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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 Patients don't need to be withdrawn from therapy at this time.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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