CENTER FOR DRUG EVALUATION AND RESEARCH

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FINAL PRINTED LABELING

Mirapex®

(pramipexole dihydrochloride)

Boehringer Ingelheim

0.125 mg, 0.25 mg, 0.5 mg, 1 mg, and 1.5 mg Tablets

Mirapex® (pramipexole dihydrochloride) Tablets

0819898004

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DESCRIPTION

MIRAPEX® (pramipexole dihydrochloride) Tablets contain pramipexole, a dopamine agonist indicated for the treatment of the signs and symptoms of idiopathic Parkinson's disease. The chemical name of pramipexole dihydrochloride is (S)-2-amino-4,5,6,7-tetrahydro-6-propylamino benzothiazole dihydrochloride monohydrate. Its empirical formula is $C_{10}H_{19}N_3S \cdot 2HCl \cdot H_2O$, and its molecular weight is 302.27. The structural formula is:

Pramipexole dihydrochloride is a white to off-white powder substance. Melting occurs in the range of 296°C to 301°C, with decomposition. Pramipexole dihydrochloride is more than 20% soluble in water, about 8% in methanol, about 0.3% in ethanol, and practically insoluble in dichloromethane.

MIRAPEX Tablets, for oral administration, contain 0.125 mg, 0.25 mg, 0.5 mg, 1.0 mg, or 1.5 mg of pramipexole dihydrochloride monohydrate. Inactive ingredients consist of mannitol, corn starch, colloidal silicon dioxide, povidone, and magnesium stearate.

CLINICAL PHARMACOLOGY

Pramipexole is a nonergot dopamine agonist with high relative in vitro specificity and full intrinsic activity at the D_2 subfamily of dopamine receptors, binding with higher affinity to D_3 than to D_2 or D_1 receptor subtypes. The relevance of D_3 receptor binding in Parkinson's disease is unknown.

The precise mechanism of action of pramipexole as a treatment for Parkinson's disease is unknown, although it is believed to be related to its ability to stimulate dopamine receptors in the striatum. This conclusion is supported by electrophysiologic studies in animals that have demonstrated that pramipexole influences striatal neuronal firing rates via activation of dopamine receptors in the striatum and the substantia nigra, the site of neurons that send projections to the striatum.

Pharmacokinetics

Pramipexole is rapidly absorbed, reaching peak concentrations in approximately 2 hours. The absolute bioavailability of pramipexole is greater than 90%, indicating that it is well absorbed and undergoes little presystemic metabolism. Food does not affect the extent of pramipexole absorption, although the time of maximum plasma concentration (T_{max}) is increased by about 1 hour when the drug is taken with a meal.

Pramipexole is extensively distributed, having a volume of distribution of about 500 L (coefficient of variation (CV)=20%). It is about 15% bound to plasma proteins. Pramipexole distributes less rad blood cells as indicated by an erythrocyte-to-plasma ratio of approximately 2.

Pramipexole displays linear pharmacokinetics over the clinical dosage range. Its terminal half-life is about 8 hours in young healthy volunteers and about 12 hours in elderly volunteers (see CLINICAL PHARMACOLOGY, *Pharmacokinetics in Special Populations*). Steady-state concentrations are achieved within 2 days of dosing.

Metabolism and elimination: Urinary excretion is the major route of pramipexole elimination, with 90% of a pramipexole dose recovered in urine, almost all as unchanged drug. Nonrenal routes may contribute to a small extent to pramipexole elimination. Although no metabolites have been identified in plasma or urine, the renal clearance of pramipexole is approximately 400 mL/min (CV=25%), approximately three times higher than the glomerular filtration rate. Thus, pramipexole is secreted by the renal tubules, probably by the organic cation transport system.

Pharmacokinetics in Special Populations

Because therapy with pramipexole is initiated at a subtherapeutic dosage and gradually titrated upward according to clinical tolerability to obtain the optimum therapeutic effect, adjustment of the initial dose based on gender, weight, or age is not necessary. However, renal insufficiency, which can cause a large decrease in the ability to eliminate pramipexole, may necessitate dosage adjustment (see CLINICAL PHARMACOLOGY, *Renal Insufficiency*).

Gender: Pramipexole clearance is about 30% lower in women than in men, but most of this difference can be accounted for by differences in body weights. There is no difference in half-life between males and females

Age: Pramipexole clearance decreases with age as the half-life and clearance are about 40% longer and 30% lower, respectively, in elderly (aged 65 years or older) compared with young healthy volunteers (aged less than 40 years). This difference is most likely due to the well-known reduction in renal function with age, since pramipexole clearance is correlated with renal function, as measured by creatinine clearance (see CLINICAL PHARMACOLOGY, *Renal Insufficiency*).

Parkinson's disease patients: A cross-study comparison of data suggests that the clearance of pramipexole may be reduced by about 30% in Parkinson's disease patients compared with healthy elderly volunteers. The reason for this difference appears to be reduced renal function in Parkinson's disease patients, which may be related to their poorer general health. The pharmacokinetics of pramipexole were comparable between early and advanced Parkinson's disease patients.

Pediatric: The pharmacokinetics of pramipexole in the pediatric population have not been evaluated.

Hepatic insufficiency: The influence of hepatic insufficiency on pramipexole pharmacokinetics has not been evaluated. Because approximately 90% of the recovered dose is excreted in the urine as unchanged drug, hepatic impairment would not be expected to have a significant effect on pramipexole elimination.

Renal Insufficiency: The clearance of pramipexole was about 75% lower in patients with severe renal impairment (creatinine clearance approximately 20 mL/min) and about 60% lower in patients with moderate impairment (creatinine clearance approximately 40 mL/min) compared with healthy volunteers. A lower starting and maintenance dose is recommended in these patients (see PRECAUTIONS and DOSAGE AND ADMINISTRATION). In patients with varying degrees of renal impairment, pramipexole clearance correlates well with creatinine clearance. Therefore, creatinine clearance can be used as a predictor of the extent of decrease in pramipexole clearance. Pramipexole clearance is extremely low in dialysis patients, as a negligible amount of pramipexole is removed by dialysis. Caution should be exercised when administering pramipexole to patients with renal disease.

CLINICAL STUDIES

The effectiveness of MIRAPEX (pramipexole dihydrochloride) Tablets in the treatment of Parkinson's disease was evaluated in a multinational drug development program consisting of seven randomized, controlled trials. Three were conducted in patients with early Parkinson's disease who were not receiving concomitant levodopa, and four were conducted in patients with advanced Parkinson's disease who were receiving concomitant levodopa. Among these seven studies, three studies provide the most persuasive evidence of pramipexole's effectiveness in the management of patients with Parkinson's disease who were and were not receiving concomitant levodopa. Two of these three trials enrolled patients with early Parkinson's disease (not receiving levodopa), and one enrolled patients with advanced Parkinson's disease who were receiving maximally tolerated doses of levodopa.

In all studies, the Unified Parkinson's Disease Rating Scale (UPDRS), or one or more of its subparts, served as the primary outcome assessment measure. The UPDRS is a four-part multitem rating scale intended to evaluate mentation (part I), activities of daily living (part II), motor performance (part III), and complications of therapy (part IV).

Part II of the UPDRS contains 13 questions relating to activities of daily living (ADL), which are scored from 0 (normal) to 4 (maximal severity) for a maximum (worst) score of 52. Part III of the UPDRS contains 27 questions (for 14 items) and is scored as described for part II. It is designed to assess the severity of the cardinal motor findings in patients with Parkinson's disease (e.g. tremor, rigidity, bradykinesia, postural instability, etc), scored for different body regions, and has a maximum (worst) score of 108.

Studies in Patients With Early Parkinson's Disease

Patients (N=599) in the two studies of early Parkinson's disease had a mean disease duration of 2 years, limited or no prior exposure to levodopa (generally none in the preceding 6 months), and were not experiencing the "on-off" phenomenon and dyskinesia characteristic of later stages of the disease.

One of the two early Parkinson's disease studies (N=335) was a double-blind, placebo-controlled, parallel trial consisting of a 7-week dose-escalation period and a 6-month maintenance period. Patients could be on selegiline, anticholinergics, or both, but could not be on levodopa products or amantadine. Patients were randomized to MIRAPEX or placebo. Patients treated with MIRAPEX had a starting daily dose of 0.375 mg and were titrated to a maximally tolerated dose, but no higher than 4.5 mg/day in three divided doses. At the end of the 6-month maintenance period, the mean improvement from baseline on the UPDRS part II (ADL) total score was 1.9 in the group receiving MIRAPEX and −0.4 in the placebo group, a difference that was statistically significant. A statistically significant difference between groups in favor of MIRAPEX was seen beginning at week 2 of the UPDRS part II (maximum dose 0.75 mg/day) and at week 3 of the UPDRS part III (maximum dose 1.5 mg/day).

The second early Parkinson's disease study (N=246) was a double-blind, placebo-controlled, parallel trial consisting of a 6-week dose-escalation period and a 4-week maintenance period. Patients could be on selegiline, anticholinergics, amantadine, or any combination of these, but could not be on levodopa products. Patients were randomized to 1 of 4 fixed doses of MIRAPEX (1.5 mg, 3.0 mg, 4.5 mg, or 6.0 mg per day) or placebo. At the end of the 14-week maintenance period, the mean improvement from baseline on the UPDRS part II total score was 1.8 in the patients treated with MIRAPEX, regardless of assigned dose group, and 0.3 in placebo-treated patients. The mean improvement from baseline on the UPDRS part III total score was 4.2 in patients treated with MIRAPEX and 0.6 in placebo-treated patients. No dose-response relationship was demonstrated. The between-treatment differences on both parts of the UPDRS were statistically significant in favor of MIRAPEX for all doses.

No differences in effectiveness based on age or gender were detected. There were too few non-Caucasian patients to evaluate the effect of race. Patients receiving selegiline or anticholinergics had responses similar to patients not receiving these drugs.

Studies in Patients With Advanced Parkinson's Disease

In the advanced Parkinson's disease study, the primary assessments were the UPDRS and daily diaries that quantified amounts of "on" and "off" time.

Patients in the advanced Parkinson's disease study (N=360) had a mean disease duration of 9 years, had been exposed to levodopa for long periods of time (mean 8 years), used concomitant levodopa during the trial, and had "on-off" periods.

The advanced Parkinson's disease study was a double-blind, placebo-controlled, parallel trial consisting of a 7-week dose-escalation period and a 6-month maintenance period. Patients were all treated with concomitant levodopa products and could additionally be on concomitant selegiline, anticholinergics, amantadine, or any combination. Patients treated with MIRAPEX had a starting dose of 0.375 mg/day and were titrated to a maximally tolerated dose, but no higher than 4.5 mg/day in three divided doses. At selected times during the 6-month maintenance period, patients were asked to record the amount of "off," "on," or "on with dyskinesia" time per day for several sequential days. At the end of the 6-month maintenance period, the mean improvement from baseline on the UPDRS part II total score was 2.7 in the group treated with MIRAPEX and 0.5 in the placebo group, a difference that was statistically significant. The mean improvement from baseline on the UPDRS part III total score was 5.6 in the group treated with MIRAPEX and 2.8 in the placebo group, a difference that was statistically significant. A statistically significant difference between groups in favor of MIRAPEX was seen at week 3 of the UPDRS part II (maximum dose 1.5 mg/day) and at week 2 of the UPDRS part III (maximum dose 0.75 mg/day). Reduction of concomitant levodopa was allowed during this study if dyskinesia (or hallucinations) developed; levodopa dosage reduction occurred in 76% of patients treated with MIRAPEX versus 54% of placebo patients. On average, the levodopa dose was reduced 27%.

The mean number of "off" hours per day during baseline was 6 hours for both treatment groups. Throughout the trial, patients treated with MIRAPEX had a mean of 4 "off" hours per day, while placebo-treated patients continued to experience 6 "off" hours per day.

No differences in effectiveness based on age or gender were detected. There were too few non-Caucasian patients to evaluate the effect of race.

INDICATIONS AND USAGE

MIRAPEX (pramipexole dihydrochloride) Tablets are indicated for the treatment of the signs and symptoms of idiopathic Parkinson's disease.

The effectiveness of MIRAPEX was demonstrated in randomized, controlled trials in patients with early Parkinson's disease who were not receiving concomitant levodopa therapy as well as in patients with advanced disease on concomitant levodopa (see CLINICAL STUDIES).

CONTRAINDICATIONS

MIRAPEX (pramipexole dihydrochloride) Tablets are contraindicated in patients who have demonstrated hypersensitivity to the drug or its ingredients.

WARNINGS

Falling Asleep During Activities of Daily Living:

Patients treated with MIRAPEX (pramipexole dihydrochloride) 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 MIRAPEX, some perceived that they had no warning signs such as excessive drowsiness, and believed that they were alert immediately prior to the event. Some of these events have been reported as late as one year after the initiation of treatment.

Somnolence is a common occurrence in patients receiving MIRAPEX at doses above 1.5 mg/day. Many clinical experts believe that falling asleep while engaged in activities of daily living always occurs in a setting of pre-existing somnolence, although patients may not give such a history. For this reason, prescribers should continually reassess patients for drowsiness or sleepiness, especially since some of the events occur well after the start of treatment. Prescribers should also be aware that patients may not acknowledge drowsiness or sleepiness until directly questioned about drowsiness or sleepiness during specific activities.

Before initiating treatment with MIRAPEX, patients should be advised of the potential to develop drowsiness and specifically asked about factors that may increase the risk with MIRAPEX such as concomitant sedating medications, the presence of sleep disorders, and concomitant medications that increase pramipexole plasma levels (e.g., cimetidine – see PRECAUTIONS, Drug Interactions). If a patient develops significant daytime sleepiness or episodes of falling asleep during activities that require active participation (e.g., conversations, eating, etc.), MIRAPEX should ordinarily be discontinued. If a decision is made to continue MIRAPEX, patients should be advised to not drive and to avoid other potentially dangerous activities. While dose reduction clearly 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.

Symptomatic 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 dopaminergic agonists ordinarily require careful monitoring for signs and symptoms of orthostatic hypotension, especially during dose escalation, and should be informed of this risk (see PRECAUTIONS, *Information for Patients*).

In clinical trials of pramipexole, however, and despite clear orthostatic effects in normal volunteers, the reported incidence of clinically significant orthostatic hypotension was not greater among those assigned to MIRAPEX Tablets than among those assigned to placebo. This result is clearly unexpected in light of the previous experience with the risks of dopamine agonist therapy.

While this finding could reflect a unique property of pramipexole, it might also be explained by the conditions of the study and the nature of the population enrolled in the clinical trials. Patients were carefully titrated, and patients with active cardiovascular disease or significant orthostatic hypotension at baseline were excluded.

Hallucinations: In the three double-blind, placebo-controlled trials in early Parkinson's disease, hallucinations were observed in 4% (25 of 328) of patients receiving MIRAPEX, compared with 2.0% (6 of 233) of patients receiving placebo. In the four double-blind, placebo-controlled trials in advanced Parkinson's disease, where patients received MIRAPEX and concomitant levodopa, hallucinations were observed in 16.3% (43 of 264) of patients receiving MIRAPEX compared with 3.7% (10 of 264) of patients receiving placebo. Hallucinations were of sufficient severity to cause discontinuation of treatment in 2.1% of the early Parkinson's disease patients and 3.7% of the advanced Parkinson's disease patients compared with about 0.4% of placebo patients in both populations.

Age appears to increase the risk of hallucinations attributable to pramipexole. In the early Parkinson's disease patients, the risk of hallucinations was 1.9 times greater than placebo in patients younger than 65 years and 6.8 times greater than placebo in patients older than 65 years. In the advanced Parkinson's disease patients, the risk of hallucinations was 3.5 times greater than placebo in patients younger than 65 years and 5.2 times greater than placebo in patients older than 65 years.

PRECAUTIONS

Rhabdomyolysis: A single case of rhabdomyolysis occurred in a 49-year-old male with advanced Parkinson's disease treated with MIRAPEX (pramipexole dihydrochloride) Tablets. The patient was hospitalized with an elevated CPK (10,631 IU/L). The symptoms resolved with discontinuation of the medication.

Renal: Since pramipexole is eliminated through the kidneys, caution should be exercised when prescribing MIRAPEX to patients with renal insufficiency (see DOSAGE AND ADMINISTRATION).

Dyskinesia: MIRAPEX may potentiate the dopaminergic side effects of levodopa and may cause or exacerbate preexisting dyskinesia. Decreasing the dose of levodopa may ameliorate this side effect.

Retinal pathology in albino rats: Pathologic changes (degeneration and loss of photoreceptor cells) were observed in the retina of albino rats in the 2-year carcinogenicity study. While retinal degeneration was not diagnosed in pigmented rats treated for 2 years, a thinning in the outer nuclear layer of the retina was slightly greater in rats given drug compared with controls. Evaluation of the retinas of albino mice, monkeys, and minipigs did not reveal similar changes. The potential significance of this effect in humans has not been established, but cannot be disregarded because elimination of a mechanism that is universally present in vertebrates (i.e., disk shedding) may be involved (see ANIMAL TOXICOLOGY).

Events Reported With Dopaminergic Therapy

Although the events enumerated below have not been reported in association with the use of pramipexole in its development program, they are associated with the use of other dopaminergic drugs. The expected incidence of these events, however, is so low that even if pramipexole caused these events at rates similar to those attributable to other dopaminergic therapies, it would be unlikely that even a single case would have occurred in a cohort of the size exposed to pramipexole in studies to date.

Withdrawal-emergent hyperpyrexia and confusion: Although not reported with pramipexole in the clinical development program, a symptom complex resembling the neuroleptic malignant syndrome (characterized by elevated temperature, muscular rigidity, altered consciousness, and autonomic instability), with no other obvious etiology, has been reported in association with rapid dose reduction, withdrawal of, or changes in antiparkinsonian therapy.

Fibrotic complications: Although not reported with pramipexole in the clinical development program, cases of retroperitoneal fibrosis, pulmonary infiltrates, pleural effusion, and pleural thickening have been reported in some patients treated with ergot-derived dopaminergic agents. While these complications may resolve when the drug is discontinued, complete resolution does not always occur.

CYP interactions: Inhibitors of cytochrome P450 enzymes would not be expected to affect pramipexole elimination because pramipexole is not appreciably metabolized by these enzymes in vivo or in vitro. Pramipexole does not inhibit CYP enzymes CYP1A2, CYP2C9, CYP2C19, CYP2E1, and CYP3A4. Inhibition of CYP2D6 was observed with an apparent Ki of 30 μM, indicating that pramipexole will not inhibit CYP enzymes at plasma concentrations observed following the highest recommended clinical dose (1.5 mg tid).

Dopamine antagonists: Since pramipexole is a dopamine agonist, it is possible that dopamine antagonists, such as the neuroleptics (phenothiazines, butyrophenones, thioxanthenes) or metoclopramide, may diminish the effectiveness of MIRAPEX.

Drug/Laboratory Test Interactions: These are no known interactions between MIRAPEX and laboratory tests.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Two-year carcinogenicity studies with pramipexole have been conducted in mice and rats. Pramipexole was administered in the diet to CD-1/NARL mice at doses of 0.3, 2, and 10 mg/kg/day (0.3, 2.2, and 11 times the highest recommended clinical dose [1.5 mg tid] on a mg/m² basis). Pramipexole was administered in the diet to Wistar rats at 0.3, 2, and 8 mg/kg/day (plasma AUCs equal to 0.1, 2.5, and 12.5 times the AUC in humans receiving 1.5 mg tid). No significant increases in tumors occurred in either species.

Pramipexole was not mutagenic or clastogenic in a battery of assays, including the in vitro Ames assay, V79 gene mutation assay for HGPRT mutants, chromosomal aberration assay in Chinese hamster ovary cells, and in vivo mouse micronucleus assay.

In rat fertility studies, pramipexole at a dose of 2.5 mg/kg/day (5.4 times the highest clinical dose on a mg/m² basis), prolonged estrus cycles and inhibited implantation. These effects were associated with reductions in serum levels of prolactin, a hormone necessary for implantation and maintenance of early pregnancy in rats.

Pregnancy: Pregnancy Category C. When pramipexole was given to female rats throughout pregnancy, implantation was inhibited at a dose of 2.5 mg/kg/day (5.4 times the highest clinical dose on a mg/m² basis). Administration of 1.5 mg/kg/day of pramipexole to pregnant rats during the period of organogenesis (gestation days 7 through 16) resulted in a high incidence of total resorption of embryos. The plasma AUC in rats dosed at this level was 4.3 times the AUC in humans receiving 1.5 mg tid. These findings are thought to be due to the prolactin-lowering effect of pramipexole, since prolactin is necessary for implantation and maintenance of early pregnancy in rats (but not rabbits or humans). Because of pregnancy disruption and early embryonic loss in these studies, the teratogenic potential of pramipexole could not be adequately evaluated. There was no evidence of adverse effects on embryo-fetal development following administration of up to 10 mg/kg/day to pregnant rabbits during organogenesis (plasma AUC was 71 times that in humans receiving 1.5 mg tid). Postnatal growth was inhibited in the offspring of rats treated with 0.5 mg/kg/day (approximately equivalent to the highest clinical dose on a mg/m² basis) or greater during the latter part of pregnancy and throughout lactation.

Selegiline: In healthy volunteers (N=11), selegiline did not influence the pharmacokinetics of pramipexole.

Amantadine: Population pharmacokinetic analysis suggests that amantadine is unlikely to alter the oral clearance of pramipexole (N=56).

Cimetidine: Cimetidine, a known inhibitor of renal tubular secretion of organic bases via the cationic transport system, caused a 50% increase in pramipexole AUC and a 40% increase in half-life (N=12).

Probenecid: Probenecid, a known inhibitor of renal tubular secretion of organic acids via the anionic transporter, did not noticeably influence pramipexole pharmacokinetics (N=12).

Other drugs eliminated via renal secretion: Population pharmacokinetic analysis suggests that coadministration of drugs that are secreted by the cationic transport system (e.g., cimetidine, ranitidine, diltiazem, triamterene, verapamil, quinidine, and quinine) decreases the oral clearance of pramipexole by about 20%, while those secreted by the anionic transport system (e.g., cephalosporins, penicillins, trimethoprim, hydrochlorothiazide, and chlorpropamide) are likely to have little effect on the oral clearance of pramipexole.

CYP interactions: Inhibitors of cytochrome P450 enzymes would not be expected to affect pramipexole elimination because pramipexole is not appreciably metabolized by these enzymes in vivo or in vitro. Pramipexole does not inhibit CYP enzymes CYP1A2, CYP2C9, CYP2C19, CYP2E1, and CYP3A4. Inhibition of CYP2D6 was observed with an apparent Ki of 30 μM, indicating that pramipexole will not inhibit CYP enzymes at plasma concentrations observed following the highest recommended clinical dose (1.5 mg tid).

Information for Patients: Patients should be instructed to take MIRAPEX only as prescribed.

Patients should be alerted to the potential sedating effects associated with MIRAPEX, including somnolence and the possibility of falling asleep while engaged in activities of daily living. Since somnolence is a frequent adverse event with potentially serious consequences, patients should be notified that they should not engage in other potentially dangerous activities until they have gained sufficient experience with MIRAPEX to gauge whether or not it affects their mental and/or motor performance adversely. Patients should be advised that if increased somnolence or new episodes of falling asleep during activities of daily living (e.g., watching television, passenger in a car, etc.) are experienced at any time during treatment, they should not drive or participate in potentially dangerous activities until they have contacted their physician. Because of possible additive effects, caution should be advised when patients are taking other sedating medications or alcohol in combination with MIRAPEX and when taking concomitant medications that increase plasma levels of pramipexole (e.g., cimetidine).

Patients should be informed that hallucinations can occur and that the elderly are at a higher risk than younger patients with Parkinson's disease.

Patients may develop postural (orthostatic) hypotension, with or without symptoms such as dizziness, nausea, fainting or blackouts, and sometimes, sweating. Hypotension may occur more frequently during initial therapy. Accordingly, patients should be cautioned against rising rapidly after sitting or lying down, especially if they have been doing so for prolonged periods and especially at the initiation of treatment with MIRAPEX.

Because the teratogenic potential of pramipexole has not been completely established in laboratory animals, and because experience in humans is limited, patients should be advised to notify their physicians if they become pregnant or intend to become pregnant during therapy (see PRECAUTIONS, *Pregnancy*).

Because of the possibility that pramipexole may be excreted in breast milk, patients should be advised to notify their physicians if they intend to breast-feed or are breast-feeding an infant.

If patients develop nausea, they should be advised that taking MIRAPEX with food may reduce the occurrence of nausea.

Laboratory Tests: During the development of MIRAPEX, no systematic abnormalities on routine laboratory testing were noted. Therefore, no specific guidance is offered regarding routine monitoring; the practitioner retains responsibility for determining how best to monitor the patient in his or her care.

Drug Interactions

Carbidopa/levodopa: Carbidopa/levodopa did not influence the pharmacokinetics of pramipexole in healthy volunteers (N=10). Pramipexole did not alter the extent of absorption (AUC) or the elimination of carbidopa/levodopa, although it caused an increase in levodopa C_{max} by about 40% and a decrease in T_{max} from 2.5 to 0.5 hours.

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There are no studies of pramipexole in human pregnancy. Because animal reproduction studies are not always predictive of human response, pramipexole should be used during pregnancy only if the potential benefit outweighs the potential risk to the fetus.

Nursing Mothers: A single-dose, radio-labeled study showed that drug-related materials were excreted into the breast milk of lactating rats. Concentrations of radioactivity in milk were three to six times higher than concentrations in plasma at equivalent time points.

Other studies have shown that pramipexole treatment resulted in an inhibition of prolactin secretion in humans and rats.

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from pramipexole, a decision should be made as to whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use: The safety and efficacy of MIRAPEX® in pediatric patients has not been established.

Geriatric Use: Pramipexole total oral clearance was approximately 30% lower in subjects older than 65 years compared with younger subjects, because of a decline in pramipexole renal clearance due to an age-related reduction in renal function. This resulted in an increase in elimination half-life from approximately 8.5 hours to 12 hours. In clinical studies, 38.7% of patients were older than 65 years. There were no apparent differences in efficacy or safety between older and younger patients, except that the relative risk of hallucination associated with the use of MIRAPEX was increased in the elderly.

ADVERSE EVENTS

During the premarketing development of pramipexole, patients with either early or advanced Parkinson's disease were enrolled in clinical trials. Apart from the severity and duration of their disease, the two populations differed in their use of concomitant levodopa therapy. Patients with early disease did not receive concomitant levodopa therapy during treatment with pramipexole; those with advanced Parkinson's disease all received concomitant levodopa treatment. Because these two populations may have differential risks for various adverse events, this section will, in general, present adverse-event data for these two populations separately.

Because the controlled trials performed during premarketing development all used a titration design, with a resultant confounding of time and dose, it was impossible to adequately evaluate the effects of dose on the incidence of adverse events.

Early Parkinson's Disease

In the three double-blind, placebo-controlled trials of patients with early Parkinson's disease, the most commonly observed adverse events (≥5%) that were numerically more frequent in the group treated with MIRAPEX (pramipexole dihydrochloride) Tablets were nausea, dizziness, somnolence, insomnia, constipation, asthenia, and hallucinations.

Approximately 12% of 388 patients with early Parkinson's disease and treated with MIRAPEX were participated in the double-blind, placebo-controlled trials discontinued treatment due to adverse events compared with 11% of 230 patients who received placebo. The adverse events most commonly causing discontinuation of treatment were related to the nervous system (hallucinations [3.1% on MIRAPEX vs 0.4% on placebo]; dizziness [2.1% on MIRAPEX vs 1% on placebo]; somnolence [1.6% on MIRAPEX vs 0% on placebo]; extrapyramidal syndrome [1.6% on MIRAPEX vs 0.4% on placebo]; headache and confusion [1.3% and 1.0%, respectively, on MIRAPEX vs 0% on placebo]); and gastrointestinal system disorders (2.1% on MIRAPEX vs 0.4% on placebo).

Adverse-event Incidence in controlled clinical studies in early Parkinson's disease: Table 1 lists treatment-emergent adverse events that occurred in the double-blind, placebo-controlled studies in early Parkinson's disease that were reported by ≥1% of patients treated with MIRAPEX and were numerically more frequent than in the placebo group. In these studies, patients did not receive concomitant levodopa. Adverse events were usually mild or moderate in intensity.

The prescriber should be aware that these figures cannot be used to predict the incidence of adverse events in the course of usual medical practice where patient characteristics and other factors differ from those that prevailed in the clinical studies. Similarly, the cited frequencies cannot be compared with figures obtained from other clinical investigations involving different treatments, uses, and investigators. However, the cited figures do provide the prescribing physician with some basis for estimating the relative contribution of drug and nondrug factors to the adverse-events incidence rate in the population studied.

Table 1: Treatment-Emergent Adverse-Event* Incidence in Double-Blind, Placebo-Controlled Trials in Early Parkinson's Disease (Events ≥5% of Patients Treated With MIRAPEX and Numerically More Frequent Than in the Placebo Group)

Body System/ Adverse Event	MIRAPEX N=388	Placebo N=235
Body as a Whole		
Asthenia	14	12
General edema	5	3
Malaise	2	1
Reaction unevaluable	2	1
Fever	1	0
Digestive System		
Nausea	26	18
Constipation	14	6
Anorexia	4	2
Dysphagia	2	0
Metabolic & Nutritional System		
Peripheral edema	5	4
Decreased weight	2	0
Nervous System		
Dizziness	25	24
Somnolence	22	9
Insomnia	17	12
Hallucinations	9	3
Confusion	4	1
Amnesia	4	2
Hypesthesia	3	1
Dystonia	2	1
Akathisia	2	0
Thinking abnormalities	2	0
Decreased libido	1	0
Abnormal dreams	1	0
Special Senses		
Vision abnormalities	3	0
Urogenital System		
Impotence	2	1

* Patients may have reported multiple adverse experiences during the study or at discontinuation; thus, patients may be included in more than one category.

Other events reported by 1% or more of patients with early Parkinson's disease and treated with MIRAPEX but reported equally or more frequently in the placebo group were infection, accidental injury, headache, pain, tremor, back pain, syncope, postural hypotension, hyperkinesia, depression, abdominal pain, anxiety, dyspepsia, flatulence, diarrhea, rash, ataxia, dry mouth, extrapyramidal syndrome, leg cramps, twitching, pharyngitis, sinusitis, sweating, rhinitis, urinary tract infection, vasodilation, flu syndrome, increased saliva, tooth disease, dyspnea, increased cough, gait abnormalities, urinary frequency, vomiting, allergic reaction, hypertension, pruritis, hypokinesia, increased creatine PK, nervousness, dream abnormalities, chest pain, neck pain, paresthesia, tachycardia, vertigo, voice alteration, conjunctivitis, paralysis, accommodation abnormalities, tinnitus, diplopia, and taste perversions.

In a fixed-dose study in early Parkinson's disease, occurrence of the following events increased in frequency as the dose increased over the range from 1.5 mg/day to 6 mg/day: postural hypotension, nausea, constipation, somnolence, and amnesia. The frequency of these events was generally 2-fold greater than placebo for pramipexole doses greater than 3 mg/day. The incidence of somnolence with pramipexole at a dose of 1.5 mg/day was comparable to that reported for placebo.

Advanced Parkinson's Disease

In the four double-blind, placebo-controlled trials of patients with advanced Parkinson's disease, the most commonly observed adverse events (≥5%) that were numerically more frequent in the group treated with MIRAPEX and concomitant levodopa were postural (orthostatic) hypotension, dyskinesia, extrapyramidal syndrome, insomnia, dizziness, hallucinations, accidental injury, dream abnormalities, confusion, constipation, asthenia, somnolence, dystonia, gait abnormality, hypertonia, dry mouth, amnesia, and urinary frequency.

Approximately 12% of 260 patients with advanced Parkinson's disease who received MIRAPEX and concomitant levodopa in the double-blind, placebo-controlled trials discontinued treatment due to adverse events compared with 16% of 264 patients who received placebo and concomitant levodopa. The events most commonly causing discontinuation of treatment were related to the nervous system (hallucinations [2.7% on MIRAPEX vs 0.4% on placebo]; dyskinesia [1.9% on MIRAPEX vs 0.8% on placebo]; extrapyramidal syndrome [1.5% on MIRAPEX vs 0% on placebo]; dizziness [1.2% on MIRAPEX vs 1.5% on placebo]; confusion [1.2% on MIRAPEX vs 2.3% on placebo]; and cardiovascular system (postural hypotonic) hypotension [2.3% on MIRAPEX vs 1.1% on placebo]).

Adverse-event Incidence in controlled clinical studies in advanced Parkinson's disease: Table 2 lists treatment-emergent adverse events that occurred in the double-blind, placebo-controlled studies in advanced Parkinson's disease that were reported by ≥1% of patients treated with MIRAPEX and were numerically more frequent than in the placebo group. In these studies, MIRAPEX or placebo was administered to patients who were also receiving concomitant levodopa. Adverse events were usually mild or moderate in intensity.

The prescriber should be aware that these figures cannot be used to predict the incidence of adverse events in the course of usual medical practice where patient characteristics and other factors differ from those that prevailed in the clinical studies. Similarly, the cited frequencies cannot be compared with figures obtained from other clinical investigations involving different treatments, uses, and investigators. However, the cited figures do provide the prescribing physician with some basis for estimating the relative contribution of drug and nondrug factors to the adverse-events incidence rate in the population studied.

Table 2: Treatment-Emergent Adverse-Event* Incidence in Double-Blind, Placebo-Controlled Trials in Advanced Parkinson's Disease (Events ≥ 1% of Patients Treated With MIRAPEX and Numerically More Frequent Than in the Placebo Group)

Body System/ Adverse Event	MIRAPEX (pramipexole dihydrochloride)† N=260	Placebo† N=264
Body as a Whole		
Accidental injury	17	15
Asthenia	10	8
General edema	4	3
Chest pain	3	2
Malaise	3	2
Cardiovascular System		
Postural hypotension	11	6
Digestive System		
Constipation	10	9
Dry mouth	7	3
Metabolic & Nutritional System		
Peripheral edema	2	1
Increased creatine PK	1	0
Musculoskeletal System		
Arthritis	3	1
Twitching	2	0
Bursitis	2	0
Myasthenia	1	0
Nervous System		
Dyskinesia	47	31
Extrapyramidal syndrome	28	26
Insomnia	27	22
Dizziness	26	25
Hallucinations	17	4
Dream abnormalities	11	10
Confusion	10	7
Somnolence	9	6
Dystonia	8	7
Gait abnormalities	7	5
Hypertonia	7	6
Amnesia	6	4
Akathisia	3	2
Thinking abnormalities	3	2
Paranoid reaction	2	0
Delusions	1	0
Sleep disorders	1	0
Respiratory System		
Dyspnea	4	3
Rhinitis	3	1
Pneumonia	2	0
Skin & Appendages		
Skin disorders	2	1
Special Senses		
Accommodation abnormalities	4	2
Vision abnormalities	3	1
Diplopia	1	0
Urogenital System		
Urinary frequency	6	3
Urinary tract infection	4	3
Urinary incontinence	2	1

* Patients may have reported multiple adverse experiences during the study or at discontinuation; thus, patients may be included in more than one category.

† Patients received concomitant levodopa.

Other events reported by 1% or more of patients with advanced Parkinson's disease and treated with MIRAPEX but reported equally or more frequently in the placebo group were nausea, pain, infection, headache, depression, tremor, hypokinesia, anorexia, back pain, dyspepsia, flatulence, ataxia, flu syndrome, thinking abnormalities, diarrhea, rhinitis, abdominal pain, anxiety, rash, paresthesia, hypertension, increased saliva, tooth disease, vomiting, hypotension, sweating, vasodilation, vomiting, increased cough, nervousness, pruritus, hypokinesia, neck pain, syncope, arthralgia, dyspraxia, palpitations, pharyngitis, vertigo, leg cramps, conjunctivitis, and lacrimation disorders.

Adverse Events; Relationship to Age, Gender, and Race: Among the treatment-emergent adverse events in patients treated with MIRAPEX, hallucination appeared to exhibit a positive relationship to age. No gender-related differences were observed. Only a small percentage (6%) of patients enrolled were non-Caucasian, therefore, an evaluation of adverse events related to race is not possible.

Other Adverse Events Observed During All Phase 2 and 3 Clinical Trials: MIRAPEX has been administered to 1,468 individuals during all clinical trials (Parkinson's disease and other patient populations), 668 of whom were in seven double-blind, placebo-controlled Parkinson's disease trials. During these trials, all adverse events were recorded by the clinical investigators using terminology of their own choosing. To provide a meaningful estimate of the proportion of individuals having adverse events, similar types of events were grouped into a smaller number of standardized categories using modified COSTART dictionary terminology. These categories are used in the listing below. The events listed below occurred in less than 1% of the 1,468 individuals exposed to MIRAPEX and occurred on at least two occasions (on one occasion if the event was serious). All reported events, except those already listed above, are included, without regard to determination of a causal relationship to MIRAPEX.

Events are listed within body-system categories in order of decreasing frequency.

Body as a whole: enlarged abdomen, death, fever, suicide attempt.
Cardiovascular system: peripheral vascular disease, myocardial infarction, angina pectoris, atrial fibrillation, heart failure, arrhythmia, atrial arrhythmia, pulmonary embolism.
Digestive system: thirst.
Musculoskeletal system: joint disorder, myasthenia.
Nervous system: agitation, CNS stimulation, hypokinesia, psychosis, convulsions.
Respiratory system: pneumonia.
Special senses: cataract, eye disorder, glaucoma.
Urogenital system: dysuria, abnormal ejaculation, prostate cancer, hematuria, prostate disorder.

Falling Asleep During Activities of Daily Living: Patients treated with MIRAPEX have reported falling asleep while engaged in activities of daily living, including operation of a motor vehicle which sometimes resulted in accidents (see Boxed WARNING).

Post-Marketing Experience: In addition to the adverse events reported during clinical trials, the following adverse reactions have been identified during post-approval use of MIRAPEX Tablets. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. Decisions to include these reactions in labeling are typically based on one or more of the following factors: (1) seriousness of the reaction, (2) frequency of reporting, or (3) strength of causal connection to MIRAPEX Tablets. Similar types of events were grouped into a smaller number of standardized categories using the *MedDRA Dictionary*: accidents (including fall), compulsive behaviors (including sexual and pathological gambling), fatigue, hallucinations (all kind), headache, hypotension (including postural hypotension), libido disorders, syncope, and blackouts.

DRUG ABUSE AND DEPENDENCE

Pramipexole is not a controlled substance. Pramipexole has not been systematically studied in animals or humans for its potential for abuse, tolerance, or physical dependence. However, in a rat model on cocaine self-administration, pramipexole had little or no effect.

OVERDOSAGE

There is no clinical experience with massive overdosage. One patient, with a 10-year history of schizophrenia, took 11 mg/day of pramipexole for 2 days; this is two to three times the maximal recommended daily dose. No adverse events were reported related to the increased dose. Blood pressure remained stable although pulse rate increased to between 100 and 120 beats/minute. The patient withdrew from the study at the end of week 2 due to lack of efficacy.

There is no known antidote for overdosage of a dopamine agonist. If signs of central nervous system stimulation are present, a phenothiazine or other butyrophenone neuroleptic agent may be indicated; the efficacy of such drugs in reversing the effects of overdosage has not been assessed. Management of overdose may require general supportive measures along with gastric lavage, intravenous fluids, and electrocardiogram monitoring.

DOSAGE AND ADMINISTRATION

In 18 clinical studies, dosage was initiated at a subtherapeutic level to avoid intolerable adverse effects and orthostatic hypotension. MIRAPEX (pramipexole dihydrochloride) Tablets should be titrated gradually in all patients. The dosage should be increased to achieve a maximum therapeutic effect, balanced against the principal side effects of dyskinesia, hallucinations, somnolence, and dry mouth.

Dosing in Patients With Normal Renal Function

Initial Treatment: Dosages should be increased gradually from a starting dose of 0.375 mg/day given in three divided doses and should not be increased more frequently than every 5 to 7 days. A suggested ascending dosage schedule that was used in clinical studies is shown in the following table:

Table 3: Ascending Dosage Schedule of MIRAPEX

Week	Dosage (mg)	Total Daily Dose (mg)
1	0.125 tid	0.375
2	0.25 tid	0.75
3	0.5 tid	1.50
4	0.75 tid	2.25
5	1.0 tid	3.0
6	1.25 tid	3.75
7	1.5 tid	4.50

Maintenance Treatment: MIRAPEX Tablets were effective and well tolerated over a dosage range of 1.5 to 4.5 mg/day administered in equally divided doses three times per day with or without concomitant levodopa (approximately 800 mg/day).

In a fixed-dose study in early Parkinson's disease patients, doses of 3 mg, 4.5 mg, and 6 mg per day of MIRAPEX were not shown to provide any significant benefit beyond that achieved at a daily dose of 1.5 mg/day. However, in the same fixed-dose study, the following adverse events were dose related: postural hypotension, nausea, constipation, somnolence, and amnesia. The frequency of these events was generally 2-fold greater than placebo for pramipexole doses greater than 3 mg/day. The incidence of somnolence reported with pramipexole at a dose of 1.5 mg/day was comparable to placebo.

When MIRAPEX is used in combination with levodopa, a reduction of the levodopa dosage should be considered. In a controlled study in advanced Parkinson's disease, the dosage of levodopa was reduced by an average of 27% from baseline.

Table 4: Patients with Renal Impairment Pramipexole Dosage in the Renally Impaired

Renal Status	Starting Dose (tid)	Maximum Dose (mg)
Normal to mild impairment (creatinine Cl = 60 mL/min)	0.125 tid	1.5 tid
Moderate impairment (creatinine Cl = 35 to 59 mL/min)	0.125 bid	1.5 tid
Severe impairment (creatinine Cl = 15 to 34 mL/min)	0.125 qd	1.5 qd
Very severe impairment (creatinine Cl = 15 mL/min and hemodialysis patients)	The use of MIRAPEX (pramipexole dihydrochloride) has not been adequately studied in this group of patients.	

Discontinuation of Treatment: It is recommended that MIRAPEX be discontinued over a period of 1 week; in some studies, however, abrupt discontinuation was uneventful.

HOW SUPPLIED

MIRAPEX (pramipexole dihydrochloride) Tablets are available as follows:

0.125 mg: white, round tablet with "U" on one side and "Z" on the reverse side.
Bottles of 63 NDC 0597-0083-53
0.25 mg: white, oval, scored tablet with "U" twice on one side and "A" twice on the reverse side.
Bottles of 90 NDC 0597-0084-90
Unit dose packages of 100 NDC 0597-0084-61
0.5 mg: white, oval, scored tablet with "U" twice on one side and "B" twice on the reverse side.
Bottles of 90 NDC 0597-0085-90
Unit dose packages of 100 NDC 0597-0085-61
1 mg: white, round, scored tablet with "U" twice on one side and "G" twice on the reverse side.
Bottles of 90 NDC 0597-0090-90
Unit dose packages of 100 NDC 0597-0090-61
1.5 mg: white, round, scored tablet with "U" twice on one side and "J" twice on the reverse side.
Bottles of 90 NDC 0597-0091-90
Unit dose packages of 100 NDC 0597-0091-61

Store at 25°C (77°F); excursions permitted to 15°-30°C (59°-86°F) [see USP Controlled Room Temperature]. Protect from light.

Store in a safe place out of the reach of children.

℞ only

ANIMAL TOXICOLOGY

Retinal Pathology in Albino Rats

Pathologic changes (degeneration and loss of photoreceptor cells) were observed in the retina of albino rats in the 2-year carcinogenicity study with pramipexole. These findings were first observed during week 16 and were dose dependent in animals receiving 2 or 8 mg/kg/day (plasma AUCs equal to 2.5 and 12.5 times the AUC in humans that received 1.5 mg tid). In a similar study of pigmented rats with 2 years exposure to pramipexole at 2 or 8 mg/kg/day retinal degeneration was not diagnosed. Animals given drug had thinning in the outer nuclear layer of the retina that was only slightly greater than that seen in control rats utilizing morphometry.

Investigative studies demonstrated that pramipexole reduced the rate of dark shedding from the photoreceptor rod cells of the retina in albino rats, which was associated with enhanced sensitivity to the damaging effects of light. In a comparative study, degeneration and loss of photoreceptor cells occurred in albino rats after 13 weeks of treatment with 25 mg/kg/day of pramipexole (56 times the highest clinical dose on a mg/m² basis) and constant light (100 lux) but not in pigmented rats exposed to the same dose and higher light intensities (500 lux). Thus, the retina of albino rats is considered to be uniquely sensitive to the damaging effects of pramipexole and light. Similar changes in the retina did not occur in a 2-year carcinogenicity study in albino mice treated with 0.3, 2, or 10 mg/kg/day (0.1, 2.2 and 11 times the highest clinical dose on a mg/m² basis). Evaluation of the retinas of monkeys given 0.1, 0.5, or 2.0 mg/kg/day of pramipexole (0.6, 2.2, and 8.6 times the highest clinical dose on a mg/m² basis) for 12 months and minipigs given 0.3, 1, or 5 mg/kg/day of pramipexole for 13 weeks also detected no changes.

The potential significance of this effect in humans has not been established, but cannot be discounted because disruption of a mechanism that is universally present in vertebrates (i.e., disk shedding) may be involved.

Fibro-osseous Proliferative Lesions in Mice

An increased incidence of fibro-osseous proliferative lesions occurred in the femurs of female mice treated for 2 years with 0.3, 2.0, or 10 mg/kg/day (0.1, 2.2, and 11 times the highest clinical dose on a mg/m² basis). Lesions occurred at a lower rate in control animals. Similar lesions were not observed in male mice or rats and monkeys of either sex that were treated chronically with pramipexole. The significance of this lesion to humans is not known.

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ATTACHMENT A

14 page(s) of draft labeling has been removed from this portion of the review.