Pharmaceutical Approval Update

Marvin M. Goldenberg, PhD, RPh, MS

Mirabegron (Myrbetriq) Tablets

Manufacturer: Astellas Pharma US, Inc., Northbrook, Ill.

Indication: Mirabegron is used in the treatment of overactive bladder (OAB) in patients with symptoms of urge urinary incontinence, urgency, and urinary frequency.

Drug Class: Mirabegron is a beta-3 adrenergic agonist. Its chemical name is 2-(2-aminothiazol-4-yl)-*N*-[4-(2-{[(2R)-2-hydroxy2-phenylethyl]amino}ethyl)phenyl]acetamide. The drug's molecular weight is 396.51.

Uniqueness of Drug: Mirabegron causes relaxation of the detrusor smooth muscle during the storage phase of the urinary bladder fill–void cycle by activation of beta-3 adrenergic receptor, which increases bladder capacity. Although mirabegron shows very low intrinsic activity for cloned human beta-1 and beta-2 adrenergic receptors, results in humans indicate that stimulation of the beta-1 adrenergic receptor occurs with a 200-mg dose.

Warnings and Precautions:

Increased blood pressure. Periodic blood pressure (BP) determinations are recommended, especially in hypertensive patients. Mirabegron is not recommended for patients with severe uncontrolled hypertension, defined as a systolic BP of 180 mm Hg or higher or a diastolic BP of 110 mm Hg or higher.

In two randomized, placebo-controlled studies of healthy volunteers, mirabegron was associated with dose-related increases in supine BP. At the maximum recommended dose of 50 mg, the mean maximum increase in systolic and diastolic BP was approximately 3.5/1.5 mm Hg greater than placebo. By contrast, in clinical trials enrolling patients with OAB, the mean increase in systolic and diastolic BP at the maximum recommended dose of mirabegron 50 mg was approximately 0.5 to 1 mm Hg greater than that with placebo. Worsening of pre-existing hypertension was reported infrequently in treated patients.

Urinary retention. In postmarketing experience with mirabegron, urinary retention was reported in patients with bladder outlet obstruction and in patients taking antimuscarinic agents for OAB. A controlled safety study did not demonstrate increased urinary retention; however, mirabegron should be used with caution in patients with clinically significant bladder outlet obstruction and in patients taking antimuscarinic medications for the treatment of OAB.

Reactions with drugs metabolized by cytochrome P450 2D6. Because mirabegron is a moderate cytochrome P450 (CYP) 2D6 inhibitor, systemic exposure to CYP2D6 substrates, such as metoprolol (e.g., Lopressor, Novartis) and desipramine (Norpramin, Sanofi), is increased with coadministration of mirabegron. Therefore, appropriate monitoring and dose adjustments may be necessary, especially with drugs that have a narrow therapeutic index and that are metabolized by CYP2D6, such as thioridazine (Mellaril, Novartis), flecainide (Tambocor, 3M), and propafenone (Rythmol, GlaxoSmithKline).

Dosage and Administration: The recommended starting dose of mirabegron is 25 mg once daily. This dose is effective within 8 weeks. Based on each patient's tolerability and the drug's efficacy, the dose may be increased to 50 mg once daily. Mirabegron should be taken with water and swallowed whole. It should not be chewed, divided, or crushed. It can also be taken with or without food.

The daily dose should not exceed 25 mg once daily in patients with severe renal impairment, defined as a creatinine clearance (CrCl) of 15 to 29 mL/minute or an estimated glomerular filtration rate of 15 to 29 mL/minute/1.73 m^2. Further, this dose should not be exceeded in patients with moderate hepatic impairment (Child–Pugh Class B). Mirabegron is not recommended for patients with end-stage renal disease or severe hepatic impairment.

Each extended-release (ER) tablet contains either 25 mg or 50 mg of mirabegron and the following inactive ingredients: polyethylene oxide, polyethylene glycol, hydroxypropyl cellulose, butylated hydroxytoluene, magnesium stearate, hypromellose, yellow ferric oxide, and red ferric oxide (in the 25-mg tablet only).

Commentary: As an ER tablet taken once daily, mirabegron (Myrbetriq) increases the bladder's storage capacity by relaxing the bladder muscle during filling. Symptoms of overactive bladder, which can be uncomfortable, embarrassing, and disruptive, include frequent and urgent urination and the involuntary leakage of urine resulting from urge urinary incontinence. Approximately 33 million Americans have OAB, according to the FDA's Center for Drug Evaluation and Research.

Sources: www.fda.gov; www.myrbetriq.com

Qsymia (Phentermine/Topiramate Extended-Release Capsules)

Manufacturer: Vivus Pharmaceuticals, Inc., Mountain View, Calif.

Indication: Qsymia capsules are indicated as an adjunct to a reduced-calorie diet and increased physical activity for chronic weight management in adults with an initial body mass index (BMI) of 30 kg/m^2 or greater (medical obesity) or 27 kg/m^2 or greater (medical overweight) if they also have at least one weight-related medical condition such as hypertension, type-2 diabetes, or high cholesterol levels. The drug's effect on cardiovascular morbidity and mortality is unknown, and its safety and effectiveness when used with other weight-loss products (e.g., prescription drugs, over-the-counter drugs, and herbal preparations) have not been established.

Drug Class: Phentermine is a sympathomimetic amine. Its pharmacological activity is similar to that of the prototype drugs of this class used for obesity, amphetamine (D- and D/L-amphetamine). Drugs of this class are commonly known as anorectic or anorexogenic agents. The effect of phentermine

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.*

on chronic weight management appears to be mediated by the release of catecholamines in the hypothalamus, resulting in reduced appetite and decreased food consumption, but other metabolic effects may also be involved.

The precise mechanism of action of topiramate (Topamax, Janssen), an antiseizure drug, on chronic weight management is not known. It might be a result of appetite suppression and satiety enhancement because of augmenting the activity of the neurotransmitter gamma-aminobutyrate (GABA), modulation of voltage-gated ion channels, inhibition of α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor AMPA (AMPA)/kainite excitatory glutamate receptors, or inhibition of carbonic anhydrase.

Uniqueness of Drug: Qsymia capsules combine immediate-release (IR) phentermine HCl (as the free base) and extended-release (ER) topiramate. The chemical name of phentermine HCl is α,α,-dimethylphenethylamine HCl, and its molecular weight is 185.7 for the hydrochloride salt and 149.2 as free base. The chemical name of topiramate is 2,3:4,5-Di-*O*-isopropylidene-β-D-fructopyranose sulfamate, and its molecular weight is 339.4.

Warnings and Precautions:

Fetal toxicity. Fetal harm has been observed in the first trimester of pregnancy in patients using Qsymia. Women must have a negative pregnancy test before taking this drug and must be tested monthly thereafter.

Elevated heart rate. Qsymia can cause an increase in resting heart rate from baseline of more than 5, 10, 15, and 20 beats/minute. Regular measurements of the resting heart rate are recommended during therapy, especially in patients with cardiac or cerebrovascular disease.

Suicidal behavior and ideation. Topiramate can increase the risk of suicidal thoughts or behavior. If a patient experiences these effects, therapy must be discontinued.

Acute-angle closure glaucoma. In previous treatment with patients, topiramate was reported to cause acute myopia associated with secondary angle-closure glaucoma. Symptoms typically occurred within 1 month of initiating treatment, but they may occur at any time. Elevated intraocular pressure of any cause, if left untreated, can lead to serious adverse events such as permanent loss of vision.

Cognitive impairment. Cognitive dysfunction, such as difficulties with concentration, memory, or speech, has been reported. High initial doses of Qsymia may be associated with higher rates of impaired attention and memory difficulty in thinking of the right word. Caution is necessary for patients who are operating automobiles or hazardous machinery.

Metabolic acidosis. Qsymia has been associated with elevated levels of serum creatinine.

Dosage and Administration: Qsymia capsules are available as phentermine 3.75 mg/topiramate 23 mg; phentermine 7.5 mg/topiramate 46 mg; phentermine 11.25 mg/topiramate 69 mg; and phentermine 15 mg/topiramate 92 mg. The capsules are taken once daily in the morning. Evening doses should be avoided to prevent insomnia.

The recommended dose is 3.75 mg/23 mg daily for 14 days. The dose is then increased to 7.5 mg/46 mg daily. If the patient does not achieve a 3% weight loss after 12 weeks with 7.5 mg/46 mg, therapy may be discontinued or the dose may be escalated. If a 5% weight loss is not achieved after 12 weeks with a maximum daily dose of 15 mg/92 mg, treatment should be discontinued.

The 15-mg/92-mg dose should be gradually discontinued to prevent possible seizures. Patients with moderate or severe renal impairment or moderate hepatic impairment should not take doses exceeding 7.5 mg/46 mg.

Commentary: Qsymia combines a stimulant and an antiseizure medication. After Qsymia was approved, some wondered whether it would be an anti-obesity wonder drug or a potentially dangerous substance likely to be recalled. The history of obesity medications is replete with unsuccessful therapies; Ephedra, Fen-Phen, phenylpropanolamine (e.g., Accutrim, Dexatrim), and sibutramine (Meridia, Abbott) were withdrawn from the market because of cardiovascular toxicity. Rimonabant (Acomplia, Sanofi) was approved for sale in Europe but was not approved in the U.S. because of its severe psychiatric side effects.

The obvious question to be answered is whether Qsymia works. Results from two trials show that after 1 year of treatment with the recommended and highest daily dose, patients had an average weight loss of 6.7% and 8.9%, respectively, compared with those receiving placebo. Approximately 62% and 69% of patients lost at least 5% of their body weight with the recommended dose and highest dose, respectively, compared with about 20% of patients receiving placebo. However, there was a potential risk of birth defects when Qsymia was used by pregnant women. Elevated heart rate and cognitive problems are also concerns.

The FDA initially rejected Qsymia in 2010 but relented after reviewing new data presented by Vivus in 2012. The agency warned that the drug should not be used by pregnant women, patients with glaucoma and an overactive thyroid gland, people taking monoamine oxidase inhibitors for depression, and those allergic to either phentermine or topiramate. Critics have noted that the stimulant in Qsymia (phentermine) was also a component in Fen-Phen, a popular drug in the 1990s that ultimately was discontinued after evidence linked it to heart valve problems.

Sources: www.fda.gov; www.qsymia.com

Ocriplasmin (Jetrea Intravitreal Injection)

Manufacturer: Thrombogenics NV, Leuven, Belgium

Indication: Ocriplasmin is indicated for the treatment of symptomatic vitreomacular adhesion (VMA), a condition that threatens vision.

Drug Class: A proteolytic enzyme, ocriplasmin is a truncated form of human plasmin produced by recombinant DNA technology in a *Pichia pastoris* expression system. The molecular weight of ocriplasmin is 27.2 kilodaltons.

Uniqueness of Drug: Ocriplasmin has proteolytic activity against protein components of the vitreous body and the vitreoretinal interface (e.g., laminin, fibronectin, and collagen), thereby dissolving the protein matrix responsible for the VMA.

Warnings and Precautions:

Ocular effects. Decreases in vision resulting from progression of VMA with traction may occur, and surgical intervention is required. Intraocular inflammation or infection, intraocular hemorrhage, and increased intraocular pressure may occur following an intravitreal injection. Patients should

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