Pharmaceutical Approval Update

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Desvenlafaxine (Pristiq)

Manufacturer: Wyeth, Philadelphia, Pa.

Indication: This product is indicated for the treatment of major depressive disorder (MDD) in adults.

Drug Class: Pristiq is an extended-release, oral once-daily tablet that contains desvenlafaxine succinate, a structurally novel serotonin–norepinephrine reuptake inhibitor (SNRI). Desvenlafaxine (*O*-desmethylvenlafaxine) is the major active metabolite of Wyeth's antidepressant venlafaxine (Effexor), which is used to treat MDD, generalized anxiety disorder, social anxiety disorder, and panic disorder. Venlafaxine XR was the first SNRI approved by the FDA for treating major depressive disorder.

Uniqueness of Drug: Desvenlafaxine delivers the major active metabolite of venlafaxine HCl (Effexor XR) in its active state without going through the cytochrome P450 (CYP 2D6) metabolic pathway. This could be beneficial if desvenlafaxine is coadministered with other commonly prescribed medications that are metabolized through that pathway. The clinical efficacy of desvenlafaxine succinate is thought to be related to the potentiation of these neurotransmitters in the central nervous system (CNS).

Black-Box Warning: Compared with placebo, antidepressants have been found to increase the risk of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults in short-term studies of MDD and other psychiatric disorders. Prescribers considering the use of desvenlafaxine or any other antidepressant in a child, adolescent, or young adult must balance this risk with the clinical need.

Short-term studies have not shown an increase in the risk of suicidality with antidepressants, compared with placebo, in adults older than 24 years of age; there was a reduction in risk with antidepressants, compared with placebo, in adults 65 years of age and older. Depression and certain other psychiatric disorders are associated with increases in the risk of suicide. Patients of all ages who begin antidepressant therapy should be monitored appropriately and observed closely for clinical worsening, suicidality, or unusual changes in behavior. Families and caregivers should be advised of the need for close observation and communication with the prescriber. Desvenlafaxine is not approved for use in pediatric patients.

Warnings and Precautions:

Clinical worsening and suicide risk. Both adults and pediatric patients may experience worsening of their depression and/or the emergence of suicidal ideation and behavior or unusual changes in behavior, whether or not they are taking antidepressant medications, and this risk may persist until significant remission occurs. Suicide is a known risk of depression and certain other psychiatric disorders, and these disorders themselves are the strongest predictors of suicide. There has been a long-standing concern, however, that antidepressants may have a role in inducing worsening of depression and the emergence of suicidality in certain patients during the early phases of treatment.

Pooled analyses of short-term placebo-controlled studies of antidepressants—the selective serotonin reuptake inhibitors (SSRIs) and others—showed that these drugs increase the risk of suicidal thinking and behavior in children, adolescents, and young adults (ages 18 to 24) with MDD and other psychiatric disorders. Short-term studies have not shown an increase in the risk of suicidality with antidepressants, compared with placebo, in adults beyond age 24; there was a reduction with antidepressants, compared with placebo, in adults aged 65 and older.

All patients using antidepressants for any indication should be monitored appropriately and observed closely for clinical worsening, suicidality, and unusual changes in behavior, especially during the initial few months of a course of drug therapy or at times of either increases or decreases in dose.

Anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia (psychomotor restlessness), hypomania, and mania have been reported in adults and pediatric patients being treated with antidepressants for MDD as well as for other indications, both psychiatric and nonpsychiatric. Although a causal link between the emergence of such symptoms and either the worsening of depression and the emergence of suicidal impulses has not been established, there is concern that such symptoms may represent precursors to emerging suicidality.

Families and caregivers of patients being treated with antidepressants for MDD or other psychiatric and nonpsychiatric indications, should be alerted about the need to monitor patients for the emergence of agitation, irritability, unusual changes in behavior, and the other symptoms described here, as well as the emergence of suicidality, and to report such symptoms immediately to health care providers.

Serotonin syndrome. The development of a potentially life-threatening serotonin syndrome may occur with desvenlafaxine, particularly with the use of other serotonergic drugs (SSRIs, SNRIs, triptans) or with drugs that impair metabolism of serotonin, including monoamine oxidase inhibitors (MAOIs). Symptoms may include mental status changes (agitation, hallucinations, coma), autonomic instability (tachycardia, labile blood pressure, hyperthermia), neuromuscular aberrations (hyperreflexia, incoordination) or gastrointestinal (GI) symptoms (nausea, vomiting, diarrhea). The concomitant use of desvenlafaxine and MAOIs is contraindicated. If concomitant treatment with desvenlafaxine and an SSRI, another SNRI, or a 5-hydroxytryptamine (5-HT) receptor agonist (triptan) is warranted, patients should be observed carefully, particularly during the beginning of treatment and with dose increases. The concomitant use of desvenlafaxine with serotonin precursors (tryptophan) is not recommended.

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Blood pressure elevations. Because sustained increases in blood pressure (BP) were noted in clinical studies, patients receiving desvenlafaxine should have regular BP monitoring. Pre-existing hypertension should be controlled before treatment with desvenlafaxine begins. Caution should be exercised in treating patients with pre-existing hypertension or other underlying conditions that might be compromised by increases in BP. Cases of elevated BP requiring immediate treatment have been reported with desvenlafaxine.

Sustained increases in BP can have adverse consequences. For patients who experience a sustained increase in BP while receiving desvenlafaxine, either the dose should be reduced or the drug should be discontinued. Treatment with desvenlafaxine at all doses, from 50 mg/day to 400 mg/day, was associated with sustained hypertension (supine diastolic BP of 90 mm Hg and 10 mm Hg or more above the baseline BP) for three consecutive on-therapy visits. Studies showed a consistent increase in the proportion of those subjects who developed sustained hypertension at all doses with a suggestion of a higher rate at 400 mg/day.

Abnormal bleeding. SSRIs and SNRIs, including desvenlafaxine, may increase the risk of bleeding. The concomitant use of aspirin, nonsteroidal anti-inflammatory drugs (NSAIDs), warfarin (Coumadin, Bristol-Myers Squibb), and other anticoagulants may add to this risk. Case reports and epidemiological studies have shown an association between use of drugs that interfere with serotonin reuptake and the occurrence of GI bleeding. Bleeding events related to SSRIs and SNRIs have ranged from ecchymosis, hematoma, epistaxis, and petechiae to life-threatening hemorrhages. Patients should be cautioned about the risk of bleeding associated with the concomitant use of desvenlafaxine and NSAIDs, aspirin, or other drugs that affect coagulation or bleeding.

Glaucoma. Mydriasis has been reported in association with desvenlafaxine; therefore, patients with elevated intraocular pressure or those at risk of acute narrow-angle (angle-closure) glaucoma should be monitored.

Mania or hypomania. During all phase 2 and 3 studies of MDD and vasomotor symptoms, mania was reported for approximately 0.1% of patients receiving desvenlafaxine. Activation of mania or hypomania has also been reported in some patients with major affective disorder who used other marketed antidepressants. As with all antidepressants, desvenlafaxine should be used cautiously in patients with a history or family history of mania or hypomania.

Heart disease. Caution is advised for patients with cardiovascular, cerebrovascular, or lipid metabolism disorders. Increases in BP and small increases in heart rates were observed in studies with desvenlafaxine. Desvenlafaxine has not been evaluated systematically in patients with a recent history of myocardial infarction, unstable heart disease, uncontrolled hypertension, or cerebrovascular disease. Patients with these diagnoses, except for cerebrovascular disease, were excluded from clinical studies.

Cholesterol and triglycerides. Dose-related elevations in fasting serum total cholesterol, low-density lipoprotein-cholesterol (LDL-C), and triglycerides were observed in controlled studies. Serum lipids should be monitored during treatment with desvenlafaxine.

Discontinuation of treatment. Abruptly discontinuing or reducing the dose of desvenlafaxine has been associated with new symptoms, including dizziness, nausea, headache, irritability, insomnia, diarrhea, anxiety, fatigue, abnormal dreams, and hyperhidrosis. In general, discontinuation events occurred more frequently with a longer duration of therapy. During marketing of SNRIs and SSRIs, there have been spontaneous reports of adverse events occurring upon discontinuation of these drugs (particularly with abrupt cessation), including dysphoric mood, irritability, agitation, dizziness, sensory disturbances (paresthesia, such as electric shock sensations), anxiety, confusion, headache, lethargy, emotional lability, insomnia, hypomania, tinnitus, and seizures. Although these events have generally been self-limiting, serious discontinuation symptoms have been reported.

Renal impairment. In patients with moderate or severe renal impairment or end-stage renal disease (ESRD), the clearance of desvenlafaxine was decreased, thus prolonging the elimination half-life of the drug. As a result, there were potentially clinically significant increases in exposures to desvenlafaxine. A dosage adjustment (50 mg every other day) is necessary in patients with severe renal impairment or ESRD. The doses should not be escalated in patients with moderate or severe renal impairment or ESRD.

Seizures. Seizures have been reported in premarketing clinical studies with desvenlafaxine even though patients with a history of seizures were excluded from premarketing clinical studies. This drug has not been systematically evaluated in patients with seizure disorders; therefore, desvenlafaxine should be prescribed with caution in these patients.

Hyponatremia. Low sodium levels may occur after treatment with SSRIs and SNRIs, including desvenlafaxine. In many cases, this hyponatremia appears to be the result of the syndrome of inappropriate antidiuretic hormone secretion (SIADH). Cases of serum sodium lower than 110 mmol/L have been reported. Elderly patients may be at greater risk for hyponatremia with SSRIs and SNRIs, and patients who are taking diuretics or who are volume-depleted can be at greater risk. Discontinuation of desvenlafaxine should be considered in patients with symptomatic hyponatremia, and appropriate medical intervention should be instituted. Signs and symptoms of hyponatremia include headache, difficulty concentrating, memory impairment, confusion, weakness, and unsteadiness, which can lead to falls. Signs and symptoms associated with more severe or acute cases have included hallucination, syncope, seizure, coma, respiratory arrest, and death.

Coadministration with venlafaxine. Desvenlafaxine is the major active metabolite of venlafaxine. Products containing desvenlafaxine and products containing venlafaxine should not be used with each other.

Lung disease and pneumonia. In rare instances, interstitial lung disease and eosinophilic pneumonia associated with venlafaxine have been reported. The possibility of these adverse events should be considered in patients receiving desvenlafaxine who present with progressive dyspnea, cough, or chest discomfort. Such patients should undergo a prompt medical evaluation, and discontinuation of desvenlafaxine should be considered.

Dosage and Administration: The recommended dose of

desvenlafaxine is 50 mg once daily with or without food. In clinical studies, doses of 50 to 400 mg/day were effective, but no additional benefits were observed at doses higher than 50 mg/day; adverse events and discontinuations were more frequent at higher doses. When discontinuing treatment, gradual dose reduction is recommended whenever possible. Tablets should be taken whole and should not be divided, crushed, chewed, or dissolved.

Renal impairment: The recommended dose in patients with moderate renal impairment is 50 mg/day. The recommended dose in patients with severe renal impairment and ESRD is 50 mg every other day. The dose should not be escalated in patients with moderate or severe renal impairment or ESRD.

Hepatic impairment: Dose escalation above 100 mg/day is not recommended. Desvenlafaxine tablets are available in strengths of 50 and 100 mg. Each tablet contains 76 mg or 152 mg of desvenlafaxine succinate, equivalent to 50 mg or 100 mg of desvenlafaxine.

Commentary: MDD is a common mental disorder, affecting about 121 million people worldwide. In the U.S., MDD affects approximately 15 million adults, or 6.7% of the U.S. population 18 years of age and older in a given year. Depression is among the leading causes of disability and the fourth leading contributor to the global burden of disease. A study estimated that the total economic burden of depression was $83.1 billion in 2000, including direct treatment costs and suicide-related and work-related costs.

The controversy among experts is whether desvenlafaxine (Pristiq) is a substantial improvement over existing antidepressants. Although the chemical formula is similar to that of venlafaxine (Effexor), it is unclear whether the new product has advantages over its predecessor. Wyeth claims that desvenlafaxine does not need to be gradually ramped up to an ideal dosage, so that patients can immediately begin taking the full dose and may see faster results. This can be crucial, because patients must often try multiple drugs before they find their way out of their depression, a process that can take many painful weeks.

A second purported advantage of desvenlafaxine is that it delivers the main metabolite of Effexor in an already active state without having to pass through the liver. This may prevent many undesirable drug–drug interactions.

Time will tell whether desvenlafaxine offers a noticeable improvement over Effexor or at least a way to avoid the terrible withdrawal symptoms. The Food and Drug Administration (FDA) approved desvenlafaxine based on four eight-week double-blind studies, but results of antidepressant trials can be easily manipulated through selective reporting. Having perhaps learned from its past mistakes, the FDA gave a conditional approval, contingent on Wyeth's promise to continue research into the drug's efficacy and safety by conducting at least one study each of sexual dysfunction, pediatric reactions, dosing differences, and relapse prevention. Ideally, the results of all of these studies will be open to public scrutiny.

Sources: www.wyeth.com; www.treatmentonline.com; http://biz.yahoo.com

Rilonacept (Arcalyst) Injection for Subcutaneous Use

Manufacturer: Regeneron, Tarrytown, N.Y.

Indication: Rilonacept, an orphan drug, is indicated for the treatment of cryopyrin-associated periodic syndromes (CAPS), including familial cold autoinflammatory syndrome (FACS) and Muckle–Wells syndrome, in adults and children 12 years of age and older.

Drug Class: This product is a targeted inhibitor of interleukin-1 (IL-1), the key driver of inflammation in cryopyrin syndromes.

Uniqueness of Product: Rilonacept (IL-1 Trap) is a recombinant biological protein-based product designed to bind the IL-1 cytokine to prevent its interaction with cell–surface receptors.

Warnings and Precautions:

Infection and immunosuppression. IL-1 blockade may interfere with immune response to infections. Serious, life-threatening infections have been reported in patients taking rilonacept. Treatment should be discontinued if a serious infection develops. Patients with active or chronic infections should not use rilonacept.

Hypersensitivity. Hypersensitivity reactions associated with rilonacept have been rare. If a hypersensitivity reaction occurs, the drug should be discontinued and appropriate therapy should be initiated.

Immunization. Live vaccines should not be given concurrently with rilonacept. Before patients begin taking rilonacept, they should receive all recommended vaccinations.

Dosage and Administration:

Adults. For adults 18 years of age and older, therapy should begin with a loading dose of 320 mg, delivered as two 2-mL, subcutaneous (SQ) injections of 160 mg on the same day at two different sites. Dosing continues with a once-weekly injection of 160 mg, given as a single 2-mL, SQ injection. Rilonacept should not be administered more often than once weekly.

Pediatric patients. For pediatric patients 12 to 17 years of age, treatment begins with a loading dose of 4.4 mg/kg, up to a maximum of 320 mg, delivered as one or two SQ injections with a maximum single-injection volume of 2 mL. Dosing is continued with a once-weekly injection of 2.2 mg/kg, up to a maximum of 160 mg, administered as a single subcutaneous injection, up to 2 mL. If the initial dose is given as two injections, both injections should be given on the same day at two different sites. Rilonacept should not be given more often than once weekly.

Commentary: CAPS includes a spectrum of rare inherited inflammatory conditions, including familial cold autoinflammatory syndrome (FCAS), Muckle–Wells syndrome, and neonatal onset multisystem inflammatory disease. These autoinflammatory disorders are characterized by spontaneous systemic inflammation. A novel feature of these conditions is that exposure to mild degrees of cold temperatures can provoke a major inflammatory episode that occurs within hours. The syndromes are caused by a range of mutations in the gene *CIAS1 (NALP3),* which encodes a protein named cryopyrin (meaning "icy-fire").

In a pivotal development program, patients receiving rilonacept experienced a greater improvement in overall symptom

scores compared with patients treated with placebo. These improvements were sustained over time with continued rilonacept treatment. The most commonly reported adverse reactions were injection-site reactions and upper respiratory tract infections. The approval of rilonacept represents a major advance in the treatment of CAPS.

Source: www.regeneron.com

Levocetirizine (Xyzal Oral Solution)

Manufacturer: Sanofi-Aventis, Bridgewater, N.J., and UCB, Brussels, Belgium

Indication: Levocetirizine dihydrochloride oral solution is indicated for the relief of symptoms associated with seasonal and perennial allergic rhinitis in adults and children six years of age and older as well as for uncomplicated skin manifestations of chronic idiopathic urticaria in adults and children six years of age and older.

Drug Class: Levocetirizine is an orally active and selective histamine H_1-receptor antagonist. The drug's chemical name is (R)-[2-[4-[(4-chlorophenyl) phenylmethyl]-1-piperazinyl] ethoxy] acetic acid dihydrochloride. It is the R enantiomer of cetirizine HCl, a racemic compound with antihistaminic properties.

Uniqueness of Drug: Levocetirizine is an antihistamine whose principal effects are mediated via inhibition of H_1 receptors. The drug's antihistaminic activity has been documented in animal and human models. *In vitro* binding studies have shown that levocetirizine has an affinity for the human H_1-receptor two-fold higher than that of cetirizine. The clinical relevance of this finding is unknown.

Warnings and Precautions:

Activities requiring mental alertness. In clinical trials, somnolence, fatigue, and asthenia have been reported in some patients receiving the oral solution. Patients should be cautioned against engaging in hazardous occupations requiring complete mental alertness and motor coordination, such as operating machinery or driving a motor vehicle. The concurrent use of levocetirizine solution with alcohol or other CNS depressants should be avoided, because of possible additional reductions in alertness and additional impairment of CNS performance.

Adverse Drug Reactions: The safety data reflect 2,549 patients with seasonal or perennial allergic rhinitis and chronic idiopathic urticaria in 12 controlled clinical trials lasting from one week to six months. Because trials were conducted under varying conditions, the rates of adverse reactions from the clinical trials of a drug cannot be directly compared with rates in a clinical trial of another drug and might not reflect the rates observed in practice.

Short-term data: The short-term data (up to six weeks) for adults and adolescents were based on eight trials in which 1,896 patients (825 males and 1,071 females aged 12 years and older) received the oral solution at a dose of 2.5, 5, or 10 mg once daily in the evening. The short-term data from pediatric patients were based upon two clinical trials in which 243 children with seasonal or perennial allergic rhinitis (162 boys and 81 girls six to 12 years of age) received the oral solution at a dose of 5 mg once daily for four to six weeks.

Long-term data: The long-term data (four to six months) were based on two trials in adults and adolescents in which 428 patients (190 males and 238 females) with allergic rhinitis received the oral solution at a dose of 5 mg once daily.

Adults and adolescents 12 years of age and older: In studies up to six weeks in duration, the mean age of the adult and adolescent patients was 32 years; 44% of the patients were men and 56% were women, and most (more than 90%) were Caucasian. In these trials, 43% and 42% of the subjects in the 2.5-mg and 5-mg groups, respectively, had at least one adverse event, compared with 43% of placebo subjects. In placebo-controlled trials of one to six weeks in duration, the most common adverse reactions were somnolence, nasopharyngitis, fatigue, dry mouth, and pharyngitis. Most of these were mild to moderate in intensity. Somnolence was the most common adverse reaction, leading to discontinuation of therapy in 0.5% of patients.

Dosage and Administration: Levocetirizine is available as an oral solution of 2.5 mg/5 mL (0.5 mg/mL), allowing for the administration of 2.5 mg if needed. That is, the 2.5-mg dose can be given, or a dose of 5 mg can be given by just doubling the volume (i.e., two teasoons instead of one teaspoon). The oral solution can be taken without regard to food consumption.

Children 6 to 11 years of age: The recommended dose is 2.5 mg (one teaspoon, or 5 mL) once daily in the evening.

Adults and children 12 years of age and older: The recommended dose is 5 mg (two teaspoons, or 10 mL) once daily in the evening. Some patients may achieve adequate control of symptoms with 2.5 mg, or one teaspoon (5 mL) of the oral solution once daily in the evening. The 2.5-mg dose should not be exceeded; a systemic exposure of 5 mg is approximately twice the exposure recommended for adults.

Commentary: Unlike the oral tablets of levocetirizine, the oral solution provides a welcome alternative for patients who have difficulty swallowing or who prefer liquid medication. This is especially helpful for younger patients. The oral solution offers potent and long-lasting allergy relief when taken once daily. In studies of allergic rhinitis patients, levocetirizine significantly reduced the symptoms of sneezing, itchy nose, runny nose, and itchy eyes. Studies of patients with chronic idiopathic urticaria showed that levocetirizine significantly reduced the severity of itching and the number and size of wheals.

Sources: www.xyzal.com; www.rxlist.com ■

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