

Mirapex® Prolonged-Release Tablets 0.375 mg & 0.75 mg & 1.5 mg

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

Treatment of the signs and symptoms of Parkinson's disease.

2 DOSAGE AND ADMINISTRATION

2.1 General Dosage Considerations

MIRAPEX PR tablets must be swallowed whole and must not be chewed, crushed, or divided.

If a significant interaction in therapy with MIRAPEX PR tablets has occurred, re-titration of therapy may be warranted.

2.2 Dosing for Parkinson's Disease

The starting dose is 0.375 mg once per day. Based on efficacy and tolerability, dosages may be increased gradually, not more frequently than every 5 to 7 days, first to 0.75 mg per day and then by 0.75 mg increasing up to a maximum recommended dose of 4.5 mg per day.

In clinical trials, dosing was initiated at 0.375 mg/day and gradually increased based on individual therapeutic response and tolerability. Doses greater than 4.5 mg/day have not been studied in clinical trials. Patients should be assessed for therapeutic response and tolerability at a minimal interval of 5 days or longer after each dose increase.

Due to the flexible dose design used in clinical trials, specific dose-response information could not be determined.

When discontinuing therapy with MIRAPEX PR, taper the dose gradually over a period of one week (see Warnings and Precautions) in order to study with immediate-release pramipexole tablets, however, abrupt discontinuation was uneventful.

Dosing in Patients with Renal Impairment

The elimination of pramipexole is dependent on renal function [see Clinical Pharmacology (12.3)].

Patients with mild renal impairment (creatinine clearance above 50 mL/min) require no reduction in daily dose.

In patients with moderate renal impairment (creatinine clearance between 30 and 50 mL/min), MIRAPEX PR tablets should be initially taken every other day. Caution should be exercised and careful assessment of therapeutic response and tolerability should be taken before increasing to daily dosing after one week, and before any additional titration to 0.375 mg increments up to 2.25 mg per day. Dose adjustment should occur no more frequently than a weekly interval.

MIRAPEX PR tablets have not been studied in patients with severe renal impairment (creatinine clearance ≤30 mL/min) or patients on hemodialysis, and are not recommended in these patients.

2.3 Switching from Immediate-Release Pramipexole Tablets to MIRAPEX PR

Patients may be switched overnight from immediate-release pramipexole tablets to MIRAPEX PR tablets at the same daily dose. When switching between immediate-release pramipexole tablets and MIRAPEX PR tablets, patients should be monitored to determine if dosage adjustment is necessary.

3 DOSAGE FORMS AND STRENGTHS

0.375mg white to off-white, round, biconvex, bevel-edged, extended-release tablets debossed with "P1" on one side and the Boehringer Ingelheim company symbol on the other side.

0.75mg white to off-white, round, biconvex, bevel-edged, extended-release tablets debossed with "P2" on one side and the Boehringer Ingelheim company symbol on the other side.

1.5mg white to off-white, oval, biconvex, extended-release tablets debossed with "P3" on one side and the Boehringer Ingelheim company symbol on the other side.

4 CONTRAINDICATIONS

Hypersensitivity to pramipexole or any other component of the product.

5 WARNINGS AND PRECAUTIONS

5.1 Falling Awake During Activities of Daily Living

Patients treated with pramipexole have reported falling asleep while engaged in activities of daily living, including the operation of motor vehicles, which sometimes resulted in accidents. Although many of these patients reported somnolence while on pramipexole tablets, some prescribers that they had no warning signs or excessive drowsiness, and believed that they were alert immediately prior to the event. Some of these events had been reported as late as one year after the initiation of treatment. In placebo-controlled clinical trials in Parkinson's disease, the sudden onset of sleep or sleep attacks were reported in 8 of 387 (2%) patients treated with MIRAPEX PR tablets compared to 2 of 281 (1%) patients on placebo.

In early Parkinson's disease, somnolence was reported in 33% of 223 patients treated with MIRAPEX PR, median dose 3.0 mg/day, compared to 15% of 103 patients on placebo. In advanced Parkinson's disease, somnolence was reported in 17% of 164 patients treated with MIRAPEX PR tablets, median dose 3 mg/day, compared to 16% of 178 patients on placebo. Many clinical experts believe that falling asleep while engaged in activities of daily living always occurs in a setting of presomnolence, although patients may not give such a history. For this reason, prescribers should continually reassess patients for drowsiness or sleepiness, especially on some of the events occur after the start of treatment. Prescribers should be aware that patients may not acknowledge drowsiness or sleepiness until directly questioned about drowsiness or sleepiness during specific activities.

When initiating treatment with MIRAPEX PR tablets, advise patients of the potential to develop drowsiness, and specifically ask about factors that may increase the risk such as the use of concomitant sedating medications or alcohol, the presence of sleep disorders, and concomitant medications that increase pramipexole plasma levels (e.g., cimetidine). If a patient develops significant daytime sleepiness or episodes of falling asleep during activities that require active participation (e.g., conversations, eating, etc.), MIRAPEX PR tablets should be discontinued. If a decision is made to continue MIRAPEX PR tablets, advise patients not to drive and to avoid other potentially dangerous activities. While dose reduction reduces the degree of somnolence, there is insufficient information to establish that dose reduction will eliminate episodes of falling asleep while engaged in activities of daily living.

5.2 Symptomatic Orthostatic Hypotension

Dopamine agonists, in clinical studies and clinical experience, appear to impair the systemic regulation of blood pressure, with resulting orthostatic hypotension, especially during dose escalation. Parkinson's disease patients, in addition, appear to have an impaired capacity to respond to an orthostatic challenge. For these reasons, Parkinson's disease patients being treated with dopamine agonists, including MIRAPEX PR, ordinarily require careful monitoring for signs and symptoms of orthostatic hypotension, especially during dose escalation, and should be informed of this risk. In placebo-controlled clinical trials in Parkinson's disease, symptomatic orthostatic hypotension was reported in 10 of 387 (3%) patients treated with MIRAPEX PR tablets compared to 3 of 281 (1%) patients on placebo. One patient of 387 on MIRAPEX PR tablets discontinued treatment due to hypotension.

5.3 Impulse Control/Compulsive Behavior

Case reports and the results of cross-sectional studies suggest that patients can experience intense urges to gamble, increased sexual urges, intense urges to spend money, binge eating, and/or other intense urges, and the inability to control these urges while taking one or more of the medications, including MIRAPEX PR, that increase central dopaminergic tone and that are generally used to treat Parkinson's disease. In some cases, although not rare, these urges were reported to have stopped when the dose was reduced or the medication was discontinued. Such urges may not recognize these behaviors as abnormal. It is important for prescribers to specifically ask patients or their caregivers about the development of new or increased gambling urges, sexual urges, uncontrolled spending or other urges while being treated with MIRAPEX PR. Physicians should consider dose reduction or stopping the medication if a patient develops such urges while taking MIRAPEX PR.

5.4 Hallucinations

In placebo-controlled clinical trials in Parkinson's disease, hallucinations (visual and auditory or mixed) were reported in 25 of 387 (6%) patients treated with MIRAPEX PR tablets compared to 5 of 281 (2%) patients receiving placebo. Hallucinations led to discontinuation of treatment in 5 of 387 (1%) patients on MIRAPEX PR tablets.

Age appears to increase the risk of hallucinations attributable to pramipexole. In placebo-controlled clinical trials in Parkinson's disease, hallucinations were reported in 15 of 162 (9%) patients ≥ 65 years of age taking MIRAPEX PR tablets compared to 10 of 225 (4%) patients < 65 years of age taking MIRAPEX PR tablets.

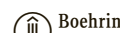
5.5 Dyskinesia

MIRAPEX PR tablets may potentiate the dopaminergic side effects of levodopa and may cause or exacerbate preexisting dyskinesia.

5.6 Renal Impairment

The elimination of pramipexole is dependent on renal function [see Clinical Pharmacology (12.3)].

Patients with mild renal impairment (creatinine clearance above 50 mL/min) require no reduction in daily dose. MIRAPEX PR tablets have not been studied in patients with moderate to severe renal impairment (creatinine clearance ≤50 mL/min) or on hemodialysis.



5.7 Rhabdomyolysis

In the clinical development program for immediate-release pramipexole tablets, a single case of rhabdomyolysis occurred in a 45-year-old male with advanced Parkinson's disease. The patient was hospitalized with an elevated CK (10,631 IU/L). The symptoms improved with discontinuation of the medication in 10 days.

Advise patients to contact a physician if they experience any unexplained muscle pain, tenderness, or weakness. These may be symptoms of rhabdomyolysis.

5.8 Refrill Changes in Alkaline Rat

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