Pharmaceutical Approval Update

Marvin M. Goldenberg, PhD, RPh, MS

Rivastigmine Transdermal System
(Exelon Patch)

Manufacturer: Novartis Pharmaceuticals Corp, East Hanover, NJ

Indication: The rivastigmine transdermal system is indicated for the treatment of mild-to-moderate dementia of the Alzheimer’s type and for mild-to-moderate dementia associated with Parkinson’s disease (PD). The dementia of PD is characterized by impairments in executive function, memory retrieval, and attention.

Drug Class: Rivastigmine is a reversible cholinesterase inhibitor and is known chemically as (S)-3-[1-(dimethylamino)ethyl]phenyl ethylmethylcarbamate.

Uniqueness of Drug: This new therapy is the first transdermal therapy for Alzheimer’s disease, a degenerative condition that affects millions of people in the U.S. Placebo-controlled clinical trials showed significant benefits to patients in terms of their memory and overall functioning.

The patch maintains steady drug levels in the bloodstream, improving tolerability and allowing a higher proportion of patients to receive therapeutic doses, compared with the capsule formulation. The transdermal system is applied to the back, chest, or upper arm, and it provides smooth, continuous delivery of medication through the skin over a period of 24 hours.

Warnings and Precautions:
Gastrointestinal adverse reactions: At higher-than-recommended doses, the patch is associated with significant gastrointestinal (GI) adverse reactions, including nausea, vomiting, diarrhea, anorexia or decreased appetite, and weight loss. For this reason, the starting dose should always be 4.6 mg per 24 hours. This dose should be titrated to the maintenance dose of 9.5 mg per 24 hours.

If treatment is interrupted for more than several days, the medication should be reinitiated with the lowest daily dose to reduce the possibility of severe vomiting and its potentially serious sequelae. In one postmarketing report, severe vomiting with esophageal rupture followed inappropriate reinitiation of treatment with a 4.5-mg dose of an oral formulation after eight weeks of interrupted treatment.

At higher-than-recommended doses, caregivers should be advised of the elevated incidence of nausea and vomiting associated with the patch as well as the possibility of anorexia and weight loss. Caregivers should be encouraged to monitor patients for these adverse events and should inform the physician if they occur. It is critical to inform caregivers that if therapy has been interrupted for more than several days, the next dose should not be administered until the physician has been consulted.

Nausea and vomiting: In the controlled clinical trial, the following patients experienced nausea: 7% of patients treated with the rivastigmine transdermal system at a dose of 9.5 mg per a 24-hour period, 23% of patients who received the rivastigmine capsule at doses up to 6 mg twice daily, and 5% of those who received placebo. In the same trial, 6% of patients treated with the patch at this dosage experienced vomiting, compared with 17% of patients who received the capsule at doses up to 6 mg twice daily and with 3% of those who received placebo.

The proportion of patients who discontinued treatment because of vomiting was 0% of patients given the patch at a dosage of 9.5 mg per 24 hours, 2% of patients who received the capsule at doses up to 6 mg twice daily, and 0% of those who received placebo. Vomiting was severe in none of the patients who received the patch 9.5 mg per 24 hours, in 1% of patients who received the capsule at doses up to 6 mg twice daily, and in none of those who received placebo.

In the same trial, 21% of patients using the higher dose of the patch at 17.4 mg per 24 hours experienced nausea and 19% experienced vomiting. The proportion of these patients who discontinued treatment as a result of vomiting was 2%. Vomiting was severe in 1% of patients wearing the patch at a dosage of 17.4 mg per 24 hours.

Weight loss: In the controlled clinical trial, the following patients had a weight loss equal to or greater than 7% of their baseline weight: 8% of those treated with the patch at a dosage of 9.5 mg per 24 hours, 11% of patients who received the rivastigmine capsule at doses up to 6 mg twice daily, and 6% of those who received placebo. In the same trial, 12% of those treated with 17.4 mg per 24 hours had weight loss equal to or greater than 7% of their baseline weight. It is not clear how much of the weight loss was related to the anorexia, nausea, vomiting, and diarrhea associated with the drug.

Diarrhea: In the controlled clinical trial, 6% of patients treated with the patch at a dosage of 9.5 mg per 24 hours developed diarrhea, compared with 5% of patients who received the rivastigmine capsule at doses up to 6 mg twice daily, 10% of those treated with 17.4 mg per 24 hours, and 3% of those who received placebo.

Anorexia and decreased appetite: In the controlled clinical trial, 3% of patients treated with the patch at a dose of 9.5 mg/24 hours experienced decreased appetite or anorexia, compared with 9% of patients who were receiving the capsule at doses up to 6 mg twice daily, 9% of those using the patch at a dose of 17.4 mg per 24 hours, and 2% of those receiving placebo.

Pep tic ulcers and GI bleeding: Because of their pharmacological action, cholinesterase inhibitors may be expected to increase gastric acid secretion caused by increased cholinergic activity. Therefore, patients should be monitored closely for symptoms of active or occult GI bleeding, especially if they are at an increased risk for developing ulcers (e.g., patients with a history of ulcer disease or those receiving concurrent

The author is President of Pharmaceutical and Scientific Services at Marvin M. Goldenberg, LLC, in Westfield, New Jersey. His e-mail address is mmgpotter@comcast.com.
nonsteroidal anti-inflammatory drugs (NSAIDs)). Clinical studies of rivastigmine have shown no significant increase, relative to placebo, in the incidence of either peptic ulcer disease or GI bleeding.

**Anesthesia:** As a cholinesterase inhibitor, rivastigmine is likely to exaggerate succinylcholine-type muscle relaxation during anesthesia.

**Cardiovascular Conditions:** Drugs that increase cholinergic activity may have vagotonic effects on the heart rate, such as bradycardia. The potential for this action may be particularly important to patients with sick sinus syndrome or other supraventricular cardiac conduction conditions. In clinical trials, rivastigmine was not associated with an increased incidence of cardiovascular adverse events, changes in heart rate or blood pressure, or electrocardiographic abnormalities.

**Genitourinary Conditions:** Although a genitourinary effect was not observed in clinical trials of rivastigmine capsules, drugs that increase cholinergic activity may cause urinary obstruction.

**Neurological Conditions:**

**Seizures.** Drugs that increase cholinergic activity are believed to have a potential for causing seizures. However, seizure activity may also be a manifestation of Alzheimer’s disease.

**Extrapyramidal symptoms:** Like other cholinomimetic agents, rivastigmine may exacerbate or induce extrapyramidal symptoms. Worsening of parkinsonian symptoms, particularly tremor, has been observed in patients with dementia associated with PD who received rivastigmine capsules.

**Pulmonary Conditions:** Like other drugs that increase cholinergic activity, rivastigmine should be used with care in patients with a history of asthma or obstructive pulmonary disease.

**Driving and Using Machines:** Dementia may cause gradual impairment of driving performance or may compromise the ability to use machinery. The administration of rivastigmine may also result in adverse events that are detrimental to these functions. Thus, the ability to continue driving or operating machinery should be routinely evaluated by the treating physician.

**Dosage and Administration:**

**Initial dose:** Treatment is started with the rivastigmine transdermal system at a dosage of 4.6 mg per 24 hours. After a minimum of four weeks of treatment and if this dose is well tolerated, it should be increased to 9.5 mg per 24 hours, the recommended effective dose.

**Maintenance dose:** Dose increases should occur only after a minimum of four weeks at the previous dose if the previous dose has been well tolerated. The maximum recommended dose is 9.5 mg per 24 hours. Higher doses confer no appreciable additional benefit and are associated with a significant increased incidence of adverse events. If these adverse effects (e.g., nausea, vomiting, diarrhea, loss of appetite) cause intolerance during treatment, patients should be instructed to discontinue treatment for several days and then to restart therapy at the same or next lower dose level. If treatment is interrupted for longer than several days, the medication should be reinitiated with the lowest daily dose and titrated as described previously.

**Switching from capsules or an oral solution:** Patients taking capsules or the oral solution may be switched to the patch as follows:

- Patients receiving a total daily dose of less than 6 mg of oral rivastigmine can be switched to the patch at a dosage of 4.6 mg per 24 hours.
- Patients receiving a total daily dose of 6 to 12 mg of oral rivastigmine may be directly switched to the patch at a dosage of 9.5 mg per 24 hours.

**General Recommendations:** Each patch is a thin, matrix-type transdermal system consisting of three layers when it is worn. A fourth layer, the release liner, covers the adhesive layer prior to use and is removed when the patch is applied to the skin.

The patch should first be applied on the day following the last oral administration. It is applied once a day to clean, dry, hairless, intact healthy skin in an area that is not in contact with tight clothing. The upper or lower back is recommended as the site of application, because patients are less likely to remove the patch when it is in this location. When sites on the back are not accessible, the patch can be applied to the upper arm or chest.

The patch should not be applied to skin that is red, irritated, or cut. The application site should be changed daily to avoid potential irritation, although consecutive patches can be applied to the same anatomic site (e.g., another spot on the upper back). The patch should be pressed down firmly until the edges stick well. Patients can wear the patch while bathing and in hot weather.

The patch should be replaced with a new one every 24 hours, but patients should not apply the new patch to the same spot for at least 14 days. Patients and caregivers should be instructed accordingly.

**Commentary:** The Exelon patch represents an innovative way to deliver what is now standard therapy for mild-to-moderate Alzheimer’s disease through a skin patch instead of an oral capsule. The patch maintains steady drug concentrations in the bloodstream, improving tolerability and allowing more patients to receive therapeutic doses, compared with the capsule. When applied to the back, chest, or upper arm, the patch provides smooth, continuous drug delivery for 24 hours.

GI side effects are commonly seen with the class of drugs called cholinesterase inhibitors. The recommended dose of the patch greatly reduces these side effects, with three times fewer reports of nausea and vomiting than with the capsule formulation.

**Source:** www.pharma.us.novartis.com

**Armodafinil (Nuvigil)**

**Manufacturer:** Cephalon, Inc., Frazer, PA

**Indication:** Armodafinil is designed to improve wakefulness in patients with excessive sleepiness associated with obstructive sleep apnea/hypopnea syndrome, narcolepsy, and shift work sleep disorder.

In obstructive sleep apnea/hypopnea syndrome, armodafinil is indicated as an adjunct to standard therapy for the underlying obstruction. If continuous positive airway pressure (CPAP) is
the treatment of choice, a maximal effort should be made to treat with CPAP for an adequate period of time before armodafinil is initiated. If armodafinil is used as an adjunct with CPAP, encouragement and periodic assessment of compliance with CPAP are essential.

In all cases, it is of the utmost importance to pay careful attention to the diagnosis and treatment of the underlying sleep disorder. Some patients might have more than one sleep disorder that is contributing to their excessive sleepiness.

**Drug Class:** Armodafinil is the R-enantiomer of modafinil (Provigil, Cephalon), which is a mixture of the R- and S-enantiomers. The chemical name for armodafinil is 2-[(R)-(diphenylmethy1)sulfinyl]acetamide.

**Uniqueness of Product:** The precise mechanism through which armodafinil and modafinil promote wakefulness is unknown.

At pharmacologically relevant concentrations, armodafinil does not bind to or inhibit several receptors and enzymes potentially relevant for sleep/wake regulation, including those for serotonin, dopamine, adenosine, galanin, melatonin, melancortin, orexin-1, orphanin, pituitary adenylate cyclase activating polypeptide (PACAP) or benzodiazepines, or transporters for gamma-butyric acid (GABA), serotonin, norpinephrine, and choline or phosphodiesterase VI, catechol-O-methyltransferase (COMT), GABA transaminase, and tyrosine hydroxylase. Modafinil does not inhibit the activity of monoamine oxidase-B or phosphodiesterases II, III, and IV.

Armodafinil and modafinil have wake-promoting actions similar to those of sympathomimetic agents, including amphetamine and methylphenidate, but their pharmacological profile differs from that of the sympathomimetic amines.

**Warnings:**

**Serious rash (including Stevens–Johnson Syndrome).** Modafinil has been associated with serious rash requiring hospitalization, and there have been reports of discontinuation of treatment in adults and children. Armodafinil has not been studied and is not approved for use in children for any indication.

In clinical trials of modafinil (the racemate), the incidence of rash resulting in discontinuation was approximately 0.8% (13 per 1,585) in pediatric patients (age younger than 17 years); these rashes included one case of possible Stevens–Johnson syndrome (SJS) and one case of apparent multiorgan hypersensitivity reaction. Several of the cases were associated with fever and other abnormalities such as vomiting and leukopenia. The median time to rash development that resulted in discontinuation was 13 days.

No such cases were observed among 380 pediatric patients who received placebo. No serious skin rashes have been reported in adult clinical trials (0 per 4,264) of modafinil. Rare cases of serious or life-threatening rash, including Stevens–Johnson syndrome, toxic epidermal necrolysis, and drug rash with eosinophilia and systemic symptoms (DRESS) have been reported in adults and children in worldwide postmarketing experience.

The reported rate of toxic epidermal necrolysis and Stevens–Johnson syndrome associated with modafinil use, which is generally considered an underestimate because of under-reporting, exceeds the background incidence rate. Estimates of the background incidence rate for these serious skin reactions in the general population range from 1 to 2 cases per million-person years.

No serious skin rashes have been reported in clinical trials of adults (0 per 1,595). However, because armodafinil is the R-isomer of racemic modafinil, a similar risk of serious rash with armodafinil cannot be ruled out.

No factors are known to predict the risk of occurrence or the severity of rash associated with modafinil or armodafinil. Nearly all cases of serious rash associated with modafinil occurred within one to five weeks after treatment began. However, isolated cases have been reported after prolonged treatment (e.g., three months). Accordingly, the duration of therapy cannot be relied upon to predict the potential risk heralded by the first appearance of a rash.

Although benign rashes also occur with armodafinil, it is not possible to predict which rashes will prove serious. Ordinarily, armodafinil should be discontinued at the first sign of a rash unless the rash is clearly not related to use of the drug. Discontinuing treatment might not prevent a rash from becoming life-threatening or permanently disabling or disfiguring.

**Angioedema and anaphylactoid reactions:** One serious case of angioedema and one case of hypersensitivity (with rash, dysphagia, and bronchospasm) were observed among 1,595 patients receiving armodafinil. Patients should be advised to discontinue therapy and to immediately notify their physician of any signs or symptoms that suggest angioedema or anaphylaxis (e.g., facial swelling, difficulty swallowing or breathing; or hoarseness).

**Multiorgan hypersensitivity reactions:** Multiorgan hypersensitivity reactions, including at least one fatality in postmarketing experience, have occurred in close temporal association with the initiation of modafinil therapy. The median time to detection was 13 days, with a range of 4 to 33 days. A similar risk of such reactions with armodafinil cannot be ruled out.

Despite a limited number of reports, these reactions may result in hospitalization or may be life-threatening. There are no factors that are known to predict the risk of occurrence or the severity of multiorgan hypersensitivity reactions associated with modafinil. Signs and symptoms of this disorder were diverse; however, patients typically—but not exclusively—presented with fever and rash associated with other organ system involvement. Other associated manifestations included myocarditis, hepatitis, liver function test abnormalities, hematological abnormalities (e.g., eosinophilia, leukopenia, thrombocytopenia), pruritus, and asthenia.

Because multiorgan hypersensitivity varies in its expression, other organ system symptoms and signs may occur. If a multiorgan hypersensitivity reaction is suspected, armodafinil should be discontinued. Although no case reports have indicated cross-sensitivity with other drugs that produce this syndrome, the experience with drugs associated with multiorgan hypersensitivity indicates such a possibility.

**Persistent sleepiness.** Patients with abnormal levels of sleepiness who take armodafinil should be advised that their level of wakefulness might not return to normal. Patients with excessive sleepiness, including those taking armodafinil, should be frequently reassessed for their degree of sleepi-
ness. If appropriate, patients should be advised to avoid driving or any other potentially dangerous activity. Prescribers should be aware that patients might not acknowledge feeling sleepy or drowsy until they are directly questioned about drowsiness or sleepiness during specific activities.

**Psychiatric symptoms:** Psychiatric adverse experiences have been reported in patients using modafinil. Because modafinil and armodafinil are closely related, the incidence and type of psychiatric symptoms associated with the drug are expected to be similar to the incidence and type of these events with modafinil.

Postmarketing adverse events associated with modafinil have included mania, delusions, hallucinations, and suicidal ideation, sometimes resulting in hospitalization. Many patients had a prior psychiatric history. In one healthy male volunteer, ideas of reference (a false belief that irrelevant things in the world have a special personal significance), paranoid delusions, and auditory hallucinations developed in association with multiple daily doses of modafinil 600 mg and sleep deprivation. There was no evidence of psychosis 36 hours after the drug was discontinued.

In the controlled trial’s armodafinil database, anxiety, agitation, nervousness, and irritability were reasons for treated patients (1.2%) to discontinue treatment, compared with those receiving placebo (0.3%). In the controlled studies, depression was also a reason for stopping treatment, more often with armodafinil (0.6% of patients) than with placebo (0.2%).

Two cases of suicidal ideation were observed in clinical trials. Caution should be exercised in patients with a history of psychosis, depression, or mania. If psychiatric symptoms develop in association with armodafinil, prescribers should consider discontinuing therapy.

**Precautions:**

**Hepatic impairment:** The pharmacokinetics and metabolism of modafinil were examined in six men and three women with cirrhosis of the liver. Three patients had stage B or B+ cirrhosis, and six patients had stage C or C+ cirrhosis (per Child-Pugh criteria). Clinically, eight of nine patients were icteric, and all had ascites. In these patients, the oral clearance of modafinil was decreased by about 60%, and the steady-state concentration was doubled, compared with normal patients. The armodafinil dose should be reduced in patients with severe hepatic impairment.

**Dosage and Administration:**

**Obstructive sleep apnea/hypopnea syndrome and narcolepsy:** The recommended dose is 150 mg or 250 mg given as a single dose in the morning. In patients with obstructive sleep apnea/hypopnea syndrome, doses up to 250 mg/day, given as a single dose, have been well tolerated, but there is no consistent evidence that additional benefit is conferred beyond a dose of 150 mg/day.

**Shift work sleep disorder:** The recommended dose is 150 mg, given daily approximately one hour prior to the start of the work shift. The dosage can be adjusted for concomitant medications that are substrates for cytochrome CYP 3A4 and 3A5, such as steroidal contraceptives, triazolam, and cyclosporine. Drugs that are eliminated largely via CYP 2C19 metabolism, such as diazepam (Valium, Roche), propranolol, and phenytoin (Dilantin, Pfizer) may have prolonged elimination upon co-administration with armodafinil. Consequently, the dosage might need to be reduced and monitored for toxicity.

**Hepatic impairment:** In patients with severe hepatic impairment, armodafinil should be administered at a reduced dose, because adequate information is lacking to determine the safety and efficacy of the drug in these patients.

**Elderly patients:** In elderly patients, elimination of armodafinil and its metabolites may be reduced as a consequence of aging. Therefore, lower doses should be considered in this population.

**Commentary:** Excessive sleepiness is the primary symptom and often the most debilitating feature in patients with narcolepsy, shift work sleep disorder, and obstructive sleep apnea/hypopnea syndrome. The defining characteristic of excessive sleepiness is a consistent inability to stay awake and alert enough to accomplish tasks of daily living safely and successfully. This condition is associated with reduced activity in the cerebral cortex of the brain. Although millions of Americans have excessive sleepiness associated with these three disorders, misdiagnosis is common. The rate of underdiagnosis ranges from 50% to 90%. Persons experiencing excessive sleepiness who seek medical attention typically complain of fatigue, tiredness, lapses of attention, lack of energy, low motivation, difficulty concentrating, disrupted sleep, snoring, or difficulties at work.

Armodafinil is the second product available for the treatment of conditions associated with excessive sleepiness. Modafinil (Provigil) is currently approved to treat excessive sleepiness associated with narcolepsy, obstructive apnea/hypopnea syndrome, and shift work sleep disorder. Provigil and Nuvigil have similar ingredients but different enantiomers. Armodafinil promotes wakefulness later in the day, suggesting that it has a long duration of action.

**Source:** www.cephalon.com

**Ambrisentan (Letairis)**

**Manufacturer:** Gilead Sciences, Inc., Foster City, CA

**Indications:** Ambrisentan is an endothelin receptor antagonist indicated for the treatment of pulmonary arterial hypertension (PAH) (World Health Organization Group 1) in patients with WHO class II or III symptoms to improve exercise capacity and delay clinical worsening. PAH is a rare, life-threatening condition characterized by continuous high blood pressure within the arteries of the lungs.

**Drug Class:** Ambrisentan, an endothelin receptor antagonist, is selective for the endothelin type-A (ETA) receptor. The chemical name is (+)-(2S)-2-[(4,6-dimethylpyrimidin-2-yl)oxy]-3-methoxy-3,3-diphenylpropanoic acid.

**Uniqueness of Drug:** Endothelin-1 (ET-1) is a potent autocrine and paracrine peptide. Two receptor subtypes, ETA and ETB, mediate the effects of ET-1 in the vascular smooth muscle and endothelium. The primary actions of ETA are vasoconstriction and cell proliferation, whereas the predominant actions of ETB are vasodilation, antiproliferation, and ET-1 clearance.

In patients with PAH, plasma ET-1 concentrations are increased as much as 10-fold, and they correlate with increased mean right atrial pressure and disease severity. ET-1 and ET-1 messenger RNA concentrations are increased as much...
as nine-fold in the lung tissue of patients with PAH, primarily in the endothelium of pulmonary arteries. These findings suggest that ET-1 may play a critical role in the pathogenesis and progression of PAH.

Ambrisentan is a high-affinity (Ki = 0.011 nM) ETA receptor antagonist with a high selectivity for the ETA versus ETB receptor (more than 4,000-fold). The clinical impact of high selectivity for ETA is not known.

**Boxed Warning:**

**Potential liver toxicity:** Ambrisentan can cause elevation of liver alanine and aspartate aminotransferases (ALT and AST) to at least three times the upper limit of normal (ULN). Ambrisentan treatment was associated with aminotransferase elevations above three times the ULN in 0.8% of patients in 12-week trials and in 2.8% of patients, including long-term open-label trials, out to one year.

One case of aminotransferase elevations above three times the ULN has been accompanied by bilirubin elevations greater than twice the ULN. Because these changes are a marker for potentially serious liver injury, serum aminotransferase levels—and bilirubin if aminotransferase levels are elevated—must be measured prior to the initiation of treatment and then monthly.

In the postmarketing period, in studies of another endothelin receptor antagonist, bosentan (Tracleer, Actelion), rare cases of unexplained hepatic cirrhosis were reported after prolonged therapy of more than 12 months. In at least one case with bosentan, a late presentation (after more than 20 months of treatment) included pronounced elevations in aminotransferases and bilirubin levels accompanied by nonspecific symptoms, all of which resolved slowly over time after discontinuation of the suspect drug. This case reinforces the importance of strict adherence to the monthly monitoring schedule for the duration of treatment.

Patients with elevations in aminotransferases require close attention. Ambrisentan should generally be avoided in patients with elevated aminotransferases (greater than three times the ULN) at baseline, because monitoring liver injury may be more difficult. If liver aminotransferase elevations are accompanied by clinical symptoms of liver injury (such as nausea, vomiting, fever, abdominal pain, jaundice, or unusual lethargy or fatigue) or increases in bilirubin greater than twice the ULN, treatment should be stopped. There is no experience with the reintroduction of ambrisentan in these circumstances.

**Contraindications:**

Pregnancy: Because ambrisentan consistently produced serious birth defects in animals, it is like to have a similar effect in pregnant women. Pregnancy must be excluded before ambrisentan is started. Thereafter, patients should avoid pregnancy by using at least two reliable methods of contraception. If a tubal sterilization has been performed or an intrauterine device (IUD), such as the Copper T 380A IUD or the levonorgestrel (LNG-20) has been inserted, no other contraception is needed. Pregnancy tests should be performed monthly.

Because of the risks of liver injury and birth defects, ambrisentan is available only through a restricted distribution program called the Letairis Education and Access Program (LEAP) (phone number: 1-866-664-LEAP). Only health care professionals and pharmacies registered with LEAP may prescribe and distribute ambrisentan. This medication may be dispensed only to patients who are enrolled in and who meet all conditions of LEAP.

**Warnings and Precautions:**

**Potential liver injury:** Treatment with endothelin receptor antagonists has been associated with dose-dependent liver injury manifested primarily by elevated serum aminotransferase (ALT or AST) levels, but is sometimes accompanied by abnormal liver function (elevated bilirubin). The combination of aminotransferase levels above three times the ULN and total bilirubin levels greater than twice the ULN are markers for potentially serious hepatic injury.

In all clinical studies with ambrisentan, liver function tests were closely monitored. For all ambrisentan-treated patients (N = 483), the 12-week incidence of aminotransferase levels that were above three times the ULN was 0.8%; the incidence of levels above eight times the ULN was 0.2%.

For placebo-treated patients, the 12-week incidence of aminotransferase levels that were more than three times the ULN was 2.3%; the incidence of levels above eight times the ULN was 0.0%.

The one-year rate of aminotransferase elevations that were above three times the ULN with ambrisentan was 2.8%; the rate above eight times the ULN was 0.5%.

One case of aminotransferase elevations above three times the ULN was accompanied by bilirubin elevations greater than two times the ULN.

Liver chemistry values must be measured before ambrisentan therapy is initiated and at least every month thereafter. If aminotransferase levels are elevated between three and five times the ULN, they should be measured again.

If the confirmed level of aminotransferase is between three and five times the ULN, the daily dose should be reduced or interrupted. These levels should continue to be monitored every two weeks until they are below three times the ULN.

If aminotransferase elevations are between five and eight times the ULN, ambrisentan should be discontinued and monitoring should be performed until levels are below three times the ULN. Ambrisentan can then be reinitiated, and aminotransferase levels should be monitored more frequently.

If aminotransferase elevations are more than eight times the ULN, treatment should be stopped and should not be introduced again.

Ambrisentan is not recommended in patients with elevated aminotransferase levels (above three times the ULN) at baseline, because monitoring liver injury may be more difficult. If aminotransferase elevations are accompanied by clinical symptoms of liver injury (anorexia, nausea, vomiting, fever, malaise, fatigue, right upper quadrant abdominal discomfort, itching, or jaundice) or if increases in bilirubin exceed twice the ULN, ambrisentan treatment should be stopped. Reintroducing ambrisentan therapy has not been studied in these circumstances.

**Hematological changes:** Decreased hemoglobin concentrations and hematocrit have occurred following the administration of other endothelin receptor antagonists, and these changes have been observed with ambrisentan. These decreases were apparent within the first few weeks of ambrisentan treatment, but they stabilized after that. The mean
Because of the exposure to ambrisentan, caution is recommended when ambrisentan is taken with ambrisentan is a substrate of P-gp, OATP, and CYP 3A. There-2C19-inhibitors (e.g., omeprazole [Prilosec, AstraZeneca]) with strong CYP 3A-inhibitors (e.g., ketoconazole) and CYP
port protein (OATP), and CYP 3A4.
failure, and the possible need for specific treatment. Should be undertaken to determine the cause, such as heart
severity. If clinically significant peripheral edema develops, with or without associated weight gain, further evaluation
should be undertaken to determine the cause, such as heart failure, and the possible need for specific treatment.
Peripheral edema: Peripheral edema is a known effect of the class of endothelin receptor antagonists, and it is a clinical
consequence of PAH and worsening PAH. In the placebo-controlled studies, the incidence of peripheral edema increased in patients receiving ambrisentan 5 or 10 mg, compared to those receiving placebo. Most edema was mild to moderate in
Coadministration of cyclosporine A: Cyclosporine is a strong inhibitor of P-glycoprotein (P-gp), organic anion transport
protein (OATP), and CYP 3A4. In vitro data indicate that ambrisentan is a substrate of P-gp, OATP, and CYP 3A. Therefore, caution is recommended when ambrisentan is taken with cyclosporine A, because cyclosporine A may cause increased exposure to ambrisentan.
Coadministration of strong CYP 3A and 2C19 inhibitors: Caution is necessary when ambrisentan is administered with strong CYP 3A-inhibitors (e.g., ketoconazole) and CYP 2C19-inhibitors (e.g., omeprazole [Prilosec, AstraZeneca]).

Prescribing and Distribution Program: Because of the risks of liver injury and birth defects, ambrisentan is available only via a program called the Letairis Education and Access Program (LEAP). To enroll in LEAP, prescribers must complete the LEAP Prescriber Enrollment and Agreement Form. All patients who receive this drug must be enrolled in LEAP and must be re-enrolled after the first six months of treatment and annually thereafter. Prescribers should review the ambrisentan medication guide and patient education brochure with all patients. All patients should be informed about the drug’s risks, including possible hepatotoxicity and terato-
 genetically.
Women of childbearing age should be instructed to use two different forms of contraception, including at least one primary form during ambrisentan treatment, and for one month after they stop treatment. If the patient has undergone a tubal sterilization or has the Copper T 380A IUD or the levonorgestrel-20 IUD, no additional contraception is needed. The primary forms of contraception include tubal sterilization, hormonal therapy (combination oral contraceptives, transdermal patch, injectables, implantables, or vaginal ring), an IUD, and a partner’s vasectomy. The IUD can be used alone without a secondary form of contraception, as can tubal sterilization.
Secondary forms of contraception include barrier methods such as latex condoms, diaphragms, and cervical caps.
For women of childbearing age, a pregnancy test is necessary before ambrisentan treatment begins and then the test should be given monthly during treatment. Patients who do not comply with LEAP requirements should be counseled. Prescribers should notify LEAP of any adverse events, including liver injury, or if any patient becomes pregnant during ambrisentan treatment.
Liver function tests (including aminotransferases and bilirubin) should be reviewed before ambrisentan therapy is begun and then monthly during treatment.
Dosage and Administration: Treatment is initiated at 5 mg once daily with or without food. Prescribers should consider increasing the dose to 10 mg once daily if 5 mg is tolerated. Tablets may be administered with or without food, and they should not be split, crushed, or chewed. Doses higher than 10 mg once daily have not been studied in patients with PAH. Liver function tests should be measured before and during treatment with ambrisentan.
Women of Childbearing Age: Ambrisentan should be prescribed for women of childbearing age only after a negative pregnancy test and only if patients are using two reliable methods of contraception (unless the patient has had a tubal sterilization or has the Copper T 380A or LNG-20 IUD). In these cases, no other contraception is needed. Pregnancy tests should be performed monthly in these patients.
Pre-existing Hepatic Impairment: Ambrisentan is not recommended for patients with moderate or severe hepatic impairment. Caution should be used for patients with mild hepatic impairment.
Commentary: The FDA approved ambrisentan as an orphan drug for patients with PAH. PAH is characterized by elevated blood pressure within the pulmonary arteries. If these small arteries become narrowed or blocked, the heart must work harder to pump the blood through them. Over time, the overworked heart muscle may become weak and lose its ability to pump enough blood through the lungs. Symptoms include shortness of breath, fatigue, chest pain, dizzy spells, and fainting. About 100,000 people in the U.S. have PAH.
In two clinical studies, ambrisentan significantly improved physical activity capacity, compared with placebo, as shown by a standard six-minute walking test, and it also delayed the worsening of PAH.
Bosentan, an earlier endothelin receptor antagonist, was approved for the treatment of PAH, but ambrisentan produces fewer drug interactions. Prostacyclin as a continuous IV infusion has also been used.
Source: www.letairis.com

www.letairis.com

Vol. 32 No. 10 • October 2007 • P&T® 557