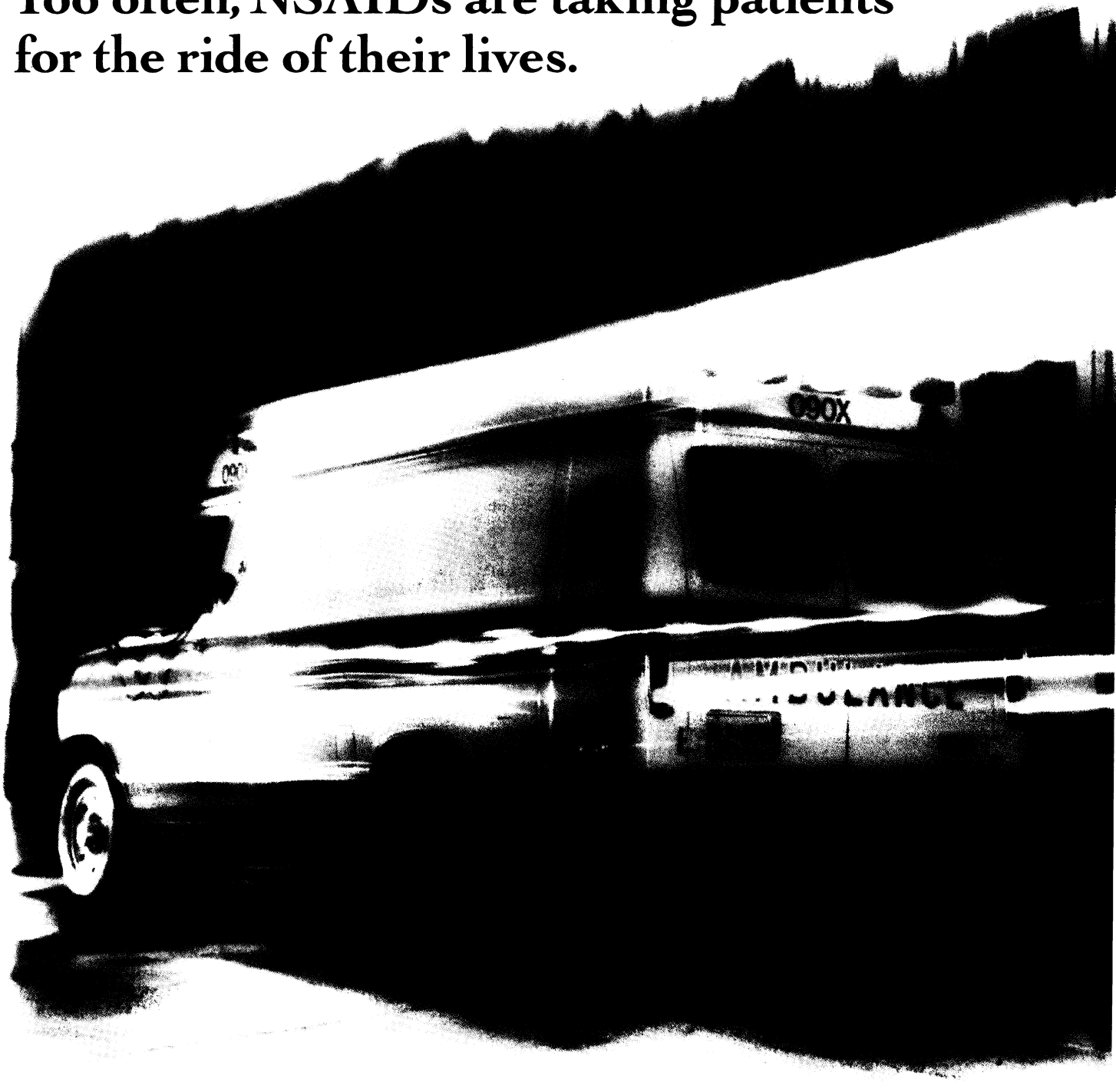
Mississauga, Ont. *Trademark ©JANSSEN, 1989

Too often, NSAIDs are taking patients for the ride of their lives.



The chances are, you are already becoming increasingly concerned for the safety of patients taking NSAID's chronically. Recent Canadian data has shown that 1 in 100 Canadian RA patients on chronic NSAID therapy may die because of NSAID-induced upper G.I. complications.[1]

It has been shown that 1 in 5 chronic NSAID users, at any given time, have an NSAID-induced gastric ulcer;[2,3] 2 out of 3 of which may remain silent until it is too late for them to be treated easily.[4]

NSAID BURN™* is now a critical question of patient safety for which many physicians are finding Cytotec to be the only effective answer.

CYTOTEC.
Improved gastric safety for patients who require NSAID relief.

Only Cytotec can protect patients by reducing the incidence of NSAID BURN™ by over 90%[5] while still allowing them to continue with NSAID therapy. After all, relieving the pain of arthritis is important, but no one should have to risk their life for it.

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(misoprostol) 100mcg 200mcg
To cool the risk of NSAID BURN.™

SEARLE
Oakville, Ontario
*"NSAID BURN™" refers to NSAID-induced gastric ulceration.

For prescribing information see page 1948

Alupent® Syrup

orciprenaline sulphate

EFFECTIVE BRONCHODILATOR THERAPY THAT'S EASY TO SWALLOW

PRESCRIBING INFORMATION

Indications
Alupent has been found useful in the following conditions: Bronchial asthma, Chronic bronchitis, pulmonary emphysema. Alupent is also useful in sarcoidosis, silicosis, carcinoma of the lung and tuberculosis when bronchospasm contributes to the disability. When used regularly, Alupent offers effective management of chronic bronchospasm with reduction in frequency and severity of acute attacks.

Dosage
As with all drugs, the ideal dosage of Alupent varies from patient to patient. The following recommended dosages represent general guidelines which will be found suitable for the majority of patients.
Tablets 20 mg
Ages 4-12, 10 mg (1/2 tablet) t.i.d.
above 12, 20 mg (1 tablet) t.i.d. — q.i.d.
Syrup 10 mg/5 ml
Ages 4-12, 10 mg (one teaspoonful) t.i.d.
above 12, 20 mg (two teaspoonsful) t.i.d. — q.i.d.
Metered Aerosol
One to two inhalations will usually provide control of an acute attack of bronchospasm for periods of 5 hours or longer. As a general rule, patients should not exceed a total of 12 inhalations per day.
Solution 5%
Hand nebulizer: 5 to 15 inhalations of 5% solution by hand nebulizer DeVilbiss No. 40 or 42 administered up to three times daily.
Intermittent positive pressure breathing: 1/2-1 ml of 5% solution diluted if desired and administered over a period of about 20 minutes.

Side Effects
In the recommended dosage, adverse reactions to Alupent are infrequent. Mild tachycardia, nausea, vomiting, palpitations, minimal hypertension, nervousness, bad taste and tremor have been reported.

Precautions
In acute tests, Alupent has shown minimal effect on blood pressure and pulse. The drug should be used with care, however, in asthmatic or emphysematous patients who also have systemic hypertension, coronary artery disease, acute and recurring congestive heart failure, diabetes mellitus, glaucoma or hyperthyroidism. Extreme care must also be exercised in the concomitant use of Alupent with epinephrine or MAO inhibitors.

Warnings
Alupent should not be administered to pregnant women or to women of childbearing potential unless, in the opinion of the physician, the expected benefits outweigh the possible risk to the foetus. Occasional patients have been reported to have developed severe paradoxical airways resistance with repeated excessive use of sympathomimetic inhalation preparations. The cause of this refractory state is unknown. It is advisable that in such instances the use of the preparation be discontinued immediately and alternative therapy instituted, since in the reported cases the patients did not respond to other forms of therapy until the drug was withdrawn. Fatalities have been reported following excessive use of isoproterenol inhalation preparations and the exact cause is unknown. Cardiac arrest was noted in several instances.
Patients should be advised to seek medical aid in the event that they do not respond to their usual dose of a sympathomimetic amine aerosol. The failure to respond may be due to retention of viscid bronchial secretions, associated with an allergic or infective exacerbation of the patient's condition. Increased airways resistance on the basis of bronchospasm alone is reversed promptly by bronchodilators, and if this does not occur, a more serious condition should be suspected. Admission to hospital for intensive support of the cardiovascular and respiratory systems may be necessary.

Contraindications
Known sensitivity to the drug or other sympathomimetic amines. The use of Alupent and other beta stimulators is generally considered to be contra-indicated in patients with cardiac arrhythmias associated with tachycardia. Beta blocking agents, e.g. propranolol, effectively antagonize the action of Alupent. Their concomitant use, except in the treatment of accidental over-dosage, is therefore contraindicated.

Availability
Alupent 20 mg tablets are available as round, white, single scored compressed tablets, printed on one side with the Boehringer Ingelheim symbol. Supplied in bottles of 100 and 500.
Alupent Syrup is clear, sugar-free and woodruff flavoured. 5 ml contains 10 mg of active ingredient. Supplied in bottles of 250 ml.
Alupent Metered Aerosol is supplied as a 15 ml metal vial (with free disposable mouthpiece) containing 300 individual doses. Each depression of the valve releases 0.75 mg of active ingredient as a micronized powder.
Alupent Solution 5% is supplied in bottles containing 10 ml.
For further information consult the Alupent Product Monograph or your Boehringer Ingelheim representative.

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More Convenient

New Naprosyn SR provides once-a-day dosing convenience which is important for long term maintenance therapy.

Naprosyn SR may help to improve compliance and minimize confusion, particularly among patients who are required to take other medications daily.

Effective

Naprosyn SR is as effective as Naprosyn on a B.I.D. dosage[1]. In fact, Naprosyn SR maintains plasma levels within a narrow range over a 24 hour period with significantly less fluctuation than with B.I.D. dosing[2].

Naprosyn SR is proven to significantly decrease the severity of pain at rest and during passive motion, and to reduce interference with patients' normal activities[1].

Proven Tolerability

Naprosyn SR is as well tolerated by patients over 60 years of age as by patients under 60 years[3].

In addition, Naprosyn SR has the same low incidence of GI, CNS, dermatological and other adverse effects as original Naprosyn[1].

once a da

Canada's Leading NSAID Therapy[4] now in a once-a-day dosage.

For more than 10 years, Naproxen has been Canada's most frequently prescribed NSAID.[4]

Naprosyn
naproxen
Prescribing Information:

Therapeutic Classification: Anti-inflammatory, analgesic and antipyretic agent. **Indications:** The treatment of osteoarthritis, rheumatoid arthritis, ankylosing spondylitis and juvenile rheumatoid arthritis. **Contraindications:** Naprosyn should not be given to patients with active peptic ulcer or active inflammatory disease of the gastrointestinal tract. It is also contraindicated for those who have shown a sensitivity to it and for patients in whom ASA or other NSAIDs induce the syndrome of asthma, rhinitis or uticaria. Sometimes severe and occasionally fatal anaphylactoid reactions have occurred in such individuals. Suppositories should not be given to patients under 12 years of age or those with inflammatory lesions of the rectum or anus.
Warnings: Peptic ulceration, perforation and gastrointestinal bleeding, sometimes severe and occasionally fatal have been reported during therapy with NSAIDs, including Naprosyn. Naprosyn should be given under close supervision to patients prone to gastrointestinal tract irritation particularly those with a history of peptic ulcer, diverticulosis or other inflammatory disease of the gastrointestinal tract. Patients taking any NSAID should be instructed to contact a physician immediately if they experience symptoms or signs suggestive of peptic ulceration or gastrointestinal bleeding. These reactions can occur without warning at any time during the treatment. Elderly, frail and debilitated patients appear to be at higher risk from a variety of adverse reactions from NSAIDs. For such patients, consideration should be given to a starting dose lower than usual. The safety of Naprosyn in pregnancy and lactation has not been established and its use is therefore not recommended.
Precautions: Naprosyn (naproxen) should not be used concomitantly with the related drug Anaprox (naproxen sodium) since they both circulate in plasma as the naproxen anion. GI system: If peptic ulceration is suspected or confirmed, or if gastrointestinal bleeding or perforation occurs Naprosyn should be discontinued, and appropriate treatment instituted. Renal effects: Patients with impaired renal function, extracellular volume depletion, sodium restrictions, heart failure, liver dysfunction, those taking diuretics, and the elderly are at greatest risk of developing overt renal decompensation. Assessment of renal function in these patients before and during therapy is recommended. Naprosyn and its metabolites are eliminated primarily by the kidneys, and therefore, a reduction in daily dosage should be anticipated to avoid the possibility of drug accumulation in patients with significantly impaired renal function.
Peripheral edema has been observed, consequently, patients with compromised cardiac function should be kept under observation when taking Naprosyn.
Naprosyn Suspension contains sodium chloride (20 mg/mL). This should be considered in patients whose overall intake of sodium must be restricted.
As with other drugs used with the elderly or those with impaired liver function it is prudent to use the lowest effective dose. Severe hepatic reactions including jaundice, and cases of fatal hepatitis have been reported with NSAIDs. The prescriber should be alert to the fact that the anti-inflammatory, analgesic and antipyretic effects of Naprosyn may mask the usual signs of infection. Periodic liver function tests and ophthalmic studies are recommended for patients on chronic therapy. Caution should be exercised by patients whose activities require alertness if they experience drowsiness, dizziness, vertigo or depression during naproxen therapy. Naprosyn may displace other albumin-bound drugs from their binding sites and may lead to drug interactions or interfere with certain laboratory tests. See Product Monograph for specific examples.

ADVERSE REACTIONS – (1) Denotes incidence of reported reaction between 3% and 9%. (2) Denotes incidence of reported reactions between 1% and 3%. See Product Monograph for reactions occurring in less than 1% of patients. **Gastrointestinal:** Heartburn (1), constipation (1), abdominal pain (1), nausea (1), diarrhea (2), dyspepsia (2), stomatitis (2), diverticulitis (2). Rectal burning (1) has been reported occasionally with the use of naproxen suppositories. **Central Nervous System:** Headache (1), dizziness (1), drowsiness (1), lightheadedness (2), vertigo (2), depression (2) and fatigue (2). **Skin:** Pruritus (1), ecchymoses (1), skin eruptions (1), sweating (2) and purpura (2). **Cardiovascular:** Dyspnea (1), peripheral edema (1) and palpitations (2). **Special senses:** Tinnitus (1) and hearing disturbances (2). **Others:** Thirst (2).

DOSAGE AND ADMINISTRATION – Adult: Oral: The usual total daily dosage for osteoarthritis, rheumatoid arthritis and ankylosing spondylitis is 500 mg (20 mL, 4 teaspoons) a day in divided doses. It may be increased gradually to 750 or 1000 mg or decreased depending on the patient's response. Patients with rheumatoid arthritis or osteoarthritis maintained on a dose of 750 mg/day in divided doses can be switched to a once daily dose of Naprosyn SR 750 mg. The single daily dose of Naprosyn SR should not be exceeded and can be administered in the morning or evening. Naprosyn SR tablets should be swallowed whole. **Rectal:** Naprosyn Suppositories (500 mg) can replace one of the oral doses in patients receiving 1000 mg of Naprosyn daily. **Juvenile Rheumatoid Arthritis:** The recommended daily dose is approximately 10 mg/kg in two divided doses.

AVAILABILITY – Naprosyn is available as: 125 mg, 250 mg, 375 mg, and 500 mg Tablets, as 750 mg Sustained-Release Tablets and 500 mg Suppositories. Suspension: Each 5 mL contains 125 mg of naproxen. Shake bottle gently before use. Pharmacists are to provide the Naprosyn Patient Information leaflet when dispensing this drug.
Product Monograph available to health professionals upon request.

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3. Cleland, L.G., Clinical Trials Journal. (1988) 25 (2): 103-108.

4. Naproxen Rx data on file 1978-1989.

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*generally well-tolerated for maintenance arthritis therapy
†compared to indomethacin[1], piroxicam[1], naproxen[2], ASA[1,3] and ketoprofen capsules[3]

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Straight to the heart of the menopause

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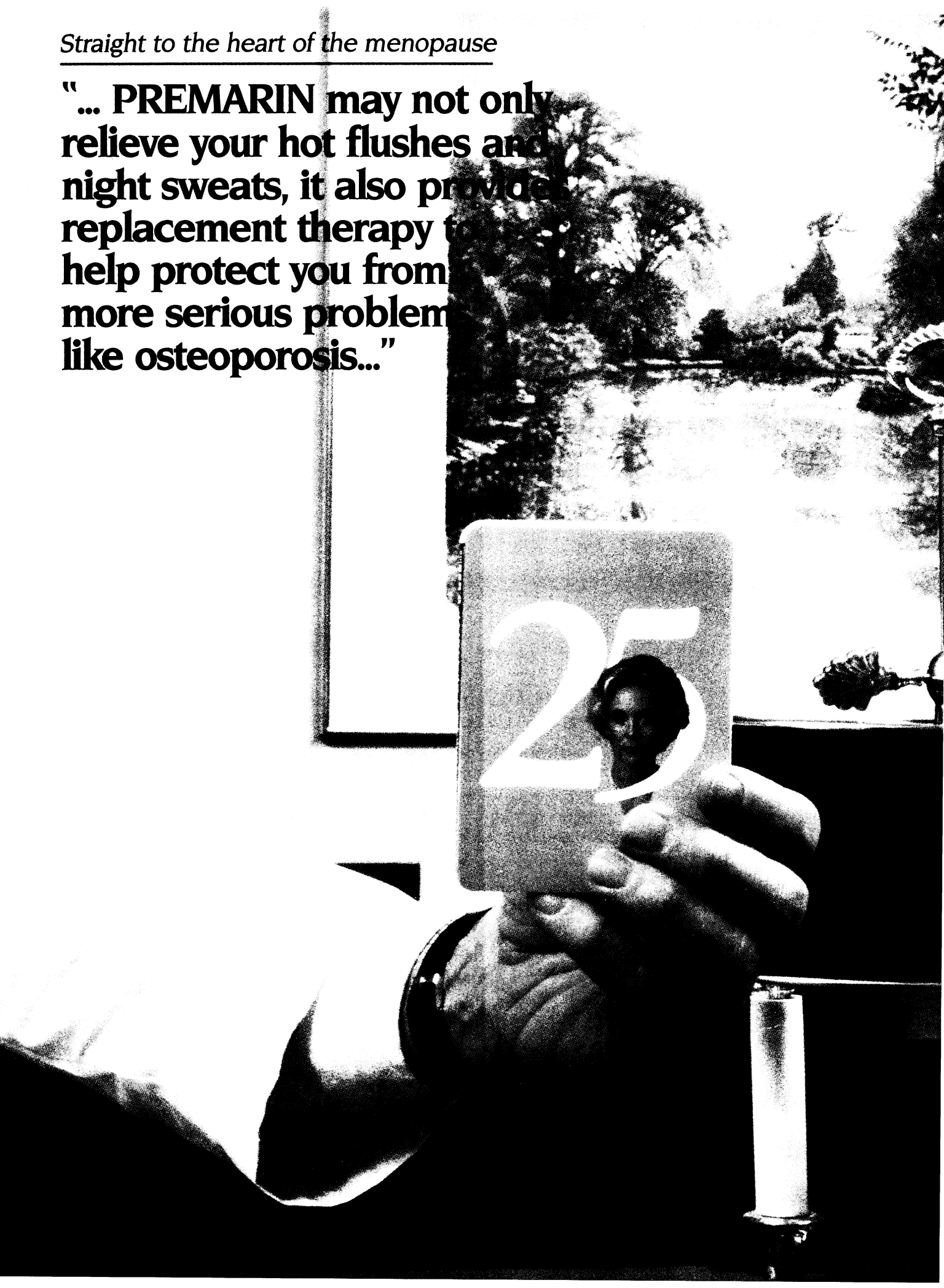

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- **PREMARIN promotes** convenience with the widest range of dosage forms and presentations, from vaginal cream to oral tablets.
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LOSEC®
FULL DISCLOSURE DOCUMENT
Effective June 1989-June 1991

Losec® (OMEPRAZOLE)

THERAPEUTIC CLASSIFICATION

H^+, K^+ –ATPase Inhibitor

Action:

LOSEC (omeprazole) inhibits the gastric enzyme H^+, K^+ –ATPase (the proton pump) which catalyzes the exchange of H^+ and K^+. It is effective in the inhibition of both basal acid secretion and stimulated acid secretion. The inhibition is dose dependent. Daily oral doses of 20 mg LOSEC and higher, showed a consistent and effective acid control. A mean reduction of 24 hour intragastric acidity of approximately 80% was achieved during repeated dosing of 20 mg daily.

LOSEC is absorbed rapidly. After an initial oral dose of LOSEC, approximately 35% of the drug is absorbed from the gastrointestinal tract. Following one week of therapy, the percentage absorbed is 43. Neither food nor antacids have any effect on the bioavailability. Peak plasma levels occur within about 4 hours. The terminal plasma half-life is about 40 minutes. Although the antisecretory effect of omeprazole is directly proportional to the AUC, it is not dependent on the plasma concentration at any given time. Omeprazole is 95% bound to plasma proteins.

Omeprazole undergoes an extensive first-pass metabolism. Following I.V. and oral administration, 80% of the dose is recovered as urinary metabolites, the remaining 20% is excreted in the feces.

Indications and Clinical Use:

LOSEC is indicated in the treatment of conditions where a reduction of gastric acid secretion is required, such as:

1) duodenal ulcer
2) gastric ulcer
3) reflux esophagitis
4) Zollinger-Ellison Syndrome (pathological hypersecretory conditions)

Contraindications:

Hypersensitivity to omeprazole or any of the components of this medication.

Warnings:

When gastric ulcer is suspected, the possibility of malignancy should be excluded before therapy with LOSEC is instituted as treatment with LOSEC may alleviate symptoms and delay diagnosis.

Use in Pregnancy: The safety of LOSEC in pregnancy has not been established. LOSEC should not be administered to pregnant women unless the expected benefits outweigh the potential risks.

Nursing Mothers: It is not known if LOSEC is secreted in human milk. LOSEC should not be given to nursing mothers unless its use is considered essential.

Use in Children: The safety and effectiveness of LOSEC in children has not yet been established.

Precautions:

Use in the Elderly: Elderly subjects showed increased bioavailability (79%), reduced total plasma clearance (229 mL/min) and prolonged (50%) elimination half-life. The daily dose in elderly patients should, as a rule, not exceed 20 mg (see DOSAGE AND ADMINISTRATION).

Patients with Hepatic Insufficiency: Patients with impaired liver function showed an increased bioavailability (to 97%), reduced total plasma clearance (75 mL/min), and a four-fold prolongation of the elimination half-life (2.7 hours). Twenty mg given once daily to these patients for 4 weeks was well tolerated, with no accumulation of omeprazole or its metabolites. The daily dose in patients with severe liver disease should, as a rule, not exceed 20 mg (see DOSAGE AND ADMINISTRATION).

Patients with Renal Insufficiency: The disposition of intact LOSEC is unchanged in patients with impaired renal function and no dose adjustment is needed in these patients (see DOSAGE AND ADMINISTRATION).

Carcinogenicity: The rat carcinogenicity study (24 months) revealed a gradual development from gastric ECL-cell hyperplasia to carcinoids at the end of their normal life span during administration with 14-140 mg/kg/day of omeprazole. No metastasis developed. No carcinoids developed during 18 months high dose treatment of mice (14-140 mg/kg/day). Similarly, administration of omeprazole up to 28 mg/kg/day in dogs for 12 months did not cause any carcinoids.

The gastric carcinoids in rats were related to sustained hypergastrinemia secondary to acid inhibition and not to omeprazole per se.

Short-term treatment (and long-term treatment in a limited number of patients for up to 5 years) to date, have not resulted in any significant pathological changes in gastric oxyntic endocrine cells.

Drug Interactions: LOSEC is metabolized in the liver. This occurs via the cytochrome P-450 system. The pharmacokinetics of the following drugs which are also metabolized through the cytochrome P-450 system have been evaluated during concomitant use of LOSEC in humans: aminopyrine, antipyrine, diazepam, phenytoin, warfarin, theophylline, and propranolol.

Aminopyrine and Antipyrine: After 14 days administration of 60 mg LOSEC once daily, the clearance of aminopyrine was reduced by 19%; the clearance of antipyrine was reduced by 14%. After 14 days administration of 30 mg once daily, no significant changes in clearance were noted.

Diazepam, Phenytoin and Warfarin: Following repeated dosing with LOSEC 40 mg once daily, the elimination half-life of diazepam was increased by 128%; the elimination half-life of phenytoin was increased by 27%. Concomitant administration of LOSEC 20 mg had no effect on plasma concentrations of the (S)-enantiomer of warfarin, but caused a slight, though statistically significant increase (12%) in the less potent (R)-enantiomer concentrations. A small but statistically significant increase (11%) in the anticoagulant effect of warfarin was also seen.

Patients should be monitored to determine if it is necessary to adjust the dosage of these drugs when taken concomitantly with LOSEC.

Theophylline and Propranolol: No effects on oral or I.V. theophylline kinetics have been observed after repeated once daily doses of 40 mg LOSEC. Similarly, no effects on propranolol kinetics were observed in a steady-state trial with 20 mg of LOSEC daily.

Adverse Reactions:

LOSEC is well tolerated. Most adverse reactions have been mild and transient and there has been no consistent relationship with the treatment. Adverse reactions have been recorded during controlled clinical investigations in 2448 patients exposed to LOSEC. In a controlled clinical trial comparing LOSEC to placebo, the prevalence of adverse events with LOSEC 40 mg once daily was similar to the placebo group. In short term comparative double-blind studies with histamine H_2-receptor antagonists, there was no significant difference in the prevalence of adverse events between LOSEC and the H_2-receptor antagonists.

The following adverse experiences (at a rate of more than one percent) have been reported in individuals receiving LOSEC therapy in controlled clinical situations: nausea (3.6%); headache (2.6%); diarrhea (2.9%); constipation (1.4%); abdominal pain (2.0%); dyspepsia (2.2%); flatulence (2.4%) and vomiting (1.9%). Skin rash has occurred in a few patients.

An extensive evaluation of laboratory variables has not revealed any significant changes during LOSEC treatment which are considered to be clinically important. Laboratory abnormalities were reported as serious adverse events in 0.2% (13/7356) *healthy subjects and patients* exposed to LOSEC. In no case was a causal relationship to the drug established. A slight, clinically insignificant increase in alkaline phosphatase S-ASAT and S-ALAT has been observed. Similar increases were also observed with histamine H_2-receptor antagonist treatments in comparative studies.

Symptoms and Treatment of Overdosage:

To date, there is no experience with deliberate overdosage. Single doses of up to 160 mg have been well tolerated. Doses of up to 360 mg per day have been used in patients with Zollinger-Ellison Syndrome with no serious adverse effects. As in all cases where overdosing is suspected, treatment should be supportive and symptomatic. Any unabsorbed material should be removed from the gastrointestinal tract, and the patient should be carefully monitored.

The oral LD_{50} of omeprazole in male and female rats and mice was greater than 4000 mg/kg. In dogs, the only sign of acute toxicity was vomiting which occurred at doses of approximately 600 mg/kg.

Dosage and Administration:

Duodenal Ulcer: ***Acute Therapy:*** The adult oral dose of LOSEC for the treatment of acute duodenal ulcer is 20 mg given once daily. Healing usually occurs within 2 weeks. For patients not healed after this initial course of therapy, an additional 2 weeks of treatment is recommended.

Refractory Patients: In patients with duodenal ulcer refractory to other treatment regimens, 20 mg and 40 mg LOSEC given once daily has been used. Healing is usually achieved within 4 weeks in such patients.

Gastric Ulcer: ***Acute Therapy:*** The recommended adult dose is 20 mg of LOSEC given once daily. Healing usually occurs within 4 weeks. For patients not healed after this initial course of therapy, an additional 4 weeks of treatment is recommended.

Refractory Patients: In patients with gastric ulcer refractory to other treatment regimens, 40 mg LOSEC given once daily has been used. Healing is usually achieved within 8 weeks.

Reflux Esophagitis: ***Acute Therapy:*** The recommended adult dose is 20 mg given once daily. In most patients, healing occurs within 4 weeks. For patients not healed after this initial course of therapy, an additional 4 weeks of treatment is recommended.

Refractory Patients: For patients with reflux esophagitis refractory to other treatment regimens, 40 mg LOSEC given once daily has been used. Healing is usually achieved within 8 weeks.

Maintenance Therapy for Duodenal, Gastric Ulcers, and Reflux Esophagitis: Experience with the long term administration of LOSEC to patients is limited and its use as maintenance therapy cannot be recommended until further data is available.

Zollinger-Ellison Syndrome: The dose of LOSEC used in the treatment of Zollinger-Ellison syndrome will vary with the individual patient. The recommended initial dose is 60 mg LOSEC, given once daily. More than 90% of the patients with the severe form of the disease and inadequate response to other therapies have been adequately controlled with doses of 20 mg to 120 mg daily. With doses greater than 80 mg, the dose should be divided and given twice daily. Doses should be adjusted to the individual patient's need and should continue as long as clinically indicated. Doses up to 120 mg t.i.d. have been administered.

Concomitant Antacid Use: Antacids may be used concomitantly if required. There is no influence on the bioavailability of omeprazole with concomitant antacid treatment.

Patients with Renal Insufficiency: No dose adjustment is required (see PRECAUTIONS).

Patients with Hepatic Insufficiency: The daily dose in patients with severe liver disease should, as a rule, not exceed 20 mg (see PRECAUTIONS).

Elderly Patients: The daily dose should, as a rule, not exceed 20 mg (see PRECAUTIONS).

The capsules should be swallowed whole with sufficient water.

Dosage Forms:

LOSEC 20 mg capsules are two-piece hard gelatin capsules with an opaque pink body and an opaque reddish-brown cap. The body is printed '20,' and the cap AS OM, in black ink.

Fourteen capsules are provided in a high density polyethylene bottle with a child resistant screw cap which contains a desiccant. The capsules should be dispensed in the original container.

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5. Sandmark, S. et al. Omeprazole vs. Ranitidine in the Treatment of Reflux Esophagitis. Scand. J. Gastroenterol 1988: 23: 625-32.

6. Omeprazole Monograph, AB Astra, 1988.

Full Product Monograph available on request from:

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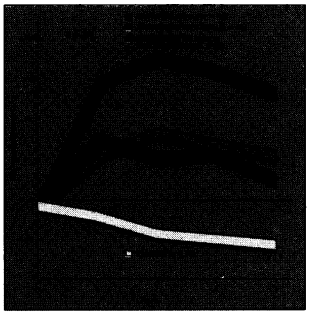

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REFERENCE: 1. Cooper, S.A.; The Relative Efficacy of Ibuprofen on Dental Pain, Compend Contin Educ Dent, Vol. VII, No 8.

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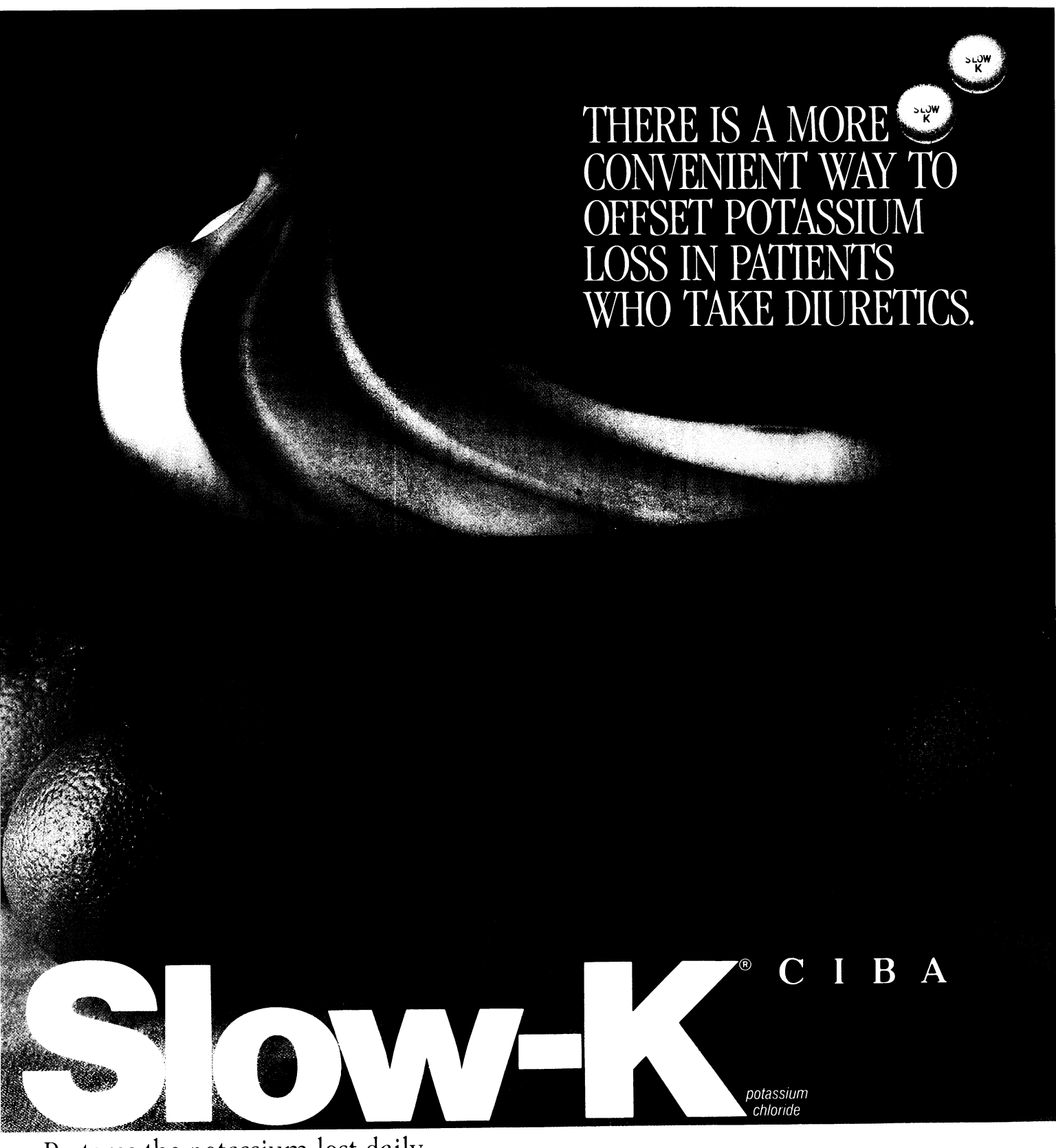

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infection. Weighing the benefits and harms. *Ann Intern Med* 1989; 110:727–33.

Voluntary screening for human immunodeficiency virus (HIV) infection may help prevent the spread of the HIV epidemic if persons who test positive alter behaviours that may transmit infection. Protecting persons from unknowing exposure to HIV infection must be balanced against respecting the autonomy of individuals being screened. Seropositive patients may be subject to discrimination if confidentiality of test results is breached. In patients without high-risk behaviours, the positive predictive value of HIV testing may be substantially increased if tests are done in reference laboratories and if further confirmatory tests are run on a second blood specimen. For persons with high-risk behaviours, HIV testing can be recommended to those who want to reduce uncertainty about their HIV status or whose medical care would change if they were seropositive. Health care workers can maximize benefits of screening and minimize harm by educating and counselling patients before HIV testing, discussing the confidentiality of HIV test results, urging patients to disclose positive results to sex partners, and advising patients on how to reduce high-risk behaviours.

Hypertension

Kligman EW, Higbee MD. Drug therapy for hypertension in the elderly. *J Fam Pract* 1989; 28:81–7.

Essential hypertension is a major health care problem in the elderly and requires effective treatment to lower morbidity and mortality. The traditional stepped-care approach to therapy consists of diuretics, sympatholytic agents, or β-blockers for all age groups. Indeed, initial therapy with these agents is effective in 50% to 60% of elderly patients, but may produce adverse effects. A high incidence of adverse responses, including sexual dysfunction and central nervous system impairment, has been reported with diuretic or β-blocker therapy, and a reduction in several measures of quality of life has been noted during therapy with methyldopa or propranolol. Administration of an angiotensin-converting enzyme (ACE) inhibitor is as effective as the traditional stepped-care approach without producing these ill effects. Combining an ACE inhibitor with a diuretic produces additive antihypertensive effects while minimizing diuretic-induced metabolic alterations. Orthostatic hypotension with the first dose can be minimized by ensuring that patients are not hypovolemic from previous diuretic therapy. Nevertheless, in controlled trials, the combination of an ACE inhibitor and a diuretic has been effective in up to 85% of patients. Also, using an ACE inhibitor may benefit the hypertensive patient with concomitant congestive heart failure. Most important, the patient's quality of life is maintained during therapy with an ACE inhibitor alone, or in combination with a diuretic.

Melanoma

Becker JK, Goldberg LH, Tschen JA. Differential diagnosis of malignant melanoma. *Am Fam Physician* 1989; 39(5):203–14.

Malignant melanoma accounts for only 3% of all skin cancers, but is responsible for two-thirds of deaths due to cutaneous malignancies. This dis-

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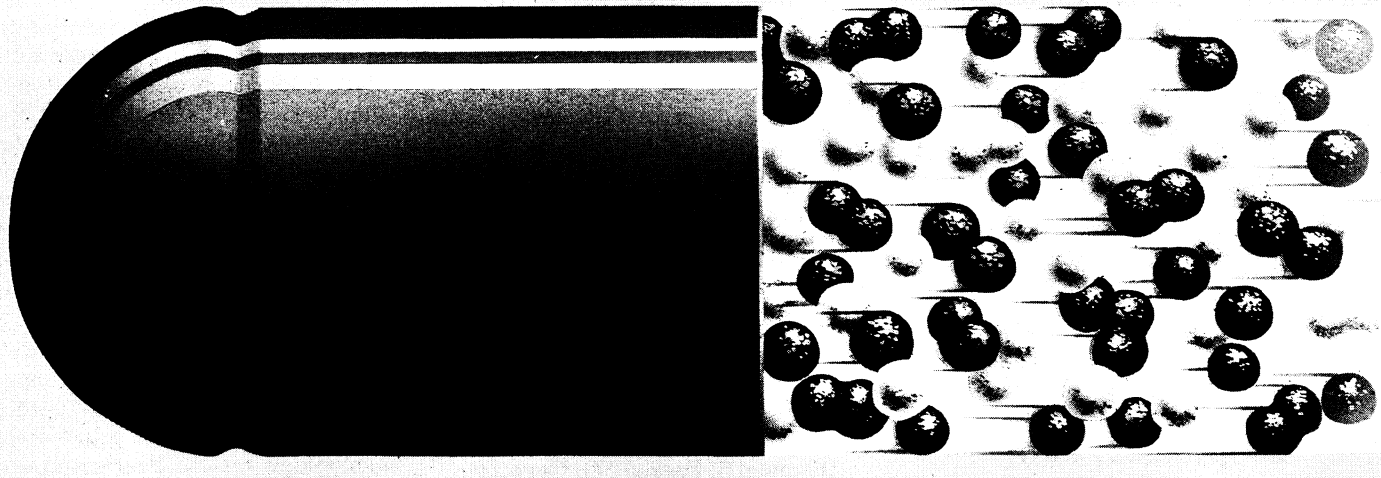

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ease has had a 500% rise in incidence over the past four decades, which is the most rapid increase in any cancer except lung cancer. Unlike most other malignancies, melanoma is a visible lesion with identifiable characteristics that make early detection an attainable goal. People have become more aware of the dangers of melanoma and look to their family physicians for evaluation of suspect lesions. Since a variety of skin tumours and conditions may resemble melanoma, knowledge of the differential diagnosis and a systematic approach to the evaluation of a suspect lesion are essential.

Obesity

Holmes MD, Zysow B, Delbanco TL. An analytic review of current therapies for obesity. *J Fam Pract* 1989; 28:610–6.

The obese adult patient poses a frustrating problem for every physician. Success in achieving sustained weight control is rare, although weight loss is a cornerstone treatment for many common diseases, such as hypertension, diabetes, heart disease, and degenerative joint disease. Substantial, prolonged weight loss is difficult to achieve. Nutrition counselling, very low calorie diets, behaviour modification, exercise, intragastric balloon, and gastric restriction surgery are interventions that physicians may recommend for obese patients. This paper analyzes the efficacy of these methods with attention to attrition rates, maximum weight loss, long-term maintenance of weight loss, and morbidity. Strategies for intervention for various classes of obese patients are recommended.

Pap Smears

Koss LG. The Papanicolaou test for cervical cancer detection. *JAMA* 1989; 261:737–43.

The complex detection system leading to finding and treating precancerous lesions and early cancer of the cervix is described in detail and discussed. By far the most difficult and underestimated component of this system is the screening and interpretation of cervical (Papanicolaou) smears. Cytologic case finding may fail because of inadequate samples, insufficient time devoted to screening, or human fatigue. Other weak points of the system, such as inadequate patient compliance, poor reproducibility of diagnoses, and ineffective aftercare are also described. For example, obtaining a second smear to confirm or refute a diagnosis of cellular atypia is often a misleading practice. The Pap smear has been effective in reducing the morbidity and mortality rates from invasive cervical cancer in appropriately screened populations. There is no evidence, however, that the Pap test has successfully eradicated this theoretically preventable disease anywhere. It is important to inform the public about the potential failures of the system and the reasons for them.

Postherpetic Neuralgia

Schmader KE, Studenski S. Are current therapies useful for the prevention of postherpetic neuralgia? A critical analysis of the literature. *J Gen Intern Med* 1989; 4:83–9.

The purpose of this study was to determine whether current therapies are useful in preventing postherpetic neuralgia (PHN), by meta-analysis of all controlled studies investigating PHN prevention in the immunocompetent host. Articles were identified through MEDLINE, *Index Medicus*,

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and bibliographic reviews of major texts and review articles. Studies meeting eligibility criteria were independently assessed using explicit methodologic criteria for validity and generalizability in clinical trials. Pooled analysis was also performed where appropriate. Twenty-one investigations met eligibility criteria and primarily addressed the use of antiviral agents and corticosteroids. Among studies with strong designs, no evidence of benefit was found for acyclovir or corticosteroids. Pooled results showed no significant effect of acyclovir on the prevention of PHN. Studies that found the strongest potential efficacy in PHN prevention involved adenosine monophosphate and idoxuridine in dimethyl sulfoxide, but problems with clinical application limit the use of these compounds. Outcome definition, compliance assessment, power estimation, and method of randomization were infrequently addressed aspects of design. The authors conclude that there is currently no proven useful therapy for the prevention of PHN. The benefits of acyclovir and corticosteroids are limited, but key questions about these medications remain. A clear consensus definition of PHN is needed to improve future investigations.

Practice Styles

Bertakis KD, Robbins JA. Utilization of hospital services. A comparison of internal medicine and family practice. *J Fam Pract* 1989; 28:91–6.

At a large university hospital, 520 new patients were randomly and prospectively assigned to receive care in either the internal medicine clinic or family practice clinic. Previous analyses of out-patient data showed that the frequency of visits to the primary care clinic, acute care clinic, emergency room, and consultant clinics for patients randomized to internal medicine were all significantly higher than for family practice. In this study, patients' charts were reviewed for information about hospitalizations. During the 3.4-year study, there were a total of 61 hospital admissions for internal medicine (35 of 249 patients), and 58 for family practice (27 of 271 patients). Age (mean 47 years) and sex of patients in both groups were equivalent. The average total cost of hospitalization for each patient was greater for those randomized to the internal medicine clinic: $7193 for internal medicine patients, compared with $5764 for family practice patients. The professional costs per hospitalization showed greater variation: $913 for internal medicine clinic patients and $629 for family practice clinic patients. The mean length of hospitalization was longer for internal medicine patients (7.5 days) than for family practice patients (6.3 days). The authors conclude that, in this clinical environment, hospitalization patterns differ for patients assigned to the internal medicine clinic compared with the family practice clinic: both cost and length of care for hospitalization are less for those followed by the family practice clinic.

Sigmoidoscopy

Selby JV, Friedman GD. Sigmoidoscopy in the periodic health examination of asymptomatic adults. *JAMA* 1989; 261:595–601.

Periodic screening sigmoidoscopic examination of asymptomatic persons has been recommended for more than 30 years as a means of reducing mortality from colorectal cancer. Evi-

Effective allergy relief. Day in,

dence supporting this practice is limited, however, and expert opinions differ as to whether sigmoidoscopy should be included in the periodic health examination (PHE). The authors review available evidence on the efficacy and effectiveness of periodic screening sigmoidoscopy in average-risk persons. The sensitivity, specificity, and acceptability of screening sigmoidoscopy are also considered, as are recommendations for screening high-risk groups. The rules of evidence used by the United States Preventive Services Task Force for ranking quality of evidence and for recommending inclusion (or exclusion) of screening tests in PHEs accompany the article. These rules have been modified from guidelines developed by the Canadian Task Force on the Periodic Health Examination.

Somatic Fixation

McDaniel SH, Campbell T, Seaburn D. Somatic fixation in patients and physicians: a biopsychosocial approach. *Fam Syst Med* 1989; 7:5–16.

Somatic fixation occurs when the patient or physician focuses exclusively on the somatic aspects of a complex disorder. This common and challenging problem results from individual, family, and cultural factors that promote communication and the expression of emotional experience through somatic symptoms. An unrewarding cycle of interactions occurs when the physician first rules out organic illness in the somatically fixated patient and then searches for psychosocial explanations. This article presents a biopsychosocial approach to somatic fixation in which the physician or a treatment team establishes a collaborative relationship with the patient system and strives to reach a mutually acceptable explanation for the symptoms. Biomedical and psychosocial evaluation are integrated from the beginning, and the patient's somatic defences and mode of communication are respected. Limited goals are established and levels of patient functioning, rather than symptoms, are monitored. Collaboration with another physician or a family therapist often helps to increase success and enjoyment of these difficult cases.

Thromboembolic Disorders

Brunader REA. Diagnosis and evaluation of thromboembolic disorders. *J Am Board Fam Pract* 1989; 2:106–18.

The most common types of thromboembolic disorders are deep venous thrombosis of the leg and pulmonary embolism. Since the effectiveness of anticoagulation therapy for deep venous thrombosis and pulmonary embolism was established in 1960, knowledge of these disorders has increased rapidly. It has become clear that the nonspecificity of symptoms and signs of these disorders has led to both overdiagnosis and undertreatment. The author reviews the natural history and clinical manifestations of deep venous thrombosis and pulmonary embolism and discusses their diagnostic evaluation.

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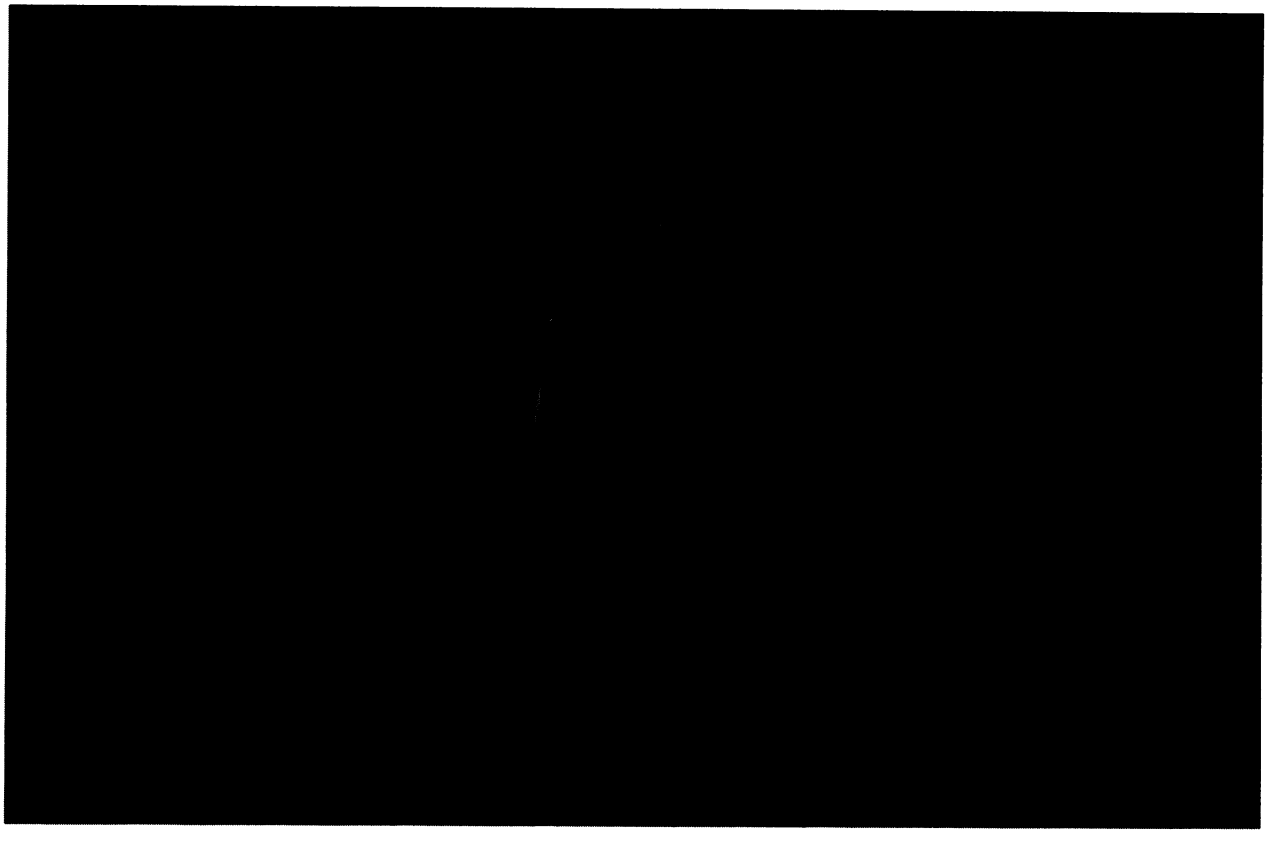
Your older patients with insomnia require extra care. Consider Restoril.



- *Low amnesic potential*[1]
- *8 to 10 hour half-life*
- *Minimal risk of accumulation*[2,3]
- *Helps avoid next day impairment*[3,4]
- *May help prevent early morning insomnia*[5]
- *Does not alter REM sleep*

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(temazepam)

An answer to the growing concern about hypnotics

Please review the Restoril prescribing information, because there are important properties to consider when selecting a benzodiazepine hypnotic.

ℙRESTORIL® (temazepam) Hypnotic

Pharmacology: Temazepam is an active benzodiazepine with hypnotic properties. In sleep laboratory studies, temazepam decreased the number of nightly awakenings but had no effect on sleep latency. Rebound insomnia was not observed after withdrawal of the drug. Temazepam decreased stage 3, and combined stage 3 and 4 sleep, accompanied by a compensatory increase in stage 2 sleep, but did not alter REM sleep.

Orally administered temazepam is well absorbed in man. Temazepam has a half-life of about 8 to 10 hours in plasma (with considerable inter-individual variability). On multiple dosing, steady state is reached usually within 3 to 5 days with excretion of the drug mainly in the urine in the form of the inactive O-conjugate metabolite.

Indications: Temazepam is a hypnotic agent useful in the short-term management of insomnia. It has no effect, however, in shortening the time taken by patients to fall asleep.

Efficacy has not been established in children under 18 years of age. As with other hypnotics, temazepam is not indicated for prolonged administration.

Contraindications: Hypersensitivity to benzodiazepines and in myasthenia gravis.

Warnings: Occupational hazards: driving, operating dangerous machinery or engaging in any activity requiring mental alertness and physical coordination after taking temazepam.

Physical and psychological dependence: Temazepam should not be administered to individuals prone to drug abuse, or that may have potential for psychological dependence. Withdrawal symptoms are similar to those manifested by patients with excessive anxiety and may appear to justify continuation of drug use.

Potentiation of drug effects: Temazepam may potentiate the effects of other CNS depressant drugs: e.g. alcohol, barbiturates, nonbarbiturate hypnotics, antihistamines, narcotics, antipsychotic and antidepressant drugs, and anticonvulsants. Different benzodiazepines should usually not be used simultaneously and careful consideration should be given if other CNS depressants are administered in combination with temazepam. Patients should be advised against the simultaneous use of other CNS depressant drugs including alcohol.

Pregnancy: Temazepam should not be used during pregnancy. If the drug is prescribed to a woman of child-bearing potential, she should be warned to consult her physician regarding discontinuation of the drug if she intends to become or suspects that she is pregnant.

Lactation: Temazepam should not be given to nursing mothers.

Precautions: Patients with emotional disorders: use temazepam with caution in patients with symptoms of depression, latent depression, or suicidal tendencies.

Elderly and debilitated patients or those with organic brain syndrome: are prone to CNS depression after even low doses of benzodiazepine and may experience paradoxical reactions to these drugs. Use temazepam only in the lowest possible dose and adjust when necessary under careful observation.

General: Temazepam is metabolized in the liver and is primarily excreted by the kidney. Caution should be exercised in administration of temazepam to patients who might have impaired hepatic and/or renal function.

Adverse Effects: Most common adverse reactions reported: dizziness, lethargy and drowsiness, confusion, euphoria, staggering ataxia and falling. Paradoxical reactions such as excitement, stimulation, hyperactivity and hallucinations are observed infrequently.

Other adverse reactions are weakness, anorexia, horizontal nystagmus, vertigo, tremor, lack of concentration, loss of equilibrium, dry mouth, blurred vision, palpitations, faintness, hypotension, depression, shortness of breath, nausea, diarrhea, abdominal discomfort, genitourinary complaints, pruritus, skin rash, urticaria, and anterograde amnesia. Abnormal liver function tests have been reported occasionally.

Dosage: An appropriate hypnotic dose should produce the desired effect while avoiding oversedation and impairment of performance the next day.

Adults: 30 mg before retiring.

Elderly and debilitated patients: initial dose should not exceed 15 mg before retiring (see Precautions).

Temazepam is not indicated in children below 18 years of age.

Temazepam is intended only for short-term use. Prescribe in quantities not exceeding those required for that cycle of administration. Prescriptions should not be renewed without further assessment of the patient's needs.

Supplied: Each maroon and blue capsule, imprinted Restoril 30 and SANDOZ contains: temazepam 30 mg. Also contains lactose. Each maroon and flesh colored capsule, imprinted Restoril 15 and SANDOZ contains: temazepam 15 mg. Also contains lactose. Bottles of 100.

Protect from moisture and excessive heat.

Full Product Monograph available to physicians and pharmacists upon request.

References

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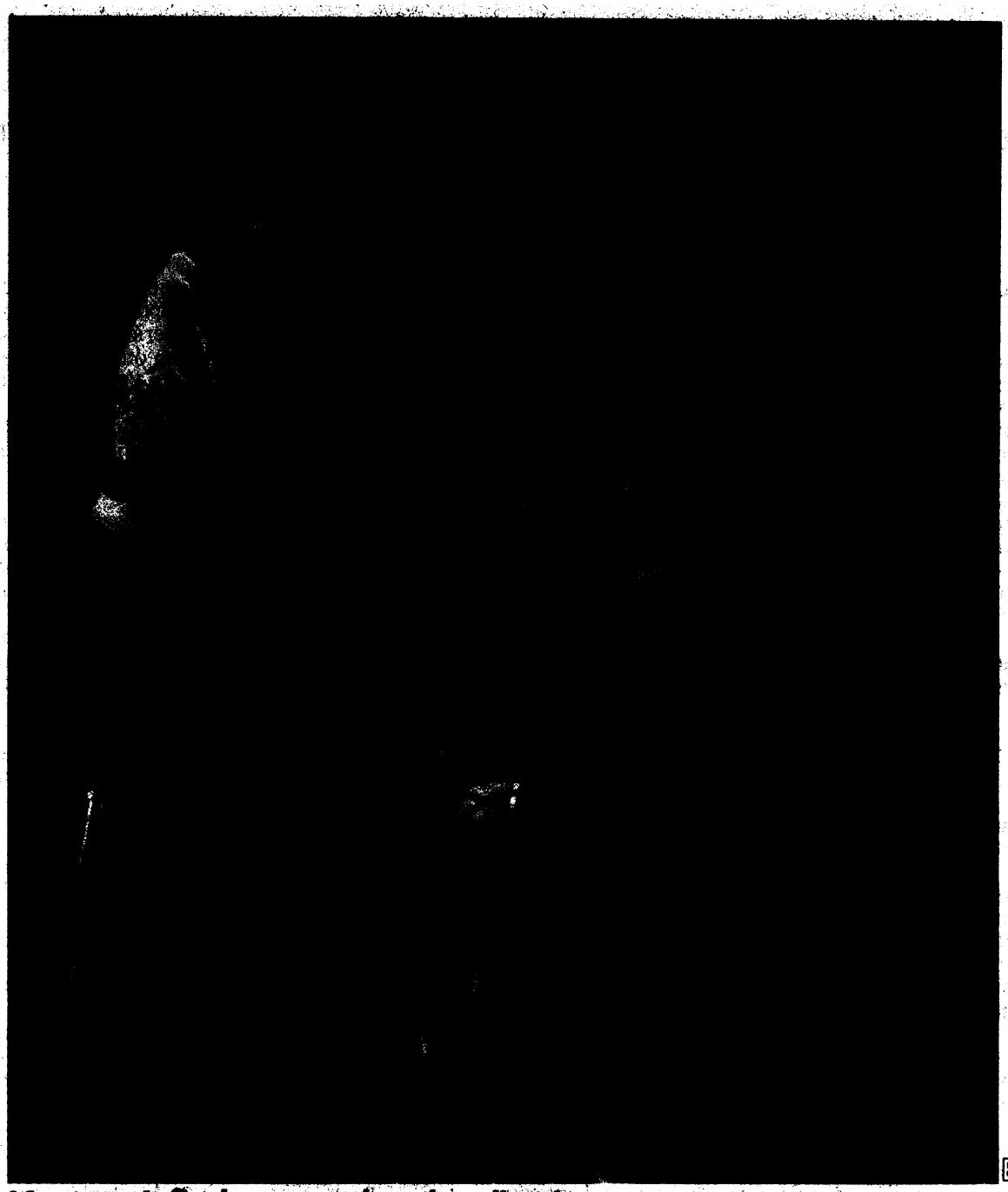

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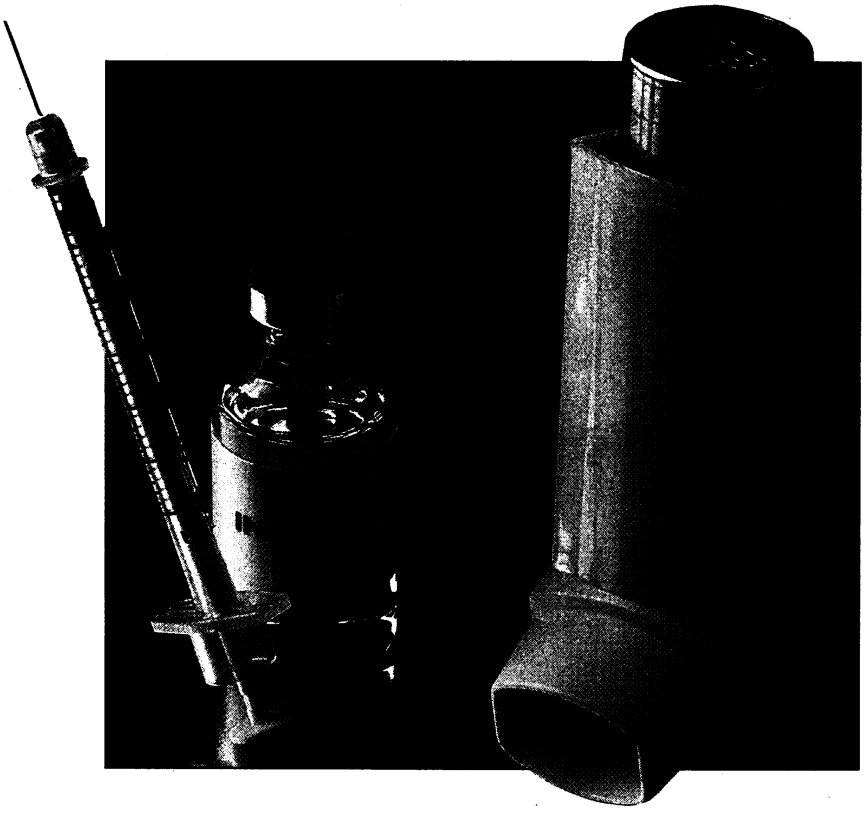

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Catapres is effective in mild to moderate hypertension when administered in low doses and has a low potential for aggravating or complicating underlying conditions of diabetes and asthma/COPD.

For the Diabetic Hypertensive
With Catapres there is no significant alteration of diabetic control[1] and virtually no interference with lipid or glucose metabolism.[2,3]

For the Asthmatic Hypertensive
With Catapres there are no contraindications in patients with asthma or COPD,[3] and Catapres has been used concomitantly with bronchodilating drugs.

When hypertension is complicated by diabetes or asthma, consider low dose Catapres first.

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They share everything. Including Otitis Media with Effusion.

By the age of 3 years, more than 1/3 of children in day care have had 3 or more episodes of OME.[1]

Ceclor benefits can be shared by children and parents alike!

Children enjoy sharing everything, but the joys of sharing toys and hand-to-hand contact amongst children in day care can readily encourage the spread of OME. For parents who rely on day care, OME can lead to a merry-go-round of office visits, prescription costs, sleepless nights, lost workdays and greater frustration at home.[1,2]

For effective symptomatic relief, consider Ceclor® as an important choice for both children and parents.[3,4,5]

Ceclor with its 9 years of proven clinical experience

- For broad single-agent coverage[6,7]
- For effective relief of OME[4]
- For convenient BID dosing[7]
- For patient compliance[7]

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50th ANNIVERSARY

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These cases, however, were not statistically significant. All patients in this study were male veterans, and it is not known what proportion of the two groups were smokers. Furthermore, the placebo groups consisted of 70% and the treatment group of 30% of the total study population;

- There is a theoretical negative effect on compliance for future treatment. Having stopped taking medications may negatively affect compliance with subsequent treatment because patients may need to re-start medication as their blood pressure returns to hypertensive levels;
- There exists a theoretical possibility of long-term complications from medication withdrawal unrelated to the return of elevated blood pressure. Antihypertensive medications may decrease the incidence of disease in ways that are unrelated to their effect on blood pressure. Patients may be at risk for cerebrovascular accidents, congestive heart failure, and so forth, even if they are able to maintain normal blood pressure levels without medications;
- There are no established protocols for medication withdrawal.

Conclusion

The growing body of evidence supporting the withdrawal of antihypertensive drugs in patients with well-controlled mild hypertension challenges the present accepted practice of life-long pharmacotherapy for hypertension. Withdrawal of antihypertensive medication for up to four years is safe.[1-9] More large long-term studies are needed to investigate the theoretical negative effects of prolonged medication withdrawal and to establish protocols. The side-effects of antihypertensive medications, however, are well documented.

The evidence clearly justifies a trial of gradual medication withdrawal in patients with well-controlled mild hypertension. These patients should be normotensive for at least six months and have no end-organ damage or associated cardiovascular risk factors. Weight loss and sodium restriction should accompany medication withdrawal.[6] ■

Acknowledgements

I thank Dr. W.E. Hogg for his assistance in preparing this manuscript.

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PRESCRIBING INFORMATION:

Benadryl*

(Diphenhydramine Hydrochloride)

Indications: The symptomatic relief of allergic diseases such as urticaria, atopic dermatitis, contact dermatitis, angioedema, pruritus, reactions to injection of contrast media, serum sickness, reactions to therapeutic preparations, gastrointestinal allergies, allergic transfusion reactions, allergic rhinitis, hayfever, vasomotor rhinitis; also post-operative nausea and vomiting, motion sickness, parkinsonism, and quieting emotionally disturbed children. Parenteral administration is indicated where, in the judgement of the physician, prompt action is necessary and oral therapy would be inadequate. Antiallergic, antiemetic and antispasmodic.

Precautions: Avoid subcutaneous or perivascular injection. Single parenteral dosage greater than 100 mg should be avoided, particularly in hypertension and cardiac disease. Safety for use in pregnancy and lactation has not been established. Its use therefore in such patients should involve consideration of expected benefits and possible risks. Patients should be cautioned not to operate vehicles or hazardous machinery until their response to the drug has been determined. Since the depressant effects of antihistamines are additive to those of other drugs affecting the central nervous system, patients should be cautioned against drinking alcoholic beverages or taking hypnotics, sedatives, psychotherapeutic agents or other drugs with CNS depressant effects during antihistaminic therapy. Diphenhydramine has an atropine-like effect which should be considered when prescribing Benadryl. Rarely, prolonged therapy with antihistamines can produce blood dyscrasias.

Adverse Effects: Drowsiness, dizziness, dryness of mouth, nausea and nervousness may occur. Other infrequently reported effects are vertigo, palpitation, blurring of vision, headache, restlessness, insomnia and thickening of bronchial secretions. Allergic reactions, diarrhea, vomiting and excitation may also occur.

Dosage: Oral: Average adult dose is 25 to 50 mg, 3 or 4 times daily. Children up to 12 years, 12.5 mg to 25 mg, 3 or 4 times daily.

Parenteral: 10 to 50 mg intravenously or deeply intramuscularly not to exceed 400 mg daily. High dosage for adults (300 to 400 mg daily) may be required in acute, generalized or chronic urticaria and allergic eczema.

Supplied: Capsules of 25 and 50 mg; Elixir, 12.5 mg per 5 mL; Ampoules, 50 mg per mL; Steri-Dose Syringes, 50 mg per mL; Steri-Vials, 10 mg or 50 mg per mL.

Product Monograph available on request.

[1]Benadryl* prescribing information.

[2]Krause, L., Shuster, S., Mechanism of action of anti-pruritic drugs: British Med J Oct. 22, 1984 (Vol. 287)

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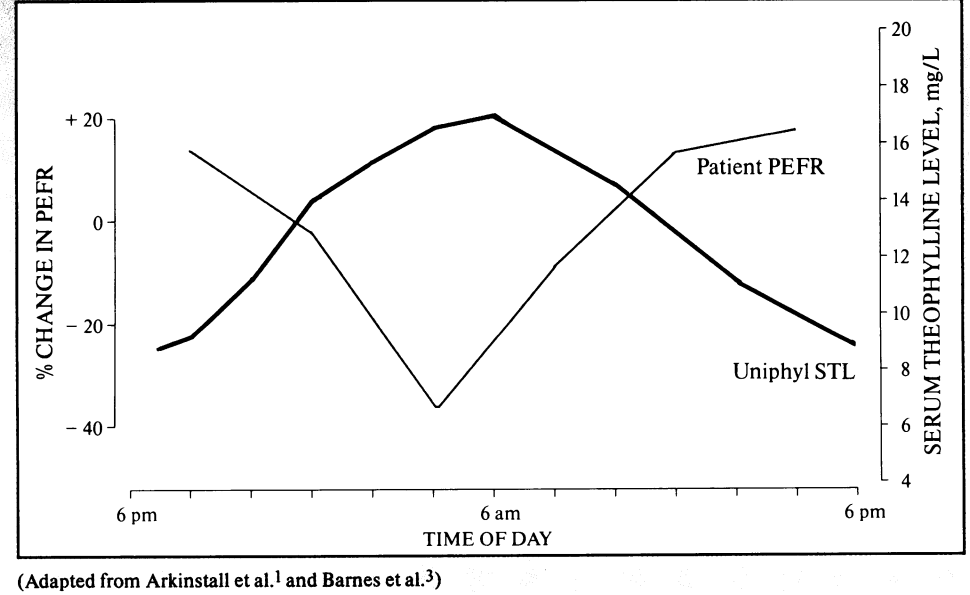
People used to think

People used to believe that asthma was best treated with medications that provided flat theophylline levels.

Timing the peak theophylline levels to the time of the patient's greatest need is becoming recognized as providing greater stabilization of the airways than seen with conventional, flat serum theophylline levels.

Uniphyl administered in the evening provides maximum theophylline levels in the early morning hours, and more effective asthma control for a full 24 hours.[1]

Clinical trials showed that with Uniphyl the patients' FEV_1 measurements were better in the morning, and significantly more stable throughout the day, than with a twice-daily theophylline preparation.[1,2]

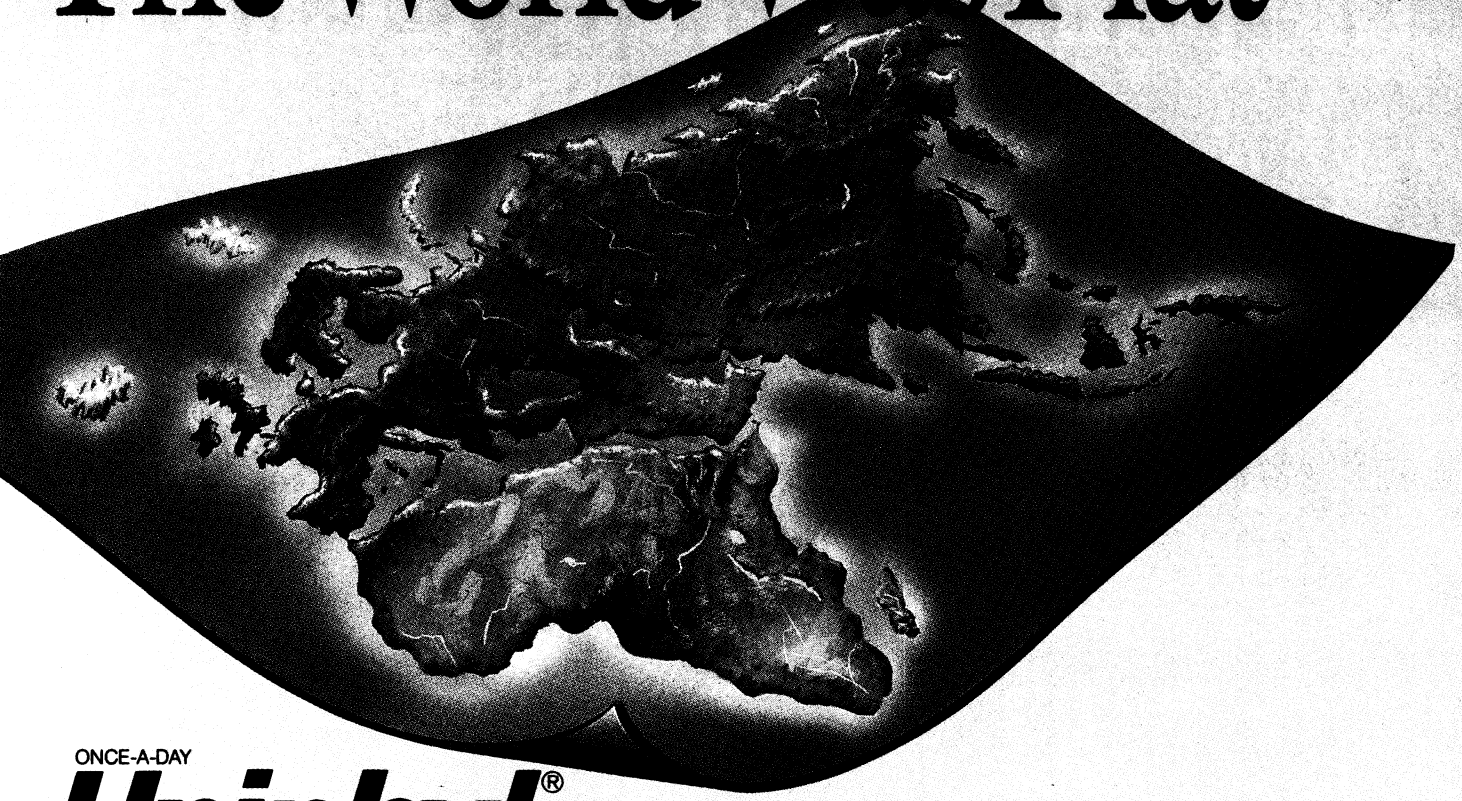


(Adapted from Arkinstall et al.[1] and Barnes et al.[3])

Asthma patients have reduced airflow at night and in the early morning;[3] Uniphyl can provide greater serum theophylline levels at this time.[1]

Most patients should take once daily Uniphyl with, or shortly following, the evening meal.

The World Was Flat



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Theophylline sustained release tablets

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Studies comparing Uniphyl administered in the evening to a conventional 12-hour, sustained-release theophylline, showed that:

- Uniphyl produced greater stabilization of airway function.[1]
- Uniphyl improved spirometry and symptoms.[1,2,4]
- There was a smooth transition from the twice-daily theophylline preparation.[4]

Patients preferred Uniphyl's 24 hour control.[1,2,4]

- When 197 asthmatics were transferred to Uniphyl, from twice-daily theophylline preparations, 155 (78.7%) said they would prefer to continue taking Uniphyl.[5]

Round out your asthma therapy with Uniphyl. More effective control 24 hours a day.

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It's not enough just to relieve pain. A pain reliever must be easy to take. And it must fit into your patient's lifestyle.

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Just one 400 mg ®Idarac (floctafenine) tablet T.I.D. can help to relieve moderate pain caused by low backaches, headaches, sprains and strains!

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REFERENCE: 1. Lomas, D.M. et al., A Double-Blind Comparative Clinical Trial of Floctafenine and Four Other Analgesics Conducted in General Practice. J. In. Med. Res. (1976) 4:179-182.

For prescribing information see page 1746

Without Benadryl*, itchiness can make them wish they were a lot handier.

Histamine and non-histamine mediated skin conditions can drive your patients to lose their patience. The constant itching and scratching can quickly make them feel like they just don't have enough hands to go around.

For you, itchy skin conditions can be equally frustrating. Determining an accurate diagnosis is sometimes difficult, yet you need this knowledge to know if a specific antipruritic will work or not. Benadryl* has both central and peripheral activity and hence, covers itching in a wider range of skin conditions than terfenadine and astemizole.[1,2]

Benadryl*
(diphenhydramine hydrochloride)
Starts from Scratch.

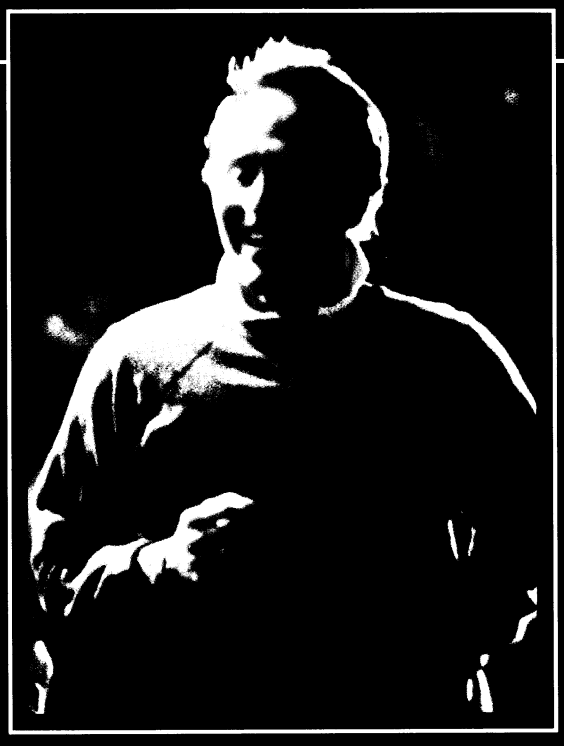
So next time pruritus gets under their skin, give them a hand. Recommend Benadryl.*

PARKE-DAVIS
PAAB CCPP Scarborough, Ontario M1L 2N3

For prescribing information see page 1831

89-22E

FOR HYPERTENSIVE PATIENTS UNABLE TO TOLERATE BETA-BLOCKER THERAPY



VASOTEC*

(enalapril maleate)

angiotensin converting enzyme inhibitor

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Frosst

Usually No Interference with Physical or Mental Activity

Certain subjective symptoms such as malaise and drowsiness, which may interfere with physical or mental activity, have not been characteristic of VASOTEC* – a fact that may be related to the specificity of action of VASOTEC* on the renin-angiotensin-aldosterone system.

Also, certain central effects, such as impairment of memory, nightmares or depression, have not been characteristic of VASOTEC*.

ACE† Inhibition That Favorably Affects Certain Hemodynamic Parameters in Many Patients

VASOTEC* has a highly specific mode of action which acts on the renin-angiotensin-aldosterone system – it blocks ACE from converting angiotensin I to angiotensin II, one of the most potent vasoconstrictors known. For many hypertensive patients, VASOTEC* favorably affects certain hemodynamic parameters: peripheral arterial resistance is reduced with an increase in cardiac output and no significant change in heart rate; sodium and water retention are also reduced.

VASOTEC* (enalapril maleate) is contraindicated in patients who are hypersensitive to this product.

Angioedema has been reported in patients treated with VASOTEC* (enalapril maleate). Angioedema associated with laryngeal edema and/or shock may be fatal. If angioedema occurs, VASOTEC* should be promptly discontinued and the patient should be observed until the swelling subsides. Where swelling is confined to the face, lips and mouth the condition will usually resolve without further treatment, although antihistamines may be useful in relieving symptoms. These patients should be followed carefully until the swelling has resolved. However, where there is involvement of the tongue, glottis or larynx, likely to cause airway obstruction, subcutaneous adrenaline (0.5 mL 1:1000) should be administered promptly when indicated.

Symptomatic hypotension has occurred after administration of VASOTEC*, usually after the first or second dose or when the dose was increased. It is more likely to occur in patients who are volume depleted by diuretic therapy, dietary salt restriction, dialysis, diarrhea, or vomiting. In patients with severe congestive heart failure, with or without associated renal insufficiency, excessive hypotension has been observed and may be associated with oliguria and/or progressive azotemia, and rarely with acute renal failure and/or death. Because of the potential fall in blood pressure in these patients, therapy should be started under very close medical supervision, usually in a hospital. Such patients should be followed closely for the first two weeks of treatment and whenever the dose of enalapril and/or diuretic is increased.

Discontinue therapy with a beta-blocker only in accordance with the recommendations in the prescribing information for that product.

†angiotensin converting enzyme

FOR SELECTED HYPERTENSIVE PATIENTS
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VASOTEC*

(enalapril maleate)

IT MAY CHANGE THE WAY YOU MANAGE MANY OF YOUR HYPERTENSIVE PATIENTS

BEFORE PRESCRIBING PLEASE CONSULT PRESCRIBING INFORMATION WHICH FOLLOWS

NEW VASOTEC*

(enalapril maleate)

Tablets 5, 10, 20 mg

Angiotensin Converting Enzyme Inhibitor

ACTIONS

VASOTEC* (enalapril maleate) is an ACE inhibitor which is used in the treatment of hypertension.

Angiotensin converting enzyme (ACE) is a peptidyl dipeptidase which catalyzes the conversion of angiotensin I to the pressor substance, angiotensin II. After absorption, enalapril, a pro-drug, is hydrolyzed to enalaprilat, its active metabolite, which inhibits ACE. Inhibition of ACE results in decreased plasma angiotensin II, which leads to increased plasma renin activity (due to removal of negative feedback of renin release) and decreased aldosterone secretion. Although the latter decrease is small, it results in a small increase in serum K^+. In patients treated with VASOTEC* and a thiazide diuretic there was essentially no change in serum potassium (see PRECAUTIONS).

ACE is identical to kininase II. Thus, VASOTEC* may also block the degradation of bradykinin, a potent vasodepressor peptide. However, the role that this plays in the therapeutic effects of VASOTEC* is unknown.

Administration of VASOTEC* to patients with hypertension results in a reduction of both supine and standing blood pressure. Abrupt withdrawal of VASOTEC* has not been associated with a rapid increase in blood pressure. In most patients studied, after oral administration of an individual dose of enalapril, the onset of antihypertensive activity is seen at one hour with peak reduction of blood pressure achieved by 4-6 hours. At recommended doses, the antihypertensive effect has been shown to be maintained for at least 24 hours. In some patients the effect may diminish towards the end of the dosing interval (see DOSAGE AND ADMINISTRATION). On occasion, achievement of optimal blood pressure reduction may require several weeks of therapy.

In hemodynamic studies in patients with essential hypertension, blood pressure reduction was accompanied by a reduction in peripheral arterial resistance with an increase in cardiac output and little or no change in heart rate. Following administration of VASOTEC*, there was an increase in renal blood flow; glomerular filtration rate was usually unchanged.

When VASOTEC* is given together with thiazide-type diuretics, its blood pressure lowering effect is approximately additive.

Administration of VASOTEC* to patients with congestive heart failure reduces afterload and preload of the heart, resulting in an increase in cardiac output, without reflex tachycardia.

Pharmacokinetics

VASOTEC* is rapidly absorbed with peak serum concentrations of enalapril occurring within one hour. Based on urinary recovery the extent of absorption of enalapril from VASOTEC* is approximately 60%.

Following absorption, enalapril is rapidly and extensively hydrolyzed to enalaprilat, a potent angiotensin converting enzyme inhibitor (which itself is poorly absorbed). Peak serum concentrations of enalaprilat occur 3 to 4 hours after an oral dose of enalapril maleate. Excretion of VASOTEC* is primarily renal. Approximately 94% of the dose is recovered in the urine and feces as enalaprilat or enalapril. The principal components in urine are enalaprilat, accounting for about 40% of the dose, and intact enalapril. Except for conversion to enalaprilat, there is no evidence of significant metabolism of enalapril. The serum concentration profile of enalaprilat exhibits a prolonged terminal phase, apparently associated with binding to ACE. The effective half-life for accumulation of enalaprilat following multiple doses of enalapril maleate is 11 hours. The absorption of enalapril is not influenced by the presence of food in the gastrointestinal tract.

INDICATIONS

VASOTEC* (enalapril maleate) is indicated in the treatment of essential or renovascular hypertension. It is usually administered in association with other drugs, particularly thiazide diuretics.

In using VASOTEC* consideration should be given to the risk of angioedema (see WARNINGS).

VASOTEC* should normally be used in those patients in whom treatment with diuretic or beta blocker was found ineffective or has been associated with unacceptable adverse effects.

VASOTEC* can also be tried as an initial agent in those patients in whom use of diuretics and/or beta blockers is contraindicated or in patients with medical conditions in which these drugs frequently cause serious adverse effects.

VASOTEC* is indicated in the treatment of congestive heart failure as adjunctive therapy in patients who have not responded adequately to digitalis and diuretics. Treatment with VASOTEC* should be initiated under close medical supervision, usually in a hospital.

CONTRAINDICATIONS

VASOTEC* (enalapril maleate) is contraindicated in patients who are hypersensitive to this product.

WARNINGS

Angioedema

Angioedema has been reported in patients treated with VASOTEC* (enalapril maleate). Angioedema associated with laryngeal edema and/or shock may be fatal. If angioedema occurs, VASOTEC* should be promptly discontinued and the patient should be observed until the swelling subsides. Where swelling is confined to the face, lips and mouth the condition will usually resolve without further treatment, although antihistamines may be useful in relieving symptoms. These patients should be followed carefully until the swelling has resolved. However, where there is involvement of the tongue, glottis or larynx, likely to cause airway obstruction, subcutaneous adrenaline (0.5 mL 1:1000) should be administered promptly when indicated.

Hypotension

Symptomatic hypotension has occurred after administration of VASOTEC*, usually after the first or second dose or when the dose was increased. It is more likely to occur in patients who are volume depleted by diuretic therapy, dietary salt restriction, dialysis, diarrhea, or vomiting. In patients with severe congestive heart failure, with or without associated renal insufficiency, excessive hypotension has been observed and may be associated with oliguria and/or progressive azotemia, and rarely with acute renal failure and/or death. Because of the potential fall in blood pressure in these patients, therapy should be started under very close medical supervision, usually in a hospital. Such patients should be followed closely for the first two weeks of treatment and whenever the dose of enalapril and/or diuretic is increased.

If hypotension occurs, the patient should be placed in supine position and, if necessary, receive an intravenous infusion of normal saline. A transient hypotensive response is not a contraindication to further doses which usually can be given without difficulty once the blood pressure has increased after volume expansion.

Neutropenia/Agranulocytosis

Agranulocytosis and bone marrow depression have been caused by angiotensin converting enzyme inhibitors. Several cases of agranulocytosis and neutropenia have been reported in which a causal relationship to enalapril cannot be excluded. Current experience with the drug shows the incidence to be rare. Periodic monitoring of white blood cell counts should be considered, especially in patients with collagen vascular disease and renal disease.

PRECAUTIONS

Impaired Renal Function

VASOTEC* (enalapril maleate) should be used with caution in patients with renal insufficiency as they may require reduced or less frequent doses (see DOSAGE AND ADMINISTRATION). Close monitoring of renal function during therapy should be performed as deemed appropriate in those with renal insufficiency. In the majority, renal function will not alter, or may improve.

Renal failure has been reported in association with VASOTEC*, mainly in patients with severe congestive heart failure or underlying renal disease, including renal artery stenosis. If recognized promptly and treated appropriately, renal failure, when associated with VASOTEC* therapy, is usually reversible.

Some hypertensive patients, with no apparent pre-existing renal disease, have developed increases in blood urea and creatinine when VASOTEC* has been given concurrently with a diuretic. Dosage reduction of VASOTEC* and/or discontinuation of the diuretic may be required.

Renal function should be assessed before initiating therapy with VASOTEC*.

Hyperkalemia

Elevated serum potassium (greater than 5.7 mEq/L) was observed in approximately one percent of hypertensive patients in clinical trials. In most cases these were isolated values which resolved despite continued therapy. Hyperkalemia was a cause of discontinuation of therapy in 0.28% of hypertensive patients. Risk factors for the development of hyperkalemia may include renal insufficiency, diabetes mellitus, and the concomitant use of agents to treat hypokalemia (see ADVERSE REACTIONS).

Valvular Stenosis

There is concern on theoretical grounds that patients with aortic stenosis might be at particular risk of decreased coronary perfusion when treated with vasodilators because they do not develop as much afterload reduction.

Surgery/Anesthesia

In patients undergoing major surgery or during anesthesia with agents that produce hypotension, enalapril blocks angiotensin II formation, secondary to compensatory renin release. If hypotension occurs and is considered to be due to this mechanism, it can be corrected by volume expansion.

Patients with Impaired Liver Function

There are no adequate studies in patients with cirrhosis or other liver dysfunction. Enalapril is a pro-drug metabolized in the liver to its active moiety. Particular caution and close monitoring of response and metabolic effects should therefore apply to such patients.

Pregnancy

Maternal and fetal toxicity occurred in some rabbits at doses of 1 mg/kg/day or more. Saline supplementation prevented the maternal and fetal toxicity seen at doses of 3 and 10 mg/kg/day, but not at 30 mg/kg/day (50 times the maximum human dose). Enalapril was not teratogenic in rabbits.

There was no fetotoxicity or teratogenicity in rats treated with up to 200 mg/kg/day of enalapril (333 times the maximum human dose). Fetotoxicity expressed as a decrease in average fetal weight, occurred in rats given 1200 mg/kg/day of enalapril, but did not occur when these animals were supplemented with saline. The drug crosses the placental barrier in rats and hamsters.

There are no studies in pregnant women. VASOTEC* should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers

In rats, it has been shown that enalapril is excreted in milk.

It is not known whether this drug is excreted in human milk. Caution should be exercised when enalapril is administered to a nursing mother and in general, nursing should be interrupted.

Pediatric Use

VASOTEC* has not been studied in children and therefore, use in this age group is not recommended.

Drug Interactions

Hypotension - Patients on Diuretic Therapy: Patients on diuretics and especially those in whom diuretic therapy was recently instituted, may occasionally experience an excessive reduction of blood pressure after initiation of therapy with enalapril. The possibility of hypotensive effects with enalapril can be minimized by either discontinuing the diuretic or increasing the salt intake prior to initiation of treatment with enalapril (see WARNINGS, and DOSAGE AND ADMINISTRATION).

Agents Increasing Serum Potassium: Since enalapril decreases aldosterone production, elevation of serum potassium may occur. Potassium sparing diuretics such as spironolactone, triamterene or amiloride, or potassium supplements should be given only for documented hypokalemia and with caution since they may lead to a significant increase in serum potassium.

Agents Causing Renin Release: The antihypertensive effect of VASOTEC* is augmented by antihypertensive agents that cause renin release (e.g. diuretics).

Agents Affecting Sympathetic Activity: Agents affecting sympathetic activity (e.g., ganglionic blocking agents or adrenergic neuron blocking agents) may be used with caution. Beta-adrenergic blocking drugs add some further antihypertensive effect to enalapril.

ADVERSE REACTIONS

In controlled clinical trials involving 2314 hypertensive patients and 363 patients with congestive heart failure, the most severe adverse reactions were: angioedema (0.2%), hypotension (2.3%) and renal failure (5 cases).

In hypertensive patients, hypotension occurred in 0.9% and syncope in 0.5%, with a discontinuation rate of 0.1%.

In congestive heart failure patients, hypotension occurred in 4.4% and syncope 0.8%, with a discontinuation rate of 2.5%.

The most frequent clinical adverse reactions in controlled clinical trials were: headache (4.8%), dizziness (4.6%) and fatigue (2.8%). Discontinuation of therapy was required in 6.0% of the 2677 patients.

Adverse reactions occurring in patients treated with VASOTEC* (enalapril maleate) in controlled clinical trials are shown below.

	HYPERTENSION (2314 PATIENTS)	CONGESTIVE HEART FAILURE (363 PATIENTS)
CARDIOVASCULAR		
Hypotension	0.9%	4.4%
Chest Pain	0.9%	1.7%
Palpitations	0.6%	0.3%
GASTROINTESTINAL		
Nausea	1.4%	1.1%
Vomiting	0.8%	1.7%
Dysphagia	0.1%	—
Diarrhea	1.4%	3.0%
Abdominal Pain	0.7%	1.4%
RENAL		
Renal Failure	0.1%	0.6%
Oliguria	1 case	—
Proteinuria†	0.1%	-
DERMATOLOGIC		
Rash	1.4%	1.9%
Pruritus	0.4%	1.4%
NERVOUS SYSTEM		
Headache	5.2%	2.2%
Dizziness	4.3%	6.6%
Insomnia	0.5%	0.3%
Nervousness	0.6%	-
Somnolence	0.6%	-
Paresthesia	0.6%	-
ALLERGIC		
Cough	1.3%	1.4%
Angioedema	0.2%	-
HEMATOLOGIC		
Anemia	0.1%	-
Leukopenia	1 case	-
MISCELLANEOUS		
Muscle Cramps	0.6%	0.3%
Dyspnea	0.6%	1.1%
Hyperhidrosis	0.7%	-
Impotence	0.4%	0.3%
Fatigue	3.0%	1.4%
Taste Disturbance	0.4%	0.3%

† Defined as >1 g/24h or >0.5 g/12h on two consecutive measurements, at least one month apart.

ABNORMAL LABORATORY FINDINGS

Hyperkalemia: (see PRECAUTIONS)

Creatinine, Blood Urea Nitrogen: Increases in serum creatinine and BUN were reported in about 20% of patients with renovascular hypertension and in about 0.2% of patients with essential hypertension treated with VASOTEC* alone.

In patients with congestive heart failure, who were also receiving diuretics and/or digitalis, increases in BUN and serum creatinine, usually reversible upon discontinuation of VASOTEC* and/or concomitant therapy, were observed in about 9.7% of patients.

Hemoglobin and Hematocrit: Decreases in hemoglobin and hematocrit (mean approximately 0.34 g% and 1.0 vol% respectively) occurred frequently in either hypertensive or congestive heart failure patients; less than 0.1% of patients discontinued therapy due to anemia.

Others: Rarely, elevations of liver enzymes and/or serum bilirubin occurred.

ADVERSE REACTIONS REPORTED IN UNCONTROLLED TRIALS AND/OR MARKETING EXPERIENCE

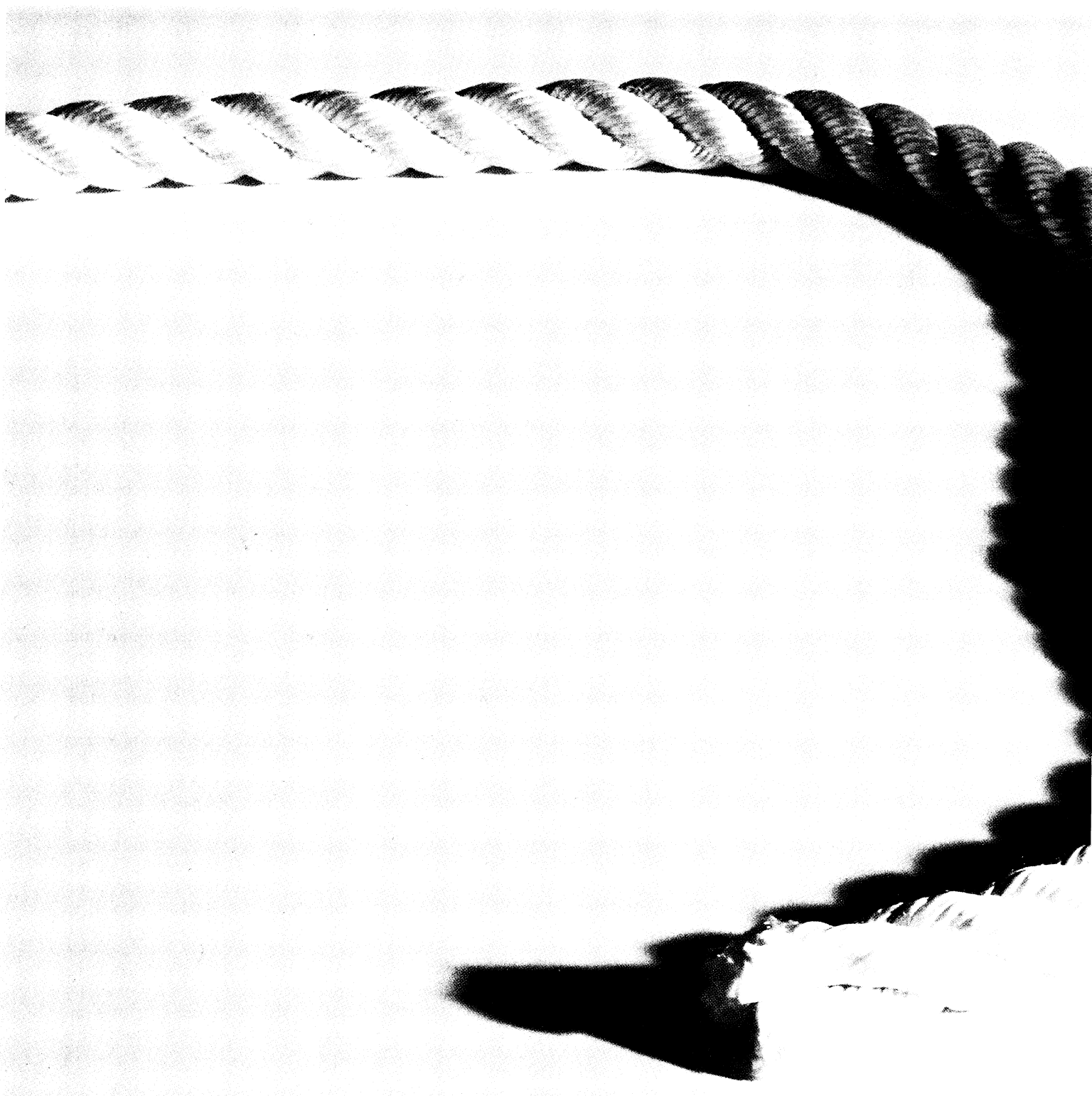
The following occurred in an incidence of 0.5 to 1.0%: insomnia, impotence, renal dysfunction, renal failure and oliguria.

Rare cases of neutropenia, thrombocytopenia, bone marrow depression and deafness have been reported.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

Limited data are available with regard to overdosage in humans. The most likely manifestation of overdosage would be hypotension, which can be treated, if necessary, by intravenous infusion of normal saline solution.

Enalaprilat may be removed from the general circulation by hemodialysis.



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Product Monograph available upon request. [1]Ryrfeldt A, et al Europ Jrnl of Respir Dis Suppl No. 122, Vol 63 1982. [2]Adelroth E, Allergy 1985; 40:58-64. [3]Stiksa G. Respiration, 48:91-93 (1985). [4]Laursen Eur J Respir Dis 1986; 68:19-28. [5]Johansson S-A, Eur J Clin Pharmacol (1982) 22:523-529.

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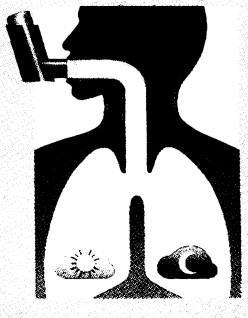

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When used promptly, ZOVIRAX interferes with viral replication[1] and helps to preempt lesion development. A prescription for ZOVIRAX Ointment 5% makes certain it's available for patients to use at the earliest onset of symptoms.

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(acyclovir)

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† ZOVIRAX Ointment 5% is indicated for limited, non-life-threatening mucocutaneous herpes infections in immunocompromised patients.

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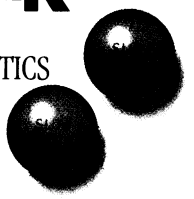

Intermediate Prescribing Information

Pr Slow-K®

(slow-release potassium chloride)

Potassium supplement

Indications

Hypokalemia with metabolic alkalosis, digitalis intoxication. Prevention of potassium depletion when dietary intake is insufficient in patients on digitalis and diuretics for the treatment of congestive heart failure, hepatic cirrhosis with ascites, selected patients on long-term diuretic therapy, hyperaldosteronism states with normal renal function, the nephrotic syndrome, certain diarrheal states.

Contraindications

Renal impairment with oliguria or azotemia, untreated Addison's disease, hyperadrenalism associated with adrenogenital syndrome, extensive tissue breakdown as in severe burns, acute dehydration, heat cramps, adynamia episodica hereditaria, hyperkalemia of any etiology, certain cardiac patients with esophageal compression due to an enlarged left atrium, dysphagia. Cause for arrest or delay in tablet passage through the gastrointestinal tract (liquid potassium should be given in such cases).

Warnings

In patients with impaired mechanisms for excreting potassium, eg. chronic renal disease, careful monitoring of serum potassium and dosage adjustment can prevent hyperkalemia and cardiac arrest. Do not treat hypokalemia with potassium salts and a potassium-sparing diuretic concomitantly, since severe hyperkalemia may result. Use an alkalinizing potassium salt such as potassium acetate, potassium bicarbonate, or potassium citrate in hypokalemia with metabolic acidosis.

A probable association exists between the use of coated tablets containing potassium salts, with or without thiazide diuretics, and the incidence of serious small bowel ulceration. Such preparations should be used only when adequate dietary supplementation is not practical, and should be discontinued if abdominal pain, distention, nausea, vomiting or gastrointestinal bleeding occurs. SLOW-K is a wax matrix tablet formulated to provide a controlled rate of release of potassium chloride and thus to minimize the possibility of a high local concentration of potassium near the bowel wall. While the reported frequency of small bowel lesions is very much less with wax matrix tablets (less than one per 100,000 patient years) than with enteric-coated potassium chloride tablets (40-50 per 100,000 patient years), a few cases associated with wax matrix tablets have been reported. Discontinue immediately and consider the possibility of bowel obstruction or perforation if severe vomiting, abdominal pain, distention or gastrointestinal bleeding occurs.

Precautions

The treatment of potassium depletion, particularly in the presence of cardiac disease, renal disease or acidosis, requires careful attention to acid-base balance and appropriate monitoring of serum electrolytes, the electrocardiogram and the clinical status of the patient.

Use with caution in diseases associated with heart block since increased serum potassium may increase the degree of block.

Adverse Reactions

Small bowel lesions: *the incidence is much lower than that reported for enteric-coated potassium chloride tablets (See WARNINGS).*

Most common: *nausea, vomiting, abdominal discomfort, and diarrhea; best avoided by increasing fluid intake when possible, taking the dose with meals or reducing the dose.*

Most severe: *hyperkalemia (See WARNINGS), esophageal and gastrointestinal obstruction, bleeding or perforation (See WARNINGS).*

Symptoms and Treatment of Overdosage

Symptoms: *especially where excretory mechanisms are impaired or if potassium is administered too rapidly intravenously, potentially fatal hyperkalemia can result (See CONTRAINDICATIONS and WARNINGS), which is usually asymptomatic and may be manifested only by an increased serum potassium concentration and characteristic electrocardiographic changes (peaking of T-waves, loss of P-wave, depression of S-T segment, and prolongation of the QT interval). Late manifestations include muscle paralysis and cardiovascular collapse from cardiac arrest. Discontinue SLOW-K immediately.*

Treatment: *(1) elimination of foods and medications containing potassium and potassium-sparing diuretics; (2) I.V. administration of 300 to 500 ml/hr of 10% dextrose solution containing 10-20 units of insulin per 1,000 ml; (3) correction of acidosis, if present, with intravenous sodium bicarbonate; (4) use of exchange resins, hemodialysis, or peritoneal dialysis; (5) calcium gluconate. In patients stabilized on digitalis, too rapid a lowering of the serum potassium concentration can produce digitalis toxicity.*

Dosage and Administration

Usual dietary intake of potassium by the average adult is 40 to 80 mEq per day. Potassium depletion sufficient to cause hypokalemia usually requires the loss of 200 or more mEq of potassium from the total body store.

Prevention of hypokalemia: *usual dosage 20 mEq daily.*

Treatment of depletion: *usual dosage 40-100 mEq daily.*

Usual dosage range: *2-6 tablets daily, preferably after meals. Do not exceed 12 tablets daily.*

Availability

SLOW-K: Pale-orange, sugar-coated tablets branded SLOW K in black ink. Each tablet contains 600 mg of potassium chloride (equivalent to 8 mEq K+) in a slow-release wax matrix core.

Product monograph available on request.

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C I B A
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Immunotherapy

The role of immunotherapy in allergic disease has been debated for many years.[9] Most investigators believe that immunotherapy acts by inducing a specific IgG antibody response to allergen. This IgG antibody can then bind to the allergen before it can interact with IgE, thereby abrogating the allergic response. Some recent evidence has suggested that immunotherapy may also alter the late response after allergic challenge of both the nose and lung.[10] This may be an important mechanism by which immunotherapy may alter the allergic response.

We do know that patients with allergic rhinitis respond well to immunotherapy for seasonal pollenosis. The data in asthma are less substantial, but there is increasing evidence that immunotherapy will alter bronchial reactivity and modulate the immune response in the bronchi.

Recent changes in immunotherapy have included the advent of modified vaccines. These vaccines have altered allergenicity, but maintain immunogenicity. They elicit an IgG-blocking antibody response, but minimize the danger of an acute allergic reaction. The only such agent currently available is a glutaraldehyde modified vaccine for both grass and ragweed. The future likely will bring a host of other modified vaccines that should demonstrate clinical efficacy with a diminished incidence of adverse reactions. The future of immunotherapy as a modulator of the immune response seems bright.

Conclusions

Our understanding of allergic disease has changed considerably during the last few years. We now understand that there is a late phase to the IgE-mediated reaction that involves a significant inflammatory component. Based on this information, allergic disease must be considered an inflammatory disease, and the approach to diagnosis and treatment should reflect these newer concepts.

From a diagnostic point of view, it has become clear that skin testing is the best technique to diagnose allergic disease. Therapeutically, anti-inflammatory agents must be considered first-line therapy in the treatment of allergic disease. Therefore, such drugs as corticosteroids and cromoglycates should be primary, rather than secondary, therapies. The role of immunotherapy has also changed over the years, and a resurgence in interest is anticipated, with the idea that one can modulate the late-phase reaction by means of allergy injections. Our concepts of allergic disease are changing rapidly, and further changes may supplant those described in this article. ■

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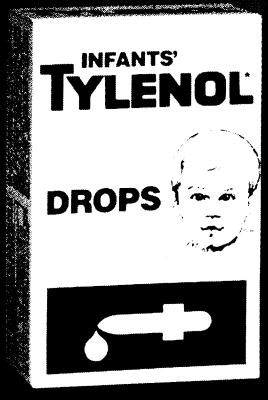

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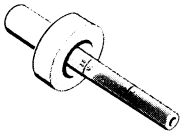

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In seasonal allergic rhinitis

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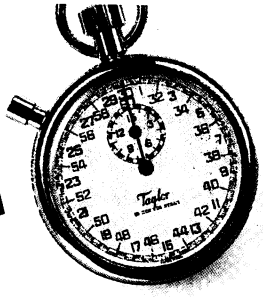

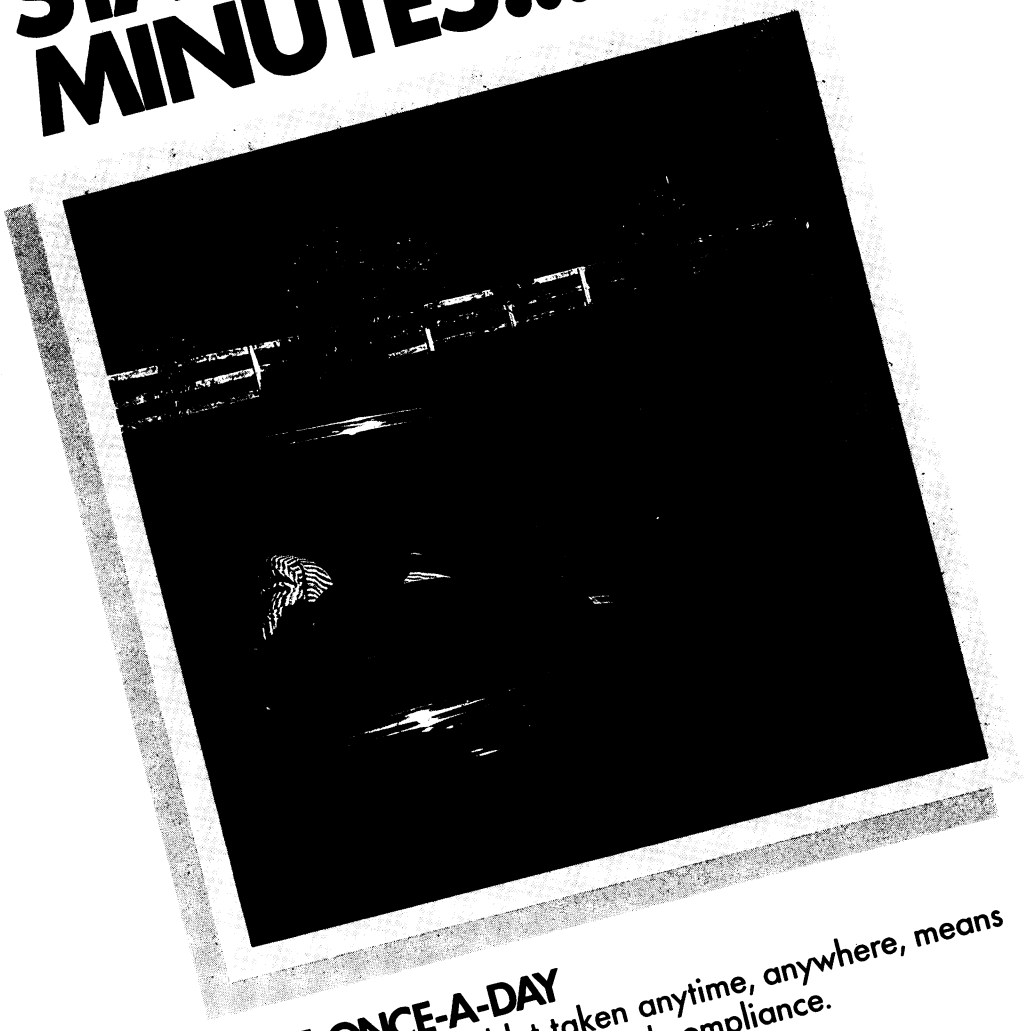

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ACTIONS:
Acetaminophen is an analgesic and anti-pyretic.

INDICATIONS:
TYLENOL* acetaminophen is indicated for the relief of pain and fever. Also as an analgesic-antipyretic in the symptomatic treatment of colds.

CONTRAINDICATIONS:
Hypersensitivity to acetaminophen.

ADVERSE EFFECTS:
In contrast to salicylates, gastrointestinal irritation rarely occurs with acetaminophen. If a rare hypersensitivity reaction occurs, discontinue the drug. Hypersensitivity is manifested by rash or urticaria. Regular use of acetaminophen has shown to produce a slight increase in prothrombin time in patients receiving oral anticoagulants, but the clinical significance of this effect is not clear.

PRECAUTIONS AND TREATMENT OF OVERDOSE:
The majority of patients who have ingested an overdose large enough to cause hepatic toxicity have early symptoms. However, since there are exceptions, in cases of suspected acetaminophen overdose, begin specific antidotal therapy as soon as possible. Maintain supportive treatment throughout management of overdose as indicated by the results of acetaminophen plasma levels, liver function tests and other clinical laboratory tests.

N-acetylcysteine as an antidote for acetaminophen overdose is recommended and is available in oral and parenteral dosage forms. More detailed information on the treatment of acetaminophen overdose with N-acetylcysteine in its oral and parenteral dosage forms is available from the manufacturers (Mucomyst, Bristol-Myers Canada Inc., and Airbron and Parvolex, Glaxo Canada Ltd., trademarks for their brands of N-acetylcysteine) or contact your nearest Poison Control/Information Centre.

DOSAGE:
Children:
Based on Weight
10-15 mg/kg every 4 to 6 hours, not to exceed 65 mg/kg in 24 hours.

SUPPLIED:
TYLENOL* Drops: Each 1.0 mL contains 80 mg acetaminophen in an orange-coloured, non-alcoholic liquid vehicle with a new improved, fruit-flavoured taste. Available in bottles containing 15 mL† and 24 mL† and a calibrated dropper.
‡sweetened with sodium cyclamate and sorbitol

TYLENOL* Elixir: Each 5 mL contains 160 mg acetaminophen in a cherry-flavoured, non-alcoholic red liquid vehicle. Available in bottles containing 100 mL † and 500 mL.

TYLENOL* Chewable Tablets 80 mg: Each round, pink tablet, scored one side and engraved "TYLENOL" the other side, contains 80 mg acetaminophen. Available in bottles of 24† tablets.

TYLENOL* Junior Strength Caplets 160 mg: Each white caplet, scored on one side and engraved "TYLENOL 160" the other side, contains 160 mg acetaminophen. Available in blister packs of 20†.
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more aware of some of the roadblocks to implementing manoeuvres of newly proven effectiveness and have begun to explore strategies to overcome these roadblocks.

There is much to be accomplished, however. Many important conditions have insufficient evidence to determine whether they do more good than harm. Family medicine can lead the evaluation of the effectiveness of such conditions. Similarly, family physicians can significantly contribute to the understanding of ways to improve prevention and early detection and to enhance patient compliance.

Perhaps a more specific challenge lies ahead for each family physician. Current evidence suggests we can improve the care we provide our patients in prevention and early detection. We have an obligation to take stock of the situation in our own practices. Are we current in our knowledge of which actions are effective and which are not? Do we know whether we are successfully implementing proven recommendations and reaching a high percentage of patients who will benefit from such care? And have we organized our practices in ways that might enhance the provision of such care?

Over the next 10 years, a major part of the challenge in prevention, early detection, and health promotion is ours to address as individual family physicians, and collectively, as a discipline. We can provide leadership and expertise in confronting these important issues. ■

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MEDIPREN*

ibuprofen tablets USP

200 mg CAPLETS/TABLETS

ANALGESIC, ANTIPYRETIC AGENT

CLINICAL PHARMACOLOGY: Ibuprofen is a member of the class of agents commonly known as non-steroidal anti-inflammatory drugs (NSAID). Consistent with this classification, ibuprofen exhibits anti-inflammatory activity at higher dosage ranges. At lower single doses relevant to a 200 mg dosage strength (200 mg to 400 mg) ibuprofen relieves pain of mild to moderate intensity and reduces fever. Analagous to acetylsalicylic acid, the prototype of this class, this analgesic/antipyretic activity of ibuprofen occurs at lower doses than necessary for anti-inflammatory effects which are thought to require sustained administration of higher individual doses. Ibuprofen is rapidly absorbed after oral administration, with peak serum or plasma levels generally appearing within 1½ to 2 hours. Oral absorption is estimated to be 80% of the dose. Both the rate of absorption and peak plasma concentrations are reduced when the drug is taken with food, but, bioavailability as measured by total area under the concentration-time curve is minimally altered. Ibuprofen has an elimination half-life of approximately two hours. It is rapidly metabolized through oxidation and glucuronic acid conjugation with urinary excretion of the inactive metabolites usually complete within 24 hours. Less than 10% is excreted unchanged in the urine.

Studies demonstrate no significant alterations in ibuprofen pharmacokinetics in the elderly. Ibuprofen pharmacokinetics has also been studied in patients with alcoholic liver disease who have been assessed to have fair to poor hepatic function. Results suggest that despite the liver being the primary organ of metabolism of ibuprofen, its kinetic parameters are not substantially altered by this condition.

The basic mechanism of the pharmacological actions of ibuprofen, like other NSAID's, has not been precisely determined. It is generally thought to be related to the inhibition of prostaglandin synthesis.

INDICATIONS AND CLINICAL USE: MEDIPREN* 200 mg (ibuprofen) is indicated for the temporary relief of headaches, minor aches and pains in muscles, bones and joints such as the pain of arthritis, sprains or strains, backache, dysmenorrhea, the aches and fever due to the common cold, dental pain, and for reduction of fever.

CONTRAINDICATIONS: MEDIPREN* (ibuprofen) should not be used in patients who have previously exhibited hypersensitivity to it or in individuals who are known to have a sensitivity manifested as asthma, bronchospasm, hypotension, angioedema, laryngeal edema, swelling, shock or urticaria to acetylsalicylic acid or other non-steroidal anti-inflammatory drugs.

MEDIPREN* ibuprofen should not be used during pregnancy, in nursing mothers or in paediatric patients because its safety under these conditions has not been established.

MEDIPREN* ibuprofen is contraindicated in patients with Systemic Lupus Erythematosus as an anaphylaxis like reaction with fever may occur, particularly when ibuprofen has been administered previously. Aseptic meningitis has also been reported.

MEDIPREN* ibuprofen should not be used in patients with acute peptic ulcer or gastrointestinal bleeding.

WARNINGS: Anaphylactoid reactions have occurred after administration of ibuprofen to patients with known acetylsalicylic acid or other NSAID sensitivity manifested as asthma, swelling, shock or hives.

Gastrointestinal side effects to ibuprofen have been reported including dyspepsia, heartburn, nausea, vomiting, anorexia, diarrhea, constipation, stomatitis, flatulence, bloating, epigastric pain, abdominal pain, and peptic ulcer with GI bleeding or perforation which could have a fatal outcome.

MEDIPREN* ibuprofen should therefore be given only under close supervision to patients with a history of upper gastrointestinal tract disease.

PRECAUTIONS: Occasionally serious gastrointestinal side effects have been associated with the anti-inflammatory uses of ibuprofen (see Warnings). Minor gastrointestinal complaints have also been reported during the clinical use of ibuprofen at analgesic doses. Therefore, if occasional and mild heartburn, upset stomach or stomach pain were to occur with its use, the administration of MEDIPREN* with food or milk is recommended. Patients should be advised to seek the consultation of a physician if gastrointestinal side effects occur, persist or appear to worsen.

MEDIPREN* ibuprofen, like other nonsteroidal anti-inflammatory agents, can inhibit platelet aggregation but the effect is quantitatively less than that seen with acetylsalicylic acid. Ibuprofen has been shown to prolong bleeding time (but within the normal range) in normal subjects. Because this prolonged bleeding effect may be exaggerated in patients with underlying haemostatis defects, MEDIPREN* ibuprofen should be avoided by persons with intrinsic coagulation defects and by those on anticoagulant therapy.

Tinnitus, blurred and/or diminished vision, scotoma, and/or changes in colour vision have been reported. If a patient develops such complaints while taking MEDIPREN*, the drug should be discontinued. Patients with any visual disturbances should have an ophthalmologic examination.

Advanced age, hypertension use of diuretics, diabetes, atherosclerotic cardiovascular disease, chronic renal failure, cirrhosis and conditions which may be associated with dehydration appear to increase the risk of renal toxicity. MEDIPREN* should therefore be used with caution when these risk factors are present.

Patients taking MEDIPREN* should be cautioned to report to their physician signs or symptoms of GI ulceration or bleeding, blurred vision or other ocular symptoms, skin rash, tinnitus, dizziness, weight gain, edema, or respiratory difficulties.

If MEDIPREN* is taken in conjunction with prolonged corticosteroid therapy and it is decided to discontinue this therapy, the corticosteroid should be tapered slowly to avoid exacerbation of disease or adrenal insufficiency.

Particular caution should be observed in elderly patients taking MEDIPREN* ibuprofen, as they are more likely to be taking other medications or have pre-existing disease states which can increase the likelihood of the complications that have been associated with ibuprofen. Elderly patients appear to be more susceptible to the central nervous system disease reactions; cognitive dysfunction (forgetfulness, inability to concentrate, a feeling of separation from the surroundings) in such patients has been reported.

Use in Obstetrics: No evidence specifically identifies exposure to analgesic doses of ibuprofen as a cause of harm to either mother or fetus during pregnancy. Non-steroidal anti-inflammatory drugs in general, however, are known to affect the action of prostaglandin synthetase which could alter a variety of the physiological functions of prostaglandins or platelets during delivery such as facilitating uterine contraction in the mother, closure of the ductus arteriosus in the fetus, and platelet-related haemostasis. Patients should therefore be advised not to use MEDIPREN* during pregnancy without the advice of a physician, particularly during the last trimester. Clinical information is limited on the effects of ibuprofen in pregnancy.

Use in Nursing Mothers: Pharmacokinetic studies indicated that following oral administration of ibuprofen 400 mg the level of drug which appeared in breast milk was below detection levels of 1 mcg/mL. The amount of ibuprofen to which an infant would be exposed through this source was considered negligible. However, since the absolute safety of ibuprofen ingested under these circumstances has not been determined, nursing mothers should be advised to consult a physician before using MEDIPREN*

Patients with Special Diseases and Conditions: Several medical conditions which can predispose patients to the adverse effects of non-steroidal anti-inflammatory drugs in general may be applicable to ibuprofen.

MEDIPREN* should be used with caution in patients with a history of cardiac failure or kidney disease because of the possibility of aggravating pre-existing states of fluid-retention and edema. Mild impairment of renal function (decreased renal blood flow or glomerular filtration rate) can occur at maximal doses of ibuprofen. Renal papillary necrosis has been reported. Also, patients with underlying medical or pharmacologically-induced hemostatic defects could experience further prolongation of bleeding time through the inhibition of platelet aggregation induced to varying degrees by this class of drugs.

Long term ingestion of combinations of analgesics has been associated with the condition analgesic nephropathy. It is therefore appropriate that patients be discouraged from long-term unsupervised consumption of analgesics, particularly in combination. Patients should therefore be directed to consult a physician if their underlying condition requires administration of MEDIPREN* for more than 5 days, nor should MEDIPREN* usually be administered along with acetaminophen or acetylsalicylic acid.

A general precaution seems appropriate for patients with any serious medical condition to consult a physician before using MEDIPREN* as an analgesic or antipyretic.

DRUG INTERACTIONS: The platelet inhibiting effects of ibuprofen, although less potent and of shorter duration than those induced by acetylsalicylic acid, warrant cautionary supervision by a physician before co-administration of MEDIPREN* and anticoagulants.

Coumarin Type Anticoagulants – Several short-term controlled studies failed to show that ibuprofen significantly affected prothrombin time or a variety of other clotting factors when administered to individuals on coumarin-type anticoagulants. However, bleeding has been reported when ibuprofen and other NSAI agents have been administered to patients on coumarin-type anticoagulants. The use of MEDIPREN* in patients who are taking anticoagulants should therefore be avoided because of the possibility of enhanced GI bleeding or an additives effect due to ibuprofen's reversible antiplatelet action.

Acetylsalicylic Acid – Animal studies show that ASA given with NSAI agents, including ibuprofen, yields a net decrease in anti-inflammatory activity with lowered blood levels of the non-ASA drug. Single dose bioavailability studies in normal volunteers have failed to show an effect of ASA on ibuprofen blood levels. Correlative clinical studies have not been done.

Other Anti-inflammatory Agents (NSAID) – The addition of MEDIPREN* to a pre-existent prescribed NSAID regimen in patients with a condition such as rheumatoid arthritis may result in increased risk of adverse effects.

Diuretics – Ibuprofen, because of its fluid retention properties, can decrease the diuretic and antihypertensive effects of diuretics, and increased diuretic dosage may be needed. Patients with impaired renal function taking potassium-sparing diuretics who develop ibuprofen-induced renal insufficiency might be in serious danger of fatal hyperkalemia.

Acetaminophen – Although interactions have not been reported, concurrent use with MEDIPREN* is not advisable.

Other Drugs – Although ibuprofen binds to a significant extent to plasma proteins, interactions with other protein-bound drugs occur uncommonly. Nevertheless, caution should be observed when other drugs also having a high affinity for protein binding sites are used concurrently. Some observations have suggested a potential for ibuprofen to interact with digoxin, phenytoin and lithium salts. However, the mechanisms and clinical significance of these observations are presently not known.

A general precaution is appropriate for patients to assure the compatibility of MEDIPREN* with their other prescribed medications through consultation with a physician.

ADVERSE REACTIONS: Experience reported with prescription use of ibuprofen has included the following adverse reactions. *Note:* Reactions listed below under Causal Relationship Unknown are those where a causal relationship could not be established; however, in these rarely reported events, the possibility of a relationship to ibuprofen also cannot be excluded.

Gastrointestinal: The adverse reactions most frequently seen with ibuprofen therapy involve the gastrointestinal system.

Incidence 3 to 9%: nausea, epigastric pain, heartburn. Incidence 1 to 3%: diarrhea, abdominal distress, nausea and vomiting, indigestion, constipation, abdominal cramps and pain, fullness of the gastrointestinal tract (bloating or flatulence). Incidence less than 1%: gastric or duodenal ulcer with bleeding and/or perforation, gastrointestinal hemorrhage, melena, hepatitis, jaundice, abnormal liver function (SGOT, serum bilirubin and alkaline phosphatase). The generally modest elevations of serum transaminase activity that has been observed are usually without clinical sequelae but severe, potentially fatal toxic hepatitis can occur.

Central Nervous System: Incidence 3 to 9%: dizziness. Incidence 1 to 3%: headache, nervousness. Incidence less than 1%: depression, insomnia. The causal relationship is unknown but paresthesias, hallucinations, dream abnormalities have been reported.

Aseptic meningitis has been reported in patients with systemic lupus erythematosus or other connective tissue disease. Aseptic meningitis and meningioencephalitis, in one case accompanied by eosinophilia, in the cerebrospinal fluids, has been reported in patients who took ibuprofen intermittently and did not have any connective tissue disease. Cognitive dysfunction has been observed in elderly patients who took ibuprofen.

Dermatologic: Incidence 3 to 9%: rash (including maculopapular type). Incidence 1 to 3%: pruritis. Incidence less than 1%: vesiculobullous eruptions, urticaria, erythema multiforme. The causal relationship is unknown but alopecia, Stevens-Johnson Syndrome have been reported.

Special Senses: Incidence 1 to 3%: tinnitus. Incidence less than 1%: amblyopia (blurred and/or diminished vision, scotomata and/or changes in colour vision). Any patient with eye complaints during ibuprofen therapy should have an ophthalmological examination. The causal relationship is unknown but conjunctivitis, diplopia, optic neuritis have been reported.

Metabolic: Incidence 1 to 3%: decreased appetite, edema, fluid retention. Fluid retention generally responds promptly to drug discontinuation.

Hematologic: Incidence less than 1%: leukopenia and decreases in hemoglobin and hematocrit. The causal relationship is unknown but rare cases of hemolytic anemia, thrombocytopenia, granulocytopenia, bleeding episodes (e.g. purpura, epistaxis, hematuria, menorrhagia) have been reported in conjunction with ibuprofen administration. Autoimmune haematologic anemia occurred in one patient taking 400 mg of ibuprofen three times a day for ten days. Fatal aplastic anaemia was reported in one patient who took 600 mg per day for eight months.

Cardiovascular: Incidence less than 1%: congestive heart failure in patients with marginal cardiac function, elevated blood pressure. Conditions such as congestive heart failure and hypertension may be aggrevated by sodium retention and edema caused by ibuprofen in such patients. The causal relationship is unknown but rare cases of arrhythmias (sinus tachycardia, sinus bradycardia, palpitations) have been reported.

Allergic: Incidence less than 1%: anaphylaxis (see CONTRAINDICATIONS). The causal relationship is unknown but fever, serum sickness, lupus erythematosus syndrome have been rarely reported in connection with ibuprofen administration.

Endocrine: Rare cases of gynecomastia, hypoglycemic reaction have been reported with ibuprofen administration. Menstrual delays of up to two weeks and dysfunctional uterine bleeding occurred in nine patients taking ibuprofen 400 mg three times a day for three days before menses.

Renal: The causal relationship is unknown but decreased creatinine clearance, polyuria, azotemia have been reported in conjunction with ibuprofen administration. Like other non-steroidal anti-inflammatory agents, ibuprofen inhibits renal prostaglandin synthesis which may decrease renal function and cause sodium retention. Renal blood flow glomerular filtration rate decreased in patients with mild impairment of renal functions who took 1200 mg/day of ibuprofen for one week. Renal papillary necrosis has been reported. A number of factors appear to increase the risk of renal toxicity (see PRECAUTIONS).

SYMPTOMS AND TREATMENT OF OVERDOSE: Clinical Features: A clear pattern of clinical features associated with accidental or intentional overdose of ibuprofen has not been established. Reported cases of overdose have often been complicated by co-ingestions or additional suicidal gestures. The range of symptoms observed has included nausea, vomiting, abdominal pain, drowsiness, nystagmus diplopia, headache, tinnitus, impaired renal function, coma and hypotension. A review of four fatalities associated with ibuprofen overdose indicates other contributing factors co-existed so it would be difficult to identify the toxicity of ibuprofen as a specific cause of death.

Post-ingestion blood levels may be useful to confirm a diagnosis and to quantify the degree of exposure but otherwise have not been helpful in predicting clinical outcome. Generally, full recovery can be expected with appropriate symptomatic management.

The following cases of overdose have been reported. A 19 month old child, 1½ hours after the ingestion of seven to ten 400 mg tablets of ibuprofen presented apnea, cyanosis and responded only to painful stimuli. After treatment with O_2, $NaHCO_3$, infusion of dextrose and normal saline, the child was responsive and 12 hours after ingestion appeared completely recovered. Blood levels of ibuprofen reached 102.9 mcg/mL, 8½ hours after the accident. Two other children weighing approx. 10 kg, had taken an estimated 120 mg/kg. There were no signs of acute intoxication or late sequelae. In one child the ibuprofen blood level at 90 minutes after ingestion was approx. 700 mcg/mL. A nineteen year old male who had ingested 8000 mg of ibuprofen reported dizziness and nystagmus was noted. He recovered with no reported sequelae after parenteral hydration and 3 days of bed rest.

Management of Overdose: General measures to reduce absorption such as gastric lavage, administration of activated charcoal or ipecac-induced emesis are appropriate particularly within one to four hours of ingestion. Routine symptomatic and supportive treatment is then recommended as follow-up.

DOSAGE AND ADMINISTRATION: Mild to moderate pain or fever.

Adults: MEDIPREN* 200 mg - 400 mg (1 - 2 tablets/caplets) as required every 4 to 6 hours, not to exceed 6 tablets/caplets in 24 hours unless directed by a physician.

Children: Clinical experience with ibuprofen to date is insufficient for labelling MEDIPREN* for use in children under 12 years of age.

Do not take for pain for more than 5 consecutive days or fever for more than 3 days unless directed by a physician. If the painful area is red or swollen, if condition deteriorates or new symptoms occur, consult a physician.

Availability: MEDIPREN* ibuprofen is available as white, 200 mg, film-coated tablets and caplets in bottles of 24, 50 and 100.

A Product Monograph is available upon request.

References:

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1. 10-year lipid Research Clinics Study-Coronary Primary Prevention Trial. JAMA 1984; 251: 385-374. 2. A Multicenter Comparison of Lovastatin and Cholestyramine Therapy for Severe Primary Hypercholesterolemia. JAMA, July 15, 1988. 3. National Cholesterol Education Program, coordinated by the National Heart, Lung and Blood Institute. NIH publication No. 88-2926, November 1987. *TM Authorized User. For complete prescribing information, see page **1943**

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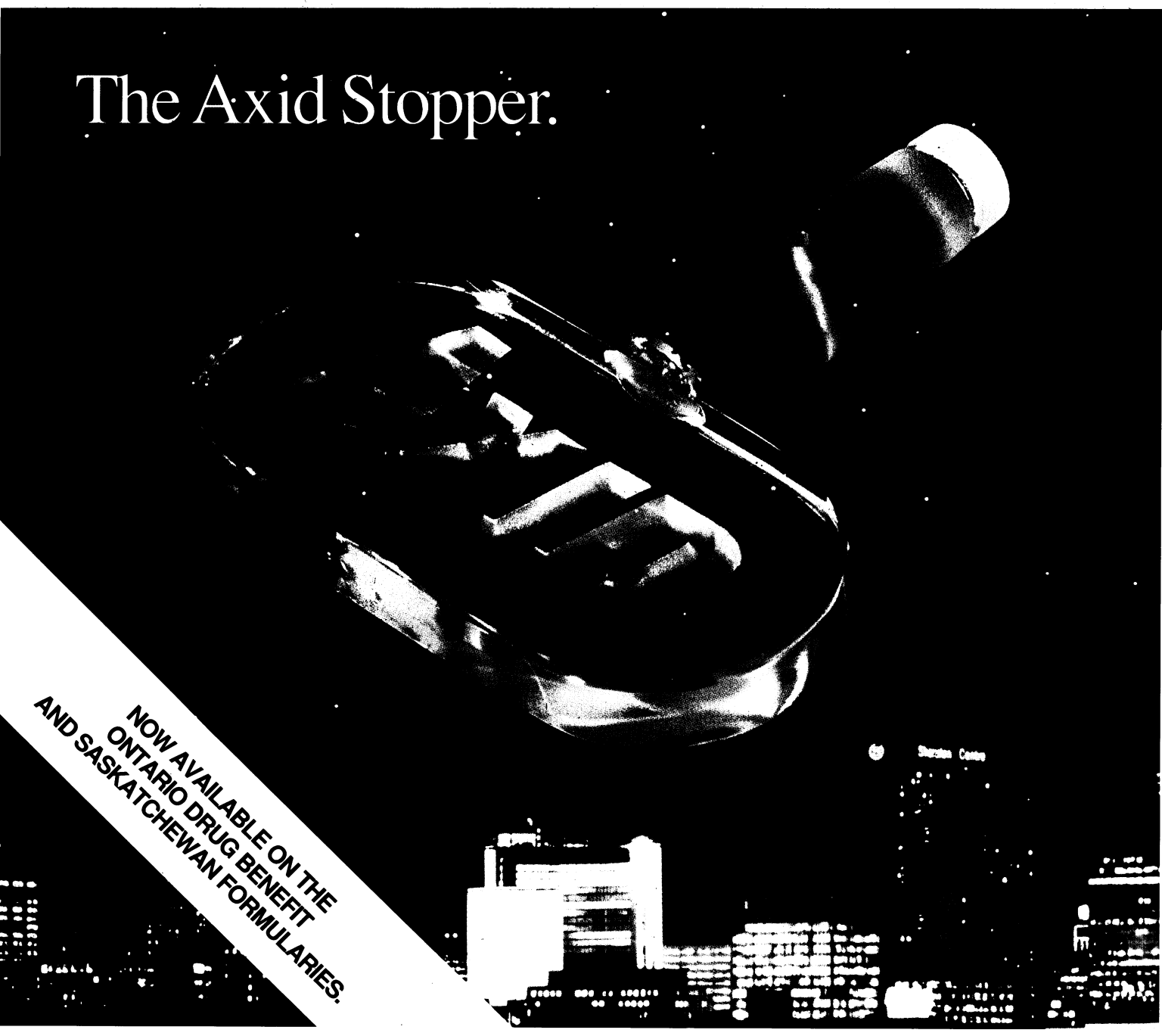

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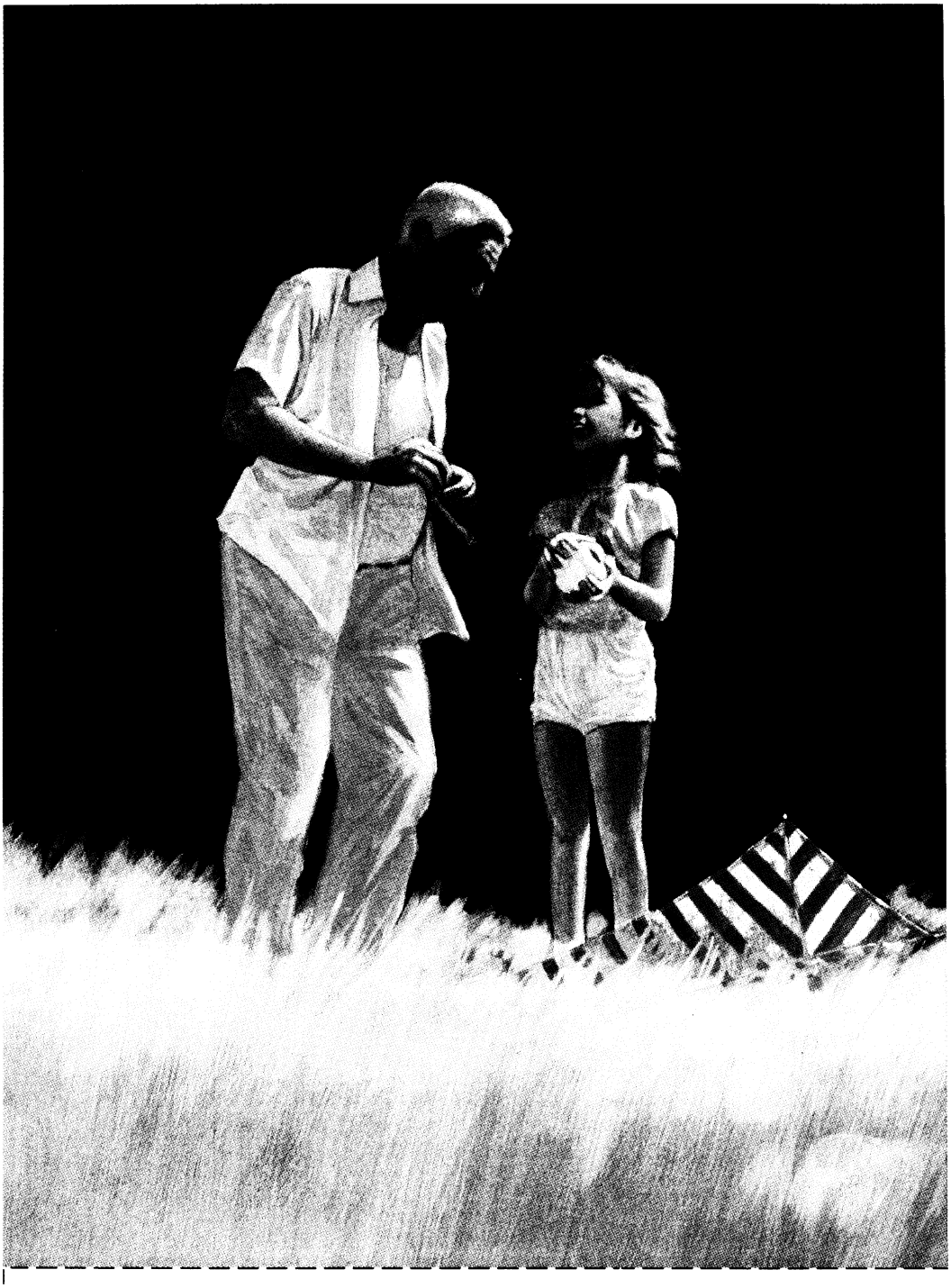

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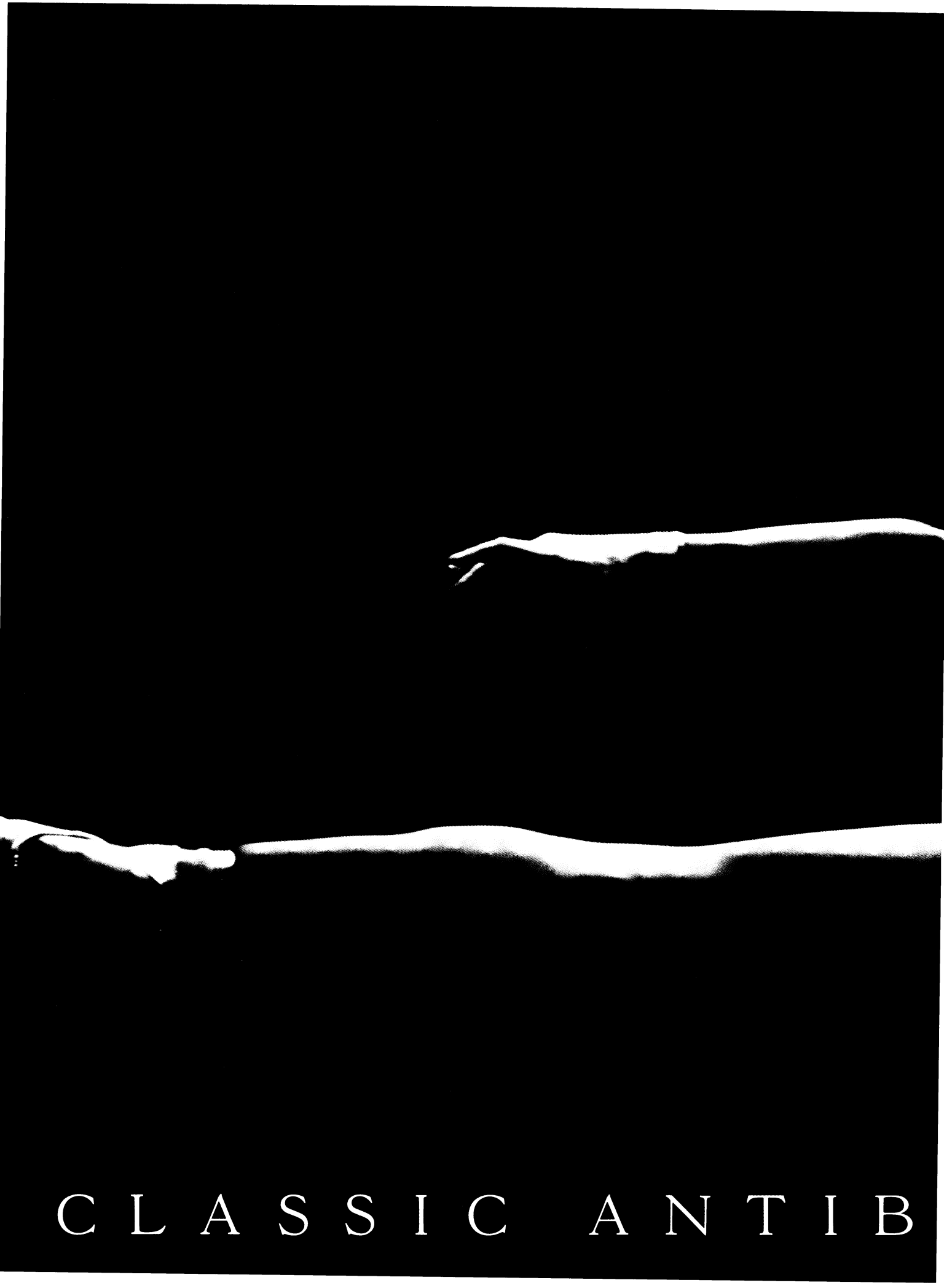
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Pneumonia: Single and multilobe pneumonia and bronchopneumonia due to susceptible strains of Pneumococcus, Streptococcus, Staphylococcus, *H. influenzae* and *Klebsiella pneumoniae*.

Other Respiratory Tract Infections: Pharyngitis, tonsillitis, sinusitis, otitis media, bronchitis caused by susceptible strains of β-hemolytic Streptococcus, Staphylococcus, Pneumococcus, and *H. influenzae*.

Gastro-intestinal Infections: caused by susceptible strains of Shigella, Salmonella and *E. coli*.

Skin and Soft Tissue Infections: Impetigo, furunculosis, cellulitis, abscess, wound sepsis, paronychia, caused by susceptible strains of *Staphylococcus aureus* and *albus*, Streptococcus, *E. coli*, and the Klebsiella-Aerobacter group.

Genitourinary Tract Infections: Pyelonephritis, cystitis, urethritis, gonococcal urethritis caused by susceptible strains of the Klebsiella-Aerobacter group, *E. coli*, Enterococcus, Staphylococcus, Streptococcus and *Neisseria gonorrhoeae*.

In adult patients with urethritis, cervicitis and vaginitis with a positive test for *Chlamydia trachomatis* and/or *Ureaplasma urealyticum*, clinical resolution and absence of detectable organisms have been observed at completion of therapy with VIBRA-TABS (doxycycline). Relapses or reinfection can occur. In these cases, limited data suggest that some patients may derive clinical benefit from the administration of VIBRA-TABS (doxycycline) or an alternative therapy. The effect on long term morbidity has not been established. For further information on the treatment of these infections, please consult VIBRA-TABS C-PAK product information.

CONTRAINDICATIONS

VIBRA-TABS (doxycycline) is contraindicated in individuals who have shown hypersensitivity to tetracyclines.

WARNINGS

As with other tetracyclines, VIBRA-TABS (doxycycline) may form a stable calcium complex in any bone-forming tissue, though *in vitro* it binds calcium less strongly than other tetracyclines. Though not observed in clinical studies to date, it should be anticipated that like other tetracyclines the use of VIBRA-TABS (doxycycline) during tooth development (last trimester of pregnancy, during lactation, neonatal period and early childhood) may cause discoloration of the teeth. Though more commonly associated with long term use of tetracyclines, this effect has also been known to occur after short courses.

PRECAUTIONS

In clinical studies to date, doxycycline administration did not lead to increased serum levels nor to an increase in the serum half-life of doxycycline in patients with impaired renal function. VIBRA-TABS (doxycycline) in normal dosage may be used to treat these patients. Although no evidence of increased toxicity has been observed in such patients, the potential for increased hepatic or other toxicity should be considered until further data on the metabolic fate of doxycycline under these conditions become available. Liver function tests should be carried out at regular intervals on patients receiving high doses for prolonged periods of time. Concurrent administration of VIBRA-TABS (doxycycline) and agents known to be hepatotoxic should be avoided if possible.

The use of antibiotics may occasionally result in overgrowth of non-susceptible organisms; thus, observation of the patient is essential. There is evidence to suggest that VIBRA-TABS (doxycycline) may have less effect on the gut flora than other tetracyclines.

Certain hypersensitive individuals may develop a photodynamic reaction to sunlight during treatment with VIBRA-TABS (doxycycline). If this or any other allergic reaction should occur, medication should be discontinued.

Increased intracranial pressure with bulging fontanelles has been observed in infants receiving therapeutic doses of tetracycline. Although the mechanism of this phenomenon is unknown, the signs and symptoms have disappeared rapidly upon cessation of treatment with no sequelae.

Esophageal injury consisting of esophagitis and esophageal ulceration have rarely been reported in patients receiving doxycycline orally. If this should occur, VIBRA-TABS (doxycycline) should be discontinued until healing occurs. Administration of antacids and/or cimetidine has provided relief in the treatment of such cases. To reduce the risk of esophageal injury, patients should be advised to take VIBRA-TABS (doxycycline) with an adequate amount of fluid while standing or sitting upright.

Use in Pregnancy and Lactation: VIBRA-TABS (doxycycline) should not be administered to pregnant and lactating women or neonates until its safety in such cases has been established beyond all reasonable doubt, unless in the judgement of the physician the potential benefit to the patient outweighs the risk to the fetus or child.

ADVERSE REACTIONS

As with other broad spectrum antibiotics, gastro-intestinal disturbances such as nausea, vomiting and diarrhoea, as well as glossitis, stomatitis and proctitis may occur, but have rarely been sufficiently troublesome to warrant discontinuation of therapy.

Rare instances of esophagitis and esophageal ulcerations in patients receiving the capsule form of doxycycline have been reported. (See PRECAUTIONS and DOSAGE AND ADMINISTRATION Sections.)

As with other tetracyclines, elevation of SGOT or SGPT values, anemia, neutropenia, eosinophilia, leukopenia or elevated BUN has been reported, the significance of which is not known.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

Gastric lavage if necessary.

DOSAGE AND ADMINISTRATION OF VIBRA-TABS

Adults: The recommended dosage of VIBRA-TABS (doxycycline) in adults for the majority of susceptible infections is a single loading dose of 200 mg on the first day of treatment followed by a maintenance dosage of 100 mg once daily at the same time each day thereafter.

As absorption is not significantly affected by food or milk VIBRA-TABS (doxycycline) should be given with or after a meal thus minimizing the possibility of gastric upset. Antacids and iron preparations impair absorption and should not be given concomitantly to patients taking VIBRA-TABS (doxycycline).

VIBRA-TABS (doxycycline) should be given to patients with adequate amounts of fluid while standing or sitting upright to reduce the risk of esophageal injury.

In severe infections in adults such as lung abscesses or osteomyelitis, and in chronic urinary tract infections, a single daily dose of 200 mg may be used throughout.

Therapy should be continued after symptoms and fever have subsided. It should be noted, however, that effective antibacterial levels are usually present 24 to 36 hours following discontinuance of VIBRA-TABS (doxycycline) therapy.

When used in streptococcal infections, therapy should be continued for 10 days to prevent the development of rheumatic fever or glomerulonephritis.

For the treatment of acute gonococcal infections, the recommended dosage is 200 mg stat. and 100 mg at bedtime, the first day, followed by 100 mg b.i.d. for 3 days.

No alteration in recommended dosage schedule need be made when treating patients with impaired renal function.

AVAILABILITY

VIBRA-TABS 100 mg are available as orange film-coated tablets containing doxycycline hyclate equivalent to 100 mg of doxycycline, supplied in bottles of 100 and 250.

Also available as the 20 tablet VIBRA-TABS C-PAK, intended for adult use as a 10 day treatment for urethral, endocervical or vaginal infections associated with *Chlamydia trachomatis* and *Ureaplasma urealyticum*.

Storage: VIBRA-TABS film-coated tablets (doxycycline) 100 mg: Protect from light. Dispense in a light-resistant container.

Product Monograph available on request.

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Pfizer Canada Inc.
Kirkland, Quebec
H9J 2M5

PAAB
CCPP

Vibra-Tabs*

(doxycycline hyclate/pfizer)

CLASSIC ANTIBIOTIC THERAPY

Stieva-A*

Tretinoin

Indications: Treatment of acne vulgaris, primarily where comedones, papules and pustules predominate.

Dosage and administration: Stieva-A should be applied to the affected area once a day before retiring. The area under treatment (not just clinical lesions) should be thoroughly cleansed with a mild soap, such as Acne-Aid* Soap, and dried, followed by application of Stieva-A with gentle rubbing motion. Application may be accompanied by a transitory feeling of warmth or a stinging sensation.

In cases where it has been necessary to discontinue therapy or to reduce the frequency of applications, therapy may be resumed when the adverse effects have ceased. Reinstitution of therapy with Stieva-A has failed in many instances to produce the adverse effects previously encountered.

In some patients, during the early weeks of therapy, an apparent exacerbation of the acne lesions may occur.

Therapeutic results may be noticed after two to three weeks of therapy; however, results may not be optimal until after eight to ten weeks of treatment. Once the acne lesions have responded satisfactorily, it may be possible to maintain the improved state with less frequent applications.

Patients being treated with Stieva-A may continue to use cosmetics; however, the area of skin to be treated should be thoroughly cleansed and dried before Stieva-A application.

Contraindications: Stieva-A (tretinoin) is contraindicated in patients with known hypersensitivity to retinoids.

Warnings: Use in pregnancy: High oral doses of vitamin A acid in animals can cause fetal abnormalities. No drug-related, toxic or teratogenic changes have been seen in studies employing subchronic dermal application of tretinoin in the rat, mouse and rabbit. However, caution is advised in prescribing tretinoin for pregnant women or sexually active women who are unprotected against conception.

Do not apply to eyelids or to the skin at the corners of the eyes and mouth. Avoid the angles of the nose and naso-labial fold (if treatment in these areas is necessary, apply very sparingly). Topical use may induce severe local erythema and peeling at the site of application. If the degree of local irritation warrants, patients should be directed to use the medication less frequently, discontinue use temporarily or discontinue use altogether. Stieva-A has been reported to cause severe irritation of eczematous skin and should only be used with utmost caution in patients with this condition.

Precautions: Concomitant topical medications should be used with caution during therapy with Stieva-A because of possible intensified reactions. Particular caution should be exercised when using preparations containing a peeling agent concomitantly (such as sulphur, resorcinol, benzoyl peroxide or salicylic acid) with Stieva-A. It may be advisable to "rest" a patient's skin until the effects of previously used peeling agents subside before initiating Stieva-A therapy.

Excessive exposure to sunlight or ultraviolet rays (sun lamps) should be avoided during Stieva-A treatment, because the additional irradiation may lead to a more intense action. If a sunburn occurs, it is advisable to interrupt therapy until the severe erythema and peeling subside. Patients whose occupations require considerable exposure to the sun should exercise particular caution.

Clinical evaluation of the photosensitivity potential of Stieva-A in one short-term study has shown the preparation to be free of phototoxic properties.

No therapeutic advantage will be obtained by using more than recommended amounts; marked redness, peeling and discomfort may occur.

Adverse reactions: The skin of certain sensitive individuals, particularly those with fair complexion, may become excessively red, edematous, blistered or crusted when exposed to Stieva-A. Pain, burning sensation, tenderness, irritation or pruritus have also been occasionally reported. If any of these effects occur, the medication should be discontinued until the integrity of the skin has been restored or the treatment schedule adjusted to the level the patient can tolerate. Temporary hyper-or hypopigmentation has been reported with repeated applications of tretinoin. To date, all adverse clinical effects of Stieva-A encountered have been reversible upon discontinuance of therapy. In many instances, reinstitution of therapy with Stieva-A failed to produce the adverse effects previously experienced.

Presentation: Stieva-A Cream: 25 g tubes containing 0.01%, 0.025%, 0.05% or Stieva-A Cream Forte 0.1% tretinoin; Stieva-A Gel: 25 g tubes containing 0.01%, 0.025% or 0.05% tretinoin; Stieva-A Solution: 50 ml bottles with snap-on applicator containing 0.025% or 0.05% tretinoin. Product monograph available upon request.

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Montreal, Quebec

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SC1-D-8907/STV/61-JA-E

Anaprox®

Indications. (naproxen sodium)

Relief of mild to moderately severe pain, accompanied by inflammation such as musculoskeletal trauma, post-dental extraction, relief of post-partum cramping and dysmenorrhea.

Contraindications.

Patients who have hypersensitivity to it or in whom ASA or other non-steroidal drugs induce asthma, rhinitis or urticaria; in active peptic ulcer or inflammatory disease of G.I. tract.

Warnings.

Not recommended in children under 16 years of age, pregnant or lactating women, because safety and dose schedule have not been established.

Precautions.

Caution is advised, in patients taking a coumarin-type anticoagulant, hydantoin, sulfonamide or sulfonylurea. Use with caution in patients with impaired renal function, compromised cardiac function and patients whose overall intake of sodium is markedly restricted. (Each tablet contains approximately 25 mg of sodium.)*

*Probenecid increases Anaprox plasma levels and half-life.

Adverse Reactions.

G.I.: nausea, heartburn, abdominal discomfort, vomiting, constipation, dyspepsia, stomatitis, diarrhea, melena, gastrointestinal bleeding (occasionally severe) and hematemesis.

C.N.S.: dizziness, headache, drowsiness, mental confusion, lightheadedness, vertigo, inability to concentrate and depression.

Special Senses: tinnitus, visual disturbances, and hearing disturbances.

Skin: itching (pruritus), skin eruptions, sweating, ecchymoses, skin rashes, urticaria and purpura.

Cardiovascular: edema, palpitations, and dyspnea were reported. In this class of drugs, other reactions seen include congestive heart failure, pyrexia, acute renal disease, hematuria, jaundice, angioneurotic edema, thrombocytopenia, eosinophilia, agranulocytosis, aplastic anemia, hemolytic anemia and peptic ulceration with bleeding and/or perforation.

Availability.

Anaprox (naproxen sodium) is available in blue filmcoated tablets of 275 mg in a bottle of 100 tablets.

Dosage.

Initial dose: 2 tablets.

Thereafter: 1 tablet every 6-8 hours as required.

Maximum daily dose: 5 tablets.

References.

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2. Smith L. Naproxen sodium in dysmenorrhea: A Canadian clinical trial. Proceedings: Telemedical Symposium "Prostaglandins and Dysmenorrhea." Sept. 10, 1980, Canada.

Product monograph available on request.

SYNTEX

*Syntex Inc.**
Mississauga, Ont./Montréal, Qué.

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PAAB CCPP

amounts of money are expended when our signatures appear at the bottom of a prescription sheet, a consultation form, or an insurance claim. Family physicians are often the chief professional resource of our health care system, and our knowledge of the family and social systems places us in a strategic position to devise effective interventions for patients suffering chronic low back pain. Family physicians can be of great help if we have time, patience, and interest. ■

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Table 2
Managing the Patient with Low Back Pain

1. Does your patient understand the condition? Acute and chronic low back pain are as different as diabetes types I and II. A clear understanding of the diagnosis will help many patients to cope with diabetes, but acquiring a coping strategy is generally difficult for patients with chronic back pain because the causes of this disorder include a complex interaction of somatic and psychogenic components.

2. Is your therapeutic strategy strongly supported by sufficient data? To search for another job is a difficult decision for a person to make, but job-related stress may be the only real issue. You will not feel confident in making such a recommendation without a record that includes pertinent socio-affective data.

3. Do you believe that your patient is a malingerer? This type of patient is rare, and you will not be able to build a positive relationship with a patient if you harbour such an assumption.

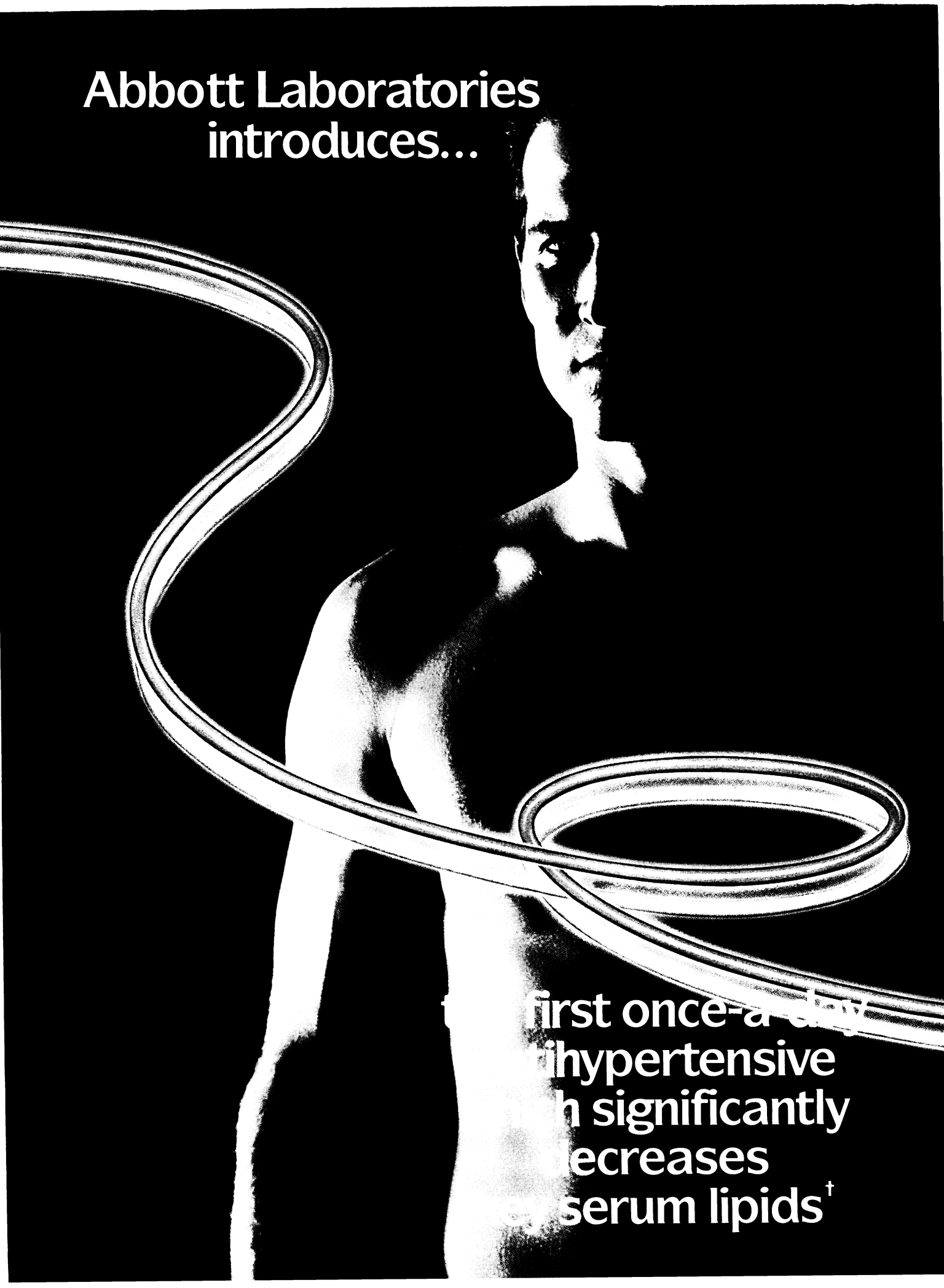
4. Are you spending enough time on a problem that requires (a) an extensive inquiry and (b) an empathic relationship built on good communication?

5. Are you giving enough consideration to material problems that can increase the anxiety of your patient and cause unexplained resistance to the treatment?

6. Are you over-investigating your patient, convincing him or her that there is a hidden organic problem that must be identified to bring about a complete cure?

7. Do you show enough conviction when you prescribe exercises and postural counselling? If not, you can expect limited compliance from your patient.

8. Does your patient believe that the problem can be completely resolved instead of that he or she will have to live with it?


Abbott Laboratories
introduces...
first once-a
ihypertensive
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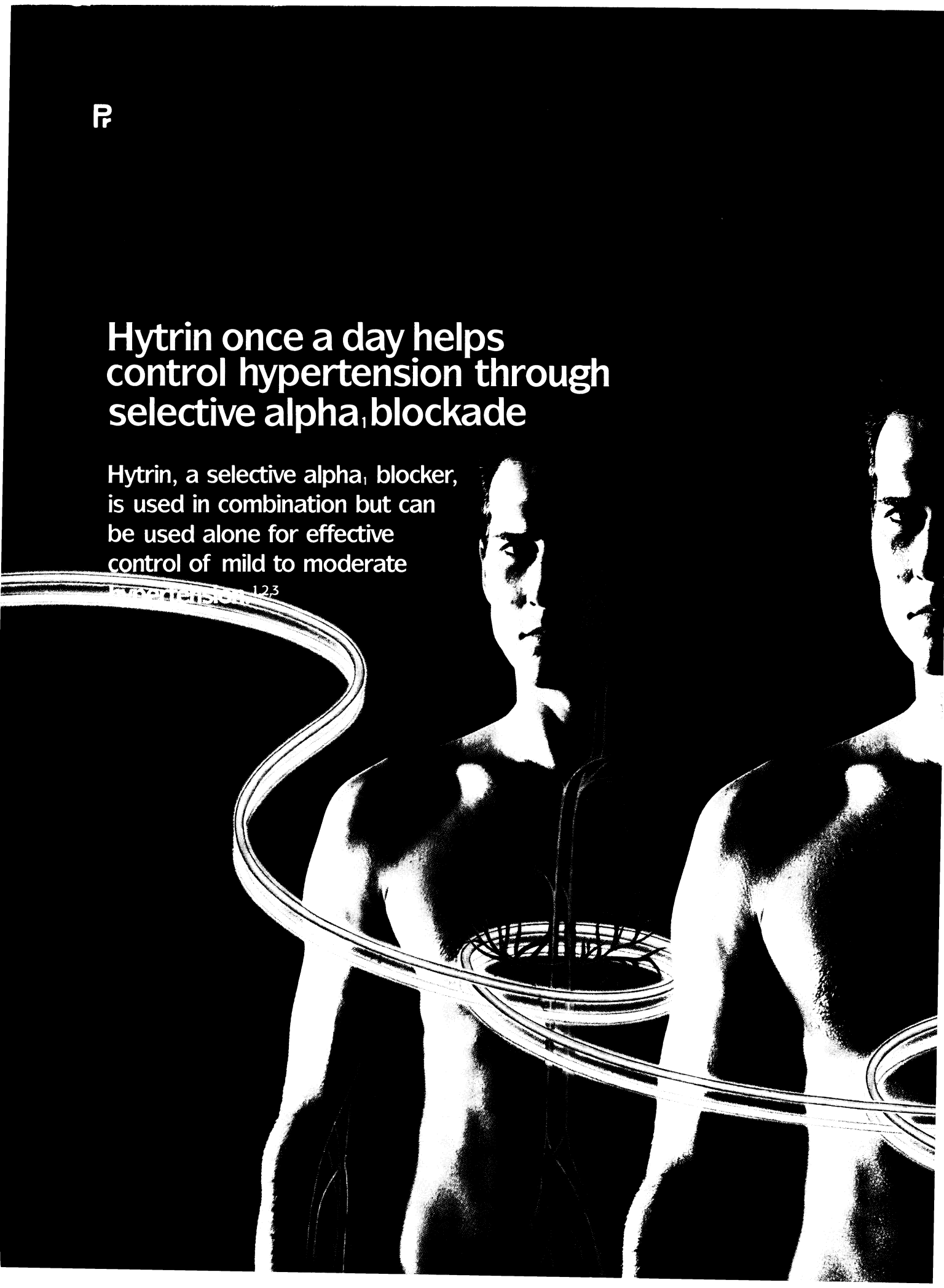
serum lipids†

Pr

Hytrin once a day helps control hypertension through selective alpha$_1$ blockade

Hytrin, a selective alpha$_1$ blocker, is used in combination but can be used alone for effective control of mild to moderate hypertension.[1,2,3]



Hytrin has lowered key serum lipids†,††

Unlike thiazide diuretics, beta-blockers, ACE inhibitors, and calcium channel blockers,[4] Hytrin can decrease total serum cholesterol levels.[5,6]

Compared to placebo, Hytrin monotherapy produced a small but statistically significant decrease of total cholesterol as well as LDL plus VLDL plasma levels.[6,††]

† Total cholesterol, LDL + VLDL levels
†† Hytrin is not indicated for the treatment of hyperlipidemia.

Hytrin is generally well tolerated for long-term compliance[7]

Hytrin has a low incidence of reflex tachycardia.[7]

Compliance-limiting side effects are seldom encountered with Hytrin.[5]

8 out of 10 responders continued with Hytrin after 2 years.[7]

Hytrin is cost effective

Hytrin is less expensive than ACE inhibitors or calcium channel blockers.[8]

The first once-a-day antihypertensive which significantly decreases key serum lipids†

HYTRIN* 1

TERAZOSIN HCl — ONCE-A-DAY

The first once-a-day antihypertensive which significantly decreases key serum lipids†

DESCRIPTION

HYTRIN* (terazosin hydrochloride) is the hydrochloride salt of 1-(4-amino-6,7-dimethoxy-2-quinazolinyl), 4-[(tetrahydro-2-furanyl)carbonyl]-piperazine, dihydrate. Terazosin hydrochloride is a white, crystalline substance, freely soluble in water and isotonic saline.

ACTIONS, CLINICAL PHARMACOLOGY

The antihypertensive effect of HYTRIN* (terazosin hydrochloride) is believed to be a direct result of peripheral vasodilation. Although the exact mechanism by which the lowering of blood pressure is achieved is not known, the relaxation of the vessels appears to be produced mainly by selective blockade of alpha-1-adrenoceptors.

Pharmacodynamics: Systolic and diastolic blood pressure is lowered in both the supine and standing positions. In clinical trials, blood pressure responses were measured at the end of the dosing interval (24 hours), with the usual supine response 5-10 mmHg systolic and 3.5-8 mmHg diastolic. The response in the standing position tended to be larger by 1-3 mmHg.

Limited measurements of peak response (2-3 hours after dosing) during chronic terazosin administration indicate that this response is somewhat greater than the trough (24 hour) response, suggesting some attenuation of response at 24 hours, presumably due to a fall in blood terazosin concentrations at the end of the dose interval.

The greater blood pressure effect associated with peak plasma concentrations appears to be more position dependent (greater in the standing position) than the effect of terazosin at 24 hours; in the standing position there is also a 6-10 beat per minute increase in heart rate in the first few hours after dosing. During the first 3 hours after dosing, 12.5% of patients had a systolic pressure fall of 30 mmHg or more from supine to standing, or standing systolic pressure below 90 mmHg with a fall of at least 20 mmHg.

During controlled clinical studies, patients receiving terazosin monotherapy had a small but statistically significant decrease (a 3% fall) compared to placebo in total cholesterol and the combined low-density and very-low density lipoprotein fractions. No significant changes were observed in high-density lipoprotein fraction and triglycerides compared to placebo.

Pharmacokinetics: Orally administered terazosin hydrochloride is essentially completely absorbed in man. Nearly all of the circulating dose is in the form of parent drug. Food has little or no effect on the bioavailability. The plasma levels of the free base peak in about 1 hour and then decline with a half-life of approximately 12 hours. Approximately 90-94% of the drug is bound to plasma proteins and binding is constant over the clinically observed concentration range.

Hepatic metabolism is extensive with major biliary elimination. Approximately 10% of an orally administered dose is excreted as parent drug in the urine and approximately 20% is excreted in the feces. The remainder is eliminated as metabolites. Overall approximately 40% of the administered dose is excreted in the urine and approximately 60% in the feces.

INDICATIONS AND CLINICAL USES

HYTRIN* (terazosin hydrochloride) is indicated in the treatment of mild to moderate hypertension. It is employed in a general treatment program in conjunction with a thiazide diuretic and/or other antihypertensive drugs as needed for proper patient response. HYTRIN* may be tried as a sole therapy in those patients in whom other agents caused adverse effects or are inappropriate.

CONTRAINDICATIONS

In individuals who have shown hypersensitivity to HYTRIN* (terazosin hydrochloride) or its analogs.

WARNINGS

Syncope and "First dose" Effect: Terazosin can cause marked hypotension, especially postural hypotension, and syncope in association with the first dose or first few doses of therapy. A similar effect can occur if therapy is reinstated following interruption for more than a few doses. Syncope has also occurred in association with rapid dosage increases or the introduction of another antihypertensive agent into the regimen of a patient taking high doses of HYTRIN*.

Syncope is believed to be due to an excessive postural hypotensive effect, although occasionally the syncopal episode has been preceded by a bout of severe supraventricular tachycardia with heart rates of 120-160 beats per minute.

In studies of terazosin the incidence of syncopal episodes was approximately 1%.

The likelihood of syncopal episodes or excessive hypotension can be minimized by limiting the initial dose of the drug to 1 mg of terazosin given at bedtime, by increasing the dosage slowly, and by introducing any additional antihypertensive drugs into the patient's regimen with caution (see "DOSAGE AND ADMINISTRATION").

Patients should be advised of the possibility of syncopal and orthostatic symptoms, and to avoid driving or hazardous tasks for 12 hours after the initial dose of terazosin, after the dose is increased and after interruption of therapy when treatment is resumed. They should be cautioned to avoid situations where injury could result should syncope occur.

If syncope occurs, place the patient in the recumbent position and institute supportive measures as necessary.

PRECAUTIONS

Orthostatic Hypotension: While syncope is the most severe orthostatic effect of HYTRIN* (terazosin hydrochloride) (see WARNINGS) other symptoms of lowered blood pressure, such as dizziness, lightheadedness and palpitations are more common with one or more of these occurring in 28% of patients in clinical trials. Patients should be advised to lie down when these symptoms occur and then wait for a few minutes before standing to prevent their recurrence.

Patients with occupations in which such events represent potential problems should be treated with particular caution.

There is evidence that the orthostatic effect of terazosin is greater, even in chronic use, shortly after dosing.

Use in Elderly: Terazosin should be used cautiously in elderly patients because of the possibility of orthostatic hypotension. There was an age-related trend towards an increased incidence of dizziness, blurred vision and syncope in elderly patients treated with this drug.

Use in Children: The use of terazosin in children is not recommended since safety and efficacy have not been established.

Use in Patients with Renal Impairment: The use of terazosin in patients with impaired renal function requires careful monitoring. Limited pharmacokinetic studies using low doses (1 mg) showed no difference in the pharmacokinetics of terazosin as compared to patients with normal renal function. Approximately 40% of oral terazosin dose is excreted by the kidney as parent drug or metabolites.

Use in Patients with Liver Impairment: No information is available on the use of terazosin in patients with impaired liver function.

Peripheral Edema: Fluid retention resulting in weight gain may occur during terazosin therapy. In placebo-controlled monotherapy trials, male and female patients receiving terazosin gained a mean of 0.8 and 1 kg respectively, compared to losses of 0.1 and 0.5 kg respectively, in the placebo group. Both differences were significant.

Use in Pregnancy: The safety of terazosin in pregnancy has not been established. HYTRIN* is not recommended during pregnancy unless potential benefits justify potential risks to mother and fetus.

Use in Nursing Mothers: It is not known whether terazosin is excreted in human milk. Because of possible adverse reactions in nursing infants, an alternate method of infant feeding should be considered when use of the drug is essential.

Drug Interactions: In controlled trials, terazosin has been added to diuretics and several beta-adrenergic blockers; except for the additive hypotensive effect, no unexpected interactions were observed. Terazosin has also been used in patients on a variety of concomitant therapies. While these were not formal interaction studies, no interactions were observed. Terazosin has been used concomitantly in at least 50 patients on the following drugs or drug classes: 1) analgesic/anti-inflammatory (e.g., acetaminophen, aspirin, codeine, ibuprofen, indomethacin); 2) antibiotics (e.g., erythromycin, trimethoprim and sulfamethoxazole); 3) anticholinergic/ sympathomimetics (e.g., phenylephrine hydrochloride, phenylpropanolamine hydrochloride, pseudoephedrine hydrochloride); 4) antigout (e.g., allopurinol); 5) antihistamines (e.g., chlorpheniramine); 6) cardiovascular agents (e.g., atenolol, hydrochlorothiazide, methyclothiazide, propranolol); 7) corticosteroids; 8) gastrointestinal agents (e.g., antacid); 9) hypoglycemics; 10) sedatives and tranquilizers (e.g., diazepam).

Laboratory Tests: Small but statistically significant decreases in hematocrit, hemoglobin, white blood cells, total protein and albumin were observed in controlled clinical trials. The magnitude of the decreases did not worsen with time. These laboratory findings suggested the possibility of hemodilution.

ADVERSE REACTIONS

The incidence of adverse reactions is derived from clinical trials involving 1,986 hypertensive patients on terazosin monotherapy or combination therapy.

The most serious adverse reaction encountered with HYTRIN* (terazosin hydrochloride) is syncope, occurring in approximately 1% of patients.

The most common reactions were dizziness (18.9%), headache (14.1%), asthenia (11%), somnolence (4.8%), nasal congestion (4.6%) and palpitation (4.6%).

The most frequently reported adverse effects which resulted in termination of HYTRIN* were dizziness (3.5%), asthenia (2.1%) and headache (1.8%).

The following events were reported in less than 1% of cases except as indicated in brackets. The order of presentation corresponds within each heading to the relative frequency of occurrence.

Body as a Whole: Headache (14.1%), asthenia (11%), peripheral edema (3.6%), chest pain (2.2%), abdominal pain (1.5%), edema (1.3%), facial edema (1.0%), allergic reactions, malaise.

Cardiovascular System: Palpitation (4.6%), tachycardia (2.9%), syncope (1%), postural hypotension, angina pectoris, arrhythmias, cerebrovascular accident, heart failure, hypotension, migraine.

Digestive System: Nausea (3.9%), dry mouth (1.7%), diarrhea (1.3%), dyspepsia, vomiting, anorexia, gastritis, liver function abnormality, jaundice.

Nervous System: Dizziness (18.9%), somnolence (4.8%), nervousness (2.2%), paresthesia (1.5%), insomnia (1.2%), incoordination, abnormal dreams, confusion, speech disorder, tremor, vertigo.

Respiratory System: Nasal congestion (4.6%), dyspnea (2.8%), rhinitis (1.2%), asthma, increased cough.

Skin and Appendages: Sweating (1.1%), pruritus, rash.

Special Senses: Blurred vision (1.4%), eye disorder (1.2%), tinnitus, taste perversion.

Urogenital system: Impotence (1.1%), urinary frequency, dysuria.

Miscellaneous: Pain in extremities (1.8%), hypokalemia, hypophosphatemia, decreased libido.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

Should administration of HYTRIN* (terazosin hydrochloride) lead to hypotension, support of the cardiovascular system is of first importance. Restoration of blood pressure and normalization of heart rate may be accomplished by keeping the patient in the supine position. If this measure is inadequate, shock should first be treated with volume expanders. If necessary, vasopressors should then be used and the renal function should be monitored and supported as needed. Laboratory data indicate that terazosin is highly protein bound; therefore, dialysis may not be of benefit.

DOSAGE AND ADMINISTRATION

The dose and the dosing intervals (12 or 24 hours) of HYTRIN* (terazosin hydrochloride) should be adjusted to the individual patient's blood pressure response.

When HYTRIN* is being added to the existing antihypertensive therapy, the patient should be carefully monitored for the occurrence of hypotension. If a diuretic or other antihypertensive agent is being added to HYTRIN* regimen, dosage reduction of HYTRIN* and retitration with careful monitoring may be necessary. The following is a guide to its administration:

Initial dose: 1 mg of terazosin at bedtime is the starting dose for all patients and this dose should not be exceeded; compliance with this initial dosage recommendation should be strictly observed to minimize the potential for acute hypotensive episodes.

Subsequent doses: The dose may be slowly increased to achieve the desired blood pressure response. The usual dose range is 1 to 5 mg once a day. Some patients may benefit from doses up to 20 mg per day which is the maximum recommended daily dose.

The blood pressure should be monitored at the end of the dosing interval to assure that control is maintained. It is also helpful to measure the blood pressure two to three hours after dosing to see if the maximum and minimum responses are similar and to evaluate symptoms.

If response to terazosin is substantially diminished at 24 hours, patients may be tried on a larger dose or twice daily dosage regimen. The latter should also be considered if adverse effects such as dizziness, palpitations or orthostatic complaints are seen two to three hours after dosing.

If terazosin administration is discontinued for several days or longer, therapy should be reinstituted using the initial dosing regimen.

DOSAGE FORMS

HYTRIN* is available as round tablets in three different dosage strengths: Terazosin 1 mg (as terazosin hydrochloride dihydrate) – white tablets; Terazosin 2 mg (as terazosin hydrochloride dihydrate) – orange tablets; Terazosin 5 mg (as terazosin hydrochloride dihydrate) – tan tablets.

Product monograph available upon request.

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PONSTAN* (mefenamic acid)

Helps stop the pain where it starts.

- The only dual action anti-prostaglandin for dysmenorrhea[1,2].
- With a fast onset of analgesia for pain relief often within 20 minutes of administration[2,3,4,5].
- Simple, short-term therapy taken at the onset of menstruation, Ponstan can be taken from age 14 for relief when needed†.

PONSTAN*

Some of the best advice you can give for dysmenorrhea.

For prescribing information see page 1940

PARKE-DAVIS
Scarborough, Ontario M1L 2N3

*T.M. Warner-Lambert Company, Parke-Davis Div., Warner-Lambert Canada Inc. auth. user.

†Ponstan, Product monograph.

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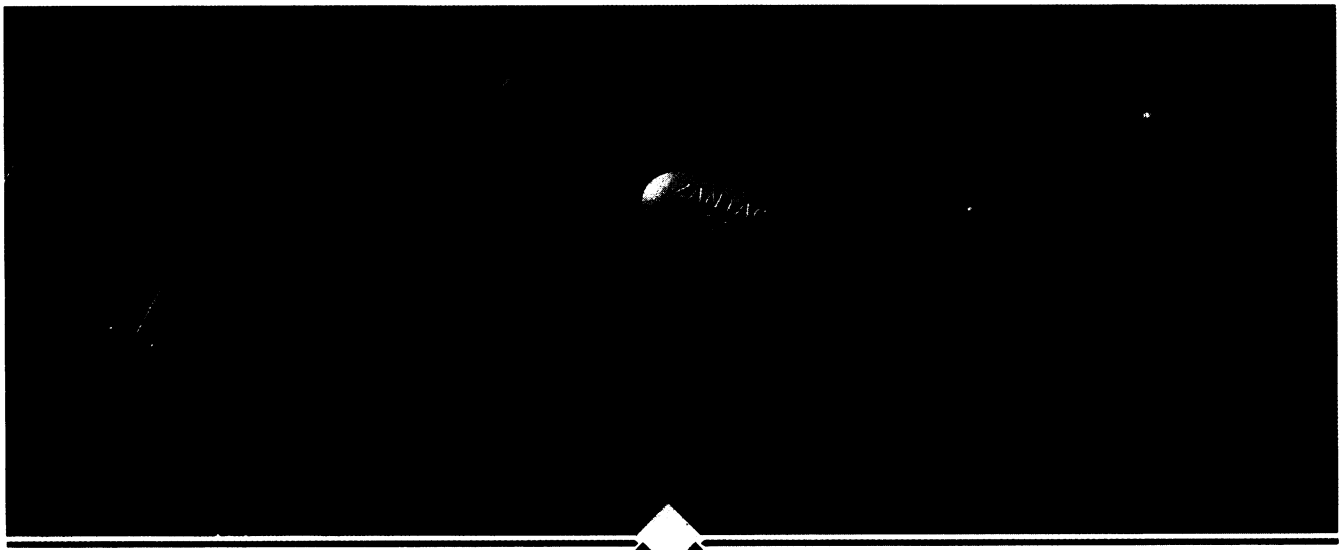
Is your ulcer treatment comfortable in a crowd?



You're already treating your patient for hypertension, asthma and depression. So you'll want to be very sure of the treatment you prescribe when an ulcer occurs.

Zantac® won't significantly interfere with P-450 hepatic drug metabolism.[3] So, unlike cimetidine, there is no appreciable interference with metabolism of most beta-blockers, calcium antagonists, theophyllines or anxiolytics.[9,10,11]

To be sure you're helping patients towards normal lives this safely, comfortably and quickly, prescribe Zantac – no substitution.

Zantac® (RANITIDINE HCl)
To be sure.

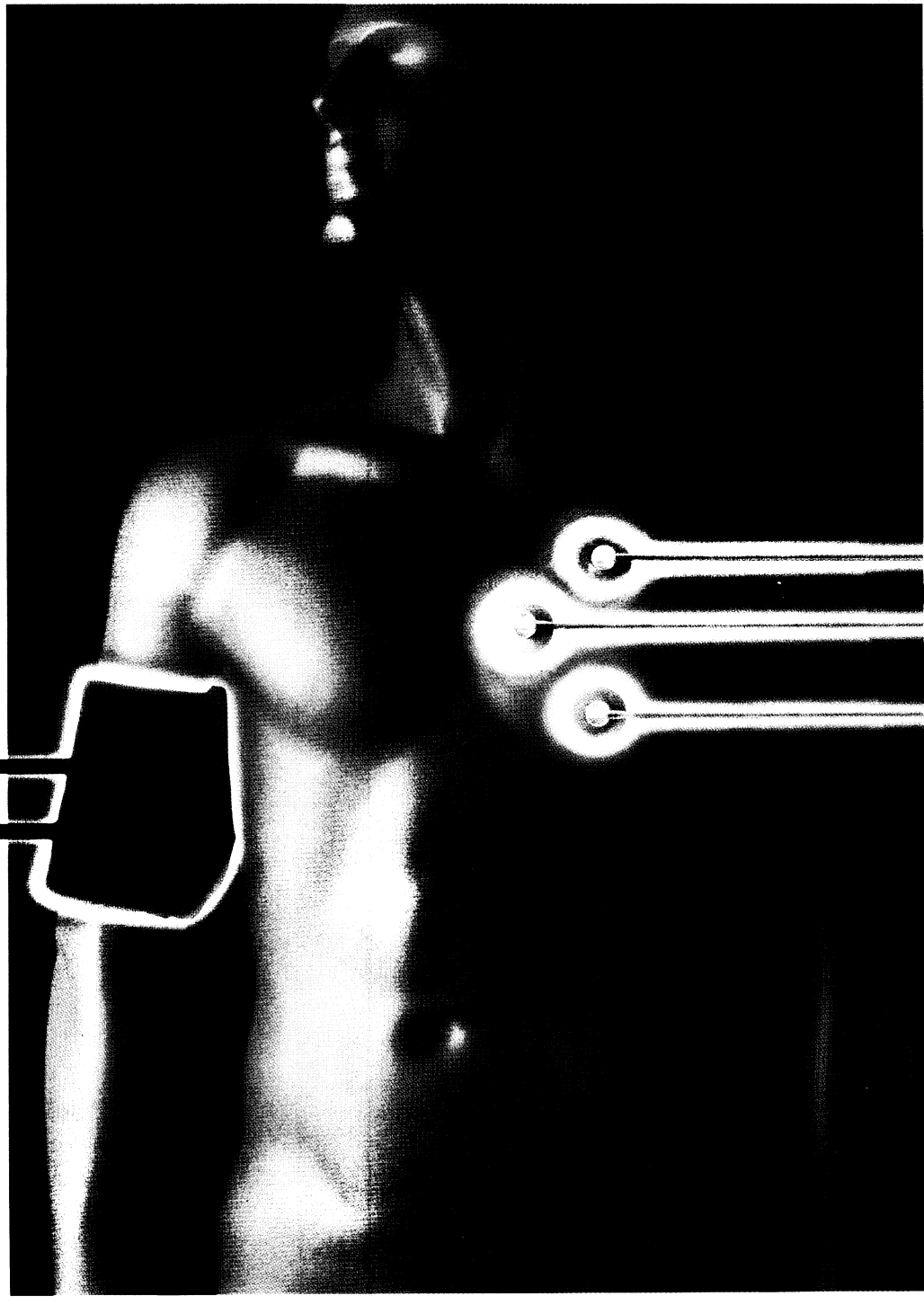
Glaxo Laboratories, A Division of Glaxo Canada Inc., Toronto, Ontario, Montreal, Quebec.

For prescribing information see page 1745

One in two hypertensives has something to get off his chest

Almost **50%** of hypertensives have a concomitant condition, coronary disease being just one possibility.[1]

DIABETES • HYPERLIPIDEMIA • ANGINA • PREVIOUS MYOCARDIAL INFARCTION • RENAL IMPAIRMENT • CONGESTIVE HEART FAILURE • CNS DISEASE • ASTHMA • LVH • CORONARY ARTERY SPASM • DEGENERATIVE ARTHRITIS • PERIPHERAL VASCULAR DISEASE



Cardizem* SR monotherapy effectively reduces high blood pressure.[2,3,4] And it is unlikely to worsen concomitant COPD, diabetes, hyperlipidemia, LVH or peripheral vascular disease.[1] It may help improve exercise tolerance.[1] And note Cardizem's demonstrated antianginal activity when treating hypertensives who also present with angina.[6]

That's why Cardizem* SR monotherapy deserves your full consideration.

CARDIZEM*SR b.i.d.

diltiazem HCl sustained release capsules/NORDIC

90 mg • 120 mg

AN EXCELLENT CHOICE, FOR SO MANY REASONS

NORDIC
NORDIC LABORATORIES INC.
Laval, Qc, Canada H7L 3M7

*Cardizem is a registered trademark of Marion Laboratories, Inc., U.S.A. SR082-0889/E

For prescribing information see page 1945

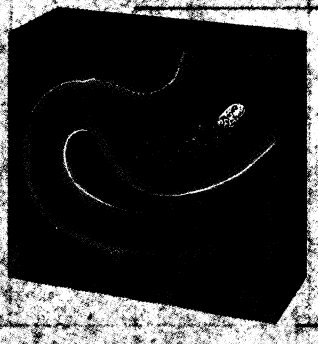
PAAB CCPP MEMBER PMAC

New from Abbott, an innovation in erythromycin technology

Available on the Ontario, Saskatchewan and Quebec Drug Formularies

pce*

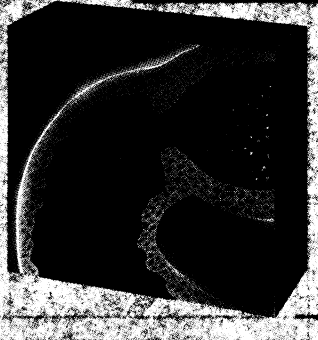
particle coated erythromycin tablets



1

Designed to increase G.I. tolerance

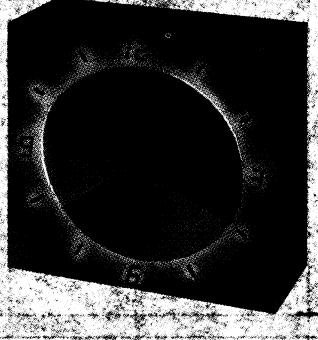
- acid-resistant polymer coating prevents direct contact between erythromycin and the gastric mucosa
- particle dispersion in the small intestine prevents high local concentrations of active base
- can be taken with food, which may further reduce potential for G.I. upset



2

Designed to increase bioavailability

- dissolves in the duodenum earlier than enteric-coated erythromycin[1,2,3,4]
- the active base is released over the area of highest absorption capacity[5,6]
- dispersion over a large surface area further enhances absorption[1,7]



3

Designed for convenience

- first and only polymer-coated t.i.d. regimen
- can be taken with or without food

pce*

333 mg t.i.d.

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1-800-363-6871

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PHARMACEUTICAL PRODUCTS DIVISION
ABBOTT LABORATORIES, LIMITED
MONTRÉAL, CANADA

PAAS

For prescribing information see page 1714

lows one to measure and compare one's own activities or standards for audits with the apparent expertise of the authors. For those less acquainted with the medical audit, the paper may be somewhat overwhelming and indeed may reinforce some of the negative emotions mentioned at the beginning of this review. Despite this reservation, this paper provides an excellent discussion of both theoretical and practical implications of practice activity analysis.

Reviewed by Dr. Mark J. Yaffe. Dr. Yaffe is an Associate Professor of Family Medicine at McGill University in Montreal, Quebec.

Anecdotal Stories of Pregnancy

Title: Being Pregnant: Conversations with Women
Author: Daphne Morrison
Publisher: New Star Books Ltd. Publishers, 2504 York Ave., Vancouver, B.C. V6K 1E3
Publication Date: July 1987
Pages: 201
Price: $9.95

This small paperback book is not designed to tell women what to do in pregnancy; it is a collection of vignettes of the lives of ordinary people. The common theme is pregnancy, the settings vary.

Fifteen women recount, in their own words, the experiences, the emotions, the pressures, the life struggles, and the practicalities of a pregnancy. These women are single, are married, or are lesbian; some are unemployed, others self-employed; they are young and old, healthy and sick. As always, real life stories strike the heart, and the reader is filled with sympathy, a feeling of importance, with a renewed belief that women will survive. The women admit to keeping many of their feelings to themselves regarding their pregnancy.

Family physician accoucheurs would benefit from reading the author's introduction and then browsing through the rest. The anecdotal nature of the book detracts from its usefulness for a busy practitioner, but it does remind us to listen closely to our patients, not to impose our values, and to provide support at all times.

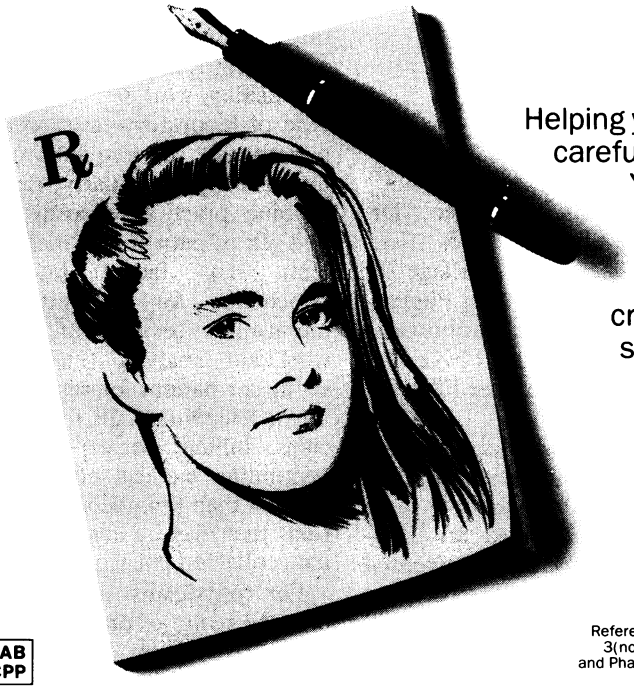
Reviewed by Dr. Verity Livingstone. Dr. Livingstone is a staff member of the General Hospital and Grace Hospital in Vancouver. She is also an Assistant Professor at the University of British Columbia.

Backache: A Book for Patients and Physicians

Title: *Beyond Backache: A Personal Guide to Back and Neck Relief*
Author: Michael Livingston, MD
Publisher: Libra Publishers, Inc., Suite 383, 3089C Clairemont Dr., San Diego, CA 92117 U.S.A.
Publication Date: 1988
Pages: 112
Price: $12.95 (U.S. Funds)

The author of this book discusses the problems encountered by people with back pain. He does so in a sensible, readable way. The book is just about the right size—thin enough so that

Sinequan and reassuring words for



Helping your patient to overcome depression takes careful evaluation based on years of experience. Years of experience that can be suddenly undermined by unforeseen changes in therapy.[1,2]
It is for this reason that for certain critical drug categories indiscriminate drug substitution is of concern to the Canadian medical community.[3]

† Recommended by the Ontario Medical Association *Committee on Drugs and Pharmacotherapy.*
References: 1. Orsulak PJ. *J Clin Psychiatry* 1986;47(10):39-49. 2. Masters AB. *Perspect Geriatr* 1987; 3(no 1):26-35. 3. Data on file, Pfizer Canada Inc. 4. Ontario Medical Association Committee on Drugs and Pharmacotherapy. *The Drug Report,* Number 23, August 1987. *Prepared by Pfizer Canada Inc. (U.I.). Pfizer Inc. TM Owner. ©Pfizer Canada Inc. 1988. Product monograph available on request.

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the reader is not intimidated—yet the volume addresses all common aspects of back pain.

In its slim 94 pages, the book discusses the multiple causes of back and neck pain. It describes a sensible course of exercise and gives detailed instructions on how to do these exercises, with proper cautions on when to stop any specific procedure if difficulties occur. The exercises are easy to do. There is no special equipment required; everything necessary can be found in any home. The time and space needed are small, and the rewards are, in most cases, rapidly apparent. Once started, the problem with compliance should be minimal.

The book is loaded with sketches illustrating the text and does an excellent job of explaining anatomical and mechanical causes for back and neck pain. Other sketches show how the exercises should be done. These make the book even more readable, and the procedures easy to follow.

The chapter on nutrition is excellent and again illustrates the author's sensible, uncomplicated approach to a topic muddied by a proliferation of fad diets, especially in the last two decades. The author even manages the difficult chapter on other treatments for back and neck pain in a commendable fashion, and that is no easy task when there are so many "cures" around for the painful back, all of which have (according to some "authorities") worked.

The author also includes a short glossary covering the few technical words used in the book and a well-constructed index. These serve to make the book complete.

This book deserves to be read by physicians treating patients with low back and neck pain, and by the patients who have the pain. I think of the book as a useful, well-illustrated manual on safe self-treatment of back pain, preferably under the supervision of the patient's physician.

Reviewed by Dr. Henry Shykoff. Dr. Shykoff is a member of staff at the Toronto East General Hospital and the Riverdale Hospital.

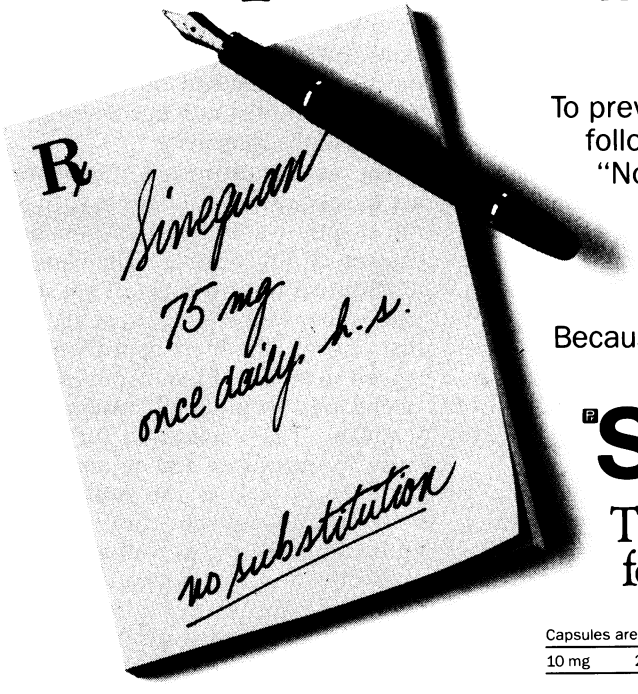
Impact of Families on Health

Title: *Review of Families and Health*
Author: William J. Doherty, Thomas L. Campbell
Publisher: SAGE Publications, Inc., 2111 Hillcrest Dr., Newbury Park, CA 91320 U.S.A.
Publication Date: 1988

Finally, a simple and crisp book about the relationship of families and health. Any teacher who is involved in the training of social workers, doctors, nurses, or any other professional involved in health services delivery will be pleased with this small book, which is a superb guide through the very recent literature on the interaction of family, health, and illness.

The main strength of this book is the authors' use of the family health and illness cycle as a way of organizing the literature and demonstrating the temporal sequence of health and illness in the family. This model represents a nice way of reviewing literature, and will be very useful to students and teachers in preparing

"no substitution"; your depressed patients.



To prevent potential therapeutic disruption, the following recommendation has been made:† "No substitution" should be indicated on all new prescriptions issued for repeated or prolonged pharmacotherapy.[4] When you prescribe clinically proven Sinequan*, specify "no substitution". Because a decision based on years of experience deserves your written reassurance.

Sinequan*
(doxepin HCl/pfizer)
There is no substitute for experience.

Capsules are available in the following strengths:

10 mg	25 mg	50 mg	75 mg	100 mg	150 mg

Pfizer
Kirkland, Quebec
H9J 2M5

Meet an age-old problem face to face

Evidence indicates that Stieva-A (tretinoin), one of the most effective topical therapies in the treatment and prevention of acne,[1,2] promotes the formation of new collagen which results in augmentation of the dermis and improved skin texture, major factors in the amelioration of skin quality.

Stieva-A is proven to:

- Promote collagen formation
- Improve the skin's surface
- Accelerate skin renewal
- Effectively treat existing acne lesions[1]
- Effectively prevent future lesions[2]

Stieva-A*

(TRETINOIN USP)

Topical therapy for an age-old problem

STIEFEL*

For prescribing information see page 1890

*Trademark

1. Mandy SH. The art of tretinoin therapy in acne. *Cutis* 1974 Dec 855-7.

2. Leyden JJ; Shalita AR. Rational therapy for acne vulgaris: An update of topical treatment. *J Am Acad Dermatol* 1986 Oct 15 (4 Pt 2 Suppl): 907-15.

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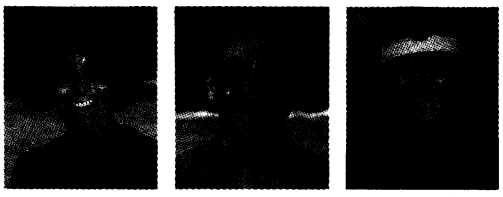
SCI-D-89-07/STV/61-JA-E

Minipress* (prazosin HCl/pfizer)

Because lowering blood pressure is not enough.



Prescribing Information

Therapeutic Classification
Antihypertensive

Indications and Clinical Use:
MINIPRESS (prazosin hydrochloride) is indicated in the treatment of hypertension. It is mild to moderate in activity.
It is employed in a general treatment program in conjunction with a diuretic and/or other antihypertensive drugs. It may be employed as the initial agent in the treatment of mild hypertension when treatment should be started with a vasodilator rather than a diuretic.

Contraindications:
MINIPRESS is contraindicated in patients with a known sensitivity to the drug.

Warnings:
MINIPRESS may cause syncope with sudden loss of consciousness. In most cases this is believed to be due to an excessive postural hypotensive effect although occasionally the syncopal episode has been associated with a bout of severe tachycardia with heart rates of 120-160 beats per minute. The incidence of syncopal episodes is approximately 0.8% when the gradual dose build up described under dosage and administration is followed. The incidence is higher if the initial dose exceeds 0.5 mg. Syncopal episodes have occurred within 30 to 90 minutes of the initial dose of the drug. They have also been reported in association with dosage increases or the introduction of MINIPRESS into the regimen of a patient taking another antihypertensive agent or a diuretic. Physicians are therefore advised to limit the initial dose of the drug to 0.5 mg b.i.d. or t.i.d., to subsequently increase the dosage slowly and to introduce any additional antihypertensive drugs into the patient's regimen with caution. Patients whose blood pressure is not adequately controlled by high doses of a beta-adrenergic blocking agent such as propranolol may develop acute hypotension when MINIPRESS is added.
To minimize the incidence of acute hypotension in such patients, the dose of beta-adrenergic blocking agent should be reduced before MINIPRESS is administered. A low initial dose of MINIPRESS is also strongly recommended (see dosage and administration).
If syncope occurs, the patient should be placed in the recumbent position and supportive measures instituted. This adverse effect is self-limiting and in most cases does not recur once a steady maintenance level is initiated. Patients should be cautioned to avoid situations where injury could result should syncope occur during MINIPRESS therapy especially in the initial dose adjustment period.
More common than loss of consciousness are the symptoms often associated with lowering of the blood pressure, namely dizziness and lightheadedness. The patient should be cautioned about these possible adverse effects and advised what measures to take should they develop.
Use During Pregnancy:
The safety of MINIPRESS use during pregnancy or lactation has not been established. In these situations, the potential benefits of the drug must be weighed against the potential risks to mother and child.
Use For Children:
MINIPRESS is not recommended for the treatment of children under the age of twelve years.

Precautions:
Use in Patients with Moderate to Severe Grades of Renal Impairment:
Therapy should be initiated at 0.5 mg daily and dose increases instituted cautiously.

Adverse Reactions:
Postural dizziness (11%), nausea (9.5%), drowsiness (8.7%), headache (8.4%), palpitations (6.6%), dry mouth (5.6%), weakness (4.6%), and fatigue/malaise (4.5%). In most instances side effects have disappeared with continued therapy or have been tolerated with no decrease in dose of drug. The following reactions have also been observed during MINIPRESS administration, some of them rarely:
Gastrointestinal: Vomiting, diarrhea, constipation, abdominal discomfort and/or pain. *Cardiovascular:* Syncope (See WARNINGS), edema, dyspnea, tachycardia. *CNS:* Nervousness, vertigo, depression, paresthesia.
Dermatologic: Rash, pruritus. *Genitourinary:* Urinary frequency, impotence. *EENT:* Blurred vision, reddened sclera, epistaxis, tinnitus, nasal congestion. *Other:* Diaphoresis.
Pigmentary mottling, serous retinopathy and cataract development have been reported, although the exact causal relationship has not been established.
In more specific slit-lamp and funduscopic studies, no drug-related abnormal ophthalmological findings have been reported.

Dosage and Administration:
NOTE: When titration is to be undertaken using the tablet formulation it will be necessary to split the 1 mg scored tablet to obtain the 0.5 mg starting dose. It is recommended that the starting dose of 0.5 mg be given with food preferably with the evening meal, at least two or three hours before retiring. The dose should be built up gradually starting with 0.5 mg given b.i.d. or t.i.d. for at least three days. Unless adverse effects occur and subject to the blood pressure lowering effect, this dose should be increased to 1 mg given b.i.d. or t.i.d. for at least a further three days. Thereafter, as determined by the patient's response, the dose should be increased gradually. Response is usually seen within one to fourteen days if it is to occur at any particular dose. When a response is seen, therapy should be continued at that dose until the degree of response has reached the optimum before the next dose increment is added. Incremental increases should be continued until a desired effect is achieved or a maximum daily dose of 20 mg is reached. The maintenance dose may be given as a twice daily dosage regimen. In patients with moderate to severe grades of renal impairment, it is recommended that therapy be initiated at 0.5 mg daily and that dose increases be instituted gradually.

Use With Other Drugs:
Patients Receiving Diuretic Therapy:
The diuretic should be reduced to a maintenance dose level for the particular agent and MINIPRESS initiated at 0.5 mg b.i.d. or t.i.d. After the initial period of observation, the dose of MINIPRESS should be gradually increased as determined by the patient's response.
Patients Receiving Other Antihypertensive Agents:
Because some additive effect is anticipated, the other agent should be reduced with appropriate precautions and MINIPRESS initiated at 0.5 mg b.i.d. or t.i.d. Subsequent dosage increase should be made depending upon the patient's response.
Patients on MINIPRESS To Whom Other Antihypertensive Agents Are Added:
When adding a diuretic or other antihypertensive agent, the dose of MINIPRESS should be reduced to 1 mg or 2 mg b.i.d. or t.i.d. and retitration then carried out.

Dosage Form:
Tablets
MINIPRESS is available as scored tablets containing prazosin hydrochloride equivalent to 1 mg (orange, flat oblong), 2 mg (white, round) or 5 mg (white, diamond) of prazosin. Bottles of 100 (all tablet strengths) and 500 (1 mg only) tablets.

Product monograph available on request.

References
1. Grimm RH and Hunninghake DB. Lipids and hypertension, implications of new guidelines for cholesterol management in the treatment of hypertension. *Am J Med* 1986;80(2A):56-63.
2. Ames RP. The influence of non beta-blocking drugs on the lipid profile: are diuretics outclassed as initial therapy for hypertension? *Am Heart J* 1987;114(4, part 2):998-1006.
3. Stokes GS. Selective alpha-inhibition: an overview of efficacy. *Clin Ther* 1987;9(suppl. D):37-45.
4. Jens TJ. Effects of smoking on the heart and peripheral circulation. *Am Heart J* 1988;115:263-266.
5. Kaplan NM. Strategies to reduce risk factors in hypertensive patients who smoke. *Am Heart J* 1988;115:288-294.

*Prepared by Pfizer Canada Inc. (R.U.)
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Pfizer
Kirkland, Quebec
H9J 2M5

sidered the household her domain, battling a bout of depression because she is suddenly out of a job. Perhaps the wife views her husband's retirement as an opportunity for renewed intimacy. His plans, however, might involve fishing trips, golf tournaments, and curling bonspiels, in the company of his male friends.

All three scenarios have the makings of marital bombshells. They give rise to feelings of resentment, 'usually by the wife,' adds the social worker, whose statement that women report marital strain more often than men is based on her own observations as well as on the findings of several American surveys. Although the resentment may simmer quietly unchecked for a while, it inevitably reaches the boiling point. According to the psychologist, it is often a matter of one spouse's not realizing the consequences of his or her actions. 'Once each partner is helped to see the situation from the other spouse's viewpoint, they can usually negotiate a mutually satisfactory compromise.'

Illness can also undermine marital harmony. 'When a spouse becomes ill, many times the other partner becomes the exclusive caregiver, shunning all help from family and friends,' the social worker contends. The supporting partner becomes overextended and, frustrated by his or her inability to cope, becomes resentful of the spouse's illness. In the same situation, the supporting spouse may be frail and find it necessary to place the other in an institution. Although the ill partners will receive the care they need, they may also feel abandoned.

Although both elderly and young couples are subject to marital stress, there is a noticeable difference in how each generation resolves conflict. Today, if a young or middle-aged couple cannot come to terms with their differences, they often divorce. While many elderly couples openly admit that they would not be together if they belonged to the younger generation, for them divorce simply isn't an option. "These are couples for whom the vow 'for better or for worse' is as sacred today as it was 25, 30, or even 50 years ago, the social worker said.

'Their marriages are based on an entirely different system of values,' the psychologist stresses 'and we as

Continued on page 1850

Are you positive she tested negative?

The false-negative problem. You may not know it, but research shows that the rate of false-negative Pap smears may be as high as 55 percent.

A major problem is the endocervical sampling device. Ordinary sampling devices—swabs and spatulas—are simply inefficient cell collectors, yielding inadequate samples up to 70% of the time.

Adequate endocervical specimens are also extremely vital in Chlamydia and other STD testing.

The Cytobrush Solution. The ZELSMYR® Cytobrush® cell collector was designed to improve the reliability of *all* endocervical testing. And it's easy to use. With just one turn, its soft bristles collect more endocervical cells and material than ordinary devices can—that's why it's known as the World's Best Celler. The cells are released more efficiently and in better condition. So you get consistently higher-quality samples, making analysis easier and more accurate. The results?

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- Reduced professional liability associated with false-negatives.
- Cost-effective testing due to fewer repeats.

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The World's Best Celler

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Patent No. 4,759,376. Zelsmyr® is a registered trademark of International Cytobrush, Inc. Cytobrush® is a registered trademark and product of Medscand Sweden. Contraindications: Do not use for endometrial sampling. Do not use on pregnant patients (due to insufficient data).

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THE CHANCES OF AN OSTEOARTHRITIC DEVELOPING AN ULCER WITH VOLTAREN® SR ARE JUST ABOUT AS SLIM.

We're not overstating the case.

You may know from experience that Voltaren SR is one of the best tolerated anti-arthritics available.

Of course, most antiarthritics are effective enough.

But consider that world wide data indicates that the incidence of gastric or duodenal ulceration and bleeding in patients on Voltaren is rare.[1]

With Voltaren SR your patients stand a good chance of being able to continue long-term therapy uninterrupted by severe gastrointestinal side effects.

So when you're treating long-term OA, remember that Voltaren SR maintenance therapy is a good way to decrease the likelihood of future complications.

TWICE DAILY Voltaren SR 75

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Sustained release diclofenac sodium

PROVEN TOLERABILITY AT MAXIMUM DOSAGE.[2]

ONCE-A-DAY 100

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Sustained release diclofenac sodium

PROVEN TOLERABILITY WHEN YOUR PATIENTS NEED LESS THAN MAXIMUM DOSAGE.

Geigy

Mississauga, Ontario
L5N 2W5

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1. Voltaren Product Monograph, July 1989.

For prescribing information see page 1942

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The College Travel Page

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Information: Quality Assurance in Health Care, Conference and Seminar Services, Humber College, 205 Humber College Blvd., Etobicoke, Ont. M9W 5L7

20–22 National Conference on Mental Health: Community Reinvestment. London, Ont. Information: Kelly McKinley, National Conference Co-ordinator, CMHA London/Middlesex Branch, 355 Princess Ave., London, Ont. N6B 2A7 Telephone: (519) 434-9178

20–Nov. 22. OHA Management Education: Series I (Wednesday Evenings). Newmarket, Ont. Information: Admissions Office, Seneca College, Newmarket Campus, 112 Yonge St. S., Newmarket, Ont. L3Y 6Y9 Telephone: (416) 898-6199

22 Prevention and Rehabilitation of Stroke. Toronto, Ont. Information: Jean Twiner, Organising Secretary, Sunnybrook Medical Centre, 2075 Bayview Ave., Toronto, Ont. M4N 3M5 Telephone: (416) 480-4287

22 Healing Co-Dependency: The Journey from Shame to Respect. Toronto, Ont. Information: LifeCycle Learning, Suite 305, 1320 Centre St., Newton, MA 02159 U.S.A. Telephone: (617) 964-5050, Fax: (617) 965-5054

22 OHA Management Education: Series I. Chesley, Ont. Information: Karen King, c/o Chesley & District Memorial Hospital, 39 2nd St. S.E., Chesley, Ont. N0G 1L0 Telephone: (519) 881-1220

22 OHA Management Education: Series I. Kingston, Ont. Information: Ontario Hospital Association, Management Education, 1st Floor, 150 Ferrand Dr., Don Mills, Ont. M3C 1H6 Telephone: (416) 429-2661, ext. 3302

22–23 Risk Management in Long-Term Care. Victoria, B.C. Information: Dr. John Maccagno, 1459 Jamaica Rd., Victoria, B.C. V8N 2C9 Telephone: (604) 477-7559

23 OHA Management Education: Series II—Long-Term Care. Waterloo, Ont. Information: Conestoga College of Applied Arts & Technology, Continuing Education, Waterloo Campus, 435 King St. N., Waterloo, Ont. N2S 2Z5 Telephone: (519) 885-0300

23 OHA Management Education: Series II. Mississauga, Ont. Information: Sheridan College, Mississauga Campus, 100 Dundas St. W., Mississauga, Ont. L5B 1H3 Telephone: (416) 279-3731

23–24 Canadian Association of Physical Medicine and Rehabilitation. Edmonton, Alta. Information: Dr. Lee Kirby, Nova Scotia Rehabilitation Centre, 1341 Summer St., Halifax, N.S. B3H 4K4

24–27 Focus on Child Abuse: Facing the Challenges Together. Toronto, Ont. Information: Dorothy Malcolm, The Institute for the Prevention of Child Abuse, 25 Spadina Rd., Toronto, Ont. M5R 2S9 Telephone: (416) 921-3151

24–28 Ninety-third Annual Meeting of the American Academy of Otolaryngology. New Orleans, GA. Information: American Academy of Otolaryngology–Head and Neck Surgery, Suite 302, 1101 Vermont Ave. N.W., Washington, DC 20005 U.S.A. Telephone: (202) 289-4607

24–30 Royal Australian College of General Practitioners Conference. Tasmania. Information: Penelope Archer, Tasmania Faculty, Royal Australian College of Gener-

◄ BRIEF PRESCRIBING INFORMATION ►

ERYC*

(encapsulated enteric-coated erythromycin pellets)

Therapeutic classification: Antibiotic.

Indications: The treatment of the following infections when caused by susceptible strains of micro-organisms: upper and lower respiratory tract infections; skin and soft tissue infections; gonorrhea; syphilis; Legionnaires' disease; pertussis; diphtheria; short term prophylaxis of bacterial endocarditis in patients hypersensitive to penicillin.

Contraindications: Known hypersensitivity to erythromycin.

Precautions: The possibility of superinfection caused by overgrowth of nonsusceptible bacteria or fungi should be kept in mind during prolonged or repeated therapy with ERYC. In such instances, the administration of ERYC should be discontinued and appropriate treatment instituted if necessary.
Erythromycin is excreted principally by the liver. Caution should be exercised when administering ERYC to patients with impaired hepatic function.
The concomitant administration of erythromycin and high doses of theophylline may be associated with increased serum theophylline levels and possible theophylline toxicity. The dose of theophylline may require reduction while patients are receiving ERYC.
The safety of ERYC for use in pregnant patients has not been established.
There is placental transfer and excretion of erythromycin in breast milk.
Adverse Effects: The most frequent side effects are gastrointestinal and are dose-related. They include nausea, vomiting, abdominal pain, diarrhea and anorexia. Symptoms of hepatic dysfunction and/or abnormal liver function test results may occur.

Serious allergic reactions have been extremely infrequent. Mild allergic reactions such as rashes with or without pruritis, urticaria, bullous eruptions and eczema have been reported with erythromycin.

DOSAGE AND ADMINISTRATION

ERYC and ERYC 125 capsules are administered one hour before meals or in the fasting state in order to obtain optimum serum concentrations of erythromycin.

Adults: The usual dose is ERYC capsule 250 mg every 6 hours. Depending on the severity of the infection, larger doses may be considered, however, a single dose should not exceed 500 mg.

Children: Age, weight, and severity of the infection are important factors in determining the proper dosage. The usual dosage is 30–50 mg/kg/day in equally divided doses. For the treatment of more severe infections, this dosage may be increased. The entire contents of an ERYC 125 capsule should be sprinkled on a small amount of applesauce, fruit jellies, or ice cream immediately prior to ingestion. SUBDIVIDING THE CONTENTS OF A CAPSULE IS NOT RECOMMENDED. If desired, ERYC capsule may be swallowed whole.

PROPHYLAXIS

For continuous prophylaxis against recurrence of streptococcal infections in persons with a history of rheumatic heart disease, the recommended dose is 250 mg twice a day. For the prevention of bacterial endocarditis due to alpha-hemolytic streptococci in penicillin-allergic patients with valvular heart disease who are to undergo dental procedures or surgical procedures of the upper respiratory tract, the adult dose is 1 g one hour prior to the procedure and 500 mg six hours later. The pediatric dose is 20 mg/kg (maximum 1 g) one hour before surgery, followed by 10 mg/kg (maximum 500 mg) six hours later.

Primary syphilis: 2–4 grams per day for a period of 10 to 15 days.

Intestinal Amoebiasis: 250 mg four times daily for 10 to 15 days for adults.

Legionnaires' Disease: Optimal doses have not been established. Doses utilized in reported clinical data were 0.5 to 1 g every 6 hours.

Pertussis: Although optimal dosage and duration of therapy have not been established, doses of erythromycin utilized in reported clinical studies were 40–50 mg/kg/day, given in divided doses for 5 to 14 days.

ERYC capsule is a two-tone clear and orange opaque capsule each containing 250 mg erythromycin base as enteric-coated pellets. Available in bottles of 100 and 500.
ERYC 125 capsule is a two-tone clear and orange opaque capsule containing 125 mg erythromycin base as enteric-coated pellets. They bear the inscription "This End Up" and "P-D" on the cap and "Eryc 125" on the body. Available in bottles of 100.
Store at room temperature below 30°C.
Protect from moisture and light.

Full prescribing information is available on request.

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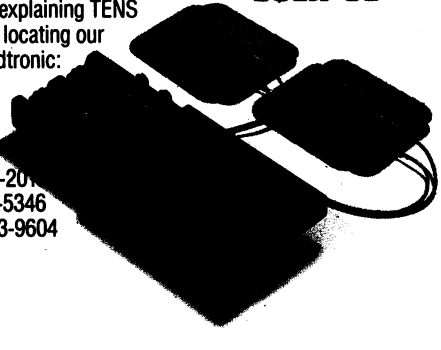

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(captopril)

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INDICATIONS: FOR THE TREATMENT OF ESSENTIAL OR RENOVASCULAR HYPERTENSION. It is usually administered in association with other drugs, particularly thiazide diuretics. The blood pressure lowering effects of captopril and thiazides are approximately additive. In using CAPOTEN (captopril), consideration should be given to the risk of neutropenia/agranulocytosis (see WARNINGS). **a) In patients with normal renal function.** CAPOTEN should normally be used in those patients in whom treatment with diuretic or beta-blockers was found ineffective or has been associated with unacceptable adverse effects. CAPOTEN can be tried as an initial agent in those patients with severe hypertension or in those in whom the use of diuretics and/or beta-blockers is contraindicated or in patients with medical conditions in which those drugs frequently cause serious adverse effects. **b) In patients with impaired renal function.** In these patients, particularly those with collagen vascular disease, captopril should be reserved for hypertensives who have either developed unacceptable side effects on other drugs, or have failed to respond satisfactorily to drug combinations (see WARNINGS). CAPOTEN is indicated in patients with heart failure who have not responded adequately to or cannot be controlled by conventional diuretic and digitalis therapy. CAPOTEN is to be used with diuretics and digitalis.

CONTRAINDICATION: Contraindicated in patients with a history of hypersensitivity to the drug.

WARNINGS: Proteinuria: Total urinary proteins greater than 1 g per day were seen in <1% of patients receiving CAPOTEN (captopril), but this has been predominantly in those who had prior renal disease, or in those receiving relatively high doses (>150 mg per day), or both. In patients without prior evidence of renal disease the incidence of proteinuria was 0.5%. In those patients without prior evidence of renal disease receiving ≤150 mg of CAPOTEN per day, the incidence was 0.2%. Parameters of renal function, such as BUN and serum creatinine were seldom altered in patients with proteinuria. In most cases, proteinuria subsided or cleared within 6 months whether or not captopril was continued. Nephrotic syndrome occurred in about one-fifth of proteinuric patients. Membranous glomerulopathy was found in biopsies taken from proteinuric patients. A causal relationship to CAPOTEN has not been established since pre-treatment biopsies were not taken and membranus glomerulopathy has been shown to occur in hypertensive patients not receiving CAPOTEN. Since most cases of proteinuria occurred by the eighth month of therapy with captopril, patients with prior renal disease or those receiving captopril at doses greater than 150 mg per day should have urinary protein estimations (dip-stick on first morning urine, or quantitative 24-hour urine) prior to therapy, at approximately monthly intervals for the first nine months of treatment, and periodically thereafter. When proteinuria is persistent, 24-hour quantitative determinations provide greater precision. For patients who develop proteinuria exceeding 1 g/day, or proteinuria that is increasing, the benefits and risks of continuing captopril should be evaluated.

Neutropenia/Agranulocytosis: Neutropenia (<1000/mm³) with myeloid hypoplasia has resulted from use of captopril. About half of the neutropenic patients developed systemic or oral cavity infections or other features of the syndrome of agranulocytosis. The risk of neutropenia is dependent on the clinical status of the patient: In clinical trials in patients with hypertension who have normal renal function (serum creatinine <1.6 mg/dL and no collagen disease), neutropenia has been seen in one patient out of over 8,600 exposed. In patients with some degree of renal failure (serum creatinine at least 1.6 mg/dL) but no collagen vascular disease, the risk of neutropenia in clinical trials was about 1 per 500, a frequency of over 15 times that for uncomplicated hypertension. Daily doses of captopril were relatively high in these patients, particularly in view of their diminished renal function. In patients with renal failure, use of allopurinol concomitantly with captopril has been associated with neutropenia. In patients with collagen vascular disease (e.g., systemic lupus erythematosus, scleroderma) and impaired renal function, neutropenia occurred in 3.7% of patients in clinical trials. While none of the over 750 patients in formal clinical trials of heart failure developed neutropenia, it has occurred during subsequent clinical experience. About half of the reported cases had serum creatinine >1.6 mg/dL and more than 75% were in patients also receiving procainamide. In heart failure, it appears that the same risk factors for neutropenia are present. The neutropenia has been detected within 3 months after captopril was started. Bone marrow examinations in patients with neutropenia consistently showed myeloid hypoplasia, frequently accompanied by erythroid hypoplasia and decreased numbers of megakaryocytes (e.g., hypo-plastic bone marrow and pancytopenia); anemia and thrombocytopenia were sometimes seen. In general, neutrophils returned to normal about 2 weeks after captopril was discontinued, and serious infections were limited to clinically complex patients. About 13% of the cases of neutropenia have ended fatally, but almost all fatalities were in patients with serious illness, having collagen vascular disease, renal failure, heart failure or immunosuppressant therapy, or a combination of these complicating factors. Evaluation of the hypertensive or heart failure patients should always include assessment of renal function. If captopril is used in patients with impaired renal function, white blood cell and differential counts should be evaluated prior to starting treatment and at approximately 2 week intervals for about 3 months, then periodically. In patients with collagen vascular disease or who are exposed to other drugs known to affect the white cells or immune response, particularly when there is impaired renal function, captopril should be used only after assessment of benefit and risk, and then with caution. Patients treated with captopril should be told to report any signs of infection (e.g., sore throat, fever). If infection is suspected, white cell counts should be performed without delay. Since discontinuation of captopril and other drugs has generally led to prompt return of the white count to normal, upon confirmation of neutropenia (neutrophil count 1000/mm³), the physician should withdraw captopril and closely follow the patient's course. Since captopril decreases aldosterone production, elevation of serum potassium may occur rarely, especially in patients with renal failure (see PRECAUTIONS – Drug Interactions).

Hypotension: Excessive hypotension was seen in hypertensive patients but is a possible consequence of captopril use in severely salt/volume depleted persons such as those treated vigorously with diuretics, for example, patients with severe congestive heart failure (see PRECAUTIONS – Drug Interactions). In heart failure, where the blood pressure was either normal or low, decreases in mean blood pressure >20% were recorded in about half of the patients. This transient hypotension may occur after any of the first several doses and produces either no symptoms or brief mild lightheadedness, although in rare instances, it has been associated with arrhythmia or conduction defects. Hypotension was the reason for discontinuation of drug in 3.6% of patients with heart failure. BECAUSE OF THE POTENTIAL FALL IN BLOOD PRESSURE IN THESE PATIENTS, THERAPY SHOULD BE STARTED UNDER CLOSE MEDICAL SUPERVISION. A low starting dose may minimize the hypotensive effect (see DOSAGE AND ADMINISTRATION). Patients should be followed closely for the first 2 weeks of treatment and whenever the dose of CAPOTEN, or diuretic, is increased. Hypotension in itself is not a reason to discontinue CAPOTEN. If associated symptoms are troublesome or persist, they are usually relieved by reducing the dose of either CAPOTEN or diuretic.

PRECAUTIONS: Impaired Renal Function: Some hypertensive patients with renal disease, particularly those with severe renal artery stenosis, have developed increases in BUN and serum creatinine after reduction of blood pressure with captopril. Captopril dosage reduction and/or discontinuation of diuretic may be required. For some, it may not be possible to normalize blood pressure and maintain adequate renal perfusion. About 20% of patients with heart failure develop stable elevations of BUN and serum creatinine 20% above normal or baseline upon long term treatment. Less than 5% of patients, generally those with severe pre-existing renal disease, required discontinuation of treatment due to progressively increasing creatinine; subsequent improvement probably depends upon the severity of the underlying renal disease (see ACTIONS, DOSAGE AND ADMINISTRATION, ADVERSE REACTIONS [Altered Laboratory Findings]).

Valvular Stenosis: There is concern, on theoretical grounds, that patients with aortic stenosis might be at particular risk of decreased coronary perfusion when treated with vasodilators because they do not develop as much afterload reduction.

Surgery/Anesthesia: In patients undergoing major surgery or during anesthesia with agents that produce hypotension, captopril will block angiotensin II formation secondary to compensatory renin release. This may lead to hypotension, which can be corrected by volume expansion.

Pregnancy: Captopril was embryocidal in rabbits when given in doses 2 to 70 times (on a mg/kg basis) the maximum recommended human dose, and low incidences of craniofacial malformations were seen. The marked embryocidal effect in rabbits was most probably due to the particularly marked decrease in blood pressure caused by the drug in this species. Captopril was also embryocidal in sheep when given in doses similar to those given in humans. Captopril given to pregnant rats as 400 times the recommended human dose continuously during gestation and lactation caused a reduction in neonatal survival. No teratogenic effects have been observed after large doses of captopril were administered to hamsters and rats. Safety of the drug in pregnant women has not been established. Since captopril crosses the human placenta, it should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: Following oral administration, concentrations of unchanged captopril in human milk are approximately 1% of those in maternal blood. The effect of low levels of captopril on the nursing infant has not been determined. Caution should be exercised when captopril is administered to a nursing woman, and, in general, nursing should be interrupted.

Pediatric Use: Safety and effectiveness in children have not been established although there is limited experience with the use of captopril in children from 2 months to 15 years of age with secondary hypertension and varying degrees of renal insufficiency. Dosage, on a weight basis, was comparable to that used in adults. CAPOTEN should be used in children only if other measures for controlling blood pressure have not been effective.

DRUG INTERACTIONS: Diuretic Therapy: Patients on diuretics and especially those in whom diuretic therapy was recently instituted, as well as those on severe dietary salt restriction or dialysis, may occasionally experience a precipitous reduction of blood pressure usually within the first hour after receiving the initial dose of captopril (see WARNINGS). When feasible the hypotensive effects may be minimized by either discontinuing the diuretic or increasing the salt intake approximately one week prior to initiation of treatment with CAPOTEN. Alternatively, provide medical supervision for at least one hour after the initial dose. If hypotension occurs, the patient should be placed in a supine position and, if necessary, receive an intravenous infusion of normal saline. This transient hypotensive response is not a contraindication to further doses which can be given without difficulty once the blood pressure has increased after volume expansion.

Agents Having Vasodilator Activity: Data on the effect of concomitant use of other vasodilators in patients receiving CAPOTEN for heart failure are not available; therefore, nitrates (as used for management of angina) or other drugs having vasodilator activity should, if possible, be discontinued before starting CAPOTEN. If resumed during CAPOTEN therapy, such agents should be administered cautiously, perhaps at lower dosage.

Agents Causing Renin Release: Captopril's effect will be augmented by antihypertensive agents that cause renin release. For example, diuretics (e.g., thiazides) may activate the renin-angiotensin-aldosterone system.

Agents Affecting Sympathetic Activity: The sympathetic nervous system may be especially important in supporting blood pressure in patients receiving captopril alone or with diuretics. Therefore, agents affecting sympathetic activity (e.g., ganglionic blocking agents or adrenergic neuron blocking agents) should be used with caution. Beta-blocking drugs add some further hypotensive effect to captopril, but the overall response is less than additive. In heart failure, special caution is necessary since sympathetic stimulation is a vital component supporting circulatory function and inhibition with beta-blockade always carries a potential hazard of further depressing myocardial contractility.

Agents Increasing Serum Potassium: Since captopril decreases aldosterone production, elevation of serum potassium may occur. Potassium-sparing diuretics or potassium supplements should be given only for documented hypokalemia, and then with caution, since they may lead to a significant increase of serum potassium. Salt substitutes which contain potassium should also be used with caution.

Drug/Laboratory Test Interaction: Captopril may cause a false-positive urine test for acetone.

Inhibitors of Endogenous Prostaglandin Synthesis: It has been reported that indomethacin may reduce the antihypertensive effect of captopril, especially in cases of low renin hypertension. Other non-steroidal anti-inflammatory agents (e.g., aspirin) may also have this effect. The blood pressure lowering effects of captopril and beta-blockers are less than additive. In patients with renal failure, the use of allopurinol concomitantly with captopril has been associated with neutropenia. In patients with heart failure, the use of procainamide concomitantly with captopril has been associated with neutropenia.

Information for Patients: Patients should report promptly any indication of infections (e.g., sore throat, fever), which may be a sign of neutropenia, or of progressive edema, which might be related to proteinuria and nephrotic syndrome. All patients should be cautioned that excessive perspiration and dehydration may lead to an excessive fall in blood pressure because of reduction in fluid volume. Other causes of volume depletion such as vomiting or diarrhea may also lead to a fall in blood pressure; patients should be advised to consult with the physician. Warn patients against interruption or discontinuation of antihypertensive medications without the physician's advice. Patients treated for severe congestive heart failure should be cautioned to increase their physical activity slowly.

SYMPTOMS AND TREATMENT OF OVERDOSAGE. In the event of overdosage, correction of hypotension would be of primary concern. Volume expansion with an intravenous infusion of normal saline is the treatment of choice for restoration of blood pressure. Captopril may be removed from the general circulation by hemodialysis.

ADVERSE REACTIONS. Reported incidences are based on clinical trials involving approximately 7000 patients.

Renal: Approximately 1% of patients developed proteinuria (see WARNINGS). Each of the following has been reported in approximately 0.1 to 0.2% of patients and are of uncertain relationship to drug use: renal insufficiency, renal failure, polyuria, oliguria, and urinary frequency.

Hematologic: Neutropenia/agranulocytosis (see WARNINGS). Cases of anemia, thrombocytopenia, and pancytopenia have been reported.

Dermatologic: A rash occurred in 8.5% of patients with normal renal function and 13% of patients with evidence of prior renal function impairment. It was dose related, having occurred in 7% of patients at doses of ≤150 mg per day. The rash is usually maculopapular, rarely urticarial, and generally occurs during the first 4 weeks of therapy. It is usually mild and disappears within a few days of dosage reduction, short term treatment with an antihistaminic agent, and/or discontinuing therapy; remission may occur even if captopril is continued. Pruritus without rash occurs in about 2% of patients. Between 7 and 10% of patients with skin rash have shown an eosinophilia and/or positive ANA titers. A reversible associated pemphigoid like lesion, and photosensitivity, have also been reported.

Angio: Angioedema of the face, mucous membranes of the mouth, or of the extremities has been observed in approximately 0.1% of patients and is reversible on discontinuance of captopril therapy. Serum sickness and bronchospasm have been reported. One case of laryngeal edema has been reported.

Cardiovascular: Hypotension may occur; see WARNINGS and PRECAUTIONS [Drug Interactions] for discussion of hypotension on initiation of captopril therapy. Tachycardia, chest pain, and palpitations have each been observed in approximately 1% of patients. Angina pectoris, myocardial infarction, Raynaud's syndrome, and congestive heart failure have each occurred in 0.2 to 0.3% of patients. Flushing or pallor has been reported in 0.2 to 0.5% of patients.

Alterations in Taste: 2% of patients receiving ≤150 mg/day of CAPOTEN developed a diminuation or loss of taste perception. At doses >150 mg per day, 7% of patients experienced this effect. Taste impairment is reversible and usually self-limited (2 to 3 months) even with continued drug administration. Weight loss may be associated with the loss of taste. The following have been reported in about 0.5 to 2% of patients:

Gastrointestinal: gastric irritation, abdominal pain, nausea, vomiting, diarrhea, anorexia, constipation, aphthous ulcers, peptic ulcer.

CNS: dizziness, headache, malaise, fatigue, insomnia, paresthesia.

Others: dry mouth, dyspnea, cough, alopecia, impotence, loss of libido, disturbed vision, and itching and/or dry eyes.

Altered Laboratory Findings: Elevations of liver enzymes have been noted in a few patients but no causal relationship to captopril use has been established. Rare cases of cholestatic jaundice, and of hepatocellular injury with or without secondary cholestasis, have been reported. Elevation of BUN and serum creatinine may occur, especially in patients who are volume-depleted or who have renovascular hypertension. In instances of rapid reduction of longstanding or severely elevated blood pressure, the glomerular filtration rate may decrease transiently, resulting in transient rises in serum creatinine and BUN. Small increases in the serum potassium concentration frequently occur, especially in patients with renal impairment (see

PRECAUTIONS).

DOSAGE AND ADMINISTRATION: CAPOTEN (captopril) should be taken one hour before meals. DOSAGE MUST BE INDIVIDUALIZED.

Adults: Hypertension: Initiation of therapy requires consideration of recent antihypertensive drug treatment, the extent of blood pressure elevation, salt restriction, and other clinical circumstances. If possible, discontinue the patient's previous antihypertensive drug regimen for one week before starting CAPOTEN. If this is impossible, especially in severe hypertension, the diuretic should be continued. The initial dose of CAPOTEN is 25 mg b.i.d. or t.i.d. If satisfactory reduction of blood pressure has not been achieved after one or two weeks, the dose may be increased to 50 mg b.i.d. or t.i.d. The dose of CAPOTEN in hypertension usually does not exceed 150 mg daily. Therefore, if the blood pressure has not been satisfactorily controlled after 1 to 2 weeks at this dose (and the patient is not already receiving a diuretic), a modest dose of a thiazide-type diuretic (e.g., hydrochlorothiazide, 25 mg daily) should be added. The diuretic dose may be increased at 1 to 2 week intervals until its highest usual antihypertensive dose is reached. If CAPOTEN is started in a patient already receiving a diuretic, CAPOTEN therapy should be initiated under close medical supervision (see WARNINGS and PRECAUTIONS (Drug Interactions) regarding hypotension), with dosage and titration of CAPOTEN as noted above. In severe hypertension, if further blood pressure reduction is required, the dose of CAPOTEN may be increased to 100 mg b.i.d. or t.i.d., and then, if necessary to 150 mg b.i.d. or t.i.d., while continuing the diuretic. The usual dose range is 25 to 150 mg b.i.d. or t.i.d. A maximum daily dose of 450 mg given in three equally divided doses should not be exceeded. For patients with accelerated or malignant hypertension, when temporary discontinuation of current antihypertensive therapy is not practical or desirable, or when prompt titration to more normotensive blood pressure levels is indicated, diuretic should be continued but other concurrent antihypertensive medication should be stopped and CAPOTEN dosage promptly initiated at 25 mg t.i.d., under close medical supervision. When necessitated by the patient's clinical condition, the daily dose of CAPOTEN may be increased every 24 hours under continuous medical supervision until a satisfactory blood pressure response is obtained or the maximum dose is reached. In this regimen, addition of a more potent diuretic, e.g. furosemide, may also be indicated. Beta-blockers may also be used in conjunction with CAPOTEN therapy, (see PRECAUTIONS — Drug Interactions) but the effects of the two drugs are less than additive.

Heart Failure: Initiation of therapy requires consideration of recent diuretic therapy and the possibility of severe salt/volume depletion. In patients with either normal or low blood pressure, who have been vigorously treated with diuretics and who may be hyponatremic and/or hypovolemic, a starting dose of 6.25 or 12.5 mg t.i.d. may minimize the magnitude or duration of the hypotensive effect (see WARNINGS, [Hypotension]). For these patients, titration to the usual daily dosage can then occur within the next several days. For most patients the usual initial daily dosage is 25 mg t.i.d. After a dosage of 50 mg t.i.d. is reached, further increases in dosage should be delayed, where possible, for at least two weeks to determine if a satisfactory response occurs. Most patients studied have had a satisfactory clinical improvement at 50 or 100 mg t.i.d. A maximum daily dose of 450 mg of CAPOTEN should not be exceeded. CAPOTEN is to be used in conjunction with a diuretic and digitalis. Therapy must be initialed under very close medical supervision.

Dosage Adjustment in Renal Impairment: Because CAPOTEN is excreted primarily by the kidneys, excretion rates are reduced in patients with impaired renal function. These patients will take longer to reach steady-state captopril levels and will reach higher steady-state levels for a given daily dose than patients with normal renal function. Therefore, these patients may respond to smaller or less frequent doses. Accordingly, for patients with significant renal impairment, initial daily dosage of CAPOTEN should be reduced, and smaller increments utilized for titration, which should be quite slow (1 to 2 week intervals). After the desired therapeutic effect has been achieved, the dose should be slowly back-titrated to determine the minimal effective dose. When concomitant diuretic therapy is required, a loop diuretic (e.g., furosemide) rather than a thiazide diuretic, is preferred in patients with impaired renal function.

The following table which is based on theoretical considerations may be useful as a guide to minimize drug accumulation.

Creatinine Clearance (mL/min/1.73 m²)	Dosage Interval (Hours)
>75	8
75-35	12-24
34-20	24-48
19-8	48-72
7-5	72-108
	(3 to 4.5 days)

Captopril is removed by hemodialysis.

AVAILABILITY: CAPOTEN (captopril) is available as tablets containing: 25 mg of captopril – white, square, quadrisect scored on one side and imprinted CAPOTEN 25 on the other. 50 mg of captopril – white, oval, biconvex with a partial bisecting score and SQUIBB imprinted on one side and imprinted CAPOTEN 50 on the other. 100 mg of captopril – white, oval, biconvex with a partial bisecting score and SQUIBB imprinted on one side and imprinted CAPOTEN 100 on the other.

Supplied: 25 mg (Bottles of 100 and 1000)
50 mg (Bottles of 100 and 500)
100 mg (Bottles of 100).

Storage: Store at room temperature. Protect from moisture. Keep bottles tightly closed.

Product monograph available to physician upon request.

SQUIBB CANADA INC., 2365 CÔTE-DE-LIESSE, MONTREAL, QUEBEC H4N 2M7 PAAB 11/88

PRESCRIBING INFORMATION

Lopid (Gemfibrozil USP)

300 mg capsules and 600 mg tablets

PHARMACOLOGICAL CLASSIFICATION

Antihyperlipidemic Agent

ACTIONS

LOPID (gemfibrozil) is a lipid regulating agent which decreases serum triglycerides and total cholesterol, and increases high density lipoprotein cholesterol. The lipid-lowering changes occur primarily in the very low density lipoprotein (VLDL) fraction (S_f20–400) rich in triglycerides and to a lesser extent in the low density lipoprotein (LDL) fraction (S_f0–20) rich in cholesterol. LOPID treatment of patients with elevated triglycerides due to Type IV hyperlipoproteinemia may cause a rise in LDL-cholesterol. In addition, LOPID increases the high density lipoprotein (HDL) cholesterol subfractions, HDL_2 and HDL_3, as well as apolipoproteins AI and AII.

Epidemiological studies have shown that both low HDL-cholesterol and high LDL-cholesterol are independent risk factors for coronary heart disease. Depending on the type of hyperlipidemia, pharmacological intervention with LOPID raises HDL-cholesterol and may lower LDL-cholesterol, and may be associated with reduced morbidity due to coronary heart disease as reported in the Helsinki Heart Study; a 5-year primary prevention Phase IV clinical trial (N. Engl. J. Med. 317: 1237-1245, 1987).

INDICATIONS

As an adjunct to diet and other therapeutic measures for the treatment of:

1. Adult patients with very high serum triglyceride levels, Fredrickson classification Type IV and V hyperlipidemias, who are at high risk of sequelae and complications (i.e. pancreatitis).

2. Patients with hypercholesterolemia, Type IIa and IIb mixed dyslipidemias, to regulate lipid levels (reduce serum triglycerides and LDL cholesterol levels and increase HDL cholesterol).

LOPID alone may not be adequate therapy in some patients with familial combined hyperlipidemia with Type IIb and IV hyperlipoproteinemia.

LOPID therapy for hyperlipidemia should include a special diet, weight reduction, and an exercise program; and for patients with diabetes mellitus, a good diabetic control.

CONTRAINDICATIONS

Hepatic or renal dysfunction, including primary biliary cirrhosis; pre-existing gallbladder disease (See Precautions); hypersensitivity to LOPID (gemfibrozil); in pregnant or lactating patients; treatment of Type I hyperlipoproteinemia.

WARNINGS

1. Drug Interactions — Severe myositis with markedly elevated creatinine kinase (CK) and myoglobinuria (rhabdomyolysis) has been reported with concomitant use of LOPID and lovastatin. When myoglobinuria is severe, acute renal failure may ensue. These drugs should not be used concomitantly.

Exercise caution when giving anticoagulants with LOPID. Reduce dosage of anticoagulant to maintain prothrombin time at desired level to prevent bleeding complications. Frequent prothrombin determinations are advised until it has been definitely determined that the prothrombin level has stabilized.

2. LOPID clinically, pharmacologically and chemically shows similarities with clofibrate. Physicians prescribing gemfibrozil should also be familiar with the risks and benefits of clofibrate.

3. Long term studies with gemfibrozil in rats and mice at one and 10 times the human dose, showed significant increases in incidence of benign liver nodules and liver carcinomas in high dose male rats. The incidence of liver carcinomas increased also in low dose males, but was not statistically significant ($p > 0.05$). There were no statistically significant differences from controls in the incidence of liver tumors in female rats, and male and female mice. Liver and testicular cell tumors were increased in male rats.

Electron microscopy studies have demonstrated a florid hepatic peroxisome proliferation following gemfibrozil administration to male rats. Such changes have not been found in the liver of patients treated with this drug.

Toxicology studies in male rats revealed a dose-related increase of benign Leydig cell tumors. Subcapsular bilateral cataracts occurred in 10% and unilateral in 6.3% of high dose males.

4. Cholelithiasis — LOPID may increase cholesterol excretion into the bile leading to cholelithiasis. If cholelithiasis is suspected, gallbladder studies are indicated. Discontinue LOPID therapy if gallstones are found.

5. Since a reduction of total mortality has not been demonstrated, LOPID should be administered only to patients described in "Indications". If a significant serum lipid response is not obtained in 3 months, LOPID should be discontinued.

If LOPID is prescribed, the physician should discuss proposed therapy and inform patient of expected benefits and potential risks which may be associated with long-term administration (See Precautions).

6. Safety and efficacy in children have not been established.

7. Women of childbearing potential must exercise strict birth control procedures. If pregnancy occurs despite birth control procedures, LOPID should be discontinued.

8. Women planning pregnancy should discontinue LOPID several months prior to conception.

9. Nursing mother — Because of the potential for tumorigenicity in rats, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

PRECAUTIONS

1. **Initial Therapy** — Before instituting LOPID (gemfibrozil) therapy, attempts should be made to control serum lipids and lipoproteins with appropriate diet, exercise, weight loss in obese patients, and control of diabetes mellitus.

2. **Long-Term Therapy** — Because long-term administration of LOPID is recommended, pretreatment clinical chemistry studies should be performed to ensure that the patient has elevated serum lipid or low HDL cholesterol levels. Periodic determinations of serum lipids and lipoproteins should be done during administration, including measurement of LDL-cholesterol/HDL-cholesterol ratio, particularly in Type IV hyperlipoproteinemic patients.

3. **Impairment of Fertility** — Administration of approx. three and 10 times the human dose to male rats for 10 weeks resulted in a dose-related decrease of fertility. Subsequent studies demonstrated that this effect was reversed after a drug-free period of about 8 weeks, and was not transmitted to their offspring.

4. **Hemoglobin Changes** — Mild hemoglobin or hematocrit decrease has been observed in occasional patients following initiation of LOPID therapy. Levels stabilize during long-term administration. Therefore, a blood count is recommended every 2 months during the first 12 months of administration.

5. **Liver Function** — Abnormal liver function tests have been observed occasionally during LOPID administration, including elevations of SGOT, SGPT, LDH, and alkaline phosphatase. These are usually reversible when LOPID is discontinued. Therefore, periodic liver function studies are recommended and LOPID therapy should be terminated if abnormalities persist.

6. **Hepatobiliary Disease** — Use LOPID with caution in patients with past history of jaundice or hepatic disorder.

7. **Cardiac Arrhythmias** — Although no clinically significant abnormalities occurred that could be attributed to LOPID, the possibility exists that they may occur.

ADVERSE REACTIONS

(i) Pre-Marketing Studies:

LOPID (gemfibrozil) has been carefully evaluated in over 3,000 patients in monitored clinical studies prior to marketing. Symptoms reported during the controlled phase in studies of 805 subjects were considered for safety. Principal symptoms for which the incidence was greater with gemfibrozil than placebo where nausea, vomiting, and abdominal and epigastric pain. However, the incidence was low: nausea, 4.3% with gemfibrozil versus 3.8% with placebo; vomiting, 2.3% versus 0.8%; abdominal pain, 6.4% versus 4.2%; and epigastric pain, 3.4% versus 1.7%.

(ii) Post-Marketing Study (Helsinki Heart Study):

The long-term safety of LOPID (gemfibrozil) was established in the Helsinki Heart Study, a 5-year primary prevention Phase IV clinical trial. In the double-blind phase of the study, 2,046 patients received LOPID for up to 5 years. Dyspepsia and abdominal pain occurred more often in the gemfibrozil group than the placebo group (19.6% versus 11.9% and 9.8% versus 5.6%, respectively, $p < 0.05$). All other adverse events were similar in frequency between the two groups.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

While there has been no reported case of overdosage, symptomatic supportive measures should be taken should overdose occur.

DOSAGE AND ADMINISTRATION

Recommended adult dose: One 600 mg tablet or two 300 mg capsules b.i.d. 30 minutes before morning and evening meal. Maximum recommended daily dose: 1500 mg.

AVAILABILITY

LOPID 300 mg — maroon and white size 0 capsule, containing 300 mg gemfibrozil. Bottles of 100 and 250.

LOPID 600 mg — white, ellipsoidal, coated tablet, containing 600 mg gemfibrozil. Bottles of 100.

Product Monograph available on request.

REFERENCES:

1. Manninen V, Elo MO, Frick MH, et al: Lipid alterations and decline in the incidence of coronary heart disease in the Helsinki Heart Study. JAMA 1988; 260:641-651.
2. Lopid Product Monograph.
3. Data on file, Medical Affairs Dept., Parke-Davis.

PARKE-DAVIS

Scarborough, Ontario M1L 2N3

*T.M. Warner-Lambert Company, Parke-Davis Division, Warner-Lambert Canada Inc. auth.user. PAAB CCPP PMAC

Mevacor®

(lovastatin)

Tablets 20 mg

Cholesterol-lowering agent

ACTIONS

MEVACOR® (lovastatin), is a cholesterol-lowering agent isolated from a strain of *Aspergillus terreus*. After oral ingestion, lovastatin, which is an inactive lactone, is hydrolyzed to the corresponding β-hydroxyacid form. This principal metabolite is a specific inhibitor of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase.

This enzyme catalyzes the conversion of HMG-CoA to mevalonate, which is an early and rate-limiting step in the biosynthesis of cholesterol.

Lovastatin reduces cholesterol production by the liver and induces some changes in cholesterol transport and disposition in the blood and tissues. The mechanism(s) of this effect is believed to involve both reduction of the synthesis of Low Density Lipoprotein (LDL), and an increase in LDL catabolism as a result of induction of the hepatic LDL receptors.

Lovastatin has complex pharmacokinetic characteristics (see PHARMACOLOGY section of Product Monograph).

INDICATIONS AND CLINICAL USE

MEVACOR® (lovastatin) is indicated as an adjunct to diet for the reduction of elevated total and Low Density Lipoprotein Cholesterol (LDL-C) levels in patients with primary hypercholesterolemia (Types IIa and IIb),† when the response to diet and other measures alone has been inadequate.

After establishing that the elevation in plasma lipids represents a primary disorder not due to secondary conditions such as poorly-controlled diabetes mellitus, hypothyroidism, the nephrotic syndrome, liver disease, or dysproteinemias, it should be determined that patients for whom treatment with lovastatin is being considered have an elevated LDL-C level as the cause for an elevated total serum cholesterol. This may be particularly relevant for patients with total triglycerides over 4.52 mmol/L (400 mg/dL) or with markedly elevated High Density Lipoprotein Cholesterol (HDL-C) values, where non-LDL lipoprotein fractions may contribute significantly to total cholesterol levels without apparent increase in cardiovascular risk. In general, LDL-C may be estimated according to the following equation:

LDL-C (mmol/L) =
Total cholesterol - [(0.37 x triglycerides) + HDL-C][x]

LDL-C (mg/dL) =
Total cholesterol - [(0.16 x triglycerides) + HDL-C]

When total triglycerides are greater than 4.52 mmol/L (400 mg/dL) this equation is not applicable. In such patients, LDL-C may be obtained by ultra-centrifugation.

CONTRAINDICATIONS

- Hypersensitivity to any component of this medication
- Active liver disease or unexplained persistent elevations of serum transaminases
- Pregnancy and lactation (see also PRECAUTIONS)

WARNINGS

The effect of lovastatin-induced changes in lipoprotein levels, including reduction of serum cholesterol, on cardiovascular morbidity or mortality has not been established.

1. **Liver Dysfunction**

In controlled clinical trials, marked persistent increases (to more than 3 times the upper limit of normal) in serum transaminases occurred in 1.6% of adult patients who received MEVACOR® (lovastatin) for at least one year (see ADVERSE REACTIONS and Laboratory Tests). When the drug was interrupted or discontinued in these patients, the transaminase levels fell slowly to pretreatment levels. The increases usually appeared 3 to 12 months after the start of therapy with MEVACOR®, and were not associated with jaundice or other clinical signs or symptoms.

Based on present clinical experience, it is recommended that liver function tests be performed at baseline and every 4-6 weeks during the first 15 months of therapy with MEVACOR® and periodically thereafter in all patients. Particular attention should be paid to patients who develop elevated serum transaminase levels, and in these patients, measurements should be repeated promptly and then performed more frequently.

If the transaminase levels show evidence of progression, particularly if they rise to three times the upper limit of normal and are persistent, the drug should be discontinued. If elevations are persistent beyond discontinuation of the drug, further investigations should be carried out and liver biopsy may be considered if necessary.

The drug should be used with caution in patients who consume substantial quantities of alcohol and/or have a past history of liver disease. Active liver disease or unexplained serum transaminase elevations are contraindications to the use of MEVACOR®; if such condition develops during therapy, the drug should be discontinued.

Moderate elevations of serum transaminases (less than three times the upper limit of normal) have been reported following therapy with MEVACOR® (see ADVERSE REACTIONS). These changes were not specific to MEVACOR® and were also observed with comparative lipid-lowering agents. They generally appeared within the first 3 months after initiation of therapy, were often transient and were not accompanied by any other symptoms. They did not necessitate interruption of treatment.

2. **Muscle Effects**

- **CPK:** Transient elevations of creatine phosphokinase (CPK) levels are commonly seen in lovastatin-treated patients but have usually been of no clinical significance.
- **Myalgia** and muscle cramps have also been associated with lovastatin therapy.
- **Rhabdomyolysis** has occurred rarely and should be considered in any patient with diffuse myalgias, muscle tenderness and/or marked elevation of creatine phosphokinase (10 times the upper limit of normal). In cardiac transplant patients who were receiving immunosuppressive drugs including cyclosporine, there have been reports of severe rhabdomyolysis that precipitated acute renal failure. **Lovastatin therapy should be discontinued if marked elevation of CPK levels occurs, and appropriate therapy should be instituted.**
- **Myopathy:** Most of the patients who have developed myopathy were receiving concomitant therapy with immunosuppressive drugs which included cyclosporine, gemfibrozil or lipid-lowering doses of niacin.
- In clinical trials, about 30% of patients on immunosuppressive therapy, including cyclosporine, developed myopathy within a year after starting therapy with lovastatin. The corresponding incidence figures for concomitant therapy with gemfibrozil and niacin were approximately 5% and 2% respectively. It is not known whether the same phenomenon occurs with concomitant use of lovastatin and fibrates other than gemfibrozil.
- **Therefore, the benefits and risks of using lovastatin concomitantly with immunosuppressive drugs, fibrates or lipid-lowering doses of niacin should be carefully considered.**
- **Interruption of therapy with lovastatin should be considered in any patient with a risk factor predisposing to the development of renal failure or rhabdomyolysis, such as severe acute infection, hypotension, major surgery, trauma, severe metabolic, endocrine or electrolyte disorders and uncontrolled seizures.**

PRECAUTIONS

General
Before instituting therapy with MEVACOR® (lovastatin), an attempt should be made to control hypercholesterolemia with appropriate diet, exercise, weight reduction in overweight and obese patients, and to treat other underlying medical problems (see INDICATIONS AND CLINICAL USE). The patient should be advised to inform subsequent physicians of the prior use of MEVACOR®.

Ophthalmological Observations
There is no unequivocal evidence that lovastatin causes human lens opacities, but lack of an effect on the lens has not been established.

Of 471 patients examined with slit lamp at baseline and during therapy with MEVACOR®, 56 had opacities reported at the final examination (2-24 months after starting lovastatin, average 14 months) that were not noted at baseline.

However, in 49 patients, opacities observed at baseline had disappeared at the final examination.

Lens Opacities

N	Baseline (%)	New	Disappeared	Final Exam (%)
471	165 (35.0)	56	49	168 (35.7)

No clinically significant change in visual acuity was reported nor was any patient discontinued from therapy because of a decrease in visual acuity.

Nevertheless, until further experience is obtained, it is recommended that patients placed on lovastatin therapy be subjected to an examination of the lens before or shortly after initiation of treatment, and annually thereafter.

Use in Homozygous Familial Hypercholesterolemia
MEVACOR® is less effective in patients with the rare homozygous familial hypercholesterolemia, possibly because these patients have no or very low levels of LDL receptor activity. MEVACOR® appears to be more likely to raise serum transaminases (see ADVERSE REACTIONS) in these homozygous patients.

Carcinogenesis
In a 21-month study in mice receiving doses of up to 500 mg/kg/day (312 times the maximum recommended human dose) an increased incidence of hepatocellular carcinomas and adenomas and, in females, pulmonary adenomas was noticed (see TOXICOLOGY section of Product Monograph). However, no evidence of a tumorigenic effect was observed in a 24-month study in rats receiving doses of up to 180 mg/kg/day (112.5 times the maximum recommended human dose).

Use in Pregnancy
MEVACOR® is contraindicated during pregnancy (see Teratogenicity and Reproductive Studies under TOXICOLOGY section of Product Monograph).

Atherosclerosis is a chronic process and the discontinuation of lipid-lowering drugs during pregnancy should have little impact on the outcome of long-term therapy of primary hypercholesterolemia. Moreover, cholesterol and other products of the cholesterol biosynthesis pathway are essential components for fetal development, including synthesis of steroids and cell membranes. Because of the ability of inhibitors of HMG-CoA reductase such as MEVACOR® to decrease the synthesis of cholesterol and possibly other products of the cholesterol biosynthesis pathway, MEVACOR® may cause fetal harm when administered to a pregnant woman.

There are no data on the use of MEVACOR® in pregnant women (see CONTRAINDICATIONS).

MEVACOR® should be administered to women of childbearing age only when such patients are highly unlikely to conceive. If the patient becomes pregnant while taking this drug, MEVACOR® should be discontinued and the patient apprised of the potential hazard to the fetus.

Nursing Mothers
It is not known whether MEVACOR® is excreted in human milk. Because many drugs are excreted in

† A disorder of lipid metabolism characterized by elevated serum cholesterol levels in association with normal triglyceride levels (Type IIa) or with increased triglyceride levels (Type IIb).
Frederickson, D.S., Levy, R.I., Lees, R.S.: Fat transport in lipoproteins - An integrated approach to mechanisms and disorders, N Engl J Med 276:148-156, Jan 1967.

[x] DeLong, D.M. et al.: A comparison of methods, JAMA 256:2372-2377, Nov 7, 1986.

human milk and because of the potential for serious adverse reactions in nursing infants from MEVACOR®, women taking MEVACOR® should not nurse their infants (see CONTRA-INDICATIONS).

Pediatric Use
Safety and effectiveness in children have not been established. Because children are not likely to benefit from cholesterol lowering for at least a decade and because experience with this drug is limited (no studies in subjects below the age of 20 years), treatment of children with lovastatin is not recommended at this time.

Use in Patients with Impaired Renal Function
Lovastatin does not undergo significant renal excretion. However, caution should be exercised in patients with significantly impaired renal function.

Drug Interactions

Concomitant Therapy with other Lipid-Lowering Agents
- Preliminary evidence suggests that the cholesterol-lowering effects of MEVACOR® and the bile acid sequestrant cholestyramine, are additive.
- There is insufficient information to date on the coadministration of MEVACOR® with other lipid-lowering agents. Therefore, caution must be exercised, particularly in the case of gemfibrozil and niacin (see WARNINGS).

Coumarin Anticoagulants: Clinically evident bleeding and/or increased prothrombin time have been reported occasionally in patients taking coumarin anticoagulants concomitantly with lovastatin. Careful monitoring of prothrombin time is therefore recommended in such cases.

Digoxin: In patients with hypercholesterolemia, concomitant administration of lovastatin and digoxin resulted in no effect on digoxin plasma concentrations.

Beta-Adrenergic Blocking Drugs: In healthy volunteers, the coadministration of propranolol and lovastatin resulted in a slight decrease of the AUC of lovastatin and its metabolites as well as in a significant decrease of the C_{max} for the lovastatin metabolites.

The clinical interpretation of this phenomenon is difficult as it may indicate a greater uptake of lovastatin by the liver.

There was no clinically relevant interaction reported in patients who have been receiving MEVACOR® concomitantly with beta-adrenergic blocking agents.

Antipyrine: Antipyrine was used as a model for drugs metabolized by the microsomal hepatic enzyme system (cytochrome P450 system). Lovastatin had no effect on the pharmacokinetics of antipyrine.

Other Concomitant Therapy: Although specific interaction studies were not performed, in clinical studies, MEVACOR® was used concomitantly with calcium-channel blockers (such as verapamil HCl, nifedipine and diltiazem HCl) and a number of diuretics and nonsteroidal anti-inflammatory drugs (NSAIDs), without evidence of clinically significant adverse interactions.

Drug/Laboratory Test Interactions
Lovastatin may elevate creatine phosphokinase and transaminase levels (see Laboratory Tests under ADVERSE REACTIONS). In the differential diagnosis of chest pain in a patient on therapy with MEVACOR®, cardiac and non cardiac fractions of these enzymes should be determined.

ADVERSE REACTIONS

Based on experience in a total of over 1300 patients, of whom about 800 were treated for one year and over 250 for 2 years or more, MEVACOR® (lovastatin) is generally well tolerated and adverse reactions are usually mild and transient.

In controlled clinical trials, less than 1% of patients were withdrawn due to adverse experiences attributable to MEVACOR®. About 2% of patients were withdrawn from all studies (controlled and uncontrolled) due to adverse experiences attributable to MEVACOR®; about one-third of these patients were withdrawn due to increases in serum transaminases.

Adverse experiences reported in patients treated with MEVACOR® in controlled clinical studies are shown in the table below:

	MEVACOR® (n = 613) %	Placebo (n = 82) %
Gastrointestinal		
Constipation	4.9	-
Diarrhea	5.5	4.9
Dyspepsia	3.9	-
Flatus	6.4	2.4
Abdominal pain/cramps	5.7	2.4
Heartburn	1.6	-
Nausea	4.7	3.7
Musculoskeletal		
Muscle cramps	1.1	-
Myalgia	2.4	1.2
Nervous System/ Psychiatric		
Dizziness	2.0	1.2
Headache	9.3	4.9
Skin		
Rash/pruritus	5.2	-
Special Senses		
Blurred vision	1.5	-
Dysgeusia	0.8	-

Laboratory Tests
Marked persistent increases of serum transaminases have been noted (see WARNINGS).

About 11% of patients had elevations of creatine phosphokinase (CPK) levels of at least twice the normal value on one or more occasions. This was attributable to the non cardiac fraction of CPK. Muscle pain or dysfunction was not usually reported. However, myopathy with large increases in CPK has occasionally occurred (see WARNINGS, Muscle Effects and PRECAUTIONS, Drug/ Laboratory Test Interactions).

Nervous System
A single case of peripheral neuropathy has been reported; the relationship to lovastatin is uncertain. Visual evoked response, nerve conduction measurements and electromyography in over 30 patients showed no evidence of neurotoxic effects of lovastatin.

Ophthalmological Observations: (see PRECAUTIONS)

SYMPTOMS AND TREATMENT OF OVERDOSAGE

Five healthy human volunteers have received up to 200 mg of lovastatin as a single dose without clinically significant adverse experiences. A few cases of accidental overdosage have been reported; no patients had any specific symptoms and all patients recovered without sequelae. The maximum dosage taken was fifty-two 20 mg tablets (1.04 g).

In the event of overdosage, treatment should be symptomatic and supportive, liver function should be monitored, and appropriate therapy instituted. Until further experience is obtained, no specific therapy of overdosage can be recommended.

The dialyzability of lovastatin and its metabolites in man is not known.

DOSAGE AND ADMINISTRATION

The patient should be placed on a standard cholesterol-lowering diet before receiving MEVACOR® (lovastatin) and should continue on this diet during treatment with MEVACOR®. If appropriate, a program of weight control and physical exercise should be implemented.

The usual starting dose is 20 mg/day given as a single dose with the evening meal. Single daily doses given with the evening meal have been shown to be more effective than the same dose given with the morning meal, perhaps because cholesterol is synthesized mainly at night. Adjustments of dosage, if required, should be made at intervals of not less than 4 weeks, to a maximum of 80 mg daily given in single doses or divided doses with the morning and evening meals. Divided doses (i.e., twice daily) tend to be slightly more effective than single daily doses.

Cholesterol levels should be monitored periodically and consideration should be given to reducing the dosage of MEVACOR® if cholesterol levels fall below the targeted range, such as that recommended by the Canadian Consensus Conference on Cholesterol.

Concomitant Therapy
Preliminary evidence suggests that the cholesterol-lowering effects of lovastatin and the bile acid sequestrant, cholestyramine, are additive. For concomitant use with other lipid-lowering agents, see WARNINGS and PRECAUTIONS.

DOSAGE FORMS AND AVAILABILITY

Ca 8180 - MEVACOR® 20 mg tablets, a light blue coloured, octagon-shaped, flat, bevelled-edge tablet engraved with 731 on one side and engraved with product name on the other side. Available in bottles of 60 tablets.

PRODUCT MONOGRAPH AVAILABLE ON REQUEST

(326-b,8,88)

MEVACOR® is a Trademark of Merck & Co., Inc./ Merck Frosst Canada Inc., Registered User

2497-98-99

MSD
MERCK SHARP & DOHME CANADA
P.O. BOX 1005, POINTE-CLAIRE
DORVAL, QUEBEC H9R 4P8

PAAB MEMBER PMAC

PONSTAN*

(Mefenamic Acid) Capsules

THERAPEUTIC CLASSIFICATION

Analgesic

INDICATIONS AND CLINICAL USES: PONSTAN (mefenamic acid) is indicated for the relief of pain of moderate severity in conditions such as muscular aches and pains, dysmenorrhea, headaches and dental pain. **CONTRAINDICATIONS:** PONSTAN (mefenamic acid) should not be used in patients who have previously exhibited hypersentivity to it. Mefenamic acid is contraindicated in patients with active ulceration or chronic inflammation of the upper or lower gastrointestinal tract. Ponstan should not be administered to patients who have previously experienced diarrhea as a result of taking the drug. Mefenamic acid should be avoided in patients with pre-existing renal disease. **WARNINGS:** In patients with a history of ulceration or chronic inflammation of the upper or lower gastrointestinal tract, PONSTAN (mefenamic acid) should be given under close supervision and only after consulting the Adverse Reactions Section. Certain patients who develop diarrhea may be unable to tolerate the drug because of recurrence of the symptoms on subsequent exposure. In these subjects, the drug should be promptly discontinued. **PRECAUTIONS:** If rash occurs, the drug should be promptly discontinued. A false-positive reaction for urinary bile, using the diazo tablet test, may result after mefenamic acid administration. If biliuria is suspected, other diagnostic procedures, such as the Harrison spot test, should be performed. In chronic animal toxicity studies PONSTAN (mefenamic acid) at 7 to 28 times the recommended human dose, caused minor microscopic renal papillary necrosis in rats, edema and blunting of the renal papilla in dogs, and renal papillary edema in monkeys. In normal human volunteers, BUN levels were slightly elevated following the prolonged administration of mefenamic acid at greater than therapeutic doses. Since mefenamic acid is eliminated primarily through the kidneys, it should not be administered to patients with significantly impaired renal function. As with other non steroidal antiinflammatory drugs, borderline elevations of liver function tests may occur. Meaningful (3 times the upper limit of normal) elevations of SGPT or SGOT occurred in controlled clinical trials in less than 1% of patients. Severe hepatic reactions including jaundice and cases of fatal hepatitis, have been reported with other nonsteroidal antiinflammatory drugs. Although such reactions are rare, if abnormal liver tests persist or worsen, if clinical signs and symptoms consistent with liver disease develop, or if systemic manifestations occur (eg. eosinophilia, rash, etc.), mefenamic acid should be discontinued. Mefenamic acid may prolong acetylsalicylic acid induced gastrointestinal bleeding. However, mefenamic acid itself appears to be less liable than acetylsalicylic acid to cause gastrointestinal bleeding. Mefenamic acid 500 mg and acetylsalicylic acid 650 mg four times a day both caused significant further lowering of the prothrombin concentration (mefenamic acid 3.48% and acetylsalicylic acid 2.75%) in patients in whom the concentration had been initially lowered by anticoagulant therapy. Caution, therefore, should be exercised in administering mefenamic acid to patients on anticoagulant therapy and should not be given when prothrombin concentrations is in the range of 10 to 20% normal. Careful monitoring of blood coagulation factors is recommended. It is recommended that estimations of hemoglobin and blood counts be carried out at regular intervals. Mefenamic acid should be used with caution in known asthmatics. **Use in pregnancy and in women of childbearing potential:** The safety of mefenamic acid on reproductive capacity and pregnancy has not been established. Thus, mefenamic acid should be used in women of childbearing potential and during pregnancy only when the potential benefits are expected to outweigh the potential risks. **Nursing mothers:** Trace amounts of mefenamic acid may be present in breast milk and transmitted to the nursing infant: thus mefenamic acid should not be taken by the nursing mother because of the effects of this class of drugs on the infant cardiovascular system. **Use in children:** Safety and effectiveness in children below the age of 14 have not been established. **ADVERSE REACTIONS:** The most frequently reported adverse reactions associated with the use of PONSTAN (mefenamic acid) involve the *gastrointestinal tract.* The following disturbances were reported in decreasing order of frequency: diarrhea (approximately 5% of patients), nausea with or without vomiting, other gastrointestinal symptoms and abdominal pain. The occurrence of the diarrhea is usually dose related. Other gastrointestinal reactions less frequently reported were anorexia, pyrosis, flatulence, and constipation. Gastrointestinal ulceration with or without hemorrhage has been reported. *Hematopoietic:* Cases of autoimmune hemolytic anemia have been associated with the continuous administration of Ponstan for 12 months or longer. Decreases in hematocrit have been noted in 2-5% of patients and primarily in those who have received prolonged therapy. Leukopenia, eosinophilia, thrombocytopenic purpura, agranulocytosis, pancytopenia and bone marrow hypoplasia have also been reported on occasion. *Nervous System:* Dizziness, drowsiness, blurred vision, insomnia, nervousness and headache have occurred. *Integumentary:* Urticaria, rash and facial edema have been reported. *Renal:* As with other nonsteriodal antiinflammatory agents, renal failure, including papillary necrosis, have been reported. In elderly patients renal failure has occurred after taking mefenamic acid for 2-6 weeks. The renal damage may not be completely reversible. Hematuria and dysuria have also been reported with mefenamic acid. *Other:* Eye irritation, ear pain, perspiration, mild hepatic toxicity and increased need for insulin in a diabetic have been reported. There have been rare reports of palpitation dyspnea and reversible loss of color vision. **DRUG INTERACTION:** Protein-bound Drugs. Because PONSTAN (mefenamic acid) is highly protein bound, it could be displaced from binding sites by, or it could displace from binding sites, other protein-bound drugs such as oral anticoagulants, hydantoins, salicylates, sulfonamide and sulfonylureas. Patients receiving mefenamic acid with any of these drugs should be observed for adverse effects. Anticoagulants and Thrombolytic Agents. Mefenamic acid enhances the hypoprothrombinemic effect of warfarin, therefore, concurrent administration of the drugs should be avoided whenever possible. If the drugs must be used concurrently, prothrombin time should be determined frequently and anticoagulant dosage adjusted accordingly; the patient should be observed for adverse effects. In addition, the ulcerogenic potential of mefenamic acid and the effect of the drug on platelet function may further contribute to the hazard of concomitant therapy with any anticoagulant or thrombolytic agent (eg. streptokinase). **DOSAGE AND ADMINISTRATION:** Administration is by the oral route, preferably with food. The recommended regimen in acute pain for adults and children over 14 years of age is 500 mg as an initial dose followed by 250 mg every 6 hours as needed, usually not to exceed one week. For the treatment of primary dysmenorrhea, the recommended dosage is 500 mg as an initial dose followed by 250 mg every 6 hours, starting with the onset of bleeding and associated symptoms. Clinical studies indicate that effective treatment can be initiated with the start of menses and should not be necessary for more than 2 to 3 days. **AVAILABILITY**: PONSTAN (mefenamic acid) is available in No. 1 Coni-snap capsule with an ivory opaque body and an aqua blue opaque cap. Each available in bottles of 100 and 500. **TEXT REFERENCES** 1. Budoff PW. Use of mefenamic acid in the treatment of primary dysmenorrhea. *JAMA* 241 (25):2713-2716, June 22, 1979. 2. Smith RP, Powell JR. The objective evaluation of dysmenorrhea therapy. *Am J Obstet Gynecol* 137 (3):314-319, 1980. 3. Powell R, Smith R.P. Treatment of primary dysmenorrhea with an antiprostaglandin agent. (In) *Symposium on "The Role of Prostaglandins in Menstrual Disorders,"* Academy of Medicine Toronto, Ontario, June 20, 1980 pp 29-37. 4. Gabka J. Ponstan dental study. Berlin. July 9, 1974. 5. Walsh et al. Ponstan bioavailability trial: granulated vs. non-granulated forms. 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*Reg. T.M. Parke, Davis & Company
Parke-Davis Canada Inc. auth. user

PARKE-DAVIS

Parke-Davis Canada Inc., Scarborough, Ontario

PMAC PAAB CCPP

NIZATIDINE **AXID®** 300 mg

COMPLETE PRESCRIBING INFORMATION

Pr AXID® Lilly

Nizatidine Histamine H_2 Receptor Antagonist

Pharmacology: Nizatidine is a competitive, reversible inhibitor of the binding of histamine to the histamine H_2 receptor of the gastric-acid secreting cells. Nizatidine is not an anticholinergic agent. It inhibits nocturnal gastric-acid secretion and gastric-acid secretion stimulated by food, caffeine, betazole and pentagastrin. Pepsin output is reduced in proportion to the reduced volume of gastric secretions. Nizatidine has little or no effect on basal serum gastrin or food induced hypergastrinemia. Nizatidine is absorbed rapidly after oral administration. Peak plasma concentrations occur from 0.5 to 3 hours after the dose. Absorption is unaffected by food or propantheline. However, antacids decrease the absorption of nizatidine by about 10%. The absolute oral bioavailability of nizatidine exceeds 90%. Approximately 35% of nizatidine is bound to plasma protein, primarily α1-glycoprotein. This binding is not influenced by other drugs such as warfarin, diazepam, acetaminophen, propranolol, or phenobarbital. Approximately 90% of an oral dose of nizatidine is excreted in the urine within 12 hours. About 60% of an oral dose and 77% of an i.v. dose of nizatidine is excreted as unchanged drug. The elimination half-life is 1 to 2 hours and the systemic plasma clearance is about 50L/hour. The volume of distribution is 0.8 to 1.5 L/kg. Since nizatidine is primarily excreted in the urine, renal impairment significantly prolongs the half-life and decreases the clearance of nizatidine. In anephric individuals with creatinine clearance less than 10mL/min., the half-life is 3.5 to 11 hours, and the plasma clearance is 7 to 14L/hour. The dose should be adjusted in patients with moderate or severe impairment of renal function (see Dosage). The pharmacokinetic profile for nizatidine in the elderly was not significantly different from the profile in younger normal subjects. Gastric acid suppression correlates directly with nizatidine doses from 75 to 350 mg. Oral doses of 100 mg or 1.3 mg/kg suppressed gastric acid secretion in sham fed volunteers for 3 hours after the dose. The duration of acid suppression directly correlates with the nizatidine dose. 300 mg nizatidine suppressed acid secretion almost entirely early in the day, and the suppression persisted about 10 hours. Nocturnal acid was suppressed for 10 to 12 hours after 300 mg nizatidine. Treatment for up to 2 weeks with nizatidine 600 mg daily did not influence the serum concentrations of gonadotropins, prolactin, growth hormone, antidiuretic hormone, cortisol, triiodothyronine, thyroxin, testosterone, 5 α-dihydrotestosterone, androstenedione or estradiol.

Drug Interactions: No interactions have been observed between nizatidine and theophylline, chlordiazepoxide, lorazepam, lidocaine, and warfarin. Nizatidine does not inhibit the cytochrome P-450-linked drug-metabolizing enzyme system; therefore, drug interactions mediated by inhibition of hepatic metabolism are not expected to occur.

Indications: Nizatidine is indicated in the treatment of conditions where a controlled reduction of gastric acid secretion is required for ulcer healing and/or pain relief. Conditions include acute duodenal ulcer, acute benign gastric ulcer, and prophylactic use in duodenal ulcer.

Contraindications: Patients with known hypersensitivity to the drug.

Precautions: Gastric ulcer: Where gastric ulcer is suspected the possibility of malignancy should be excluded before therapy with nizatidine is instituted.

Pregnancy and Lactation: Safety of nizatidine during pregnancy has not been established. Reproduction studies performed in rats and rabbits at doses up to 300 times the human dose have revealed no evidence of impaired fertility or teratogenicity. If the administration of nizatidine is considered to be necessary, its use requires that the potential benefits be weighed against possible hazards to the patient and the fetus. Nizatidine is secreted in the milk of lactating rats, it is assumed to be secreted in human milk and caution should be exercised when nizatidine is administered to nursing mothers.

Impaired Renal Function: As nizatidine is excreted via the kidney, dosage should be adjusted in patients with moderately or severely impaired renal function (see Dosage).

Hepatic Dysfunction: Nizatidine is partially metabolized in the liver; however, in patients with uncomplicated hepatic dysfunction, disposition of nizatidine is similar to that of normal subjects.

Geriatrics: Ulcer healing rates in elderly patients are similar to those in younger age groups. The incidence rates of adverse events and laboratory test abnormalities are also similar to those seen in other age groups. Age alone is not an important factor in the disposition of nizatidine. Elderly patients may have reduced renal function (see Dosage).

Children: Safety and effectiveness of nizatidine in children has not been established.

Adverse Effects: In double-blind, placebo-controlled clinical trials in over 2,300 patients, the overall incidence of adverse events reported by patients treated with nizatidine was no greater than in the placebo group. Clinical pharmacology studies and controlled clinical trials showed no evidence of antiandrogenic activity or other adverse hormonal effects.

Headache, asthenia, chest pain, myalgia, abnormal dreams, somnolence, rhinitis, pharyngitis, cough and pruritus were reported with a slightly higher frequency by nizatidine-treated patients than by the placebo group. A relationship to nizatidine administration has not been established. Excessive sweating may be related to administration and has been reported by 1.1% of patients.

Laboratory Values: Patients treated with placebo and those receiving nizatidine therapy had mild, transient, asymptomatic elevations of transaminases; rare instances of marked elevations (>500 IU/L) occurred in nizatidine-treated patients, although causality has not been established. These abnormalities were asymptomatic and readily reversible after discontinuation of the drug. Other laboratory variables which were statistically different from placebo in the nizatidine-treated group, include serum cholesterol, serum uric acid, platelet count, serum creatinine, and white blood cell count. The clinical significance of these differences is not clear.

Laboratory Tests: False positive tests for urobilinogen with Multistix® may occur during therapy with nizatidine.

Overdose: Treatment: There is no clinical experience with deliberate overdosage of nizatidine in humans. Should overdosage occur, the usual measures to remove unabsorbed material from the gastrointestinal tract should be employed along with clinical monitoring and supportive therapy. The amount of nizatidine absorbed from the gastrointestinal tract can be reduced by activated charcoal.

Dosage: Duodenal or Gastric Ulcer: One 300 mg capsule or two 150 mg capsules once daily at bedtime. Treatment should be given for 4 to 8 weeks, but the duration of the treatment may be shortened if healing can be documented. Healing occurs within 4 weeks in most cases of duodenal ulcer.

Maintenance Dosage in Duodenal Ulcer: One 150 mg capsule once daily at bedtime for 6 to 12 months depending on the severity of the condition. Antacids may be given concomitantly if needed.

Dosage Adjustment in Renal Impairment:

Renal Function	Creatine Clearance (mL/min)	Dosage: Acute	Dosage: Maintenance
Normal	>50	300 mg/ day	150 mg/day
Moderate Impairment	20-50	150 mg/day	150 mg/2nd day
Severe Impairment	<20	150 mg/2nd day	150 mg/3rd day

Supplied:

300 mg: Each pale yellow and brown Pulvule 3145 contains nizatidine 300 mg. Bottles of 30 and 100.

150 mg: Each pale yellow and dark yellow Pulvule 3144 contains: nizatidine 150 mg. Bottles of 30.

Product monograph available on request.

New Product 1987.

References:

1. Jones DB, et al. Acid suppression in duodenal ulcer: a meta-analysis to define optimal dosing with antisecretory drugs. Gut 1987;**28**:1120-27.
2. Dammann HG, et al. Topics in peptic ulcer disease. Perspective on digestive diseases, Cortina Internation, Verona, Italy 1987;**1**:19-27.
3. Howden CW, et al. Relationship between gastric secretion and infection. Gut 1987;**28**:96-107.
4. Simon B, et al. 300mg nizatidine at night versus 300mg ranitidine at night in patients with duodenal ulcer. Scand Jrnl Gastroenterol 1987;**22** (Suppl 136):61-70.
5. Data on file, Eli Lilly Canada Inc.
6. AXID® Product Monograph.

PAAB CCPP PMAC ACIM

Lilly Eli Lilly Canada Inc. Scarborough, Ontario.

SILENCE FEAR. SILENCE INFECTION.

ZOVIRAX® (acyclovir) OINTMENT 5% (4g and 15g tubes)

INDICATIONS AND CLINICAL USE: ZOVIRAX Ointment 5% is indicated for the management of initial episodes of genital herpes simplex infections. It is also indicated in the management of nonlife-threatening cutaneous herpes simplex virus infections in immunocompromised patients. The prophylactic use of this preparation has not been established.

In genital herpes, appropriate examinations should be performed to rule out other sexually transmitted diseases.

These indications are based on the results of a number of double-blind, placebo-controlled studies which examined changes in virus excretion, healing of lesions and relief of pain. Because of the wide biological variations inherent in herpes simplex infections, the following summary is presented merely to illustrate the spectrum of responses observed to date. As in the treatment of any infectious disease, the best response may be expected when therapy is begun at the earliest possible moment.

In immunocompromised patients, 93% were virus negative after 5 days of topical ZOVIRAX therapy, whereas only 35% of placebo recipients were virus negative at the same time.

In patients with herpes labialis, there was a significantly greater decrease in the amount of virus excreted after one day of therapy in those receiving ZOVIRAX within 8 hours of the onset of cold sores when compared to identically treated placebo patients.

Because complete re-epithelialization of herpes-disrupted integument necessitates recruitment of several complex repair mechanisms, the physician should be aware that the disappearance of visible lesions is somewhat variable and will occur later than the cessation of virus shedding. All immunocompromised patients who received topical ZOVIRAX had healed their lesions 23 days after the initiation of a 10-day course of therapy. 75% of placebo patients had healed lesions at that point. Some placebo patients continued to have visible lesions for more than 30 days.

Pain associated with herpes infections is highly variable in frequency and intensity. One hundred percent of the ZOVIRAX-treated immunocompromised patients were pain-free by day 23 versus 70% of placebo-treated patients.

Whereas cutaneous lesions associated with herpes simplex infections are often pathognomonic, Tzanck smears prepared from lesion exudate or scrapings may assist in the diagnosis. Positive cultures for herpes simplex virus offer the only absolute means for confirmation of the diagnosis.

CONTRAINDICATIONS: ZOVIRAX Ointment 5% is contraindicated for patients who develop hypersensitivity or chemical intolerance to any of the components of the formulation, such as polyethylene-glycol.

WARNINGS: ZOVIRAX Ointment 5% is intended for topical use only and should not be used in the eye or on mucous membranes.

PRECAUTIONS: The recommended dosage, frequency of application and duration of treatment of ZOVIRAX Ointment 5% should not be exceeded.

It is not known whether acyclovir is excreted in human milk.

Because many drugs are excreted in human milk, caution should be exercised when ZOVIRAX is administered to a nursing mother.

ZOVIRAX Ointment 5% should be used during pregnancy only if the physician feels the benefit will outweigh the possible harm to the fetus.

Safety of use of ZOVIRAX Ointment 5% in children has not been established.

There exist no data, at this time, which demonstrate that the use of ZOVIRAX Ointment 5% will prevent transmission of infection to other persons.

Since most cutaneous herpes simplex virus infections result from reactivation of latent virus, it is unlikely that ZOVIRAX Ointment 5% will prevent recurrence of infections when applied in the absence of signs and symptoms. ZOVIRAX Ointment 5% should not be applied in an attempt to prevent recurrences: application should commence only at the earliest prodromal sign of disease onset.

Although clinically significant viral resistance associated with the use of ZOVIRAX Ointment 5% has not been observed, this possibility exists.

ADVERSE REACTIONS: Because ulcerated genital lesions are characteristically tender and sensitive to any contact or manipulation, patients may experience discomfort upon application of ointment. In the controlled clinical trials, mild pain (including transient burning and stinging) was reported by 103 (28.3%) of 364 patients treated with ZOVIRAX Ointment 5% and by 115 (31.1%) of 370 patients treated with placebo; treatment was discontinued in 2 of these patients. Other local reactions among acyclovir-treated patients included pruritus in 15 (4.1%), rash in 1 (0.3%) and vulvitis in 1 (0.3%). Among the placebo-treated patients, pruritus was reported by 17 (4.6%) and rash by 1 (0.3%).

In all studies, there was no significant difference between the drug and placebo group in the rate or type of reported adverse reactions.

SYMPTOMS AND TREATMENT OF OVERDOSAGE: Overdosage by topical application of ZOVIRAX Ointment 5% is unlikely because of limited transcutaneous absorption.

DOSAGE AND ADMINISTRATION: Apply ZOVIRAX Ointment 5% liberally to the affected area 4 to 6 times daily for up to 10 days. A sufficient quantity of ointment should be applied to adequately cover all lesions. A finger cot or rubber glove should be used while applying ZOVIRAX in order to prevent:

(1) autoinoculation of other body sites or
(2) transmission of infection to other persons.

Therapy should be initiated as early as possible following onset of signs and symptoms.

AVAILABILITY: ZOVIRAX Ointment 5% is available in tubes of 4 g and 15 g. Each gram contains 50 mg acyclovir in a polyethylene-glycol base. ZOVIRAX Ointment 5% is for topical administration.

Product Monograph available on request.

Reference:

1. Whitley RJ, Levin M, Barton N, et al: Infections caused by herpes simplex virus in the immunocompromised host: Natural history and topical acyclovir therapy. *J Infect Dis* 1984;150:323-329.

PAAB CCPP

*Trade Mark
ZOV-8808

WELLCOME MEDICAL DIVISION
BURROUGHS WELLCOME INC.
KIRKLAND, QUÉ.

ONCE A DAY CLARITIN® (loratadine)

Allergy relief starting in minutes.

CLARITIN®
(loratadine)
Tablets — 10 mg

THERAPEUTIC CLASSIFICATION
Histamine H_1 receptor antagonist

ACTIONS
Loratadine is a long-acting antihistamine with selective peripheral H_1 receptor antagonistic activity. It exhibits a dose-related inhibition of the histamine-induced skin wheal and flare response in humans which is rapid in onset, occurs within the first hour and persists throughout the 24 hour observation period. Single oral doses up to 160 mg and repeat daily doses of 40 mg for up to 13 weeks were well tolerated with the incidence of sedation and dry mouth being no different from placebo.

^{14}C-loratadine is rapidly absorbed reaching Cmax values (4.7, 10.8 and 26.1 ng/mL) at 1.5, 1.0 and 1.3 hours for the 10, 20, and 40 mg dose, respectively. The loratadine elimination half-life (T-1/2$_\beta$) ranged from 7.8-11.0 hours. Descarboethoxyloratadine, the major active metabolite, reached Cmax values (4.0, 9.9 and 16.0 ng/mL) at 3.7, 1.5 and 2.0 hours after a dose of 10, 20 and 40 mg, respectively. Its T-1/2$_\beta$ ranged from 17 to 24 hours. The accumulation indices, calculated by Cmax and the area under the curve (AUC) ratios did not change after the 5th day, indicating little or no accumulation of either loratadine or its metabolite after a multiple once per day dosage regimen. The T-1/2$_\beta$ at steady state levels for loratadine and its metabolite were 14.4 and 18.7 hours, respectively, similar to that reported following a single oral dose.

Approximately 82% of the ^{14}C-loratadine dose is excreted in the urine (40%) and feces (42%) over a 10-day period. Approximately 27% of the dose is eliminated in the urine during the first 24 hours largely in the conjugated form. Unchanged drug is present only in trace quantities in the urine and the active metabolite descarboethoxyloratadine represents only 0.4 to 0.6% of the administered loratadine dose.

INDICATIONS AND CLINICAL USES
CLARITIN (loratadine) Tablets are indicated for the relief of symptoms associated with seasonal allergic rhinitis, such as sneezing, nasal discharge and itching, and ocular itching and burning.

CONTRAINDICATIONS
Contraindicated in patients who have shown hypersensitivity or idiosyncrasy to the drug or its components.

PRECAUTIONS
Use in Pregnancy and in Nursing Mothers: The safe use of CLARITIN (loratadine) Tablets during pregnancy or lactation has not been established and therefore the compound should be used only if the potential benefit justifies the potential risk to fetus or infant. (See PRODUCT MONOGRAPH for information on secretion into breast milk).

ADVERSE REACTIONS
Adverse experiences with CLARITIN (loratadine) occurred with approximately the same frequency as that with placebo control treatment, and included fatigue, headache, dry mouth and sedation.

SYMPTOMS AND TREATMENT OF OVERDOSAGE
To date, overdosage has not occurred with CLARITIN (loratadine). In the event of overdosage, treatment, which should be started immediately, is symptomatic and supportive. Discontinuation of use, gastric lavage or induction of emesis (except in patients with impaired consciousness) and support of vital functions are advised.

DOSAGE AND ADMINISTRATION
Adults and Children 12 years of age and over: One CLARITIN (loratadine) Tablet, 10 mg, once daily.

SUPPLIED
10 mg tablets for oral use. White, oval, shallow tablet with deep score. The flask and dish logo are above the score, and the number 10 below the score. Blister packaged in 10's, and in bottles of 100's. Product monograph available on request.

Starts fast, and lasts.

SCHERING CANADA INC.
Pointe Claire (Quebec) H9R 1B4

PAAB

NEW VOLTAREN® SR 75 mg TWICE DAILY

Intermediate Prescribing Information

Voltaren® (diclofenac sodium)

VOLTAREN 25 and 50 mg Enteric Coated Tablets
VOLTAREN 75 and 100 mg Slow Release Tablets
VOLTAREN 50 and 100 mg Suppositories

Anti-inflammatory Analgesic Agent

INDICATIONS AND CLINICAL USE
Symptomatic treatment of rheumatoid arthritis and osteoarthritis, including degenerative joint disease of the hip.

CONTRAINDICATIONS
Patients with active, or recent history of inflammatory diseases of the gastrointestinal tract such as peptic ulcer, gastritis, regional enteritis, or ulcerative colitis, patients who have shown hypersensitivity to the drug, patients in whom acetylsalicylic acid or other non-steroidal anti-inflammatory agents have induced asthma, rhinitis, or urticaria. Fatal anaphylactoid reactions have occurred in such individuals.
The suppositories are contraindicated in patients with any inflammatory lesions of rectum or anus and in patients with recent history of rectal or anal bleeding.

WARNINGS
Peptic ulceration, perforation and gastrointestinal bleeding, sometimes severe and occasionally (rarely) fatal have been reported during therapy with NSAIDs) including VOLTAREN.
Give VOLTAREN under close medical supervision to patients prone to gastrointestinal tract irritation particularly those with a history of peptic ulcer, melena, diverticulosis or other inflammatory disease of the gastrointestinal tract (such as ulcerative colitis or Crohn's disease). Physician must weigh the benefits of treatment against the possible hazards. (See CONTRAINDICATIONS and ADVERSE REACTIONS sections.)
Instruct patients to contact physician immediately if they experience symptoms or signs suggestive of peptic ulceration or gastrointestinal bleeding. Reactions can occur at any time during treatment, without warning symptoms or signs.
Use in Pregnancy and Lactation: The safety of VOLTAREN in pregnancy and lactation has not been established and its use is not recommended.
VOLTAREN readily crosses the placental barrier and had been detected in breast milk.
Use in Elderly, Frail and Debilitated: Use special care as advancing years appears to increase the possibility of adverse reactions. Reduce dosage to the lowest level that provides control of symptoms.
Use in Children: Not recommended in children under 16 years of age.
Central Nervous System: Headache, dizziness, lightheadedness, and mental confusion have been reported. Caution patients with these symptoms against operating machinery or motor vehicles.

PRECAUTIONS
If peptic ulceration or gastrointestinal bleeding occur, immediately withdraw the drug, institute appropriate treatment and monitor the patient closely. Use caution in patients with a history of blood dyscrasias or disorders of coagulation (see Adverse Reactions).
Periodic evaluation of the hemopoietic system and hemoglobin estimations are advised with long-term treatment. Abnormalities of bone marrow function and anemia secondary to gastrointestinal tract toxicity can occur.
Fluid retention and edema have been reported; use with caution in patients with cardiac decompensation, hypertension and renal diseases, and in those recovering from surgical operations under general anesthesia and other conditions predisposing to fluid retention.
Monitor periodically serum electrolytes during long-term therapy, especially in those patients at risk.
In humans, acute interstitial nephritis with hematuria, proteinuria, and occasionally nephrotic syndrome have been reported.
In patients with prerenal conditions leading to reduction in renal blood flow or blood volume, where renal prostaglandins have a supportive role in the maintenance of renal perfusion, administration of non-steroidal anti-inflammatory agents may precipitate overt renal decompensation due to a dose-dependent reduction in prostaglandin formation. Patients at greatest risk are those with impaired renal function, heart failure, liver dysfunction, those taking diuretics, and the elderly.
Discontinuation of non-steroidal anti-inflammatory therapy is usually followed by recovery to the pre-treatment state.
Clinical signs of adverse renal effects have rarely been observed with VOLTAREN, therefore monitor renal function. Use caution in patients with impaired renal function, as VOLTAREN and its metabolites are eliminated primarily by the kidneys, and reduce the dose accordingly.
During long-term therapy, kidney function should be monitored periodically.
As with other non-steroidal anti-inflammatory drugs, borderline elevations of one or more liver tests may occur. A patient with symptoms and/or signs suggestive of liver dysfunction, or in whom an abnormal liver test has occurred, should be evaluated. Severe hepatic reactions including jaundice and cases of fatal hepatitis have been reported. Although rare, if abnormal liver function tests persist or worsen, if clinical signs consistent with liver disease develop, or if systemic manifestations occur, discontinue treatment. Monitor liver function during long-term treatment.
Use caution in patients with hepatic porphyria, since VOLTAREN may trigger an attack.
The anti-inflammatory, antipyretic, and analgesic effects of VOLTAREN may mask the usual signs of infection and the physician should be alert to the development of infection.
Blurred and/or diminished vision has been reported. If such symptoms develop discontinue VOLTAREN and perform an opthalmologic examination; periodic ophthalmological examinations are recommended for patients on long-term therapy with non-steroidal anti-inflammatory agents.
Allergic reactions, including anaphylactic/anaphylactoid reactions, can occur without prior exposure to drug; therefore, question patients for a history of asthma, nasal polyps, urticaria, and hypotension associated with non-steroidal anti-inflammatory drugs before starting therapy.
Drug Interactions: Acetylsalicylic acid reduces the VOLTAREN serum levels when taken simultaneously. The bioavailability of ASA is reduced by diclofenac. There is no proven advantage in using these drugs concomitantly in the treatment of rheumatological conditions.
When administered concomitantly with lithium, VOLTAREN increases the lithium plasma concentration. Lithium dosage adjustment may be required.
VOLTAREN may increase the plasma concentration of digoxin; dosage adjustment of digoxin may be required.
Pharmacodynamic studies have shown no potentiation of oral hypoglycemic drugs due to concurrent administration with VOLTAREN; however, there are isolated reports of both hypoglycemic and hyperglycemic effects in the presence of VOLTAREN, which necessitated changes in the dosage of hypoglycemic agents. There are isolated reports of an increased risk of hemorrhage with the combined use of VOLTAREN and Sintrom anticoagulant therapy. Use special caution. Perform frequent laboratory tests to ensure anticoagulant response is maintained. At therapeutic doses, VOLTAREN has little effect on spontaneous platelet aggregation. Non-steroidal anti-inflammatory agents may inhibit the activity of diuretics. Concomitant treatment with potassium-sparing diuretics may be associated with increased serum potassium levels, thus making it necessary to monitor the latter.
Concomitant administration of glucocorticoids may aggravate gastrointestinal side effects. Concurrent oral treatment with two or more non-steroidal antirheumatic drugs may promote the occurrence of side effects.
Exercise caution when non-steroidal anti-inflammatory drugs are administered less than 24 hours before or after treatment with methotrexate, since the methotrexate blood concentration may rise and increase its toxicity.
Increased nephrotoxicity of cyclosporin may occur through effects of non-steroidal anti-inflammatory drugs on renal prostaglandins.
Persistently abnormal or worsening renal, hepatic or hematological test values should be followed up carefully since they may be related to therapy.

ADVERSE REACTIONS:
Adverse reactions reported in clinical trials and spontaneous reports are:
Gastrointestinal System: 15.2% – Epigastric or abdominal discomfort, pressure, heaviness, or distention 6%. Epigastric, gastric, or abdominal pain 5%; nausea 2%; anorexia 1%. Diarrhea, vomiting, flatulence or constipation 1%. Gastric and duodenal ulcerations and bleeding 0.2%. Rare (<1%) peptic ulcer with perforation, bloody diarrhea, melena, hematemesis. In isolated cases (<0.001%): lower gut disorders (e.g. non-specific hemorrhagic colitis and exacerbation of ulcerative colitis or Crohn's protocolitis), hyperacidity, stomatitis, glossitis, coated tongue, esophageal lesions.
Central Nervous System: 9% – Dizziness 5%; headache 3%; vertigo, malaise, insomnia, drowsiness, impaired concentration, tiredness: 1%. In isolated cases (<0.001%): irritability, sweating, disturbances of sensation including paresthesia, impaired hearing, tinnitus, convulsions, memory disturbance, disorientation, depression, anxiety, nightmares, tremor, psychotic reactions, taste alteration disorders.
Cardiovascular System: 4.5% – Palpitation 2.5%; angina, arrhythmias 2%. In isolated cases (<0.001%): exacerbation of cardiac failure, hypertension.
Dermatologic System: 4% – Rash 2%; pruritus 1.5%; skin eruption, eczema, urticaria, erythema less than 0.5%. In isolated cases (<0.001%): photosensitivity reactions, loss of hair, erythema multiforme and variants (Stevens-Johnson syndrome, Lyell syndrome); erythroderma, purpura including allergic purpura.
Edema and Water Retention: 2.5% – Facial edema: 2%; general edema: 0.5%; peripheral edema.
Renal System: In isolated cases (<0.001%): renal failure, nephrotic syndrome, urinary abnormalities (eg. hematuria), interstitial nephritis, papillary necrosis.
Hematologic System: Anemia secondary to gastrointestinal bleeding. In isolated cases (<0.001%): leukopenia, thrombocytopenia, agranulocytosis, hemolytic anemia, aplastic anemia.
Respiratory System: Asthma in patients sensitive to ASA.
Hepatic: Occasional (<10%): elevation of serum aminotransferase enzymes (SGOT, SGPT). Rare (<1%): liver function disorders including hepatitis with or without jaundice. In isolated cases (<0.001%): fulminant hepatitis.
Ophthalmological: In isolated cases (<0.001%): disturbances of vision (blurred vision, diplopia).
Allergic: Rare (<1%): Hypersensitivity reactions (e.g. bronchospasm, anaphylactic/anaphylactoid systemic reactions including hypotension).
Administration of suppositories may occasionally give rise to local irritation, rarely local bleeding, exacerbation of hemorrhoids.
In isolated cases (<0.001%): impotence (association with VOLTAREN intake doubtful).

DOSAGE AND ADMINISTRATION
VOLTAREN Tablets 25 mg and 50 mg (enteric coated) Rheumatoid arthritis: initiate treatment with 75 to 150 mg per day in 3 divided doses, depending on the severity of the condition. Maintenance: reduce dose to minimum amount that provides control of symptoms, usually 75 to 100 mg daily in 3 divided doses.
Osteoarthritis: starting and maintenance dose is usually 75 mg/day in 3 divided doses. Adjust dose individually to the minimum dose that will provide control of symptoms.
Maximum recommended daily dose is 150 mg.
Take with food. Swallow tablets whole.
VOLTAREN SR 75 and 100 mg (slow-release tablets)
Treatment should be initiated and individual titration carried out using VOLTAREN enteric coated tablets. Rheumatoid arthritis or osteoarthritis patients on a maintenance dose of 75 mg per day may be changed to a once-daily dose of VOLTAREN SR 75 mg tablets, administered morning or evening.
Patients on a maintenance dose of 100 mg per day may be changed to a once-daily dose of VOLTAREN SR 100 mg tablets, administered morning or evening.
Patients on a maintenance dose of 150 mg per day may be changed to a twice-daily dose of one VOLTAREN SR 75 mg tablet, administered morning and evening.
Maximum daily dose of VOLTAREN should not exceed 150 mg. Swallow VOLTAREN SR tablets whole with liquid, preferably at mealtimes.
VOLTAREN Suppositories
VOLTAREN suppositories, 50 or 100 mg, may be given as substitute for the last of the 3 oral daily doses, to a total daily dose not greater than 150 mg.

AVAILABILITY
VOLTAREN (diclofenac sodium) Tablets 25 mg: yellow, round, slightly biconvex, enteric-coated, bevelled-edged tablets. Printed "25" on one side and "VOLTAREN" on the other.
VOLTAREN (diclofenac sodium) Tablets 50 mg: light brown, round, slightly biconvex, enteric-coated, bevelled-edged tablets. Printed "50" on one side and "VOLTAREN" on the other.
VOLTAREN (diclofenac sodium) Slow-Release Tablets 75 mg: light pink, triangular, biconvex, bevelled-edged, film-coated tablets. Printed "VOLTAREN" on one side and "SR" on the other.
75
VOLTAREN (diclofenac sodium) Slow-Release Tablets 100 mg: pink, round, slightly biconvex, film-coated, bevelled-edged, imprinted "VOLTAREN SR" on one side and "100" on the other.
Store tablets at room temperature, and protect from heat and humidity.
VOLTAREN (diclofenac sodium) Suppositories 50 mg and 100 mg: torpedo-shaped suppositories with smooth surface; yellowish-white in colour.
Protect suppositories from heat.
Product Monograph available on request. July, 1989

1. Voltaren Product Monograph, July 1989.
2. Unpublished data on file, CIBA-GEIGY CANADA LTD.

VOLTAREN® SR 75 mg
Twice Daily.
Proven tolerability at maximum dosage.[1]

VOLTAREN® SR 100 mg
Once-a-day.
Proven tolerability for maintenance therapy when your patients need less than maximum dosage.

VOLTAREN® SR 75 mg
Once Daily.
Proven tolerability for patients who need minimum dosage.[1]

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CHOLESTEROL CONTROL

QUESTRAN. THE ONLY DRUG THAT REDUCES THE RISK OF CHD NON-SYSTEMICALLY BY UP TO 39·3%

THERAPEUTIC CLASSIFICATION
Antidiarrheal and antihypercholesterolemic

ACTION
Cholesterol is probably the sole precursor of bile acids. During normal digestion, bile acids are secreted into the intestines. A major portion of the bile acids is absorbed from the intestinal tract and returned to the liver via the enterohepatic circulation. Only very small amounts of bile acids are found in normal serum.
QUESTRAN resin absorbs and combines with the bile acids in the intestine to form an insoluble complex which is excreted in the feces. This results in a partial removal of bile acids from the enterohepatic circulation by preventing their absorption.
The increased fecal loss of bile acids due to QUESTRAN administration leads to an increased oxidation of cholesterol to bile acids, a decrease in beta lipoprotein or low density lipoprotein plasma levels and a decrease in serum cholesterol levels. Although in man QUESTRAN (cholestyramine resin) produces an increase in hepatic synthesis of cholesterol, plasma cholesterol levels fall.

INDICATIONS AND CLINICAL USE
QUESTRAN is indicated as adjunctive therapy to diet and exercise for the reduction of elevated serum cholesterol in patients with primary hypercholesterolemia (elevated low density lipoproteins); such reduction of serum cholesterol may reduce the risks of atherosclerotic coronary artery disease and myocardial infarction. QUESTRAN may be useful to lower elevated cholesterol in patients with combined hypercholesterolemia and hypertriglyceridemia but it is not indicated where hypertriglyceridemia is the abnormality of most concern.
QUESTRAN is indicated as a symptomatic control of bile acid induced diarrhea due to short bowel syndrome.
QUESTRAN is indicated for the relief of pruritus associated with partial biliary obstruction.

CONTRAINDICATIONS
QUESTRAN is contraindicated in patients with complete biliary obstruction where bile is not excreted into the intestine and in those individuals who have shown hypersensitivity to any of its components.

WARNINGS
QUESTRAN SHOULD NOT BE TAKEN IN ITS DRY FORM. ALWAYS MIX QUESTRAN WITH WATER OR OTHER FLUIDS BEFORE INGESTING.
SINCE QUESTRAN MAY BIND OTHER DRUGS GIVEN CONCURRENTLY, PATIENTS SHOULD TAKE OTHER DRUGS AT LEAST ONE HOUR BEFORE OR 4-6 HOURS AFTER QUESTRAN (OR AT AS GREAT AN INTERVAL AS POSSIBLE) TO AVOID IMPEDING THEIR ABSORPTION.

Pregnancy
Since QUESTRAN is not absorbed systemically, it is not expected to cause fetal harm when administered during pregnancy in recommended dosages. There are, however, no adequate and well controlled studies in pregnant women and, the known interference with absorption of fat soluble vitamins may be detrimental even in the presence of supplementation.

Nursing Mothers
Caution should be excercised when QUESTRAN is administered to a nursing mother. The possible lack of proper vitamin absorption described in the "Pregnancy" section may have an effect on nursing infants.

Pediatric Use
The effects of long term drug administration, as well as its effect in maintaining lowered cholesterol levels in pediatric patients, are unknown. A pediatric dosage schedule has not been established.

Carcinogenesis and Mutagenesis
Studies were conducted in rats in which cholestyramine resin was used as a tool to investigate the role of various intestinal factors (e.g. fat, bile salts and microbial flora). The incidence of intestinal tumors, induced by potent carcinogens, was observed to be greater in cholestyramine resin treated rats, than in control rats. This observation was not evident in all studies conducted in rats, as results from one study indicated a statistically insignificant increase in tumor incidence whereas a more recent study did not demonstrate any presence of tumors following ingestion of cholestyramine.
The relevance of this laboratory observation from studies in rats to the clinical use of QUESTRAN is not known.

PRECAUTIONS
Before instituting therapy with QUESTRAN (cholestyramine resin) an attempt should be made to control serum cholesterol by appropriate dietary regimen, weight reduction, and the treatment of any underlying disorder which might be the cause of hypercholesterolemia. A favorable trend in cholesterol reduction should occur during the first month of QUESTRAN therapy. The therapy should be continued to sustain cholesterol reduction.
Chronic use of QUESTRAN may be associated with increased bleeding tendency due to hypoprothrombinemia associated with Vitamin K deficiency. This will usually respond promptly to parenteral Vitamin K_1 and recurrences can be prevented by oral administration of Vitamin K_1.
Reduction of serum or red cell folate has been reported over long term administration of QUESTRAN. Supplementation with folic acid should be considered in these cases.
There is a possibility that prolonged use of QUESTRAN, since it is a chloride form of anion exchange resin, may produce hyperchloremic acidosis. This would especially be true in younger and smaller patients where the relative dosage may be higher.
QUESTRAN may produce or worsen pre-existing constipation. Dosage should be reduced or discontinued in such cases. Fecal impaction and aggravation of hemorrhoids may occur. Every effort should be made to avert severe constipation and its inherent problems in those patients with clinically symptomatic coronary artery disease.

Laboratory Tests
Serum cholesterol levels should be determined frequently during the first few months of therapy and periodically thereafter. Serum triglyceride levels should be measured periodically to detect whether significant changes have occurred.

Drug Interactions
QUESTRAN may delay or reduce the absorption of concomitant oral medication such as phenylbutazone, warfarin, chlorothiazide (acidic), as well as tetracycline, penicillin G, phenobarbital, thyroid and thyroxine preparations, and digitalis. The discontinuance of QUESTRAN (cholestyramine resin) could pose a hazard to health if a potentially toxic drug such as digitalis has been titrated to a maintenance level while the patient was taking QUESTRAN.
Because cholestyramine binds bile acids, QUESTRAN may interfere with normal fat digestion and absorption and thus may prevent absorption of fat soluble vitamins such as A, D and K. When QUESTRAN is given for long periods of time, concomitant supplementation of water-miscible parenteral forms of vitamins A and D should be considered.

ADVERSE REACTIONS
The most common adverse reaction is constipation. When used as a cholesterol lowering agent predisposing factors for most complaints of constipation are high dose and increased age (more than 60 years old.) Most instances of constipation are mild, transient, and controlled with conventional therapy. Some patients require a temporary decrease in dosage or discontinuation of therapy.
Less frequent adverse reactions: Abdominal discomfort, flatulence, nausea, vomiting, diarrhea, heartburn, anorexia, indigestive feeling and steatorrhea, bleeding tendencies due to hypoprothrombinemia (Vitamin K deficiency) as well as Vitamin A (one case of night blindness reported) and D deficiencies, hyperchloremic acidosis in children, osteoporosis, rash and irritation of the skin, tongue and perianal area.
Occasional calcified material has been observed in the biliary tree, including calcification of the gall bladder, in patients to whom cholestyramine resin has been given. This may be a manifestation of the liver disease and not drug related.
Other adverse reactions (not necessarily drug related) reported in patients taking QUESTRAN include:
Gastrointestinal – GI - rectal bleeding, black stools, hemorrhoidal bleeding, bleeding from unknown duodenal ulcer, dysphagia, hiccups, ulcer attack, sour taste, pancreatitis, rectal pain, diverticulitis.
Hematologic – Increased prothrombin time, ecchymosis, anemia, dental bleeding.
Hypersensitivity – Urticaria, asthma, wheezing, shortness of breath. (This may be due to the allergic potential of FD&C yellow # 5, (tartrazine) contained in the product.)
Musculoskeletal – Backache, muscle and joint pains, arthritis.
Neurologic – Headache, anxiety, vertigo, dizziness, fatigue, tinnitus, syncope, drowsiness, femoral nerve pain, paresthesia.
Eye – Uveitis.
Renal – Hematuria, dysuria, burnt odor of urine, diuresis.

SYMPTOMS AND TREATMENT OF OVERDOSAGE
Overdosage of QUESTRAN has not been reported. Should overdosage occur, the chief potential harm would be obstruction of the gastrointestinal tract. The location of such potential obstruction, the degree of obstruction, and the presence or absence of normal gut motility would determine treatment.

DOSAGE AND ADMINISTRATION
To familiarize the patient with QUESTRAN and to minimize gastrointestinal side effects, it is desirable to begin all therapy with one dose of QUESTRAN daily. Dosage is then increased within a day or two to the desired level for effective control.
Motivation of the patient to continue the prescribed regimen in spite of gastrointestinal problems is important. Physician encouragement and supervision are essential for successful management.
The recommended adult dose is 4 grams of cholestyramine resin, one to six times daily. Dosage may be adjusted as required to meet the patient's needs. A pediatric dosage schedule has not been established.
QUESTRAN should not be taken in its dry form. Always mix QUESTRAN Powder with water or other fluids before ingesting. See Preparation Instructions.

PREPARATION
The color of QUESTRAN (cholestyramine resin) may vary somewhat from batch to batch but this variation does not affect the performance of the product. Mix contents of one packet or one level scoop of QUESTRAN with 120 mL – 180 mL of a preferred beverage (water, milk, fruit juice or other noncarbonated beverage).
QUESTRAN may also be mixed with highly fluid soups or pulpy fruits with high moisture content such as applesauce or crushed pineapple.

AVAILABILITY
QUESTRAN is available in cartons of thirty packets (each packet contains one dose of Questran), or in cans containing 378 g (42 doses of Questran). Each dose of QUESTRAN contains 4 grams of anhydrous cholestyramine resin. Tartrazine is used as the colouring agent.

Questran*

YOUR FIRST COURSE AFTER DIET.

Product monograph available on request.

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NEW TRANSDERM-NITRO™

(0.2 and 0.4 patches)

FOR LONG TERM THERAPY. TRANSDERM-NITRO CAN ALSO BE USED WITH CALCIUM ANTAGONISTS OR BETA BLOCKERS.

Brief Prescribing Information

®Transderm-Nitro™ 0.2 (nitroglycerin)

®Transderm-Nitro™ 0.4 (nitroglycerin)

Transdermal Therapeutic System

Actions The principal pharmacological action of nitroglycerin is relaxation of vascular smooth muscle, producing a vasodilator effect on both peripheral arteries and veins, with more prominent effects on the latter. Dilation of the post-capillary vessels, including large veins, promotes peripheral pooling of blood and decreases venous return to the heart, thereby reducing left ventricular end-diastolic pressure (preload). Arteriolar relaxation reduces system vascular resistance and arterial pressure (afterload). Dilation of the coronary arteries also occurs. The relative importance of preload reduction, afterload reduction, and coronary dilation remains undefined.

When TRANSDERM-NITRO is applied to the skin, nitroglycerin is absorbed directly into the systemic circulation. Thus, the active drug reaches target organs before inactivation by the liver. The transdermal absorption of nitroglycerin occurs in a continuous and well-controlled manner. Nitroglycerin is rapidly metabolized, principally by a liver reductase, to form glycerol nitrate metabolites and inorganic nitrate. Two active major metabolites, the 1,2- and 1,3-dinitroglycerols, the products of hydrolysis, appear to be less potent than nitroglycerin as vasodilators but have longer plasma half-lives. The dinitrates are further metabolized to mononitrates (biologically inactive with respect to cardiovascular effects) and ultimately to glycerol and carbon dioxide. There is extensive first-pass deactivation by the liver following gastrointestinal absorption.

Single-blind, placebo-controlled studies in healthy volunteers revealed that uniform steady state plasma concentrations were reached within two hours after application of the patch and remained at the same level until removal of the patch at 24 hours. Between 2 and 24 hours, the mean concentration was 0.16 ±0.03 ng/ml (1 × 10 cm² patch), 0.25 ± 0.04 ng/ml (2 × 10 cm² patch), and 0.57 ±0.11 ng/ml (4 × 10 cm² patch), the area under the curve showing a linear correlation between drug-release area and plasma concentration. Within one hour of removal of the patch, the plasma concentration declines to about 50% of steady state concentration and to undetectable concentrations by two hours.

Although dosing regimens for most chronically used drugs are designed to provide plasma concentrations that are continuously greater than a minimally effective concentration, such a strategy is probably inappropriate for organic nitrates. Some controlled clinical trials using exercise tolerance testing have shown maintenance of effectiveness when patches are worn continuously. The large majority of such controlled trials, however, have shown the development of tolerance (i.e. complete loss of effect as measured by exercise testing) within the first day. Tolerance has appeared even when doses greater than 4 mg/hour were delivered continuously. This dose is far in excess of the effective dose of 0.2 to 0.8 mg/hour applied intermittently.

Efficacy of organic nitrates is restored after a period of absence of nitrates from the body. Drug-free intervals of 10 to 12 hours are known to be sufficient to restore response. Several studies have demonstrated that when nitroglycerin is administered according to an intermittent regimen, doses of TRANSDERM-NITRO 0.4 - 0.8 mg/hr (20 - 40 cm²) have increased exercise capacity for up to 8 hours, with a trend of increased exercise capacity to 12 hours. One controlled clinical trial suggested that the intermittent use of nitrates may be associated with a decreased, in comparison to placebo, exercise tolerance during the last part of the nitrate-free interval; the clinical relevance of this observation is unknown. In another clinical trial there was an increase in nocturnal angina attacks during the drug-free period in some patients treated with nitroglycerin as compared to placebo. Therefore the possibility of increased frequency or severity of angina during the nitrate-free interval should be considered.

Indications TRANSDERM-NITRO (nitroglycerin) used intermittently (see Actions) is indicated for the prevention of anginal attacks in patients with stable angina pectoris associated with coronary artery disease. It can be used in conjunction with other antianginal agents such as beta-blockers and/or calcium antagonists.

TRANSERM-NITRO is not intended for the immediate relief of acute attacks of angina pectoris. Sublingual nitroglycerin preparations should be used for this purpose.

Contraindications

1. Known hypersensitivity to nitroglycerin and related organic nitrate compounds.
2. Acute circulatory failure associated with marked hypotension (shock and states of collapse).
3. Postural hypotension.
4. Myocardial insufficiency due to obstruction (e.g. in the presence of aortic or mitral stenosis or of constrictive pericarditis).
5. Increased intracranial pressure.
6. Increased intraocular pressure.
7. Severe anemia.

Warnings TRANSDERM-NITRO must be removed before cardioversion or DC defibrillation is attempted, as well as before applying diathermy treatment, since it may be associated with damage to the paddles and burns to the patient.

The benefits and safety of transdermal nitroglycerin in angina patients with acute myocardial infarction of congestive heart failure have not been established. If one elects to use TRANSDERM-NITRO in these conditions, careful clinical or hemodynamic monitoring must be used to avoid the potentially deleterious effects of induced hypotension.

Precautions Headaches or symptoms of hypotension, such as weakness or dizziness, particularly when arising suddenly from a recumbent position, may occur. A reduction in dose or discontinuation of treatment may be necessary.

Caution should be exercised when using nitroglycerin in patients prone to, or who might be affected by hypotension. The drug therefore should be used with caution in patients who may have volume depletion from diuretic therapy or in patients who have low systolic blood pressure (e.g. below 90 mmHg). Paradoxical bradycardia and increased angina pectoris may accompany nitroglycerin-induced hypotension.

Nitrate therapy may aggravate the angina caused by hypertrophic cardiomyopathy.

In industrial workers who have had long-term exposure to unknown (presumably high) doses of nitroglycerin, tolerance clearly occurs. There is moreover, physical dependence since chest pain, acute myocardial infarction, and even sudden death have occurred during temporary withdrawal of nitroglycerin from these workers. In clinical trials of angina patients, there are reports of anginal attacks beings more easily provoked and of rebound in the hemodynamic effects soon after nitrate withdrawal. The importance of these observations to the routine clinical use of nitroglycerin has not been fully elucidated, but patients should be monitored closely for increased anginal symptoms during drug-free periods.

Caution should be exercised in patients with arterial hypoxemia due to anemia (see Contraindications), because in such patients the biotransformation of nitroglycerin is reduced. Similarly, caution is called for in patients with hypoxemia and a ventilation/perfusion imbalance due to lung disease of ischemic heart failure. Patients with angina pectoris, myocardial infarction, or cerebral ischemia frequently suffer from abnormalities of the small airways (especially alveolar hypoxia). Under these circumstances vasconstriction occurs within the lung to shift perfusion from areas of alveolar hypoxia to better ventilated regions of the lung. As a potent vasodilator, nitroglycerin could reverse this protective vasoconstriction and thus result in increased perfusion to poorly ventilated areas, worsening of the ventilation/perfusion imbalance, and a further decrease in the arterial partial pressure of oxygen.

Tolerance to nitroglycerin with cross tolerance to other nitrates or nitrites may occur (see Actions). As tolerance to nitroglycerin patches develops, the effect of sublingual nitroglycerin on exercise tolerance, although still observable, is somewhat blunted.

As patients may experience faintness and/or dizziness, reaction time when driving or operating machinery may be impaired, especially at the start of treatment.

Pregnancy: There are no animal reproduction studies. It is not known whether nitroglycerin can cause fetal harm when administered to a pregnant woman. Therefore use TRANSDERM-NITRO only if the potential benefit justifies the risk to the fetus.

Lactation: It is not known whether nitroglycerin is excreted into breast milk. Benefits to the mother must be weighed against the risks to the child.

Pediatric Use: Safety and effectiveness have not been established in children.

Drug Interactions: Concomittant treatment with other vasodilators, calcium antagonists, ACE inhibitors, beta-blockers, diuretics, antihypertensives, tricyclic antidepressants, and major tranquilizers may potentiate the blood pressure lowering effect of TRANSDERM-NITRO. Dose adjustment may be necessary.

Alcohol may enhance sensitivity to the hypotensive effects of nitrates.

Concurrent administration of TRANSDERM-NITRO with dihydroergotamine may increase the bioavailability of dihydroergotamine. Special attention should be paid to this point in patients with coronary artery disease, because dihydroergotamine antagonizes the effect of nitroglycerin and may lead to coronary vasoconstriction.

The possibility that the ingestion of acetylsalicylic acid and nonsteroidal anti-inflammatory drugs might diminish the therapeutic response to nitrates and nitroglycerin cannot be excluded.

Adverse Reactions Headache, which may be severe, is the most commonly reported side effect. Headache may be recurrent with each daily dose, especially at higher doses of nitroglycerin. Headaches may be treated with concomitant administration of mild analgesics. If such headaches are unresponsive to treatment, the nitroglycerin dosage should be reduced or the product discontinued. Transient episodes of lightheadedness, occasionally related to blood pressure changes, may also occur. Hypotension occurs infrequently, but in some patients it may be severe enough to warrant discontinuation of therapy.

Reddening of the skin, with or without a mild local itching or burning sensation, as well as allergic contact dermatitis may occasionally occur. Upon removal of the patch, any slight reddening of the skin will usually disappear within a few hours. The application site should be changed regularly to prevent local irritation.

Less frequently reported adverse reactions include dizziness, faintness, facial flushing, postural hypotension which may be associated with reflex tachycardia. Syncope, crescendo angina, and rebound hypertension have been reported but are uncommon. Rarely nausea, and vomiting.

Symptoms and Treatment of Overdosage Nitroglycerin overdose may result in severe hypotension, persistent throbbing headache, vertigo, palpitations, visual disturbances, flushing and perspiring skin, anorexia, nausea and vomiting, syncope (especially in the upright posture), methemoglobinemia with cyanosis, hyperpnea, dyspnea and slow breathing, slow pulse (dicrotic and intermittent), heart block, increased intracranial pressure with cerebral symptoms of fever, confusion, and coma possibly followed by paralysis, clonic convulsions and death due to circulatory collapse.

Treatment of Overdose: Keep the patient recumbent in a shock position and comfortably warm. Remove the TRANSDERM-NITRO patch. Passive movement of the extremities may aid venous return. Administer oxygen and artificial ventilation if necessary. Epinephrine is ineffective in reversing the severe hypotensive events associated with overdose; it and related compounds are contraindicated in this situation.

Methemoglobin: Case reports of clinically significant methemoglobinemia are rare at conventional doses of nitroglycerin. The formation of methemoglobin is dose-related, and in the case of genetic abnormalities of hemoglobin that favour methemoglobin formation, even conventional doses of organic nitrates can produce harmful concentrations of methemoglobin. If methemoglobinemia is present, administration of methylene blue (1% solution), 1 to 2 mg/kg intravenously, may be required.

Dosage and Administration

Daily Dosage Schedule: The daily dosage schedule is based on intermittent therapy to prevent the development of tolerance to nitroglycerin. The optimal dose should be selected based upon the clinical response, side effects, and the effects of therapy on blood pressure.

Starting dose is one TRANSDERM-NITRO 0.2 patch (10 cm²), usually applied in the morning. If 0.2 mg/hour (10 cm²) is well tolerated, the dose can be increased to 0.4 mg/hour (20 cm²) if required. A maximum of 0.8 mg/hour (40 cm²) may be used.

Prevention of Tolerance: Although some controlled clinical trials using exercise tolerance testing have shown maintenance of effectiveness when patches are worn continuously, the large majority of such controlled trials have shown the development of tolerance (i.e. complete loss of effect) within the first 24 hours after therapy was initiated. Dose adjustments even to levels much higher than generally used did not prevent the development of tolerance.

Tolerance can be prevented or attenuated by use of an intermittent dosage schedule. Although the minimum nitrate-free interval has not been defined, clinical trials have demonstrated that an appropriate dosing schedule for nitroglycerin patches would provide for a daily patch-on period of 12-14 hours and a daily patch-off period of 10-12 hours. The patch-free time should coincide with the period in which angina pectoris is least likely to occur (usually at night). Patients should be watched carefully for an increase of angina pectoris during the patch-free period. Adjustment of background medication may be required.

The dose of TRANSDERM-NITRO should be periodically reviewed in relation to continuing antianginal control.

Site of Application: TRANSDERM-NITRO can be applied to any area of skin *except* the distal extremities. Many patients prefer the chest. Each successive application should be to a different site.

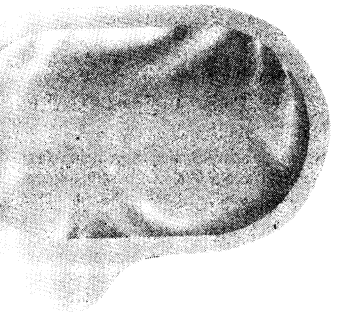
The area should be clean, dry, and preferably hairless. If hair is likely to interfere with patch adhesion or removal, clipping may be necessary prior to application. Take care to avoid areas with skin irritations.

Availability Each TRANSDERM-NITRO 0.2 (10 cm²) contains 25 mg of nitroglycerin and delivers approximately 0.2 mg of active substance per hour. The code "CG DOO" is printed on the tan-coloured backing layer. Each TRANSDERM-NITRO 0.4 (20 cm²) contains 50 mg of nitroglycerin and delivers approximately 0.4 mg of active substance per hour. The code "CG DPD" is printed on the tan-coloured backing layer.

Each system is individually sealed in a separate pouch. Store system below 25°C.

Product monograph available to physicians upon request.

FOR MORE INFORMATION: 1-800-387-[illegible]
IN TORONTO: 821-4420



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TRANSDERM-NITRO™

THE ANTIANGINAL THERAPY WITH ONCE-A-DAY APPLICATION.

CARDIZEM* SR

(diltiazem HCl, sustained release) Capsules 90 and 120mg, Antihypertensive Agent

ACTION AND CLINICAL PHARMACOLOGY: Cardizem is a calcium ion influx inhibitor (calcium entry blocker or calcium ion antagonist). MECHANISM OF ACTION: Therapeutic effect of this group of drugs believed to be related to their specific cellular action of selectively inhibiting transmembrane influx of calcium ions into cardiac muscle and vascular smooth muscle. Contractile processes of these tissues depend upon movement of extracellular calcium into cells through specific ion channels. Diltiazem blocks transmembrane influx of calcium through slow channel without significant effect on transmembrane influx of sodium through fast channel. This results in a reduction of free calcium ions available within cells of above tissues. Diltiazem does not alter total serum calcium. HYPERTENSION: Antihypertensive effect of Cardizem SR is believed to be brought about largely by vasodilatory action on peripheral blood vessels with resultant decrease in peripheral vascular resistance. HEMODYNAMIC AND ELECTROPHYSIOLOGIC EFFECTS: Diltiazem produces antihypertensive effects both in supine and standing positions. Resting heart rate usually slightly reduced. During dynamic exercise, increases in diastolic pressure inhibited while maximum achievable systolic pressure usually unaffected. Heart rate at maximum exercise reduced. Studies to date, primarily in patients with normal ventricular function, have shown cardiac output, ejection fraction and left ventricular end-diastolic pressure not affected. Chronic therapy with diltiazem produces no change, or an increase, in circulating plasma catecholamines. No increased activity of renin-angiotensin-aldosterone axis observed. Diltiazem inhibits renal and peripheral effects of angiotensin II. In man, intravenous Cardizem in doses of 20 mg prolongs AH conduction time and AV node functional and effective refractory periods by approx. 20%. Chronic oral administration of doses up to 360 mg per day has resulted in small increases in PR interval. Second and third degree AV block have been observed (see WARNINGS). In patients with sick sinus syndrome, Cardizem significantly prolongs sinus cycle length (up to 50% in some cases). PHARMACOKINETICS: Diltiazem is well absorbed from the GI tract and is subject to an extensive first-pass effect giving absolute bioavailability (compared to intravenous dosing) of about 40%. Therapeutic blood levels appear to be in the 50-200 ng/mL range and plasma elimination half-life (beta-phase) following single or multiple administration is approx. 3.5 to 6.0 hours. In vitro human serum binding studies revealed 70 to 80% of Cardizem bound to plasma proteins. Following extensive hepatic metabolism, only 2-4% of the drug appears unchanged in urine and 97% appears as metabolites. Major metabolite desacetyl diltiazem present in plasma at levels 10-20% of parent drug and is 25-50% as potent in terms of coronary vasodilation. CARDIZEM SR CAPSULES: Diltiazem is absorbed from slow release (SR) capsule formulation to about 93% of the tablet form at steady-state. Single 120 mg dose of capsule resulted in detectable plasma levels within 2 to 3 hours and peak plasma levels at 7 to 11hours. Apparent elimination half-life after single or multiple dosing is 5 to 7 hours. There is departure from linearity similar to that observed with Cardizem tablet. As dose of Cardizem SR capsules increased from daily dose of 120 mg (60 mg BID) to 240 mg (120 mg BID), there is an increase in bioavailability of 2.6 times. When dose increases from 240 mg to 360 mg daily there is an increase in bioavailability of 1.8 times. Average plasma levels of capsule dosed twice daily at steady-state equivalent to tablets dosed 4 times daily when same total daily dose administered. A study comparing patients with normal hepatic function to liver cirrhosis patients noted an increase in half-life and a 69% increase in bioavailability in hepatically impaired patients. Single dose study in patients with severely impaired renal function showed no difference in half-life of diltiazem as compared to those with normal renal function. (see PRECAUTIONS and DOSAGE AND ADMINISTRATION).

INDICATIONS AND CLINICAL USE: CARDIZEM SR CAPSULES. Indicated in treatment of mild to moderate essential hypertension. Should normally be used in those patients in whom treatment with diuretics or beta-blockers has been associated with unacceptable adverse effects. Can be tried as initial agent in patients in whom use of diuretics and/or beta-blockers contraindicated or in patients with medical conditions in which these drugs frequently cause serious adverse effects. Combination of Cardizem SR with a diuretic found to be compatible and showed additive antihypertensive effect. In a single clinical study concomitant use of Cardizem with captopril also found to be compatible. Safety of concurrent use with other antihypertensive agents not established and such use cannot be recommended at this time.

CONTRAINDICATIONS: In patients with: 1. sick sinus syndrome except in presence of functioning ventricular pacemaker; 2. second or third degree AV block; 3. hypersensitivity to diltiazem; 4. severe hypotension (less than 90 mm Hg systolic); 5. in pregnancy and women of child-bearing potential.

WARNINGS: CARDIAC CONDUCTION. Diltiazem HCl prolongs AV node refractory periods without significantly prolonging sinus node recovery time, except in patients with sick sinus syndrome. This may rarely result in abnormally slow heart rates (particularly in patients with sick sinus syndrome) or 2nd- or 3rd-degree AV block (6 of 1208 patients or 0.5%). Concomitant use of diltiazem with beta-blockers or digitalis may result in additive effects on cardiac conduction. CONGESTIVE HEART FAILURE. Because diltiazem has negative inotropic effect in vitro and affects cardiac conduction, it should only be used with caution and under careful medical supervision in patients with congestive cardiac failure.USE WITH BETA-BLOCKERS. Combination of diltiazem and beta-blockers warrants caution since in some patients, additive effects on heart rate, AV conduction, blood pressure or left ventricular function observed. Close medical supervision recommended. [illegible] to patients with [illegible] done by gradual reduction of dose of [illegible]. HYPOTENSION. Since diltiazem lowers peripheral vascular resistance, decreases in blood pressure may occasionally result in symptomatic hypotension. In patients with angina or arrhythmias using antihypertensive drugs, additional hypotensive effect of diltiazem should be considered. ACUTE HEPATIC INJURY. In rare instances, significant elevations in alkaline phosphatase, CPK, LDH, SGOT, SGPT and symptoms consistent with acute hepatic injury observed. These reactions reversible upon discontinuation of drug. Although a causal relationship to diltiazem not established in all cases, drug induced hypersensitivity reaction suspected (see ADVERSE REACTIONS). As with any drug given over prolonged periods, laboratory parameters should be monitored at regular intervals.

PRECAUTIONS: IMPAIRED HEPATIC OR RENAL FUNCTION. Because diltiazem HCl is extensively metabolized by the liver and excreted by the kidneys and in the bile, monitoring of laboratory parameters and cautious dosage titration recommended in patients with impaired hepatic or renal function. (see ADVERSE REACTIONS). PEDIATRIC USE. Safety of diltiazem in children not yet established. NURSING MOTHERS. Diltiazem reported to be excreted in human milk. One report suggests concentrations in breast milk may approximate serum levels. Since diltiazem safety in newborns not established, should not be given to nursing mothers. USE IN THE ELDERLY. Administration of diltiazem to elderly patients (65 years or over) requires caution. Incidence of adverse reactions approx. 13% higher in this group. Most frequent adverse reactions include: peripheral edema, bradycardia, [illegible], dizziness, rash and polyuria. [illegible] particular [illegible] (see DOSAGE AND ADMINISTRATION).

DRUG INTERACTIONS: DIGITALIS: [illegible] digitalis glycosides may have additive effect in prolonging AV conduction. In clinical trials concurrent administration of diltiazem and digoxin have resulted in increases in serum digoxin levels with prolongation of AV conduction. This increase may result from decrease in renal clearance of digoxin. Patients on concomitant therapy, especially those with renal impairment, should be carefully monitored. Dose of digoxin may need downward adjustment. BETA-BLOCKERS. Concomitant administration of diltiazem with beta adrenergic blocking drugs warrants caution and careful monitoring. Such association may have additive effect on heart rate, AV conduction or blood pressure. (see WARNINGS). Appropriate dosage adjustments may be necessary. A study in [illegible] subjects showed diltiazem increased propranolol bioavailability by approx. 50%. SHORT AND LONG-ACTING NITRATES. Diltiazem may be safely co-administered with nitrates, but few controlled studies done to evaluate antianginal effectiveness of combination. OTHER CALCIUM ANTAGONISTS. Limited clinical experience suggests that in certain severe conditions not responding adequately to verapamil or nifedipine, using diltiazem in conjunction with either drug may be beneficial.

ADVERSE REACTIONS: CARDIZEM SR CAPSULES. Safety evaluations of controlled and open label studies have been carried out. In 611 hypertensive patients treated with Cardizem SR alone or in combination with other antihypertensive agents, adverse effects reported in 34.2% of patients, requiring discontinuation of therapy in 7.2%. Most common adverse effects: peripheral edema (8.3%); headache (4.9%); dizziness (4.7%); asthenia (3.9%), vasodilation (flushing) (2.3%) and bradycardia (2.1%). Percentage of adverse effects, divided by system: CARDIOVASCULAR. Edema peripheral (8.3%;) vasodilation (flushing) (2.3%;) bradycardia (2.1%); AV block (first degree) (1.6%); palpitations (1.3%); arrhythmia (1.0%); heart failure right (0.5%). CENTRAL NERVOUS SYSTEM. Headache (4.9%); dizziness (4.7%); asthenia (3.9%); somnolence (1.0%); nervousness (anxiety) (0.8%); paresthesia (0.7%); insomnia (0.5%); depression (0.5%); dream abnormality (0.5%); tinnitus (0.5%). GASTROINTESTINAL. Dyspepsia (1.1%); nausea (1.1%); constipation (0.7%). DERMATOLOGIC. Rash (1.6%). LABORATORY TESTS. Increased alkaline phosphatase (0.7%). OTHER. Impotence (1.6%); musculoskeletal pain (1.5%); nocturia (1.1%); polyuria (1.0%); rhinitis (0.5%). Additional adverse effects with an incidence of less than 0.5% in clinical trials: syncope, AV block, postural hypotension, chest pain, dyspnea, tremor, gait abnormality, vertigo, taste alteration, anorexia, increased appetite, dry mouth, vomiting, diarrhea, increased saliva, acute hepatic injury, pruritus, urticaria, conjunctivitis, amblyopia, ejaculation abnormality, malaise, fever. Abnormal laboratory findings rarely reported: increased SGOT/SGPT, bilirubinemia, hyperproteinemia, hypercholesteremia, hyperlipidemia, hyperglycemia, hypokalemia, urin abnormality (see PRECAUTIONS).

SYMPTOMS AND TREATMENT OF OVERDOSAGE: Overdosage with oral diltiazem observed in 9 cases. Eight (8) patients recovered without sequelae over a few days. One patient who had ingested an unknown amount of diltiazem, [illegible]ide and alcohol experienced a fatal cardiac arrest. [illegible] ranged from 1.8 to 10.8 g. Bradycardia, AV block and hypotension noted in most patients. In the event of overdosage or exaggerated response, appropriate supportive measures should be employed in addition to gastric lavage. The following measures may be considered: BRADYCARDIA. Administer atropine. If no response to vagal blockade, administer isoproterenol cautiously. HIGH DEGREE AV BLOCK. Treat as for bradycardia above. Fixed high degree AV block should be treated with cardiac pacing. CARDIAC FAILURE. Administer inotropic agents (isoproterenol, dopamine or dobutamine) and diuretics. HYPOTENSION. Vasopressors (e.g., dopamine or levarterenol bitartrate). Actual treatment and dosage should depend on severity of clinical situation.

DOSAGE AND ADMINISTRATION: CARDIZEM SR CAPSULES. HYPERTENSION. Dosage must be individualized depending on patient's tolerance and responsiveness to Cardizem SR capsules and to concomitant antihypertensive medications (see INDICATIONS and PRECAUTIONS). Adult dose range 120 to 360 mg/day administered in 2 equally divided doses. Although individual patients may respond to any dosage level, average optimum dosage range in clinical trials is between 240 and 360 mg/day. Maximum antihypertensive effect usually observed by 2nd to 4th week of chronic therapy, therefore dosage adjustments should be scheduled accordingly. Maximum daily dose of 360 mg should not be exceeded. Evidence that effective dose in elderly (over 65 years) somewhat lower than in younger patients (average dose: 255 mg vs 288 mg respectively); therefore Cardizem SR should be administered cautiously to elderly patients and dosage should be carefully and gradually adjusted depending on patient tolerance and response (see PRECAUTIONS). Cardizem SR has additive antihypertensive effect when used concomitantly with other antihypertensive agents. Therefore, it may be necessary to decrease dose of Cardizem SR and/or dose of the concomitant antihypertensive drug when adding one to the other (see INDICATIONS and WARNINGS). Cardizem SR should not be used in severe hepatic or renal dysfunction.

AVAILABILITY: CARDIZEM SR CAPSULES. Cardizem SR 90 mg capsules (gold/brown). Cardizem SR 120 mg capsules (caramel/brown). Bottles of 100. Each capsule imprinted with distinctive CARDIZEM logo on one end and CARDIZEM SR 90 mg and 120 mg respectively on opposite end.

Product monograph available on request.

References:

1. Materson BJ: Drug Therapy 1985; 15(11): 177-188.
2. Frishman WH, Zawada ET, Kent-Smith L, et al.: Am. J. Cardiol. 1987; 59: 615-623.
3. Szlachcic J, Hirsch AT, Tubau JF, et al.: Am. J. Cardiol. 1987; 59: 393-399.
4. Data on file, Nordic Laboratories, Inc.
5. Lindenberg BS et al.: Am. J. Cardiol. 1983; 2(6): 1129-1133.
6. CARDIZEM* SR/CARDIZEM* Product Monograph.

*Cardizem is a registered trademark of Marion Laboratories, Inc., U.S.A.

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MONTREAL, CANADA

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ONCE A DAY

Orudis® SR

ENTERIC-COATED SUSTAINED-RELEASE KETOPROFEN 200 mg

Therapeutic classification: Anti-inflammatory analgesic agent.

Indications: ORUDIS (ketoprofen) is indicated in the treatment of rheumatoid arthritis, ankylosing spondylitis and osteoarthritis.

Contraindications: ORUDIS (ketoprofen) is contraindicated in patients with active peptic ulcers or active inflammatory diseases of the gastrointestinal tract; suppositories should not be used in patients with any inflammatory lesions of rectum or anus and in patients with a recent history of rectal or anal bleeding.

ORUDIS is also contraindicated in patients who have demonstrated hypersensitivity to the drug. Because of the existence of cross sensitivity, ketoprofen should not be given to patients in whom aspirin and other nonsteroidal anti-inflammatory drugs induce symptoms of asthma, rhinitis or urticaria. Severe, rarely fatal anaphylactic reactions have been reported in such patients.

Warnings: As with other steroidal and nonsteroidal anti-inflammatory drugs, peptic ulcerations and gastrointestinal bleeding have been reported in patients using ORUDIS (ketoprofen). Unlike most adverse reactions, which usually manifest themselves in the first month if they are going to occur in an individual, new peptic ulcers keep appearing in patients under treatment with ketoprofen at a rate of greater than 1% per year.

Use in Pregnancy: The safety of ORUDIS when administered to pregnant or nursing women has not been determined and therefore such use is not recommended. Pregnant rats who received ketoprofen 6 and 9 mg/kg/day p.o. from day 15 of gestation, showed dystocia and increased pup mortality.

Use in Children: The conditions for safe and effective use of ORUDIS in children under 12 years of age have not been established and the drug is therefore not recommended in this age group.

Precautions: Use with caution and careful supervision in patients with a history of gastrointestinal inflammatory disorders or ulceration. Gastrointestinal bleeding sometimes severe and occasionally fatal, and peptic ulcer have occurred in patients receiving ORUDIS (ketoprofen).

Suppositories should be given with caution to patients with any rectal or anal pathology.

ORUDIS in common with other NSAIDs can produce undesirable renal effects including interstitial nephritis, nephrotic syndrome, and overt renal failure. A second form of renal toxicity has been seen in patients with conditions leading to a reduction in renal blood flow or blood volume, where renal prostaglandins have a supportive role in the maintenance of renal blood flow. In these patients administration of a nonsteroidal anti-inflammatory drug results in a dose-dependent decrease in prostaglandin synthesis and, secondarily, in renal blood flow which may precipitate overt renal failure. Patients at greatest risk of this reaction are those with impaired renal function, heart failure, liver dysfunction, those taking diuretics, and the elderly. Discontinuation of nonsteroidal anti-inflammatory drug therapy is typically followed by recovery to the pre-treatment state. Renal function should be monitored periodically in patients on long-term treatment with ORUDIS.

Since ketoprofen is primarily eliminated by the kidneys and its pharmacokinetics are altered by renal failure, ORUDIS should be used with caution and close supervision in patients with significantly impaired renal function, and the dosage adjusted accordingly; a reduction of dosage should be anticipated to avoid accumulation of ketoprofen and/or its metabolites.

As with other nonsteroidal anti-inflammatory drugs, borderline elevations of one or more liver-function tests may occur in up to 15% of patients. These abnormalities may progress, may remain essentially unchanged, or may disappear with continued therapy. The SGPT (ALT) test is probably the most sensitive indicator of liver dysfunction. Meaningful (3 times the upper limit of normal) elevations of SGPT or SGOT (AST) occurred in controlled clinical trials in less than 1% of patients. A patient with symptoms and/or signs suggesting liver dysfunction, or in whom an abnormal liver test has occurred, should be evaluated for evidence of the development of a more severe hepatic reaction while on therapy with ketoprofen. Serious hepatic reactions including jaundice, have been reported from postmarketing experience with ketoprofen as well as with other nonsteroidal anti-inflammatory drugs. Liver function should be monitored during long-term treatment with this drug. The safety of ORUDIS in patients with liver disease has not been established.

Elderly patients, particularly women, appear to be at higher risk from a variety of adverse reactions from nonsteroidal anti-inflammatory drugs and tolerate gastrointestinal side effects less well; consideration should be given to a starting dose that is lower than usual and to increase only if symptoms remain uncontrolled. These patients should be carefully followed. (See Pharmacokinetics and DOSAGE and ADMINISTRATION).

Anemia is commonly observed in rheumatoid arthritis and is sometimes aggravated by nonsteroidal anti-inflammatory drugs, which may produce fluid retention or minor gastrointestinal blood loss in some patients. Therefore, patients with initial hemoglobin values of 10 g/dL or less who are to receive long-term therapy should have hemoglobin values determined frequently.

Fluid retention and peripheral edema have been reported in approximately 2% of patients taking ORUDIS; therefore ORUDIS should be used with caution in patients with cardiac decompensation, hypertension, renal diseases and fluid retention.

Blurred and/or diminished vision has been reported with the use of ORUDIS and other NSAIDs. If a patient develops such complaints while receiving ORUDIS, the drug should be discontinued and an ophthalmological examination carried out. ORUDIS, because of its analgesic and antipyretic properties, may mask signs of infection. This should be kept in mind so that any delay in diagnosing and treating infection in patients receiving ORUDIS may be avoided.

Drug Interactions: 1. *Methotrexate:* The concomitant administration of ketoprofen and high-dose methotrexate has been associated with prolonged and marked enhancement of serum methotrexate levels resulting in severe methotrexate toxicity. This may also apply to some other nonsteroidal anti-inflammatory drugs. There were no abnormalities in methotrexate kinetics or evidence of toxicity when ketoprofen was given at least 12 hours after completion of high-dose methotrexate infusion. ORUDIS should not be used in patients receiving high-dose methotrexate.

The potential for severe toxicity should be kept in mind when prescribing ketoprofen and low-dose methotrexate concurrently. ORUDIS should not be administered within 12 hours of methotrexate infusion.

2. *Oral anticoagulants:* ORUDIS has been shown to depress platelet coagulation and it can prolong bleeding time by approximately 3 to 4 minutes from baseline values. However, a study conducted in twenty patients undergoing therapy with coumarin and simultaneously receiving ORUDIS, failed to demonstrate potentiation of anticoagulant effect. Nevertheless, close monitoring of patients is recommended when ORUDIS is given concomitantly with anticoagulants.

3. *Aspirin:* concurrent administration of aspirin decreased ketoprofen protein binding and increased its plasma clearance. The overall result was a 40% reduction in the AUC of ketoprofen. ORUDIS does not alter aspirin absorption.

4. *Diuretics:* hydrochlorothiazide, given concomitantly with ORUDIS, produces a reduction in urinary potassium and chloride excretion compared to hydrochlorothiazide alone. Patients taking diuretics are at greater risk of developing renal failure secondary to a decrease in renal blood flow caused by prostaglandin inhibition.

5. *Probenecid:* concurrent administration of probenecid increases both free and bound ketoprofen through reducing the plasma clearance of ketoprofen to about one-third as well as decreasing its protein binding. ORUDIS is not recommended in association with probenecid.

6. *Antacids:* concomitant administration of magnesium hydroxide and aluminum hydroxide does not interfere with the rate or extent of the absorption of ketoprofen.

7. *Lithium:* nonsteroidal anti-inflammatory agents have been reported to increase steady-state plasma lithium levels. It is recommended that plasma lithium levels be monitored when ORUDIS is coadministered with lithium.

8. ORUDIS is extensively (99%) protein bound to human serum albumin and may compete for binding sites with drugs such as sulfonamides, oral hypoglycemic agents, phenytoin or lithium. Although no significant interaction has been documented, patients with such combination therapy should be monitored.

Drug/Laboratory Test Interactions: The presence of ORUDIS and its metabolites in urine has been shown to interfere with certain tests which are used to detect albumin, bile salts, 17-ketosteroids or 17-hydroxycorticosteroids in urine and which rely upon acid precipitation as an end point or upon color reactions for carbonyl groups. No interference was seen in the tests for proteinuria using Albustix, Hema-Combistix or Labstix Reagent Strips.

ORUDIS decreases platelet adhesion and aggregation. Therefore, it can prolong bleeding time by approximately 3 to 4 minutes from baseline values. There is no significant change in platelet count, prothrombin time, partial thromboplastin time, or thrombin time.

Adverse reactions: In clinical trials involving 1542 patients, the most common side effects reported were gastrointestinal (22%). The most severe were peptic ulcer or GI bleeding which occurred in controlled clinical trials in less than 1% of 1076 patients; however, in open label continuation studies in 1292 patients, the rate was greater than 2%.

The detailed breakdown of side effects with their corresponding frequencies (not indicated when <1%) is given herewith. That includes rare adverse reactions collected from foreign reports to manufacturers and regulatory agencies, publications and U.S. clinical trials:

Gastrointestinal (22%): dyspepsia (12.8%), nausea (4.0%), indigestion and flatulence (2.8%), vomiting (2.0%), constipation (2.0%), diarrhea (1.4%), anorexia, ulcer, GI bleeding and perforation, melena, hematemesis, stomatitis. Rectal administration was associated with a lower incidence of upper gastrointestinal reactions (12%) with the exception of ulceration, the incidence of which was the same. However, ano-rectal reactions presenting as local pain, burning, pruritus, tenesmus and rare instances of rectal bleeding occurred in 16.5% of subjects. Five percent of patients discontinued rectal therapy because of these local reactions.

Central Nervous System (3-5%): headache (1.7%), fatigue (1%), dizziness, tension, anxiety, depression, drowsiness, impotence, vertigo, migraine, paresthesia.

Dermatological (< 3%): rashes (1.7%), pruritus, flushing, excessive perspiration, alopecia, bullous rash, exfoliative dermatitis, photosensitivity, purpuric rash.

Allergic: urticaria, angioedema, asthma, life threatening bronchospasm.

Cardiovascular: peripheral edema (2%), palpitation, congestive heart failure, hypertension.

Hepatic: hepatic dysfunction, jaundice.

Renal: interstitial nephritis, hematuria, nephrotic syndrome, impairment of renal function, acute renal failure.

Special senses: tinnitus, hearing impairment, visual disturbance, conjunctivitis, conjunctivitis sicca, taste perversion.

Hematological: hypocoagulability, agranulocytosis, anemia, hemolysis, purpura, thrombocytopenia.

Laboratory tests: Abnormal alkaline phosphatase, lactic dehydrogenase, glutamic oxaloacetic transaminase and blood urea nitrogen values were found in some patients receiving ORUDIS therapy. The abnormalities did not lead to discontinuation of treatment and, in some cases, returned to normal while the drug was continued. There have been sporadic reports of decreased hematocrit and hemoglobin values without progressive deterioration on prolonged administration of the drug.

Symptoms and treatment of overdosage: *Symptoms:* Of 20 cases of overdosage (up to 5,000 mg) reported in Great Britain (5 children, 14 adolescents or young adults, and 1 elderly), only 4 had mild symptoms (vomiting in 3, drowsiness in 1 child).

Treatment: Administer gastric lavage or an emetic and treat symptomatically: compensate for dehydration, monitor urinary excretion and correct acidosis if present.

The drug is dialyzable; therefore, hemodialysis may be useful to remove circulating drug and to assist in case of renal failure.

Dosage and administration: ***Adults:*** *Oral:* The usual dosage for ORUDIS (ketoprofen) capsules or enteric-coated tablets is 150 to 200 mg per day in 3 or 4 divided doses.

Once the maintenance dosage has been established, patients may be tried on a twice daily dosing regimen. Clinical trials, however, show that some rheumatoid arthritis patients respond better to more frequent dosing. The usual maintenance dose is 100 mg twice daily.

Initial dosage should be reduced by ⅓ to ½ in patients with impaired renal function and the elderly.

Patients with rheumatoid arthritis or osteoarthritis on a maintenance dose of 200 mg/day may be changed to a once daily dose of ORUDIS SR-200 tablets administered in the morning or evening. ORUDIS SR-200 tablets should be swallowed whole.

ORUDIS-E tablets and ORUDIS SR-200 provide alternative presentations for those who may prefer these dosage forms. No difference in toxicity profile was documented.

Rectal: ORUDIS suppositories offer an alternative route of administration for those patients who prefer it. Administer one suppository morning and evening or one suppository at bedtime supplemented as needed by divided oral doses. The total daily dose of ORUDIS capsules, tablets and suppositories should not exceed 200 mg per day. When the patient's response warrants it, the dose may be decreased to the minimum effective level.

In severe cases, during a flare-up of rheumatic activity or if a satisfactory response cannot be obtained with the lower dose, a daily dosage in excess of 200 mg may be used. However, a dose of 300 mg per day should not be exceeded.

Children: ORUDIS is not indicated in children under 12 years of age because clinical experience in this group of patients is insufficient.

Availability: ORUDIS (ketoprofen) is available as:

Capsules: 50 mg ivory and dark green capsules printed with ORUDIS-50 and the logo ⊛. Bottles of 100 and 500.

Enteric-coated tablets: 50 mg and 100 mg yellow, round, biconvex, enteric-coated tablets, marked with the logo ⊛ on one side and identified 50 or 100 on the other. Bottles of 100 and 500.

Slow-release tablets: 200 mg white, round, biconvex, enteric-coated tablets, marked with the logo ⊛ on one side and identified ORUDIS SR-200 on the other. Bottles of 100 and 500.

Suppositories: 100 mg white to off-white suppositories. Boxes of 30. Store below 30°C.

References: **1.** Paulus, HE: Clinical Pharmacology of the Antirheumatic Drugs. *Primer on the Rheumatic Diseases* 1988;9:283. **2.** Magnusson B, Solvell L, Arvidsson B: A comparative study of gastrointestinal bleeding during administration of ketoprofen and naproxen. *Scand J Rheumatol* 1977;6:62. **3.** Ranlov PJ, Nielson SP, Barenholdt O: Faecal blood loss during administration of acetylsalicylic acid, ketoprofen and two new ketoprofen sustained-release compounds. *Scand J Rheumatol* 1983; 12:280-284. **4.** Teule M: Double-blind comparative multicenter study of the efficacy and safety of a slow-release tablet of 200-mg ketoprofen once daily and a 50-mg ketoprofen capsule four times daily. *Curr Ther Res* 1986; 40:1129-1146.

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PARLODEL® (bromocriptine mesylate)

Because quality of life is the issue

ACTIONS Parlodel (bromocriptine mesylate) is a dopaminomimetic ergot derivate with D_2 type dopamine receptor agonist activity, and has also D_1 dopamine receptor antagonist properties. The dopaminomimetic activity of bromocriptine in the striatum is considered responsible for the clinical benefits seen in selected patients with Parkinson's disease, when low doses of the drug are gradually added to levodopa therapy in patients on long-term treatment who develop late side effects of levodopa or no longer respond to the medication. Excessive dopaminomimetic drive may, however, provoke psychotic and other adverse reactions.

The extreme variability in G.I. tract absorption and the extensive and individually variable first-pass metabolism are responsible for the broad variability in plasma concentrations of bromocriptine and, in part, for the variability in dose response.

INDICATIONS* Parkinson's Disease: Parlodel (bromocriptine mesylate) has been found to be clinically useful as an adjunct to levodopa (usually with a decarboxylase inhibitor), in the symptomatic management of selected patients with Parkinson's disease who experience prominent dyskinesia or wearing off reactions on long-term levodopa therapy.

Patients on long-term treatment who are beginning to deteriorate on levodopa therapy may be controlled by reducing the dose of levodopa and adjusting the frequency and schedule of drug administration. Patients maintained on optimal dosages of levodopa who still experience prominent dyskinesia and/or end-of-dose failure may benefit from the concomitant use of Parlodel, by decreasing the occurrence and/or severity of these manifestations. Since rapid escalation of bromocriptine doses causes severe adverse reactions, it is recommended to combine a slow increase of Parlodel, usually with a concomitant, gradual and limited reduction of levodopa dosage. Continued efficacy of bromocriptine for more than two years has not been established and there is some evidence that its efficacy tends to wane. Evidence available indicates that there is no consistent benefit from bromocriptine in patients who have not responded previously to levodopa, and studies have shown significantly more adverse reactions in bromocriptine-treated patients than in patients treated with levodopa. Parlodel is not recommended in the treatment of newly diagnosed patients or as the sole medication in Parkinson's disease.

CONTRAINDICATIONS Other than sensitivity to ergot alkaloids, no absolute contraindications to treatment with Parlodel (bromocriptine mesylate) are known. For procedure during pregnancy see "Use in Pregnancy" under Precautions.

WARNINGS Long-term treatment (6-36 months) with Parlodel in doses of 20 to 100 mg/day has been associated with pulmonary infiltrates, pleural effusion and thickening of the pleura in a few patients. Where Parlodel was discontinued, these changes slowly reverted to normal.

PRECAUTIONS Parlodel (bromocriptine mesylate) may cause hypotension, primarily postural; periodic monitoring of the blood pressure, particularly during the first days of therapy, is advisable. In some patients dizziness (vertigo) may occur with Parlodel; patients should therefore be cautioned against activities requiring rapid and precise responses, such as driving an automobile or operating dangerous machinery, until their response has been determined.

Care should be exercised when administering Parlodel concomitantly with phenothiazines or antihypertensive agents. Due to drug interaction at the receptor site, dosage should be adjusted accordingly.

Alcohol should be avoided during treatment with Parlodel. In some patients, the concomitant use of Parlodel and alcohol has given rise to alcohol intolerance and an increase in the severity and incidence of Parlodel's possible adverse reactions.

Parlodel should always be taken with food. In cases where severe adverse effects, such as nausea, vomiting, vertigo or headaches are severe or persisting, the therapeutic dosage of Parlodel should be reduced to half of one tablet daily (1.25 mg) and increased gradually to that recommended. The dopamine antagonist domperidone may be useful in the control of severe gastrointestinal side effects in parkinsonian patients receiving Parlodel (see Drug Interactions).

As with all medication, Parlodel should be kept safely out of the reach of children.

Use in Pregnancy: If the patient wishes to become pregnant, Parlodel (bromocriptine mesylate) should be stopped as soon as possible after conception is suspected. In this event immunological confirmation should be done immediately. When pregnancy is confirmed, Parlodel, like all other drugs, should be discontinued unless, in the opinion of the treating physician, the possible benefit to the patient outweighs the potential risk to the fetus.

In human studies with Parlodel (reviewed by Turkalj, I.), there were 1410 reported pregnancies, which yielded 1236 live and 5 stillborn infants from women who took Parlodel (bromocriptine mesylate) during early pregnancy. Among the 1241 infants, 43 cases (31 minor and 12 major) of congenital anomalies were reported. The incidence (3.46%) and type of congenital malformations and the incidence of spontaneous abortions (11.13%) in this group of pregnancies does not exceed that generally reported for such occurrences in the population at large.

Use in Parkinson's Disease: Use of Parlodel (bromocriptine mesylate), particularly in high doses, may be associated with mental confusion and mental disturbances. Since patients with Parkinson's disease may manifest varying degrees of dementia, caution should be exercised when treating such patients with Parlodel.

Parlodel administered alone or concomitantly with levodopa may cause visual or auditory hallucinations. These usually resolve with dosage reduction, but discontinuation of Parlodel may be required in some cases. Rarely, after high doses, hallucinations have persisted for several weeks following discontinuation of Parlodel. Caution should be exercised when administering Parlodel to patients with a history of myocardial infarction, particularly if they have a residual atrial, nodal or ventricular arrhythmia.

Symptomatic hypotension can occur and, therefore, caution should be exercised when administering Parlodel, particularly in patients receiving antihypertensive medication. Periodic evaluation of hepatic, hematopoietic, cardiovascular and renal function is recommended.

Drug Interactions: The concomitant use of erythromycin may increase bromocriptine plasma levels.

Domperidone, a dopamine antagonist, may cause increases in serum prolactin. In so doing, domperidone may antagonise the therapeutically relevant prolactin lowering effect of Parlodel. It is possible that the antitumorigenic effect of Parlodel in patients with prolactinomas may be partially blocked by domperidone administration.

ADVERSE REACTIONS The most frequently observed adverse reactions are nausea, vomiting, headache and gastrointestinal side effects such as abdominal pain, diarrhea and constipation. All these effects may be minimized or even prevented by giving small initial doses of bromocriptine and by taking it with food.

Postural hypotension which can, on rare occasions, lead to fainting and "shock-like" syndromes has been reported in sensitive patients. This is most likely to occur during the first few days of Parlodel treatment.

When bromocriptine is added to levodopa therapy, the incidence of adverse reactions may increase. The most common newly appearing adverse reactions in combination therapy were: nausea, abnormal involuntary movements, hallucinations, confusion, "on-off" phenomenon, dizziness, drowsiness, faintness, fainting, vomiting, asthenia, abdominal discomfort, visual disturbance, ataxia, insomnia, depression, hypotension, shortness of breath, constipation and vertigo.

Less common adverse reactions include anorexia, anxiety, blepharospasm, dry mouth, dysphagia, edema of the feet and ankles, erythromelalgia, epileptiform seizures, fatigue, headache, lethargia, mottling of skin, nasal stuffiness, nervousness, nightmares, parethesia, skin rash, urinary frequency, urinary incontinence, urinary retention and rarely signs or symptoms of ergotism such as tingling of fingers, cold feet, numbness, muscle cramps of feet and legs or exacerbation of Raynaud's syndrome.

Abnormalities in laboratory tests may include elevation of blood urea nitrogen, SGOT, SGPT, GGPT, CPK, alkaline phosphatase and uric acid, which are usually transient and not of clinical significance.

The occurrence of adverse reactions may be lessened by temporarily reducing dosage to one-half tablet two or three times daily.

SYMPTOMS AND TREATMENT OF OVERDOSE There have been several reports of acute overdosage with Parlodel (bromocriptine mesylate) in children and adults. No life threatening reactions have occurred. Symptoms reported included nausea, vomiting, dizziness, drowsiness, hypotension, sweating and hallucinations. Management is largely symptomatic; the cardiovascular system should be monitored. Metoclopramide can be used to antagonize the emesis and hallucinations in patients who have taken high doses.

DOSAGE AND ADMINISTRATION Parlodel (bromocriptine mesylate) should always be taken with food.

Although Parlodel (bromocriptine mesylate) has been found clinically useful in decreasing the severity and frequency of "on-off" fluctuations of late levodopa therapy, the decision to use bromocriptine as adjunctive treatment and the selection of dosage must be individualized in each case. A low dose is recommended. The initial dose of Parlodel is one half of a 2.5 mg tablet (1.25 mg) at bedtime with food to establish initial tolerance. Thereafter, the recommended dosage is 2.5 mg daily in two divided doses, with meals, (half a 2.5 mg tablet twice daily). The dosage may be increased very gradually, if necessary, by adding an additional 2.5 mg per day, once every 2 to 4 weeks, to be taken always in divided doses with meals. Increments should usually not exceed 2.5 mg. Clinical assessments are recommended at two week intervals or less during dosage titration, to ensure that the lowest effective dosage is not exceeded. The usual dosage range is from a few milligrams to 40 mg daily in two or three divided doses with meals. The median dose varies with the experience of individual investigators, but can be around 10 mg daily or higher. During initial titration it is recommended that the dosage of levodopa should be maintained, if possible. Subsequently, it might be desirable to combine a slow increase of bromocriptine with a concomitant, limited and gradual reduction of levodopa.

AVAILABILITY
TABLETS each containing 2.5 mg bromocriptine, as mesylate, available in bottles of 100.
CAPSULES each containing 5 mg bromocriptine, as mesylate, available in bottles of 100.

**For information on other approved indications, please consult the Parlodel product monograph, available to physicians and pharmacists on request.*

SANDOZ

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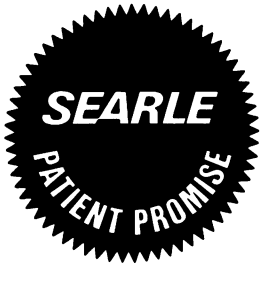


ONLY

Pr CYTOTEC®

(misoprostol) 100mcg 200mcg

PRESCRIBING INFORMATION

THERAPEUTIC CLASSIFICATION
Cytoprotective Agent

ACTIONS
CYTOTEC (misoprostol) is a synthetic analogue of prostaglandin E_1. In animals and man, it has both gastric antisecretory and cytoprotective effects. Its antisecretory activity is mediated by a direct action on the parietal cells. CYTOTEC exerts a cytoprotective effect by enhancing natural mucosal defense mechanisms. Studies conducted in animals and clinical trials in humans have demonstrated that CYTOTEC can protect the gastric mucosa against various irritants such as alcohol, aspirin, naproxen, tolmetin and sodium taurocholate. In addition, CYTOTEC has been shown to increase mucus production and to increase bicarbonate secretion in the duodenum. Misoprostol has local and systemic activity.

Following administration of a single 200 mcg dose of misoprostol to six healthy male subjects, the mean Cmax, AUC (0-24) and Tmax of the primary biologically active acid metabolite were: 309 pg/mL, 355 pg.hr/mL and 0.5 hours, respectively. After administration of tritiated misoprostol the elimination half-life of misoprostol acid was 20.6 minutes, and the elimination half-life of total organic extractable radioactivity was 1.5 to 1.7 hours. The duration of antisecretory activity is greater than 3 but less than 6 hours.

INDICATION
CYTOTEC (misoprostol) is indicated in the treatment and prevention of NSAID-induced gastric ulcers (defined as ≥ 0.3 cm in diameter) and in the treatment of duodenal ulcers.

CONTRAINDICATIONS
Known sensitivity to prostaglandins, prostaglandin analogues, or excipients (microcrystalline and hydroxypropyl methylcellulose, sodium starch and hydrogenated castor oil).

Contraindicated in pregnancy. (See CLINICAL PHARMACOLOGY.)

Women should be advised not to become pregnant while taking CYTOTEC. If pregnancy is suspected, use of the product should be discontinued, and the pregnancy followed very closely (weekly) for the next four weeks.

WARNINGS
Women of childbearing potential should employ adequate contraception (i.e., oral contraceptives or intrauterine devices) while receiving CYTOTEC. (See CONTRAINDICATIONS.)

Nursing Mothers: It is unlikely that CYTOTEC is excreted in human milk since it is rapidly metabolized throughout the body. However, it is not known if the active metabolite (misoprostol acid) is excreted in human milk. Therefore, CYTOTEC should not be administered to nursing mothers because the potential excretion of misoprostol acid could cause significant diarrhea in nursing infants.

Pediatric Use: Safety and effectiveness in patients below the age of 18 have not been established.

SUGGESTED REGIMEN FOR INITIATING THERAPY FOR PREVENTION OR TREATMENT OF NSAID-INDUCED GASTRIC ULCERS	
AM One 200 mcg tablet after food	PM One 200 mcg tablet after food
Dosage can be increased according to patient need up to 800 mcg per day in divided doses.	

100 mcg and 200 mcg tablets available

PRECAUTIONS
Selection of Patients: Before treatment is undertaken, a positive diagnosis of duodenal ulcer or NSAID-induced gastric ulcer should be made. In addition, the general health of the patient should be considered. Misoprostol is rapidly metabolized by most body tissues to inactive metabolites. Nevertheless, caution should be exercised when patients have impairment of renal or hepatic function. Experience to date with such patients is limited.

DRUG INTERACTIONS:
- The serum protein binding of misoprostol acid was not affected by: indomethacin, ranitidine, digoxin, phenylbutazone, warfarin, diazepam, methyldopa, propranolol, triamterene, cimetidine, acetaminophen, ibuprofen, chlorpropamide, and hydrochlorothiazide.
- Salicylic acid (300 mcg/mL) lowered the protein binding of misoprostol from 84% to 52%; this is not considered clinically significant since the binding of misoprostol acid is not extensive and its elimination half-life is very short.
- In laboratory studies, misoprostol has shown no significant effect on the cytochrome P450-linked hepatic mixed function oxidase system, and therefore should not affect the metabolism of theophylline, warfarin, benzodiazepines or other drugs normally metabolized by this system.
- No drug interactions attributable to misoprostol have been observed to date.

Some prostaglandins and prostaglandin analogues have the capacity to produce hypotension through peripheral vasodilation. The results of clinical trials to date indicate that CYTOTEC (misoprostol) has not produced hypotension at dosages effective in promoting the healing of ulcers. Nevertheless, CYTOTEC should be used with caution in the presence of disease states where hypotension might precipitate severe complications, e.g., cerebral vascular disease or coronary artery disease.

Epileptic seizures have been reported with prostaglandins and prostaglandin analogues administered by routes other than oral. Therefore, misoprostol tablets should be used in known epileptics only when their epilepsy is adequately controlled and then only when expected benefits outweigh potential risks.

Symptomatic responses to CYTOTEC do not preclude the presence of gastric malignancy.

ADVERSE REACTIONS
Gastrointestinal: In subjects receiving CYTOTEC (misoprostol) 400 or 800 mcg daily in clinical trials, the most frequent gastrointestinal adverse events were diarrhea, abdominal pain and flatulence. The average incidences of these events were 11.4%, 6.8% and 2.9%, respectively. The events were usually transient and mild to moderate in severity.

Diarrhea, when it occurred, usually developed early in the course of therapy, was self-limiting and required discontinuation of CYTOTEC in less than 2% of the patients. The incidence of diarrhea can be minimized by adjusting the dose of CYTOTEC, by administering after food and by avoiding coadministration of CYTOTEC with magnesium-containing antacids.

Gynecological: Women who received CYTOTEC during clinical trials reported the following gynecological disorders: spotting (0.7%), cramps (0.6%), hypermenorrhea (0.5%), menstrual disorder (0.3%), and dysmenorrhea (0.1%).

Elderly: There were no significant differences in the safety profile of CYTOTEC in approximately 500 ulcer patients who were 65 years of age or older compared with younger patients.

Incidence greater than 1%: In clinical trials, the following adverse reactions were reported by more than 1% of the subjects receiving CYTOTEC and may be casually related to the drug: nausea (3.2%), headache (2.4%), dyspepsia (2.0%), vomiting (1.3%), and constipation (1.1%). However, there were no clinically significant differences between the incidences of these events for CYTOTEC and placebo.

SYMPTOMS AND TREATMENT OF OVERDOSAGE
The toxic dose of CYTOTEC (misoprostol) in human beings has not been determined. Cumulative total daily doses of 1,600 mcg have been tolerated with only symptoms of gastrointestinal discomfort being reported. In animals, the acute toxic effects are similar to those reported for other prostaglandins and prostaglandin analogues: relaxation of smooth muscle, respiratory difficulties, and depression of the central nervous system. Possible clinical signs that may indicate an overdose may include: sedation, tremor, fever, convulsions, dyspnea, abdominal pain, diarrhea, palpitations, hypotension, or bradycardia. Treatment should be symptomatic and supportive.

It is not known if misoprostol acid is dialyzable. However, because misoprostol is metabolized like a fatty acid, it is unlikely that dialysis would be appropriate treatment for overdosage.

DOSAGE AND ADMINISTRATION
Treatment and Prevention of NSAID-Induced Gastric Ulcers: The recommended adult oral dosage of CYTOTEC for the prevention and treatment of NSAID-induced gastric ulcer is 400 to 800 mcg a day in divided doses. NSAIDs should be taken according to the schedule prescribed by the physician. When appropriate, CYTOTEC and NSAIDs are to be taken simultaneously. CYTOTEC should be taken after food.

Duodenal Ulcer: The recommended adult oral dosage of CYTOTEC (misoprostol) for duodenal ulcer is 200 mcg four times a day (after meals and at bedtime) for 4 weeks. Antacids (aluminum based) may be used as needed for relief of pain. Treatment should be continued for a total of 4 weeks unless healing in less time has been documented by endoscopic examination. In the small number of patients who may not have fully healed after 4 weeks, therapy with CYTOTEC may be continued for a further 4 weeks.

AVAILABILITY
CYTOTEC 200 mcg tablets are white, scored, hexagonal with SEARLE 1461 engraved on one side.

CYTOTEC 100 mcg tablets are white to off-white, round tablets with SEARLE engraved on one side and CYTOTEC on the other.

Store below 30°C (86°F).

Pharmacist: Dispense with Patient Insert.

1. Mitchell DM, Spitz PW, Young DY, et al: Survival, prognosis, and causes of death in rheumatoid arthritis. Arthritis Rheum 1986;29:706-14. 2. Graham DY, Agrawal NM, Roth SH: Prevention of NSAID-induced gastric ulcer with misoprostol: Multicentre, double-blind placebo-controlled trial. Lancet 1988; 2:1277-1280. 3. Skander M, Ryan F: Nonsteroidal anti-inflammatory drugs and pain free peptic ulceration in the elderly. British Medical Journal, 1988; Vol. 297:834. 4. Armstrong CP, Blower AL: Nonsteroidal anti-inflammatory drugs and life threatening complications of peptic ulceration. Gut 1987; 28:526-532. 5. Graham DY, Agrawal NM, Roth SH: Prevention of NSAID-induced gastric ulcer with misoprostol: Multicentre, double-blind placebo-controlled trial. Lancet 1988; 2:1277-1280.

SEARLE
Searle Canada Inc.
400 Iroquois Shore Road
Oakville, Ontario L6H 1M5

February 1989

Product Monograph Available on Request

PREMARIN... STRAIGHT TO THE HEART OF THE MENOPAUSE

PREMARIN* Tablets
Conjugated Estrogens C.S.D.

INDICATIONS: For replacement therapy in naturally occurring or surgically induced estrogen deficiency states associated with menopausal and postmenopausal symptoms, particularly hot flushes, senile vaginitis and kraurosis vulvae, with or without pruritus, female hypogonadism; amenorrhea; abnormal uterine bleeding due to hormonal imbalance in the absence of organic pathologic changes such as submucosal fibroids or uterine cancer; primary ovarian failure; and for estrogen deficiency induced osteoporosis, when combined with other important therapeutic measures such as diet, calcium, physiotherapy, and good general health promoting measures.

For inoperable progressing prostatic cancer (for palliation only when castration is not feasible, or when castration failures or delayed escape following a response to castration have occurred), breast cancer (for palliation only in women more than 5 years past the menopause with progressing inoperable or roentgen resistant disease).

CONTRAINDICATIONS: Estrogens should not be administered to patients with active hepatic dysfunction or disease, especially of the obstructive type; or a personal history of breast or endometrial cancer, except in special circumstances, or in patients with endometrial hyperplasia unless a progestogen is administered concomitantly.

Estrogens are also contraindicated in the following situations: undiagnosed vaginal bleeding; a history of cerebrovascular accident, coronary thrombosis, or in the presence of classical migraine; a history of thrombophlebitis or thromboembolic disease; partial or complete loss of vision or diplopia due to ophthalmic vascular disease; suspected pregnancy.

WARNINGS: Before estrogens are administered, the patient should have a complete physical examination with specific reference to pelvic organs and breasts and including blood pressure determination.

The first followup examination should be done preferably within 6 months after initiation of treatment. Thereafter, examinations should be made once a year and should include those procedures outlined above.

If any surgical procedures are performed, advise the pathologist of the patient's therapy when specimens are sent for examination. Liver function tests should be made periodically in subjects who have, or are suspected of having, hepatic disease.

If abnormal vaginal bleeding occurs during therapy, suction aspiration or curettage should be performed to rule out uterine malignancy.

Although the estrogen content of oral contraceptive therapy has been associated with an increased risk of various thromboembolic, thrombotic and vascular diseases, to date no such increased risk in postmenopausal users of estrogens has been detected. Nevertheless, the physician should be alert to the earliest manifestations of thrombotic disorders (thrombophlebitis, retinal thrombosis, cerebral embolism and pulmonary embolism). If these occur or are suspected, estrogen therapy should be discontinued immediately.

In patients with metastatic carcinoma and hypercalcemia, estrogen medication should be used with caution.

Three independent retrospective studies have reported an association between postmenopausal estrogen therapy and an increased risk of endometrial carcinoma. These studies, however, lacked information regarding certain important intrinsic risk factors of the patients (especially pretreatment endogenous hormonal status) and the mode of administration of estrogen. The potential relationship of estrogen to endometrial carcinoma under clinical conditions has to be considered. However, a cause and effect relationship between estrogen administration and endometrial carcinoma cannot be established by these data at this time.

PRECAUTIONS: Estrogen may cause sodium and water retention. Therefore, particular caution is indicated in cardiac or renal dysfunction, epilepsy or asthma.

Development of sudden enlargement, pain, or tenderness of uterine fibroids requires discontinuation of medication.

Elevation of blood pressure in previously normotensive or hypertensive patients generally necessitates cessation of therapy.

Diabetic patients or those with a predisposition to diabetes should be observed closely to detect any alterations in carbohydrate metabolism.

When liver or endocrine function tests are indicated, the results should not be considered reliable unless therapy has been discontinued for 2 to 4 months.

ADVERSE EFFECTS: The following adverse reactions have been reported with the use of estrogens in general. Some of these (indicated in brackets) have been documented with oral contraceptives specifically, and have not, up to now, been associated with cyclic menopausal or postmenopausal conjugated estrogens therapy.

Gastrointestinal: nausea, (anorexia, vomiting, abdominal cramps, bloating) cholestatic jaundice, increase or decrease in body weight.

Genitourinary: breakthrough bleeding, spotting and withdrawal bleeding, increased cervical mucus, endometrial hyperplasia, reactivation of endometriosis, (cystitis like syndrome).

Endocrine and Metabolic: sodium and water retention, breast swelling and tenderness, increased blood sugar levels, and decreased glucose tolerance; in males: gynecomastia, reduced potency and feminization.

CNS: headaches, increase or decrease of libido, (mental depression, nervousness, dizziness, fatigue, irritability).

Dermatologic — hypersensitivity: allergic reactions and rashes, chloasma, (loss of scalp hair, hemorrhagic eruption, itching, erythema nodosum and erythema multiforme, pigmentation of the skin).

Cardiovascular: an increase in blood pressure in susceptible individuals and aggravation of migraine headaches.

Hematologic: A statistically significant association has been demonstrated between the use of oral contraceptive preparations containing estrogens and the following serious reactions: thrombophlebitis, pulmonary embolism and cerebral thrombosis. Although available evidence is suggestive of an association, such a relationship has been neither confirmed nor refuted for the following serious reactions: coronary thrombosis and neuroocular lesions (e.g., retinal thrombosis and optic neuritis); altered coagulation tests (increase in prothrombin and Factors VII, VIII, IX, X).

OVERDOSE: Symptoms: Excessive doses may result in nausea, vomiting and abdominal cramps, headache, dizziness and general malaise.

TREATMENT: Remove ingested drug by gastric lavage and give symptomatic treatment.

DOSAGE: In general, estrogen should be given cyclically (21 to 25 days followed by a 5 to 7 day rest period) and in some cases with progestogen or androgen to avoid overstimulation of breast and endometrial tissues. The addition of sufficient progestogen to promote conversion of the endometrium is mandatory in those patients who are receiving sufficient unopposed estrogen to cause vaginal bleeding or endometrial hyperplasia. Obviously, abnormal vaginal bleeding in such patients is an indication for prompt diagnostic measures.

Use the lowest effective dosage and reassess periodically the requirement for estrogen therapy.

Menopausal syndrome: 0.625 - 1.25 mg daily, cyclically. Adjust dosage upward or downward according to severity of symptoms and patient response. For maintenance, adjust dosage to lowest level providing effective control.

If the patient has not menstruated within the last 2 months or more, cyclic administration is started arbitrarily. If the patient is menstruating, cyclic administration is started on day 5 of bleeding. If breakthrough bleeding (bleeding or spotting during estrogen therapy) occurs, increase the dosage as needed to stop bleeding. In the following cycle, the same dosage should be administered as that used to stop breakthrough bleeding in the previous cycle. In subsequent cycles. the dosage should be gradually reduced to the lowest level which will maintain the patient symptom free.

In some patients the combination of estrogen with methyltestosterone, administered cyclically, may be preferable to estrogen alone. If planned withdrawal bleeding is desirable, a progestogen may be added during the last 5 to 10 days of the usual recommended estrogen regimen.

Postmenopause: for the treatment of estrogen deficiency induced degenerative changes (e.g., osteoporosis, atrophic vaginitis, kraurosis vulvae): 0.3 to 1.25 mg daily and cyclically. Adjust dosage to lowest effective level.

Hypogenitalism: in an attempt to attain sexual and somatic maturation: 2.5 to 7.5 mg daily, in divided doses for 21 days, followed by a rest period of 10 days. If bleeding does not occur at the end of this period, the same dosage schedule is repeated. The number of courses of estrogen therapy necessary to produce bleeding may vary depending on the responsiveness of the endometrium.

If bleeding occurs before the end of the 10 day period, a 20 day estrogen-progestogen cyclic regimen, as in amenorrhea, is recommended.

Amenorrhea: to reproduce the hormone pattern of the ovary, i.e., bleeding from a progestational endometrium, begin a 20 day estrogen-progestogen cyclic regimen: 2.5 to 7.5 mg daily in divided doses, for 20 days. During the last 5 days of estrogen therapy, oral progestogen is added. If bleeding occurs before this regimen is concluded, therapy is discontinued and may be resumed on the fifth day of bleeding.

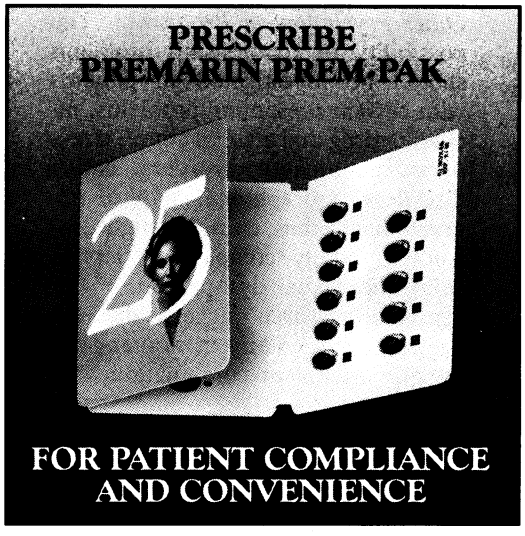
Mammary carcinoma: (for palliation in women with progressing inoperable or roentgen resistant disease more than 5 years after the menopause): 10 mg 3 times daily for a period of at least 3 months.

Prostatic carcinoma: (for palliation when castration is not feasible or when castration failure or delayed escape has occurred): 1.25 to 2.5 mg 3 times daily. The effectiveness of therapy can be judged by phosphatase determination as well as by the patient's symptomatic improvement.

SUPPLIED: Each oval, sugar-coated tablet is imprinted with "Premarin". Each tablet contains conjugated estrogens, C.S.D.:

† 0.3 mg (green) in bottles of 100 and 500;
† 0.625 mg (maroon) in bottles of 100 and 1000;
† 0.9 mg (pink) in bottles of 100;
† 1.25 mg (yellow) in bottles of 100 and 1000;
2.5 mg (purple) in bottles of 100.
† Also available in PREM-PAKS containing 25 tablets in push through blister paks.

Product Monograph available on request.



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Official publication of The College of Family Physicians of Canada

Send insertion orders to: Classified Ads, 4000 Leslie St., Willowdale, Ontario M2K 2R9 Telephone orders: (416) 493-7513 Fax number: (416) 493-3224

Positions Vacant

General Practitioner Required to join five-man unopposed rural practice in central British Columbia with view to partnership. 40-bed hospital adjacent to clinic, specialist facilities available at regional hospital one hour by road. Surgical skills a definite advantage. *Interested applicants write to: Dr. B. Grobbelaar, Omineca Clinic, R.R. #2, Vanderhoof, B.C. V0J 3A0 or telephone (604) 567-2201.* (9-31)

Family Physician required to join four family doctors and one surgeon at Wainwrights's only medical clinic. Wainwright is 200 km east of Edmonton and has a health care complex of 46 general and 75 auxiliary beds, serving 10 000 people. The area has a varied economic base with good facilities; an indoor recreational complex, active service clubs, theatre group, craft centre, separate and public schools. Applicants should be trained for family medicine. Obstetrical or surgical skills would be added assets. We encourage continuing medical education and share on-call duties equally. *For further information please contact: Dr. Kevin Hay, Box 1060, Wainwright, Alta. T0B 4P0. Telephone: (403) 842-3341.* (9-36)

King & University Medical-Dental Clinic. Physician wanted to establish downtown storefront clinic. Prestigious location in fast growing, high density area. Close to University Avenue hospitals. Subway at doorstep. Unique opportunity to establish practice quickly in heart of Toronto. *Call: (416) 593-5677 or (416) 242-6840 (evenings).* (9-40)

Family Physicians — Denver, Colorado. Seeking CCFP/BC/BE Family Practice Physician to join a Dalhousie trained CCFP, BC, FP physician in southwest Denver. Practice is a very busy, rapidly growing, caring, patient-centered practice covering all ages. Teaching orientation. Four person call group. Financial arrangements flexible and will assist in establishment. Beautiful office facility, 14 minutes from a large, full service hospital. *Send resume to: Sally Robertson, 1650 Fillmore St., Denver, CO 80206 U.S.A. Telephone: (303) 393-3639* (9-43)

Family Physicians — Denver, Colorado. Seeking CCFP/BC/BE Family Physicians for excellent opportunities in group and solo family practices in the Denver area. Experience skiing and the most livable climate in the U.S. Financial assistance available. *Send resume to: Sally Robertson, 1650 Fillmore St., Denver, CO 80206 U.S.A.* (9-44)

Family Physician — Ontario. Excellent opportunity in rapidly growing satellite community of 8000, without physician's office, on shores of Lake Huron. 15 minutes from major hospitals. Medical building opening January 1990 seeking physicians to rent. Laboratory and X-ray probable. *Reply to: Dr. Winegard, 900 Allandale Dr., Sarnia, Ont. N7S 3E4 Telephone: (519) 542-5304.* (9-58)

Queen's University Moose Factory Program

Full-time family physicians are required to provide general practice services at Moose Factory General Hospital and associated coastal nursing stations. Competitive remuneration. (7-CW4)

Please contact:

Dr. Brian F. Kain, Co-ordinator
Queen's University, Moose Factory Program
Family Medicine Centre
P.O. Box 8888
Kingston, Ont.
K7L 5E9
Telephone: (613) 542-9592

Clinical Associate

Joseph Brant Memorial Hospital, in association with the Ontario Cancer Foundation has developed a new position for a physician to develop a consulting service regarding care of the terminally ill and also to assist with the medical management of the oncology patient.

Interested candidates must be eligible to practice medicine in Ontario. A vision regarding care for the terminally ill and the motivation to achieve same are also necessary. An attractive remuneration package including office support is available. (9-41)

Applicants are invited to send their curriculum vitae by September 30, 1989 to:

Search Committee
c/o Allison J. Stuart
Associate Executive Director
Joseph Brant Memorial Hospital
1230 North Shore Blvd.
Burlington, Ontario
L7R 4C4

Family Medicine Faculty Sunnybrook Medical Centre University of Toronto

An opportunity exists to become a full-time faculty member group with strong academic commitment. Group is organized as a physician-sponsored HSO.

Broad clinical experience and CCFP essential. Teaching and research experience desirable. Special area of interest an asset.

Good compensation package with salary and fringe benefits. (9-47)

Apply before October 31, 1989 to:

Dr. Peter G. Norton, Head
Department of Family and Community Medicine
Sunnybrook Medical Centre, Room E-349
2075 Bayview Avenue
North York, Ontario
M4N 3M5
Telephone: (416) 480-4585

One or Two Physicians needed to join three other physicians in a group practice in a small town just north of Whitby, about 45 minutes from downtown Toronto. The area is developing very quickly and the current practice is extremely busy. A new practice would fill immediately. Opportunities for obstetrics, geriatrics, emergency work, pediatrics available. Varied and interesting practice, pleasant community. Shared call, opportunity for partnership in one year. *Call Dr. B. Cairns or Dr. D. McIntosh at (416) 655-3321.* (9-46)

GP for Four-Physician Rural Practice. Billing number available. *Contact: Mr. M. Crawford, Administrator, Ashcroft & District General Hospital, P.O. Box 488, Ashcroft, B.C. V0K 1A0. Telephone: (604) 453-2211.* (9-48)

Family Physician: Ontario — Progressive, busy group of two family physicians seeks a family physician to join them with a view to full partnership. Modern medical complex with on-site diagnostic facilities including X-ray, ultrasound, audiology, PFTs, and ECGs. Excellent staff with fully computerized office equipment. The practice consists of rounds at the nearby Brockville hospitals, out-patient procedures, nursing home visits, or assists and a busy office practice. Willingness to share in provision of obstetrical care is preferred. On-call duties one in eight. Emergency call is voluntary and is dictated by one's interest. *If interested, please contact: Dr. Jamie Chillcott or Dr. Gun Bhatt, 555 King St. W., Box 1750, Prescott, Ont. K0E 1T0. Telephone: Dr. Bhatt (613) 925-4620 or Dr. Chillcott (613) 625-5134.* (9-50)

Family Physician — Northwestern Ontario to replace a solo physician in Red Rock, on the north shore of Lake Superior, 100 km east of Thunder Bay. A busy family practice with modern office and home combined. Full hospital privileges in nearby hospital, shared on call. Low overhead. Eligible for Ministry of Health Underserviced Area Grant. Starting date July 1st 1989. *Reply to: Dr. M.L. Jackson-Hughes, P.O. Box 279, Nipigon, Ont. P0T 2J0. Telephone: (807) 887-3836 (home), or (807) 887-2992 (office).* (9-51)

Family Physician — Ontario. Group of family physicians seeks a replacement for a recently retired doctor. Fully furnished and computerized office with experienced staff. Office located in a medical building which features X-ray, ultrasound, nuclear medicine, lab, pharmacy, physiotherapy. Weekend rota one in six. Hospital privileges available. No investment necessary. Immediate parity. Windsor is a university city of 200 000 with excellent schools, sporting, and cultural facilities. *Contact: John Shaw at (519) 258-3200 (collect).* (9-52)

Physicians Needed for weeknight emergency shifts (1800-0800 hours) at the Whitby General Hospital (just outside of metro Toronto). ACLS and ATLS certification required. *Please telephone the medical staff office: (416) 668-6831.* (8-52)

Georgian Bay Area, Ontario — (two hours from downtown Toronto). A solo practitioner in Durham requires a general practitioner (obstetrics an asset) as an associate for his busy family practice with its newly renovated facilities. Excellent income potential. Durham has a 35-bed accredited hospital with a general surgeon on staff. Good on-call schedule. The town/region offers excellent recreational facilities and reasonably priced housing. *For further information please call Dr. A.G. Denyer at (519) 369-2032 (office) or (519) 369-2839 (home), or forward your resume to him at P.O. Box 970, Durham, Ont. N0G 1R0* (8-38)

Northern British Columbia — G.P. Anesthetic needed early in 1990 to join unopposed three doctor group, small town in northeastern British Columbia. Very well equipped 50-bed hospital (pulse oxymetre, real time ultrasound, fiberoptic scopes, blood gasses, etc.). One surgeon in group plus second G.P. anesthetist. All share equally in practice rota – one night per week and one weekend per month. Beautiful Rocky Mountains 40 minutes away by road. Daily jet to Vancouver/Edmonton. Good quality housing available, modest prices. Pretty golf course. Excellent indoor/outdoor recreation. Good stipend during introductory period. Principalship available with no premium. *Send CV to: Fort Nelson Medical Clinic, Box 594, Fort Nelson, B.C. V0C 1R0 or telephone collect: (606) 774-3171.* (9-58)

Opportunity for a Family Physician to join an established three physician group in village medical centre, 25 km north of Brockville, Ontario. Two local physicians retiring. Situated on the St. Lawrence River, Brockville is one hour from both Kingston and Ottawa. Brockville has two active treatment hospitals with a full compliment of specialists. On-call rotation would be one in eight with emergency shifts available and obstetrics optional. *Please reply to: Athens District Health Centre, P.O. Box 99, Athens, Ont. K0E 1B0.* (9-45)

Family Practitioner, Anesthetist — Saskatchewan — Fantastic opportunity for a physician to expand a well-established five-doctor group in central Saskatchewan. Anesthesia and low risk obstetrics desirable. Attractive on-call system. Brand new 70-bed accredited hospital with full laboratory, ultrasound, radiologist plus physiotherapy facilities. Town of 5000 people with serviced area of 15 to 20 000. Recreation facilities include boating, fishing, golfing, squash, and numerous parks within easy access. *Replies: Nipawin Medical Group, P.O. Box 2135, Nipawin, Sask. S0E 1E0* (6-98)

Busy Family Practice Group of four physicians seeking full-time associate. Located in northwest metro Toronto. Close to hospital. Excellent opportunity. *Telephone: (416) 741-0310.* (8-43)

Unique opportunity for full-time physician available in established preventive medicine practice. *Address resume or inquiries to: Janet Shute, 367 Princess Ave., London, Ont. N6B 2A7. Telephone: (519) 432-1884.* (9-56)

Physicians Needed — for medical walk-in clinic located 25 minutes from Toronto. Evening and weekend hours; income guaranteed. *Contact: A.S. Vakil, 220 Dundas St. W., Whitby, Ont. L1N 8M7 Telephone: (416) 666-1644.* (5-75)

Family Physician wanted to join established seven-person group. Light on-call schedule. Excellent back-up. Anesthetic/surgical/ obstetrical skills and opportunities available. Office practice is oriented towards women and children. Summer locum and/or partnership available. *Apply: Box 2327, Hinton, Alta. T0E 1C0, or telephone: (403) 865-3338* (8-54)

Sackville Memorial Hospital, Sackville, N.B. — Two family physicians needed in this university town of 5000 population with catchment area of 15 000. We are seven GPs in town and have a new 55-bed hospital. Emergency experience essential. *Contact: Dr. Ross Thomas (506) 536-3053.* (2-12)

Département de médicine familiale
Université Laval
Québec

Au cours de la prochaine année, des postes de professeurs réguliers seront disponibles dans notre département. Nos priorités sont la recherche en médecine familiale, la formation professorale et le développement du programme de médecine familiale, incluant l'urgence. Ceux qui sont intéressés à joindre notre équipe, veuillez envoyer un curriculum vitae avant le 15 octobre 1989 au: (8-59)

Directeur du Département de médecine familiale
Faculté de médecine
Pavillon Vandry
Université Laval
Québec (Québec)
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or telephone collect, (416) 963-1176.

This advertisement is directed to Canadian citizens and permanent residents of Canada.

Family Physician — Mississauga, Ontario. Associate required to join busy well-established female physician. Pleasant newly-decorated and furnished offices in a well maintained building. Excellent location, close to Mississauga Hospital. Good on-call schedule. Contact: Dr. Marilyn LaFave, Camilla Road Medical Associates, 2024 Camilla Rd., Mississauga, Ont. L5A 2J6 Telephone: (416) 897-3003. (7-65)

Family Physician(s) — two required to join rural practice in Bashaw, Alberta. 130 km south of Edmonton. Obstetrics and skills in anesthesia or surgery would be an asset but not essential. 30-bed active treatment hospital with 25-bed nursing home addition in late planning stages. Positions available immediately. *Apply to: Administrator, Bashaw General Hospital, Box 449, Bashaw, Alta. T0B 0H0, or telephone: (403) 372-3731* (8-65)

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The University of Toronto Sioux Lookout Program requires short-term and full-time family physicians immediately. Obstetrical experience and an interest in teaching is required for full-time physicians. Locums also available in outlying communities: no obstetrics required.

Zone Hospital, 50-bed accredited general hospital with full services at Sioux Lookout, Ontario with air travel to 25 outlying native communities. Full-time residents in pediatrics and family and community medicine, University of Toronto. Visiting consultants in all specialties at regular intervals.

Excellent CME including telemedicine (audiovisual) linkage with The Hospital for Sick Children and Sunnybrook Medical Centre, Toronto.

Unique opportunity to become familiar with native culture and be involved with community development as part of a primary health care team.

Competitive remuneration and benefits, and furnished housing provided. Must be licensed in the Province of Ontario. (7-CW2)

Send resume to:

Dr. Robert Haslam
Program Chairman
University of Toronto
Sioux Lookout Program
The Hospital for Sick Children
555 University Ave.
Toronto, Ont. M5G 1X8
Telephone: (416) 598-6933

Family Physician/General Practitioner — Manitoba. Hamiota District Health Centre requires a salaried full-time family physician as of September 18, 1989. The centre has acute care, personal care, elderly persons housing, an outreach department, and a medical clinic. The centre has a 4.5 staffing with weekend on-call shared between two facilities approximately 20 minutes apart. The weekend rotation is one in six. Salary range $75 000 to $90 000 with excellent benefits including six weeks vacation and two weeks study leave a year. This is a practice opportunity which allows one to enjoy a rural lifestyle yet experience enough colleague support that isolation is not a problem. This practice offers a very rewarding and interesting experience for the right candidate. *For further information please contact: Dr. John Guilfoyle or Ross Sheardown, Administrator, Hamiota, Man. R0M 0T0 Telephone: (204) 764-2412.* (8-42)

Associate Required — to join a busy family practitioner in greater Vancouver. Fifteen minutes to downtown. Mixed practice with patients of all ages. Good potential. Obstetrics required. *Please apply to Box 3330, Canadian Family Physician, 4000 Leslie St., Willowdale, Ont. M2K 2R9.* (8-37)

Rural Community in southeastern Saskatchewan requires two physicians to share a medical clinic. Population of the hospital district is about 3200. 21-bed hospital and well equipped clinic. Guaranteed minimum and incentives program available. The town of Oxbow is well known for its excellent schools and recreational facilities. *For further information please contact: Ross Irvine, Oxbow, Sask., Telephone: (306) 483-2262; or Hospital Administrator, Box 268, Oxbow, Sask. S0C 2B0 Telephone: (306) 483-2612* (7-50)

General/Family Practitioner — Required for small town and surrounding area. New 10-bed hospital. Accredited acute care with five-bed extended care under construction. Active medical staff committee with neighbouring hospital. Situated next to two resort lakes and is just one-half hour away from the city of Red Deer. *Reply to: Dr. Ron Keller, Bentley General Hospital, Box 30, Bentley, Alta. T0C 0J0 Telephone: (403) 748-4014 (office), or (403) 748-4293 (residence).* (8-44)

Family Physician — Busy practice on north shore of Lake Huron requires third doctor. Newly renovated office, computerized OHIP billing, on call coverage for private clinic patients only, no obstetrics. Excellent remuneration, opportunity for early partnership. New hospital scheduled for completion 1991. Attractive year round recreational and outdoor facilities. *Reply to: Dr. M. Bishop, Family Health Clinic, Box 1869, Blind River, Ont. P0R 1B0 Telephone: (business) (705) 356-1666, (residence) (705) 849-2400.* (7-53)

Family Physician — Alberta. Needed to fill vacancy in five-member family group practice. Town of 10 000 with modern 40-bed hospital. Obstetrical and anesthetic experience an asset. *Reply to: Dr. W. E. Schneider, Box 6270, Hinton, Alta. T7V 1X6 Telephone: (403) 865-2203 or (403) 865-4085.* (8-51)

Family Medicine — Established group seeks fifth member. Recently renovated office is across the road from a full service hospital with good specialist backup. Affiliated with McGill Department of Family Medicine. Beautiful countryside, skiing, golf. One hour from Montreal. *Telephone: Dr. William Barakett, Dr. Robert Pincott, or Dr. David Tector, at (514) 263-2929, or write to them at 1005 Main St., Cowansville, Que. J2K 1K4* (7-64)

Reach Community Health Centre requires a sixth family physician to join a multi-disciplinary team in an established East Vancouver clinic. Obstetrics required. *Contact: Dr. Sandy Witherspoon, Reach Community Health Centre, 1145 Commercial Dr., Vancouver, B.C. V5L 3X3 Telephone: (604) 254-1354.* (8-32)

China Town, Toronto — Medical clinic requires GP/FP for part-time or full-time associate or partnership. Speaking Chinese or Vietnamese essential. *Please reply to: P.O. Box 3278, Canadian Family Physician, 4000 Leslie St., Willowdale, Ont. M2K 2R9* (7-CW)

For Sale or Rent

Family Practice available September 1, 1989 — Orillia, Ontario. *Contact: (705) 326-3549 (office), (705) 762-5300 (home).* (9-30)

Ottawa — For Sale. Stable family practice. Office located in modern medical building with full investigation facilities. Reliable coverage group, reasonable office overhead expenses. *Telephone: (613) 521-6742.* (9-33)

Practice for Sale — Solo established family practice in Cochrane, Alta., (fifteen miles west of Calgary). Fully equipped office in new professional building. Call rotation with other local doctors if desired. Ranching country close to mountain recreation areas. *Telephone: (403) 249-7117.* (9-35)

Family Practice and House for Sale — Willowdale, Ontario — as practitioner approaching retirement. Five-room bungalow with office in basement, long established solo practice, plus excellent investment opportunity in thriving Willowdale area (soaring real estate — as much as 64% over past year). Practice has tremendous growth potential for active physician. Will help introduce. Practice and house $550 000. Excellent terms. Telephone: (416) 223-0331 (evenings). (9-38)

Family Practice for Sale — Victoria, British Columbia. Excellent location and congenial call group. Terms negotiable. *Reply in confidence to: Box 3332, Canadian Family Physician, 4000 Leslie St., Willowdale, Ont. M2K 2R9.* (9-39)

Family Practice — Calgary. Selling family practice in private community clinic, containing physicians, optometrists, lab, X-ray, and physio. Weekends and evenings available. Terms negotiable. *Reply to: Doctor, Box 4, Site 27, R.R.#8, Calgary, Alta. T2J 2T9* (9-53)

Ottawa, Ontario — General Practice for Sale. Well established solo practice. No obstetrics. Lab on site. Reasonable terms. Call group of seven. Potential for further growth. *Contact: Dr. Joan Campbell (613) 820-7820 (evenings).* (9-55)

Established Vancouver family practice for sale. Low overhead. Good location. *Telephone: (604) 731-2338.* (9-57)

Practice for Sale. Not a walk-in Clinic. Excellent opportunity to purchase vigorous, established family practice. Recently renovated store front in desirable Scarborough location. Overhead shared with two part-time associates. *Contact: Dr. S. Tulk at (416) 699-8795.* (8-68)

Lucrative Medical Practice in southeastern Saskatchewan town of 3000 people with a drawing area of 10 000 for sale or lease. 40-bed accredited hospital with excellent laboratory, pharmacy and radiology services. *Reply in confidence to: Box 3322, Canadian Family Physician, 4000 Leslie St., Willowdale, Ont. M2K 2R9* (6-50)

Physician Vacancy

Queen's University
Student Health Service

Queen's University Student Health Service requires a full-time physician to provide primary health care to students. Work heavily oriented towards office gynaecology, dermatology, infectious diseases, psychiatry and preventive medicine. Interest in sports medicine an asset, interest in care of young adults is essential. Certificant of College of Family Physicians preferred. Appointment commencing *1 Sept. 1989*

Salary plus employee benefits package, pleasant working conditions, full support staff, call rota, attractive fringe benefits of University appointment.

Applications with curriculum vitae and the names and addresses of three referees to:

Dr James A. McSherry
Director, Student Health Service
Queen's University
Kingston, Ontario K7L 3N6

Senior Medical Officer

Newhook Medical Clinic
Whitbourne, Newfoundland

A family physician is being sought for the position of Senior Medical officer at Newhook Medical Clinic in Whitbourne, Newfoundland. This will be a joint appointment with the discipline of Family Practice of the Faculty of Medicine at Memorial University.

The Newhook Medical Clinic is a community medical service staffed by four family physicians, all of whom are full-time appointees within the Faculty of Medicine. The clinic's role is to provide health services to a rural area approximately 80 km. from St. John's and to conduct programs in medical education at the postgraduate and undergraduate levels.

The successful candidate will be a physician experienced in rural medicine with license to practice in Newfoundland and a certificant of the College of Family Physicians of Canada. Experience in a medical management role will be considered a major asset.(9-42)

Please apply with a curriculum vitae and the names of three references to:

Carl W. Robbins, M.D., C.C.F.P., M.B.A.
Chairman, Discipline of Family Practice
Memorial University of Newfoundland
Health Sciences Centre
St. John's, Nfld.
A1B 3V6.

Locum Tenens

Associate or long term locum required for well established medical practice in Cambridge. Fully furnished office with experienced staff. *Please contact: John Bannister (519) 653-8736.* (9-32)

Family Practice of Five Physicians is seeking a locum tenens with view to a long term association. Lower Fraser Valley practice includes emergency room and obstetric care. Position available immediately. *Contact: Dr. A. Karmali, 11948–227th St., Maple Ridge, B.C. V2X 6J3. Or call: (604) 467-3434 (office).* (9-34)

Locum required for October 1, 1989, excellent remuneration. Obstetrics a necessity, 25-bed hospital. *Please call: Dr. R.K. How, (604) 949-8110 (home), (604) 949-8119 (office). Or write to: Box 1619, Port Hardy, B.C. V0N 2P0* (9-37)

Locum Required Immediately for four-physician rural practice until March 1990. *Contact: Dr. S. Mann, Ashrcroft, B.C. V0K 1A0 Telephone: (604) 453-9191.* (9-49)

Locum Tenens — Kapuskasing, Ontario. December 14 to January 4. House, vehicle and skidoo available. Two minute walk from cross country ski trails. Emergency one in seven, and obstetrics. Finances negotiable. *Contact: Gordon Hutchings (705) 337-1622 (office).* (9-54)

St. Mary's General Hospital Timmins, Ontario

St. Mary's General Hospital, a 181-bed active treatment facility, has immediate vacancies for the following medical specialists:

- Certified Anesthetist
- General Internists (two)
- Orthopedic Surgeon

Timmins is a prosperous community serving an immediate population of 50 000 residents and the hospital functions as a district referral centre for northeastern Ontario. A new, 319-bed district hospital is scheduled to commence construction in the spring of 1989 with a completion date of September 1991. (7-CW3)

Interested candidates should make inquiries and/or send a complete curriculum vitae to:

Mrs. Irene Krys, Executive Director
or
Dr. R. Williams, Chief of Staff
St. Mary's General Hospital
41 Pine St. N.
Timmins, Ont.
P4N 6K7
Telephone: (705) 267-2131

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And MAXENAL [illegible] decongestant, without the potential of anti[illegible] combination products to cause sedation.

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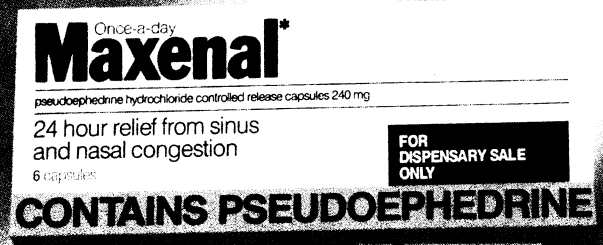
astemizole



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1. Data on file, 1988.
2. Bioavailability data, MAXENAL* N.D.S., Data on file, Janssen Pharmaceutica.
3. Dickerson J. et al, European Journal of Clinical Pharmacology, 14, 253-259, (1978).
4. van Bavel J. et al, Data on file, Janssen Pharmaceutica.
5. Paull B., Data presented at The American Academy of Family Physicians, New Orleans, La., October 1988.
6. Hindmarch I., Human Psychopharmacology Research Unit, University of Leeds, Data on file, Janssen Pharmaceutica.

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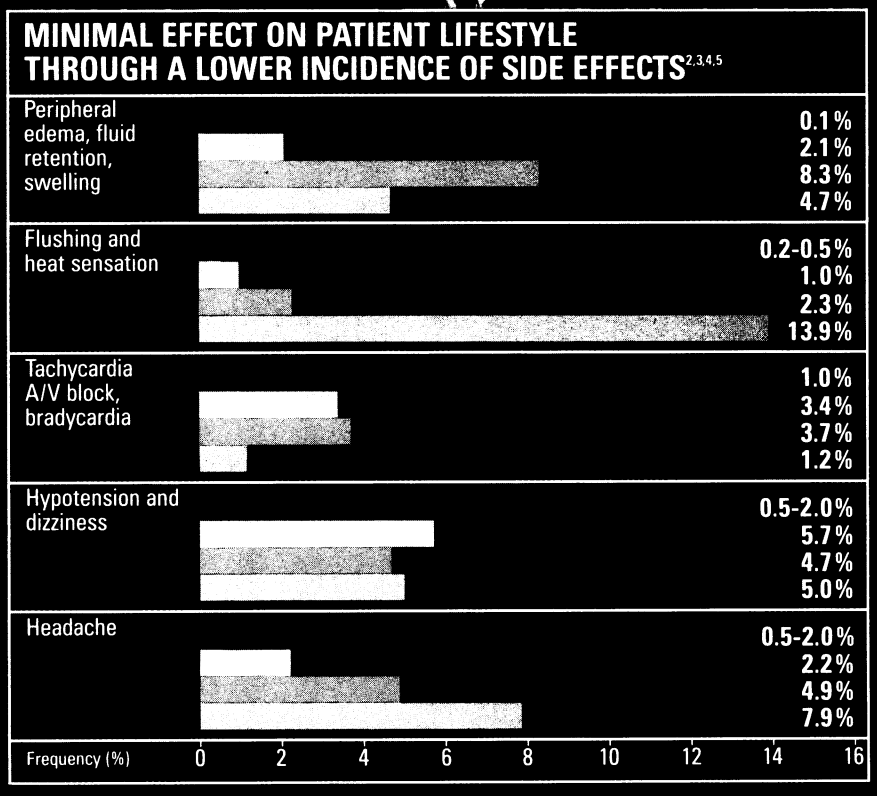
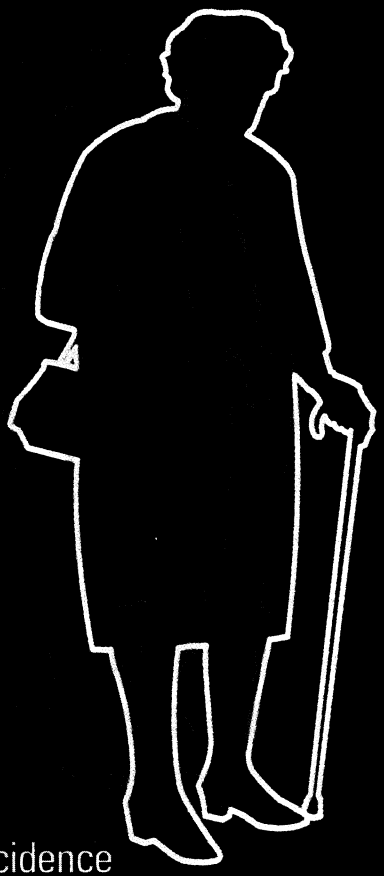
THE CAPOTEN REVOLUTION

More and more Canadian physicians are turning to Capoten...

for efficacy with minimal effect on patient lifestyle[1]
vs. calcium antagonists[2,3,4] in elderly hypertensive patients



CAPOTEN® (captopril)
Sustained release verapamil HCl
Sustained release diltiazem HCl
Prolonged action nifedipine



The incidence of adverse effects with calcium channel blockers can be significantly higher in elderly patients.[2,3,4]

*Adverse effects such as taste disturbances (2%) and skin rash (7%) are associated with Capoten; these are usually reversible and self-limiting.[6]

SQUIBB
Innovators in cardiovascular medicine

(captopril)
The World's #1 ACE Inhibitor†

bid®

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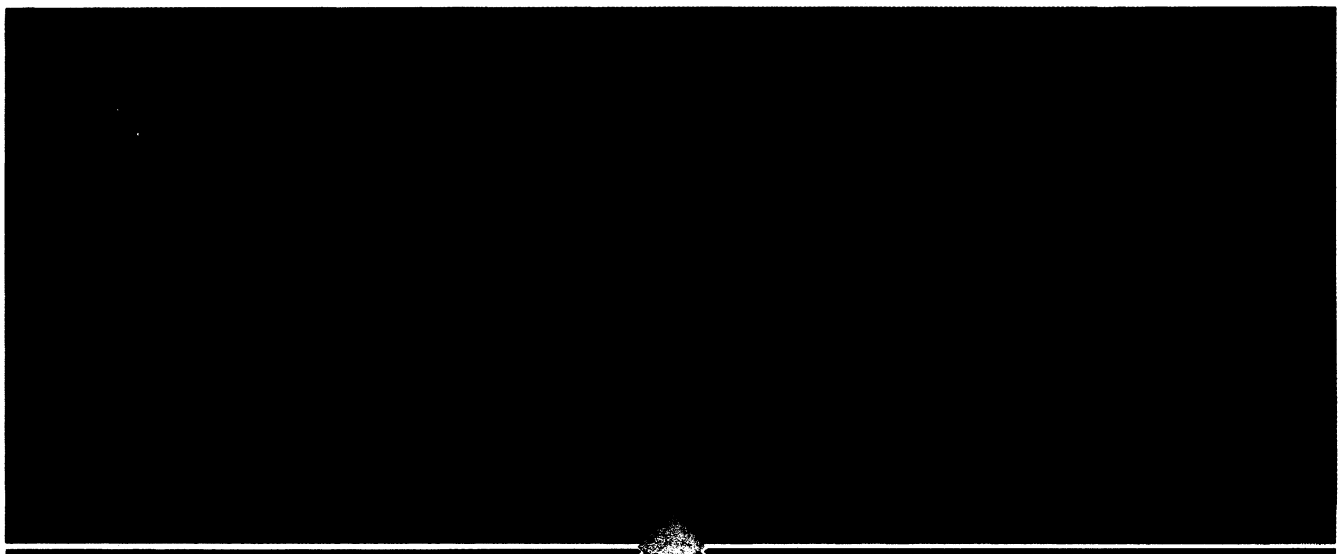
NEW DOSAGE RECOMMENDATION FOR REFLUX ESOPHAGITIS ZANTAC 300mg h.s.

Can you count on antacids after midnight?



You can control the symptoms of reflux esophagitis all night long with just a single 150 mg dose of Zantac instead of multiple doses of antacids.[3] In fact you'll be suppressing the production of acid, rather than repeatedly neutralizing it after its formation.

And a convenient regimen of Zantac® 300 mg h.s. or 150 mg b.i.d. can control the painful symptoms of reflux esophagitis round the clock.[3] To be sure you're helping patients toward a comfortable night's sleep this conveniently and reliably, prescribe Zantac—no substitution.

Zantac® (RANITIDINE HCl) To be sure.

Glaxo
Glaxo Canada Inc.

For prescribing information see page 1745

With its unique rate-limiting membrane, new Transderm-Nitro delivers a highly predictable, controlled nitrate dosage and prevents first-pass liver effects.

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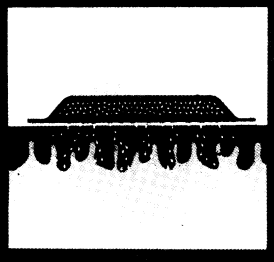

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When a therapy is this easy to handle, they're much more likely to stay on course.

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