

PRAMIPEXOLE DIHYDROCHLORIDE - pramipexole dihydrochloride tablet
STAT RX USA LLC

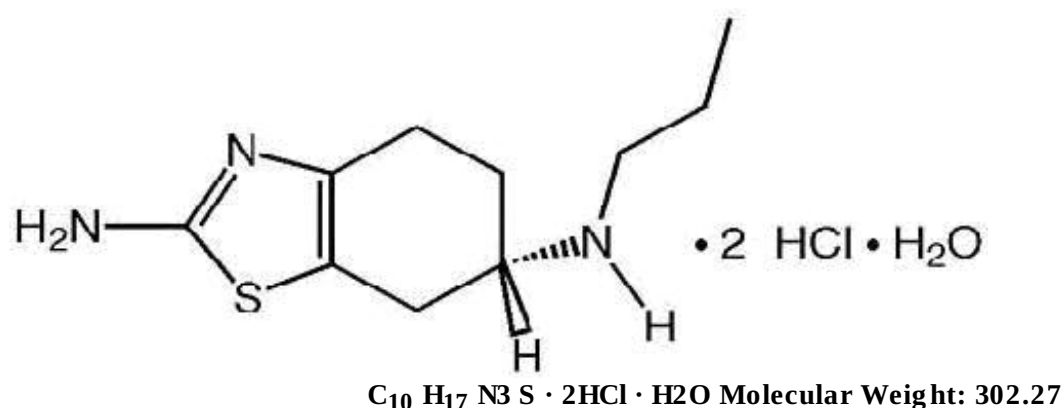
PRAMIPEXOLE DIHYDROCHLORIDE 0.125 mg, 0.25 mg, 0.5 mg, 1 mg, and 1.5 mg Tablets

PRESCRIBING INFORMATION

DESCRIPTION

Pramipexole dihydrochloride tablets contain pramipexole, a nonergot dopamine agonist. The chemical name of pramipexole dihydrochloride is (S)-2-amino-4,5,6,7-tetrahydro-6-(propylamino) benzothiazole dihydrochloride monohydrate.

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 0.5% in ethanol, and practically insoluble in dichloromethane.

Pramipexole dihydrochloride tablets, for oral administration, contain 0.125 mg, 0.25 mg, 0.5 mg, 1 mg, or 1.5 mg of pramipexole dihydrochloride monohydrate. Inactive ingredients consist of corn starch, hydrogenated vegetable oil, mannitol, povidone and pregelatinized corn starch.

CLINICAL PHARMACOLOGY

Mechanism of Action

Pramipexole is a nonergot dopamine agonist with high relative *in vitro* specificity and full intrinsic activity at the D₂ subfamily of dopamine receptors, binding with higher affinity to D₃ than to D₂ or D₄ receptor subtypes.

Parkinson's Disease: 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. The relevance of D₃ receptor binding in Parkinson's disease is unknown.

Pharmacokinetics

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.

Absorption

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.

Distribution

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 into red blood cells as indicated by an erythrocyte to plasma ratio of approximately two.

Metabolism and Elimination

The terminal half-life of pramipexole is about 8 hours in healthy volunteers and 12 hours in elderly volunteers.

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 dihydrochloride tablets is initiated at a low dose 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 weight. 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. Also, it took longer to achieve steady-state. A lower starting and/or maintenance dose may be appropriate 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

Parkinson's Disease

The effectiveness of 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 multi-item rating scale intended to evaluate mentation (part I), Activities of Daily Living (ADL) (part II), motor performance (part III), and complications of therapy (part IV).

Part II of the UPDRS contains 13 questions relating to 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 pramipexole dihydrochloride tablets or placebo. Patients treated with pramipexole dihydrochloride tablets 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 pramipexole dihydrochloride tablets and -0.4 in the placebo group, a difference that was statistically significant. The mean improvement from baseline on the UPDRS part III total score was 5.0 in the group receiving pramipexole dihydrochloride tablets and -0.8 in the placebo group, a difference that was also statistically significant. A statistically significant difference between groups in favor of pramipexole dihydrochloride tablets 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=264) 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 pramipexole dihydrochloride tablets (1.5 mg, 3 mg, 4.5 mg, or 6 mg per day) or placebo. At the end of the 4-week maintenance period, the mean improvement from baseline on the UPDRS part II total score was 1.8 in the patients treated with pramipexole dihydrochloride tablets, 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 pramipexole dihydrochloride tablets 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 pramipexole dihydrochloride tablets 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 pramipexole dihydrochloride tablets 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 pramipexole dihydrochloride tablets 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 pramipexole dihydrochloride tablets and 2.8 in the placebo group, a difference that was statistically significant. A statistically significant difference between groups in favor of pramipexole dihydrochloride tablets 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). Dosage reduction of levodopa was allowed during this study if dyskinesia (or hallucinations) developed; levodopa dosage reduction occurred in 76% of patients treated with pramipexole dihydrochloride tablets 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 pramipexole dihydrochloride 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

Parkinson's Disease

Pramipexole dihydrochloride tablets are indicated for the treatment of the signs and symptoms of idiopathic Parkinson's disease.

The effectiveness of pramipexole dihydrochloride tablets 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

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 pramipexole dihydrochloride tablets 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 dihydrochloride tablets, 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 had been reported as late as one year after the initiation of treatment.

Somnolence is a common occurrence in patients receiving pramipexole dihydrochloride tablets at doses above 1.5 mg/day (0.5 mg TID) for Parkinson's disease. Many clinical experts believe that falling asleep while engaged in activities of daily living always occurs in a setting of preexisting 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 pramipexole dihydrochloride tablets, patients should be advised of the potential to develop drowsiness and specifically asked about factors that may increase the risk with pramipexole dihydrochloride tablets 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.), pramipexole dihydrochloride tablets should ordinarily be discontinued. If a decision is made to continue pramipexole dihydrochloride tablets, 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, both 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 (also see Patient Package Insert)).

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 pramipexole dihydrochloride tablets than among those assigned to placebo. This result, especially with the higher doses used in Parkinson's disease, 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 very 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 9% (35 of 388) of patients receiving pramipexole dihydrochloride tablets, compared with 2.6% (6 of 235) of patients receiving placebo. In the four double-blind, placebo-controlled trials in advanced Parkinson's disease, where patients received pramipexole dihydrochloride tablets and concomitant levodopa, hallucinations were observed in 16.5% (43 of 260) of patients receiving pramipexole dihydrochloride tablets compared with 3.8% (10 of 264) of patients receiving placebo. Hallucinations were of sufficient severity to cause discontinuation of treatment in 3.1% of the early Parkinson's disease patients and 2.7% 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 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 pramipexole dihydrochloride tablets to patients with renal insufficiency (see DOSAGE AND ADMINISTRATION).

Dyskinesia

Pramipexole dihydrochloride tablets 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 disruption 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 may not have 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, pericarditis, and cardiac valvulopathy 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.

Although these adverse events are believed to be related to the ergoline structure of these compounds, whether other, nonergot derived dopamine agonists can cause them is unknown.

A small number of reports have been received of possible fibrotic complications, including peritoneal fibrosis, pleural fibrosis, and pulmonary fibrosis in the postmarketing experience for pramipexole. While the evidence is not sufficient to establish a causal relationship between pramipexole and these fibrotic complications, a contribution of pramipexole cannot be completely ruled out in rare cases.

Melanoma

Epidemiological studies have shown that patients with Parkinson's disease have a higher risk (2- to approximately 6-fold higher) of developing melanoma than the general population. Whether the increased risk observed was due to Parkinson's disease or other factors, such as drugs used to treat Parkinson's disease, is unclear.

For the reasons stated above, patients and providers are advised to monitor for melanomas frequently and on a regular basis when using pramipexole dihydrochloride tablets for *any* indication. Ideally, periodic skin examinations should be performed by appropriately qualified individuals (e.g., dermatologists).

Information for Patients (also see Patient Package Insert)

Patients should be instructed to take pramipexole dihydrochloride tablets only as prescribed.

Patients should be alerted to the potential sedating effects associated with pramipexole dihydrochloride tablets, 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 neither drive a car nor engage in other potentially dangerous activities until they have gained sufficient experience with pramipexole dihydrochloride tablets 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 pramipexole dihydrochloride tablets 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.

There have been reports of patients experiencing intense urges to gamble, increased sexual urges, and other intense urges and the inability to control these urges while taking one or more of the medications that increase central dopaminergic tone, that are generally used for the treatment of Parkinson's disease, including pramipexole dihydrochloride. Although it is not proven that the medications caused these events, these urges were reported to have stopped in some cases when the dose was reduced or the medication was stopped. Prescribers should ask patients about the development of new or increased gambling urges, sexual urges or other urges while being treated with pramipexole dihydrochloride. Patients should inform their physician if they experience new or increased gambling urges, increased sexual urges or other intense urges while taking pramipexole dihydrochloride. Physicians should consider dose reduction or stopping the medication if a patient develops such urges while taking pramipexole dihydrochloride.

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 pramipexole dihydrochloride tablets.

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 pramipexole with food may reduce the occurrence of nausea.

Laboratory Tests

During the development of pramipexole dihydrochloride tablets, 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.

Selegiline

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

Amantadine

Population pharmacokinetic analysis suggest that amantadine may slightly decrease the oral clearance of pramipexole.

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, indomethacin, 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 K_i of 30 μ M, indicating that pramipexole will not inhibit CYP enzymes at plasma concentrations observed following the clinical dose of 4.5 mg/day (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 pramipexole dihydrochloride tablets.

Drug/Laboratory Test Interactions

There are no known interactions between pramipexole dihydrochloride tablets 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 Chbb:NMRI mice at doses of 0.3, 2, and

10 mg/kg/day [0.3, 2.2, and 11 times the maximum recommended human dose [MRHD of 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 were 0.3, 2.5, and 12.5 times the AUC in humans at the MRHD). 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 times the MRHD 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

Teratogenic Effects

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 times the maximum recommended human dose (MRHD) 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 at this dose was 4 times the AUC in humans at the MRHD. 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 at the MRHD). Postnatal growth was inhibited in the offspring of rats treated with 0.5 mg/kg/day (approximately equivalent to the MRHD on a mg/m² basis) or greater during the latter part of pregnancy and throughout lactation.

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 pramipexole dihydrochloride tablets 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 with Parkinson's disease patients, 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 pramipexole dihydrochloride tablets was increased in the elderly.

ADVERSE REACTIONS

Parkinson's Disease

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 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 pramipexole dihydrochloride tablets who participated in the double-blind, placebo-controlled trials discontinued treatment due to adverse events compared with 11% of 235 patients who received placebo. The adverse events most commonly causing discontinuation of treatment were related to the nervous system (hallucinations [3.1% on pramipexole dihydrochloride tablets vs. 0.4% on placebo]; dizziness [2.1% on pramipexole dihydrochloride tablets vs. 1% on placebo]; somnolence [1.6% on pramipexole dihydrochloride tablets vs. 0% on placebo]; extrapyramidal syndrome [1.6% on pramipexole dihydrochloride tablets vs. 6.4% on placebo]; headache and confusion [1.3% and 1.0%, respectively, on pramipexole dihydrochloride tablets vs. 0% on placebo]); and gastrointestinal system (nausea [2.1% on pramipexole dihydrochloride tablets 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 $\geq 1\%$ of patients treated with pramipexole dihydrochloride tablets 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-event 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 $\geq 1\%$ of Patients Treated With Pramipexole Dihydrochloride Tablets and Numerically More Frequent Than in the Placebo Group)

Body System/Adverse Event	Pramipexole dihydrochloride 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	28	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
Myoclonus	1	0
Special Senses		
Vision abnormalities	3	0
Urogenital System		
Impotence	2	1

Other events reported by 1% or more of patients with early Parkinson's disease and treated with pramipexole dihydrochloride tablets but reported equally or more frequently in the placebo group were infection, accidental injury, headache, pain, tremor, back pain, syncope, postural hypotension, hypertonia, 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 pramipexole dihydrochloride tablets 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 pramipexole dihydrochloride tablets 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 pramipexole dihydrochloride tablets vs 0.4% on placebo]; dyskinesia [1.9% on pramipexole dihydrochloride tablets vs 0.8% on placebo]; extrapyramidal syndrome [1.5% on pramipexole dihydrochloride tablets vs 4.9% on placebo]; dizziness [1.2% on pramipexole dihydrochloride tablets vs 1.5% on placebo]; confusion [1.2% on pramipexole dihydrochloride tablets vs 2.3% on placebo]); and cardiovascular system (postural [orthostatic] hypotension [2.3% on pramipexole dihydrochloride tablets 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 $\geq 1\%$ of patients treated with pramipexole dihydrochloride tablets and were numerically more frequent than in the placebo group. In these studies, pramipexole dihydrochloride tablets 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 $\geq 1\%$ of Patients Treated with Pramipexole Dihydrochloride Tablets and Numerically More Frequent Than in the Placebo Group)

Body System/ Adverse Event	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	53	48
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 received concomitant levodopa.

Other events reported by 1% or more of patients with advanced Parkinson's disease and treated with pramipexole dihydrochloride tablets 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, sinusitis, diarrhea, myalgia, abdominal pain, anxiety, rash, paresthesia, hypertension, increased saliva, tooth disorder, apathy, hypotension, sweating, vasodilation, vomiting, increased cough, nervousness, pruritus, hypesthesia, neck pain, syncope, arthralgia, dysphagia, palpitations, pharyngitis, vertigo, leg cramps, conjunctivitis, and lacrimation disorders.

General

Adverse Events; Relationship to Age, Gender, and Race

Among the treatment-emergent adverse events in patients treated with pramipexole dihydrochloride tablets, hallucination appeared to exhibit a positive relationship to age in patients with Parkinson's disease. Although no gender-related differences were observed in Parkinson's disease patients. Less than 4% of patients enrolled were noncaucasian, therefore, an evaluation of adverse events related to race is not possible.

Other Adverse Events Observed During All Phase 2 and 3 Clinical Trials

Pramipexole dihydrochloride tablets have been administered to 1,620 Parkinson's disease patients in Phase 2 and 3 clinical trials. During these trials, all adverse events were recorded by the clinical investigators using terminology of their own choosing; similar types of events were grouped into a smaller number of standardized categories using MedDRA dictionary terminology. These categories are used in the listing below. Adverse events which are not listed above but occurred on at least two occasions (one occasion if the event was serious) in the 2,509 individuals exposed to pramipexole dihydrochloride tablets are listed below. The reported events below are included without regard to determination of a causal relationship to pramipexole dihydrochloride tablets.

Blood and lymphatic system disorders

anemia, iron deficiency anemia, leukocytosis, leukopenia, lymphadenitis, lymphadenopathy, thrombocythaemia, thrombocytopenia

Cardiac disorders

angina pectoris, arrhythmia supraventricular, atrial fibrillation, atrioventricular block first degree, atrioventricular block second degree, bradycardia, bundle branch block, cardiac arrest, cardiac failure, cardiac failure congestive, cardiomegaly, coronary artery occlusion, cyanosis, extrasystoles, left ventricular failure, myocardial infarction, nodal arrhythmia, sinus arrhythmia, sinus bradycardia, sinus tachycardia, supraventricular extrasystoles, supraventricular tachycardia, tachycardia, ventricular fibrillation, ventricular extrasystoles, ventricular hypertrophy

Congenital, familial and genetic disorders

atrial septal defect, congenital foot malformation, spine malformation

Ear and labyrinth disorders

deafness, ear pain, hearing impaired, hypoacusis, motion sickness, vestibular ataxia

Endocrine disorders

goiter, hyperthyroidism, hypothyroidism

Eye disorders

amaurosis fugax, blepharitis, blepharospasm, cataract, dacryostenosis acquired, dry eye, eye hemorrhage, eye irritation, eye pain, eyelid edema, eyelid ptosis, glaucoma, keratitis, macular degeneration, myopia, photophobia, retinal detachment, retinal vascular disorder, scotoma, vision blurred, visual acuity reduced, vitreous floaters

Gastrointestinal disorders

abdominal discomfort, abdominal distension, aphthous stomatitis, ascites, cheilitis, colitis, colitis ulcerative, duodenal ulcer, duodenal ulcer hemorrhage, enteritis, eructation, fecal incontinence, gastric ulcer, gastric ulcer hemorrhage, gastritis, gastrointestinal hemorrhage, gastroesophageal reflux disease, gingivitis, haematemesis, haematochezia, hemorrhoids, hiatus hernia, hyperchlorhydria, ileus, inguinal hernia, intestinal obstruction, irritable bowel syndrome, esophageal spasm, esophageal stenosis, esophagitis, pancreatitis, periodontitis, rectal hemorrhage, reflux esophagitis, tongue edema, tongue ulceration, toothache, umbilical hernia

General disorders

chest discomfort, chills, death, drug withdrawal syndrome, face edema, feeling cold, feeling hot, feeling jittery, gait disturbance, impaired healing, influenza-like illness, irritability, localized edema, edema, pitting edema, thirst

Hepatobiliary disorders

biliary colic, cholecystitis, cholecystitis chronic, cholelithiasis

Immune system disorders

drug hypersensitivity

Infections and infestations

abscess, acute tonsillitis, appendicitis, bronchiolitis, bronchitis, bronchopneumonia, cellulitis, cystitis, dental caries, diverticulitis, ear infection, eye infection, folliculitis, fungal infection, furuncle, gangrene, gastroenteritis, gingival infection, herpes simplex, herpes zoster, hordeolum, intervertebral discitis, laryngitis, lobar pneumonia, nail infection, onychomycosis, oral candidiasis, orchitis, osteomyelitis, otitis externa, otitis media, paronychia, pyelonephritis, pyoderma, sepsis, skin infection, tonsillitis, tooth abscess, tooth infection, upper respiratory tract infection, urethritis, vaginal candidiasis, vaginal infection, viral infection, wound infection

Injury, poisoning and procedural complications

accidental falls, drug toxicity epicondylitis, road traffic accident, sunburn, tendon rupture

Metabolism and nutrition disorders

cachexia, decreased appetite, dehydration, diabetes mellitus, fluid retention, gout, hypercholesterolemia, hyperglycemia, hyperlipidemia, hyperuricemia, hypocalcemia, hypoglycemia, hypokalemia, hyponatremia, hypovitaminosis, increased appetite, metabolic alkalosis

Musculoskeletal and connective tissue disorders

bone pain, fasciitis, flank pain, intervertebral disc disorder, intervertebral disc protrusion, joint effusion, joint stiffness, joint swelling, monoarthritis, muscle rigidity, muscle spasms, musculoskeletal stiffness, myopathy, myositis, nuchal rigidity, osteoarthritis, osteonecrosis, osteoporosis, polymyalgia, rheumatoid arthritis, shoulder pain, spinal osteoarthritis, tendonitis, tenosynovitis

Neoplasms benign, malignant and unspecified

abdominal neoplasm, adenocarcinoma, adenoma benign, basal cell carcinoma, bladder cancer, breast cancer, breast neoplasm, chronic lymphocytic leukemia, colon cancer, colorectal cancer, endometrial cancer, gallbladder cancer, gastric cancer, gastrointestinal neoplasm, hemangioma, hepatic neoplasm, hepatic neoplasm malignant, lip and/or oral cavity cancer, lung neoplasm malignant, lung cancer metastatic, lymphoma, malignant melanoma, melanocytic naevus, metastases to lung, multiple myeloma, oral neoplasm benign, neoplasm, neoplasm malignant, neoplasm prostate, neoplasm skin, neuroma, ovarian cancer, prostate cancer, prostatic adenoma, pseudo lymphoma, renal neoplasm, skin cancer, skin papilloma, squamous cell carcinoma, thyroid neoplasm, uterine leiomyoma

Nervous system disorders

ageusia, akinesia, anticholinergic syndrome, aphasia, balance disorder, brain edema, carotid artery occlusion, carpal tunnel syndrome, cerebral artery embolism, cerebral hemorrhage, cerebral infarction, cerebral ischemia, chorea, cognitive disorder, coma, convulsion, coordination abnormal, dementia, depressed level of consciousness, disturbance in attention, dizziness postural, dysarthria, dysgraphia, facial palsy, grand mal convulsion, hemiplegia, hyperaesthesia, hyperkinesia, hyperreflexia, hyporeflexia, hypotonia, lethargy, loss of consciousness, memory impairment, migraine, muscle contractions involuntary, narcolepsy, neuralgia, neuropathy, nystagmus, parosmia, psychomotor hyperactivity, sciatica, sedation, sensory disturbance, sleep phase rhythm disturbance, sleep talking, stupor, syncope vasovagal, tension headache

Psychiatric disorders

affect lability, aggression, agitation, bradyphrenia, bruxism, suicide, delirium, delusional disorder persecutory type, disorientation, dissociation, emotional distress, euphoric mood, hallucination auditory, hallucination visual, initial insomnia, libido increased, mania, middle insomnia, mood altered, nightmare, obsessive thoughts, obsessive-compulsive disorder, panic reaction, parasomnia, personality disorder, psychotic disorder, restlessness, sleep walking, suicidal ideation

Renal and urinary disorders

chromaturia, dysuria, glycosuria, hematuria, urgency, nephrolithiasis, neurogenic bladder, nocturia, oliguria, pollaciuria, proteinuria, renal artery stenosis, renal colic, renal cyst, renal failure, renal impairment, urinary retention

Reproductive system and breast disorders

amenorrhea, breast pain, dysmenorrhea, epididymitis, gynaecomastia, menopausal symptoms, menorrhagia, metrorrhagia, ovarian cyst, priapism, prostatitis, sexual dysfunction, uterine hemorrhage, vaginal discharge, vaginal hemorrhage

Respiratory, thoracic and mediastinal disorders

apnea, aspiration, asthma, choking, chronic obstructive pulmonary disease, dry throat, dysphonia, dyspnea exertional, epistaxis, haemoptysis, hiccups, hyperventilation, increased bronchial secretion, laryngospasm, nasal dryness, nasal polyps, obstructive airways disorder, pharyngolaryngeal pain, pleurisy, pneumonia aspiration, pneumothorax, postnasal drip, productive cough, pulmonary embolism, pulmonary edema, respiratory alkalosis, respiratory distress, respiratory failure, respiratory tract congestion, rhinitis allergic, rhinorrhea, sinus congestion, sleep apnoea syndrome, sneezing, snoring, tachypnea, wheezing

Skin and subcutaneous tissue disorders

acne, alopecia, cold sweat, dermal cyst, dermatitis, dermatitis bullous, dermatitis contact, dry skin, ecchymosis, eczema, erythema, hyperkeratosis, livedo reticularis, night sweats, periorbital edema, petechiae, photosensitivity allergic reaction, psoriasis, purpura, rash erythematous, rash maculo-

papular, rash papular, rosacea, seborrhea, seborrheic dermatitis, skin burning sensation, skin discoloration, skin exfoliation, skin hyperpigmentation, skin hypertrophy, skin irritation, skin nodule, skin odor abnormal, skin ulcer, urticaria

Vascular disorders

aneurysm, angiopathy, arteriosclerosis, circulatory collapse, deep vein thrombosis, embolism, hematoma, hot flush, hypertensive crisis, lymphoedema, pallor, phlebitis, Raynaud's phenomenon, shock, thrombophlebitis, thrombosis, varicose vein

Falling Asleep During Activities of Daily Living

Patients treated with pramipexole dihydrochloride tablets have reported falling asleep while engaged in activities of daily living, including operation of a motor vehicle which sometimes resulted in accidents (see bolded 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 pramipexole dihydrochloride tablets, primarily in Parkinson's disease patients. 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 pramipexole tablets. Similar types of events were grouped into a smaller number of standardized categories using the MedDRA dictionary: abnormal behavior, abnormal dreams, accidents (including fall), blackouts, fatigue, hallucinations (all kinds), headache, hypotension (including postural hypotension), increased eating (including binge eating, compulsive eating, and hyperphagia), libido disorders (including increased and decreased libido, and hypersexuality), pathological gambling, syncope, and weight increase.

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 in a clinical trial to evaluate the effect of pramipexole in schizophrenic patients. 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

Parkinson's Disease

In all clinical studies, dosage was initiated at a subtherapeutic level to avoid intolerable adverse effects

and orthostatic hypotension. 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 Pramipexole Dihydrochloride Tablets for Parkinson's Disease

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 tid	3
6	1.25 tid	3.75
7	1.5 tid	4.50

Maintenance Treatment

Pramipexole dihydrochloride 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 pramipexole dihydrochloride tablets 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 pramipexole dihydrochloride tablets are 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.

Dosing in Patients With Renal Impairment

Table 4: Pramipexole Dosage in Parkinson's Disease Patients With Renal Impairment

Renal Status	Starting Dose (mg)	Maximum Dose (mg)
Normal to mild impairment (creatinine Cl > 60 mL/min)	0.125 tid	1.5 tid
Moderate impairment	0.125 bid	1.5 bid

(creatinine Cl = 35 to 59 mL/min)		
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 pramipexole dihydrochloride tablets has not been adequately studied in this group of patients.	

Discontinuation of Treatment

It is recommended that pramipexole dihydrochloride tablets be discontinued over a period of 1 week; in some studies, however, abrupt discontinuation was uneventful.

HOW SUPPLIED

Pramipexole Dihydrochloride tablets are available as follows:

0.125 mg: White, round unscored tablet. Debossed with stylized b on one side and C2 on the other side. Available in bottles of:

63 Tablets	NDC 0555-0617- 62
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0.25 mg: White, oval tablet scored on both sides. Debossed with stylized b on one side and C|3 on the other side.

Available in bottles of:

90 Tablets	NDC 0555-0612- 14
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0.5 mg: White, oval tablet scored on both sides. Debossed with stylized b on one side and C|4 on the other side.

Available in bottles of:

90 Tablets	NDC 0555-0613- 14
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1 mg: White, round tablet scored on both sides. Debossed with stylized b on one side and C|5 on the other side.

Available in bottles of:

90 Tablets	NDC 0555-0614- 14
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1.5 mg: White, round tablet scored on both sides. Debossed with stylized b on one side and C|6 on the other side.

Available in bottles of:

KEEP THIS AND ALL MEDICATIONS OUT OF THE REACH OF CHILDREN.

Dispense in a tight, light-resistant container as defined in the USP, with a child-resistant closure (as required).

Store at 20° to 25°C (68° to 77°F) [See USP Controlled Room Temperature].

Protect from light.

PHARMACIST: PLEASE DISPENSE WITH ATTACHED PATIENT INFORMATION LEAFLET

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 76 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 disk 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 (54 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 (0.3, 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 mg/kg/day of pramipexole (0.4, 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 disregarded because disruption of a mechanism that is universally present in vertebrates (ie, 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, or 10 mg/kg/day (0.3, 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.

Manufactured By:
BARR LABORATORIES, INC.
Pomona, NY 10970

Manufactured For:
TEVA PHARMACEUTICALS USA

PATIENT INFORMATION ABOUT PRAMIPEXOLE DIHYDROCHLORIDE TABLETS

Read the Patient Information that comes with pramipexole before you start taking it and each time you get a refill. There may be some new information. This leaflet does not take the place of talking with your doctor about your medical condition or your treatment.

What is the most important information I should know about pramipexole?

Pramipexole may cause you to fall asleep while you are doing daily activities such as driving, talking with other people, watching TV, or eating.

- Some people taking pramipexole have had car accidents because they fell asleep while driving.
- Some patients did not feel sleepy before they fell asleep while driving. You could fall asleep without any warning.

Do not drive a car, operate a machine, or do anything that needs you to be alert until you know how pramipexole affects you.

Tell your doctor right away if you fall asleep while you are doing activities such as talking with people, watching TV, eating, or driving, or if you feel sleepier than is normal for you.

What is pramipexole?

Pramipexole is a prescription medicine to treat

- signs and symptoms of Parkinson's disease.

Pramipexole has not been studied in children.

Who should not take pramipexole?

Do not take pramipexole if you are allergic to pramipexole or any of the inactive ingredients of pramipexole. See the end of this leaflet for a complete list of ingredients in pramipexole.

What should I tell my doctor before taking pramipexole?

Tell your doctor about all of your medical conditions, including if you

- feel sleepy during the day from a sleep problem.
- have low blood pressure, or if you feel dizzy or faint, especially when getting up from a lying or sitting position.
- have trouble controlling your muscles (dyskinesia).
- have kidney problems.
- are pregnant or plan to become pregnant. It is not known if pramipexole will harm your unborn baby.
- are breast-feeding. It is not known if pramipexole will pass into your breast milk. You and your doctor should decide if you will take pramipexole or breast-feed. You should not do both.
- drink alcohol. Alcohol can increase the chance that pramipexole will make you feel sleepy or fall asleep when you should be awake.

Tell your doctor about all the medicines you take, including prescription and non-prescription medicines, vitamins, and herbal supplements. Especially tell your doctor if you take any other medicines that make you sleepy. Pramipexole and other medicines may interact with each other causing side effects. Pramipexole may affect the way other medicines work, and other medicines may affect how pramipexole works.

How should I take pramipexole?

- Take pramipexole exactly as your doctor tells you to. Your doctor will tell you how many pramipexole tablets to take and when to take them.
- Your doctor may change your dose until you are taking the right amount of medicine to control your

symptoms. Do not take more or less pramipexole than your doctor tells you to.

- Pramipexole can be taken with or without food. Taking pramipexole with food may lower your chances of getting nausea.
- If you miss a dose, **do not double your next dose**. Skip the dose you missed and take your next regular dose.
- Be sure to tell your doctor right away if you stop taking pramipexole for any reason. Do not start taking pramipexole again before speaking with your doctor. If you have Parkinson's disease and are stopping pramipexole, you should stop pramipexole slowly over 7 days.

What should I avoid while taking pramipexole?

- **Do not drive a car, operate a machine, or do anything that needs you to be alert until you know how pramipexole affects you.** See "What is the most important information I should know about pramipexole?" at the beginning of this leaflet.
- Do not drink alcohol while taking pramipexole. It can increase your chances of feeling sleepy or falling asleep when you should be awake.

What are the possible side effects of pramipexole?

Pramipexole can cause serious side effects, including

- **falling asleep during normal daily activities.** See "What is the most important information I should know about pramipexole?"
- **low blood pressure when you sit or stand up quickly.** You may have dizziness, nausea, fainting, or sweating. Sit and stand up slowly after you have been sitting or lying down for awhile.
- **hallucinations.** You may see, hear, feel, or taste something that isn't there. You have a higher chance of having hallucinations if you are over 65 years old.

The most common side effects in people taking pramipexole for Parkinson's disease are nausea, dizziness, sleepiness, constipation, hallucinations, insomnia, muscle weakness, confusion, and abnormal movements.

These are not all the possible side effects of pramipexole. For more information ask your doctor or pharmacist.

Be sure to talk to your doctor about any side effects that bother you or that do not go away.

Other Information about pramipexole

Studies of people with Parkinson's disease show that they may be at an increased risk of developing melanoma, a form of skin cancer, when compared to people without Parkinson's disease. It is not known if this problem is associated with Parkinson's disease or the medicines used to treat Parkinson's disease. Pramipexole is one of the medicines used to treat Parkinson's disease, therefore, patients being treated with pramipexole should have periodic skin examinations.

There have been reports of patients taking certain medicines to treat Parkinson's disease, including pramipexole, that have reported problems with gambling, compulsive eating, and increased sex drive. It is not possible to reliably estimate how often these behaviors occur or to determine which factors may contribute to them. If you or your family members notice that you are developing unusual behaviors, talk to your doctor.

How should I store pramipexole?

- Store at 20° to 25° C (68° to 77° F) [See USP Controlled Room Temperature].
- Protect from light.
- **Keep pramipexole and all medicines out of the reach of children.**

General information about pramipexole

Medicines are sometimes prescribed for purposes other than those listed in this Patient Information

Leaflet. Do not take pramipexole for a condition for which it was not prescribed. Do not share pramipexole with other people, even if they have the same symptoms you do. It may harm them.

This Patient Information Leaflet summarizes the most important information about pramipexole. For more information, talk with your doctor or pharmacist. They can give you information about pramipexole that is written for health care professionals.

What are the ingredients in pramipexole?

Active Ingredient: pramipexole dihydrochloride monohydrate

Inactive Ingredients: corn starch, hydrogenated vegetable oil, mannitol, povidone and pregelatinized corn starch.

Manufactured By:
BARR LABORATORIES, INC.
Pomona, NY 10970

Manufactured For:
TEVA PHARMACEUTICALS USA
Sellersville, PA 18960

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PACKAGE LABEL

PRAMIPEXOLE LABEL IMAGE



PRAMIPEXOLE DIHYDROCHLORIDE

pramipexole dihydrochloride tablet

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	Item Code (Source)	NDC:16590-409(NDC:0555-0613)
Route of Administration	ORAL		

Active Ingredient/Active Moiety				
Ingredient Name		Basis of Strength	Strength	
PRAMIPEXOLE DIHYDROCHLORIDE (UNII: 3D867NP06J) (PRAMIPEXOLE - UNII:83619PEU5T)		PRAMIPEXOLE DIHYDROCHLORIDE	0.5 mg	
Inactive Ingredients				
Ingredient Name		Strength		
STARCH, CORN (UNII: O8232NY3SJ)				
MANNITOL (UNII: 3OWL53L36A)				
POVIDONE (UNII: FZ989GH94E)				
Product Characteristics				
Color	white	Score	2 pieces	
Shape	OVAL	Size	11mm	
Flavor		Imprint Code	b;C;4	
Contains				
Packaging				
#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:16590-409-30	30 in 1 BOTTLE		
2	NDC:16590-409-40	40 in 1 BOTTLE		
3	NDC:16590-409-50	50 in 1 BOTTLE		
4	NDC:16590-409-60	60 in 1 BOTTLE		
5	NDC:16590-409-90	90 in 1 BOTTLE		
Marketing Information				
Marketing Category	Application Number or Monograph Citation		Marketing Start Date	Marketing End Date
ANDA	ANDA077724		01/01/2010	

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Establishment			
Name	Address	ID/FEI	Business Operations
STAT RX USA LLC		786036330	repack, relabel