By Diane S. Aschenbrenner, MS, RN

POSSIBLE HEART FAILURE WITH PRAMIPEXOLE USE

- The Parkinson's disease drug pramipexole (Mirapex) may increase the risk of heart failure.
- The Food and Drug Administration will release more information as data from additional investigation are collected and analyzed.

The Food and Drug Administration (FDA) is investigating the risk of heart failure associated with the use of pramipexole (Mirapex), a drug used with or without levodopa in the treatment of Parkinson's disease. Originally approved for the treatment of restless legs syndrome, pramipexole works by stimulating dopamine receptors. Peripheral edema has always been listed as a possible adverse effect on the drug's label, although it isn't common. The FDA began its review of pramipexole after two epidemiologic studies suggested that the drug increased the risk of heart failure in patients with Parkinson's disease. The FDA notes various methodologic limitations of these studies that make it difficult for the agency to draw conclusions related to the drug's safety. One of the studies, for example, included patients with conditions other than Parkinson's disease; in both studies, review of some patients' medical charts was insufficient to confirm the development of heart failure; in one, too, there were differences in the number of cardiovascular risk factors between patients in the experimental arm and patients in the control arm of the study. One of the studies showed an increased risk of heart failure but only in the first three months of treatment with pramipexole; because heart failure normally develops chronically, this finding is difficult to interpret.

The FDA also evaluated a pooled analysis of randomized clinical trials. Heart failure was more frequent with pramipexole use than with placebo use, but not to a statistically significant extent. As of this writing, the FDA is still investigating and hasn't concluded that pramipexole definitely increases the risk of heart failure. Patients don't need to be withdrawn from therapy at this time. The FDA encourages health care providers to be prudent, following labeling recommendations, educating patients on the risk of heart failure and its symptoms and instructing them to contact the prescriber if they develop any symptoms of fluid overload. Health care providers should contact the FDA MedWatch program at www.fda.gov/Safety/MedWatch if they believe a patient has experienced adverse effects of pramipexole.

NEW MS DRUG APPROVED

- Teriflunomide (Aubagio) has been approved to treat adults with relapsing multiple sclerosis.
- The drug label carries boxed warnings that teriflunomide can produce hepatotoxicity and that its use during pregnancy can cause birth defects.

A new drug is now available to help treat adult patients with relapsing forms of multiple sclerosis. Teriflunomide (Aubagio), a pyrimidine synthesis inhibitor that has antiinflammatory effects, is an oral tablet given once daily. In clinical studies the annual relapse rate was significantly reduced with the use of teriflunomide. Although the exact mechanism of action isn't known, it's believed to be related to a reduction in the number of activated lymphocytes in the central nervous system. Teriflunomide has a long half-life—18 to 19 days—and takes about three months to reach steady state. The drug is eliminated primarily unchanged through the gastrointestinal tract, although some metabolites are also excreted in the urine.

Teriflunomide carries two boxed warnings and several nonboxed warnings on its label. One boxed warning is that teriflunomide can produce severe liver toxicity. The drug is contraindicated in patients with severe hepatic impairment. Baseline transaminase and bilirubin levels should be obtained within the six months before therapy is started, and follow-up measurements should be taken at least monthly for six months. If a drug-induced liver injury is suspected, the drug should be discontinued and an accelerated-elimination procedure started. Options for such a procedure include the administration of the anticholesterol drug cholestyramine, 8 mg every eight hours for 11 days, or the administration of oral activated charcoal powder, 50 g every 12 hours for 11 days.

The second boxed warning is related to teratogenicity. Teriflunomide is a pregnancy category X drug, meaning that in animal studies the drug caused major birth defects when used during pregnancy. The birth defects that occurred in animals receiving teriflunomide included craniofacial and axial and appendicular skeletal defects; embryofetal deaths also occurred. Maternal toxicity from the drug

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wasn't present when these teratogenetic effects occurred. Male-mediated fetal toxicity studies haven't been conducted. The drug is contraindicated in pregnant women, as well as in women of childbearing age unless they're using reliable birth control. Men taking teriflunomide should make sure that they and their partners use reliable contraception.

Teriflunomide is contraindicated in pregnant women.

Other warnings and precautions include elevated risks of hypertension, a decrease in white blood cell count, peripheral neuropathy, acute renal failure and hyperkalemia, and (rarely) a severe skin reaction such as Stevens–Johnson syndrome or toxic epidermal necrolysis. The most common adverse effects of teriflunomide are alopecia, diarrhea, influenza, nausea, paresthesia, and increases in alanine aminotransferase levels.

Nurses who prescribe or work with patients taking teriflunomide should confirm that the baseline liver-function studies (bilirubin and transaminase levels) have been performed and that levels are within normal ranges. Patient education should emphasize the importance of repeated blood work to assess liver function. The signs and symptoms of liver disease (unexplained nausea, vomiting, abdominal pain, fatigue, anorexia, jaundice, or dark urine) should also be explained, as should the importance of reporting them at once to the prescriber. Nurses should confirm that the patient isn't pregnant at the time teriflunomide therapy is begun. They should include information on the importance of continuing effective birth control use while receiving the drug and during the washout period if the drug is discontinued. Breastfeeding should also be avoided. Because patients are at risk for infections secondary to a low white blood cell count, they should be carefully assessed for signs of infection. Patients should be instructed to report fever or other symptoms of infection. Nurses should monitor the patient's blood pressure throughout therapy. Because of the risk of serious adverse effects, all teriflunomide prescriptions come with a medication guide that provides the most current information about the drug's safety and gives guidance to patients on how they can help monitor themselves for serious adverse effects. Nurses should emphasize the importance of reading the entire medication guide each time a prescription is filled.

For the Food and Drug Administration news release regarding teriflunomide, as well as links to other resources, go to http://1.usa.gov/NoROVM.

CHILDREN WITH PULMONARY HYPERTENSION SHOULDN'T RECEIVE REVATIO

- The labeling of the vasodilating drug Revatio (a formulation of sildenafil) has been revised to say that the drug shouldn't be used off label to treat children with pulmonary hypertension.
- Clinical trials in pediatric patients have found that the drug increases the risk of death from pulmonary hypertension when it's taken in large doses.
- It's currently not known whether the risk of death is greater in adults taking Revatio for pulmonary hypertension. The Food and Drug Administration has ordered the manufacturer to conduct clinical trials to answer that question.

Revatio is a formulation of sildenafil, a phosphodiesterase-5 inhibitor that promotes vasodilation. Taken in 20-mg doses three times a day, it improves exercise ability and delays clinical worsening of pulmonary hypertension in adults and is approved for that indication. Clinicians have also used Revatio off label to treat children with pulmonary hypertension, but the Food and Drug Administration (FDA) now recommends against this. The recommendation is based on data from a long-term pediatric clinical trial that found a higher risk of death when a large dose of Revatio was used; the trial also found that there were no signs of improvement in exercise ability when a lower dose was used. A warning and information from the trial will be added to Revatio's label.

Other dosages of this drug (25 mg, 50 mg, and 100 mg) are sold under the trade name Viagra, which is used to treat erectile dysfunction.

The risk of death in adults from long-term use of Revatio isn't currently known. The FDA has now required the drug's manufacturer to evaluate that risk, but adult patients with pulmonary hypertension who are taking Revatio don't need to discontinue the drug. The FDA doesn't believe these safety concerns apply when the drug is used to treat erectile dysfunction because both the dosing regimen and the patient population are different than when the drug is used to treat pulmonary hypertension.

Nurses who prescribe or work with patients taking Revatio should provide education to both patients and families regarding this information from the FDA. To read the *FDA Drug Safety Communication* regarding Revatio, go to http://1.usa.gov/Pvw1Jg. ▼

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