Vortioxetine (Brintellix) Tablets

Manufacturer: Lundbeck, Deerfield, Ill./Takeda, Osaka, Japan

Indication: Vortioxetine was approved in September 2013 for adults with major depressive disorder (MDD).

Drug Class: Vortioxetine is a serotonin modulator and stimulator. The empirical formula is 1-{2-[(2,4-dimethyl-phenylsulfanyl)-phenyl-piperazine, hydrobromide. The molecular mass is 298.45 g/mol, and the molecular weight is 379.36 as hydrobromide.

Uniqueness of Drug: The drug’s role as an inhibitor of serotonin (5-HT) reuptake is thought to be a mechanism of its antidepressant action. Vortioxetine is also an agonist at 5-HT1A receptors; a partial agonist at 5-HT1B receptors; and an antagonist at 5-HT3, 5-HT3, and 5-HT7 receptors. This is considered to be the first compound with this combination of pharmacodynamic activity.

Boxed Warning: Suicidal thoughts and behaviors. In short-term studies, antidepressants increased the risk of suicidal thoughts and behavior in children, adolescents, and adults younger than 24 years of age. A trend toward a reduced risk in patients 65 years of age and older was observed. Patients of all ages who begin antidepressant therapy should be closely monitored for any worsening or emergence of suicidal thoughts and behaviors. Families and caregivers should be advised of the need for close observation and communication with the prescriber. Vortioxetine has not been evaluated in pediatric patients.

Warnings and Precautions:

Clinical worsening and suicide risk. All patients using antidepressants should be monitored appropriately and observed for suicidality and unusual changes in behavior, especially during the initial few months of therapy and during dosage increases or decreases. If symptoms of depression persist or worsen, the clinician should consider changing or discontinuing the medication. Symptoms might include anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia, hypomania, and mania. Families and caregivers of patients who take antidepressants for MDD or other psychiatric and nonpsychiatric indications should be alerted about the need to monitor patients daily.

Serotonin syndrome. The development of a potentially life-threatening serotonin syndrome has been reported with serotoninergic antidepressants, including selective serotonin reuptake inhibitors (SSRIs) and serotonin norepinephrine reuptake inhibitors (SNRIs). The syndrome has occurred with these agents alone or with other serotonergic drugs (e.g., triptans, tricyclic antidepressants, fentanyl, lithium, tramadol, tryptophan, buspirone, and St. John’s wort), as well as with drugs that impair serotonin metabolism (e.g., monoamine oxidase inhibitors).

Symptoms of serotonin syndrome may include agitation, hallucinations, delirium, and coma; tachycardia, labile blood pressure, dizziness, diaphoresis, flushing, and hyperthermia; neuromuscular problems such as tremor, rigidity, myoclonus, hyperreflexia, and incoordination; seizures; and nausea, vomiting, and diarrhea. If any of these symptoms occur, therapy should be discontinued and supportive treatment should be initiated. If the concomitant use of vortioxetine is warranted, patients should be monitored for a potential increased risk of serotonin syndrome, especially at the beginning of treatment and at dosage increases.

Abnormal bleeding. Serotonergic antidepressants may increase the risk of excessive bleeding. Patients should be cautioned about this risk when vortioxetine is taken with nonsteroidal anti-inflammatory drugs (NSAIDs), aspirin, or other medications that affect coagulation.

Mania or hypomania. Activation of mania or hypomania can occur with antidepressants. Before antidepressant treatment begins, patients should be screened for bipolar disorder. As with all antidepressants, vortioxetine should be prescribed with caution in patients with a personal or family history of bipolar disorder, mania, or hypomania.

Hyponatremia. In many cases, hyponatremia appears to be the result of the syndrome of inappropriate hormone secretion (SIADH). Elderly patients and patients taking diuretics or who are otherwise volume-depleted can be at greater risk. More severe events have included hallucinations, syncope, seizures, coma, respiratory arrest, and death. Vortioxetine should be discontinued in patients with symptomatic hyponatremia, and appropriate medical intervention should be instituted.

Dosage and Administration: The recommended starting dose of vortioxetine is 10 mg once daily without regard to meals. The dose should then be increased to 20 mg/day. The tablets are sold in strengths of 5 mg, 10 mg, and 20 mg.

Commentary: According to The World Health Organization, fewer than half of people with depression worldwide are receiving treatment, and the burden of depression is expected to continue to rise globally. Because MDD is a heterogeneous disorder that does not consistently respond to therapy, it is important for patients to work with a health care professional to help find a treatment plan that works for them.

In six placebo-controlled clinical studies, vortioxetine relieved depression. In another study, it decreased the likelihood of recurrent depression after treatment of an MDD episode. Common side effects reported included nausea, constipation, and vomiting.

Sources: www.lundbeck.com/us; www.fda.gov; www.marketwatch.com

Ustekinumab (Stelara) Injection


Indication: Ustekinumab, a human interleukin (IL)-12 and IL-23 antagonist, is now approved by the FDA for adults 18 years of age or older with active psoriatic arthritis (PsA), a chronic

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autoimmune disease. This medication can be used alone or with methotrexate. Ustekinumab was previously approved in 2009 for the treatment of adults with moderate-to-severe plaque psoriasis who were candidates for phototherapy or systemic therapy.

**Drug Class:** Ustekinumab is the first anti-IL therapy for adults with PsA. The estimated molecular mass ranges from 148,079 to 149,690 daltons.

**Uniqueness of Drug:** IL-12 and IL-23 are naturally occurring proteins that are believed to play a role in inflammatory conditions.

**Warnings and Precautions:**

**Infection.** Ustekinumab may increase the risk of infections (bacterial, fungal, and viral) and may reactivate latent infections. Patients with any active infection should not use this drug until the infection is resolved or is adequately treated. Patients should be advised to consult with a health care practitioner if signs or symptoms suggesting an infection develop. Prescribers should exercise caution when considering ustekinumab for patients with a chronic infection or a history of recurrent infection.

Serious infections requiring hospitalization have been reported, including cellulitis, diverticulitis, osteomyelitis, gastrointestinal, and pneumonia. Viral and urinary tract infections were also observed.

**Vulnerability to infections.** Individuals with a genetic deficiency of IL-12/IL-23 are particularly vulnerable to disseminated infections from mycobacteria (including nontuberculous, environmental mycobacteria), salmonella (including non-typhi strains), and Bacille Calmette-Guérin (BCG) vaccinations. Serious infections and fatal outcomes have been reported in such patients. It is not known whether patients with pharmacological blockade of IL-12/IL-23 by ustekinumab will be susceptible to these types of infections. Appropriate diagnostic testing by tissue sampling or stool culture should be considered.

**Evaluation for tuberculosis.** Patients should be evaluated and treated for tuberculosis (TB) before they receive ustekinumab. This drug should not be given to patients with active TB. Patients should be monitored closely for signs and symptoms of active TB during and after treatment.

**Malignancy.** Ustekinumab, an immunosuppressant, may increase the risk of malignancy. In rodent models, inhibition of IL-12/IL-23p40 increased this risk. The safety of ustekinumab has not been evaluated in patients with a previous or a current malignancy.

Postmarketing reports have cited the rapid appearance of multiple cutaneous squamous cell carcinomas in patients receiving ustekinumab who had pre-existing risk factors for non-melanoma skin cancer. All patients should be monitored for the appearance of non-melanoma skin cancer. Patients older than 60 years of age, those who have received prolonged immunosuppressant therapy, and those who have been treated with ultraviolet light therapy should be monitored closely.

**Hypersensitivity reactions.** Anaphylaxis and angioedema have been cited in postmarketing reports. If an anaphylactic or other clinically significant hypersensitivity reaction occurs, ustekinumab should be discontinued and appropriate therapy should be initiated.

**Neurological disorders.** Reversible posterior leukoencephalopathy syndrome (RPLS) was observed in one patient (n = 3,523) who had received 12 doses of ustekinumab over a period of 2 years. After no additional injections were administered, the patient fully recovered with appropriate treatment and experienced no more headache, seizures, or confusion. RPLS (also known as reversible posterior cerebral edema syndrome, hyperperfusion encephalopathy, and brain capillary leak syndrome) is not caused by demyelination or a known infectious agent. It has been associated with pre-eclampsia, eclampsia, acute hypertension, cytotoxic agents, and immunosuppressive therapy. Fatal outcomes have been reported. RPLS is not always “reversible.” If RPLS is suspected, ustekinumab should be discontinued and appropriate treatment should be administered.

**Immunizations.** Before ustekinumab therapy is initiated, patients should receive all immunizations appropriate for their age. Patients should not receive live vaccines during therapy. BCG vaccines should not be given during treatment with ustekinumab or for 1 year before treatment begins or 1 year after treatment was stopped. Caution is advised when live vaccines are administered to household contacts of patients receiving ustekinumab because of the potential risks of viral shedding from the contact and of transmission to patient. Non-live vaccinations received during a course of ustekinumab treatment might not elicit an immune response sufficient to prevent disease.

**Concomitant therapies.** The safety of ustekinumab, in combination with other immunosuppressive agents or phototherapy, has not been evaluated. Ultraviolet-induced skin cancers developed earlier and more frequently in mice genetically manipulated to be deficient in IL-12 and IL-23 or in IL-12 alone.

**Dosage and Administration:** Ustekinumab is administered by subcutaneous injection. The dose for patients with PsA is 45 mg at weeks 0 and 4, then every 12 weeks thereafter.

**Commentary:** PsA is a chronic immune-mediated inflammatory disease characterized by joint inflammation and the skin lesions associated with psoriasis. The disease causes pain, stiffness, and swelling in and around the joints and commonly appears between the ages of 30 and 50, although it can develop at any time. It affects up to 37 million people worldwide. Genes, the immune system, and environmental factors are believed to play a role in the onset of the disease.

Ustekinumab is a fully human monoclonal antibody that targets two cytokines, IL-12 and IL-23. The FDA’s approval of the new indication for ustekinumab in patients with PsA was based on the findings of two phase 3 studies, SUMMIT 1 (Phase 3 Multicenter, Randomized, Double-blind, Placebo-controlled trials of Ustekinumab, a Fully Human Anti-IL-12/23p40 Monoclonal Antibody, AdMinistered Subcutaneously), and SUMMIT II.

The new indication for ustekinumab represents the first treatment option for this complex disease since the introduction of anti-TNF biologic medicines more than a decade ago.

**Sources:** www.fda.gov; www.jnj.com

**Dabrafenib Mesylate (Tafinlar) Capsules**

**Manufacturer:** GlaxoSmithKline, Research Triangle Park, N.C.

**Indication:** Dabrafenib is indicated for patients with unresectable or metastatic melanoma with a BRAF V600E genetic mutation, as detected by an FDA-approved test. Dabrafenib
Dabrafenib is a kinase inhibitor. The chemical name is \( N-[3-[5-(2-	ext{amino-4-pyrimidinyl})-2-(1,1-	ext{dimethylethyl)}-1,3-	ext{thiazol-4-yl]}-2-	ext{fluorophenyl}]-2,6-	ext{difluorobenzene sulfonamide}, \) methanesulfonate salt. The molecular weight is 615.68.

**Drug Class:** Dabrafenib is a kinase inhibitor.

**Uniqueness of Drug:** Dabrafenib inhibits some mutated forms of BRAF kinases with in vitro half-maximal inhibitory concentration (IC\(_{50}\)) values of 0.65, 0.5, and 1.84 nM for BRAF V600E, BRAF V600K, and BRAF V600D enzymes, respectively. Dabrafenib also inhibits wild-type BRAF and CRAF kinases with IC\(_{50}\) values of 3.2 and 5.0 nM, respectively, and other kinases such as SIK1, NEK11, and LIMK1 at higher concentrations. Some mutations in the BRAF gene, including those that result in BRAF V600E, can result in activated BRAF kinases that may stimulate tumor cell growth. Dabrafenib inhibits BRAF V600 mutation-positive melanoma cell growth in vitro and in vivo.

**Warnings and Precautions:**

**Malignancy.** Dabrafenib has resulted in an increased incidence of cutaneous squamous cell carcinoma (SCC), keratoacanthoma, and (paradoxically) melanoma. In one trial, cutaneous SCCs and cutaneous keratoacanthomas were seen in 14/187 patients (7%) receiving dabrafenib and in none of the patients receiving dacarbazine (DTIC-Dome, Bayer), an alkylating agent. In clinical trials of dabrafenib (n = 586), the incidence of cutaneous SCC was 11%. The median time to first case of cutaneous SCC was 9 weeks (range, 1 to 53 weeks). Approximately 33% of patients who developed a cutaneous SCC developed one or more cancers with continued dabrafenib therapy.

The incidence rate of new primary malignant melanomas in 3 of 187 dabrafenib patients was 2%. No new primary malignant melanomas were noted in any chemotherapy-treated patients.

Dermatological evaluations should be performed before dabrafenib is given, every 2 months during therapy, and for up to 6 months after therapy is discontinued.

**Tumor promotion.** In vitro experiments have demonstrated a paradoxical activation of MAP-kinase signaling and increased cell proliferation in BRAF wild-type cells exposed to BRAF inhibitors. Evidence of BRAF V600E mutation status should be confirmed before therapy begins.

**Febrelic drug reactions.** In the first trial, serious cases of fever occurred in 3.7% (7/187) of patients who received dabrafenib but in none of the patients receiving dacarbazine. The incidence of serious and non-serious fever was 28% with dabrafenib and 10% with dacarbazine. The median duration of fever was 3 days (range, 1 to 129 days).

Dabrafenib should be withheld if the patient has a fever of 101.3°F or higher or if any serious febrile drug reaction develops. Patients should be evaluated for signs and symptoms of infection. Prophylaxis with an antipyretic agent may be required when dabrafenib is resumed.

**Hyperglycemia.** Patients may require an increase in the dose of, or may need to start, insulin or an oral hypoglycemic agent. In the trial, five of 12 patients with a history of diabetes required more intensive hypoglycemic therapy while they were taking dabrafenib. The incidence rates of grade 3 hyperglycemia, based on laboratory values, were 6% (12/187) in the dabrafenib patients and 0% in the dacarbazine-treated patients.

Serum glucose levels should be monitored during treatment with dabrafenib in patients with pre-existing diabetes or hyperglycemia. Patients should be advised to report symptoms of severe hyperglycemia (e.g., excessive thirst or any increase in the volume or frequency of urination).

**Ocular inflammation.** In clinical trials, uveitis (including iritis) occurred in 6 of 586 patients (1%) who were treated with dabrafenib. Symptomatic treatment included steroid and mydriatic ophthalmic drops. Patients should be monitored for signs and symptoms of uveitis, such as a change in vision, photophobia, and eye pain.

**G-6-PD deficiency.** Dabrafenib, which contains a sulfonamide moiety, confers a potential risk of hemolytic anemia in patients with glucose-6-phosphate dehydrogenase (G-6-PD) deficiency. Patients with this deficiency should be observed for signs of hemolytic anemia.

**Embryofetal toxicity.** Dabrafenib can cause fetal harm when taken by pregnant women. The medication was teratogenic and embryotoxic in rats at doses three times greater than the human exposure at the recommended dose. If dabrafenib is used during pregnancy or if the patient becomes pregnant while taking this drug, she should be apprised of the potential hazard to the fetus. Women should use a highly effective nonhormonal method of contraception during treatment and for 4 weeks after treatment, because dabrafenib can render hormonal contraceptives ineffective. Patients should be advised to contact their health care provider if they become pregnant or if they suspect that they are pregnant while they are taking dabrafenib.

**Dosage and Administration:** The recommended dose of dabrafenib is 150 mg orally taken twice daily, approximately 12 hours apart, either at least 1 hour before or at least 2 hours after a meal. Therapy should continue until disease progression or unacceptable toxicity occurs.

A missed dose may be taken up to 6 hours before the next scheduled dose. The capsules should not be opened, crushed, or broken.

**Commentary:** Melanoma is usually a cancer of the skin. It begins in melanocytes, the cells that produce the pigment melanin that colors the skin, hair, and eyes. Melanocytes also form moles. Having moles can be a risk factor for melanoma, but most moles do not become melanoma.

Nearly 65% of melanoma cases can be linked to exposure to ultraviolet rays from natural or artificial sources, such as sunlight and indoor tanning beds. However, because melanoma can occur in all melanocytes throughout the body, even those that are never exposed to the sun, ultraviolet light cannot be solely responsible for a diagnosis, especially in cases of mucosal and ocular melanoma. Current research points to a combination of family history, genetics, and environmental factors as a cause.

Dabrafenib, a kinase inhibitor, was approved for adults who carry the BRAF V600E mutation and who have unresectable stage III or stage IV melanoma. In a large clinical trial, progression-free survival was 5.1 months with dabrafenib versus 2.7 months with standard chemotherapy (with dacarbazime). In the phase 3 clinical trial, 52% of all dabrafenib-treated patients experienced tumor shrinkage compared with 17% of the chemotherapy patients.

**Sources:** www.fda.gov; www.gsksource.com