Mirapex®

(pramipexole dihydrochloride)

0.125 mg, 0.25 mg, 0.5 mg, 0.75 mg, 1 mg, and 1.5 mg Tablets

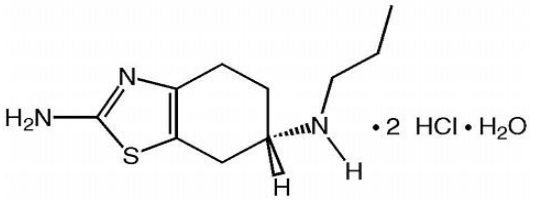
Rx only

Prescribing Information

DESCRIPTION

MIRAPEX 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. Its empirical formula is $C_{10}H_{17}N_3S \cdot 2HCl \cdot H_2O$, 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 0.5% in ethanol, and practically insoluble in dichloromethane.

MIRAPEX tablets, for oral administration, contain 0.125 mg, 0.25 mg, 0.5 mg, 0.75 mg, 1 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

Mechanism of Action

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_4 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

MIRAPEX®

(PRAMIPEXOLE DIHYDROCHLORIDE)

FORMULARY SUBMISSION DOSSIER

BOEHRINGER INGELHEIM PHARMACEUTICALS, INC.

Table of Contents

1. Product Information……3
1.1. PRODUCT DESCRIPTION 3
1.1.1 Product Overview 3
1.1.2 Pharmacology 4
1.1.3 Pharmacokinetics 4
1.1.4 Contraindications 5
1.1.5 Warnings (Please also see the enclosed MIRAPEX Package Insert) 5
1.1.6 Precautions 7
1.1.7 *Drug Interactions (See the enclosed Mirapex Package Insert for additional information* 7
1.1.8 Adverse Events 7
1.1.9 Dosage and Administration 9
1.2. PLACE OF MIRAPEX® IN THERAPY 10
1.2.1 Pramipexole as Initial Therapy (without concomitant levodopa/carbidopa): 15
1.2.2 Pramipexole as Adjunct Therapy to Levodopa/Carbidopa 15
1.2.3 Restless Legs Syndrome 15

2. Supporting Clinical and Economic Information…… 17
2.1. OVERVIEW OF CLINICAL TRIAL PROGRAM 17
2.1.1 Patients with Early PD (not treated with levodopa/carbidopa) 18
2.1.2 Patients with Advanced PD Concomitantly Treated with Levodopa/carbidopa 20
2.1.3 Restless Leg Syndrome 23
2.2. CLINICAL AND DISEASE MANAGEMENT INTERVENTION STRATEGIES 50
2.3. ECONOMIC EVALUATION SUPPORTING DATA 50

3. Modeling report of Mirapex in RLS……53

3.1 BUDGET IMPACT MODEL……...53
3.2 COST-EFFECTIVENESS MODEL……..……..……..56

4. Clinical Value and Overall Cost…….. 57

5. References…… 61

1. Product Information

1.1. Product Description

1.1.1 Product Overview

MIRAPEX® (pramipexole dihydrochloride) is a dopamine agonist classified under Miscellaneous Central Nervous System Agents (28:92:00) by the American Hospital Formulary Service (AHFS).[1] It is one of the "newer" nonergot-derived dopamine agonists, which typically avoid the serious retroperitoneal, pulmonary and valvulopathy adverse events more commonly associated with the older, ergot-derived agents.[2-4] It is approved by the FDA for the treatment of the signs and symptoms of idiopathic Parkinson's disease (PD) and for the treatment of moderate-to-severe primary Restless Leg Syndrome (RLS).[5]

The dosage forms, national drug code, and average wholesale price (AWP) of pramipexole and the other nonergot dopamine agonist in its class—Requip® (ropinirole hydrochloride)—are summarized in Table 1.[6] The daily-weighted average cost of Mirapex® was lower than that of Requip® (Table 7 in Section 3).

Table 1 Dosage Forms, National Drug Code (NDC) Numbers, and Prices for Mirapex® and Requip®* [6]

Mirapex®				Requip®			
Strength	**Package size**	**NDC**	**AWP**	**Strength**	**Package size**	**NDC**	**AWP**
0.125 mg	90	0597-0183-90	$193.65	**0.25 mg**	100	00007-4890-20	$223.69
0.25 mg	90	0597-0184-90	$193.79	**0.5 mg**	100	00007-4891-20	$223.69
				1 mg	100	00007-4892-20	$223.69
0.5 mg	90	0597-0185-90	$232.44	**2 mg**	100	00007-4893-20	$223.69
				3 mg	100	00007-4895-20	$267.30
1 mg	90	0597-0190-90	$232.44	**4 mg**	100	00007-4896-20	$267.30
1.5 mg	90	0597-0191-90	$232.44	**5 mg**	100	00007-4894-20	$267.30

*April 2007 prices published by First DataBank through Analy$ource[6]

Other Potential Uses of Mirapex®

Mirapex has also been studied for the treatment of patients with fibromyalgia and for the treatment of patients with depression.[7,8]

1.1.2 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_4 receptor subtypes.

Parkinson's Disease: The precise mechanism of action of pramipexole as a treatment for PD is unknown, although electrophysiological studies in animals have demonstrated that pramipexole stimulates dopamine receptors in the striatum. The relevance of D_3 receptor binding in PD is unknown.[5]

Restless Legs Syndrome: The precise mechanism of action of pramipexole as a treatment for Restless Legs Syndrome (RLS) is unknown although neuropharmacological evidence suggests primary dopaminergic system involvement. Positron Emission Tomographic (PET) studies suggest that a mild striatal presynaptic dopaminergic dysfunction may be involved in the pathogenesis of RLS.[5,9]

1.1.3 Pharmacokinetics

Pramipexole displays linear pharmacokinetics over the clinical dosage range. Its terminal half-life is about 8 hours in young healthy adult volunteers and about 12 hours in elderly volunteers. Steady-state concentrations are achieved within 2 days of dosing. Table 2 illustrates the pharmacokinetic profiles of pramipexole and ropinirole.

- ***Absorption:*** Pramipexole is rapidly absorbed, reaching peak concentrations in approximately 2 hours with an absolute bioavailability of greater than 90%. Food does not affect the extent of 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%). Approximately 15% of systemic pramipexole is bound to plasma proteins.
- ***Metabolism and elimination:*** Urinary excretion is the major route of elimination; 90% of a pramipexole dose is recovered in the urine, almost all as unchanged drug. The renal clearance of

pramipexole is approximately 400 mL/min (CV = 25%), approximately 3 times higher than the glomerular filtration rate. 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.[5] Pramipexole clearance is extremely low in dialysis patients, as a negligible amount is cleared by dialysis. It is not appreciably metabolized by cytochrome P450 enzymes as most (approximately 90% of dose) is recovered in urine and almost all as unchanged drug.

Table 2 Select Pharmacokinetic Parameters of Non-Ergot Dopamine Receptor Agonists* [10]

Drug	Absolute bioavail-ability (%)	Protein Binding (%)	Half-life (hours)	Clearance (mL/min)	P450 metabolism
Mirapex®	>90	15	8(12**)	400mL/min	Not appreciably metabolized by CYP P450; ~ 90% of dose is recovered in urine and almost all as unchanged drug
Requip®	55	30-40	6	783mL/min	Extensive (CYP1A2); 1% to 2% excreted unchanged

*Drug Facts and Comparisons®. 2004. Page 1270.
**In elderly patients >65 years of age

1.1.4 Contraindications

Like all dopamine agonists, pramipexole is contraindicated in patients who have demonstrated hypersensitivity to the drug or its ingredients.

1.1.5 Warnings (Please also see the enclosed MIRAPEX Package Insert)

- ***Falling Asleep during Activities of Daily Living:*** Patients treated with pramipexole dihydrochloride have reported falling asleep while engaged in activities of daily living including the operation of motor vehicles, which sometimes resulted in accidents. Somnolence is a common occurrence in patients receiving MIRAPEX tablets at doses above 1.5mg/day for Parkinson's disease. In controlled clinical trials in RLS, patients treated with MIRAPEX tablets at doses of 0.25-0.75mg once a day, the incidence of somnolence was 6% compared to an incidence of 3% for placebo-treated patients. Before initiating therapy with MIRAPEX tablets, patients should be advised of the potential to develop drowsiness and specifically asked about factors that may increase the risk such as concomitant sedating medications, the presence of sleep disorders, and concomitant medications that increase pramipexole plasma levels. If a patient develops

significant daytime sleepiness or episodes of falling asleep during activities that require active participation, MIRAPEX tablets should ordinarily be discontinued. If a decision is made to continue MIRAPEX 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.[5]

- ***Symptomatic Hypotension:*** Dopamine agonists, in general, appear to impair the systemic regulation of blood pressure, with resulting orthostatic hypotension especially during dose escalation. Parkinson's disease patients in addition, appear to have an impaired capacity to respond to an orthostatic challenge. For these reasons, Parkinson's disease patients being treated with dopamine agonists ordinarily require careful monitoring for signs and symptoms of orthostatic hypotension especially during dose escalation, and should be informed of this risk. However, despite clear orthostatic effects in normal volunteers, in clinical trials the reported incidence of clinically significant orthostatic hypotension was not greater among those assigned to pramipexole 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. Also, clinical trials in patients with RLS did not incorporate orthostatic challenges with intensive blood pressure monitoring done in close temporal proximity to dosing. [5]
- ***Hallucinations:*** Hallucinations were observed in a greater number of patients receiving pramipexole than placebo. In the 3 double-blind, placebo-controlled trials in early PD, and the 4 double-blind, placebo-controlled trials in advanced PD, hallucinations were of sufficient severity to cause discontinuation of treatment in 3.1% of the early PD patients and 2.7% of the advanced PD patients compared with approximately 0.4% of placebo patients in both populations. Age appears to increase the risk of hallucinations attributable to pramipexole. In the RLS clinical program, one pramipexole-treated patient (of 889) reported hallucinations; this patient discontinued treatment and the symptoms resolved.[5]

1.1.6 Precautions

- ***Renal:*** Since pramipexole is eliminated through the kidneys, caution should be exercised when prescribing it to patients with renal insufficiency. (see Dosage and Administration)
- ***Dyskinesia:*** Pramipexole may potentiate the dopaminergic adverse events of levodopa/carbidopa and may cause or exacerbate preexisting dyskinesia. Decreasing the dose of levodopa/carbidopa may ameliorate this adverse event.[5]
- ***Pregnancy:*** Pramipexole is in the FDA pregnancy category C.

1.1.7 Drug Interactions (See the enclosed Mirapex Package Insert for additional information)

Drug-Drug Interactions: Pramipexole caused an increase in levodopa/carbidopa C_{max} by approximately 40% and a decrease in T_{max} from 2.5 to 0.5 hours. 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.

Food-Drug Interactions: Food does not affect the extent of pramipexole absorption, although the time of maximum plasma concentration (Tmax) is increased by about 1 hour when the drug is taken with a meal.

1.1.8 Adverse Events

Given the differential risks for patients with early PD, advanced PD, and RLS, the adverse event data is presented separately for these 3 populations.

Early PD

In the 3 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 were nausea, dizziness, somnolence, insomnia, constipation, asthenia, and hallucinations.[11-13] Approximately 12% of 388 patients treated with pramipexole discontinued treatment due to adverse events compared with 11% of 235 patients who received placebo. The package insert provides additional details on treatment-emergent adverse events in these trials.[5]

Advanced PD

In the 4 double-blind, placebo-controlled trials of patients with advanced PD, the most commonly observed adverse events (>5%) that were numerically more frequent in the group treated with pramipexole and concomitant levodopa/carbidopa were postural (orthostatic) hypotension, dyskinesia, extra pyramidal syndrome, insomnia, dizziness, hallucinations,

accidental injury, dream abnormalities, confusion, constipation, asthenia, somnolence, dystonia, gait abnormality, hypertonia, dry mouth, amnesia, and urinary frequency.[14-16]

Approximately 12% of 260 patients with advanced PD who received pramipexole and concomitant levodopa/carbidopa discontinued treatment due to adverse events compared with 16% of 264 patients who received placebo and concomitant levodopa/carbidopa. The package insert provides additional details on treatment-emergent adverse events in these trials.[5]

RLS

MIRAPEX tablets for the treatment of RLS have been evaluated for safety in 889 patients, including 427 treated for over six months and 75 for over one year. The overall safety assessment focuses on the results of 3 double-blind, placebo-controlled trials, in which 575 patients with RLS were treated with MIRAPEX tablets for up to 12 weeks. The most commonly observed adverse events in the treatment of RLS (observed in > 5% of pramipexole-treated patients and at a rate at least twice that observed in placebo-treated patients) were nausea and somnolence. Occurrences of nausea and somnolence in clinical trials were generally mild and transient.

Approximately 7% of 575 patients treated with MIRAPEX tablets during the double-blind periods of the 3 placebo-controlled trials discontinued treatment due to adverse events compared to 5% of 223 patients who received placebo. The adverse event most commonly causing discontinuation of the treatment was nausea (1%). The package insert provides additional details on treatment-emergent adverse events in these trials.[5]

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, 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.

1.1.9 Dosage and Administration

Dosing in PD Patients with Normal Renal Function

In all clinical studies, dosage was initiated at a subtherapeutic level to avoid intolerable adverse events and orthostatic hypotension. Pramipexole should be titrated gradually in all patients. The dosage should be increased to achieve a maximum therapeutic effect, balanced against the principal adverse events of dyskinesia, hallucinations, somnolence, and dry mouth.[5]

Initial Treatment: Dosages should be increased gradually from a starting dose of 0.375 mg/day given in 3 divided doses and should not be increased more frequently than every 5 to 7 days (Table 3).

Table 3 Ascending Dosage Schedule of Pramipexole

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: Pramipexole is effective and well tolerated over a dosage range of 1.5 to 4.5 mg/day administered in equally divided doses 3 times per day with or without concomitant levodopa/carbidopa (approximately 800 mg/day of levodopa).

Dosing in PD Patients with Renal Impairment

The dosing schedule for various degrees of renal impairment is presented in Table 4.

Table 4 Pramipexole Dosage in the Renally Impaired

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 (creatinine Cl = 35 to 59 mL/min)	0.125 bid	1.5 bid
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 has not been adequately studied in this group of patients.	

Dosing in RLS Patients with Normal Renal Function

The recommended starting doses of MIRAPEX tablets is 0.125mg taken once daily 2-3 hours before bedtime. For patients requiring additional symptomatic relief, the dose may be increased by 0.125mg daily every 4 to 7 days. Although the dose of MIRAPEX tablets was increased to 0.75mg in some patients during long-term open-label treatment, there is no evidence that the 0.75mg dose provides additional benefit beyond the 0.5mg dose. [5]

Dosing in RLS Patients with Renal Impairment

The duration between titration steps should be increased to 14 days in RLS patients with severe and moderate renal impairment (creatinine clearance 20-60mL/min) (see Clinical Pharmacology, Renal Insufficiency in package insert) [5]

1.2. Place of Mirapex® in Therapy

PD is a chronic, progressive, degenerative condition of the central nervous system, resulting from an impairment of dopamine-producing brain cells. The disease affects 100 to 200 per 100,000 people in North America.[17] Its prevalence is growing as the population continues to age and as patients live longer due to better therapy.[18]

PD is characterized by symptoms such as resting tremor, muscle rigidity, bradykinesia, and postural reflex impairment.[18] Patients usually experience one or two of these symptoms, which progressively worsen. The actual triggers and precise etiology of PD is still unknown, although, in recent years, certain environmental and genetic risk factors have been identified as potential causes.[19,20] Generally, the average age of onset of PD is in the late 50s to early 60s.[21,22]

In addition to the characteristic motor symptoms, PD patients also exhibit several non-motor features including depression, dementia, anxiety, psychosis, sleep disturbances, autonomic disturbance, sexual dysfunction and apathy.[23] Depression, which strongly influences a patient's quality of life, is common in PD patients and its prevalence ranges from 11% to 44%. [23] Dementia- a syndrome of global decline of intellect, memory and personality, is reported in approximately 20%-44% of patients and is more common in patients with late onset disease (after 65 years of age).[24] Anxiety, which affects nearly a third of the PD patients, can be a part of depression and manifests as panic attacks, phobia, and/or as generalized anxiety disorder.[23,25] Psychosis is also common in PD patients and results in poor quality of life for patient and caregiver, early institutionalization and increased mortality.[23]

Pharmacological treatment has been shown to improve clinical outcome in PD patients. Levodopa/carbidopa (Sinemet®) is commonly used to replace the lack

of dopamine within the substantia nigra. Many patients require levodopa/carbidopa therapy for 10-20 years and sometimes even longer. A major disadvantage of levodopa/carbidopa is that it loses its effectiveness over time.[26] In addition, long-term use of levodopa/carbidopa is associated with serious motor response complications.[26] To reduce these complications and delay dependence on levodopa/carbidopa, medical practitioners are increasingly using nonergot-derived dopamine agonists. The use of "newer," nonergot-derived agents such as pramipexole and ropinirole is more common, as they typically avoid the serious retroperitoneal and pulmonary adverse events more commonly associated with the older, ergot-derived agents.[27] Pramipexole has a longer half-life than other available nonergot dopamine agonists in the United States and is not extensively metabolized through the liver.

The effectiveness of pramipexole has been demonstrated in randomized controlled trials in patients with early and advanced PD. In early PD, fewer patients developed motor complications when initiated on pramipexole over those on levodopa.[28] Thus, pramipexole is commonly used as monotherapy during the early stages of PD as part of a levodopa/carbidopa-sparing strategy and is later used in combination with levodopa/carbidopa to allow for lower doses of levodopa/carbidopa and longer "on" periods. [15,16,29,30]

The multinational drug development program for pramipexole consisted of four pivotal phase III studies – two in early PD: Shannon et al (1997), and Parkinson's Study Group (1997); and two in advanced PD: Lieberman et al (1997) and Guttman et al (1997).[11,12,15,16] These trials demonstrated improvements in several domains of the Unified PD Rating Scale (UPDRS), which evaluates mentation, ADL, motor function, complications, clinician global assessment, and patient global assessment. Sections 1.2.1 and 1.2.2 summarize the major benefits of pramipexole in the treatment of PD.

RLS is a neurological disorder characterized by unpleasant sensations in the legs and an irresistible urge to move the legs to relieve the discomfort. RLS can lead to profound disruption of sleep and associated daytime drowsiness, fatigue, and disruption of normal functioning and quality of life.[31]

The diagnostic criteria for RLS were updated in 2003 following a National Institute of Health (NIH) sponsored workshop.[9,31-35] The criteria were rephrased to incorporate new scientific findings and to better reflect the working interpretation of symptoms. Supportive criteria (e.g. family history, dopamine responsiveness, periodic leg movements or PLMs[9,31-35]) are not required for diagnosis but help to "resolve diagnostic uncertainty". Associated features were also outlined to highlight many significant clinical features of RLS (course, sleep disturbance, physical examination) but again, are not required for diagnosis. In addition, new diagnostic criteria were developed for cognitively

impaired elderly and children, and criteria were developed for augmentation, a common adverse event of pharmacologic therapies. In sum, these diagnostic criteria included in Table 5 remain the international standard for the diagnosis of RLS[31].

Table 5 Diagnostic Criteria for Restless Legs Syndrome[31]

Diagnostic features (required)

1. An urge to move the legs usually accompanied or caused by uncomfortable and unpleasant sensations in the legs.
2. The urge to move or unpleasant sensations begin or worsen during periods of rest or inactivity, such as lying or sitting.
3. The urge to move or unpleasant sensations are partially or totally relieved by movement, such as walking or stretching.
4. The urge to move or unpleasant sensations are worse in the evening or night than during the day or only occur in the evening or night.

Supportive clinical features

- Positive family history
- Positive response to dopaminergic therapy
- Presence of periodic limb movements (PLMs) during wakefulness or sleep

Associated clinical features

- Variable clinical course, waxing and waning in mild forms or chronic and progressive in moderate to severe forms
- Sleep disturbance and its related daytime tiredness and fatigue
- Normal physical examination in primary and familial forms

Polysomnography (laboratory sleep study) recordings of PLMs have traditionally been used as an objective measure of RLS severity. PLMs occur in more than 80% of people with RLS. PLMs are also significantly associated with worsening of RLS symptoms. Typically, the number of PLMs per hour (PLM index) and the number of PLM associated arousals per hour (PLM arousal index) are collected. A PLM arousal index > 5 is considered abnormal. While recording PLMs provides an objective measure of sleep disruption, it is not a reliable measure for all RLS patients. Not all RLS patients have PLMs and not all patients experience sleep disruption (with or without PLMs).

The IRLS was developed by the International RLS Study Group to provide a quantitative measure of RLS symptoms and their impact on quality of life. It is not intended to be a diagnostic instrument but instead to measure RLS severity after a diagnosis is made. The IRLS is a 10-item questionnaire completed by the patient or through clinician interview with a patient. Each item is rated for severity, by the patient, on a five-point scale: none (0 points) to very severe (4 points). Scores are totaled and RLS severity is categorized as none (0 points),

mild (1-10 points), moderate (11-20 points), severe (21-30 points), very severe (31-40 points). The IRLS has been found to have high internal consistency ($r=0.93$, $p<0.001$) and test-retest reliability ($r=0.87$, $p<0.0001$).[35] The IRLS was found to be significantly correlated with the Clinical Global Impressions Scale (CGI: $r=0.74$, $p<0.001$) and to successfully discriminate RLS patients from normal controls.[35] In addition, the IRLS exhibited excellent item response characteristics. The IRLS has become the most frequently use RLS severity instrument in research studies.

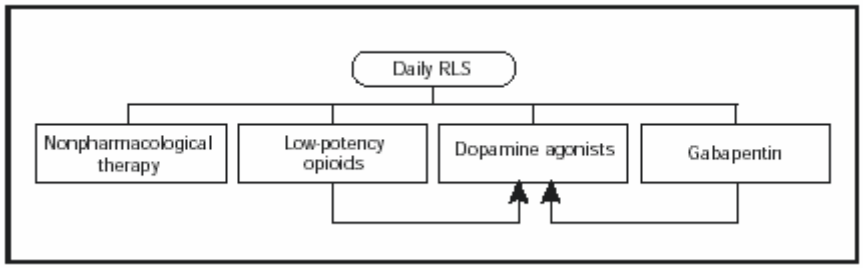
Although the cause of RLS is still under investigation, several important developments in understanding the mechanisms involved in RLS have been made. The high incidence of RLS in family members (approximately 50%) and the high concordance in identical twins (83%) suggests RLS has a genetic cause.[36,37] The prevailing theory is that individuals who develop RLS have a genetic predisposition for the disorder that is triggered or initiated by an environmental or physical condition, such as pregnancy, iron deficiency, or other condition.[36,37]

Drugs that increase dopamine activity in the brain (dopamine precursors and receptor agonists) have been found to be effective in treating the symptoms of RLS.[37-39]

RLS is also commonly associated with iron-deficiency.[40] Concentrations of ferritin are reduced and transferrin increased in RLS patients, which suggest low brain iron content.[41-43]

RLS can start at any age, although in about one-third of patients RLS starts before 20 years of age. Peak onset is in middle age. In more than 60% of patients, symptoms worsen over time while for others symptoms may remain stable.[31] Less than 15% of patients experience spontaneous remission. According to recent reports prevalence of RLS in adults and elderly ranges from 5% to 15%. The Medical Advisory Board of the Restless Legs Syndrome Foundation recommends dopamine agonists as the drugs of choice for *daily restless legs syndrome*.[44] (See Figure 1) The nonergot agonists such as pramipexole and ropinirole are generally preferred to the ergot agonists such as pergolide because of their more favorable adverse effect profile. Pramipexole has been studied in 4 randomized, double-blind, placebo-controlled trials involving a total of approximately 1000 adult RLS patients.[45-48]

Figure 1 Algorithm for the Management of DAILY RLS[44]



Nonpharmacological therapies include treating any underlying disorders. In some cases treatment of an associated condition (e.g. renal disease, iron deficiency) can alleviate symptoms and therefore should be tried first.

A number of studies, many of them placebo-controlled but with small sample sizes, have confirmed the efficacy of levodopa, particularly in combination with a carboxylase inhibitor.[50] Levodopa improves patient reported symptoms of RLS.[50] In contrast to dopamine agonists, however, levodopa does not have a significant impact on sleep efficiency and subjective sleep quality.[51]

Ergot derived dopamine agonists such as bromocriptine or pergolide have been studied and shown to be effective in RLS. Bromocriptine is not well tolerated by patients due to nausea and hypotension. Augmentation occurs in a moderate proportion of patients taking pergolide (approximately 15 to 25% of patients).[50]

Anticonvulsants like gabapentin and carbamazepine have been studied for RLS. The toxicities associated with carbamazepine limit its use. Gabapentin has been evaluated in small placebo-controlled trials. Although study results demonstrate a reduction of PLMs and RLS severity, the use of gabapentin is limited because of its tendency to produce daytime sleepiness, fatigue and ist short duration of action necessitating more frequent dosing.

Benzodiazepines and opiods have been used for many years for RLS, except for a few rare cases are considered second-line therapy.

The clinical development of pramipexole for RLS included four registration studies: two studies with a fixed-dose design and two studies with a flexible-dose design. The duration of the double-blind phase of the trials ranged from 3 weeks to 12 weeks and involved approximately 1000 patients with moderate-to-severe primary RLS. Three of the studies had extension phases ranging from 26 to 46 weeks. The pramipexole doses studied ranged from 0.125mg to 0.75mg

per day. Section 1.2.3 summarizes the major benefits of pramipexole in the treatment of RLS.[45-48]

1.2.1 Pramipexole as Initial Therapy (without concomitant levodopa/carbidopa):

In a multicenter, parallel group, double-blind, randomized controlled 4-year trial involving 301 patients with early PD, initial treatment with pramipexole resulted in significantly lower rates of dopaminergic complications (wearing-off, or dyskinesias) compared with levodopa/carbidopa ($p<0.03$).[28] In addition, a recently concluded imaging study showed that patients initially treated with pramipexole had a significantly slower rate of decline in striatal β-CIT uptake versus patients initially treated with levodopa/carbidopa.[52,53] The mean percentage loss from baseline of striatal β-CIT uptake in pramipexole vs levodopa/carbidopa groups was 16.0% vs 25.5% at 46 months ($P = 0.01$).[52,53] A key therapeutic issue is whether the effects of pramipexole and levodopa on the rate of loss of β-CIT uptake are associated with a persistent change in clinical function in patients with PD. In several cross-sectional studies of PD cohorts, the reduction in β-CIT correlates with the increasing severity measured by the UPDRS. However, in prior longitudinal studies, there has been no clear correlation between change in β-CIT uptake and the change in UPDRS score.[52,53]

1.2.2 Pramipexole as Adjunct Therapy to Levodopa/Carbidopa

When administered concomitantly or as an adjunct to levodopa/carbidopa, pramipexole enhances patient functioning, increases "on" time (time when Parkinson's symptoms are adequately controlled) and decreases "off" time (time when Parkinson's symptoms are not adequately controlled),[16] reduces tremor,[54] and reduces the daily levodopa dosage.[29] In a 12-week multicenter, double-blind, randomized, placebo-controlled trial ($N = 84$), patients taking pramipexole experienced a mean decrease in total tremor score of 5.8 compared to 1.5 in those taking placebo ($P<.0001$).[54] Pinter et al (2000), in a 12-week multicenter trial involving 90 advanced PD patients, found a mean reduction of 219.1 mg in adjusted levodopa/carbidopa dose after pramipexole use.[29]

1.2.3 Restless Legs Syndrome

A 3-week study monitoring periodic limb movements during the time in bed (PLMI) using polysomnography found median reductions ranged from -26.55 to -52.70, compared to placebo (-3.00) at fixed pramipexole doses of 0.125mg to 0.75mg ($p< 0.001$).[45] Improvements in the severity of RLS symptoms was evaluated using the International Restless Legs Severity Scale (IRLS) in the double-blind phases of three of the studies. Pramipexole significantly reduced the severity of symptoms in all three of the studies with a mean change in IRLS score from baseline ranging from

-11.87 to -17.01 compared to those who received placebo who ranged from -6.08 to -9.3 ($p \leq 0.01$ for all comparisons).[45-47] In a 6-week European study and a 12-week U.S. study, the proportion of CGI responders (patients who were deemed to be "improved" or "much improved" on the clinician-rated Clinical Global Impression Improvement scale) was significantly greater among the pramipexole-treated patients compared to placebo (62.9 to 72% compared to 32.5 to 51.2% respectively; $p \leq 0.0005$).[46,47]

2. Supporting Clinical and Economic Information

2.1. Overview of Clinical Trial Program

The clinical efficacy and safety of pramipexole in the treatment of PD was evaluated in a multinational drug development program consisting of 7 randomized controlled trials—3 in patients with early PD and 4 in patients with advanced PD. These trials, along with those completed in recent years, are reviewed in this section. To date there have been no head-to-head trials comparing pramipexole with ropinirole.

Overall, the safety and efficacy trials for pramipexole in the treatment of PD demonstrated that:

- Pramipexole enhances patient functioning (eg, UPDRS Part II, ADL subscale scores) in early PD [13]
- Pramipexole reduces tremor (eg, tremor score calculated as a sum of UPDRS items 16, 20, and 21)[54]
- Pramipexole reduces the daily levodopa dosage[29]

As initial therapy in early PD:

- Pramipexole treatment arm had significantly fewer patients that developed dopaminergic complications than the levodopa arm[28]
- Pramipexole significantly reduced the risk of developing dyskinesias and wearing-off[28]
- Pramipexole may slow the loss of dopaminergic neurons (measured as change in striatal [^{123}I]β-CIT uptake)[53]

As adjunct therapy in advanced PD:

- Pramipexole increases “on” time and decreases “off” time[16]
- Pramipexole enhances patient functioning (eg, UPDRS Part II, ADL subscale scores)[15,16]
- Pramipexole had a higher percentage of improvement in parkinsonian motor signs than placebo[15]

The clinical efficacy and safety of pramipexole in the treatment of RLS was evaluated in four multinational, placebo-controlled, double-blind, randomized registration studies involving approximately 1000 patients with moderate-to-severe primary RLS. The two 12-week studies were pivotal trials and the 3-week and 6-week studies were supportive trials.[45-48]

Overall, the safety and efficacy trials of pramipexole in RLS demonstrated that:

- After 3 weeks of treatment the mean PLMI values were significantly smaller in the pramipexole group compared to placebo ($p < 0.0001$)[45]

- After 6 week and 12 weeks, the mean IRLS score was significantly reduced and significantly more patients improved as demonstrated by the CGI-I in the pramipexole group compared to placebo group ($p < 0.0001$)[46,47]
- After 6 months of successful pramipexole treatment, the withdrawal of pramipexole resulted in rapid deterioration of RLS symptoms[48]

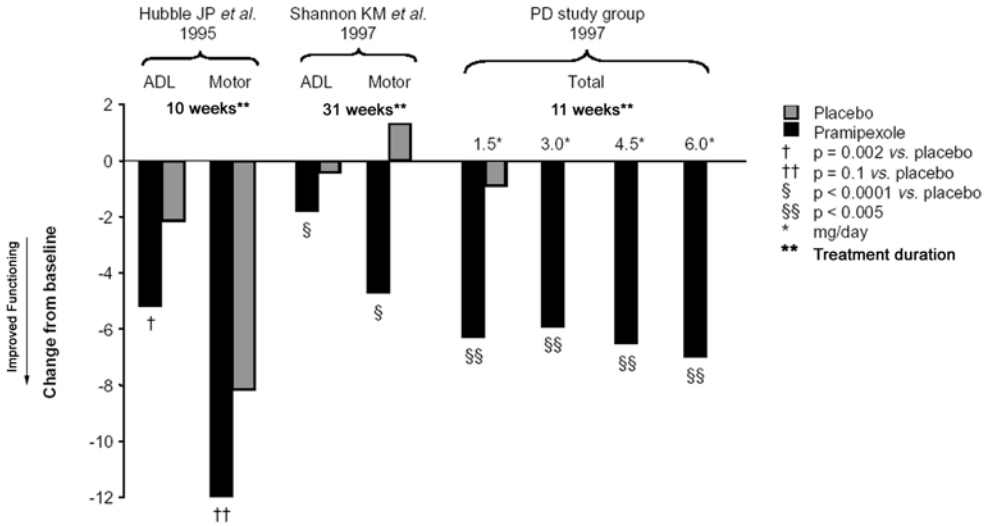
2.1.1 Patients with Early PD (not treated with levodopa/carbidopa)

Three randomized double-blind placebo-controlled trials involving approximately 650 subjects evaluated the efficacy of pramipexole in early PD. Selected patients did not use levodopa/carbidopa or dopamine agonist 60 days prior to enrollment. Use of selegiline and anticholinergics, however, were permitted. In 2 trials pramipexole was titrated to a dose of 4.5 mg daily over a period of 6-7 weeks,[11,13] whereas in the Parkinson Study Group (PSG) different doses of pramipexole 1.5 mg, 3.0 mg, 4.5 mg, and 6.0 mg/day were compared to placebo.[12]

In all 3 studies, the Unified PD Rating Scale (UPDRS) or one or more of its subparts served as the primary outcome assessment measure. The UPDRS is a 4-part multi-item 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 PD (eg, tremor, rigidity, bradykinesia, postural instability), scored for different body regions, and has a maximum (worst) score of 108.

Figure 2 provides the results for the major outcomes evaluated in these trials. Shannon et al found that UPDRS ADL and motor scores were significantly improved in the pramipexole group compared to placebo.[11] Hubble et al reported significant improvements in the UPDRS ADL score for the pramipexole group compared to placebo.[13] In the PSG trial, after 10 weeks of treatment, subjects treated with pramipexole showed a 20% improvement in total UPDRS scores compared to placebo.[12]

Figure 2 Change from Baseline in Unified PD Rating Scale with Pramipexole Versus Placebo in Early PD.[55]



- **As Initial Therapy Compared to Levodopa/carbidopa (Review Nos. 4A, 4B, & 5)** [28,52,53]

  Pramipexole was compared to levodopa/carbidopa as initial treatment in early PD in one large scale, multicenter, randomized, double-blind trial conducted at 22 sites in the US and Canada.[52] Selected patients were 30 years or older with idiopathic PD for less than 7 years. Pramipexole was administered as 0.25 mg, 0.5 mg, or 1.0 mg tablets or matching placebo tablets, and carbidopa/levodopa was administered as 12.5/50 mg or 25/100 mg capsules or matching placebo capsules three times a day. Doses were escalated over a 10-week period, initially to a daily dosage of 1.5mg of pramipexole or 75/300mg of carbidopa/levodopa and further, if needed, to 3mg or 4.5mg of pramipexole or 112.5/450mg or 150/600mg of carbidopa/levodopa. Time to first occurrence of dopamine complications (wearing off, dyskinesias, or on-off fluctuations) and change in scores on the UPDRS, the PD Quality of Life Scale, and EuroQol were the major outcome measures evaluated. Results indicated that over a 2-year period, compared to levodopa/carbidopa, pramipexole reduced the risk of developing dopaminergic motor complications by 55%. Pramipexole, however, was not as potent as levodopa/carbidopa in improving parkinsonian features as measured by the UPDRS. After 4 years, the pramipexole arm had significantly fewer patients that developed dopaminergic complications than the levodopa arm (52% vs 74%, 0.48; p<.001), and patients treated with pramipexole showed significant reduction in the risk of developing dyskinesias (24.5% vs 54%; hazard ratio, 0.37; 95% CI: 0.25-0.56; *P*<.001)

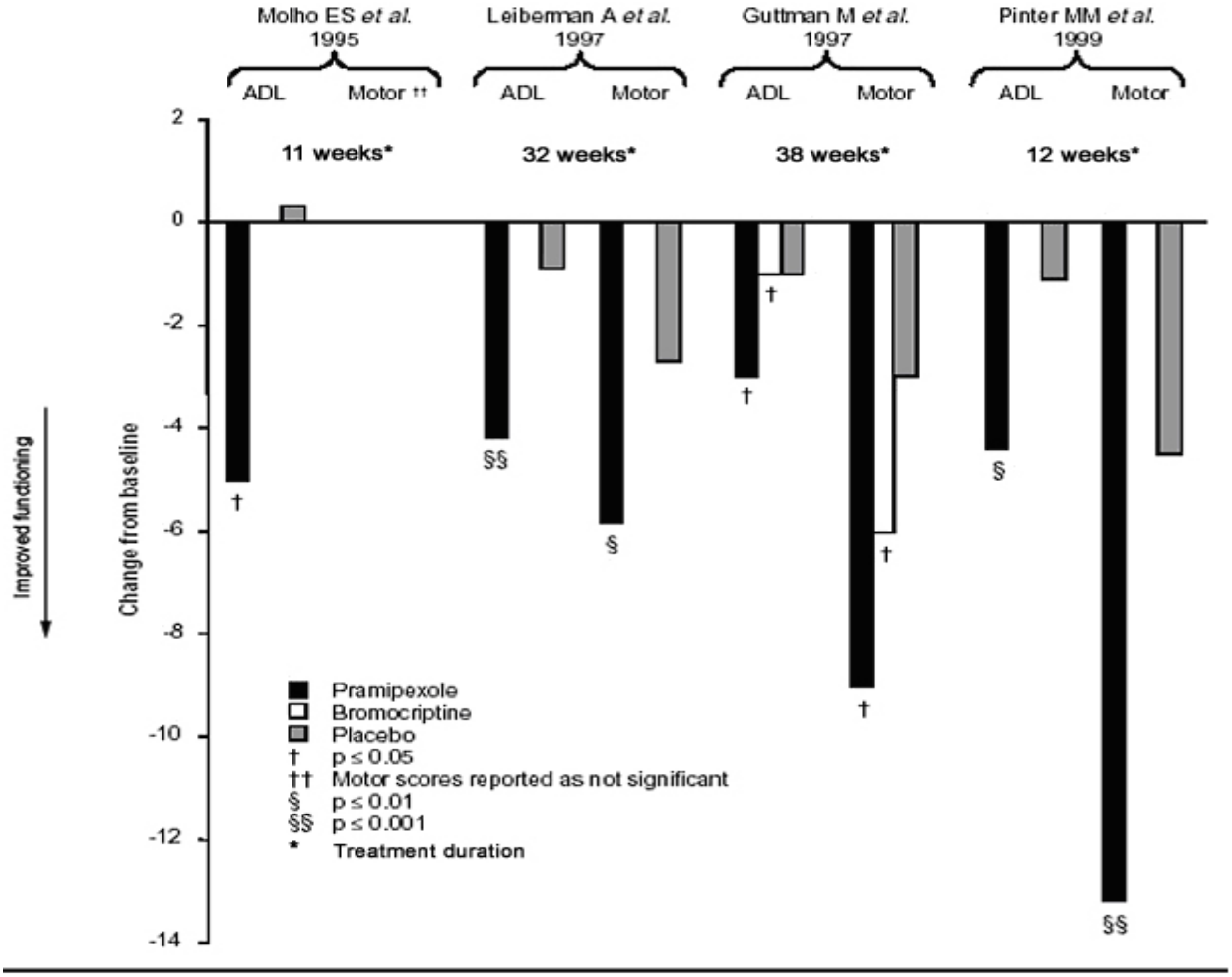
and wearing off (47% vs 62.7%; hazard ratio, 0.68; 95% CI, 0.49-0.63; *P* = .02).[28] A subset of these patients initially treated with pramipexole (N = 42) demonstrated a reduction in loss of striatal β-CIT uptake, a marker of dopamine neuron degeneration, compared with those initially treated with levodopa, during a 46-month period.[53]

2.1.2 Patients with Advanced PD Concomitantly Treated with Levodopa/carbidopa

- **Placebo-Controlled Trials (Review Nos. 6-10)[14-16,30,56]**

  Four randomized, double-blind, placebo-controlled trials based in the US and Europe evaluated the efficacy of pramipexole as adjuvant therapy to levodopa/carbidopa in patients with advanced PD. Approximately, 700 patients were evaluated in these trials, which ranged in duration from 11 to 36 weeks. During enrollment, selected patients were on levodopa/carbidopa and experiencing motor complications. Change in UPDRS scores was the primary measure of efficacy. Additionally, QOL, FSQ, and EuroQol were measured in one study.[16] Figure 3 summarizes the major findings from these trials. Specifically, Molho et al (1995) found that, from baseline to maintenance, pramipexole significantly improved ADL "off" scores and decreased levodopa/carbidopa dose by 30%.[30] Lieberman et al (1997) reported that pramipexole administered concurrently with levodopa/carbidopa significantly improved motor function as measured by UPDRS Part III ("on" period) and reduced disability (Schwab-England Disability Scale) compared to placebo.[15] In a study by Guttman et al (1997), pramipexole significantly improved (lowered) UPDRS scores on the ADL and motor subscales.[16] Scores on the FSQ Basic ADL, Intermediate ADL, and Mental Health Scales were significantly different between pramipexole and placebo groups. Pinter et al (1999) found that pramipexole significantly reduced total UPDRS scores compared to placebo.[14] Total scores for UPDRS II and III were significantly reduced for pramipexole compared to placebo in patient with advanced PD (Review No. 10).[56]

Figure 3 Change from Baseline Unified PD Rating Scale with Pramipexole Versus Placebo in Advanced PD.[55]



- **Levodopa/carbidopa Sparing Capacity (Review No. 11)** [29]

  The levodopa/carbidopa dose-sparing capacity of pramipexole was evaluated in a 12-week open label multicenter trial involving 90 European patients. 47% of patients had a levodopa dose reduction (adjusted) of more than 40% while maintaining or improving their level of efficacy.

- **Tremor control (Review No. 12 & 13)**[54,57]

  Two European, randomized, double-blind, placebo-controlled, multicenter trials examined the role of pramipexole in 114 patients with Parkinsonian tremor. Enrolled patients had marked tremor and were previously on antiparkinsonian therapy. Results from both trials showed that compared to placebo, pramipexole significantly reduced tremor in patients with idiopathic PD.

- **Depressive symptoms related to PD (Review No. 14 and 15)[58,59]**
  Rektorova and colleagues found that pramipexole appeared to have antidepressive effects in 41 nondemented patients with mild to moderate depression and advanced PD. Post hoc-analyses of a double-blind trial with open-label follow-up in advanced PD patients showed that pramipexole significantly improved the subitems motivation/initiative and depression in a subpopulation with increased UPDRS I scores at the time of inclusion.[59] Depression is not an FDA-approved indication of MIRAPEX.

2.1.3 Restless Legs Syndrome (RLS)[45-48]

Table 6 Clinical Trial Design Summary

	3-wk EU Study	6-wk EU Study	12-wk US Study	12-wk EU Study
Location/Phase	Europe/Phase 2	Europe/Phase 3	U.S./Phase 3	Europe/Phase 3
Subjects (N)	109	345	344	224 (150 in DB)
Design (DB = double-blind; OL = open-label)	3 week DB; 26 week OL follow-up	6 week DB; 46 week DB (responders) or OL (nonresponders) follow-up	12 week DB	26 week OL; 12 week DB (withdrawal of pramipexole)
Pramipexole dosages (mg)	0.125 – 0.75 mg/day Fixed dose	0.125 – 0.75 mg/day Flexible dose	0.25 – 0.75 mg/day Fixed dose	0.125 – 0.75 mg/day Flexible dose
Primary outcome measure	PLMI	IRLS CGI-I	IRLS CGI-I	Time to target event after randomization (by IRLS + CGI-I)
Secondary outcome measures	IRLS CGI PGI ESS Subjective sleep quality PSG SF-36	PGI ESS SF-36 VAS	PGI ESS VAS ASRS RLSQOL	IRLS CGI PGI ESS VAS ASRS RLSQOL

Description of the efficacy scales used in the RLS clinical trial program

- **International restless legs severity scale (IRLS) scale:** a 10-item questionnaire completed by the patient or physician interview. Each item is rated for severity by the patient on a 4-point scale with a range from none (0points) to very severe (4 points). The scores are totaled and the severity of RLS is then categorized as:

None	0 points
Mild	1-10 points
Moderate	11-20 points
Severe	21 -30 points
Very severe	31-40 points

- **Clinical Global Impressions Scale (CGI):** a well-validated clinician-rated tool including 2 items rated on a 7-point scale: change in illness severity and global improvement from "very much improved" to "very much worse". Two other items are rated on a 4-point scale: therapeutic effect and side effects.

- **Patient Global Impression of Improvement (PGI):** a 7-point, patient-rated questionnaire that asks how much they have improved since starting treatment from 1 being "very much better" to 7 being "very much worse".

- **Medical Outcomes Study 36-item Short Form Health Survey (SF-36):** a general health status questionnaire that assesses health related quality of life. This tool covers 8 areas: limitations in physical activities because of health problems, limitations in social activities because of physical or emotional problems, limitations in usual activities because of physical health problems, bodily pain, general mental health, limitations in usual activities because of emotional problems, vitality (energy and fatigue), and general health perceptions.

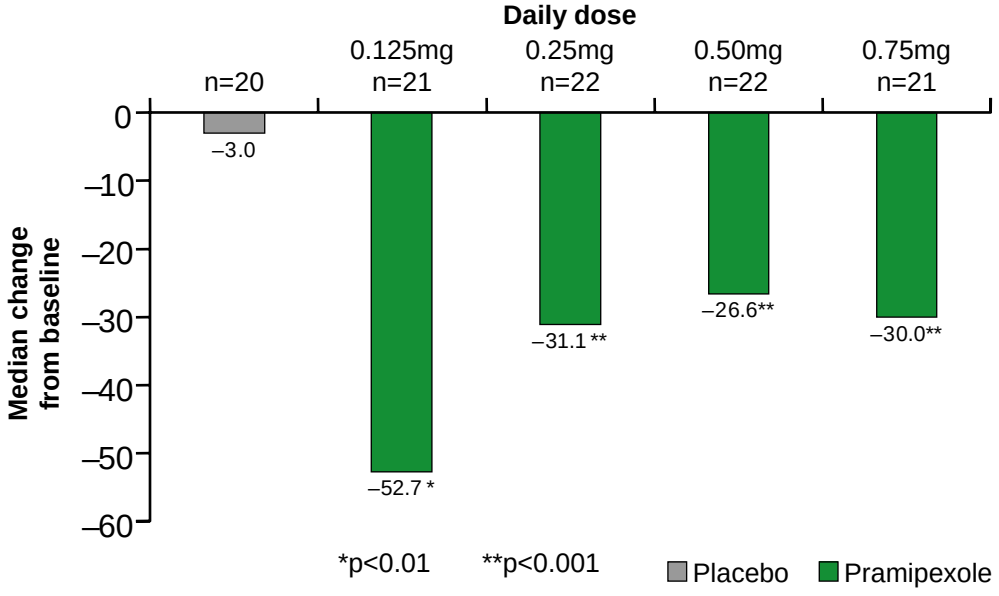
- **Restless Legs Syndrome Quality of Life (RLS-QoL):** a patient questionnaire developed by the International RLS Study Group which consists of 18 items that assess the extent to which RLS impacted daily activity, concentration, sexual activity, and work during the previous month.

- **Visual Analog Scale (VAS):** an internationally utilized scale that records patients' perception of disease or satisfaction with treatment on a 100mm scale. A low score means "not present or very satisfied" and a high score means "severe or very dissatisfied". This scale is used to measure RLS severity while getting to sleep, severity of symptoms during the night, severity of symptoms during the day, and sleep satisfaction.

- **Three-week European Trial (Review 16)[45]**

  The 3-week European trial compared 4 fixed doses of MIRAPEX tablets, 0.125mg, 0.25mg, 0.5mg and 0.75mg, to placebo in a randomization of 1:1:1:1:1. Approximately 20 patients were in each dose group for a total of 109 patients. Polysomnography was performed to determine the effect of pramipexole on the Periodic Limb Movements during time in bed index (PLMI). Pramipexole significantly reduced the PLMI from baseline to week 3 compared with placebo in all dose groups ($p<0.01$ to $p<0.001$) (see Figure 4). The mean improvement from baseline on the IRLS Scale total score and the percentage of CGI-I responders for each of the MIRAPEX tablet treatment groups was compared to placebo. The 0.125mg dose group was not significantly different from placebo. On average, the 0.5mg dose group performed better than the 0.25mg dose group, but there was no difference between the 0.5mg and the 0.75mg dose groups.

Figure 4 Change in PLMI from Baseline to Week 3 in 3-wk European Trial[45]

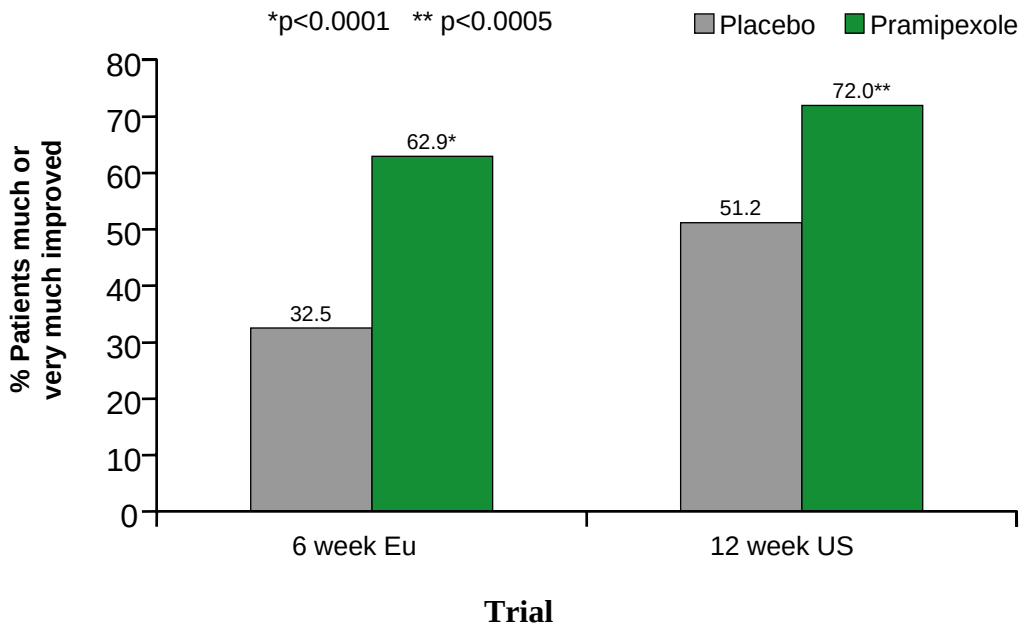


- **Six-week European Trial (Review 17)[46]**

  The 6-week European trial involved 345 patients randomized in a 2:1 ratio to a flexible dose of MIRAPEX tablets or placebo. The distribution of achieved doses was as follows: 35 on 0.125mg, 51 on 0.25mg, 65 on 0.5mg, and 69 on 0.75mg. The mean improvement from baseline on the IRLS Scale total score was -12 for MIRAPEX-treated patients and -6 for placebo-treated

patients(p<0.0001) with a median dose of 0.35mg/day of pramipexole. As shown below in Figure 5, the proportion of CGI-I responders was 63% for pramipexole-treated patients and 32% for placebo-treated patients (p<0.0001). The difference between these groups was statistically significant for both measures. For all secondary endpoints, pramipexole showed superior results.

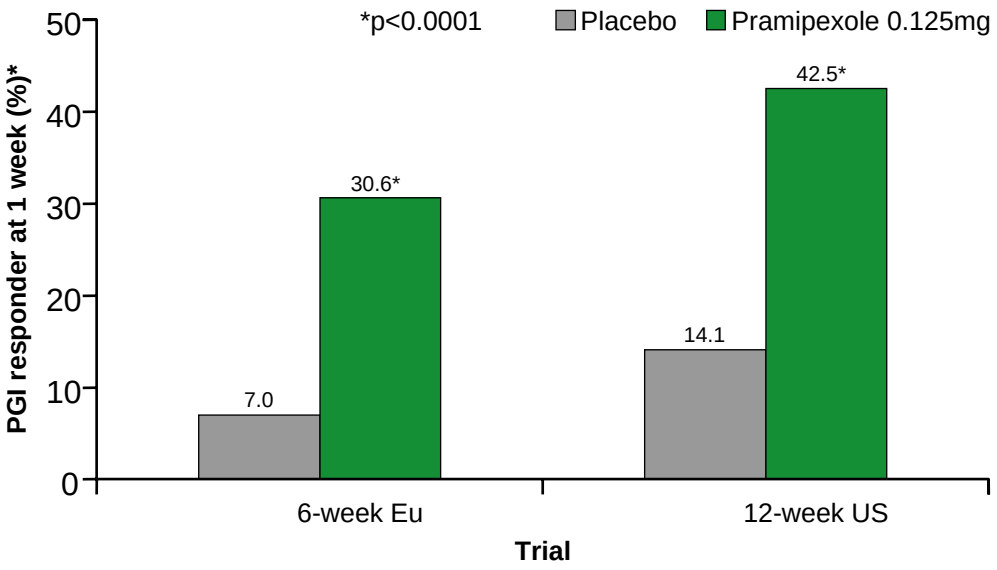
Figure 5 CGI Responders in the 6-wk European and the 12-wk US Trials[46,47]



The PGI is a 7-point patient rated assessment scale which asks the patient how much they have improved since starting treatment. The number of PGI responders or patients who rated their overall condition as "much better" or "very much better" on the PGI – was calculated at each study visit.

Figure 6 below shows the PGI-responder rates after 1 week in the 6-week European trial and the 12-week US trial. An increase in the number of responders was apparent after 1 week even at the starting dose of pramipexole: 30.6% and 42.5% of pramipexole-treated patients met the criteria for PGI responders compared with 7.0% and 14.1% of patient on placebo (p<0.0001 for all comparisons). This demonstrates the early effects of the low starting dose (0.125mg) of pramipexole.

Figure 6 PGI Responders in the 6-wk European and 12-wk US Trials[46,47]



*PGI responder-rating of 'much better' or 'very much better'.

- **Twelve-week United States Trial (Review 18)[47]**

  The 12-week US trial evaluated fixed doses of pramipexole in 344 patients up-titrated over 3 weeks to 0.25mg/day, 0.5mg/day or 0.75mg/day. As shown in Figure 7, after 12 weeks of treatment in the US trial, the IRLS score had changed from baseline -9.3 for placebo, compared with a change of -12.8 for 0.25mg/day, -13.8 for 0.5mg/day, and -14.0 for 0.75mg/day. The adjusted mean difference was -4.3 points in favor of pramipexole ($p<0.0001$)

  As seen in Figure 5, CGI–I responder rates (the proportion of patients who were “improved” or “much Improved”) were 72.0% with pramipexole, compared with 51.2% with placebo ($p<0.0005$).

  In this study pramipexole significantly improved RLS-related quality of life as assessed by the RLS-QoL (Figure 8). Significant improvements in the mean RLS-QoL score were seen after 6 weeks of pramipexole treatment (+20.0 points) compared with placebo (+12.8 points; $p<0.0001$): The improvements were maintained after 12 weeks.

  Pramipexole was well tolerated and the most frequent adverse events with a higher occurrence in the pramipexole group were nausea (19% vs. 4.7%) and somnolence (10.1 vs 4.7%).

Figure 7 Change in IRLS Total Score Compared to Placebo in the 12-wk US Trial[47]

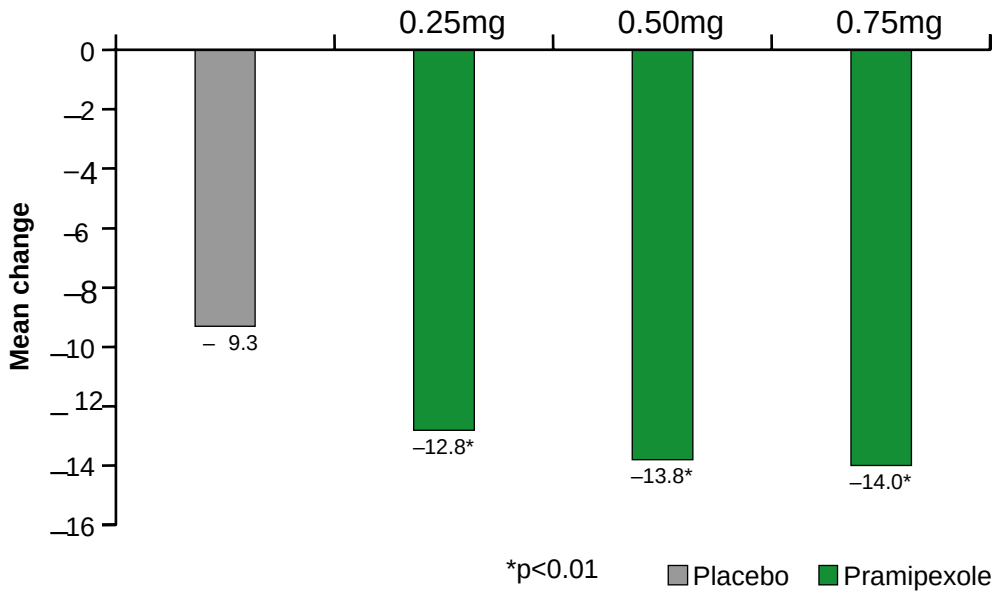
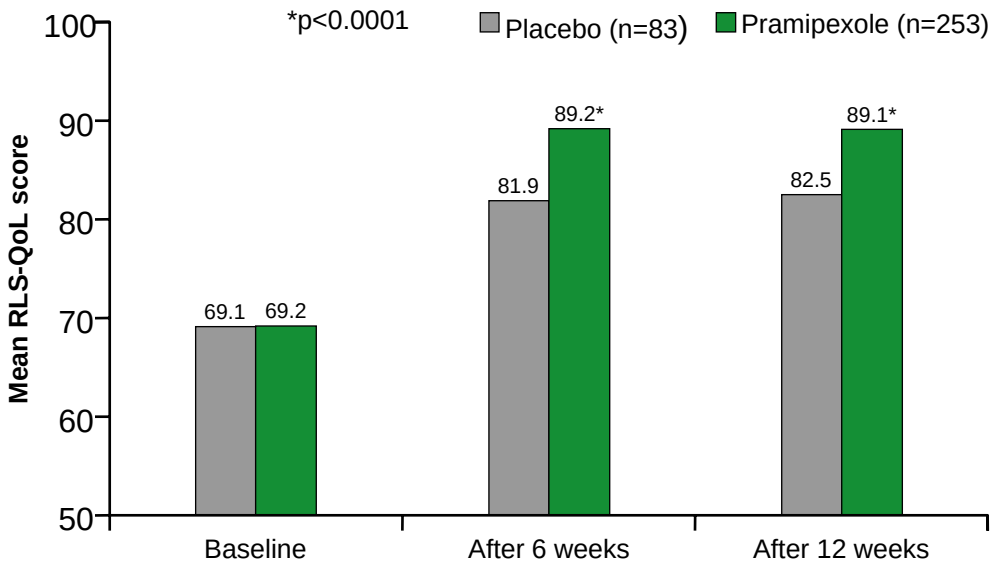


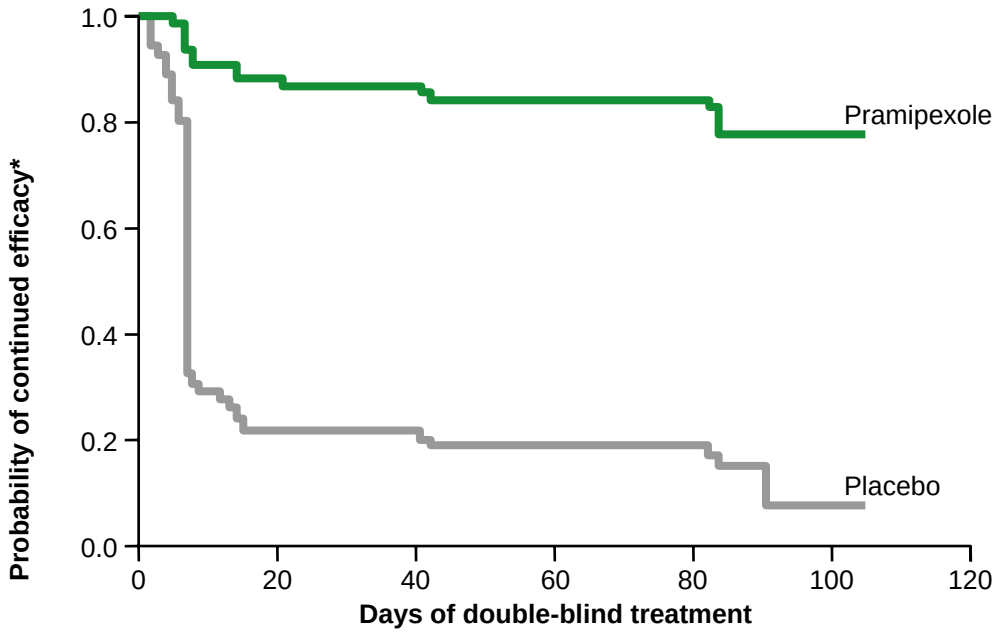
Figure 8 RLS related Quality of Life in the 12-wk US Trial[47]



- **Twelve-week European Withdrawal Trial (Review 19)[48]**

  During a 6-month run-in period, open-label pramipexole was up-titrated to individually optimized doses of 0.125mg, 0.25mg, 0.5mg, or 0.75mg given once daily 2-3 hours before bedtime. At the end of this phase, patients with an IRLS score ≤ 15 and a CGI-I rating of "very much improved" or "much improved" were considered responders. There were 150 responders who were then randomized to receive active treatment or placebo in a ratio of 1:1. For this second period, the primary endpint was the time to a target event representing an insufficient response. This insufficient response was defined a CGI-I score of "minimally" or "much" or "very much" worse (compared to the score at the start of this period) and an increase in the IRLS to a score > 15. By Kaplan-Meier analysis (Figure 9) and log-rank test, the time to a survival estimate of 0.85 was 5 days for placebo, and the time to an estimate of 0.50 was 7 days. For pramipexole, the corresponding times were 42 days and >84 days (p<0.0001). This latter interval could not be calculated exactly because less than 50% of the pramipexole patients reached the target event.

Figure 9 Kaplan-Meier Analysis of Time to Target Events for the 12-wk European Trial[48]



*Kaplan-Meier estimate.

Review #1:	**Efficacy of Pramipexole, a Novel Dopamine Agonist, as Monotherapy in Mild to Moderate PD.**[11]
Author, Year	Shannon et al, 1997
Journal	Neurology; 49:724-728
Study Sites:	18 US sites
Study Period:	Dates unspecified; ascending dose phase (7 weeks); maintenance phase (24 weeks);
Primary Objectives:	Assess the efficacy and tolerability of pramipexole in patients with mild to moderate PD who were not receiving levodopa/carbidopa.
Methodology:	Randomized, placebo-controlled, double-blind, multicenter clinical trial
Diagnosis and Main Criteria for Inclusion:	• Patients older than 25 years of age with idiopathic PD in Hoehn and Yahr (HY) stages I to III who were levodopa/carbidopa-free for 60 days prior to study entry.
Number of Subjects (planned and analyzed):	• 164 patients were randomized to active treatment and 171 were randomized to placebo. • 136 (83%) active-treatment subjects completed the study and 137 (80%) placebo subjects completed the study. • An intent-to-treat (ITT) analysis was performed on all patients at weekly intervals. Missing data were estimated using the last observation carried forward (LOCF) method.
Treatment Regimens:	• Pramipexole dihydrochloride titrated over a period of 7 weeks from 0.375 mg to 4.5 mg daily in 3 divided doses. A maintenance dose of 4.5 mg was given daily.
Criteria for Evaluation:	• Changes in UPDRS parts II (ADL) and III (motor) scores between baseline and the end of the maintenance period were the primary outcome variables. • Secondary outcomes included changes from baseline in the individual components of UPDRS, HY stage, and number of days until failure

Clinical Results:

- UPDRS ADL and motor scores were significantly lower at the end of the maintenance interval (mean ADL 6.4; mean motor 14.1) compared to baseline (mean ADL 8.2; mean motor 18.8) in the pramipexole group ($P<.05$).
- Compared with the placebo, there was a significant improvements in ADL and motor subscores of the UPDRS scale at each visit ($P<.0001$) beginning with week 3 of the ascending-dose interval.
- The magnitude of benefit, during the maintenance period, ranged from 22% to 29% for ADL and 25% to 31% for motor scores.

Safety Results:

- Nausea (active drug 39% vs placebo 20.5%; $P = .0002$), insomnia (25.6% vs 12.9%, $P = .0034$), constipation (17.7% vs 6.4%, $P = .0021$), somnolence (18.3% vs 8.8%, $P = .015$), and visual hallucinations (9.7% vs 2.3%, $P = .0048$) occurred significantly more frequently in the pramipexole treatment group compared with placebo patients.
- Forty percent of the pramipexole patients experienced hallucinations and had to discontinue the medication.
- Eighteen pramipexole-treated and 8 placebo-treated patients discontinued the study due to adverse events.
- Common reasons for discontinuation included gastrointestinal complaints (10 patients), hallucinations (7 patients) and sleepiness or fatigue (5 patients).

Conclusion:

- The results indicated that pramipexole is safe and effective in the treatment of early PD.

Review #2:	**Pramipexole in Patients with Early PD.**[13]
Author, Year	Hubble et al, 1995
Journal	Clinical NeuroPharmacology; 18:338-347
Study sites:	4 US sites
Study Period:	Dates unspecified; 9 weeks (first 6 weeks on an ascending dose schedule; 3 weeks on maintenance phase)
Primary Objectives:	Evaluate the efficacy, tolerability, safety, and pharmacokinetics of pramipexole in early PD.
Methodology:	Randomized, parallel-group, multicenter, placebo-controlled trial
Diagnosis and Main Criteria for Inclusion:	• Selected patients were 21 years or older and had a diagnosis of early idiopathic PD (Stages I-III by the Modified Hoehn and Yahr Scale). • All patients received selegiline (10 mg/day) but were not treated with levodopa/carbidopa.
Number of Subjects (planned and analyzed):	• Pramipexole (28 patients); placebo (27 patients) • All patients, except one in the placebo group, completed the trial.
Treatment Regimens:	• Pramipexole dihydrochloride titrated over a period of 6 weeks from 0.30 mg to 4.5 mg daily in 3 divided doses. Maintenance dose of 4.5 mg daily
Criteria for Evaluation:	• The primary end point was mean change from baseline at end of maintenance period in UPDRS Part II and Part III scores. • The secondary measure was mean change in score from baseline to the average score over the 3-week maintenance period for UPDRS Parts II and III.

Clinical Results:

- For the UPDRS Part II score, the change from baseline to end of the maintenance period, adjusted by center and center-by-treatment interaction, was significantly higher in the pramipexole group (5.19) compared to the placebo group (2.16, *P* = .002).
- Similarly, change from baseline to average during the maintenance period in UPDRS Part II score, adjusted by center and center-by-treatment interaction, was significantly higher in the pramipexole group (4.84) compared to the placebo group (2.29, *P* = .005).
- The change in score from baseline to final measurement on UPDRS Part III (motor examination) was not significantly different (P = 0.10), although the trend favored the pramipexole group.

Safety Results:

- All patients in both groups experienced at least one drug-related adverse event.
- Four patients (14.3%) in the pramipexole group and 0 in the placebo group experienced hallucinations.
- Seven patients (25%) in the pramipexole group and 5 (18.5%) in the placebo group showed symptoms of orthostatic hypertension
- At one of three interim visits, there was a significant difference in supine systolic blood pressure between pre- and postdose measurements compared to placebo (7.5 mm Hg, p=0.04)
- Reports of asymptomatic orthostatic hypotension: 207 episodes in the pramipexole arm and 180 episodes in the placebo arm

Conclusion:

- Pramipexole is effective and tolerable in the treatment of early PD.

Review #3:	**Safety and Efficacy of Pramipexole in Early Parkinson Disease: A Randomized Dose-Ranging Study.** [12]
Author, Year	Parkinson Study Group, 1997
Journal	JAMA; 278:125-130
Study Sites:	20 US and Canadian sites
Study Period:	April 1994-September 1994
Primary Objectives:	To evaluate dose-response relationships for tolerability, safety, and efficacy of pramipexole.
Methodology:	Multicenter, multidosage, parallel-group, double-blind, placebo-controlled, randomized clinical trial
Diagnosis and Main Criteria for Inclusion:	• Adults age 30 or older with idiopathic PD for less than 7 years that did not require anti-PD treatment with levodopa/carbidopa or dopamine agonists and had not taken such medication within the 3 years prior to the study and were in Hoehn and Yahr stages I, II, III.
Number of Subjects (planned and analyzed):	• Planned enrollment is 250 subjects, actually enrolled 264, completed 239.
Treatment Regimens:	Placebo, pramipexole 1.5 mg/day, 3.0 mg/day, 4.5 mg/day, 6.0 mg/day; 6-week dose escalation, 4-week maintenance, 1-week treatment withdrawal
Criteria for Evaluation:	• Subjects were evaluated at 2, 4, 6, 8, 10, and 11 weeks after baseline visit. • The primary measure of efficacy was the change in the total UPDRS score between baseline and 10 weeks. • The secondary measure of efficacy was changes between baseline and 8 and 10 weeks in the mental, motor, and activities of daily living (ADL) subscale scores of the UPDRS, and changes between baseline and 10 weeks in Hoehn and Yahr score. • The primary outcome measure of tolerability was whether the subject completed the study on the originally assigned medication dosage. • The secondary measure of tolerability included whether subjects completed the study with at most 1 dosage reduction and whether subjects completed the study regardless of dosage reductions.

Clinical Results:

- The proportion of subjects completing the study on the originally assigned dosage was 98% for placebo and 81% for the 1.5 mg/day, 92% for the 3.0 mg/day, 78% for the 4.5 mg/day, and 67% for the 6.0 mg/day treatment groups.
- After 10 weeks of treatment, pramipexole-treated subjects showed a 20% improvement in total UPDRS scores, with mean improvements in scores ranging from 5.9 to 7.0 units among active treatment groups, compared with 0.9 units for the placebo group ($P<.005$ for each comparison with placebo).
- Treatment effects were more pronounced in subjects with worse disease at baseline.

Safety Results:

- There was a trend toward more clinical adverse experiences in the higher dosage groups. In particular, in the 6.0 mg/day group there was a higher incidence of moderate and severe adverse experiences (p=.002)
- There were higher incidences of nausea, somnolence, and hallucinations in the pramipexole group than in the placebo arm, but the differences among treatment groups for any specific adverse event were not statistically significant.

Conclusion:

- Pramipexole is safe and effective as a short-term monotherapy in patients with early PD who are not receiving levodopa/carbidopa.

Review #4A:	**Pramipexole vs Levodopa/carbidopa as Initial Treatment for Parkinson Disease: A Randomized Controlled Trial.** [52]
Author, Year	Parkinson Study Group, 2000
Journal	JAMA; 284:1931-1938
Study Sites:	22 sites in US and Canada
Study Period:	October 1996-August 1997
Primary Objectives:	To compare the development of dopaminergic motor complications after initial treatment of early PD with pramipexole vs levodopa/carbidopa
Methodology:	Randomized, controlled, double-blind, multicenter trial
Diagnosis and Main Criteria for Inclusion:	• Adults age 30 or older with idiopathic PD for less than 7 years, requiring dopaminergic antiparkinsonian therapy at time of enrollment • Hoehn and Yahr stage I, II, III
Number of Subjects (planned and analyzed):	• The planned sample size was 300; 150 for each treatment group • Pramipexole: 128 completed the trial • Levodopa/carbidopa: 131 completed the trial
Treatment Regimens:	• Pramipexole 0.25 mg, 0.5 mg, or 1.0 mg or matching placebo 3 times a day • Carbidopa/levodopa 12.5/50 mg or 25/100 mg or matching placebo 3 times a day • Doses were escalated over a 10-week period, initially to a daily dosage of 1.5mg of pramipexole or 75/300mg of carbidopa/levodopa and further, if needed, to 3 or 4.5 mg of pramipexole or 112.5/450mg or 150/600mg of carbidopa/levodopa.
Criteria for Evaluation:	• The primary outcome was the time from randomization until the first occurrence of any of 3 specified dopaminergic complications: wearing off, dyskinesias, or on-off fluctuations. • Secondary outcome variables included changes in scores on the UPDRS, the PD Quality of Life scale (PDQUALIF), the EuroQol, and the need for supplemental levodopa/carbidopa. • Measures of safety included the frequency and severity of individual adverse experiences. • A subset of patients was enrolled in single photon emission computed tomography imaging with β-CIT looking at the ratio of specific to nondisplaceable striatal β-CIT uptake.

Clinical Results:

- Dopaminergic end point—28% of subjects assigned to pramipexole treatment reached the primary end point by 23.5 months compared to 51% in the levodopa/carbidopa group (hazard ratio [HR], 0.45; 95%CI, 0.30-0.66; *P*<.001). The reduced risk was observed in each of the four 6-month study periods (0-6 month HR, 0.46; 6-12 month HR, 0.27; 12-18 month HR, 0.56; 18-24 month HR, 0.65) and for specific dopaminergic complications of wearing off and dyskinesias.
- Mean change from baseline to month 23.5 in UPDRS score was greater in the levodopa/carbidopa group compared to the pramipexole group. (*P*≤.002).
- Quality-of-life scores improved in both groups initially and then declined over time. The PDQUALIF score was significantly higher in the levodopa/carbidopa group. (P = 0.006)
- Mean decline in β-CIT uptake did not differ between the 2 treatment groups.

Safety Results:

- Significantly more patients in the pramipexole group experienced somnolence (*P* = .003), hallucinations (*P* = .03), and both generalized (*P* = .01) and peripheral edema (*P* = .002) compared with those in the levodopa/carbidopa group.
- The differences in somnolence and hallucinations between the 2 groups emerged during the escalation phase of the trial, whereas the differences for edema emerged during the maintenance phase of the trial.

Conclusion:

- Pramipexole as initial therapy in patients with early PD reduced the risk of developing dopaminergic motor complications by 55% compared to initiating therapy with levodopa/carbidopa over a 2-year period.
- Both pramipexole and levodopa/carbidopa improved parkinsonian features, as measured by UPDRS, but pramipexole was not as potent as levodopa/carbidopa in improving these features.

Review #4B:	**Pramipexole vs Levodopa/carbidopa as Initial Treatment for Parkinson Disease: A 4 Year Randomized Controlled Trial.[28]**
Author, Year	Parkinson Study Group, 2004
Journal	Archives of Neurology
Study Sites:	22 sites in US and Canada
Study Period:	Enrolled between October 1996-August 1997 and observed until August 2001
Primary Objectives:	To compare initial treatment with pramipexole vs levodopa/carbidopa in early PD
Methodology:	Randomized controlled, double-blind, multicenter parallel group trial
Diagnosis and Main Criteria for Inclusion:	• Adults age 30 or older with idiopathic PD for less than 7 years, requiring dopaminergic antiparkinsonian therapy at time of enrollment • Hoehn and Yahr stage I, II, III
Number of Subjects (planned and analyzed):	• Planned sample size was 300; 150 for each treatment group • Pramipexole: 151 • Levodopa/carbidopa: 150
Treatment Regimens:	• Pramipexole 0.25 mg, 0.5 mg, or 1.0 mg or matching placebo 3 times a day (10-week dose escalation) • Levodopa/carbidopa 50/12.5 mg or 100/25 mg or matching placebo 3 times a day • Doses were escalated over a 10-week period, initially to a daily dosage of 1.5mg of pramipexole or 75/300mg of carbidopa/levodopa and further, if needed, to 3 or 4.5 mg of pramipexole or 112.5/450mg or 150/600mg of carbidopa/levodopa.
Criteria for Evaluation:	• Primary outcome was the time from randomization until the first occurrence of any of 3 specified dopaminergic complications: wearing off, dyskinesias, or on-off fluctuations. • Secondary outcome variables included changes in scores on the UPDRS, the PDQUALIF, the EuroQol, and the need for supplemental levodopa/carbidopa. • Measures of safety included the frequency and severity of individual adverse experiences.

Clinical Results:

- 52% of subjects assigned to pramipexole treatment reached the primary end point of developing dyskinesias, wearing off, or on-off fluctuations compared with 74% of the levodopa group (HR, 0.48; 95% CI, 0.35-0.66; P<0.001).
- Patients treated with pramipexole showed significant reduction in the risk of developing dyskinesias (24.5% vs 54%; hazard ratio, 0.37; 95% CI: 0.25-0.56; *P*<.01) and wearing off (47% vs 62.7%; hazard ratio, 0.68; 95% CI, 0.49-0.63; *P* = .02).
- Mean change from baseline to 48 months in total UPDRS scores was significantly greater in the levodopa/carbidopa group than in the pramipexole group (2 ±15.4 points vs -3.2 ± 17.3 points, *P* = .003).
- Mean changes in quality-of-life scores did not differ between the 2 groups.

Safety Results:

- Somnolence (36% vs 21%, *P* = .05), cellulitis (4.6% vs 0.0%, P=0.01) and edema (42% vs 15%, *P*<.001) were more common in pramipexole-treated subjects than in levodopa/carbidopa-treated subjects.
- Urinary frequency (3% vs 11%, *P* = .01) and hernia (1% vs 8%, *P* = .002) were more common in the levodopa group.

Conclusion:

- Initial treatment with pramipexole resulted in lower incidences of dyskinesias and wearing off compared with initial treatment with levodopa/carbidopa.

Review #5:	**Dopamine Transporter Brain Imaging to Assess the Effects of Pramipexole vs Levodopa/carbidopa on Parkinson Disease Progression.[53]**
Author, Year	Parkinson Study Group, 2002
Journal	JAMA; 287:1653-1661
Study Sites	17 sites in US and Canada
Study Period	Enrollment period November 1996 to August 1997
Primary Objectives	To compare rates of dopamine neuron degeneration after initial treatment with pramipexole or levodopa/carbidopa in early PD by means of dopamine transporter imaging
Methodology	Substudy of a parallel-group double-blind randomized clinical trial
Diagnosis and Main Inclusion Criteria:	• Patients of both sexes, 30 years and older, with PD (Hoehn and Yahr stage I-III) • Duration of PD for 7 years or less • Patients required antiparkinsonian therapy but were excluded if had taken levodopa/carbidopa or another dopamine agonist in the 2 months prior to enrollment
Number of Subjects:	• Eighty-two patients with early PD
Treatment Regimens	• Randomly assigned to receive pramipexole 0.5 mg 3 times per day (n = 42) or levodopa/carbidopa, 100/25 mg 3 times per day (n = 40) • Doses were escalated over a 10-week period, initially to a daily dosage of 1.5mg of pramipexole or 75/300mg of carbidopa/levodopa and further, if needed, to 3 or 4.5 mg of pramipexole or 112.5/450mg or 150/600mg of carbidopa/levodopa.
Primary Outcomes	• Percentage change from baseline in striatal [123] β-CIT uptake after 46 months • Secondary outcomes: percentage changes and absolute changes in striatal, putamen, and caudate[123]β-CIT uptake after 22 and 34 months

Clinical Results:

- The mean (SD) percentage loss in striatal [123]β-CIT uptake from baseline was significantly reduced in patients initially treated with pramipexole compared to those initially treated with levodopa/carbidopa: 7.1% (9.0%) vs 13.5% (9.6%) at 22 months (*P* = .004); 10.9% (11.8%) vs 19.6% (12.4%) at 34 months (*P* = .009); and 16.0% (13.3%) vs 25.5% (14.1%) at 46 months (*P* = .01).
- At the 46-month evaluation, percentage loss from baseline in striatal [123]β-CIT uptake correlated significantly with the change from baseline in UPDRS (r = -0.40; *P* = .001)

Conclusion:

- Patients initially treated with pramipexole demonstrated a reduction in loss of striatal [123] β-CIT uptake, a marker of dopamine neuron degeneration, compared with those initially treated with levodopa/carbidopa, during a 46-month period.

Review #6:	**The Use of Pramipexole, A Novel Dopamine Agonist, in Advanced PD.[30]**
Author, Year	Molho et al, 1995
Journal	Journal of Neural Transmission; 45:225-230
Study Sites:	2 US sites (Miami and New York)
Study Period	11 weeks
Primary Objectives	To evaluate the tolerability, safety, and efficacy of pramipexole in PD patients experiencing motor fluctuations on levodopa/carbidopa therapy
Methodology	Single-blind, parallel group, randomized, placebo-controlled trial
Diagnosis and Main Inclusion Criteria	• Enrolled patients had Stage II-IV PD on the Hoehn and Yahr Scale • Experiencing motor fluctuations • Treated with levodopa/carbidopa at the time of enrollment
Number of Subjects	24 patients randomized to placebo (n = 12) and pramipexole (n = 12)
Treatment Regimens	• Pramipexole, ascending dose schedule up to 1.5 mg 3 times daily (in 7 weeks); 3 weeks maintenance phase
Criteria for Evaluation	• Primary efficacy endpoints: ADL (part II) of UPDRS and mean hours "off" (diary results) • Also, patients were evaluated weekly on the following measures: o UPDRS, Modified Schwab and England disability scale o Modified Hoehn and Yahr Scale o Parkinson's Dyskinesia Scale

Clinical Results:

- Pramipexole- treated patients showed a statistically significant improvement in their ADL "off" scores when compared to baseline. The placebo group patients showed no significant improvement in their ADL "off" scores.
- ADL "on" scores were not significantly improved in either group
- In the pramipexole group, UPDRS motor subscale scores were 12% lower (improved) during maintenance phase compared to baseline ($P>.05$). In the placebo group, this reduction was 26% ($P<.05$).
- Levodopa/carbidopa dose decreased significantly (by 30%) from baseline to maintenance in the pramipexole group.

Safety Results:

Major adverse events	Pramipexole (n = 12)	Placebo (n = 12)
Increased Dyskinesia	6	2
Confusion	3	1
Hallucinations	3	2
Insomnia	3	4

Conclusion:

- Pramipexole is efficacious and safe in the treatment of advanced PD with motor fluctuations

Review #7:	**Clinical Evaluation of Pramipexole in Advanced PD: Results of a Double-blind, Placebo-controlled, Parallel Group Study.[15]**
Author, Year	Lieberman et al, 1997
Journal	Neurology; 49:162-168
Study Sites	26 centers (22 in the US and 4 in Canada)
Study Period:	Dates unspecified; 32 weeks (7 weeks ascending dose phase; 24 weeks maintenance phase)
Primary Objectives:	Compare the efficacy, safety, and tolerability of pramipexole with placebo in advanced PD patients with motor fluctuations under levodopa/carbidopa treatment.
Methodology:	Randomized, placebo-controlled, double-blind, multicenter investigation
Diagnosis and Main Criteria for Inclusion:	• Patients at least 30 years of age with advanced idiopathic PD in stage II to IV as measured by the Hoehn and Yahr scale during an "on" period. • Patients must have continued to experience motor fluctuations specifically characterized as an end-of-dose phenomenon or a "wearing-off" effect while receiving a stable dosage of levodopa/carbidopa for at least 30 days prior to entering the study.
Number of Subjects (planned and analyzed):	• 181 patients were randomized to active treatment and 179 were randomized to placebo. • 151 (83.4%) active treatment subjects and 140 (78.2%) placebo subjects completed the study • An intent-to-treat (ITT) analysis was performed on all patients at each visit. Missing data were estimated using the last observation carried forward (LOCF) method.
Treatment Regimens:	• Pramipexole dihydrochloride was titrated over a period of 7 weeks from 0.375 mg to 4.5 mg daily in 3 divided doses. Maintenance dose of 4.5 mg daily
Criteria for Evaluation:	• Changes in the average of the "on" and "off" ratings for the UPDRS parts II (ADL) and III (motor) scores between baseline and the end of the maintenance period were the primary outcome measures. • Secondary endpoints included UPDRS Part II for "on" and "off" periods; average percentage of "off" time; average severity of "off" time; dosage of concomitant levodopa/carbidopa; Schwab-England Disability Scale; Modified Hoehn and Yahr Scale for "on" and "off" periods; UPDRS parts I to IV; Parkinson Dyskinesia Scale; and timed walking test

Clinical Results:

- The difference between pramipexole and placebo for the average UPDRS Part II "off" and "on" data and the motor part of UPDRS III for the "on" period was statistically significant ($P<.05$).
- The difference between pramipexole and placebo on the Schwab-England Disability Scale for both the "off" and "on" periods were statistically significant ($P<.05$).
- Mean changes from baseline to end of maintenance in mentation (measured on the UPDRS Part I), dyskinesias (measured on the Parkinson Dyskinesia Scale), or timed walking in the pramipexole group, were not statistically significantly different from mean changes in the placebo group.
- Severity of the "off" periods decreased significantly with pramipexole compared with placebo ($P < 0.05$).

Safety Results:

- Common drug-related adverse events in the pramipexole group included: dyskinesia (61.3%), asymptomatic orthostatic hypotension (48.1%), dizziness (36.5%), insomnia (22.7%), hallucinations (19.3%), nausea (17.7%), symptomatic orthostatic hypotension (16.0%) and confusion (11.0%).
- In the placebo group, the common drug-related adverse events were asymptomaic orthostatic hypotension (48.0%), dyskinesia (40.8%),dizziness (31.8%), nausea (16.7%), insomnia (15.6%), tremor (12.3%), symptomatic orthostatc hypotension (11.2%), headache (10.6%) and pain (10.1%).
- Differences in insomnia, confusion, agitation, paranoia, and depression between pramipexole and placebo were not clinically significant.
- Hallucinations were statistically significantly higher in the pramipexole group (21%) versus the placebo group (5.6%, $P\leq.0001$)

Conclusions:

The study demonstrated that pramipexole administered concurrently with levodopa/carbidopa improves ADL, and motor function and reduces disability and disease severity compared to placebo.

Review #8:	**Double-Blind Comparison of Pramipexole and Bromocriptine Treatment with Placebo in Advanced PD.[16]**
Author, Year	Guttman et al, 1997
Journal	Neurology; 49:1060-1065
Study Sites:	34 sites in 6 European countries and Canada
Study Period:	36 weeks
Primary Objectives:	Evaluate the efficacy, tolerance, and safety of pramipexole versus placebo in patients with advanced PD with motor fluctuations.
Methodology:	Randomized, double-blind, multicenter, placebo-controlled, parallel-group trial
Diagnosis and Main Criteria for Inclusion:	• Patients were at least 30 years of age and had idiopathic PD with Hoehn and Yahr stages II to IV during an "on" period. Patients received an optimized dose of levodopa/carbidopa and were stable for 30 days prior to the initial administration of study medication.
Number of Subjects (planned and analyzed):	• A total of 246 patients were randomized to pramipexole (n = 79), bromocriptine (n = 84) and placebo (n = 83) groups. The study was not powered to compare pramipexole and bromocriptine.
Treatment Regimens:	• Pramipexole, up to 4.5 mg per day; bromocriptine, up to 30 mg per day; and placebo.
Criteria for Evaluation:	• Primary end points were the UPDRS part II Activities of Daily Living Scale (average of "on" and "off" scores) and the UPDRS part III Motor Examination Scale. Change from baseline to 6 months of maintenance medication was assessed. • Secondary end points included the UPDRS I, UPDRS IV, modified Hoehn and Yahr staging both "on" and "off", modified Schwab and England Disability Scale, Parkinson Dyskinesia Scale, timed walking test, global clinical assessment of efficacy, patient diary records, FSQ, and EuroQoL

Clinical Results:

- Reduction in UPDRS II and III subscales was significantly higher in the pramipexole group (26.67% and 34.88% respectively) compared to the placebo group (4.76% [*P* = .0002] and 5.71% [*P* = .0006], respectively). Bromocriptine treatment was also significantly better than placebo on these measures, but the magnitude of the response was less than that observed with pramipexole.
- On average, percentage of "off" time was significantly lower in the pramipexole group compared to placebo.
- The pramipexole group had a 15% reduction in the awake hours "off" time, which resulted in approximately 2.5 more hours of "on" time each day (P = 0.007)
- The bromocriptine group did not experience a significant change in its average percentage of "off" time (P=0.2)
- FSQ Basic Activities of Daily Living, Intermediate Activities of Daily Living, and Mental Health Scale scores for the pramipexole and bromocriptine groups were significantly better than placebo.

Safety Results:

- 16 (20%) patients in the pramipexole group and 33 (40%) patients in the placebo group dropped out of the study due to adverse events.

Conclusion:

- In advanced PD patients, pramipexole and bromocriptine were both significantly better than placebo for both primary end points.

Review #9:	**Efficacy, Safety, and Tolerance of the Non-Ergoline Dopamine Agonist Pramipexole in the Treatment of Advanced PD: A Double Blind, Placebo Controlled, Randomized, Multicenter Study.[14]**
Author, Year	Pinter et al, 1999
Journal	Journal of Neurology and Neurosurgery Psychiatry; 66:436-441
Study Sites	9 sites in Europe
Study Period:	7 week dose titration interval and 4 week maintenance period
Primary Objectives:	Assess the efficacy, safety, and tolerance of pramipexole as an add-on drug in patients with advanced PD with motor fluctuations.
Methodology:	Randomized, double-blind, multicenter, placebo-controlled trial
Diagnosis and Main Criteria for Inclusion:	• Patients with idiopathic PD classified according to the UK PD Society Brain Bank; who experienced motor fluctuations or abnormal involuntary movements on a stable levodopa/carbidopa regimen. • Patients with Hoehn and Yahr classification stages II and IV were included.
Number of Subjects (planned and analyzed):	• 34 patients were randomized to pramipexole and 44 to placebo. • One patient was dropped from the ITT analysis as he was inadvertently randomized twice. • 29 pramipexole patients and 38 placebo patients completed the study according to protocol.
Treatment Regimens:	Pramipexole (dose titration period: 0.2 to 5.0 mg/day; maintenance period 5 mg/day); placebo
Criteria for Evaluation:	• The primary endpoint was the change in the UPDRS total score at the end of the maintenance period compared with baseline. • Secondary end points were changes in sub scores (4 parts): part I (mentation, behavior and mood), part II (activities of daily living), part III (motor examination), and part IV (complications of therapy), Hoehn and Yahr scale, the Schwab and England scale, and the Parkinson dyskinesia scale, the patients' diary, and global clinical assessment at the end of maintenance interval compared with baseline.

Clinical Results:

- UPDRS total score was reduced by 20.1 (37.3%) in the pramipexole group compared to 5.9 (13.1%) in the placebo group ($P<.001$).
- Differences in UPDRS total scores between treatment and placebo were significant at the end of Week One and remained significant until the end of the maintenance period.
- Median change in UPDRS part II subscore and part III subscore from baseline to end of maintenance was significantly different between treatment and placebo.
- Hoehn and Yahr staging improved in 6 (18%) patients in the pramipexole group and 12 (27%) patients in the placebo group.
- Hoehn and Yahr staging deteriorated in 2 (6%) patients in the pramipexole group and 4 (9%) patients in the placebo group.
- For the Schwab and England scale, pramipexole, compared to placebo, showed improvements in the "on" period in 52% of patients versus 18%; and in the "off" period in 54% of patients versus 27%.

Safety Results:

- Fifty percent of the patients treated with pramipexole and 45% of those treated with placebo experienced a drug-related adverse event.
- Fourteen patients (41%) in the pramipexole versus 7 patients (16%) in the placebo group experienced psychiatric adverse events (mainly vivid dreams and visual hallucinations).
- Common (> 10%) adverse events in the pramipexole group were fatigue (29.4%), dyskinesia (14.7%), agitation (11.8%), and vivid dreams (11.8%). In the placebo group these were headache (18.2%), dizziness (27.3%) and aggravated parkinsonism (13.4%)

Conclusion:

- Pramipexole is efficacious and tolerated in patients with advanced PD, with an improvement in activities of daily living, motor function, and treatment-associated complications.

Review #10:	**Randomized, Double-Blind Study of Pramipexole with Placebo and Bromocriptine in Advanced PD.[56]**
Author, Year	Mizuno et al, 2003
Journal	Movement Disorders; 18:1149-1156
Study Sites:	38 sites throughout Japan
Study Period	April 1999 – March 2000
Primary Objectives	To determine whether the efficacy of adjunctive pramipexole is superior to placebo and not inferior to bromocriptine in patients with advanced PD.
Methodology	Multicenter, double-blind, randomized, 3-arm parallel-group clinical trial
Diagnosis and Main Inclusion Criteria	• Patients 20 years and older with PD • Included patients with continuing problems on levodopa/carbidopa (eg, wearing-off, on-off, and freezing phenomena) • Stability on levodopa/carbidopa therapy for at least 28 days
Number of Subjects	• 325 randomized, 315 received treatment, 313 included in analysis
Treatment Regimens	• Placebo • Pramipexole, ascending dose schedule up to 4.5 mg/day • Bromocriptine, ascending dose schedule up to 22.5 mg/day • 12-week trial with an 8-week ascending dose period and a 4-week maintenance dose period
Criteria for Evaluation	• Comparisons were made between baseline score and evaluation at the 12-week endpoint. Assessments also were made every 2 weeks during the study period. • Primary endpoints included the total score of the UPDRS II (ADL Scale) and the total score of the UPDRS III (Motor Examination Scale). • Secondary endpoints included the total score of the UPDRS I, UPDRS IV, modified Hoehn and Yahr Staging Scale, Clinical Global Impression on Efficacy (CGI), and responder analysis on the changes of UPDRS II, III, and I to IV total scores. • The safety assessment was based on the frequency of adverse events and abnormal laboratory and physical findings.

Clinical Results:

- Compared to placebo, total scores for both the UPDRS II and III were reduced in the pramipexole group (*P*<.001). Mean change in UPDRS II: placebo, -2.03; pramipexole, -3.98. Mean change in UPDRS III: placebo, -5.55; pramipexole, -11.75.
- Bromocriptine also was significantly superior to placebo, although the magnitude of the response was less than pramipexole (not statistically significant).
- Proportion of responders showing a 30% or more reduction in UPDRS II and III, I to IV total scores from baseline, were significantly larger in the pramipexole group than the placebo group for each variable (P <0.001).
- Secondary endpoints: On CGI, pramipexole was significantly better than both bromocriptine and placebo; 61.8%, 47.1%, and 28.0% were evaluated as having an effective or very effective response, respectively.
- No significant difference for the pramipexole group, when compared to placebo and bromocriptine in the analysis of UPDRS I
- Significant difference favoring placebo over pramipexole in the analysis of UPDRS IV (p=0.006); no significant difference between pramipexole and bromocriptine in this analysis

Safety Results:

- Adverse events were reported by 85.3% of patients taking pramipexole (including 8 withdrawals), 90.5% of those taking bromocriptine (12 withdrawals), and 76.9% of those taking placebo (9 withdrawals). The rates of AEs, however, were not significantly different between the groups.
- None of the patients in the pramipexole group had serious adverse events attributable to the medication.

Conclusions:

- Pramipexole was superior to placebo in terms of reducing UPDRS II (ADL) and III (Motor) scores.
- Analysis of 2° endpts indicates pramipexole might be superior to bromocriptine and warrants further investigation.

Review #11:	**An open-label, multicentre clinical trial to determine the levodopa/carbidopa dose-sparing capacity of Pramipexole in patients with idiopathic PD.[29]**
Author, Year	Pinter et al., 2000
Journal	Journal of Neural Transmission; 107:1307-1323
Study Sites:	14 sites (4 in Austria, 4 in Germany, 4 in Netherlands, and 2 in Switzerland)
Study Period:	Dates unspecified; 12-week trial
Primary Objectives	To determined the levodopa-sparing capacity of pramipexole when used as an add-on treatment in patients with advanced PD
Methodology	Multicenter, open-label, baseline-controlled clinical trial in Europe
Diagnosis and Main Inclusion Criteria	• Patients of both sexes with PD (Hoehn and Yahr stage II-IV) • Stability on levodopa therapy (250-1500 mg/day) for at least 28 days • Patients stratified according to levodopa dose (>500 mg/day, ≤500 mg/day)
Number of Subjects	• 98 screened, 93 entered trial, 90 included in intention-to-treat (ITT) analysis, 87 completed trial, 61 included in per-protocol (PP) analysis • 59 patients in low-levodopa subgroup, 31 in high-levodopa subgroup
Treatment Regimens	• Pramipexole, ascending dose schedule up to 4.5 mg/day • 12-week trial including a 3-week titration phase, a 4-week dose-adjustment phase, a 2-week maintenance phase
Criteria for Evaluation	• The primary endpoint was the change in levodopa dose at the end of the maintenance period compared with baseline among patients whose efficacy and tolerability remained relatively unchanged. • Safety was assessed by laboratory and physical findings, blood pressure evaluation, 12-lead ECG, and documentation of adverse events.

Clinical Results:

- The mean reduction of adjusted levodopa dose was 219.1 mg (43.6%) in the per-protocol group and 202.9 mg (42.2%) in the ITT group.
- In the ITT group, 72.2% of patients were classified as responders (20% or more reduction in levodopa dose).
- 47% of patients experienced a levodopa reduction of at least 40% while remaining stable or improving in terms of parkinsonian symptoms (sum of UPDRS II and III).

Safety Results:

- Adverse events were common (84.9% of patients), and 13 patients were excluded from PP analysis based on drug-related adverse events (eg, dizziness, dyskinesias, visual hallucinations, vasovagal syncope, akinesia, stomach pain, sleep disturbances, knee pain).
- The occurrence of asymptomatic hypotension (15.1%) was higher than symptomatic hypotension (1.1%) in the pramipexole group.

Conclusion:

- Results indicate that add-on pramipexole can reduce levodopa/carbidopa dose while maintaining or even improving parkinsonian symptoms.

Review #12:	**Pramipexole in patients with PD and marked drug resistant tremor: A randomized, double blind, placebo-controlled, multicenter study.[54]**
Author, Year	Pogarell et al, 2002
Journal	Journal of Neural Neurosurgery and Psychiatry; 72:713-720
Study Sites	Four sites in 2 European Countries
Study Period	Up to 12 weeks
Primary Objectives	To determine the effectiveness of adjunctive pramipexole in controlling tremor among patients with early or advanced PD presenting with marked, drug-resistant tremor
Methodology	Multicenter, double-blind, randomized, placebo-controlled clinical trial in Europe
Diagnosis and Main Inclusion Criteria	• Patients of both sexes with PD (Hoehn and Yahr stage I-IV) as determined by UK PD brain bank criteria • Patients had to have marked and drug-resistant tremor • Stability on antiparkinsonian therapy for at least 30 days
Number of Subjects	90 registered, 84 randomized, 83 included in intention-to-treat analysis, 82 completed protocol
Treatment Regimens	• Placebo (N = 40) • Pramipexole, ascending dose schedule up to 4.5 mg/day (N = 44) • 12-week trial with a 7-week ascending dose period, a 4-week maintenance dose period, and a 1-week dose reduction period
Criteria for Evaluation	• The primary endpoint was the change in total tremor score during "on" periods from baseline to end of maintenance period. Tremor score was the sum of UPDRS items 16, 20, and 21. • The secondary endpoints included change in individual tremor score items, change in 2 tremor self-rating scales, change in long-term tremor occurrence as measured by EMG, and a global assessment of tremor change. • Safety was assessed by laboratory and physical findings, blood pressure evaluation, 12-lead ECG, documentation of adverse events, and a global impression of tolerance.

Clinical Results:

- Patients taking pramipexole experienced a mean decrease in total tremor score of -5.8 compared to -1.5 in those taking placebo (*P*<.0001). The difference in mean relative change was -34.7%.
- Pramipexole also was superior to placebo for individual tremor items (*P*<0.01) and all other secondary endpoints (*P*<.0001). EMG scores showed a mean relative change of -45.7%. The sum of the UPDRS II and III scores had a percentage difference of -30.9%, in favor of pramipexole.

Safety Results:

- The global clinical impression of tolerance was rated as good in 94% of patients and did not differ between the two groups.
- Patients taking pramipexole were more likely to report adverse effects compared to patients taking placebo (93.2% versus 77.5%, *P* = .06).
- One patient in the pramipexole group experienced a serious drug-related adverse effect (orthostatic hypotension with a short loss of consciousness).
- While a higher percentage of patients in the pramipexole group experienced fatigue (22.7%), dizziness (18.2%), insomnia (20.5%), nausea (15.9%), abdominal pain(13.6%) and headache (13.6%) than those in the placebo group, the differences were not statistically significant.

Conclusions:

- Add-on therapy with pramipexole resulted in a reduction in tremor among patients with previously drug-resistant and marked tremor.

Review #13:	**Randomized, double-blind, 3-month parallel study of the effects of pramipexole, pergolide, and placebo on Parkinsonian tremor.[57]**
Author, Year	Navan et al, 2003
Journal	Movement Disorders; 18(11):1324-1331
Study Sites:	2 hospitals in London and Essex
Study Period:	February 2001 – November 2001
Primary Objectives:	To compare the antitremor effect of pramipexole, pergolide, or placebo in PD
Methodology:	Double-blind, randomized controlled, parallel clinical trial in Europe
Diagnosis and Main Inclusion Criteria:	• Patients with idiopathic PD (UK PD Society brain bank criteria) • Symptomatic tremor of an upper limb that reached at least grade 2/10 in severity on a validated tremor rating • Had not previously taken any direct-acting dopamine agonist class medication, although other antiparkinsonian medications were permitted
Number of Subjects:	• 40 screened, 30 included in the trial • 10 patients in each arm (pramipexole, pergolide, or placebo)
Treatment Regimens:	• Placebo, pergolide, or pramipexole (doses escalated to 1.5 mg 3 times daily over 3 months) • Patents were pre-treated with domperidone 10 mg orally with each dose of (placebo or active) treatment for the first week.
Criteria for Evaluation:	• Primary outcomes were final (3-month) UPDRS III and a Tremor Index (TI; TI equal to the sum of measured tremor scores for rest tremor, postural tremor, and spiral tremor). TI score ranged from 0 to 30. • Secondary outcomes included scores on rest tremor, postural tremor, tremor in spirals, accelerometry (rest and postural tremor), nine-hole peg-test, Becks Depression Rating Scale/HADS, Euroquol EQ-5D health status scores, sitting and standing blood pressure, and pulse rate. • Safety was assessed by sitting and standing blood pressure and pulse rate, and documentation of adverse events. • Patients were assessed for each outcome at baseline and then for approximately 1 hour on 3 separate mornings at monthly intervals, commencing at the same time of day on each occasion.

Clinical Results

- UPDRS III scores decreased more over time in the groups receiving active treatment. TI scores decreased over time in each group, although more in those on active treatment.
- Analysis of covariance demonstrated evidence for a treatment effect on both TI ($F(2, 20) = 6.53$; $P = 0.007$) and UPDRS III ($F(2, 20) = 10.11$; $P = 0.001$).
- No significant difference between active treatments on either TI or UPDRS III.
- Pergolide had a significantly greater ($P<.01$) antipostural tremor effect than placebo, while pramipexole did not.
- Effect of treatment on spirals was not significant.
- No significant differences were found between treatments in their effects on the nine-hole peg test performance, Euroquol-EQ-5D health status scores or total scores for HADS or Beck's depression inventory.

Safety Results:

- Most patients in each treatment group experienced an adverse effect (placebo, n = 5; pergolide, n = 10; pramipexole, n = 9).
- Sitting diastolic blood pressure fell more on pergolide (mean ± SD, 60.8 ± 10.7 mm Hg) than on pramipexole (76.0 ± 15.1 mm Hg) at the final assessment ($P<.05$).

Conclusions

Pergolide and pramipexole (1.5 mg 3 times daily) have similar anti-PD tremor and UPDRS III actions that are significantly superior to placebo.

Review #14:	**Pramipexole and Pergolide in the Treatment of Depression in PD: A National Multicenter Prospective Randomized Study.**[58] (Depression is not an FDA-approved indication of MIRAPEX.)
Author, Year	Rektorova et al (2003)
Journal	European Journal of Neurology; 10:399-406
Study Sites	Multicenter
Study Period:	8 months
Primary Objectives:	Compare the effects of pramipexole and pergolide as add-on to levodopa on depressive symptoms in patients with Parkinson's disease
Methodology:	Multicenter, prospective randomized study
Diagnosis and Main Criteria for Inclusion:	• Nondemented patients with advanced PD and mild or moderate depression.
Number of Subjects (planned and analyzed):	• 41 nondemented patients (25 men, 16 women) with mild or moderate depression and advanced PD • 19 pramipexole and 17 pergolide patients completed the study
Treatment Regimens:	• Pramipexole (recommended 3 mg; range 1.5 to 4.5 mg/day); Pergolide (recommended 3 mg; range 1.5 to 4.5 mg/day)
Outcome Measures:	• Montgomery-Asberg Depression Rating Scale (MADRS); These scores were measured at the first and sixth (final) visit. • UPDRS II, III, and IV. III and IV scores were measured at all 6 visits.

Clinical Results:

- Eight of 18 (44%) pramipexole patients and 3 of 16 (18.7%) pergolide patients had at least a 50% reduction in MADRS scores from first to last (sixth) visit.
- Average value of MADRS scores decreased in both groups (pramipexole:statistically significant decrease from 15.11 at first visit to 9.28 at the sixth; pergolide: from 11.25 at the first to 10.06 to the last)
- Average UPDRS II, III and IV scores decreased significantly from first to last (sixth) visit (at the 1% significance level) in both groups.

Safety:

- The most frequent adverse effects, occurring in 13 pramipexole and 14 pergolide patients, were sleep disturbances, aggravation of dyskinesias, nausea, orthostatic hypotension, and hallucinations.

Conclusions:

- Pramipexole appears to have antidepressive effects in patients with advanced PD.

Review #15:	**Long-term efficacy and safety of pramipexole in advanced Parkinson's disease: results from a European multicenter trial.[59]**
Author, Year	Moller et al 2004
Journal	In press
Study Sites	European Multicenter
Study Period:	32 week trial with an open label extension of 57 months
Primary Objective:	Compare the efficacy, safety, and tolerability of pramipexole with that of placebo in advanced PD
Methodology:	Multicenter, double-blind, placebo-controlled, parallel group study
Diagnosis and Main Criteria for Inclusion:	• PD patients at least 30 years of age who experienced motor fluctuations characterized as "end of dose" phenomena while receiving an individually adjusted stable dosage of levodopa for atleast 3 days prior to entering the study..
Number of Subjects (planned and analyzed):	• Double-blind study: pramipexole N = 174; placebo N = 180 • Open-label study: pramipexole N = 146; placebo N = 116
Treatment Regimens:	• Pramipexole or placebo was administered 3 times a day as an adjunct to levodopa in seven dosages from 0.375 – 4.5mg per day
Outcome Measures:	Primary endpoints: • Change from baseline to end-of-maintenance (1) of the average sum score of the "on" and "off" ratings for UPDRS II and (2) of the average sum score of the "on" ratings for UPDRS III. Secondary endpoints: • Change from baseline to end-of-maintenance for the following scales: UPDRS II during "on" periods only; UPDRS I and IV and the total UPDRS score; average percentage and severity of "off" time during waking hours according to the patients' records; modified Schwab-England Disabilit Scale of "on" and "off" periods; dosage of concomitant levodopa; modified Hoehn and Yahr Scale for "on" and for "off" periods; Parkinson dyskinesia scale to assess dyskinesia and dystonia during "on" periods; timed walking test to supplement UPDRS III; individual items of UPDRS II and III; and Global Clinical Assessment.

Clinical Results:

- Pramipexole improved UPDRS sum scores of parts II and III by 30% and "off" times by approximately 2.5 hours per day.
- Post hoc-analyses revealed that patients with pronounced resting tremor derived a clear benefit from pramipexole treatment compared with placebo.
- Pramipexole significantly improved the subitems motivation/initiative and depression in a subpopulation with increased UPDRS I scores at the time of inclusion. (Depression is not an FDA-approved indication of MIRAPEX.)
- Pramipexole showed statistically significant improvements in all of the above listed secondary end points except Parkinson dyskinesia scale and Modified Hoehn and Yahr in "on" period.

Safety:

- In the double-blind study 3 (1.7%) of the pramipexole patients and 4(2.2%) of the placebo patients experienced somnolence
- Common drug-related events in the double-blind phase (> 10%) included dyskinesias (30%-Ppx vs 8.7% Placebo), asymptomatic orthostatic hypotension 23.3%-Ppx vs 20.2%-Placebo), nausea (16.1%-Ppx vs 12.0%-Placebo), visual hallucinations (11.1%-Ppx vs 4.4%-Placebo), and dizziness (10.6%-Ppx vs 7.1%-Placebo)

Conclusions:

- Pramipexole is efficacious in the treatment of advanced PD and may have tremorlytic and antidepressive properties

Review #16:	**Efficacy and safety of pramipexole in idiopathic restless legs syndrome: A polysomnographic dose-finding study—the PRELUDE study.[45]**
Author, Year	Partinen et al (2006)
Journal	Sleep Medicine
Study Sites:	conducted in Finland
Study Period	3 weeks plus 26 week OL follow-up
Objectives	• To determine the optimal dose of pramipexole in patients with idiopathic restless leg syndrome by polysomnography • To evaluate clinical improvement in RLS symptoms with use of pramipexole
Methodology	Double-blind, placebo-controlled, parallel-group, fixed-dose trial design
Diagnosis and Main Inclusion Criteria	Patients with idiopathic restless leg syndrome; age = 18-80; baseline IRLS score >15
Number of Subjects	• 109 patients randomized to placebo (n = 22) or different daily doses of pramipexole: 0.125 mg (n = 21), 0.25 mg (n = 22), 0.5 mg (n = 22), or 0.75 mg (n = 22)
Treatment Regimens	• Either placebo or different daily doses of pramipexole (0.125 mg, 0.25 mg, 0.5 mg, 0.75 mg). For higher dose groups doses were increased stepwise (day 5: 0.25 mg; day 9: 0.05 mg; day 13: (0.75 mg)
Criteria for Evaluation	• Primary endpoint: reduction in the periodic limb movements during time in bed index (PLMI) • Secondary endpoint: change in the RLS symptom severity score (RLSRS, max : 40 points) and Clinical Global Impression Scale of Improvement (CGI-I) score

Clinical Results

Dose/Group Very Improved	Mean PLMIs		Mean Reduction In RLSRS**	% patients with ≥50% Reduction in RLSRS	% Patients with Much/Much CGI at Week 3
	Baseline	End of 3 weeks			
Placebo	42.1	35.5	6.2 points	33.3	42.9
0.125mg	42.1	6.9*	11.7 points***	61.9	61.9
0.25mg	32.8	5.0*	15.3 points***	68.2	68.2
0.5mg	34.5	4.9*	17.6 points***	77.3	86.4 (P=0.003)
0.75mg	34.1	7.6*	15.2 points***	76.2	85.7 (P=0.0088)

**P*<.0001 vs placebo for all dose groups; **from baseline to end of 3 weeks; ***P*<.0054 vs placebo for all dose groups,

Safety Results

- Nausea: 4.5% in placebo and 14.9% in all pramipexole dose groups
- Somnolence: Three patients all in the 0.125mg dose group
- Orthostatic hypotension: One patient (0.125 mg)

Conclusions

- Pramipexole was efficacious in relieving RLS symptoms over the range of 0.125 mg/day to 0.75 mg/day within 3 weeks of therapy.
- Safety and tolerability were favorable in all groups tested.

Review #17	**Efficacy of pramipexole in restless legs syndrome (RLS): A 6-week, multicenter, randomized,double-blind study (effect-RLS study)[46]**
Author, Year	Oertel et al (2006)
Journal	Movement Disorders
Study Sites:	37 sites in Austria, Germany, Norway, Sweden and the Netherlands
Study Period	6-week DB plus 46 week DB (responders) or OL (nonresponders) follow up
Objectives	Evaluate the efficacy of pramipexole (0.125mg-0.175mg/day) versus placebo in RLS for 6 wks
Methodology	Multicenter, double-blind, placebo-controlled, flexible-dose design
Diagnosis and Main Inclusion Criteria	Patients with idiopathic restless leg syndrome; age = 18-80; baseline IRLS score >15
Number of Subjects	345 patients randomized 1:2 to placebo (n=115) or pramipexole (n=230)
Treatment Regimens	The starting dose was 0.125mg or matched placebo. During the first 4 weeks, the daily dose was titrated at weekly intervals to 0.25mg, 0.5mg, or 0.75mg as tolerated by the patient. At week 6, 14.8% of the pramipexole-treated patients received 0.125mg/day, 26.5% received 0.25mg/day, 28.7% received 0.5mg/day and 30% received 0.75mg/day.
Criteria for Evaluation	• Primary endpoints were a reduction in the IRLS score and improvement in the CGI-I scale • Secondary endpoints were PGI, SF-36, VAS

Clinical Results

- Primary endpoints: After 6 weeks of treatment the IRLS score was reduced by an adjusted mean difference (±SE) in favor of pramipexole of -6.6 (±1.1) with a 95% CI of -8.6 to -4.5 ($p < 0.0001$). The analysis of CGI-I at week 6, 32.5% of patients in the placebo group and 62.9% of those in the pramipexole group were assessed as either "much improved" or "very much improved" compared with baseline ($p < 0.0001$)
- Secondary endpoints: At 6 weeks, the proportions of PGI responders were 31.6% for placebo and 61.6% for pramipexole ($p < 0.0001$). VAS assessments at 6 weeks showed symptom severity slightly reduced with placebo bul substantially lowered with pramipexole. Increase in daytime sleepiness, referred to as "augmentation," was neither specifically assessed nor spontaneously reported by patients in either group.

Safety Results

- The most frequent drug-related AE's were nausea (5.2% vs. 9.6%), fatigue (4.3% vs. 9.1%), headache (6.1% vs. 7.0%), and dizziness (3.5% vs. 3.5%) in the placebo and pramipexole groups, respectively.
- No patients experienced sudden onset of sleep, 2.6% of patients in each group reported daytime sleepiness.
- Analysis of the CGI side effects subscale revealed that the vast majority of patients in both treatment groups were not impaired by side effects (97.4% with placebo vs. 93.3% with pramipexole).

Conclusions

- Both primary assessments demonstrated significant improvement in RLS severity in pramipexole-treated patients compared with patients who received placebo.
- During the entire study period pramipexole was well tolerated with a greater proportion of patients in the placebo group discontinuing because of AEs than with pramipexole.
- After 1 week of treatment, 30.6% of patients in the pramipexole group assessed their condition as "much/very much better" (PGI responders) compared with 7% in the placebo group.

Review #18	**Efficacy and safety of pramipexole in RLS.**[47]
Author, Year	Winkelman et al (2006)
Journal	Neurology
Study Sites:	43 sites in the United States
Study Period	12-weeks
Objectives	Evaluate the efficacy and safety of pramipexole in moderate-to-severe RLS over 12 weeks
Methodology	Multicenter, double-blind, randomized, placebo-controlled trial of fixed doses of pramipexole (0.25mg, 0.5mg, and 0.75mg/day)
Diagnosis and Main Inclusion Criteria	Patients with idiopathic restless leg syndrome
Number of Subjects	344 patients
Treatment Regimens	Patients were uptitrated to their randomized dose over 3 weeks. Placebo (n=86), 0.25mg/day (n=88), 0.5mg/day (n=80), and 0.75mg/day (n=90)
Criteria for Evaluation	• Primary endpoints were a reduction in the IRLS score and improvement in the CGI-I scale • Secondary endpoints were PGI, VAS, ESS, ASRS, and RLS-QOL

Clinical Results

- Primary endpoints: The mean IRLS change from baseline at 12 weeks was greater in patients receiving each pramipexole dose than patients receiving placebo (0.25mg, p= 0.0086; 0.5mg, p= 0.0011; 0.75mg. p= 0.0005) with no significant differences among the doses. 72% of pramipexole patients were assessed as CGI-I responders after the 12 weeks compared to 51.2% of the placebo group (p=0.0005)
- Secondary endpoints: Across all pramipexole doses, 61.4% of patients were PGI responders vs. 44.7% for placebo (p=0.0056) after 12 weeks. All VAS ratings had improved significantly in the pramipexole group vs. placebo group by week 12. At week 12 the adjusted mean reduction for the ESS was not a significant difference between the pramipexole and placebo groups with the 0.25mg dose being the only dose with a trend toward reduction in daytime sleepiness. Pramipexole-related improvement was present at week 6 and persisted without diminishing through week 12 , for the RLS-QOL with adjusted mean changes from baseline that were highly statistically significant compared to placebo at all doses.

Safety Results

- The frequency of drug-related AEs and other AEs of severe intensity was higher in the pramipexole group, but a dose effect with a specific AE was only evident with nausea.
- Withdrawal from the study due to AEs was more common with the 0.5mg and 0.75mg doses than with the 0.25mg or placebo possibly because of forced titration to a fixed dose. Some patients may have received larger doses than needed had they been able to individualize their dose to response.
- Daytime sleepiness was not reported more commonly in the pramipexole group than the placebo group

Conclusions

- As rated by patients and clinicians, pramipexole doses of 0.25mg, 0.5mg. and 0.75mg/day were effective and safe in reducing the symptoms of moderate-to-severe RLS.
- RLS symptoms were improved by a significant amount compared to placebo as measured by the primary endpoints of a change in patient-rated symptom severity (the IRLS score) and clinician ratings of improvement (percentage of CGI-I responders).
- PGI responder rate, RLS-QOL ratings, and VAS ratings related to sleep satisfaction and symptom severity were secondary outcomes that showed significant treatment effects with pramipexole.

Review #19	**Controlled withdrawal of pramipexole after 6 months of open-label treatment in patients with Restless Legs Syndrome.**[48]
Author, Year	Trenkwalder et al (2006)
Journal	Movement Disorders
Study Sites:	13 sites in Germany
Study Period	12 week DB phase (phase 2) plus 26 week OL run-in phase (phase 1)
Objectives	Evaluate the sustained efficacy of pramipexole against RLS during 12 wks of placebo-controlled, double-blind treatment of patients who had responded to a 6-month open-label trial
Methodology	Multicenter, randomized, double-blind, placebo-controlled, parallel-group study
Diagnosis and Main Inclusion Criteria	For phase 1: Patients with idiopathic restless leg syndrome; age=18-80; IRLS score > 15 For phase 2: Responded to pramipexole in phase 1 with a CGI-I rating of "very much improved" or "much improved" and an IRLS total score ≤ 15; had a ≥80% compliance rate; had no dosage adjustments during the final 12 weeks of phase 1.
Number of Subjects	150 patients were randomized
Treatment Regimens	Placebo (n=72) or the optimized dosage of pramipexole (n=78
Criteria for Evaluation	• Primary endpoint was the time to a target event representing insufficient response as defined by concurrence of two independently rated parameters: a CGI-I score of "minimally," "much," or "very much," worse (compared with the score at the start of phase 2) and an increase of the IRLS to a score >15. • Secondary endpoints were other CGI subscales, PGI, RLS-QOL, VAS, ESS

Clinical Results

- **Primary endpoint**: By a Kaplan-Meier analysis and log-rank test, the survival estimate dropped to 0.85 at 5 days for placebo and the time to an estimate of 0.5 was 7 days. For pramipexole it took 42 days to reach a drop to 0.85 in survival estimate. Because less than 50% of the pramipexole group reached a target worsened event, the number of days to 0.5 could not be calculated.
- **Secondary endpoints:**
- Number of target events: In the placebo group 85.5% of patients reached the target event compared to 20.5% of patients in the pramipexole group (p< 0.0001)
- IRLS: The adjusted mean change from baseline (start of phase 2) was +14.9 for placebo and +2.0 for pramipexole (p< 0.0001) the divergence being evident after just one week of treatment.
- CGI-I: Clinically significant worsening of the CGI-I scale was evident within the first week;
- PGI: At the end of phase 2, 70.5% of the pramipexole group deemed themselves unchanged ans 10.3% felt they were worse. Of the placebo group, 63.8% felt they were worse and 30.4% felt they were unchanged.
- RLS-QOL: At the end of phase 2, the pramipexole group was unchanged (score of 90/100) whereas the placebo group experienced a clinically significant decrease of 12.5 points (p< 0.0001)
- ESS: No significant changes between treatment group differences at the end of phase 2

Safety Results

- A high proportion of placebo patients left phase 2 prematurely (placebo patients had a median of 13 days of participation compared to a median of 84 days for pramipexole recipients), thus the overall incidence of AEs was higher for pramipexole (39.7%) than for placebo (23.6%).
- There were no cases of augmentation and no cases of sudden onset of sleep
- Among the pramipexole patient AEs, there was no dose dependency and no associations with clinically relevant changes in laboratory parameters, vital signs, physical examination, or electrocardiogram.

Conclusions

This study demonstrates sustained efficacy of pramipexole at evening doses of 0.125mg to 0.75mg to treat moderate-to-severe RLS as rated by both patients (IRLS) and clinicians (CGI-I) with resultant improvement in sleep and quality of life for up to 9 months. The results also show the rapid decline in efficacy once pramipexole is withdrawn.

2.2. Clinical and Disease Management Intervention Strategies

No formal disease management or care management intervention strategies have been implemented for pramipexole.

2.3. Economic Evaluation Supporting Data

To date, there are no head-to-head trials comparing economic outcomes between pramipexole and ropinirole. However, cost-effectiveness of pramipexole in the treatment of early and advanced PD has been evaluated in one modeling study, which found that adding pramipexole to the treatment regimen of early and advanced PD patients improved health utility but also increased costs.[60] Details of this modeling study are summarized in Review #20.

In a cost-effectiveness analysis of randomized clinical trial data, Noyes and colleagues (2005) found that pramipexole is likely to be cost-effective compared to levodopa/carbidopa.[61] The trial compared pramipexole to levodopa/carbidopa in 301 patients with early PD. Patients were followed every 6 months for 4 years. Health care resource use (physician visits, hospitalizations, outpatient procedures, use of medical devices, off-trial medications, and time lost from work), obtained from patients utilization diaries, were converted into 2002 costs in US dollars and discounted at an annual rate of 3%. For pramipexole versus levodopa, the base-case incremental cost effectiveness ratio was $42,989/QALY, indicating that pramipexole was a fairly cost-effective alternative to levodopa over 4 years in early PD patients. Additional details of this study are summarized in Review #21.

Review #20	**Cost Effectiveness of Pramipexole in PD in the US.**[60]
Author, Year	Hoerger TJ, 1998
Journal	Pharmacoeconomics
Objective:	Estimate the costs and cost effectiveness (cost utility) of Pramipexole compared with baseline treatment in patients with early and advanced PD.
Economic Perspective:	Societal perspective
Drug Regimens	Pramipexole Vs No-pramipexole treatment; Pramipexole was also compared to other dopamine agonists including bromocriptine and pergolide
Methodology	Cost-effectiveness Model that linked UPDRS part II and III scores to costs and QALYs. Separate disease progression paths were developed for treatment with or without pramipexole and for early and advanced PD.
Data Sources	• Disease progression data obtained from clinical trials, literature review and review of health resource utilization in 193 neurology clinic outpatients
Number of Subjects	• 193 patients
Model Assumptions	• US data model that linked UPDRS Part II and III scores to disease progression, costs and patient utility. • Early-stage PD patients were defined as those who have not yet begun to use levodopa/carbidopa. These patients received pramipexole initially and had levodopa/carbidopa added later on in the course of therapy. • Advanced-stage PD patients were defined as those who were already receiving levodopa/carbidopa therapy and had pramipexole added to their current regimen. • In the model, a typical PD patient experiences the disease at age 55 years and lives for 16 years after the onset of PD. Levodopa/carbidopa is introduced with the disease reaches a pre-defined severity level.
Cost measures	• Direct costs included: hospital visits, emergency room visits, physician visits, other medical providers, prescription drugs, home health visits, special aids or equipment, nursing home care, domestic help, formal home care, community services • Indirect costs included: productivity/income (earnings loss)
Effectiveness/Utility Measures:	Cost/quality-adjusted life years (QALY); incremental cost/QALY
Analyses performed:	Cost-utility analyses; sensitivity analyses; incremental cost-effectiveness
Findings:	• The incremental CE ratio, based on total costs including productivity loss, for pramipexole in early and advanced PD was $8,837/QALY and $12,294 respectively (1997 values). • If only direct costs are considered, the incremental CE ratio is $34,423/QALY and $31,528/QALY (1997 values).
Conclusions:	For patients with early and advanced PD, treatment with pramipexole had higher costs but was more effective (improved health utility) than baseline treatment. However, inherent limitations of cost-effectiveness modeling should be considered before interpreting these results.

Review #21	**Pramipexole and Levodopa in Early Parkinson's Disease[61]**
Author, Year	Noyes et al, 2005
Journal	Pharmacoeconomics; 23(12): 1257-70
Main Objective:	Assess cost effectiveness of pramipexole compared with levodopa over the first 4 years of treatment
Economic Perspective:	US Societal perspective
Drug Regimens	Initial treatment with pramipexole versus initial levodopa treatment in early PD patients.
Methodology	Quality of life measured by EuroQoL (EQ)-5D and a healthcare resource utilization diary were collected alongside the multicenter CALM-PD clinical trial every 3 months over 4 years
Data Sources	• Disease progression data obtained from CALM-PD clinical trials and literature review • Healthcare utilization was collected by patient diary • Health resource utilization costs were estimated from the Medicare reimbursement schedule by DRG and CPT codes, US Census data, estimates from the National Nursing Home Survey, local facility rates, and the Drug Topics Red Book • To value time lost from work, current population census data was used stratified by patients' age and gender
Number of Subjects	• 301 patients
Model Assumptions	• Expert judgment used to estimate the number of neurologist visits over the 4-year trial period • Missingness at random was used for imputed EQ-5D missing data • Cost data was considered missing when subjects were lost to follow-up
Cost measures	• Cost data was adjusted to reflect 2002 values by the Consumer Price Index • Direct costs were used for six categories: provider visits, outpatient procedures and diagnostic tests, acute hospitalizations, emergency department visits, outpatient surgeries. Also collected were medication use, durable medical equipment, need for home help, and long-term care and rehabilitation services • Days of gainful employment lost
Effectiveness/Utility Measures:	• Cost/quality-adjusted life years (QALY); incremental cost/QALY (ICER)
Analyses performed:	• Cost-utility analyses; sensitivity analyses; incremental cost-effectiveness; sub-group analyses; Dynamic changes in net benefit (NB) based on willingness to pay: Healthcare payer analysis
Findings:	• ICER for pramipexole versus initial levodopa decreased over time from 1 to 4 years. At year 4, the ICER was $42,989 per QALY with societal view and $46,218 per QALY from a healthcare payer viewpoint (direct costs only) • Net benefit was higher for pramipexole in the following subgroups: low baseline EQ-5D and depression at baseline
Conclusions:	• In the treatment of early PD, the cost effectiveness of pramipexole versus levodopa improved over a 4 year time period. In subgroups, pramipexole was found to be more cost effective for patients with depression and a low baseline HRQoL score.

3. Modeling report of Mirapex in RLS

3.1 Budget Impact Model

Purpose

The interactive Budget Impact Model (BIM) for the treatment of RLS presents the change in pharmaceutical and medical costs to the payer with respect to the market shares (MS) of two FDA-approved treatments for RLS: pramipexole and ropinirole. Along with current and new MS for the prescription drug treatments, the user can adjust other model inputs, such as the number of plan enrollees, percentage of patients diagnosed with RLS, percentage of patients receiving dopamine agonists, age, drug costs, discounts, and co-payments. The BIM provides a simulation that is consistent with current treatment practices and can be tailored to individual health plan characteristics. The model assumes that only patients with moderate to severe RLS receive treatment. Of these patients, a percentage will receive the dopamine agonists, pramipexole or ropinirole.

Health Plan Simulation Inputs

RLS Patients

Using adjustable health plan demographics and RLS prevalence rates from literature, the number of new annual RLS cases is projected. The number of men and women in 10-year age groups is calculated using rates from US Census Data (US Census Bureau). The proportion of male to female patients, the proportion of patients over the age of 65 (Medicare patients), and the prevalence rates of RLS can be varied.

Once the number of patients in each age group is calculated, the number of patients with RLS is found using age- and sex-specific RLS prevalence rates. The prevalence rates for each group are as follows: males ages 20-65, 4.8%; males ages 65 or greater, 8%; females ages 20-65, 8.3%; females 65 or greater, 10.8%. These rates were derived from prevalence estimates based on the REST General Population Study with RLS defined as those that experience all 4 diagnostic symptoms of RLS at any frequency.[62]

RLS Treatment

The percentage of patients with symptoms severe enough to warrant treatment (2.7% of respondents were RLS "sufferers" or 37.34% of those with RLS) is also derived from the REST General Population Study. RLS sufferers were defined as those that met the 4 diagnostic criteria and had reported that these symptoms that were moderately to severely distressing and occurred at least twice weekly over the past 12 months.[62] In actual practice, rates of diagnosis and treatment of RLS are much lower due to study design and low awareness of RLS. These percentages can be user-adjusted to reflect actual practice. However, the default rates used are kept consistent to measure effect based solely on change in MS.

In actual practice, dopamine agonists are used as initial treatment for RLS symptoms 67.1% of the time. According to BIPI market forecasts, this rate is expected to increases to 89% in 5 years. Although the model allows the user to change the growing rate of patients receiving dopamine agonists, the default rates are kept consistent to determine effect in MS.

Market Share Scenario

The primary pharmacologic treatments for RLS are considered to be pramipexole and ropinirole. Current market shares were estimated using MS data from IMS Health, measured as moving annual total (MAT) New Prescriptions. National Disease and Therapeutic Index (NDTI) Factors for Prescriptions Data from IMS were used to find MS figures specific to the RLS market. BIPI market share forecasters predicted the anticipated change in percent MS of pramipexole relative to ropinirole over the next 5 years. Defaults MS for pramipexole in Year 1 is 37%. It is estimated that pramipexole will increase to 46% of MS by year 2.

Pharmacy Costs

Cost-per-pill, average daily costs-per-patient, and annual pharmacy costs-per-patient is calculated using fixed AWPs, RLS-specific strength mix, as well as modifiable discounts percentages. AWPs are based on April of 2007 prices published by First DataBank through Analy$ource. Drug costs can be altered by the user by changing the cost-per-pill directly, discount percentages, or applied monthly co-payments. The default average daily costs-per-patient are $2.30 for pramipexole and $2.25 for ropinirole.

Medical Costs

There are medical costs associated with initiating prescription drug therapies. The number of physician visits per year for patients with varying degrees of RLS was determined by expert opinion. In the BIM, it is assumed that a patient with no or mild RLS sees a general practitioner once annually. Those with moderate RLS see a general practitioner twice yearly, are referred to specialists (i.e., neurologist, sleep specialist, psychologist), seen 4 times within the first 3 months for drug titration, and seen 1 more time per each subsequent 3 months. Patients with severe RLS are seen by a general practitioner 3 times during each 3 month period, and a specialist 4 times in the first 3 months and twice during each subsequent 3 month period. Patients with very severe RLS are seen by a general practitioner once every 3 months, a specialist 4 times in the first 3 months, and 3 times during each subsequent 3 month period, and a quarter of these patients require a second specialist once every 3 months. The cost of a general practitioner visit is $50.29 and the cost of a specialist visit is $78.87 according to Essential Resource-Based Relative Value Scale (RBRVS).

Health state probabilities (the probability of being an RLS patient with mild symptoms or severe symptoms and so on) were extrapolated from the Oertel trial, a 6-week double-blinded trial evaluating flexible dose pramipexole versus placebo in

patients with mild to moderate RLS. Although the Oertel trial is used as the default, one may chose to run the model based on health state probabilities of other trials, as well. The model uses the following health states: "no RLS" represents patients with IRLS scores of 0; "mild RLS" represents an IRLS score between 1 and 10; "moderate RLS" represents between 11 and 20; "severe RLS" falls between 21 and 30; "very severe RLS" falls between 31 and 40; and death from all causes. The probability of moving from one state to another was also derived from the Oertel trial. In the trial, mean IRLS was reduced by 12.4 points with pramipexole and 6.1 points with placebo, demonstrating that pramipexole has double the effect size. This treatment effect was sustained to the end of the 46-week open-labeled extension period. Therefore, in the BIM, patients treated with pramipexole are more likely to move from a higher to lower health state (e.g., severe RLS to mild RLS) than patients receiving no treatment.

A meta-analysis conducted by Quilici, et al. directly and indirectly compared the efficacy of pramipexole and ropinirole by pooling the results of randomized, double-blind, placebo-controlled trials of patients with idiopathic RLS. [63] Direct meta-analysis demonstrated that both treatments were significantly superior to placebo. Mean reduction in IRLS versus placebo for pramipexole was -5.5 (95% CI, -7.7 to -3.2) and for ropinirole was -3.2 (95% CI, -4.3 to -2.1). The Bayesian indirect comparison demonstrated a superior reduction in IRLS for pramipexole versus ropinirole or -2.3 points. In addition, the odds of responding, defined as reporting "much improved" or "very much improved" on the Clinical Global Impressions – Improvements Scale (CGI-I), were 1.5 times higher with pramipexole, both with the observed probability of ≥97%. In the BIM, the resulting percentage of patients transitioning from a higher health state to a lower health state will be slightly greater with pramipexole than for ropinirole.[63]

The probability of treatment discontinuation for pramipexole is also derived from the Oertel trial, which has the longest timeframe of all trials and is, therefore, the more appropriate source of discontinuation data. The probability of patients discontinuing ropinirole is taken from a similarly-conducted trial by Walters, et al. [64]

The percentage of patients developing an adverse event is based on the Oertel trial for pramipexole and, for ropinirole, the trial by Walters, et al. In practice, because both agents are both relatively well-tolerated, there is rarely a cost associated with experiencing an adverse event. Therefore, the BIM makes an assumption that only those that experience a "severe" or "very severe" event, as defined within these trials, were considered severe enough to warrant visiting a physician. These few patients incurred the cost of visiting a general practitioner. Treatments for side effects common to dopamine agonists (nausea, vomiting, dizziness, etc.) are typically dopamine antagonists, which are not recommended for RLS patients and are not included in the BIM. Patients experiencing severe sleep disturbance were prescribed zolpidem ($4.08/pill) or eszopiclone ($3.70).

Base Case Results Summary

The results of running the model with the default inputs show that increasing the relative MS of pramipexole by 9 percentage points, as is predicted from Year 1 to Year 2 and, as a result, reducing MS of ropinirole by 9 percentage points reduces the health plan's total costs by $98,122 for 9,855 RLS patients receiving dopamine agonists. Pharmacy costs increase slightly due to a higher average daily cost with pramipexole. Medical costs are reduced due to a higher probability of responding, lower discontinuation rates, and better tolerability with pramipexole leading less need for physician visits. The costs differences are presented as follows:

- Per member per month (PMPM) costs changed from $1.37 to $1.37 for a difference of $-0.01
- Per treated member per month (PTMPM) costs changed from $106.41 to $106.96 for a difference of $-0.55
- Total cost for 9,855 RLS patients on dopamine agonists changed from $16,492,247 to $16,407,150 for a difference of -$85,097.

3.2 Cost-Effectiveness Model

The underlying structure of the BIM described in the previous section mirrors that of the cost-utility model developed to assess the cost-effectiveness of pramipexole relative to other treatments for idiopathic RLS. The model incorporates data from the clinical trials of pramipexole and published reports of trials for the key comparators (Trenkwalder et al, 2004; Walters et al, 2004; Benes et al, 1999).[64-66] Resource use, unit cost and utility data were derived from expert opinion and the literature. The model was originally designed to produce analyses for the UK (NICE) but can be adapted to other countries [described in Review #19]. The US-adapted model takes a US-based health care system perspective.

Similar to the BIM, the model population consists of patients with a diagnosis of idiopathic RLS and an IRLS score of greater than 15 (at least moderate disease severity). Model outputs are presented as changes in quality adjusted life years (QALYs) to allow comparison with other published models in this disease area, as well as changes in time spent in less severe health states.

The results of the model show that the incremental cost per QALY gained with pramipexole over no treatment is $9,236 over a three-year period. In addition, pramipexole is $205 less expensive and slightly more effective than ropinirole over the three year period. These results indicate that pramipexole is a highly cost-effective treatment option for idiopathic RLS. A range of one-way and probabilistic sensitivity analyses indicate that variation in the value of key parameters does not change the conclusion that pramipexole is a cost-effective alternative to no treatment or ropinirole for the management of idiopathic RLS.

The cost-effectiveness of pramipexole over levodopa treatment was also evaluated. For the first year of treatment, pramipexole is $106 less expensive and more effective than levodopa indicating that pramipexole is highly cost-effective relative to levodopa the first year of treatment. At 3-years, pramipexole is more effective with an incremental cost of $196, which yields an incremental cost per QALY gained is $3,669, regarded as highly cost-effective.

4. Clinical Value and Overall Cost

Parkinson's disease (PD) is caused by a slow, gradual loss of dopamine-producing brain cells, which limits a person's ability to control some of his or her muscles. The disease affects over 1 million people in North America and its prevalence is growing as the population continues to age.[18] Between 100 to 200 per 100,000 people in North America have PD.[17] Generally, the average age of onset of PD is in the late 50s to early 60s.[21] PD causes involuntary shaking of arms and legs, muscle rigidity, bradykinesia, and postural reflex impairment. The actual triggers and precise etiology of PD is still unknown although in recent years, certain environmental and genetic risk factors have been identified as potential causes.[19,20]

Despite medical intervention, PD symptoms progressively worsen, putting a significant burden on patients and their families. PD results in reduced quality of life, higher susceptibility to depression and cognitive impairment, increased risk for comorbidities such as pneumonia, increased medical expenses (physician visits and emergency care), and caregiver burden and risk of early nursing-home placement.[67-69] Combined annual direct and indirect cost of PD to patient and family has been estimated at $25,000. Comorbidity cost ratios reveal 2 to 3 times higher charges for dementia, broken bones, broken hips, and diabetes.[70] Among men with PD aged 55 to 64 years, only 51.2% were still employed, compared with 81.5% of the general population.[67] Among PD patients the greatest single cost relates to lost earnings in younger patients and long-term institutional care in older patients.[67] Patient's quality of life is compromised as the disease progresses and mortality rates are nearly 5 times higher in patients with this disease.

To date there is no cure for PD, but there have been significant advances in the treatment of this disease that can effectively manage its symptoms. Pramipexole, a non-ergot-based dopamine agonist, has been found effective without levodopa/carbidopa in treating early PD patients, and in combination with levodopa/carbidopa in treating advanced PD patients.

Overall safety and efficacy of pramipexole in Parkinsons Disease

- Pramipexole reduces tremor (eg, tremor score calculated as a sum of UPDRS items 16, 20, and 21)[54]
- Pramipexole reduces the daily levodopa dosage[29]
- Pramipexole enhances patient functioning in early PD (UPDRS Part II)[13]

As initial therapy in early PD

- Pramipexole treatment arm had significantly fewer patients that developed dopaminergic complications than the Levodopa arm[28]
- Pramipexole significantly reduced the risk of developing dyskinesias & wearing-off[28]
- Pramipexole may slow the loss of dopaminergic neurons (measured as change in striatal [^{123}I]β-CIT uptake)[53]

As adjunct therapy in advanced PD

- Pramipexole increases "on" time and decreases "off" time"[16]
- Pramipexole enhances patient functioning (eg, UPDRS Part II, ADL subscale scores)[15,16]
- Pramipexole had a higher percentage of improvement in parkinsonian motor signs than placebo[15]

In the treatment of Parkinsonian tremor PD:

- Compared to placebo, pramipexole significantly reduced tremor in patients with idiopathic Parkinson's disease (data from 2 European studies)[54,57]

PD-related depressive symptoms (Depression is not an FDA-approved indication of MIRAPEX.)

- Pramipexole appeared to have antidepressive effects in 41 nondemented patients with mild to moderate depression and advanced PD[58]
- Post hoc-analyses of a double-blind trial with open-label follow-up in advanced PD patients showed that pramipexole significantly improved the subitems motivation/initiative and depression in a subpopulation with increased UPDRS I scores at the time of inclusion[59]

Overall safety and efficacy of pramipexole in Restless Leg Syndrome

- After 3 weeks of treatment the mean PLMI values were significantly smaller in the pramipexole group compared to placebo ($p < 0.0001$)[45]
- After 6 week and 12 weeks, the mean IRLS score was significantly reduced and significantly more patients improved as demonstrated by the CGI-I in the pramipexole group compared to placebo group ($p < 0.0001$)[46,47]
- After 6 months of successful pramipexole treatment, the withdrawal of pramipexole resulted in rapid deterioration of RLS symptoms[48]

Economic value of Pramipexole

The economic value of Mirapex® (pramipexole) has been demonstrated and quantified in several analyses. However, the overall value is based on the fact that pramipexole is one of a few very effective treatments available for early or advanced PD and RLS. Pramipexole has a very favorable side-effect profile as it is associated with relatively low rates of nausea, dizziness, somnolence and vomiting, the most common side-effects associated with nonergot-derived dopamine agonists, characteristics which may result in good tolerability and potentially reduced health resource utilization relative to ropinirole.

- Average Wholesale Price (AWP) comparisons (April 2007 values) between pramipexole and ropinirole are provided in Table 1 on page 3. The market share (percent) and daily average consumption for each dose for pramipexole and ropinirole are compared below (Table 7) along with the daily-weighted average dose.

Table 7 Daily and Daily-Weighted Average Costs for Ropinirole and Pramipexole*

Mirapex®				Requip®			
Strength	**% Share**	**Dacon****	**Daily Weighted Average Cost**	**Strength**	**% Share**	**Dacon****	**Daily Weighted Average Cost**
0.125 mg	19.9	2.21	**$5.48**	**0.25 mg**	19.2	2.13	**$4.13**
0.25 mg	28.6	2.13		**0.5 mg**	17.0	1.80	
				1 mg	37.3	1.40	
0.5 mg	24.4	2.27		**2 mg**	12.5	1.62	
				3 mg	7.3	2.39	
1 mg	18.1	2.52		**4 mg**	3.9	2.29	
1.5 mg	9.0	2.65		**5 mg**	2.7	2.75	

* January 2007 prices published by First DataBank through Analy$ource[6]

** Dacon - daily average consumption

- In a cost analysis of trial data comparing pramipexole to levodopa in 301 early PD patients, the base-case incremental cost-effectiveness ratio was $42,989/QALY for pramipexole versus levodopa. Indicating that pramipexole was a fairly cost-effective alternative to levodopa over 4 years in early PD patients.[61] There is no official accepted

standard for cost per QALY in the United States, but under $50,000 per QALY is usually deemed appropriate value.[71]

5. References

1. American Hospital Formulary Service (AHFS) Drug Information. 2005.

2. Horvath J, Fross RD, Kleiner-Fisman G, Lerch R, Stalder H, Liaudat S et al. Severe multivalvular heart disease: a new complication of the ergot derivative dopamine agonists. Mov Disord 2004; 19(6):656-662.

3. Baseman DG, O'Suilleabhain PE, Reimold SC, Laskar SR, Baseman JG, Dewey RB, Jr. Pergolide use in Parkinson disease is associated with cardiac valve regurgitation. Neurol 2004; 63(2):301-304.

4. Van Camp G, Flamez A, Cosyns B, Weytjens C, Muyldermans L, Van Zandijcke M et al. Treatment of Parkinson's disease with pergolide and relation to restrictive valvular heart disease. Lancet 2004; 363(9416):1179-1183.

5. Mirapex Package Insert. Boehringer Ingelheim Pharmaceuticals, Inc. 2006.

6. March 2006 prices published by First DataBank through Analy$ource. 2006.

7. Holman AJ, Myers RR. A randomized, double-blind, placebo-controlled trial of pramipexole, a dopamine agonist, in patients with fibromyalgia receiving concomitant medications. Arthritis Rheum 2005;52(8):2495-2505.

8. Corrigan MH, Denahan AQ, Wright CE, et al: Comparison of pramipexole, fluoxetine, and placebo in patients with major depression. Depress Anxiety 2000;11:58-65.

9. NIH fact sheet - www.ninds.nih.gov/health. 2006.

10. Drug Facts and Comparisons. 2006.

11. Shannon KM, Bennett JP, Jr., Friedman JH. Efficacy of pramipexole, a novel dopamine agonist, as monotherapy in mild to moderate Parkinson's disease. The Pramipexole Study Group. Neurol 1997; 49(3):724-728.

12. Safety and efficacy of pramipexole in early Parkinson disease. A randomized dose-ranging study. Parkinson Study Group. JAMA 1997; 278(2):125-130.

13. Hubble JP, Koller WC, Cutler NR, Sramek JJ, Friedman J, Goetz C et al. Pramipexole in patients with early Parkinson's disease. Clin Neuropharmacol 1995; 18(4):338-347.

14. Pinter MM, Pogarell O, Oertel WH. Efficacy, safety, and tolerance of the non-ergoline dopamine agonist pramipexole in the treatment of advanced Parkinson's disease: a double blind, placebo controlled, randomised, multicentre study. J Neurol Neurosurg Psychiatry 1999; 66(4):436-441.

15. Lieberman A, Ranhosky A, Korts D. Clinical evaluation of pramipexole in advanced Parkinson's disease: results of a double-blind, placebo-controlled, parallel-group study. Neurol 1997; 49(1):162-168.

16. Guttman M. Double-blind comparison of pramipexole and bromocriptine treatment with placebo in advanced Parkinson's disease. International Pramipexole-Bromocriptine Study Group. Neurol 1997; 49(4):1060-1065.

17. Tanner CM, Ben Shlomo Y. Epidemiology of Parkinson's disease. Adv Neurol 1999; 80:153-159.

18. Parkinson's Disease Foundation. Parkinson's disease: an overview. Available at: http://www.pdf.org/aboutdisease/overview/index.html.

19. Hicks AA, Petursson H, Jonsson T, Stefansson H, Johannsdottir HS, Sainz J et al. A susceptibility gene for late-onset idiopathic Parkinson's disease. Ann Neurol 2002; 52(5):549-555.

20. Warner TT, Schapira AH. Genetic and environmental factors in the cause of Parkinson's disease. Ann Neurol 2003; 53 Suppl 3:S16-S23.

21. National Institute of Neurological Disorders and Stroke. Parkinson's disease backgrounder. Available at: http://www.ninds.nih.gov/health_and_medical/pubs/parkinson's_disease_backgrounder.htm.

22. DeStefano AL, Lew MF, Golbe LI, Mark MH, Lazzarini AM, Guttman M et al. PARK3 influences age at onset in Parkinson disease: a genome scan in the GenePD study. Am J Hum Genet 2002; 70(5):1089-1095.

23. Thanvi BR, Munshi SK, Vijaykumar N, Lo TC. Neuropsychiatric non-motor aspects of Parkinson's disease. Postgrad Med J 2003; 79(936):561-565.

24. Cummings JL. Intellectual impairment in Parkinson's disease: clinical, pathologic, and biochemical correlates. J Geriatr Psychiatry Neurol 1988; 1(1):24-36.

25. Walsh K, Bennett G. Parkinson's disease and anxiety. Postgrad Med J 2001; 77(904):89-93.

26. Tolosa E, Marti MJ, Valldeoriola F, Molinuevo JL. History of levodopa and dopamine agonists in Parkinson's disease treatment. Neurol 1998; 50(6 Suppl 6):S2-10.

27. Bhatt MH, Keenan SP, Fleetham JA, Calne DB. Pleuropulmonary disease associated with dopamine agonist therapy. Ann Neurol 1991; 30(4):613-616.

28. Holloway RG, Shoulson I, Fahn S, Kieburtz K, Lang A, Marek K et al. Pramipexole vs levodopa as initial treatment for Parkinson disease: a 4-year randomized controlled trial. Arch Neurol 2004; 61(7):1044-1053.

29. Pinter MM, Rutgers AW, Hebenstreit E. An open-label, multicentre clinical trial to determine the levodopa dose-sparing capacity of pramipexole in patients with idiopathic Parkinson's disease. J Neural Transm 2000; 107(11):1307-1323.

30. Molho ES, Factor SA, Weiner WJ, Sanchez-Ramos JR, Singer C, Shulman L et al. The use of pramipexole, a novel dopamine (DA) agonist, in advanced Parkinson's disease. J Neural Transm Suppl 1995; 45:225-230.

31. Allen RP, Picchietti D, Hening WA, et al. Restless legs syndrome; diagnostic criteria, special considerations and epidemiology. A report from the restless legs syndrome diagnosis and epidemiology workshop at the National Institutes of Health. Sleep Med 2003;**4:**101-119.

32. Montplaisir J, Boucher S, Poirier G, Lavigne G, Lapierre O, Lesperance P. Clinical, polysomnographic, and genetic characteristics of restless legs syndrome: a study of 133 patients diagnosed with new standard criteria. Mov Disord 1997;12:61-5.

33. Garcia-Borreguero D, Larrosa O, de la Llave Y, Jose Granizo J, Allen R. Correlation between rating scales and sleep laboratory measurements in restless legs syndrome. Sleep Med 2004;5:561-565.

34. International classification of sleep disorders, revised: diagnostic and coding manual. Rochester, MN: American Sleep Disorders Association, 1997.

35. International Restless Legs Syndrome Study Group. Validation of the International Restless Legs Syndrome Study Group rating scale for restless legs syndrome. Sleep Med 2003;4:121-132.

36. Winkelmann J, Wetter TC, Collado-Seidel V, Gasser T, Dichgans M, Yassouridis A, Trenkwalder C. Clinical characteristics and frequency of the hereditary restless legs syndrome in a population of 300 patients. Sleep 2000;23:597-602.

37. Allen RP, Earley CJ. Defining the phenotype of the restless legs syndrome (RLS) using age-of-symptom-onset. Sleep Med. 2000;1:11-19.

38. Schapira AH. Restless legs syndrome: an update on treatment options. Drugs 2004;64:149-58.

39. Lesage S, Hening WA. The restless legs syndrome and periodic limb movement disorder: a review of management. Semin Neurol. 2004 ;24:249-59

40. Walters AS. Stilling the nighttime intruder: Innovations in treatment of restless legs syndrome (RLS). Part 1 of 4: Overview of restless legs syndrome. Available at www.projectsinknowledge.com/RLS/

41. Allen RP, Barker PB, Wehrl F, Song HJ, Earley CJ. MRI measurement of brain iron in patients with restless legs syndrome. Neurol 2001;56:263-5.

42. Ruottinen HM, Partinen M, Hublin C, Bergman J, Haaparanta M, Solin O, Rinne JO. An FDOPA PET study in patients with periodic limb movement disorder and restless legs syndrome. Neurol 2000;54:502-4.

43. Earley CJ, Connor JR, Beard JL, Malecki EA, Eptstein DK, Allen RP. Abnormalities in CSF concentrations of ferritin and transferrin in restless legs syndrome. Neurol 2000;54:1698-700.

44. Silber MH, Ehrenberg BL, Allen RP, Buchfuhrer MJ, Earley CJ, Hening WA et al. An algorithm for the management of restless legs syndrome. Mayo Clin Proc 2004; 79(7):916-922.

45. Partinen M, Hirvonen K, Jama L, Alakuijala A, Hublin C, Tamminen I, Koester J, Reess J. Efficacy and safety of pramipexole in idiopathic restless legs syndrome: A polysomnographic dose-finding study – The PRELUDE study. Sleep Med 2006;7:407-417.

46. Oertel W, Stiasny-Kolster K, Bergtholdt B, et al.. Efficacy of pramipexole in restless legs syndrome: A six-week, multicenter, randomized, double-blind study (effect-RLS study) Mov Disord 2006; E-Pub ahead of print, Nov. 28, 2006.

47. Winkelman JW, Sethi KD, Kushida CA, Becker PM, Koester J, Cappola JJ, Reese J. Efficacy and safety of pramipexole in RLS. Neurol 2006;67:1034-1039.

48. Trenkwalder C, Stiasny-Kolster K, Kupsch A, et al. Controlled withdrawal of pramipexole after 6 months of open-label treatment in patients with Restless Legs Syndrome. Mov Disord 2006;21(9):1404-1410.

49. Allen RP, Earley CJ. Restless Legs syndrome. A review of clinical and pathophysiologic features. J Clin Neurophysiol 2001;18(2):128-147.

50. Schapira AH. Restless legs syndrome: an update on treatment options. Drugs 2004;64:149-58.

51. Saletu M, Anderer P, Hogl B, Saletu-Zyhlarz G, Kunz A, Poewe W, Saletu B. Acute double-blind, placebo-controlled sleep laboratory and clinical follow-up studies with a combination treatment of rr-L-dopa and sr-L-dopa in restless legs syndrome. J Neural Transm 2003;110:611-626.

52. Pramipexole vs levodopa as initial treatment for Parkinson disease: A randomized controlled trial. Parkinson Study Group. JAMA 2000; 284(15):1931-1938.

53. Dopamine transporter brain imaging to assess the effects of pramipexole vs levodopa on Parkinson disease progression. JAMA 2002; 287(13):1653-1661.

54. Pogarell O, Gasser T, van Hilten JJ, Spieker S, Pollentier S, Meier D, et al. Pramipexole in patients with Parkinson's disease and marked drug resistant tremor: a randomised, double blind, placebo controlled multicentre study. J Neurol Neurosurg Psychiatry 2002; 72(6):713-720.

55. Biglan KM, Holloway RG. A review of pramipexole and its clinical utility in Parkinson's disease. Expert Opin Pharmacother 2002; 3(2):197-210.

56. Mizuno Y, Yanagisawa N, Kuno S, Yamamoto M, Hasegawa K, Origasa H et al. Randomized, double-blind study of pramipexole with placebo and bromocriptine in advanced Parkinson's disease. Mov Disord 2003; 18(10):1149-1156.

57. Navan P, Findley LJ, Jeffs JA, et al. Randomized, double-blind, 3-month parallel study of the effects of pramipexole, pergolide, and placebo on parkinsonian tremor. Mov Disord 2003;18(11):1324-1331.

58. Rektorova I, Rektor I, Bares M, Dostal V, Ehler E, Fanfrdlova Z et al. Pramipexole and pergolide in the treatment of depression in Parkinson's disease: a national multicentre prospective randomized study. Eur J Neurol 2003; 10(4):399-406.

59. Moller JC. Long-term efficacy and safety of pramipexole in advanced Parkinson's disease: results from a European multicenter trial. In Press . 2004.

60. Hoerger TJ, Bala MV, Rowland C, Greer M, Chrischilles EA, Holloway RG. Cost effectiveness of pramipexole in Parkinson's disease in the US. Pharmacoeconomics 1998; 14(5):541-557.

61. Noyes K, Dick AW, Holloway RG. Pramipexole and levodopa in early Parkinson's disease: dynamic changes in cost effectiveness. Pharmacoeconomics 2005; 23(12):1157-1170.

62. Allen RP, Walters AS, Montplaisir J, et al. Restless Legs Syndrome prevalence and impact: REST general population study. Arch Intern Med 2005;165:1286-1292.

63. Quilici S, Nicolas A, Abrams K, Martin M, Petit C, LLeu P-L, Finnern HW. Meta-analysis of the efficacy and tolerability of pramipexole and ropinirole in Restless Leg Syndrome (RLS). abstract presented at the Movement Disorders Society.

64. Walters AS, Ondo WG, Dreykluft T, et al. Ropinirole is effective in the treatment of Restless Legs Syndrome. TREAT RLS 2: A 12-week, double-blind, randomized, parallel-group, placebo-controlled study. Mov Disord 2004;19(12):1414-23.

65. Trenkwalder C, Garcia-Borreguero D, Montagna P, Lainey E, et al. Ropininirole in the treatment of restless legs syndrome: results from the TREAT RLS 1 study, a 12 week, randomised, placebo controlled study in 10 European countries. Journal of Neurology 2004; Neurosurgery and Psychiatry 75:92-97.

66. Benes H, Kurella B, Kummer J, Kazenwadel J, Selzer R, Kohnen R. Rapid onset of action of levodopa in restless legs syndrome: A double-blind, randomized, multicenter, crossover trial. Sleep 1999;22(8):1073-81.

67. Dodel RC, Berger K, Oertel WH. Health-related quality of life and healthcare utilisation in patients with Parkinson's disease: impact of motor fluctuations and dyskinesias. Pharmacoeconomics 2001; 19(10):1013-1038.

68. Parashos SA, Maraganore DM, O'Brien PC, Rocca WA. Medical services utilization and prognosis in Parkinson disease: a population-based study. Mayo Clin Proc 2002; 77(9):918-925.

69. Carter JH, Stewart BJ, Archbold PG, Inoue I, Jaglin J, Lannon M et al. Living with a person who has Parkinson's disease: the spouse's perspective by stage of disease. Parkinson's Study Group. Mov Disord 1998; 13(1):20-28.

70. Pressley JC, Louis ED, Tang MX, Cote L, Cohen PD, Glied S et al. The impact of comorbid disease and injuries on resource use and expenditures in parkinsonism. Neurology 2003; 60(1):87-93.

71. Neumann PJ. Using cost-effectiveness analyses to improve health care: Opportunities and barriers. Oxford University Press 2005: 157-158.

neurons that send projections to the striatum. The relevance of D_3 receptor binding in Parkinson's disease is unknown.

Restless Legs Syndrome (RLS): The precise mechanism of action of Mirapex® (pramipexole dihydrochloride) tablets as a treatment for Restless Legs Syndrome (RLS) is unknown. Although the pathophysiology of RLS is largely unknown, neuropharmacological evidence suggests primary dopaminergic system involvement. Positron Emission Tomographic (PET) studies suggest that a mild striatal presynaptic dopaminergic dysfunction may be involved in the pathogenesis of RLS.

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 2.

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.

Pharmacodynamics

In a clinical trial with healthy volunteers, where pramipexole was titrated faster than recommended (every 3 days) up to 4.5 mg per day, an increase in blood pressure and heart rate was observed.

Although mean values remained within normal reference ranges throughout the study, supine systolic blood pressure (SBP), diastolic blood pressure (DBP), and pulse rate for subjects treated with pramipexole generally increased during the up-titration phase, up to 10 mmHg, 7 mmHg, and 10 bpm higher than placebo, respectively. Higher SBP, DBP, and pulse rates compared to placebo were maintained until the pramipexole doses were tapered; values on the last day of tapering were generally similar to baseline values. Such effects have not been observed in clinical studies with Parkinson's disease patients, and are most likely due to the forced up-titration every 3 days.

Pharmacokinetics in Special Populations

Because therapy with MIRAPEX 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.

Restless Legs Syndrome Patients

A cross-study comparison of data suggests that the pharmacokinetic profile of pramipexole administered once daily in RLS patients is similar to the pharmacokinetic profile of pramipexole in healthy volunteers.

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 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 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 Mirapex® (pramipexole dihydrochloride) tablets or placebo. Patients treated with MIRAPEX 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 MIRAPEX 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 MIRAPEX tablets and -0.8 in the placebo group, a difference that was also statistically significant. A statistically significant difference between groups in favor of MIRAPEX 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 MIRAPEX tablets (1.5 mg, 3.0 mg, 4.5 mg, or 6.0 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 MIRAPEX 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 MIRAPEX 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 MIRAPEX 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 MIRAPEX 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 Mirapex® (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 MIRAPEX tablets and 2.8 in the placebo group, a difference that was statistically significant. A statistically significant difference between groups in favor of MIRAPEX 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 MIRAPEX 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 MIRAPEX tablets 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.

Restless Legs Syndrome

The efficacy of MIRAPEX tablets in the treatment of Restless Legs Syndrome (RLS) was evaluated in a multinational drug development program consisting of 4 randomized, double-blind, placebo-controlled trials. This program included approximately 1000 patients with moderate to severe RLS; patients with RLS secondary to other conditions (e.g., pregnancy, renal failure, and anemia) were excluded. All patients were administered MIRAPEX tablets (0.125 mg, 0.25 mg, 0.5 mg, or 0.75 mg) or placebo once daily 2-3 hours before going to bed. Across the 4 studies, the mean duration of RLS was 4.6 years (range of 0 to 56 years), mean age was approximately 55 years (range of 18 to 81 years), and approximately 66.6% were women.

The two outcome measures used to assess the effect of treatment were the International RLS Rating Scale (IRLS Scale) and a Clinical Global Impression - Improvement (CGI-I) assessment. The IRLS Scale contains 10 items designed to assess the severity of sensory and motor symptoms, sleep disturbance, daytime somnolence, and impact on activities of daily

living and mood associated with RLS. The range of scores is 0 to 40, with 0 being absence of RLS symptoms and 40 the most severe symptoms. The CGI-I is designed to assess clinical progress (global improvement) on a 7-point scale.

In Study 1, fixed doses of MIRAPEX tablets were compared to placebo in a study of 12 weeks duration. A total of 344 patients were randomized equally to the 4 treatment groups. Patients treated with MIRAPEX tablets (n=254) had a starting dose of 0.125 mg/day and were titrated to one of the three randomized doses (0.25, 0.5, 0.75 mg/day) in the first three weeks of the study. The mean improvement from baseline on the IRLS Scale total score and the percentage of CGI-I responders for each of the MIRAPEX tablets treatment groups compared to placebo are summarized in Table 1. All treatment groups reached statistically significant superiority compared to placebo for both endpoints. There was no clear evidence of a dose-response across the 3 randomized dose groups.

Table 1 Mean Changes from Baseline to Week 12 in IRLS Score and CGI-I (Study 1)

	MIRAPEX 0.25 mg	**MIRAPEX 0.5 mg**	**MIRAPEX 0.75 mg**	**MIRAPEX Total**	**Placebo**
No. Patients	88	79	87	254	85
IRLS score	-13.1	-13.4	-14.4	-13.6	-9.4
CGI-I responders*	74.7%	67.9%	72.9%	72.0%	51.2%

*CGI-I responders = "much improved" and "very much improved"

Study 2 was a randomized-withdrawal study, designed to demonstrate the sustained efficacy of pramipexole for treatment of RLS after a period of six months. RLS patients who responded to Mirapex® (pramipexole dihydrochloride) tablets treatment in a preceding 6-month open label treatment phase (defined as having a CGI-I rating of "very much improved" or "much improved" compared to baseline and an IRLS score of 15 or below) were randomized to receive either continued active treatment (n=78) or placebo (n=69) for 12 weeks. The primary endpoint of this study was time to treatment failure, defined as any worsening on the CGI-I score along with an IRLS Scale total score above 15.

In patients who had responded to 6-month open label treatment with MIRAPEX tablets, the administration of placebo led to a rapid decline in their overall conditions and return of their RLS symptoms. At the end of the 12-week observation period, 85% of patients treated with placebo had failed treatment, compared to 21% treated with blinded pramipexole, a difference that was highly statistically significant. The majority of treatment failures occurred within 10 days of randomization. For the patients randomized, the distribution of doses was: 7 on 0.125 mg, 44 on 0.25 mg, 47 on 0.5 mg, and 49 on 0.75 mg.

Study 3 was a 6-week study, comparing a flexible dose of MIRAPEX tablets to placebo. In this study, 345 patients were randomized in a 2:1 ratio to MIRAPEX tablets or placebo. The mean improvement from baseline on the IRLS Scale total score was -12 for Mirapex-treated patients and -6 for placebo-treated patients. The percentage of CGI-I responders was 63% for Mirapex-treated patients and 32% for placebo-treated patients. The between-group

differences were statistically significant for both outcome measures. For the patients randomized to MIRAPEX tablets, the distribution of achieved doses was: 35 on 0.125 mg, 51 on 0.25 mg, 65 on 0.5 mg, and 69 on 0.75 mg.

Study 4 was a 3-week study, comparing 4 fixed doses of MIRAPEX tablets, 0.125 mg, 0.25 mg, 0.5 mg, and 0.75 mg, to placebo. Approximately 20 patients were randomized to each of the 5 dose groups. The mean improvement from baseline on the IRLS Scale total score and the percentage of CGI-I responders for each of the MIRAPEX tablets treatment groups compared to placebo are summarized in Table 2. In this study, the 0.125 mg dose group was not significantly different from placebo. On average, the 0.5 mg dose group performed better than the 0.25 mg dose group, but there was no difference between the 0.5 mg and 0.75 mg dose groups.

Table 2 Mean Changes from Baseline to Week 3 in IRLS Score and CGI-I (Study 4)

	MIRAPEX 0.125 mg	**MIRAPEX 0.25 mg**	**MIRAPEX 0.5 mg**	**MIRAPEX 0.75 mg**	**MIRAPEX Total**	**Placebo**
No. Patients	21	22	22	21	86	21
IRLS score	-11.7	-15.3	-17.6	-15.2	-15.0	-6.2
CGI-I responders*	61.9%	68.2%	86.4%	85.7%	75.6%	42.9%

*CGI-I responders = “much improved” and “very much improved”

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

Mirapex® (pramipexole dihydrochloride) tablets are indicated for the treatment of the signs and symptoms of idiopathic Parkinson's disease.

The effectiveness of MIRAPEX 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**).

Restless Legs Syndrome

MIRAPEX tablets are indicated for the treatment of moderate-to-severe primary Restless Legs Syndrome (RLS).

Key diagnostic criteria for RLS are: an urge to move the legs usually accompanied or caused by uncomfortable and unpleasant leg sensations; symptoms begin or worsen during periods of rest or inactivity such as lying or sitting; symptoms are partially or totally relieved by

movement such as walking or stretching at least as long as the activity continues; and symptoms are worse or occur only in the evening or night. Difficulty falling asleep may frequently be associated with symptoms of RLS.

CONTRAINDICATIONS

MIRAPEX 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) 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 MIRAPEX 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 MIRAPEX tablets at doses above 1.5 mg/day (0.5 mg TID) for Parkinson's disease. In controlled clinical trials in RLS, patients treated with MIRAPEX tablets at doses of 0.25-0.75 mg once a day, the incidence of somnolence was 6% compared to an incidence of 3% for placebo-treated patients (see ADVERSE EVENTS, Table 5). 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 tablets, patients should be advised of the potential to develop drowsiness and specifically asked about factors that may increase the risk with MIRAPEX 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.), MIRAPEX tablets should ordinarily be discontinued. If a decision is made to continue MIRAPEX 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 and RLS 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® (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. Also, clinical trials in patients with RLS did not incorporate orthostatic challenges with intensive blood pressure monitoring done in close temporal proximity to dosing.

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 MIRAPEX 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 MIRAPEX tablets and concomitant levodopa, hallucinations were observed in 16.5% (43 of 260) of patients receiving MIRAPEX 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.

In the RLS clinical program, one pramipexole-treated patient (of 889) reported hallucinations; this patient discontinued treatment and the symptoms resolved.

PRECAUTIONS

Rhabdomyolysis

A single case of rhabdomyolysis occurred in a 49-year-old male with advanced Parkinson's disease treated with MIRAPEX 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® (pramipexole dihydrochloride) tablets to patients with renal insufficiency (see **DOSAGE AND ADMINISTRATION**).

Dyskinesia

MIRAPEX 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 post-marketing experience for Mirapex® (pramipexole dihydrochloride) tablets. While the evidence is not sufficient to establish a causal relationship between MIRAPEX tablets and these fibrotic complications, a contribution of MIRAPEX tablets 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 MIRAPEX tablets for *any* indication. Ideally, periodic skin examinations should be performed by appropriately qualified individuals (e.g., dermatologists).

Impulse Control/Compulsive Behaviors

Cases of pathological gambling, hypersexuality, and compulsive eating (including binge eating), and compulsive shopping have been reported in patients treated with dopamine agonist therapy, including pramipexole therapy. As described in the literature, such behaviors are generally reversible upon dose reduction or treatment discontinuation.

Rebound and Augmentation in RLS

Reports in the literature indicate treatment of RLS with dopaminergic medications can result in a shifting of symptoms to the early morning hours, referred to as rebound. Rebound was not reported in the clinical trials of MIRAPEX tablets but the trials were generally not of sufficient duration to capture this phenomenon. Augmentation has also been described during therapy for RLS. Augmentation refers to the earlier onset of symptoms in the evening (or even the afternoon), increase in symptoms, and spread of symptoms to involve other extremities. In a controlled trial of MIRAPEX tablets for RLS, approximately 20% of both the Mirapex- and the placebo-treated patients reported at least a 2-hour earlier onset of symptoms during the day by the end of 3 months of treatment. The frequency and severity of

augmentation and/or rebound after longer-term use of MIRAPEX tablets and the appropriate management of these events have not been adequately evaluated in controlled clinical trials.

Information for Patients (also see Patient Package Insert)

Patients should be instructed to take MIRAPEX tablets only as prescribed.

Patients should be alerted to the potential sedating effects associated with MIRAPEX 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 Mirapex® (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 MIRAPEX 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. In clinical trials, patients with RLS treated with pramipexole rarely reported hallucinations.

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 MIRAPEX tablets. 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 MIRAPEX tablets. Patients should inform their physician if they experience new or increased gambling urges, increased sexual urges or other intense urges while taking MIRAPEX tablets. Physicians should consider dose reduction or stopping the medication if a patient develops such urges while taking MIRAPEX tablets.

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 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 MIRAPEX tablets with food may reduce the occurrence of nausea.

Laboratory Tests

During the development of MIRAPEX 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 analyses 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 Ki of 30 μM, 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 Mirapex® (pramipexole dihydrochloride) tablets.

Drug/Laboratory Test Interactions

There are no known interactions between MIRAPEX 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) (MRHD of 1.5 mg TID on a mg/m^2 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/m^2 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 Effect: *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 MRHD on a mg/m^2 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/m^2 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 Mirapex® (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 MIRAPEX tablets was increased in the elderly. In clinical studies with RLS patients, 22% of patients were at least 65 years old. There were no apparent differences in efficacy or safety between older and younger patients.

ADVERSE EVENTS

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 MIRAPEX tablets were nausea, dizziness, somnolence, insomnia, constipation, asthenia, and hallucinations.

Approximately 12% of 388 patients with early Parkinson's disease and treated with MIRAPEX 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 MIRAPEX tablets vs 0.4% on placebo]; dizziness [2.1% on MIRAPEX tablets vs 1% on placebo]; somnolence [1.6% on MIRAPEX tablets vs 0% on placebo]; extrapyramidal syndrome [1.6% on MIRAPEX tablets vs 6.4% on placebo]; headache and confusion [1.3% and 1.0%, respectively, on Mirapex® (pramipexole dihydrochloride) tablets vs 0% on placebo]); and gastrointestinal system (nausea [2.1% on MIRAPEX tablets vs 0.4% on placebo]).

Adverse-event Incidence in Controlled Clinical Studies in Early Parkinson's Disease

Table 3 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 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 3 Treatment-Emergent Adverse-Event* Incidence in Double-Blind, Placebo-Controlled Trials in Early Parkinson's Disease (Events ≥1% of Patients Treated with MIRAPEX tablets 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	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

*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® (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 MIRAPEX 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 Mirapex® (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 MIRAPEX tablets vs 0.4% on placebo]; dyskinesia [1.9% on MIRAPEX tablets vs 0.8% on placebo]; extrapyramidal syndrome [1.5% on MIRAPEX tablets vs 4.9% on placebo]; dizziness [1.2% on MIRAPEX tablets vs 1.5% on placebo]; confusion [1.2% on MIRAPEX tablets vs 2.3% on placebo]); and cardiovascular system (postural [orthostatic] hypotension [2.3% on MIRAPEX tablets vs 1.1% on placebo]).

Adverse-event Incidence in Controlled Clinical Studies in Advanced Parkinson's Disease

Table 4 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 tablets and were numerically more frequent than in the placebo group. In these studies, MIRAPEX 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 4 Treatment-Emergent Adverse-Event* Incidence in Double-Blind, Placebo-

Controlled Trials in Advanced Parkinson's Disease (Events ≥1% of Patients Treated with MIRAPEX tablets 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	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 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® (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.

Restless Legs Syndrome

MIRAPEX tablets for treatment of RLS have been evaluated for safety in 889 patients, including 427 treated for over six months and 75 for over one year.

The overall safety assessment focuses on the results of three double-blind, placebo-controlled trials, in which 575 patients with RLS were treated with MIRAPEX tablets for up to 12 weeks. The most commonly observed adverse events with MIRAPEX tablets in the treatment of RLS (observed in > 5% of pramipexole-treated patients and at a rate at least twice that observed in placebo-treated patients) were nausea and somnolence. Occurrences of nausea and somnolence in clinical trials were generally mild and transient.

Approximately 7% of 575 patients treated with MIRAPEX tablets during the double-blind periods of three placebo-controlled trials discontinued treatment due to adverse events

compared to 5% of 223 patients who received placebo. The adverse event most commonly causing discontinuation of treatment was nausea (1%).

Table 5 lists treatment-emergent events that occurred in three double-blind, placebo-controlled studies in RLS patients that were reported by ≥ 2% of patients treated with MIRAPEX tablets and were numerically more frequent than in the placebo group.

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 5 Treatment-Emergent Adverse-Event* Incidence in Double-Blind, Placebo-Controlled Trials in Restless Legs Syndrome (Events ≥ 2% of Patients Treated with MIRAPEX tablets and Numerically More Frequent than in the Placebo Group)

Body System/ Adverse Event	MIRAPEX 0.125 – 0.75 mg/day (N=575) %	Placebo (N=223) %
Gastrointestinal disorders		
Nausea	16	5
Constipation	4	1
Diarrhea	3	1
Dry mouth	3	1
General disorders and administration site conditions		
Fatigue	9	7
Infections and infestations		
Influenza	3	1
Nervous system disorders		
Headache	16	15
Somnolence	6	3

*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 2% or more of RLS patients treated with Mirapex® (pramipexole dihydrochloride) tablets but equally or more frequently in the placebo group, were: vomiting, nasopharyngitis, back pain, pain in extremity, dizziness, and insomnia.

Table 6 summarizes data for adverse events that appeared to be dose related in the 12-week fixed dose study.

Table 6 Dose Related Adverse Events in a 12-Week Double-Blind, Placebo-Controlled Fixed Dose Study in Restless Legs Syndrome (Occurring in

≥ 5% of all Patients in the Treatment Phase)

Body System/ Adverse Event	MIRAPEX 0.25 mg (N=88) %	MIRAPEX 0.5 mg (N=80) %	MIRAPEX 0.75 mg (N=90) %	Placebo (n=86) %
Gastrointestinal disorders				
Nausea	11	19	27	5
Diarrhea	3	1	7	0
Dyspepsia	3	1	4	7
Infections and infestations				
Influenza	1	4	7	1
General disorders and administration site conditions				
Fatigue	3	5	7	5
Psychiatric disorders				
Insomnia	9	9	13	9
Abnormal dreams	2	1	8	2
Respiratory, thoracic and mediastinal disorders				
Nasal congestion	0	3	6	1
Musculoskeletal and connective tissue disorders				
Pain in extremity	3	3	7	1

General

Adverse Events; Relationship to Age, Gender, and Race

Among the treatment-emergent adverse events in patients treated with MIRAPEX 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, nausea and fatigue, both generally transient, were more frequently reported by female than male RLS patients. Less than 4% of patients enrolled were non-Caucasian, therefore, an evaluation of adverse events related to race is not possible.

Other Adverse Events Observed During Phase 2 and 3 Clinical Trials

MIRAPEX tablets have been administered to 1620 Parkinson's disease patients and to 889 RLS 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 2509 individuals exposed to MIRAPEX tablets are listed below. The reported events below are included without regard to determination of a causal relationship to MIRAPEX 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, monarthritis, 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, pollakiuria, 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 Mirapex® (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 MIRAPEX 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, compulsive shopping, 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, pruritus, syncope, vomiting, 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. 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 7 Ascending Dosage Schedule of MIRAPEX 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	3.0
6	1.25 TID	3.75
7	1.5 TID	4.50

Maintenance Treatment

Mirapex® (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 MIRAPEX 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 MIRAPEX 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 8 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 (creatinine Cl = 35 to 59 mL/min)	0.125 BID	1.5 BID
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 tablets has not been adequately studied in this group of patients.	

Discontinuation of Treatment

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

Restless Legs Syndrome

The recommended starting dose of MIRAPEX tablets is 0.125 mg taken once daily 2-3 hours before bedtime. For patients requiring additional symptomatic relief, the dose may be increased every 4-7 days (Table 9). Although the dose of MIRAPEX tablets was increased to 0.75 mg in some patients during long-term open-label treatment, there is no evidence that the 0.75 mg dose provides additional benefit beyond the 0.5 mg dose.

Table 9 Ascending Dosage Schedule of MIRAPEX tablets for RLS

Titration Step	Duration	Dosage (mg) to be taken once daily, 2-3 hours before bedtime
1	4-7 days	0.125
2*	4-7 days	0.25
3*	4-7 days	0.5

*if needed

Patients with Renal Impairment

The duration between titration steps should be increased to 14 days in RLS patients with severe and moderate renal impairment (creatinine clearance 20-60 mL/min) (see **CLINICAL PHARMACOLOGY**, ***Renal Insufficiency***).

Discontinuation of Treatment

In clinical trials of patients being treated for RLS with doses up to 0.75 mg once daily, Mirapex® (pramipexole dihydrochloride) tablets were discontinued without a taper.

HOW SUPPLIED

MIRAPEX tablets are available as follows:

0.125 mg: white, round tablet with "BI" on one side and "83" on the reverse side.
Bottles of 90 NDC 0597-0183-90

0.25 mg: white, oval, scored tablet with "BI BI" on one side and "84 84" on the reverse side.
Bottles of 90 NDC 0597-0184-90
Unit dose packages of 100 NDC 0597-0184-61

0.5 mg: white, oval, scored tablet with "BI BI" on one side and "85 85" on the reverse side.
Bottles of 90 NDC 0597-0185-90
Unit dose packages of 100 NDC 0597-0185-61

0.75 mg: white, oval, debossed tablet with "BI" on one side and "101" on the reverse side.

Bottles of 90	NDC 0597-0101-90

1 mg: white, round, scored tablet with "BI BI " on one side and "90 90" on the reverse side.

Bottles of 90	NDC 0597-0190-90
Unit dose packages of 100	NDC 0597-0190-61

1.5 mg: white, round, scored tablet with "BI BI" on one side and "91 91" on the reverse side.

Bottles of 90	NDC 0597-0191-90
Unit dose packages of 100	NDC 0597-0191-61

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.

Address medical inquiries to: http://us.boehringer-ingelheim.com, (800) 542-6257 or (800) 459-9906 TTY.

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/m^2 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/m^2 basis). Evaluation of the retinas of monkeys given 0.1, 0.5, or 2.0 mg/kg/day of pramipexole (0.4, 2.2, and 8.6 times the highest clinical dose on a mg/m^2 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 (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 (0.3, 2.2, and 11 times the highest clinical dose on a mg/m^2 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.

Distributed by:
Boehringer Ingelheim Pharmaceuticals, Inc.
Ridgefield, CT 06877 USA

Licensed from:
Boehringer Ingelheim International GmbH

Trademark under license from:
Boehringer Ingelheim International GmbH

U.S. Patent Nos. 4,886,812; 6,001,861; and 6,194,445.

©2009, Boehringer Ingelheim International GmbH
ALL RIGHTS RESERVED

Rev: April 2009

OT1317PC2409
2001/05

OT1338H
10003128/08

IT1322G
10003129/07

Mirapex®

(pramipexole dihydrochloride)

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

Boehringer Ingelheim

Patient Information

Mirapex® **/mîr′-ah-pĕx/** (pramipexole dihydrochloride) tablets

Read the Patient Information that comes with MIRAPEX 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 MIRAPEX?

MIRAPEX 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 MIRAPEX 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 MIRAPEX 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 MIRAPEX?

MIRAPEX is a prescription medicine to treat

- primary Restless Legs Syndrome.
- signs and symptoms of Parkinson's disease.

MIRAPEX has not been studied in children.

Who should not take MIRAPEX?

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

What should I tell my doctor before taking MIRAPEX?

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

- feel sleepy during the day from a sleep problem other than Restless Legs Syndrome.
- 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 MIRAPEX will harm your unborn baby.
- are breast feeding. It is not known if MIRAPEX will pass into your breast milk. You and your doctor should decide if you will take MIRAPEX or breastfeed. You should not do both.
- drink alcohol. Alcohol can increase the chance that MIRAPEX 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. MIRAPEX and other medicines may interact with each other causing side effects. MIRAPEX may affect the way other medicines work, and other medicines may affect how MIRAPEX works.

How should I take MIRAPEX?

- Take MIRAPEX exactly as your doctor tells you to. Your doctor will tell you how many MIRAPEX 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 MIRAPEX than your doctor tells you to.

- MIRAPEX can be taken with or without food. Taking MIRAPEX 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 MIRAPEX for any reason. Do not start taking MIRAPEX again before speaking with your doctor. If you have Parkinson's disease and are stopping Mirapex, you should stop Mirapex slowly over 7 days.

What should I avoid while taking MIRAPEX?

- **Do not drive a car, operate a machine, or do anything that needs you to be alert until you know how MIRAPEX affects you.** See "**What is the most important information I should know about MIRAPEX?**" at the beginning of this leaflet.

- Do not drink alcohol while taking MIRAPEX. It can increase your chances of feeling sleepy or falling asleep when you should be awake.

What are the possible side effects of MIRAPEX?

MIRAPEX may cause serious side effects, including

- **falling asleep during normal daily activities**. See "**What is the most important information I should know about MIRAPEX?**"

- **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 a while.

- **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 MIRAPEX for Restless Legs Syndrome are nausea and sleepiness.

The most common side effects in people taking MIRAPEX 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 MIRAPEX. 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 MIRAPEX

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. MIRAPEX is one of the medicines used to treat Parkinson's disease, therefore, patients being treated with MIRAPEX should have periodic skin examinations.

There have been reports of patients taking certain medicines to treat Parkinson's disease or RLS, including MIRAPEX, that have reported problems with gambling, compulsive eating, compulsive shopping, 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 MIRAPEX?

- Store MIRAPEX tablets at room temperature [77°F (25°C)]. Short-term exposure to higher or lower temperatures [from 59°F (15°C) to 86°F (30°C)] is acceptable. Ask your doctor or pharmacist if you have any questions about storing your tablets.
- Keep MIRAPEX out of light.
- **Keep MIRAPEX and all medicines out of the reach of children.**

General information about MIRAPEX

Medicines are sometimes prescribed for purposes other than those listed in this Patient Information leaflet. Do not take MIRAPEX for a condition for which it was not prescribed. Do not share MIRAPEX 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 MIRAPEX. For more information, talk with your doctor or pharmacist. They can give you information about MIRAPEX that is written for healthcare professionals. **For additional information, you may also call Boehringer Ingelheim Pharmaceuticals, Inc. at 1-800-542-6257, or (TTY) 1-800-459-9906. You may also request information through the company website at http://us.boehringer-ingelheim.com.**

What are the ingredients in MIRAPEX?
Active Ingredient: pramipexole dihydrochloride monohydrate

Inactive Ingredients: mannitol, corn starch, colloidal silicon dioxide, povidone, and magnesium stearate

Distributed by:
Boehringer Ingelheim Pharmaceuticals, Inc.
Ridgefield, CT 06877 USA

Licensed from:
Boehringer Ingelheim International GmbH

Trademark under license from:
Boehringer Ingelheim International GmbH

U.S. Patent Nos. 4,886,812; 6,001,861; and 6,194,445

©2009, Boehringer Ingelheim International GmbH
ALL RIGHTS RESERVED

Rev: April 2009

OT1317PC2409
2001/05

OT1338H
10003128/08

IT1322G
10003129/07