

Press Release

FDA approves MIRAPEX for the treatment of moderate-to-severe primary Restless Legs Syndrome

RIDGEFIELD, Conn., Nov. 10, 2006 – Boehringer Ingelheim Pharmaceuticals, Inc. today announced that the U.S. Food and Drug Administration (FDA) has approved Mirapex® (pramipexole dihydrochloride) tablets for the treatment of moderate-to-severe primary Restless Legs Syndrome (RLS).¹ RLS is a common, yet often undiagnosed,² neurological sensorimotor disorder.³ While symptoms can vary from person to person, they are typically described as an urge to move the legs accompanied by burning, creeping, crawling, aching, tingling, or tugging sensations in the legs.⁴ Symptoms begin or worsen during periods of rest or inactivity – for example, when lying down or sitting in a movie – and generally are worse at night.² Up to ten percent of the U.S. adult population is affected by RLS.⁵

“RLS patients may experience daytime tiredness, mood disturbance, and an impaired ability to perform daily activities,” said Professor John W. Winkelman, MD, PhD, Medical Director of the Sleep Health Center of Brigham and Women’s Hospital, Boston, Massachusetts. “Oftentimes sufferers don’t realize that they have an underlying treatable medical condition that is causing these symptoms as well as sleep disturbance. With MIRAPEX, physicians now have another option to help manage their patients’ RLS symptoms.”

For the treatment of RLS, MIRAPEX is approved in varying doses and should be taken once daily 2-3 hours before bedtime.¹ MIRAPEX is also approved to treat the signs and symptoms of idiopathic Parkinson’s disease,¹ and is supported by nearly a decade of real-world experience in the treatment of Parkinson’s disease.⁶

Clinical Trials

The FDA approval was based on safety and efficacy data from four randomized, double-blind, placebo-controlled clinical trials involving approximately 1,000 patients with primary moderate-to-severe RLS who were administered MIRAPEX (0.125mg, 0.25mg, 0.5mg and 0.75mg) or placebo once daily, 2-3 hours before going to bed.¹ In controlled clinical trials, patients were treated with MIRAPEX for periods of three weeks up to nine months.¹ In clinical studies, patients taking MIRAPEX experienced statistically and clinically significant improvements in short- and long-term efficacy versus placebo.¹ In three clinical studies, the mean change from baseline in total International RLS Rating (IRLS) scores for patients treated with MIRAPEX demonstrated a statistically significant greater improvement compared with placebo-treated patients.⁷ In a fourth study, efficacy was sustained with MIRAPEX over a period of nine months, including a six-month open label treatment period followed by a 12-week placebo-controlled withdrawal period.¹

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Highlights from the clinical trials program in support of the approval include:

- In a 12-week study, patients treated with Mirapex® (pramipexole dihydrochloride) tablets reached superiority compared to placebo on both The Clinical Global Impression – Improvement (CGI-I) and the IRLS Scale.¹
 - Total IRLS scores at week 12 demonstrated a statistically significant improvement with MIRAPEX (13.6 point improvement) versus placebo (9.4 point improvement).¹ The IRLS Scale is designed to assess the severity of sensory and motor symptoms, sleep disturbance, daytime somnolence, and impact on activities of daily living and mood associated with RLS.¹
 - The CGI-I rating scale measurements showed statistically significant RLS symptom improvement in patients taking MIRAPEX (72 percent) versus patients taking placebo (51 percent) after 12 weeks of treatment. The CGI-I is designed to assess clinical progress (global improvement).¹
 - Efficacy was demonstrated at even the lowest doses, as 75 percent of patients on 0.25mg of MIRAPEX responded to therapy as measured by the CGI-I.¹
 - In the same 12-week study, the Patient Global Impressions (PGI) scale was also used to rate symptom improvement, and patients reported significantly improved PGI ratings relative to placebo.⁸
- A second study demonstrated the sustained efficacy of MIRAPEX for the treatment of RLS in a nine-month study consisting of a six-month open label treatment period followed by a 12-week placebo-controlled withdrawal period.¹
 - Long-term improvements were demonstrated with MIRAPEX, as at the end of the 12-week withdrawal period, 79 percent of patients who showed improvements on MIRAPEX after six months of treatment had maintained response through nine months versus 15 percent of patients treated with placebo.¹
 - The administration of placebo to patients who had previously responded to MIRAPEX therapy in the six-month open-label treatment period, led to a rapid decline in the patients' overall conditions and return of their RLS symptoms.¹

About Restless Legs Syndrome (RLS)

RLS is a common, yet often undiagnosed², neurological sensorimotor disorder.³ Up to 10 percent of U.S. adults are affected by RLS.⁵ Patients with RLS often experience an urge to move their legs at night due to uncomfortable leg sensations that worsen during periods of rest or inactivity, often interfere with the ability to sleep, and are partially or totally relieved with movement, such as walking or stretching.^{2,9} Additionally, people with RLS will often have difficulty falling asleep.¹⁰ Approximately one-third of sufferers experience symptoms more than twice weekly causing moderate-to-severe distress.¹¹

As a direct result of RLS, patients may experience daytime tiredness, mood disturbance, and an inability to perform daily activities.⁴

Despite many years of research and increased disease recognition, RLS still remains underdiagnosed or misdiagnosed to this day. RLS may be diagnosed with positive answers to the following criteria, which were developed by participants in the RLS Diagnosis & Epidemiology workshop at the National Institutes of Health in collaboration with members of the International Restless Legs Syndrome Study Group (IRLSSG)²:

- Do you have an urge to move your legs, usually accompanied by uncomfortable leg sensations?²
- Do your symptoms begin or worsen during rest or inactivity, such as lying down or sitting?²
- Are your RLS symptoms partially or totally relieved by movement, such as walking or stretching?²
- Are your RLS symptoms worse in the evening or at night, or do they only occur in the evening and at night?²

About Mirapex® (pramipexole dihydrochloride) tablets

In addition to now being approved for RLS, MIRAPEX, a compound from Boehringer Ingelheim research, is also approved for the treatment of the signs and symptoms of idiopathic Parkinson's disease.¹ MIRAPEX is supported by nearly a decade of real-world experience in the treatment of Parkinson's disease,⁶ and approximately 9.1 million prescriptions for MIRAPEX have been written in the U.S. since its launch in 1997.^{12,6}

MIRAPEX may cause patients to fall asleep without any warning, even while doing normal daily activities such as driving.

When taking MIRAPEX hallucinations may occur and sometimes patients may feel dizzy, sweaty or nauseated upon standing up. The most common side effects in clinical trials for RLS were nausea (15% vs. 5% with placebo), headache (16% vs. 15% with placebo), fatigue (9% vs. 7% with placebo) and somnolence (6% vs. 3% with placebo). The most commonly reported adverse events in early and late Parkinson's disease in clinical trials were dizziness, involuntary movement, hallucinations, headache, difficulty falling asleep, sleepiness, and nausea.

Patients and caregivers should be informed that impulse control disorders/compulsive behaviors may occur while taking medicines, including MIRAPEX, to treat Parkinson's disease and RLS.

Boehringer Ingelheim Pharmaceuticals, Inc.

Boehringer Ingelheim Pharmaceuticals, Inc., based in Ridgefield, CT, is the largest U.S. subsidiary of Boehringer Ingelheim Corporation (Ridgefield, CT) and a member of the Boehringer Ingelheim group of companies.

The Boehringer Ingelheim group is one of the world's 20 leading pharmaceutical companies. Headquartered in Ingelheim, Germany, it operates globally with 143 affiliates in 47 countries and approximately 37,500 employees. Since it was founded in 1885, the family-owned company has been committed to researching, developing, manufacturing and marketing novel products of high therapeutic value for human and veterinary medicine.

In 2005, Boehringer Ingelheim posted net sales of US \$11.8 billion (9.5 billion euro) while spending approximately one-fifth of net sales in its largest business segment, Prescription Medicines, on research and development.

For more information, please visit <http://us.boehringer-ingelheim.com>.

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¹ Mirapex® prescribing information (Rev. 11/7/2006)

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³ Abetz L, Allen R, Follet A, et al. Evaluating the quality of life of patients with restless legs syndrome. *Clin Ther* 2004;26:925-935.

⁴ National Heart, Lung and Blood Institute Working Group on Restless Legs Syndrome. Restless legs syndrome: detection and management in primary care. *Am Fam Physician* 2000;62:108-114.

⁵ Hening W, Walters AS, Allen RP, et al. Impact, diagnosis, and treatment of restless legs syndrome (RLS) in a primary care population: the REST (RLS epidemiology, symptoms, and treatment) primary care study. *Sleep Med* 2004;5:237-246.

⁶ Mirapex (PD) FDA Approval Letter (7/1/1997)

⁷ Data on file, Boehringer Ingelheim Pharmaceuticals, Inc.

⁸ Corbin, Ann E.; Sethi, Kapil D.; Kushida, Clete A et al. Pramipexole treatment rapidly improves patient ratings of Restless Legs Syndrome symptoms. Submitted abstract. Associated Professional Sleep Societies Annual Meeting, June 2006.

⁹ Comella CL. Restless legs syndrome: treatment with dopaminergic agents. *Neurology* 2002;58(suppl 1):S87-S92.

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¹¹ Allen RP, Walters AS, Montplaisir J, Hening W, Myers A, Bell TJ, Ferini-Stambi L et al. Restless legs syndrome prevalence and impact: REST general population study. *Arch Intern Med* 2005;165:1286-1292

¹² IMS Data on file, Boehringer Ingelheim Pharmaceuticals, Inc.