U.S. Food and Drug Administration
Protecting and Promoting *Your* Health

Drug Safety Communications

FDA Drug Safety Communication: FDA warns of serious skin reactions with the anti-seizure drug Onfi (clobazam) and has approved label changes

Safety Announcement

[12-3-2013] The U.S. Food and Drug Administration (FDA) is warning the public that the anti-seizure drug Onfi (clobazam) can cause rare but serious skin reactions that can result in permanent harm and death. We have approved changes to the Onfi drug label and the patient Medication Guide to describe the risk of these serious skin reactions. Patients taking Onfi should seek immediate medical treatment if they develop a rash, blistering or peeling of the skin, sores in the mouth, or hives. Health care professionals should discontinue use of Onfi and consider an alternate therapy at the first sign of rash, unless it is clearly not drug-related.

These rare but serious skin reactions, called Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), can occur at any time during Onfi treatment. However, the likelihood of skin reactions is greater during the first 8 weeks of treatment or when Onfi is stopped and then re-started. All cases of SJS and TEN in the FDA case series have resulted in hospitalization, one case resulted in blindness, and one case resulted in death.

Onfi is a benzodiazepine medication used in combination with other medicines to treat seizures associated with a severe form of epilepsy called Lennox-Gastaut Syndrome. Serious skin reactions have not generally been associated with other benzodiazepines.

Patients should not stop taking Onfi without first talking to their health care professionals. Stopping Onfi suddenly can cause serious withdrawal problems, such as seizures that will not stop, hallucinations (hearing or seeing things that are not real), shaking, nervousness, and stomach or muscle cramps.

The Onfi drug label has been revised to add information about the risk for serious skin reactions to the *Warnings and Precautions* section and to the Medication Guide.

Facts about Onfi (clobazam)

- Approved as an adjunctive treatment (to be added to other anti-seizure medicines) for patients 2 years and older with Lennox-Gastaut Syndrome (LGS), a severe form of epilepsy.
- From drug approval in October 2011 through September 2013, approximately 31,000 patients received a dispensed prescription for clobazam from U.S. outpatient retail pharmacies.[1] Based on U.S. sales distribution data, the majority of all clobazam bottles (82% of clobazam sales) were distributed to U.S. outpatient retail pharmacies.[2]

- Has been marketed outside the United States for approximately 40 years under various brand names for the treatment of anxiety and seizures.

Additional Information for Patients and Caregivers

Onfi can cause serious skin reactions. These skin reactions, known as Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), can result in permanent harm and death.

- Patients taking Onfi should seek immediate medical treatment if they develop rashes, blistering or peeling of the skin, sores in the mouth, or hives.
- Onfi should be stopped only under the careful guidance of a health care professional. Stopping Onfi suddenly can cause serious withdrawal problems, such as seizures that will not stop, hallucinations (hearing or seeing things that are not real), shaking, nervousness, and stomach or muscle cramps.
- Talk to your health care professional if you have any questions or concerns about Onfi or other seizure medications.
- Carefully read the patient Medication Guide that comes with the filled prescription.
- Report side effects from Onfi to the FDA MedWatch program, using the information in the Contact FDA box at the bottom of this page.

Additional Information for Health Care Professionals

- Onfi can cause serious skin reactions such as Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN).
- Patients should be closely monitored for signs or symptoms of SJS/TEN, especially during the first 8 weeks of treatment or when re-introducing therapy.
- Patients should be informed about the signs and symptoms of serious skin reactions and told that they should seek immediate medical treatment at the first appearance of a skin rash or any other sign of hypersensitivity.
- Onfi should be discontinued at the first sign of rash, unless the rash is clearly not drug-related. If signs or symptoms suggest a serious skin reaction, use of Onfi should not be resumed and alternative therapy should be considered.
- When assessing patients with potentially drug-induced skin reactions, Onfi should be considered as a possible cause, along with other drugs already known to have such an association. Some other antiepileptic drugs can also cause serious skin reactions, and health care professionals should consider this when changing from one antiepileptic drug to another.
- Health care professionals should encourage patients to read the Medication Guide they receive with every filled prescription.
- Adverse events involving Onfi should be reported to the FDA MedWatch program, using the information in the Contact FDA box at the bottom of this page.

Data Summary

FDA reviewed the FDA Adverse Event Reporting System (FAERS) database, the medical literature, and information submitted by the manufacturer (Lundbeck) of Onfi for evidence of a causal association between Onfi (clobazam) and the serious skin reactions

known as Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN). Because FAERS is a spontaneous and voluntary reporting system for adverse events, the exact incidence of SJS or TEN with Onfi cannot be calculated.

FDA identified 20 cases of SJS/TEN (6 U.S. cases and 14 foreign cases) in FAERS. One additional case of TEN was identified in the literature. Five of the six U.S. cases involved children. All of the cases resulted in hospitalization, with one case resulting in blindness. Two deaths occurred, one of which was deemed possibly related to Onfi. The relation to Onfi could not be assessed in the other death. Nineteen cases reported use of one or more concomitant drugs associated with SJS/TEN, including other antiepileptic drugs (n=18), beta-lactam antibiotics (n=3), or sulfasalazine (n=2). The report of TEN from the medical literature concerned a patient treated with Onfi monotherapy. Although some patients received previous or concomitant therapy with a drug thought to increase the risk of SJS and TEN, the evidence available in many of these cases indicated that Onfi was the likely cause of the serious skin reaction. Patients had been treated with the other suspect medications for prolonged durations without developing SJS/TEN, whereas there was a close temporal relationship (within two months) between initiation of Onfi and development of the serious skin reaction for 14 of the 17 cases that provided specific timing information. Moreover, many of the cases indicated that patients improved after stopping Onfi and, in some instances, after continuing or re-starting the other suspect medications.

In conclusion, FDA has approved an updated drug label for Onfi that includes a *Warnings and Precautions* statement and an addition to the Medication Guide describing the risk of serious skin reactions including SJS and TEN. Patients taking Onfi should seek immediate medical treatment and talk to their health care professional if they develop rashes, blistering or peeling of the skin, mouth sores, or hives. Serious skin reactions can happen at any time during Onfi treatment, but are more likely to happen within the first 8 weeks of treatment or when Onfi is discontinued and then re-started. Onfi should be discontinued at the first sign of rash, unless it is clearly not drug-related. If signs or symptoms suggest a serious skin reaction, use of Onfi should not be resumed and alternative therapy should be considered.

References

1. IMS Vector One: Total Patient Tracker (TPT). October 2011-September 2013. Extracted October 2013.
2. IMS Health National Sales Perspectives. October 2011-September 2013. Extracted October 2013