

Pharmaceutical Approval Update

Marvin M. Goldenberg, PhD, RPh, MS

Lorcaserin (Belviq)

Manufacturer: Arena Pharmaceuticals, San Diego, Calif.

Indication: An appetite suppressant, lorcaserin is used in the treatment of obesity and overweight patients. The drug is approved for people 18 years of age and older with a body mass index (BMI) of 30 or higher or in adults with a BMI of at least 27 who also have a weight-related condition, such as type-2 diabetes or hypertension.

Drug Class: Lorcaserin is a selective 5-hydroxytryptamine (5-HT_{2C}) receptor agonist. *In vitro* testing of the drug showed reasonable selectivity for 5-HT_{2C} over other related targets. 5-HT_{2C} receptors are located almost exclusively in the brain and can also be found in the choroid plexus, cortex, hippocampus, cerebellum, amygdala, thalamus, and hypothalamus.

The activation of 5-HT_{2C} receptors in the hypothalamus is thought to stimulate pro-opiomelanocortin (POMC) production and, consequently, promote weight loss through satiety. The 5-HT_{2C} receptors appear to help regulate appetite, mood, and endocrine secretion, but the exact mechanism of appetite regulation is not known.

Uniqueness of Drug: Lorcaserin promotes satiety by selectively activating 5-HT_{2C} receptors on anorexigenic POMC neurons in the hypothalamus. Lorcaserin has shown 100:1 affinity for 5-HT_{2C} when compared with other receptors.

Warnings and Precautions:

Serotonin syndrome or neuroleptic malignant syndrome-like reactions. Lorcaserin is a serotonergic drug. The development of a potentially life-threatening serotonin syndrome or neuroleptic malignant syndrome (NMS)-like reactions has been reported with the use of serotonergic drugs, such as serotonin-norepinephrine reuptake inhibitors (SNRIs), selective serotonin reuptake inhibitors (SSRIs), tricyclic antidepressants (TCAs), bupropion (Wellbutrin, GlaxoSmithKline), triptans, St. John's wort, and tryptophan. Other examples include drugs that impair serotonin metabolism such as monoamine oxidase (MAO) inhibitors, dextromethorphan (a cough suppressant), lithium, tramadol (Ultram, Janssen), and anti-psychotic agents or other dopamine antagonists, particularly when used in combination.

Symptoms of serotonin syndrome may include agitation, hallucinations, coma, tachycardia, labile blood pressure, hyperthermia, hyperreflexia, incoordination, nausea, vomiting, and diarrhea. In its most severe form, serotonin syndrome can resemble NMS. Symptoms of NMS include hyperthermia, muscle rigidity, autonomic instability with possible rapid fluctuation of vital signs, and changes in mental status. Patients should be monitored for the emergence of serotonin syndrome or NMS-like signs and symptoms.

The safety of lorcaserin, when coadministered with other

serotonergic or anti-dopaminergic agents (including anti-psychotic agents) or drugs that impair metabolism of serotonin (including MAO inhibitors), has not been systematically evaluated or established.

If the concomitant administration of lorcaserin with an agent that affects the serotonergic neurotransmitter system is warranted, extreme caution and careful observation of the patient are advised, particularly when treatment begins and when the dose is increased. Lorcaserin and any concomitant serotonergic or antidopaminergic agents (including antipsychotic drugs) should be discontinued immediately if any of these events occur. Supportive symptomatic treatment should be initiated.

Valvular heart disease. Regurgitant cardiac valvular disease, primarily affecting the mitral or aortic valves, has been reported in patients who took serotonergic drugs with 5-HT_{2B} receptor agonist activity. The cause is thought to be activation of 5-HT_{2B} receptors on cardiac interstitial cells. At therapeutic concentrations,

lorcaserin is selective for 5-HT_{2C} receptors, compared with 5-HT_{2B} receptors. In clinical trials lasting 1 year, 2.4% of patients receiving lorcaserin and 2.0% of patients receiving placebo developed echocardiographic criteria for valvular regurgitation, although none of these patients had symptoms.

Lorcaserin has not been studied in patients with congestive heart failure or hemodynamically significant valvular heart disease. Preliminary data suggest that 5HT_{2B} receptors might be overexpressed in congestive heart failure; therefore, lorcaserin should be used with caution in patients with this condition.

Lorcaserin should not be used with serotonergic and dopaminergic drugs that are potent 5-HT_{2B} receptor agonists and that increase the risk for cardiac valvulopathy, such as cabergoline (Dostinex, Pfizer).

Patients who experience signs or symptoms of valvular heart disease (including dyspnea, dependent edema, congestive heart failure, or a new cardiac murmur) during lorcaserin therapy should be evaluated, and discontinuation of the drug should be considered.

Cognitive impairment. In clinical trials lasting at least 1 year, impairments in attention and memory were reported. Adverse reactions were observed in 1.9% of patients receiving lorcaserin and in 0.5% of patients receiving placebo. These reactions led to discontinuation of treatment in 0.3% and 0.1% of these patients, respectively. Other adverse reactions in clinical trials included confusion, somnolence, and fatigue. Patients should be cautioned against operating hazardous machinery and driving until they are certain that lorcaserin therapy does not affect them adversely.

Psychiatric disorders. In short-term studies, euphoria, hallucinations, and dissociation were seen with lorcaserin at supratherapeutic doses. The dose of lorcaserin should not exceed 10 mg twice daily.

Some drugs that target the central nervous system (CNS) have been associated with depression or suicidal ideation. Patients using lorcaserin should be monitored for the emer-



A member of P&T's editorial board, the author is President of Pharmaceutical and Scientific Services at Marvin M. Goldenberg, LLC, in Westfield, N.J. His e-mail address is marvinmgoldenberg@verizon.net.

Pharmaceutical Approval Update

gence or worsening of depression, suicidal thoughts or behavior, or any unusual changes in mood or behavior. Therapy should be stopped if patients experience suicidal thoughts or behavior.

Hypoglycemia. Weight loss may increase the risk of hypoglycemia in patients with type-2 diabetes mellitus who are using insulin or insulin secretagogues, such as sulfonylureas. Hypoglycemia was observed in clinical trials with lorcaserin therapy. Lorcaserin has not been studied in combination with insulin. Blood glucose levels should be measured before and during lorcaserin treatment in patients with type-2 diabetes. Decreases in the dosage of antidiabetic medications that are non-glucose-dependent should be considered in order to mitigate the risk of hypoglycemia. If hypoglycemia develops, appropriate changes should be made to the antidiabetic drug regimen.

Priapism. Painful erections lasting longer than 6 hours can be an effect of 5-HT_{2C} receptor agonists. If not treated promptly, priapism can result in irreversible damage to the erectile tissue. Men who have an erection lasting longer than 4 hours, whether painful or not, should discontinue taking lorcaserin immediately and should seek emergency medical attention.

Lorcaserin should be used with caution in men with conditions that might predispose them to priapism (sickle cell anemia, multiple myeloma, or leukemia) or in men with anatomical deformation of the penis (angulation, cavernosal fibrosis, or Peyronie's disease). Experience with lorcaserin and medications for erectile dysfunction (e.g., phosphodiesterase type-5 inhibitors) is limited; therefore, the combination of lorcaserin and these medications should be used with caution.

Bradycardia. In clinical trials lasting at least 1 year, the mean change in heart rate was -1.2 beats per minute (bpm) in lorcaserin patients and -0.4 bpm in placebo patients without diabetes. The decrease in heart rate was 2.0 bpm in lorcaserin patients and 0.4 bpm in placebo patients with type-2 diabetes. The incidence of heart rate below 50 bpm was 5.3% in lorcaserin patients and 3.2% in placebo patients without diabetes; these rates were 3.6% in lorcaserin patients and 2.0% in placebo patients with type-2 diabetes. In the combined population, bradycardia occurred in 0.3% of lorcaserin patients and in 0.1% of placebo patients. Lorcaserin should be used with caution in patients with bradycardia or with a history of heart block greater than first degree.

Hematological changes. In clinical trials lasting at least 1 year, decreases in white blood cell (WBC) count (leukopenia, lymphopenia, and neutropenia) were reported in 0.4% of patients who received lorcaserin compared with 0.2% of patients who were treated with placebo. Decreases in red blood cell (RBC) count (anemia and decreased hemoglobin and hematocrit) were reported in 1.3% of lorcaserin patients and in 1.2% of placebo patients. Periodic monitoring of the complete blood count should be considered during treatment with lorcaserin.

Prolactin elevation. Lorcaserin causes moderate elevations in prolactin levels. In a subset of placebo-controlled clinical trials lasting at least 1 year, elevations of prolactin above the upper limit of normal (ULN), two times the ULN, and five times the ULN, measured both before and 2 hours after administration, occurred in 6.7%, 1.7%, and 0.1% of lorcaserin-treated patients, respectively, and in 4.8%, 0.8%, and 0.0% of placebo-

treated patients, respectively. During the trial, a prolactinoma developed in one patient being treated with lorcaserin. The relationship of lorcaserin to prolactinoma in this patient was unknown. Prolactin should be measured when symptoms and signs of prolactin excess (e.g., galactorrhea and gynecomastia) are suspected.

Pulmonary hypertension. Some centrally acting weight-loss agents that act on the serotonin system have been associated with pulmonary hypertension, a rare but lethal disease. Clinical trial experience with lorcaserin is inadequate to determine whether lorcaserin increases the risk of pulmonary hypertension.

Dosage and Administration: The recommended dose of lorcaserin is 10 mg orally twice daily. Lorcaserin can be taken with or without food. If the patient has not lost at least 5% of baseline body weight by week 12, the drug should be discontinued because clinically meaningful weight loss is not likely to be achieved or sustained with continued treatment.

Commentary: Lorcaserin (Belviq) is the first prescription weight-loss treatment approved in the U.S. in 13 years. According to the Centers for Disease Control and Prevention, more than two-thirds of adults in the U.S. are either overweight or obese, and the percentage of obese people more than doubled (from 15% to 36%) between 1980 and 2010.

Lorcaserin activates a brain receptor that helps to promote satiety with less food intake. It was evaluated in a study of nearly 8,000 patients.

The drug stimulates parts of the 5-HT_{2C} serotonin receptors in the hypothalamus. Fenfluramine/phentermine (Fen-Phen, Wyeth), fenfluramine (Pondimin, American Home Products/Wyeth) and dexfenfluramine (Redux, Wyeth/Interneuron) had been approved to aid in weight loss by altering the serotonin levels in the brain to suppress feelings of hunger. However, these drugs were withdrawn from the market in 1997 because of the development of heart valve disease and pulmonary hypertension.

The molecular structure of lorcaserin is similar to that of dexfenfluramine; unlike fenfluramine, however, lorcaserin works more selectively and has not shown the destructive heart problems that were associated with fenfluramine.

Sources: http://us.eisai.com/package_inserts/BelviqPI.pdf; www.fda.gov

Pertuzumab (Perjeta)

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

Indication: As a HER-2/neu receptor antagonist, pertuzumab is infused with trastuzumab (Herceptin) and docetaxel (Taxotere, Sanofi) for patients with late-stage, HER-2-positive metastatic breast cancer who have not received anti-HER-2 therapy or chemotherapy for this disease. HER-2/neu, a type of receptor tyrosine kinase, is also known as ErbB-2 and human epidermal growth factor receptor (EGFR) 2.

Biological Class: Pertuzumab is a humanized monoclonal antibody that inhibits HER-2 dimerization.

Uniqueness of Biological: Like trastuzumab, pertuzumab attaches to the HER-2 receptor on a cancer cell's surface. It differs from trastuzumab by binding to a distinct part of the molecule, and its mechanism of action complements that of

Pharmaceutical Approval Update

trastuzumab. The HER protein family members are complex signaling molecules that span cell membranes. HER-1, the EGF receptor, is turned on when it is bound by its partner, or molecular ligand, EGF. EGFR is also known as ErbB-1 and HER-1 in humans. Mutations affecting HER-1 activity can result in cancer. HER-1 and HER-2/neu are both measured in tumor tissue and are evaluated for overexpression (amplification).

An increase in HER-1 or in HER-2/neu indicates a more aggressive tumor and a poorer prognosis. HER-1 and HER-2/neu are used to evaluate different types of cancer. HER-2/neu is used in the diagnosis and prognosis of breast cancer.

Boxed Warning: Exposure to pertuzumab can result in embryo-fetal death and birth defects. Animal studies have reported oligohydramnios, delayed renal development, and death. Patients should be advised of these risks and of the need for effective contraception.

Warnings and Precautions:

Embryo-fetal toxicity. Fetal harm can occur when pertuzumab is administered to pregnant women.

Left ventricular dysfunction. Patients with left ventricular dysfunction should be monitored, and therapy should be withheld if appropriate.

Infusion and hypersensitivity reactions. Patients should be monitored for signs and symptoms of infusion-related reactions and anaphylaxis. If a significant infusion-associated reaction occurs, the infusion should be slowed or interrupted and appropriate medical therapies should be administered.

HER-2 testing. FDA-approved tests should be performed by laboratories with demonstrated proficiency.

Dosage and Administration: The initial dosage of pertuzumab is 840 mg, delivered as a 60-minute intravenous (IV) infusion, followed every 3 weeks thereafter by 420 mg, administered as a 30- to 60-minute IV infusion. When trastuzumab is given with pertuzumab, the recommended initial trastuzumab dose is 8 mg/kg, given as a 90-minute IV infusion, followed every 3 weeks by 6 mg/kg, given as a 30- to 90-minute IV infusion. When administered with pertuzumab, the recommended initial docetaxel dose is 75 mg/m², administered as an IV infusion. The dose may be escalated to 100 mg/m² and can be given every 3 weeks if the initial dose is well tolerated.

Commentary: Approximately 20% of breast cancers have increased amounts of HER-2 protein. Pertuzumab is administered with trastuzumab (Herceptin)—the first FDA-approved HER-2 therapy—and with the chemotherapy agent docetaxel (Taxol). Pertuzumab is indicated for patients with metastatic HER-2–positive breast cancer who have not received previous treatment with either chemotherapy or HER-2–targeted therapy.

The cost of pertuzumab is \$5,900 per month, or about \$71,000 per year; trastuzumab costs \$4,500 per month, or \$54,000 per year. Thus, the total cost for the combination is \$115,000 for 1 year.

When pertuzumab, trastuzumab, and chemotherapy were given together, median progression-free survival was 18.5 months, compared with 12.4 months for trastuzumab plus chemotherapy (hazard ratio = 0.62; $P < 0.0001$). The combination also brought about a 38% reduction in the risk of disease, disease progression, or death, compared with trastuzumab plus chemotherapy plus placebo (HR = 0.62; $P < 0.0001$).

Sources: www.gene.com; www.fda.com; www.drugs.com/perjeta.html

MenHibrix Vaccine

Manufacturer: GlaxoSmithKline, Rixensart, Belgium

Indication: MenHibrix vaccine is used to prevent invasive disease caused by *Neisseria meningitidis* serogroups C and Y and *Haemophilus influenzae* type b in children 6 weeks through 18 months of age.

Biological Class: MenHibrix is a tetanus toxoid conjugate vaccine.

Uniqueness of Biological: Antigenic capsular polysaccharides (meningococcal serogroups A and C, *H. influenzae* type b) in the vaccine convey active immunity by stimulating endogenous antibody production. Antibodies are associated with protection against invasive meningococcal disease.

Warnings and Precautions:

Guillain-Barré syndrome. If Guillain-Barré syndrome occurs within 6 weeks after the patient receives a prior vaccine containing tetanus toxoid, the decision to give any tetanus toxoid-containing vaccine, including MenHibrix, should be based on consideration of the potential benefits and risks. Syncope can occur with injectable vaccines, including MenHibrix. Procedures should be in place to avoid injuries from falls and to restore cerebral perfusion following syncope.

Apnea. Apnea following intramuscular (IM) vaccination has been observed in some infants born prematurely. The decision about when to administer MenHibrix should be based on the medical status of the premature infant and the potential benefits and risks of vaccination.

Dosage and Administration: Four doses are given to infants starting at 2 months of age, then at 4 and 6 months. The final dose is given when the infant is between 12 and 15 months of age. The first dose can also be given as early as 6 weeks of age, and the last dose can be given as late as 18 months.

Commentary: MenHibrix, a combination vaccine, is effective against two potentially life-threatening bacteria for infants and toddlers 6 weeks through 18 months of age: *N. meningitidis* serogroups C and Y and *H. influenzae* type b, which commonly present as meningitis in children. Unvaccinated infants and toddlers younger than 2 years of age can be at particular risk from these illnesses. The early symptoms of these diseases are often difficult to distinguish from the symptoms of other common childhood illnesses.

Serogroup distribution may vary from year to year, but serogroups B, C, and Y cause most cases of meningococcal disease in the U.S. The most common vaccine-preventable serogroups are C and Y, but no vaccine is available in the U.S. to protect against serogroup B. *H. influenzae* type b most commonly presents as meningitis and was the leading cause of bacterial meningitis in the U.S. among children younger than 5 years of age before effective *H. influenzae* vaccines were introduced.

The vaccine was tested in more than 7,500 infants in the U.S., Germany, Belgium, Mexico, and Australia. Adverse effects included irritability, fever, pain, and swelling and redness at the injection site.

For the *H. influenzae* b component, MenHibrix was as effective as another FDA-approved vaccine for invasive *H. influenzae* type b disease. The meningococcal component produced antibodies in sufficient quantities to protect against invasive meningococcal disease caused by serogroups C and Y.

Sources: www.fda.gov; www.empr.com; www.gsk.com

Pharmaceutical Approval Update

Icosapent Ethyl (Vascepa) Capsules

Manufacturer: Amarin Corp., Bedminster, N.J.

Indication: Icosapent ethyl is an adjunct to diet to reduce triglyceride levels in adults with severe triglyceridemia (triglyceride levels above 500 mg/dL).

Drug Class: Formerly known as AMR101, this ultra-pure form of omega-3 fatty acids contains at least 96% of eicosapentaenoic acid (EPA) in a 1-g capsule.

Uniqueness of Drug: In the MARINE trial, the drug was found to reduce triglyceride levels without elevating low-density lipoprotein-cholesterol (LDL-C) levels. Very high triglyceride levels pose a cardiovascular risk.

Warnings and Precautions:

Monitoring of laboratory tests. In patients with hepatic impairment, alanine aminotransferase and aspartate aminotransferase levels should be monitored periodically during therapy with this medication.

Fish allergy. Vascepa contains ethyl esters of the omega-3 fatty acid of EPA, obtained from the oil of fish. It is not known whether patients with allergies to fish or shellfish are at increased risk for an allergic reaction to Vascepa; therefore, this medication should be used with caution in patients with a hypersensitivity to fish or shellfish.

Dosage and Administration: The daily dose is 4 g, administered orally. No more than four capsules should be taken each day. The capsules should be taken whole, not broken, crushed, dissolved, or chewed. Patients can take a missed dose as soon as they remember, but the dose should not be doubled when it is taken.

Commentary: Patients with severe hypertriglyceridemia have very high serum levels of triglycerides (500 mg/dL or more). Approximately 4 million people in the U.S. are thought to have this condition.

According to the American Heart Association Scientific Statement on Triglycerides and Cardiovascular Disease (2011), triglycerides provide important information as a marker associated with the risk of heart disease and stroke, especially when a patient also has low levels of high-density lipoprotein-cholesterol (HDL-C) and elevated levels of LDL-C. The effect of Vascepa on cardiovascular mortality and morbidity in patients with severe hypertriglyceridemia has not been determined.

The active moiety in GlaxoSmithKline's Lovaza, a similar agent for the treatment of hypertriglyceridemia, is a mixture of omega-3-acid ethyl esters that includes icosapent ethyl (EPA), docosahexaenoic acid (DHA), and a few others. Without requiring GlaxoSmithKline to specify which ester helps to lower triglycerides, the FDA considered the mixture of EPA and DHA as the active moiety that is responsible for the physiological and pharmacological action of Lovaza. Vascepa might have an advantage over Lovaza; it does not increase LDL-C levels, which has sometimes been observed with Lovaza.

It is not yet known whether Vascepa will be considered a new chemical entity. It contains only EPA but not DHA, and it does not contain any appended portions of both EPA and DHA that cause them to be an ester, salt, or other non-covalent derivative. Therefore, its active moiety has not been previously approved by the FDA in any other application submitted under Section 505(b) of the Federal Food, Drug, and Cosmetic Act.

Sources: www.vascepa.com; www.thepharmaletter.com

Acclidinium Bromide Inhalation Powder (Tudorza Pressair)

Manufacturer: Forest Pharmaceuticals, Inc., St. Louis, Mo.

Indication: Tudorza Pressair is indicated for the long-term maintenance treatment of bronchospasm associated with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and emphysema.

Drug Class: As a long-acting anticholinergic agent, the product is also referred to as a long-acting muscarinic antagonist (LAMA).

Uniqueness of Drug: When given by inhalation, acclidinium produces bronchodilation by inhibiting the muscarinic M₃ receptor in the airway's smooth muscle. Acclidinium is rapidly hydrolyzed in human plasma into two major inactive metabolites.

A multiple-dose inhaler delivers 60 doses of acclidinium bromide powder for inhalation. A colored control window and an audible click confirm that the dose has been inhaled successfully. A dose indicator indicates how many doses remain in the inhaler.

Warnings and Precautions: Tudorza Pressair is not indicated as rescue therapy for the initial treatment of acute episodes of bronchospasm. Inhaled drugs, including Tudorza, may cause paradoxical bronchospasm. If this occurs, treatment should be stopped and other treatments should be considered.

Tudorza should be used with caution in patients with narrow-angle glaucoma or urinary retention. Patients should be advised to consult a physician immediately if they experience any signs or symptoms of narrow-angle glaucoma, prostatic benign hyperplasia, or bladder-neck obstruction.

If a hypersensitivity reaction occurs after administration of Tudorza, therapy should be stopped at once and alternative treatments should be considered. Patients with a history of hypersensitivity reactions to atropine should be closely monitored for similar hypersensitivity reactions to Tudorza. This agent should be prescribed with caution in patients with severe hypersensitivity to milk proteins.

Common adverse reactions have included headache, nasopharyngitis, and cough.

Dosage and Administration: Tudorza 400 mcg is administered twice daily as a dry-powder inhalation.

Commentary: Tudorza Pressair is used to treat symptoms of COPD, including chronic bronchitis and emphysema. Patients usually experience easier breathing on the first day of therapy, but it may take longer for the full effects of the drug to be felt. This medication may work best when it is used every day.

The powder is not a rescue medication and should not be used for treating sudden breathing problems. Before therapy is initiated, the patient should be encouraged to inform the physician of any ocular problems, especially glaucoma; a severe allergy to milk proteins; or any prostate or bladder problems, because Tudorza Pressair may exacerbate these conditions.

Women should inform the physician if they are pregnant or plan to become pregnant. It is not known whether Tudorza Pressair can harm the fetus. Women who are breast-feeding or planning to breast-feed should also inform their health care providers, because Tudorza may pass into breast milk.

Sources: www.frx.com/pi/tudorza_pi.pdf; www.drugs.com/tudorza.html ■