Azilsartan medoxomil, belimumab, and lurasidone hydrochloride

Daniel A. Hussar and Anokhi Shah

Antihypertensive agent

Azilsartan medoxomil (Edarbi—Takeda) is the eighth angiotensin II receptor blocker (ARB) to be marketed in the United States, joining candesartan cilexetil (Atacand), eprosartan (Teveten), irbesartan (Avapro), losartan (e.g., Cozaar), olmesartan medoxomil (Benicar), telmisartan (Micardis), and valsartan (Diovan). The ARBs directly block the binding of the potent vasoconstrictor angiotensin II to its receptor sites, thereby causing a reduction in blood pressure. All of the ARBs selectively block the AT_1 subtype angiotensin II receptors.

The form of azilsartan that is used in its tablet formulation is the potassium salt of azilsartan medoxomil, which also is known as azilsartan kamedoxomil. Like candesartan cilexetil and olmesartan medoxomil, azilsartan medoxomil is a prodrug, and the new agent is hydrolyzed to azilsartan in the gastrointestinal tract during absorption.

As with the other ARBs, azilsartan is indicated for the treatment of hypertension and may be used alone or in combination with other antihypertensive agents, most often a diuretic. In studies in which it was compared with olmesartan and valsartan, azilsartan was more effective in lowering 24-hour blood pressure. The reduction in the 24-hour mean systolic blood pressure was 14.3 mm Hg with azilsartan (80 mg once a day), compared with reductions of 11.7 and 10 mm Hg with olmesartan (40 mg/day) and valsartan (320 mg/day), respectively. As with the other ARBs, azilsartan was less effective in lowering blood pressure in black patients.

In addition to hypertension, certain of the ARBs also have been approved for additional indications (e.g., valsartan for the treatment of heart failure in patients who are intolerant of angiotensin-converting enzyme inhibitors [ACEIs], candesartan and losartan for the treatment of diabetic nephropathy in patients with type 2 diabetes and hypertension). However, these are not labeled indications for azilsartan at the present time.

Like the other ARBs, azilsartan is well tolerated, with diarrhea (2%) being the most common adverse event reported in the clinical studies. Although the ARBs are not likely to cause symptomatic hypotension, caution should be exercised when azilsartan is used in volume- or salt-depleted patients (e.g., those using diuretics), and the use of a lower dosage should be considered. The ARBs have a potential to cause changes in renal function, and azilsartan should be used with caution in patients who are at greatest risk of such a response (e.g., those with preexisting renal impairment or renal artery stenosis). The concurrent use of a nonsteroidal anti-inflammatory drug (NSAID) may result in a deterioration of renal function in at-risk patients. In addition, the antihypertensive effect of azilsartan may be reduced by NSAIDs.

Neonatal morbidity and death are risks if either an ARB or ACEI is used during the second or third trimesters of pregnancy, and this is addressed in a boxed warning in the labeling for these agents. Like the other agents, azilsartan is classified in Pregnancy Categories C (first trimester) and D (second and third trimesters). If a woman treated with one of these agents becomes pregnant, treatment should be discontinued as soon as possible.

Whether azilsartan is excreted in human milk is unknown; therefore, in nursing mothers, a decision should me made whether to discontinue nursing or not use the drug. The effectiveness and safety of azilsartan in pediatric patients have not been established.

Following oral administration, azilsartan medoxomil is rapidly hydrolyzed to azilsartan, the absolute bioavailability of which is approximately 60%. It is metabolized to two primary metabolites, primarily via the cytochrome P450 (CYP)2C9 pathway, but the metabolites do not contribute to the activity of the drug. Approximately 55% of the drug is recovered in the feces and approximately 40% in the urine. Dosage adjustment is not considered necessary in patients with impaired renal function or in patients with mild or moderate hepatic impairment. The new drug has not been studied in patients with severe hepatic impairment.

The recommended dosage of azilsartan is 80 mg once a day, with or without food. In patients who are also being treated with a diuretic in a high dosage, consideration should be given to initiating treatment with azilsartan in a dosage of 40 mg once a day.

Azilsartan kamedoxomil is supplied in tablets in quantities representing the equivalent of 40 and 80 mg of azilsartan medoxomil. The tablets should be dispensed and stored in the original container to protect the drug from light and moisture and should not be repackaged. A combination formulation that also includes a diuretic is under development.

Agent for systemic lupus erythematosus

Systemic lupus erythematosus (SLE; lupus) is a serious and potentially fatal autoimmune disease that attacks healthy tissues, including the joints, skin, kidneys, lungs, heart, and brain. The symptoms that are most commonly experienced (flare) are joint pain and inflammation, light sensitivity, fever, fatigue, chest pain, and hair loss. More than 300,000 Americans are afflicted with lupus. It most often affects women

The **New Drugs** column informs readers about new chemical and biologic entities approved for marketing by the U.S. Food and Drug Administration. The column is written by Contributing Editor Daniel A. Hussar, PhD, Remington Professor of Pharmacy, Philadelphia College of Pharmacy, University of the Sciences in Philadelphia.

and usually develops between 15 and 44 years of age. The incidence in black women is approximately three times higher than in white women.

Standard therapies for lupus have included nonsteroidal anti-inflammatory drugs (NSAIDs), corticosteroids (e.g., prednisone), immunosuppressives (e.g., azathioprine, methotrexate, mycophenolate), and antimalarials (hydroxychloroquine [Plaquenil]). However, in some patients, these agents have been of limited effectiveness and serious complications are experienced.

Belimumab (Benlysta—Human Genome Sciences; GlaxoSmithKline) is the first new drug to be approved for the treatment of lupus since 1955, when hydroxychloroquine and corticosteroids were approved for this disease. It is thought that abnormal B cells may be responsible, in part, for symptoms and complications associated with lupus and that these cells may contribute to the formation of autoantibodies. Belimumab is a human monoclonal antibody produced by recombinant DNA technology that is specific for soluble human B lymphocyte stimulator protein (BLyS), a B-cell survival factor. As a BLyS-specific inhibitor, the new drug blocks the binding of soluble BLyS to its receptors on B-cells. This action inhibits the survival of B-cells, including autoreactive B-cells, and reduces the differentiation of B-cells into immunoglobulin-producing plasma cells.

Belimumab is administered intravenously and is specifically indicated for the treatment of adult patients with active, autoantibody-positive, systemic lupus erythematosus who are receiving standard therapy. In the clinical studies, patients received belimumab plus standard therapy or placebo plus standard therapy. Patients receiving belimumab experienced less disease activity than those receiving placebo. Some patients treated with belimumab had a reduced likelihood of severe flares, and in some, it was possible to reduce the dosage of the corticosteroid that was included as part of their standard therapy; however, the data were insufficient to establish these responses as definitive benefits of the new drug. Black patients who participated in the studies did not appear to benefit from belimumab treatment, although the numbers of these patients were not large enough to reach definite conclusions and additional studies will be conducted in black patient populations.

Patients with severe active lupus nephritis and severe active central nervous system lupus were excluded from the clinical trials, as were patients who were being treated with other biologics or intravenous cyclophosphamide. Therefore, the use of belimumab is not recommended in these situations.

Hypersensitivity reactions and infusion reactions have been experienced by some patients treated with belimumab but at an incidence not much greater than in patients receiving placebo. In the clinical studies, hypersensitivity reactions were reported in 13% and 11% of those receiving belimumab and placebo, respectively, and anaphylaxis was observed in 0.6% and 0.4%, respectively. The use of the new agent is contraindicated in patients who have previously experienced anaphylaxis to the drug. Infusion reactions (e.g., headache, nausea, skin reactions) were reported in 17% of patients treated with belimumab and 15% of those receiving placebo. Because of the overlap in signs and symptoms, distinguishing between hypersensitivity reactions and infusion reactions was not always possible. Some patients were provided with premedication, but data were insufficient to determine whether premedication diminished the frequency or severity of hypersensitivity or infusion reactions.

As with other agents with immunosuppressive activity, a risk of serious infections exists with use of belimumab. Infections were reported in 71% and 67% of the patients receiving belimumab and placebo, respectively, in the clinical trials, and infections resulting in death occurred in 0.3% and 0.1% of patients, respectively. Treatment with belimumab should not be initiated in patients receiving therapy for a chronic infection, and in patients undergoing treatment with belimumab who develop a new infection, interruption of therapy should be considered. During the controlled period of clinical trials, more deaths were reported (e.g., from infections, cardiovascular disease, suicide) with belimumab than with placebo.

Because belimumab may interfere with the response to immunizations, live vaccines should not be given for 30 days before or concurrently with the new drug.

Psychiatric adverse events (e.g., depression, anxiety) were reported more frequently in patients treated with belimumab (16%) in the clinical trials than those who were receiving placebo (12%). Although most of the patients who experienced these events had a history of these problems and were being treated with psychoactive medications, patients treated with belimumab should be instructed to report new or worsening depression, suicidal thoughts, or other mood changes.

The most frequently experienced adverse events in the clinical studies with belimumab included nausea (15%), diarrhea (12%), pyrexia (10%), nasopharyngitis (9%), bronchitis (9%), insomnia (7%), pain in extremity (6%), depression (5%), migraine (5%), and pharyngitis (5%). Although anti-belimumab antibodies were detected in only a small percentage of patients, a potential exists for the development of neutralizing antibodies.

Belimumab is classified in Pregnancy Category C, and women of childbearing potential should use adequate contraception during treatment with the drug and for at least 4 months following the final treatment. For women who are pregnant during the time period in which they are being treated with belimumab, enrollment in the Pregnancy Registry (877-681-6296) is encouraged. Whether belimumab is excreted in human milk is not known, and a decision should be made to discontinue nursing or not use the drug. The effectiveness and safety of belimumab in pediatric patients have not been evaluated.

Belimumab is administered via intravenous infusion over a period of 1 hour and must not be administered as an intravenous push or bolus. The recommended dosage is 10 mg/kg at 2-week intervals for the first three doses and