The Pharmacist Activist

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Editorial

The Restrictive and Risky Mail-order Distribution Program for Qsymia Must be Rescinded

The Food and Drug Administration (FDA) has recently approved two products for the management of overweight and obesity. Lorcaserin (Belviq) is a new drug that was approved on June 27, and the other new product (Qsymia) is actually a combination of two older drugs, the appetite suppressant phentermine and the antiepileptic drug topiramate, and was approved on July 17. Both Belviq and Qsymia 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 (obese) or 27 kg/m^2 or greater (overweight) in the presence of at least one weight-related comorbid condition such as hypertension, dyslipidemia, or type 2 diabetes mellitus. The review and approval process for both products was considerably delayed, primarily as a result of concerns about their safety, and some continue to believe that the risks of the products outweigh the benefits and that the FDA should not have approved the products. Indeed, the Indications and Usage section of the package insert for both products includes a section designated "Limitations of Use" that notes that the effect of the products on cardiovascular morbidity and mortality has not been established, and that the safety and effectiveness of the products in combination with other products intended for weight loss have not been established.

Lorcaserin is currently being reviewed by the Drug Enforcement Administration with respect to its probable classification as a controlled substance, and Qsymia is classified in Schedule IV because of its phentermine component. The potential for misuse/abuse, as well as numerous other warnings for each product, warrants caution in the selection of patients for whom the products are prescribed and in the monitoring of treatment.

Qsymia via mail-order

On the website containing information about Qsymia (www.qsymia.com) there is a section designated as the Pharmacy Network. Under the heading, "How patients will obtain the medication," the following statements are included:

> "Qsymia is not yet available, but when it becomes available, it will be distributed only by mail order through certified pharmacies in the Qsymia Home Delivery Network."
>
> "If patients ask you about Qsymia availability, please direct them to Qsymia.com where they can sign up to be notified when Qsymia becomes available."

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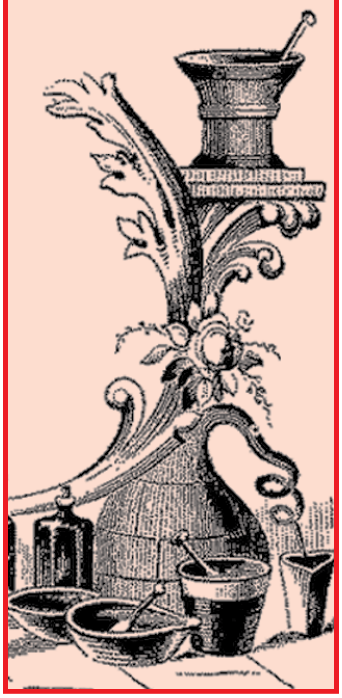

Similar information is also included in the last section (Section 17 – Patient Counseling Information) of the lengthy package insert for Qsymia. The following statements are included:

> "Qsymia is only available through certified pharmacies that are enrolled in the Qsymia certified pharmacy network. Advise patients on how to access Qsymia through certified pharmacies. Additional information may be obtained via the website www.QsymiaREMS.com or by telephone at 1-888-998-4887."

I called the company (Vivus) at the designated number to inquire when the drug would become available and to learn the reasons for which the product would be distributed only by mail order. I learned that the product will be available in the fourth quarter of 2012 but the individual with whom I spoke responded that she did not have information regarding the reasons for the mail-order distribution. She took my contact information so that someone from the company could respond to me (I am still waiting).

The lack of an explanation for restricting the distribution of the product to mail-order pharmacies invites speculation as to the reasons for doing so. Possible reasons that come to mind first pertain to safety considerations relating to use of the product, and marketing/economic reasons from which the company would benefit.

I can think of no safety reasons for which the distribution of Qsymia should be restricted. Both phentermine and topiramate have been available as single agents for decades and pharmacists are well aware of their properties and risks. Pharmacists in local pharmacies are well prepared to assume the responsibilities related to the new combination product and the new use. Indeed, I would contend that the restriction of distribution to mail-order pharmacies *adds risk* to the use of Qsymia. Even if the mail-order distribution includes a telephone conversation between a pharmacist and a patient (which is a rare occurrence in other mail-order prescription programs), there is not the face-to-face communication that often results in the disclosure of additional pertinent information. In addition, the local pharmacist is much more likely than the mail-order pharmacist to know the other prescription and nonprescription medications, herbal products, etc. that the patient is using and that might interact with Qsymia. This is of particular importance in view of the prominent statement in the package insert that the effectiveness and safety of the concurrent use of other products intended for weight loss have not been established. The planned mail-order distribution arrangement also fragments the care for patients, making it more difficult to identify and prevent drug-related and other problems. For example, a patient may be obtaining certain medications at a local pharmacy, be required or incentivized by his prescription plan to obtain medications for chronic conditions from its mail-order pharmacy (a major problem in itself), and have to obtain Qsymia from yet another mail-order pharmacy. And who is to stop other companies from developing their own restricted distribution systems for their drugs?

Because I can't identify any safety reasons that warrant the restricted mail-order distribution system that is planned, I become suspicious that there are marketing/economic reasons that have motivated this plan. Another action that leads me to conclude that marketing/economic strategies are paramount is the strange quantities of topiramate (23 mg, 46 mg, 69 mg, 92 mg) that are included in the Qsymia formulations. Does anyone really think that there will be a difference in weight loss if 46 mg of topiramate is used instead of 50 mg? Or could the quantity of 46 mg have been selected to prevent the use of less expensive generic formulations containing 50 mg of topiramate in combination with generic phentermine?

The FDA role

It is difficult to understand the extent of the FDA's role with respect to the establishment of a restricted distribution system for a medication. It would be inappropriate for the FDA to take or concur with an action that is based on the marketing/economic strategies of a pharmaceutical company. Therefore, the FDA's request for or agreement with a restricted distribution program would be presumably based on reasons related to safety and/or appropriate use of a medication. These reasons have been used to justify restricted distribution of certain specialty pharmaceuticals, the use, preparation, and administration of which require advanced expertise and/or technologies. However, an increasing number of orally-administered medications (e.g., certain anticancer drugs) that do not require advanced expertise with regard to their appropriate use have been approved and supplied in restricted distribution programs. The characteristic of these drugs that results in their designation as "specialty" pharmaceuticals is their very high cost.

In the case of Qsymia, did the FDA have a passive role in agreeing to a mail-order distribution program that was designed by Vivus, or did it have a participatory role in proposing and/or identifying the parameters of the program? If Qsymia is considered safe enough to be used for chronic weight management, it is safe enough to be distributed in local pharmacies! If Qsymia is not considered safe enough to be distributed in local pharmacies, it is not safe enough to be available at all!

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New Drug Review

Ezogabine
(Potiga – GlaxoSmithKline; Valeant)

Antiepileptic Drug

New Drug Comparison Rating (NDCR) = 3

(no or minor advantages/ disadvantages) in a scale of 1 to 5 with 5 being the highest rating

Indication:
Adjunctive treatment of partial-onset seizures in patients aged 18 years and older.

Comparable drugs:
Carbamazepine (e.g., Tegretol), oxcarbazepine (Trileptal), lamotrigine (e.g., Lamictal), levetiracetam (e.g., Keppra).

Advantages:
- Reduced seizure frequency in some patients in whom previous treatment did not provide adequate control;
- Has a unique mechanism of action (stabilizes potassium channels in an "open" position);
- Less likely to cause certain serious adverse events (compared with carbamazepine that has a boxed warning regarding serious dermatologic reactions, aplastic anemia, and agranulocytosis; lamotrigine that has a boxed warning regarding rashes; and oxcarbazepine that may cause serious dermatologic reactions and anaphylaxis/ angioedema);
- Less likely to interact with other drugs (compared with carbamazepine);
- Is in Pregnancy Category C (compared with carbamazepine that is in Category D).

Disadvantages:
- Has not been directly compared with comparable drugs in clinical studies;
- Labeled indication does not include use as monotherapy (compared with carbamazepine, oxcarbazepine, and lamotrigine);
- Labeled indications are more limited (compared with carbamazepine that is also indicated for generalized tonic-clonic seizures, mixed seizure patterns, bipolar disorder, and trigeminal neuralgia; lamotrigine that is also indicated for tonic-clonic seizures, Lennox-Gastaut syndrome, and bipolar disorder; and levetiracetam that is also indicated for tonic-clonic seizures and myoclonic seizures);
- Labeled indication does not include patients less than 18 years of age (compared with levetiracetam that is indicated for use in children as young as 4 years of age; lamotrigine and oxcarbazepine in children as young as 2 years of age; and carbamazepine with which there has been extensive experience in pediatric patients);
- May prolong the QT interval of the electrocardiogram;
- More likely to cause urinary retention;
- Is a controlled substance (Schedule V);
- Is administered three times a day (compared with formulations of levetiracetam [Keppra XR] and lamotrigine [Lamictal XR] that are administered once a day, and oxcarbazepine that is administered twice a day).

Most important risks/adverse events:
Suicidal behavior and ideation (patients, their families, and caregivers should be cautioned about being alert for symptoms of depression, unusual changes in mood or behavior, or the emergence of suicidal thoughts or behavior); neuropsychiatric symptoms (e.g., confusional state, psychotic symptoms, hallucinations); potential for misuse (classified in Schedule V); central nervous system effects (e.g., somnolence, dizziness); prolongation of the QT interval (patients at greatest risk include those with known prolonged QT interval, congestive heart failure, hypokalemia, hypomagnesemia, and those being treated with other medications known to prolong the QT interval [e.g., moxifloxacin, ziprasidone]); urinary retention (some patients required catheterization; urologic symptoms should be monitored, particularly in patients with other risk factors such as those with benign prostatic hyperplasia or who are being treated with anticholinergic agents); withdrawal symptoms (treatment should not be abruptly discontinued); action may be reduced by the concurrent use of carbamazepine or phenytoin; may increase serum digoxin concentrations; action is increased by the consumption of alcoholic beverages; may cause falsely elevated readings for serum and urine bilirubin.

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Recommended actions

Qsymia is not yet available and there is time to rescind the mail-order distribution program and plan for the inclusion of local pharmacies in the distribution system. The following specific actions are recommended:

1. Individual pharmacists should voice their concerns to Vivus, the FDA, and their professional associations.

2. The American Pharmacists Association, National Community Pharmacists Association, and National Association of Chain Drug Stores, preferably working together, should strongly protest the restricted mail-order distribution program to Vivus and FDA, and request that it be rescinded.

3. The FDA should withdraw its approval of any language in the package insert and other product materials that refers to a restricted distribution program.

4. Vivus should abandon its restricted distribution program and plan to distribute Qsymia using the traditional system for supplying prescription medications.

5. Pharmacists should advise patients who wish to lose weight about the nonpharmacologic and nonprescription medication options that will help attain this goal.

Qsymia should not be distributed at all until a plan that will include local pharmacies is ready to be implemented!

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NEWS-Line PUBLISHING

New Drug Review (cont.)

Most common adverse events:

Dizziness (23%), somnolence (22%), fatigue (15%), confusional state (9%), tremor (8%), vertigo (8%), abnormal coordination (7%), diplopia (7%), disturbance in attention (6%), memory impairment (6%), asthenia (5%), blurred vision (5%).

Usual dosage:

Initially, 100 mg three times a day; dosage is increased gradually at weekly intervals by no more than 50 mg three times a day up to a maintenance dosage of 200 mg to 400 mg three times a day; in geriatric patients and in patients with moderate or greater renal or hepatic impairment, the recommended initial dosage is 50 mg three times a day; recommended maximum dosage in geriatric patients and patients with moderate hepatic impairment is 250 mg three times a day; recommended maximum dosage in patients with severe hepatic impairment or moderate or greater renal impairment is 200 mg three times a day; if treatment is to be discontinued, the dosage should be reduced gradually over a period of at least 3 weeks.

Products:

Tablets – 50 mg, 200 mg, 300 mg, 400 mg.

Comments:

Ezogabine is thought to act by reducing brain excitability by stabilizing potassium channels in an "open" position. The results of in vitro studies suggest that it may also reduce the occurrence of seizures through augmentation of GABA-mediated currents. Its effectiveness was demonstratred in three studies in patients with partial-onset seizures with or without secondary generalization and who were not adequately controlled with one to three concomitant antiepileptic drugs. Following baseline evaluations, ezogabine or placebo was added to the regimen and the 28-day seizure frequency was reduced, as compared with placebo, in patients receiving ezogabine in all three studies.

The N-acetyl metabolite of ezogabine (NAMR) exhibits antiepileptic activity but is less potent than the parent compound. This metabolite is a P-glycoprotein inhibitor and may inhibit the renal clearance of digoxin and increase serum digoxin concentrations.

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