FDA Drug Safety Communication: Ongoing safety review of Parkinson’s drug Mirapex (pramipexole) and possible risk of heart failure

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Safety Announcement

[9-19-2012] The U.S. Food and Drug Administration (FDA) is informing the public about a possible increased risk of heart failure with Mirapex (pramipexole), a drug used to treat Parkinson’s disease and restless legs syndrome. Results of recent studies suggest a potential risk of heart failure that needs further review of available data.

FDA evaluated a pooled analysis of randomized clinical trials and found that heart failure was more frequent with Mirapex than with placebo; however, these results were not statistically significant. FDA also evaluated two epidemiologic studies that suggested an increased risk of new onset of heart failure with Mirapex use. However, study limitations make it difficult to determine whether excess heart failure was related to Mirapex use or other influencing factors (see Data Summary below for a detailed discussion of the studies).

Because of the study limitations, FDA is not able to determine whether Mirapex increases the risk of heart failure. FDA is continuing to work with the manufacturer to clarify further the risk of heart failure with Mirapex and will update the public when more information is available.

Health care professionals should continue to follow the recommendations in the drug label when prescribing Mirapex. Patients should continue to take their Mirapex as directed and should contact their health care professional if they have any questions or concerns.

Additional Information for Patients

- Do not stop taking your Mirapex unless told to do so by your health care professional.
- FDA has not concluded that Mirapex increases the risk of heart failure. The Agency is continuing to review this safety concern and will update the public when more information is available.
- Talk to your health care professional if you have any questions or concerns about Mirapex.
- Contact your health care professional if you experience any symptoms of heart failure while taking Mirapex, such as shortness of breath – with exercise or at rest; swelling of the feet, ankles, legs, or abdomen; fatigue and weakness, rapid or irregular heart beat; chest pain; or persistent cough or wheezing with white or pink blood-tinged phlegm. Patients have reported swelling of the ankles and/or feet without other signs of heart failure while taking Mirapex.
- Report side effects from Mirapex to FDA’s MedWatch program, using the information in the "Contact FDA" box at the bottom of this page.

Additional Information for Health Care Professionals

- FDA has not concluded that Mirapex increases the risk of heart failure. The Agency is continuing to
review this safety concern and will update the public when more information is available.

- Continue to follow the recommendations in the drug label when prescribing Mirapex.
- Discuss the benefits and potential risks of Mirapex with your patients.
- Counsel patients to seek medical attention if they experience symptoms of heart failure while taking Mirapex.
- Report adverse events involving Mirapex to FDA’s MedWatch program using the information in the "Contact FDA" box at the bottom of this page.

Data Summary

A pooled analysis of randomized, placebo-controlled, parallel phase 2 and 3 clinical trials of Mirapex, first submitted by the manufacturer to FDA in 2008 and later updated in 2010, found that the incidence of newly diagnosed heart failure was more frequent in patients taking Mirapex (n=12/4157) than in patients receiving placebo (n=4/2820); however, the difference in incidence was not statistically significant.

To evaluate a possible association of Mirapex with heart failure, the manufacturer sponsored an epidemiologic study using the United Kingdom General Practice Research Database (GPRD). This was a case-control study in a cohort of users of anti-Parkinsonian drugs, aged 40 to 89 years. Seven hundred and eighty-three heart failure cases were matched to 7,454 controls. The results showed that current use of any dopamine agonist, versus no use of a dopamine agonist, was associated with a statistically significant increase in risk for heart failure (risk ratio [RR] = 1.58; 95% confidence interval [CI]: 1.26-1.96). Among the individual dopamine agonists, a statistically significant association was found for Mirapex (RR = 1.86; 95% CI: 1.21-2.85) and cabergoline (RR = 2.07; 95% CI: 1.39-3.07), compared to no use of these specific drugs.

The results of a second epidemiologic study to investigate the risk of heart failure associated with dopamine agonist use was recently published. This second study was a case-control study nested in a cohort of Parkinson’s disease patients who were new users of a dopamine agonist or levodopa. Researchers used data from four population-based European databases. A total of 518 incident heart failure cases were matched to 38,641 controls. Findings of this study did not suggest that current use of ergot dopamine agonists as a class, or current use of non-ergot dopamine agonists as a class, were associated with an increased risk of heart failure when compared to use of levodopa. However, among individual non-ergot dopamine agonists, only current use of Mirapex was associated with an increased risk of heart failure when compared to levodopa (odds ratio [OR] = 1.61; 95% CI: 1.09-2.38). The increased risk for heart failure was present within the first three months of therapy (OR = 3.06; 95% CI: 1.74-5.39) and in patients aged 80 years and older (OR = 3.30; 95% CI: 1.62-7.13); the increased risk for heart failure was not significant in those who used Mirapex longer than three months.

The epidemiologic studies had a number of limitations. In the GPRD study, the primary analysis did not restrict the study population by Parkinson’s disease diagnosis, and all users of anti-Parkinsonian drugs were included (i.e., users of these drugs for Parkinson’s disease, restless legs syndrome, treatment of hyperprolactinemia, and for unidentified reasons), which likely resulted in a more heterogeneous study population. Another important limitation is that there was limited or no validation of the heart failure cases by medical chart review. Both studies had an imbalance in the percentage of patients with cardiovascular risk factors (such as a history of ischemic heart disease, chronic obstructive pulmonary disease, and arrhythmia) that were more frequent in cases than controls. Although both reports included a sensitivity analysis excluding patients with peripheral edema, the presence of peripheral edema may still cause bias in detecting heart failure in both studies. Mirapex is associated with peripheral edema, which may lead to increased testing and detection of heart failure cases. There is also the potential influence of an increasing risk for heart failure with older age (80 years and older) in the general population.

The results from the published Mokhles et al. study, showing an increased risk for heart failure only in the first three months of therapy, are difficult to explain, since heart failure is generally considered to develop chronically.

FDA is continuing to work with the manufacturer to clarify further the risk of heart failure with Mirapex. FDA will update the public when more information is available.

This communication is in keeping with FDA's commitment to inform the public about its ongoing safety review of drugs.

References


**Related Information**

- FDA Drug Safety Podcast: Ongoing safety review of Parkinson’s drug Mirapex (pramipexole) and possible risk of heart failure
- Mirapex (pramipexole) Information
- Comunicado de la FDA sobre la seguridad de los medicamentos: Estudio de seguridad en curso sobre el medicamento Mirapex (pramipexole) para la enfermedad de Parkinson y el posible riesgo de insuficiencia cardíaca

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