Pharmaceutical Approval Update

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Obinutuzumab (Gazyva)

Manufacturer: Genentech/Roche, South San Francisco, Calif.

Indication: Obinutuzumab is intended for use in combination with chlorambucil to treat patients with previously untreated chronic lymphocytic leukemia (CLL).

Biologic Class: As a humanized anti-CD20 monoclonal antibody of the immunoglobulin G_1 (IgG_1) subclass, obinituzumab recognizes a specific epitope of the CD20 molecule found on B cells. The molecular mass of the antibody is approximately 150 kilodaltons.

Obinutuzumab is produced by mammalian (Chinese hamster ovary) cell suspension culture. It is a sterile, clear, colorless to slightly brown, preservative-free liquid concentrate for intravenous (IV) administration.

Uniqueness of Biologic: Obinutuzumab targets the CD20 antigen expressed on the surface of pre B-lymphocytes and mature B-lymphocytes. Upon binding to CD20, obinutuzumab mediates B-cell lysis through engagement of immune effector cells by directly activating intracellular death signaling pathways and/or activation of the complement cascade. The immune effector cell mechanisms include antibody-dependent cellular cytotoxicity and antibody-dependent cellular phagocytosis.

Boxed Warning:

Hepatitis B virus reactivation and PML. Hepatitis B virus (HBV) reactivation, in some cases resulting in fulminant hepatitis, hepatic failure, and death, can occur in patients receiving CD20-directed cytolytic antibodies, including obinutuzumab. All patients should be screened for HBV infection before treatment begins. HBV-positive patients should be monitored during and after treatment. Obinutuzumab and concomitant medications should be discontinued if HBV reactivation occurs. Progressive multifocal leukoencephalopathy (PML), including fatal PML, can occur in patients receiving obinutuzumab.

Warnings and Precautions:

Hepatitis B virus reactivation. HBV reactivation, in some cases resulting in fulminant hepatitis, hepatic failure and death, can occur in patients receiving anti-CD20 antibodies such as obinutuzumab. HBV reactivation has been reported in patients who are hepatitis B surface antigen (HBsAg)–positive and in patients who are HbsAg-negative but who are hepatitis B core antibody (anti-HBc)–positive. Reactivation has also occurred in patients in whom the infection appeared to have resolved.

HBV reactivation is defined as an abrupt increase in HBV replication, manifesting as a rapid increase in serum HBV DNA level, or the detection of HBsAg in a person who was previously HbsAg-negative and anti-HBc–positive. Reactivation of HBV replication is often followed by hepatitis, characterized by an increase in transaminase levels and, in severe cases, an increase in bilirubin levels, liver failure, and death.

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For patients who show evidence of HBV infection, the clinician should consult a physician with expertise in HBV monitoring and antiviral therapy. Patients with evidence of current or previous HBV infection should be monitored for clinical and laboratory signs of hepatitis or HBV reactivation during, and for several months following, treatment with obinutuzumab. HBV reactivation has been reported for other CD20-directed cytolytic antibodies following the completion of therapy.

If HBV infection is reactivated during therapy with obinutuzumab, the drug and any concomitant chemotherapy should be immediately discontinued and appropriate treatment should be instituted. Whether to resume obinutuzumab if HBV reactivation resolves should be discussed with physicians with expertise in managing HBV infection. The data are insufficient to determine whether it is safe to resume obinutuzumab in the case of HBV reactivation.

PML. John Cunningham virus (JCV) infection resulting in PML, which can be fatal, was observed in patients who received obinutuzumab. The diagnosis of PML should be considered in any patient presenting with new-onset or changes to pre-existing neurological manifestations. Evaluation of PML includes consultation with a neurologist, brain magnetic resonance imaging, and lumbar puncture. Obinutuzumab should be discontinued, and stopping or reducing any concomitant chemotherapy or immunosuppressive therapy should be considered if PML develops.

Infusion reactions. Obinutuzumab can cause severe and life-threatening infusion reactions. Two-thirds of patients experienced a reaction to the first 1,000-mg infusion. Infusion reactions can also occur with subsequent infusions. Symptoms may include hypotension, tachycardia, dyspnea, and respiratory events (e.g., bronchospasm, laryngeal and throat irritation, wheezing, laryngeal edema). Other common symptoms include nausea, vomiting, diarrhea, hypertension, flushing, headache, pyrexia, and chills.

Patients may receive premedication with acetaminophen, an antihistamine, and a glucocorticoid. Glucocorticoids, epinephrine, bronchodilators, and/or oxygen may be given for infusion reactions as needed. Patients should be closely monitored during the entire infusion. Infusions reactions within 24 hours of receiving obinutuzumab have occurred.

For patients with a grade 4 infusion reaction, including but not limited to anaphylaxis, acute life-threatening respiratory symptoms, or other life-threatening infusion reaction, the infusion should be stopped and obinutuzumab therapy should be stopped permanently.

For a grade 3 reaction, therapy should be interrupted until symptoms resolve.

For a grade 1 or 2 reaction, the rate of the infusion should be interrupted or reduced and symptoms should be managed.

For patients with pre-existing cardiac or pulmonary conditions, monitoring should be performed more frequently during the infusion and post-infusion period because of a higher risk of a more severe reaction. Hypotension may occur with an

infusion reaction. The clinician should consider withholding antihypertensive treatments for 12 hours before and during each infusion and for the first hour after administration until blood pressure is stable.

For patients at an increased risk of hypertensive crisis, the benefits and the risks of withholding hypertensive medications should be considered.

Tumor lysis syndrome. Acute renal failure, hyperkalemia, hypocalcemia, hyperuricemia, and/or hyperphosphatemia from tumor lysis syndrome can occur within 12 to 24 hours after the first infusion. Patients with a high tumor burden or a high circulating lymphocyte count (above 25×10^9/L) are at greater risk for the syndrome and should receive appropriate prophylaxis with an antihyperuricemic agent such as allopurinol (e.g., Zyloprim, formerly Burroughs-Wellcome) and hydration beginning 12 to 24 hours before the fusion. For the treatment of tumor lysis syndrome, electrolyte abnormalities should be corrected, renal function and fluid balance should be monitored, and supportive care, including dialysis, should be administered as indicated.

Infection. Serious bacterial, fungal, and new or reactivated viral infections can occur during and following obinutuzumab therapy. This medication should not be given to patients with an active infection. Patients with a history of recurring or chronic infections may be at an increased risk of infection.

Neutropenia. In trials of obinutuzumab combined with chlorambucil, therapy resulted in grade 3 or 4 neutropenia in 34% of patients. Patients with grade 3 to 4 neutropenia should be monitored frequently with regular laboratory tests until neutropenia resolves. Symptoms or signs of developing infection should be anticipated, evaluated, and treated. Neutropenia can also be late in onset (occurring more than 28 days after completion of treatment) or prolonged (lasting longer than 28 days). Patients with neutropenia should receive antimicrobial prophylaxis throughout treatment. Antiviral and antifungal prophylaxis should be considered.

Thrombocytopenia. In trials of obinutuzumab combined with chlorambucil, 12% of patients experienced grade 3 or 4 thrombocytopenia. In 5% of patients, obinutuzumab led to acute thrombocytopenia occurring within 24 hours after the infusion. In patients with grade 3 or 4 thrombocytopenia, platelet counts should be monitored more frequently until resolution. Platelet transfusions may be necessary.

Immunization. The safety and efficacy of immunization with live or attenuated viral vaccines during or following obinutuzumab therapy has not been studied. Immunization with live virus vaccines is not recommended during treatment and should be postponed until B-cell recovery.

Dosage and Administration: Each IV dose of obinutuzumab is 1,000 mg except for the first infusions in cycle 1, which are administered on day 1 (100 mg) and on day 2 (900 mg) (Table 1). Obinutuzumab will be available in a 1,000-mg/40-mL (25-mg/mL) strength as a single-use vial.

Commentary: Coupled with chlorambucil, obinutuzumab is expected to be the successor to rituximab (Rituxan, Genentech), a cancer therapy responsible for $6 billion in sales; however, rituximab is beginning to be threatened by competitors.

The approval of obinutuzumab was based on CLL11, a phase 3 trial. Patients who received obinutuzumab plus chlorambucil had significantly reduced risk of disease progression or death and lived significantly longer without disease worsening compared with those who received chlorambucil alone (median progression-free survival, 23.0 months vs. 11.1 months).

Table 1 Doses of Obinutuzumab Administered During Six Treatment Cycles Every 28 Days

Cycle 1	Day 1	100 mg	25 mg/hour over 4 hours; do not increase infusion rate.
	Day 2	900 mg	50 mg/hour. Infusion rate may be escalated in increments of 50 mg/hour every 30 minutes to a maximum rate of 400 mg/hour.
	Day 8	1,000 mg	Infusions may start at rate of 100 mg/hour and may be increased by 100 mg/hour increments every 30 minutes to a maximum of 400 mg/hour.
	Day 15	1,000 mg	
Cycles 2–6	Day 1	1,000 mg	

Obinutuzumab showed improved efficacy over rituximab when combined with chlorambucil. Both drugs target cancer cells, but obinutuzumab also has unique sugar molecules that trigger the immune system to attack tumors. This drug was approved with the FDA's new breakthrough therapy designation, a label that the agency grants according to the life-threatening nature of disease and initial clinical evidence indicating significant improvement over current therapies.

Sources: www.gazyva.com/hcp; www.gene.com

Ibrutinib (Imbruvica) Capsules

Manufacturer: Pharmacyclics, Sunnyvale, Calif./ Janssen Biotech, Inc., Raritan, N.J.

Indication: Ibrutinib is designed to treat patients with mantle-cell lymphoma (MCL) who have received at least one therapy. This indication is based on overall response rate (ORR). An improvement in survival or disease-related symptoms has not been established.

Drug Class: Ibrutinib was first designed and synthesized at Celera Genomics as an approach for creating a series of small molecules that inactivate Bruton's tyrosine kinase (BTK) through covalent binding to cysteine-481 near the adenosine triphosphate (ATP) binding domain of BTK. These small molecules irreversibly inhibited BTK by using a Michael acceptor for binding to the target cysteine. In April 2006, Pharmacyclics acquired Celera's small-molecule BTK inhibitor discovery program, which included a compound, PCI-32765. This compound was subsequently chosen for further preclinical development based on the discovery of anti-lymphoma properties *in vivo*.

The chemical formula is 1-[(3*R*)-3-[4-amino-3-(4-phenoxyphenyl)pyrazolo[3,4-d]pyrimidin-1-yl]piperidin-1-yl]prop-2-en-1-one.

Uniqueness of Drug: Ibrutinib is an inhibitor of BTK, a key signaling molecule of the B-cell receptor signaling complex, which plays an important role in the survival of malignant B cells. The medication blocks signals that stimulate malignant

B cells to grow and divide uncontrollably.

Warnings and Precautions:

Hemorrhage. Five percent of patients with MCL had grade 3 or higher bleeding events (subdural hematoma, gastrointestinal bleeding, and hematuria). Bruising of any grade occurred in 48% of patients with MCL who received 560 mg daily. The cause of the bleeding events is not well understood. The risks and benefits of ibrutinib in patients requiring antiplatelet or anticoagulant therapies, and the benefits and risks of withholding ibrutinib for at least 3 to 7 days before and after surgery, depend on the type of surgery and the bleeding risk.

Infections. Fatal and nonfatal infections have occurred. At least 25% of patients with MCL had grade 3 infections or higher. Patients should be monitored for fever and infections and should be evaluated promptly.

Myelosuppression. Treatment-emergent grade 3 or 4 cytopenias were reported in 41% of patients. These included neutropenia (29%), thrombocytopenia (17%), and anemia (9%). A complete blood count (CBC) should be obtained monthly.

Renal toxicity. Fatal and serious cases of renal failure have occurred. Treatment-emergent increases in creatinine levels up to 1.5 times the upper limit of normal (ULN) occurred in 67% of patients and from 1.5 to three times the ULN in 9% of patients. Creatinine levels should be monitored periodically, and hydration should be maintained.

Second primary malignancies. Malignancies (5%) have occurred in patients with MCL who received ibrutinib, including skin cancers (4%) and other carcinomas (1%).

Embryofetal toxicity. On the basis of animal studies, ibrutinib can cause fetal harm in pregnant women. Pregnancy should be avoid during ibrutinib therapy. If this drug is used during pregnancy or if the patient becomes pregnant while taking it, she should be apprised of the potential hazard to the fetus.

Dosage and Administration: Four 140-mg capsules (560 mg) are taken orally once daily and at approximately the same time each day. The capsules should be swallowed whole with a glass of water; they should not be opened, broken, or chewed.

Commentary: Ibrutinib was approved under the FDA's accelerated approval program, which provides earlier patient access to promising new drugs while the company conducts confirmatory clinical trials. The FDA also granted a priority review and an orphan product designation for ibrutinib.

Because MCL affects only 2,900 patients in the U.S. per year, insurers may be better able to absorb the high cost. As an orphan drug, ibrutinib is relatively less expensive than other drugs for rare diseases (at more than $90 per capsule). At four capsules per day, the cost is about $130,000 per year.

Alexion's ecluzumab (Soliris), approved for paroxysmal nocturnal hemoglobinuria and other rare disorders, bears an annual price tag of $400,000 or more. Agalsidase beta (Fabrazyme for Fabry disease) and imiglucerase (Cerezyme for Gaucher's disease), both made by Sanofi/Genzyme, cost about $200,000 per year. Ivacaftor (Kalydeco, Vertex), which is approved to treat cystic fibrosis, costs about $290,000.

Sources: www.imbruvica.com; www.fiercepharma.com

Sofosbuvir (Sovaldi)

Manufacturer: Gilead Sciences, Inc., Foster City, Calif.

Indication: Sofosbuvir is designed to treat chronic hepatitis C virus (HCV) infection. It is the first drug that has demonstrated safety and efficacy to treat certain types of HCV infection without the need to co-administer interferon.

Drug Class: This nucleotide analogue inhibitor blocks a specific protein needed by the virus to replicate. The drug's efficacy was established in subjects with HCV genotypes 1, 2, 3, or 4 infection, including patients with hepatocellular carcinoma that met Milan criteria (awaiting liver transplantation) and those with HCV/HIV-1 co-infection.

Uniqueness of Drug: Sofosbuvir can be used as a component of a combination antiviral treatment regimen for chronic HCV infection. Depending on the type of HCV infection, the treatment regimen may include sofosbuvir with ribavirin or sofosbuvir, ribavirin, and peginterferon-alfa.

Warnings and Precautions:

Pregnancy. Ribavirin should not be used unless a pregnancy test result is negative immediately before therapy begins. Female patients of childbearing age and their male partners must use two forms of nonhormonal contraception during treatment and for at least 6 months after therapy has concluded. Routine monthly pregnancy tests must be performed during this time.

***Use with potent P-glycoprotein inducers*:** Rifampin and St. John's wort should not be used with sofosbuvir, because they may significantly decrease the plasma concentration of the drug, reducing its therapeutic effect.

Dosage and Administration: One 400-mg tablet is taken once daily with or without food. Sofosbuvir should be used in combination with ribavirin or in combination with pegylated interferon and ribavirin for the treatment of chronic hepatitis C.

Commentary. Hepatitis C is a viral disease that causes inflammation of the liver. It can lead to diminished liver function or liver failure. Most infected patients have no symptoms until liver damage becomes apparent, which may take several years. In some patients, scarring and cirrhosis develop over many years. This can lead to bleeding, jaundice, fluid accumulation in the abdomen, infections, or liver cancer. According to the Centers for Disease Control and Prevention, about 3.2 million Americans are infected with HCV.

In clinical trials, a regimen containing sofosbuvir was effective for multiple types of HCV infection. The medication also demonstrated efficacy in participants who could not tolerate or take an interferon-based treatment regimen and in participants with liver cancer awaiting liver transplantation; sofosbuvir therefore addressed unmet medical needs in these populations.

Sofosbuvir is the third drug with a "breakthrough therapy" designation granted by the FDA and the second drug (approved in November 2013) to treat chronic HCV infection. Simeprevir (Olysio, Janssen) is an NS3/4A protease inhibitor intended to be used in combination with two standard HCV medications, pegylated interferon, and ribavirin. It is the first such agent that can be taken once a day.

Of concern is the wholesale cost of sofosbuvir: $28,000 for 4 weeks—or $1,000 per day. This translates to $84,000 for the 12 weeks of treatment recommended for most patients, and $168,000 for the 24 weeks needed for a hard-to-treat strain of the virus.

Sources: www.gilead.com; http://finance.yahoo.com; *The New York Times*, December 7, 2013 ■