Vemurafenib (Zelboraf) Tablets

Manufacturer: Hoffmann-LaRoche Inc., Nutley, N.J.

Indication: Vemurafenib is designed to treat patients who have unresectable or metastatic melanoma with the BRAF\(^{V600E}\) genetic mutation. The FDA-approved cobas 4800 BRAF V600 Mutation Test is a companion diagnostic that helps to determine whether a patient’s melanoma cells have the BRAF\(^{V600E}\) mutation.

Drug Class: The chemical formula is propane-1-sulfonic acid \([3-[5-(4-chlorophenyl)-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]-2,4-difluoro-phenyl]-amide. The molecular formula is \(C_{23}H_{18}ClF_2N_3O_3S\), and the molecular weight is 489.9.

Uniqueness of Drug: Vemurafenib received the FDA’s early approval and is the first drug for treating advanced melanoma by targeting a specific genetic mutation. The medication is designed to destroy cancer cells by blocking the mutated BRAF gene, which is found in 40% to 60% of all melanoma patients. BRAF is a member of the Raf kinase family of serine/threonine-specific protein kinases. This protein plays a role in regulating the MAP kinase/ERKs signaling pathway, which affects cell division, differentiation, and secretion. Vemurafenib is a low-molecular-weight inhibitor of some mutated forms of BRAF serine–threonine kinase, including BRAF\(^{V600E}\). The drug also inhibits other kinases in vitro such as CRAF, ARAF, wild-type BRAF, SRMS, ACK1, MAP4K5, and FGR at similar concentrations. Some mutations in the BRAF gene, including V600E, result in constitutively activated BRAF proteins, which can cause cell proliferation in the absence of growth factors that would normally be required for proliferation.

Warnings and Precautions:

Cutaneous squamous cell carcinoma. Cases of cutaneous squamous cell carcinoma (SCC), including SCCs of the skin as well as keratoacanthomas, have been reported in patients who received vemurafenib. In one trial, the incidence of cutaaneous SCC in vemurafenib-treated patients was 24%. Cutaneous SCC usually occurred early in the course of treatment with a median time of 7 to 8 weeks to the first appearance. Of those patients who developed cutaneous SCC, approximately 33% experienced more than one occurrence, with a median time between occurrences of 6 weeks. It is recommended that all patients receive a dermatological evaluation before beginning therapy and every two months while they are receiving therapy.

Hypersensitivity reactions. Serious reactions, including anaphylaxis, have been reported in association with vemurafenib and upon reinitiation of treatment.

Dermatological reactions. Severe reactions have been reported in patients receiving vemurafenib, including one case of Stevens–Johnson syndrome and one case of toxic epidermal necrolysis in trial 1. This drug should be discontinued permanently if patients experience a severe dermatological reaction.

Prolongation of the QT interval. Exposure-dependent QT prolongation was observed in an uncontrolled, open-label phase 2 substudy in previously treated patients with BRAF\(^{V600E}\) mutation-positive metastatic melanoma. A prolonged QT interval may lead to an increased risk of ventricular arrhythmias, including torsades de pointes. Vemurafenib is not recommended if patients have uncorrectable electrolyte abnormalities or long QT syndrome or if they are taking medicinal products known to prolong the QT interval.

Electrocardiograms (ECGs) and electrolytes, including potassium, magnesium, and calcium, should be monitored before patients receive vemurafenib and after any dose modification. If the corrected QT interval (QTc) exceeds 500 milliseconds (msec) during treatment, according to common terminology for adverse events (CTC–AE grade 3 or above), therapy should be temporarily interrupted, electrolyte abnormalities should be corrected, and cardiac risk factors for QT prolongation (e.g., congestive heart failure, bradyarrhythmias) should be controlled. Treatment should be reinitiated at a lower dose after the QTc drops to below 500 msec. Treatment should be permanently discontinued if, after associated risk factors are addressed, the increase in the QTc meets values of more than a 500-msec and more than a 60-msec change from pretreatment values.

Liver abnormalities. Hepatic laboratory abnormalities have occurred with vemurafenib therapy. Liver enzymes (transaminases and alkaline phosphatase) and bilirubin should be monitored before treatment begins and monthly during treatment or as clinically indicated. Abnormal laboratory values should be managed with dose reductions, interruption of therapy, or discontinuation of treatment.

Photosensitivity. In clinical trials, mild-to-severe photosensitivity was reported in patients receiving vemurafenib. All patients should be advised to avoid sun exposure during vemurafenib therapy. To guard against sunburn, patients should wear protective clothing and use a broad-spectrum ultraviolet A/B sunscreen and lip balm with a sun protection factor (SPF) of 30 or higher when they are outdoors. Dose modifications are recommended for intolerable grade 2 photosensitivity (tender erythema covering 10% to 30% of body surface area) or more.

Ophthalmologic reactions. In the first clinical trial, five cases of uveitis were reported in treated patients. Patients should be routinely monitored for signs and symptoms of uveitis, and steroid and mydriatic ophthalmic drops may be required. Five patients also had blurry vision, five patients had iritis, and six patients had photophobia. In the second trial, one case of retinal vein occlusion was reported.

New primary malignant melanoma. In the first trial, eight
skin lesions in seven patients were reported as new primary malignant melanomas. These melanomas were managed with excision, and patients continued treatment without dose adjustments. Skin lesions should be closely monitored every two months during therapy.

**Pregnancy.** As a Pregnancy Category D agent, vemurafenib may cause fetal harm when administered during pregnancy. No adequate or well-controlled studies have been conducted in pregnant women. If vemurafenib is taken during pregnancy or if the patient becomes pregnant while taking it, she should be apprised of the potential hazard to the fetus.

**BRAF**<sup>V600E</sup> **Testing.** Confirmation of **BRAF**<sup>V600E</sup> mutation-positive melanoma, as detected by the cobas 4800 **BRAF**<sup>V600E</sup> Mutation Test, is required in order to select appropriate candidates for vemurafenib; these are the only patients who have been studied and who might benefit. In two studies (trial 1 and trial 2), all enrolled patients tested positive when their tumor tissue was assessed with the cobas test, which is designed to detect **BRAF**<sup>V600E</sup> mutations in DNA isolated from formalin-fixed, paraffin-embedded human melanoma tissue. The safety and efficacy of vemurafenib have not been evaluated in patients with a negative test result.

**Adverse Reactions:** Most adverse reactions (affecting 30% of patients or more) are arthralgia, rash, alopecia, fatigue, photosensitivity reaction, nausea, pruritus and skin papilloma.

**Dosage and Administration:** Available as 240-mg oral tablets, vemurafenib is taken approximately 12 hours apart with or without a meal. The recommended dose is 960 mg twice daily. The tablets should be swallowed whole with a glass of water and should not be chewed or crushed. If symptomatic adverse drug reactions occur, the dose may need to be reduced or treatment may need to be interrupted or discontinued. Dose reductions below 480 mg twice daily are not recommended.

**Commentary:** Targeted therapies have been used to block the growth and spread of breast cancer, pancreatic cancer, and non–small-cell lung cancer (NSCLC). Vemurafenib is the first FDA-approved drug using this approach to treat melanoma. The agency approved it six months early. This action, it is recommended.

**Peripheral neuropathy.** Vemurafenib results in peripheral neuropathy that is predominantly sensory. The neuropathy is cumulative. Patients experiencing new or worsening peripheral neuropathy may require a delay in therapy, a change in the dose, or discontinuation of treatment. Cases of peripheral motor neuropathy have also been reported.

**Infusion reactions.** Infusion-related reactions, including anaphylaxis, have occurred with vemurafenib. Patients should be monitored during infusions. If an infusion reaction occurs, the infusion should be interrupted and appropriate management should be instituted. If anaphylaxis occurs, the infusion should be discontinued immediately and medical therapy should be given.

**Neutropenia.** Complete blood counts should be taken before each dose of vemurafenib is given. If grade 3 or 4 neutropenia develops, a dose delay, a dose reduction, or discontinuation of therapy may be required. Prolonged, severe neutropenia lasting 1 week or more can occur with this medication.

**Tumor lysis syndrome.** Patients with a rapidly proliferating tumor and a high tumor burden may be at increased risk for the development of tumor lysis syndrome. Close monitoring is recommended.

**Stevens–Johnson syndrome.** Stevens–Johnson syndrome has been reported with vemurafenib. If this syndrome develops, treatment should be stopped and appropriate medical therapy should be administered.

**Progressive multifocal leukoencephalopathy.** A fatal case of progressive multifocal leukoencephalopathy was reported in a patient who received four chemotherapy regimens before receiving vemurafenib.

**Dosage and Administration:** The recommended dose is 1.8 mg/kg, administered only as an intravenous (IV) infusion continued on page 650

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**Brentuximab Vedotin (Adcetris) Infusion**

**Manufacturer:** Seattle Genetics, Inc., Bothell, Wash.

**Indication:** Brentuximab vedotin is designed to treat patients with Hodgkin’s lymphoma who have not responded to autologous stem-cell transplantation (ASCT); patients who did not respond to at least two previous multiagent chemotherapy regimens and who are not candidates for ASCT; and patients with systemic anaplastic large-cell lymphoma (ALCL) who have not responded to at least one multiagent chemotherapy regimen.

**Drug Class:** This selective bradykinin B<sub>2</sub> receptor antagonist is a CD30-directed, antibody–drug conjugate.

**Uniqueness of Drug:** Brentuximab vedotin comprises an anti-CD30 monoclonal antibody attached by a protease-cleavable linker to a microtubule-disrupting agent, monomethyl auristatin E (MMAE). The linker system is designed to be stable in the bloodstream, but it also releases MMAE upon internalization into CD30-expressing tumor cells. It consists of three components: (1) the chimeric immunglobulin G<sub>1</sub> (IgG<sub>1</sub>) antibody cAC10, specific for human CD30; (2) the microtubule-disrupting agent MMAE; and (3) a protease-cleavable linker that covalently attaches MMAE to cAC10.

**Warnings and Precautions:**

**Peripheral neuropathy.** Brentuximab vedotin results in peripheral neuropathy that is predominantly sensory. The neuropathy is cumulative. Patients experiencing new or worsening peripheral neuropathy may require a delay in therapy, a change in the dose, or discontinuation of treatment. Cases of peripheral motor neuropathy have also been reported.

**Infusion reactions.** Infusion-related reactions, including anaphylaxis, have occurred with brentuximab vedotin therapy. Patients should be monitored during infusions. If an infusion reaction occurs, the infusion should be interrupted and appropriate management should be instituted. If anaphylaxis occurs, the infusion should be discontinued immediately and medical therapy should be given.

**Neutropenia.** Complete blood counts should be taken before each dose of brentuximab vedotin is given. If grade 3 or 4 neutropenia develops, a dose delay, a dose reduction, or discontinuation of therapy may be required. Prolonged, severe neutropenia lasting 1 week or more can occur with this medication.

**Tumor lysis syndrome.** Patients with a rapidly proliferating tumor and a high tumor burden may be at increased risk for the development of tumor lysis syndrome. Close monitoring is recommended.

**Stevens–Johnson syndrome.** Stevens–Johnson syndrome has been reported with brentuximab vedotin. If this syndrome develops, treatment should be stopped and appropriate medical therapy should be administered.

**Progressive multifocal leukoencephalopathy.** A fatal case of progressive multifocal leukoencephalopathy was reported in a patient who received four chemotherapy regimens before receiving brentuximab vedotin.

**Dosage and Administration:** The recommended dose is 1.8 mg/kg, administered only as an intravenous (IV) infusion continued on page 650
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over 30 minutes every 3 weeks. The medication should not be
given as an IV push or bolus. Treatment should be continued
until the patient has received a maximum of 16 cycles, until
disease progression, or until unacceptable toxicity.

Adverse Reactions: Common adverse reactions (affecting
20% or more patients) have included neutropenia, peripheral
sensory neuropathy, fatigue, nausea, anemia, upper respiratory
tract infection, diarrhea, pyrexia, rash, thrombocytopenia,
cough, and vomiting.

Commentary: Brentuximab vedotin is recommended for
patients with Hodgkin’s lymphoma whose disease has pro-
gressed after autologous stem-cell transplantation or after two
previous chemotherapy treatments for those who cannot
receive a transplant. This medication may also be used in
patients with ALC L whose disease has progressed after one
previous chemotherapy cycle.

The indications for the FDA’s approval were based on
response rates. No data have shown improvement in patient-
reported outcomes or survival with this therapy. Brentuximab
vedotin is the first drug approved by the FDA for Hodgkin’s
lymphoma in more than 30 years, providing a therapeutic
alternative for these patients and for those with systemic ALC L.

The cost might be more than $100,000 for a course of treat-
ment, or $4,500 per vial. Patients typically need three vials in
one dose, and from seven to nine doses per course of treatment,
a cost ranging from $94,500 to $121,500.

Sources: www.fda.gov; http://dailymed.nlm.nih.gov/daily
med/drugInfo.cfm?id=50872; www.medicalnewstoday.com/
articles/233141.php

Icatibant (Firazyr) Injection

Manufacturer: Shire PLC, Lexington, Mass.

Indication: Icatibant is used to treat acute attacks of heredi-
tary angioedema (HAE) in adults 18 years of age and older.

Drug Class: As a peptidomimetic drug consisting of 10
amino acids, icatibant is a selective and specific antagonist of
bradykinin B2 receptors.

Uniqueness of Drug: Icatibant acts as a bradykinin inhib-
itor by blocking the binding of native bradykinin to the brady-
kinin B2 receptor. Bradykinin is a peptide-based hormone that
is formed locally in tissues, often in response to a trauma. It
increases vessel permeability, dilates blood vessels, and causes
smooth muscle cells to contract. Bradykinin plays an important
role as the mediator of pain. A surplus of bradykinin is respon-
sible for the typical symptoms of inflammation, such as
swelling, redness, overheating, and pain. These symptoms
are mediated by activation of bradykinin B2 receptors.

Nonclinical Toxicology:

Ischemic heart disease. Under ischemic conditions, a
deterioration of cardiac function and a decrease in coronary
blood flow may arise from antagonism of bradykinin receptor
type 2. Caution should therefore be observed when icatibant
is prescribed for patients with acute ischemic heart disease or
unstable angina pectoris.

Stroke. Although there is evidence to support a beneficial
effect of B2 receptor blockade immediately following a stroke,
it is possible that icatibant might attenuate the positive late-
phase neuroprotective effects of bradykinin. Accordingly,
caution should be observed in the weeks following a stroke.

Warnings and Precautions: Laryngeal attack. If a laryngeal attack occurs after icat-
ibant therapy, patients should be advised to seek medical
attention immediately.

Dosage and Administration: Each prefilled syringe of
3 mL contains icatibant acetate equivalent to 30 mg of icatibant.
Each milliliter of the solution contains 10 mg of icatibant. The
recommended dose is 30 mg injected subcutaneously in the
abdominal area. If the patient’s response is inadequate or if
symptoms recur, additional injections of 30 mg may be given
at intervals of at least 6 hours. No more than three injections
should be administered in 24 hours. Patients may self-
administer the drug if they recognize that they are having a
HAE attack.

Adverse Reactions: Almost all subjects who were treated
with icatibant in clinical trials developed reactions at the in-
jection site, characterized by skin irritation, swelling, pain,
itchiness, erythema, and a burning sensation. Caution should
be observed when icatibant is administered to patients with
acute ischemic heart disease or unstable angina pectoris and
in the weeks following a stroke.

Commentary: HAE is a debilitating disease, characterized
by recurrent, sometimes disfiguring, and often painful episodes
of acute swelling of the skin or the mucous membranes. The
attacks, which can be life-threatening, can affect any part of the
body but usually occur in the face, gastrointestinal tract, extre-
mities, or genitals. Laryngeal attacks can be fatal because of
the risk of suffocation.

HAE is caused by low levels of or a dysfunction of C1 ester-
ase inhibitor (C1-INH). Reduced C1-INH activity can lead to
elevated plasma levels of bradykinin, which is thought to be
responsible for HAE symptoms. Unlike angioedema that is
called by allergic reactions, signs and symptoms (e.g., hives
and itching) do not occur in HAE. Signs and symptoms of
HAE do not respond to standard treatments for allergic
angioedema, such as the use of epinephrine, corticosteroids,
or antihistamines.

The approval of icatibant was based on data from three
double-blind, randomized controlled clinical trials. FAST 1 and
FAST 2 included a total of 61 patients who received icatibant.
FAST 3 was a placebo-controlled study of 98 adults. The me-
dian time to 50% reduction in symptoms for patients with cutan-
eous or abdominal attacks who were treated with icatibant
(n = 43), compared with placebo (n = 45), was 2 hours versus
19.8 hours (P < 0.001). The median times to almost complete
symptom relief were 8 hours for icatibant and 36 hours for
placebo. In all three trials, the median time for icatibant to
achieve a 50% reduction in baseline symptoms ranged from
2 to 2.3 hours.

Until a few years ago, no effective agents for treating HAE
acute attacks had existed in the U.S. Now several medications
are available. Approved in 2009, ecallantide (Kalbitor, Dyax)
and Berinert (C1 esterase inhibitor, human, Behring) must be
given in a medical setting. Cinryze (C1 esterase inhibitor
(n = 43), compared with placebo (n = 45), was 2 hours versus
19.8 hours (P < 0.001). The median times to almost complete
symptom relief were 8 hours for icatibant and 36 hours for
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tions are available. Approved in 2009, ecallantide (Kalbitor, Dyax)
and Berinert (C1 esterase inhibitor, human, Behring) must be
given in a medical setting. Cinryze (C1 esterase inhibitor,
human, ViroPharma/Lev) was approved in 2008, and others
are in the midst of the FDA’s approval process.

Source: http://pi.shirecontent.com/PI/PDFS/Firazyr_USA_ENG.PDF; www.drugs.com/nda/firazyr_110228.html