Ibrutinib (Imbruvica)

**Manufacturer:** Pharmacycics Inc., Sunnyvale, California

**Date of Approval:** February 12, 2014

**Indication:** Ibrutinib has been approved for the treatment of chronic lymphocytic leukemia (CLL) in patients who have received at least one previous therapy.

**Drug Class:** Ibrutinib is 1-(3R)-3-[4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl]piperidine-1-yl)prop-2-en-1-one with a molecular mass of 440.497.

**Uniqueness of Drug:** Ibrutinib is an orally administered, selective, and covalent inhibitor of the enzyme Bruton’s tyrosine kinase (BTK).

In an in vitro study, treatment of activated CLL cells with ibrutinib resulted in inhibition of BTK tyrosine phosphorylation and also effectively abrogated downstream survival pathways activated by this kinase, including ERK1/2, PI3K, and NF-κB. Additionally, ibrutinib inhibited proliferation of CLL cells in vitro, effectively blocking survival signals provided externally to CLL cells from the microenvironment, including soluble factors (CD40L, BAFF, IL-6, IL-4, and TNF-α), fibronectin engagement, and stromal cell contact.

**Warnings and Precautions:**

**Hemorrhage.** Five percent of patients with mantle cell lymphoma (MCL) and 6% of patients with CLL had grade 3 or higher bleeding events (subdural hematoma, ecchymoses, gastrointestinal bleeding, and hemaeturia). Overall, bleeding events including bruising of any grade occurred in 48% of patients with MCL treated with 560 mg daily and 65% of patients with CLL treated with 420 mg daily.

The mechanism for the bleeding events is not well understood. Ibrutinib may increase the risk of hemorrhage in patients receiving antiplatelet or anticoagulant therapies. Consider the benefit and risk of withholding ibrutinib for at least three to seven days before and after surgery depending upon the type of surgery and the risk of bleeding.

**Infections.** Fatal and nonfatal infections have occurred with ibrutinib therapy. At least 25% of patients with MCL and 35% of patients with CLL had infections of grade 3 or greater using National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE). Monitor patients for fever and infections and evaluate promptly.

**Myelosuppression.** Treatment-emergent grade 3 or 4 cytopenias were reported in 41% of patients with MCL and 35% of patients with CLL. These included neutropenia (29%), thrombocytopenia (17%), and anemia (9%) in patients with MCL and neutropenia (27%) and thrombocytopenia (10%) in patients with CLL. Monitor complete blood counts monthly.

**Renal toxicity.** Serious and fatal cases of renal failure have occurred with ibrutinib therapy. Treatment-emergent increases in creatinine levels up to 1.5 times the upper limit of normal occurred in 67% of patients with MCL and 23% of patients with CLL. Increases in creatinine 1.5 to three times the upper limit of normal occurred in 9% of patients with MCL and 4% of patients with CLL. Periodically monitor creatinine levels. Maintain hydration.

**Second primary malignancies.** Other malignancies have occurred in 5% of patients with MCL and 10% of patients with CLL who have been treated with ibrutinib. Four percent of patients with MCL had skin cancers, and 1% had other carcinomas. Eight percent of patients with CLL had skin cancers and 2% had other carcinomas.

**Embryofetal toxicity.** Based on findings in animals, ibrutinib can cause fetal harm when administered to a pregnant woman. Advise women to avoid becoming pregnant while taking ibrutinib. If this drug is used during pregnancy or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to a fetus.

**Dosage and Administration:** The recommended dose and schedule of ibrutinib for patients with CLL is 420 mg (three 140-mg capsules) taken orally once daily.

Patients should swallow ibrutinib capsules whole with a glass of water without opening, breaking, or chewing them. They should take ibrutinib at about the same time each day. Advise patients who miss a dose of ibrutinib to take it as soon as they remember on the same day. They should take their next dose at their regular time on the next day. Patients should not take two doses of ibrutinib on the same day to make up for a missed dose.

**Commentary:** CLL is a rare blood and bone marrow disease that usually worsens slowly over time, causing a gradual increase in white blood cells called B lymphocytes, or B cells. In November 2013, the FDA granted Imbruvica accelerated approval to treat patients with MCL, a rare and aggressive type of blood cancer, if those patients had received at least one prior therapy. The current approval provides an important new treatment option for CLL patients whose cancer has progressed despite having undergone previous therapy.

The NCI estimates that 15,680 Americans were diagnosed with CLL and 4,580 died from the disease in 2013. That is a significant pool for a drug that is priced at more than $90 a pill—meaning a year of treatment is expected to run $98,400. Because it takes more pills to treat MCL, a year’s regimen is projected to cost about $130,000. Of course, those are prices before discounts. Pharmacycics will offer two months’ worth of the drug for free to MCL patients who have trouble with insurance reimbursement. The company is also setting up copay assistance plans for patients who can’t afford their share of the cost. Because of its improved benefits, ibrutinib is expected to be in demand, putting pressure on payers to make it available under insurance plans. According to EvaluatePharma, analysts have forecast annual sales reaching $1.3 billion in 2018.

**Sources:** www.imbruvica.com, www.fda.gov
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Tasimelteon Capsules (Hetlioz)

Manufacturer: Vanda Pharmaceuticals Inc., Washington, D.C.

Date of Approval: January 31, 2014

Indication: Tasimelteon is a melatonin receptor agonist for the treatment of non-24-hour sleep–wake disorder (non-24) in the totally blind. Non-24 is a chronic circadian rhythm (body clock) disorder in the blind that causes problems with the timing of sleep.

Drug Class: Tasimelteon, (1R, 2R)-N-[2-(2,3-dihydrobenzofuran-4-yl)cyclopropylmethyl]propanamide, is a CYP3A4 substrate: avoid coadministration with CYP3A4 inducers because of a potentially large decrease in tasimelteon exposure with reduced efficacy.

Uniqueness of Drug: Tasimelteon is a melatonin receptor agonist with highly selective affinity for MT1 and MT2 receptors in the suprachiasmatic nucleus of the brain. MT1 and MT2 are thought to synchronize the body’s melatonin and cortisol circadian rhythms with the day–night cycle in patients with non-24.

Warnings and Precautions:

Somnolence. Tasimelteon can impair performance of activities that require complete mental alertness.

Smoking. Smoking causes induction of CYP1A2 levels; tasimelteon exposure in smokers was lower (approximately 40%) than in nonsmokers, and therefore the medication’s efficacy may be reduced.

Age. Risk of adverse reactions may be greater in patients more than 65 years old compared with younger patients because exposure to tasimelteon is increased by approximately twofold.

Alcohol. In clinical trials, coadministration with alcohol showed a trend toward additive sedation.

Dosage and Administration: The recommended dosage of tasimelteon is 20 mg per day taken before bedtime at the same time every night.

Commentary: Non-24-hour sleep–wake disorder occurs in persons who are completely blind. Because light does not enter their eyes, they cannot synchronize their body clock to the 24-hour light–dark cycle.

People with the disorder may have difficulty falling asleep or staying asleep, and may wake up groggy or feeling as if they need more rest. People with non-24 may find their sleep or staying asleep, and may wake up groggy or feeling as if they need more rest. People with non-24 may find their sleep

The product contains approximately equal units of factor VIII inhibitor bypassing activity and prothrombin complex factors. In addition, one to six units of factor VIII coagulant antigen (FVIII C:Ag) per mL are present. The preparation contains only traces of factors of the kinin generating system. It contains no heparin.

Uniqueness of Drug: Feiba VH Anti-Inhibitor Coagulant Complex, Vapor Heated (AICC) is a freeze-dried sterile human plasma fraction with factor VIII inhibitor bypassing activity.

Factor VIII inhibitor bypassing activity is expressed in arbitrary units. One immuno unit of activity is defined as that amount of Feiba VH (AICC) that shortens the activated partial thromboplastin time (APTT) of a high titer factor VIII inhibitor reference plasma to 50% of the blank value. The product is intended for intravenous administration.

Warnings and Precautions:

Thromboembolic Events. Thromboembolic events (including venous thrombosis, pulmonary embolism, myocardial infarction, and stroke) can occur with Feiba, particularly following the administration of high doses (above 200 units per kilogram of body weight per day) and/or in patients with thrombotic risk factors.

Infusion of Feiba should not exceed a dose of 100 U/kg every six hours and daily doses of 200 U/kg. Monitor patients receiving more than 100 U/kg for the development of disseminated intravascular coagulation (DIC), acute coronary ischemia, and signs and symptoms of other thromboembolic events. If clinical signs or symptoms occur, such as chest pain or pressure; shortness of breath; altered consciousness, vision, or speech; or limb or abdomen swelling and/or pain, discontinue the infusion and initiate appropriate diagnostic and therapeutic measures.

Hypersensitivity and allergic reactions. Hypersensitivity and allergic reactions, including severe anaphylactoid reactions, can occur following the infusion of Feiba. The symptoms include urticaria, angioedema, gastrointestinal manifestations, bronchospasm, and hypotension. These reactions can be severe and systemic. Other infusion reactions, such as chills, pyrexia, and hypertension have also been reported. If signs and symptoms of severe allergic reactions occur, immediately discontinue administration of Feiba and provide appropriate supportive care. The use of Feiba is contraindicated in patients with known anaphylactic or severe hypersensitivity reactions to Feiba or any of its components, including factors of the kinin-generating system.

Infectious agents. Because Feiba is made from human plasma, it may carry a risk of transmitting infectious agents, e.g., viruses, the variant Creutzfeldt-Jakob disease (vCJD) agent, and, theoretically, the Creutzfeldt-Jakob disease (CJD) agent.

Dosage and Administration: The dosage and duration of therapy depends upon the severity of the disorder, the location and extent of the bleeding, and the patient’s clinical condition. Dosage and frequency of administration should always be guided by clinical efficacy in each individual case.

As a general guideline, a dose of 50 to 100 U/kg is recommended. However, a single dose of 100 U/kg body weight and a maximum daily dose of 200 U/kg body weight must not be exceeded unless the severity of bleeding warrants and justifies the use of higher doses.

Commentary: Feiba is formulated with multiple active components that quickly induce thrombin generation and maintain

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the coagulation process. It provides both factor II (prothrombin) and factor Xa for rapid and sustained thrombin generation and contains additional factors that target multiple sites within the coagulation system to help sustain activity.

Thrombotic and thromboembolic events, including disseminated intravascular coagulation (DIC), venous thrombosis, pulmonary embolism, myocardial infarction, and stroke have occurred in the course of treatment with Feiba, particularly after administration of doses above the maximum daily dose and/or prolonged application or in patients with other risk factors for thromboembolic events.

In patients with impaired liver function, coronary heart disease, acute thrombosis, and/or embolism, the use of Feiba is indicated only if no reaction to treatment with suitable blood coagulation factor concentrates can be expected. As with any intravenously administered plasma product, allergic-type hypersensitivity reactions may occur; patients should be informed of the early signs of hypersensitivity reactions.

Sources: www.feiba.com, www.baxter.com