

Pharmaceutical Approval Update

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Apremilast (Otezla)

Manufacturer: Celgene, Summit, New Jersey

Date of Approval: March 21, 2014

Indication: Apremilast is indicated for the treatment of adults with active psoriatic arthritis (PsA).

Drug Class: Chemically, apremilast is *N*-{2-[(1*S*)-1-(3-Ethoxy-4-methoxyphenyl)-2-(methylsulfonyl)ethyl]-1,3-dioxo-2,3-dihydro-1*H*-isoindol-4-yl}acetamide with a molecular mass of 460.500 g/mol.

Uniqueness of Drug: Apremilast is an orally available small-molecule inhibitor of phosphodiesterase 4 (PDE4) that intracellularly modulates a network of pro-inflammatory and anti-inflammatory mediators and inhibits spontaneous production of TNF α from human rheumatoid synovial cells, resulting in increased intracellular cyclic adenosine monophosphate (cAMP) concentrations. PDE4 is the major enzyme class responsible for the hydrolysis of cAMP, an intracellular second messenger that controls this network of pro-inflammatory and anti-inflammatory mediators. With PDE4 inhibition, and the resulting increases in cAMP concentrations in immune and nonimmune cell types, expression of this network can be modulated.

The specific mechanism by which apremilast exerts its therapeutic action in PsA is not well defined.

Warnings and Precautions:

Depression. Treatment with apremilast is associated with an increase in depression. Apremilast should be used with caution in patients with a history of depression and/or suicidal thoughts or behavior. Patients, caregivers, and families should be advised of the need to be alert for the emergence or worsening of depression, suicidal thoughts, or other mood changes, and they should contact their health care provider if this occurs.

Weight decrease. Patients taking apremilast should have their weight monitored regularly. Patients should see their health care providers if they are losing weight and the weight loss cannot be explained. They may need to stop taking apremilast.

Drug interactions. Apremilast is known to interact with cytochrome P450 enzyme inducers such as rifampin, phenobarbital, carbamazepine, and phenytoin. Patients should not take these drugs while taking apremilast.

Dosage and Administration: To reduce the risk of gastrointestinal symptoms associated with initial therapy, patients should titrate to the recommended dose (30 mg orally twice daily) according to the following schedule:

- Day 1: 10 mg in the morning
- Day 2: 10 mg in the morning and 10 mg in the evening
- Day 3: 10 mg in the morning and 20 mg in the evening
- Day 4: 20 mg in the morning and 20 mg in the evening

- Day 5: 20 mg in the morning and 30 mg in the evening
- Day 6: 30 mg in the morning and 30 mg in the evening

In patients with severe renal impairment (creatinine clearance less than 30 mL/min), reduce the dose to 30 mg orally once a day. No dosage adjustment is required for patients with mild-to-moderate renal impairment or with hepatic impairment.

Commentary: An estimated 125 million people worldwide have psoriasis, approximately 30% of whom may also develop psoriatic arthritis. PsA is a chronic disorder with progressive and additive joint inflammation that can lead to deleterious effects on quality of life and increased work disability. In addition to psoriatic

skin lesions, common signs and symptoms of PsA include pain, stiffness, and swelling in several to many joints, as well as inflammation of the spine. Patients often experience psoriasis on average for 10 years before the onset of joint symptoms, and many PsA patients go undiagnosed.

Apremilast is the only FDA-approved oral treatment for PsA. In the three clinical trials, treatment with apremilast resulted in improvement in dactylitis and enthesitis in patients with these pre-existing symptoms. Dactylitis and enthesitis are specific disease manifestations related to PsA. The studies included a wide spectrum of patients with active PsA, including those who had previously been treated with oral disease-modifying antirheumatic drugs and/or biologics, as well as patients who had previously failed a tumor necrosis factor blocker.

Source: <http://reference.medscape.com>

Omalizumab (Xolair)

Manufacturer: Genentech, South San Francisco, California; and Novartis Pharmaceuticals, East Hanover, New Jersey

Date of Approval: March 21, 2014

Indication: For treatment of chronic idiopathic urticaria (CIU), a form of chronic hives, in people ages 12 years or older who continue to have symptoms despite treatment with antihistamines. Omalizumab is also used for patients with moderate-to-severe persistent allergic asthma caused by year-round allergens in the air who have a positive skin test or *in vitro* reactivity to a perennial aeroallergen and whose symptoms are inadequately controlled with inhaled corticosteroids.

Biological Class: Omalizumab is a recombinant DNA-derived humanized IgG1k monoclonal antibody that specifically binds to free human immunoglobulin E (IgE) in the blood and interstitial fluid and to the membrane-bound form of IgE (mIgE) on the surface of mIgE-expressing B lymphocytes. Unlike an ordinary anti-IgE antibody, omalizumab does not bind to IgE that is already bound by the high-affinity IgE receptor (Fc ϵ RI) on the surface of mast cells, basophils, and antigen-presenting dendritic cells. IgE is commonly involved in type I hypersensitivity, which manifests in the most prevalent allergic diseases.

Uniqueness of Drug: Omalizumab is the first and only licensed therapy in the U.S. for the nearly 50% of patients with CIU who do not respond to approved doses of H₁ antihistamines

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and corticosteroids. Omalizumab reduces sensitivity to inhaled or ingested allergens.

Boxed Warning: Anaphylaxis presenting as bronchospasm, hypotension, syncope, urticaria, and/or angioedema of the throat or tongue has been reported to occur after administration of omalizumab. Anaphylaxis has occurred as early as the first dose of omalizumab, but also has occurred more than a year after beginning regular treatment. Because of the risk of anaphylaxis, health care providers should observe patients closely for an appropriate period after omalizumab administration and should be prepared to manage anaphylaxis that can be life-threatening. Inform patients of the signs and symptoms of anaphylaxis and instruct them to seek immediate medical care should symptoms occur.

Warnings and Precautions:

Anaphylaxis. Anaphylaxis has been reported to occur after administration of omalizumab in premarketing clinical trials and in postmarketing spontaneous reports. Signs and symptoms in these cases have included bronchospasm, hypotension, syncope, urticaria, and/or angioedema of the throat or tongue. Some events have been life-threatening. In premarketing clinical trials, the frequency of anaphylaxis attributed to omalizumab use was estimated to be 0.1%. In postmarketing spontaneous reports, the frequency of anaphylaxis attributed to omalizumab use was estimated to be at least 0.2% of patients based on an estimated exposure of about 57,300 patients from June 2003 through December 2006. Anaphylaxis has occurred as early as after the first dose of omalizumab, but also has occurred beyond one year after beginning regularly scheduled treatment.

Omalizumab should only be administered in a health care setting by providers prepared to manage anaphylaxis that can be life-threatening. Patients should be closely observed for an appropriate period after administration of omalizumab, taking into account the time to onset of anaphylaxis seen in premarketing clinical trials and postmarketing spontaneous reports. Patients should be informed of the signs and symptoms of anaphylaxis and instructed to seek immediate medical care should signs or symptoms occur.

Omalizumab should be discontinued in patients who experience a severe hypersensitivity reaction.

Malignancy. Malignant neoplasms were observed in 20 of 4,127 (0.5%) omalizumab-treated patients compared with five of 2,236 (0.2%) control patients in clinical studies of asthma and other allergic disorders. The observed malignancies in omalizumab-treated patients were a variety of types, with breast, nonmelanoma skin, prostate, melanoma, and parotid cancer occurring more than once, and five other types occurring once each. The majority of patients were observed for less than one year. The impact of longer exposure to omalizumab or use in patients at higher risk for malignancy (e.g., the elderly, current smokers) is not known.

Dosage and Administration: Omalizumab 150 mg to 375 mg is administered subcutaneously (SC) every two or four weeks. Because the solution is slightly viscous, the injection may take five to 10 seconds to administer. Dosages and dosing frequency are determined by serum total IgE concentration (IU/mL), measured before the start of treatment, and by body weight. Doses of more than 150 mg are divided among more than one injection site to limit injections to no more

than 150 mg per site. The need for continued therapy should be periodically reassessed based upon the patient's disease severity and level of asthma control.

Omalizumab for SC administration should be prepared using only sterile water for injection, USP. It is for single use and contains no preservatives. The solution should be used for SC administration within eight hours following reconstitution when stored in the vial at 2 to 8 degrees Celsius (36 to 46 degrees Fahrenheit), or within four hours of reconstitution when stored at room temperature.

Commentary: Chronic idiopathic urticaria (CIU) is an unpredictable and debilitating skin disease that is known as chronic spontaneous urticaria (CSU) outside of the U.S. In the U.S., omalizumab is indicated for CIU in adults and adolescents (12 years of age and above) who remain symptomatic despite H₁ antihistamine treatment. Until now, H₁ antihistamines have been the only approved therapy for CIU in the U.S. At any given time, the prevalence of chronic urticaria is up to 1% of the world's population, and up to two-thirds of these patients have CIU/CSU. In the U.S. it is estimated that approximately 1.5 million people suffer from CIU. Women are twice as likely as men to have the condition, and most people develop symptoms between the ages of 20 and 40 years. CIU can be difficult to manage because its causes are unknown, and other approved medicines aren't effective enough for many patients.

However, clinical reports show that anaphylaxis may occur in patients taking omalizumab. Those reports include new users of omalizumab and patients who have been taking the asthma drug for longer than one year. The FDA notes that due to the risk of anaphylaxis, omalizumab should only be administered to patients under direct medical supervision by health care workers who are aware of omalizumab's anaphylaxis risk, monitor patients while taking omalizumab, and are prepared to treat anaphylaxis. The FDA approval of omalizumab is primarily based on positive and consistent results from two landmark phase 3 studies, Asteria I and II, which involved CIU/CSU patients who were not responding to approved doses of H₁ antihistamines.

Sources: www.xolair.com, Xolair prescribing information

Grass Pollen Allergen Extract (Oralair)

Manufacturer: Stallergenes S.A., Antony, France; and Greer Laboratories, Lenoir, North Carolina

Date of Approval: April 2, 2014

Indication: Immunotherapy for the treatment of grass pollen-induced allergic rhinitis with or without conjunctivitis confirmed by positive skin test or *in vitro* testing for grass pollen-specific IgE antibodies for any of the five grass species contained in the product. Oralair is approved for use in persons 10 through 65 years of age.

Drug Class: Oralair contains a mixture of freeze-dried extracts from the pollens of five grasses, including Sweet Vernal, Orchard, Perennial Rye, Timothy, and Kentucky Blue Grass.

Uniqueness of Drug: Oralair offers a unique delivery mechanism in that it is a sublingual tablet (the first sublingual immunotherapy in the U.S. to treat multiple grass pollens) and can be administered by the patient in his or her own home. The current standard treatment for grass pollen allergy sufferers in the U.S. is subcutaneous immunotherapy, a series of

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shots given in doctor's offices over a span of several years.

Boxed Warning: Oralair can cause life-threatening allergic reactions, such as anaphylaxis and severe laryngopharyngeal edema. The product is contraindicated in patients with severe, unstable, or uncontrolled asthma or with a history of any severe systemic or local reaction to sublingual allergen immunotherapy. The first dose should be taken in a doctor's office and the patient should be observed for at least 30 minutes. Patients should be prescribed auto-injectable epinephrine, trained on its appropriate use, and instructed to seek immediate medical care after its use. Oralair may be unsuitable for patients who have some medical conditions or use some medications.

Warnings and Precautions:

Allergic reactions. Treatment with grass pollen allergen extract should only be prescribed and initiated by physicians with adequate training and experience in the treatment of respiratory allergic diseases. In the case of pediatric treatment, the physicians should have the corresponding training and experience with children.

The first tablet must be taken at the physician's office under medical supervision and the patient must be monitored for at least 30 minutes. Extra precautions must be taken while treating pediatric patients. Each time a dose is given, an adult must supervise the child for at least 30 minutes.

Treatment with the allergen extract exposes the patient to an allergen that causes allergic symptoms. Therefore, mild or moderate local allergic reactions are to be expected during the treatment period. Patients should be instructed in recognizing adverse reactions and their possible severity. If the patient experiences moderate local adverse reactions from the treatment, antihistamines should be considered. If severe allergic reactions occur, such as anaphylactic shock, they should be treated with epinephrine.

Grass pollen allergen extract tablets contain lactose. Patients who are allergic to lactose should not use grass pollen allergen extract tablets.

Dosage and Administration:

Treatment with Oralair should begin four months before the start of pollen season and should be continued throughout the season. It is recommended that the first

dose of Oralair be given under medical supervision and that the patient be monitored for 30 minutes afterward.

Oralair is given with increasing doses over three days until the maintenance dose is reached. The following dosing regimen is for patients 5 years of age and older:

- Day 1: Take one 100-mg tablet. The tablet must be placed under the tongue and allowed to dissolve.
- Day 2: Dissolve two 100-mg tablets at once under the tongue.
- Day 3: Dissolve one 300-mg tablet under the tongue.

Providers and patients should wash their hands thoroughly after handling Oralair.

Commentary: Allergic rhinitis with or without conjunctivitis is a chronic disease affecting approximately 30 million children and adults in the U.S. and more than 500 million persons worldwide. The disease is often caused by sensitivity to grass pollen. Affected people may suffer from repetitive sneezing, nasal itching, runny nose, nasal congestion, and itchy and watery eyes. Allergy immunotherapy in the U.S. has traditionally been administered via a series of subcutaneous injections in an allergy specialist's office. The approval of Oralair provides an additional option for allergy specialists and patients to consider for treating grass allergies.

Grass allergies are the most common seasonal allergy in the U.S., and most people are allergic to more than one type of grass. Oralair is the only FDA-approved oral allergy immunotherapy tablet that includes a five-grass mixed pollens allergen extract. These five grasses provide a wide range of grass allergy coverage in the U.S.

Across all studies, patients who began taking Oralair four months before and during a grass pollen season experienced a 16% to 30% reduction in symptoms and in the need for medications compared with those who received placebo.

Sources: www.paladinlabs.com, www.fda.gov ■