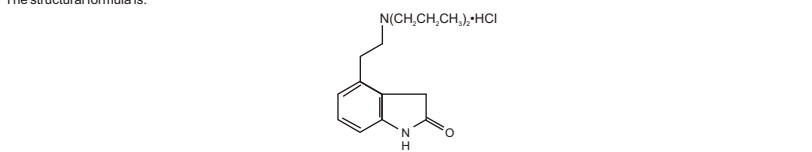


Ropinirole Hydrochloride Tablets

Rx only

DESCRIPTION
Ropinirole hydrochloride is an orally administered non-ergoline dopamine agonist. It is the hydrochloride salt of 4-[2-(dipropylamino)ethyl]-1,3-dihydro-2H-indolo-2-one monohydrochloride and has a molecular formula of C₂₀H₂₆N₂O•HCl. The molecular weight is 296.84 (260.38 as the free base).



Ropinirole hydrochloride is a white to cream-colored crystalline powder with a melting range of 241° to 245°C and a solubility of 133 mg/mL in water. Each ropinirole hydrochloride tablet intended for oral administration contains ropinirole hydrochloride equivalent to 0.25 mg or 0.5 mg or 1 mg or 2 mg or 3 mg or 4 mg or 5 mg of ropinirole. In addition, each tablet contains the following inactive ingredients: croscarmellose sodium, hydroxytoluene, lactose monohydrate, microcrystalline cellulose, polyethylene glycol and titanium dioxide. Additionally, each 0.5 mg tablet contains: FD&C blue# 2, iron oxide red and iron oxide yellow; each 1 mg tablet contains: FD&C blue#2 and iron oxide yellow; each 2 mg tablet contains: iron oxide red and iron oxide yellow; each 3 mg tablet contains carmine, FD&C blue # 2 and FD&C yellow # 6; each 4 mg tablet contains: iron oxide black, iron oxide red and iron oxide yellow and each 5 mg tablet contains: FD&C blue# 2.

CLINICAL PHARMACOLOGY
Mechanism of Action:
Ropinirole hydrochloride is a non-ergoline dopamine agonist with high relative *in vitro* specificity and full intrinsic activity at the D₂ and D₃ dopamine receptor subtypes, binding with higher affinity to D₂ than to D₁ or D₄ receptor subtypes. Ropinirole has moderate *in vitro* affinity for opioid receptors. Ropinirole and its metabolites have negligible *in vitro* affinity for dopamine D₁, 5-HT_{1A}, benzodiazepine, GABA, muscarinic, alpha-, alpha₁-, and beta-adrenoceptors.

Parkinson's Disease:
The precise mechanism of action of ropinirole hydrochloride as a treatment for Parkinson's disease is unknown, although it is believed to be due to stimulation of postsynaptic dopamine D₂-type receptors within the caudate-putamen in the brain. This conclusion is supported by studies that show that ropinirole improves motor function in various animal models of Parkinson's disease. In particular, ropinirole attenuates the motor deficits induced by the esterase inhibitor, deprenyl, in a dopaminergic pathway with the neurotoxin 1-methyl-4-phenyl-1,2,3,4-tetrahydropyridine (MPTP) in primates. The relevance of D₂ receptor binding in Parkinson's disease is unknown.

Restless Legs Syndrome (RLS):
The precise mechanism of action of ropinirole hydrochloride as a treatment for Restless Legs Syndrome (also known as Ekbom Syndrome) is unknown. Although the pathophysiology of RLS is largely unknown, neuropharmacological evidence suggests primary dopaminergic system involvement. Position emission tomographic (PET) studies suggest that a mild striatal presynaptic dopaminergic dysfunction may be involved in the pathogenesis of RLS.

Clinical Pharmacologic Studies:
In healthy nonobese subjects, single oral doses of ropinirole hydrochloride in the range 0.01 to 2.5 mg had little or no effect on supine blood pressure and heart rate. Upon standing, ropinirole hydrochloride caused decreases in systolic and diastolic blood pressure at doses above 0.25 mg. In some subjects, these changes were associated with the emergence of orthostatic symptoms, bradycardia, and, in one case, transient sinus arrest with syncope. With repeat dosing and slow titration up to 4 mg once daily in healthy volunteers, postural hypotension or hypotension-related adverse events were noted in 13% of subjects on ropinirole hydrochloride and none of the subjects on placebo.

The mechanism of postural hypotension induced by ropinirole hydrochloride is presumed to be due to a D₂-mediated blunting of the noradrenergic response to standing and subsequent decrease in peripheral vascular resistance. Nausea is a common concomitant symptom of orthostatic signs and symptoms.

At oral doses as low as 0.2 mg, ropinirole hydrochloride suppressed serum prolactin concentrations in healthy male volunteers. Ropinirole hydrochloride had no dose-related effect on ECGs wave form and rhythm in young, healthy, male volunteers in the range of 0.01 to 2.5 mg. Ropinirole hydrochloride had no dose- or exposure-related effect on mean QT intervals in healthy male and female volunteers titrated to doses up to 4 mg/day. The effect of ropinirole hydrochloride on QT intervals at higher exposures achieved either due to drug interactions or at doses used in Parkinson's disease has not been systematically evaluated.

Pharmacokinetics:
Absorption, Distribution, Metabolism, and Elimination:
The pharmacokinetics of ropinirole are similar in Parkinson's disease patients and patients with Restless Legs Syndrome. Ropinirole is rapidly absorbed after oral administration, reaching peak concentration in approximately 1-2 hours. In clinical studies, over 88% of a radiolabeled dose was excreted in urine and the absolute bioavailability was 55%, suggesting a first-pass effect. Relative bioavailability from a tablet compared to an oral solution is 85%. Food does not affect the extent of absorption of ropinirole, although its T_{max} is increased by 2.5 hours and its C_{max} is decreased by approximately 25% when the drug is taken with a high-fat meal. The clearance of ropinirole after oral administration to patients is 47 L/hr (cv = 45%) and its elimination half-life is approximately 6 hours. Ropinirole is extensively metabolized by patients to inactive metabolites and displays linear kinetics over the therapeutic dosing range of 1 to 8 mg 3 times daily. Steady-state concentrations are expected to be achieved within 2 days of dosing.

Accumulation upon multiple dosing is predictive from single dosing.

Ropinirole is widely distributed throughout the body, with an apparent volume of distribution of 7.5 L/kg (cv = 32%). It is up to 40% bound to plasma proteins and has a blood-to-plasma ratio of 1:1. The major metabolic pathways are N-despropylation and hydroxylation to form the inactive N-despropyl and hydroxy metabolites. *In vitro* studies indicate that the major cytochrome P₄₅₀ isozyme involved in the metabolism of ropinirole is CYP1A2, an enzyme known to be stimulated by smoking and omeprazole, and inhibited by, for example, fluvoxamine, mexiletine, and the older fluorquinolones such as ciprofloxacin and norfloxacin. The N-despropyl metabolite is converted to carbamyl glucuronide, carboxylic acid, and N-despropyl hydroxy metabolites. The hydroxy metabolite of ropinirole is rapidly glucuronidated. Less than 10% of the administered dose is excreted as unchanged ropinirole in urine. The predominant metabolite found in urine (40%), followed by the carboxylic acid metabolite (10%), and the glucuronide of the hydroxy metabolite (10%).

P₄₅₀ Interaction:
In vitro metabolism studies showed that CYP1A2 was the major enzyme responsible for the metabolism of ropinirole. Inhibitors or inducers of this enzyme have been shown to affect its clearance when administered with ropinirole. Therefore, if therapy with a drug known to be a potent inhibitor of CYP1A2 is stopped or started during treatment with ropinirole hydrochloride, adjustment of the dose of ropinirole hydrochloride may be required.

Population Subgroups:
Because therapy with ropinirole hydrochloride 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.

Age:
Oral clearance of ropinirole is reduced by 30% in patients above 65 years of age compared to younger patients. Dosage adjustment is not necessary in the elderly (above 65 years), as the dose of ropinirole is to be individually titrated to clinical response.

Gender:
Male and female patients showed similar oral clearance.

Race:
The influence of race on the pharmacokinetics of ropinirole has not been evaluated.

Cigarette Smoking:
Smoking is expected to increase the clearance of ropinirole since CYP1A2 is known to be induced by smoking. In a study in patients with RLS, smokers (n = 7) had an approximate 30% lower C_{max} and a 38% lower AUC than did nonsmokers (n = 11), when those parameters were normalized for dose.

Renal Impairment:
Based on population pharmacokinetic analysis, no difference was observed in the pharmacokinetics of ropinirole in patients with moderate renal impairment (creatinine clearance between 30 to 50 mL/min) compared to age-matched population with creatinine clearance above 50 mL/min. Therefore, no dosage adjustment is necessary in moderately renally impaired patients. The use of ropinirole hydrochloride in patients with severe renal impairment has not been studied.

The effect of hemodialysis on drug removal is not known, but because of the relatively high apparent volume of distribution of ropinirole (525 L), the removal of the drug by hemodialysis is unlikely.

Hepatic Impairment:
The pharmacokinetics of ropinirole have not been studied in hepatically impaired patients. These patients may have higher plasma levels and lower clearance of the drug than patients with normal hepatic function. The drug should be titrated with caution in this population.

Other Diseases:
Population pharmacokinetic analysis revealed no change in the oral clearance of ropinirole in patients with concomitant diseases such as hypertension, depression, osteoporosis/arthritis, and insomnia compared to patients with Parkinson's disease only.

Clinical Trials:
Parkinson's Disease:
The effectiveness of ropinirole hydrochloride in the treatment of Parkinson's disease was evaluated in a multinational drug development program consisting of 11 randomized, controlled trials. Four were conducted in patients with early Parkinson's disease and no concomitant levodopa (L-dopa), and 7 were conducted in patients with advanced Parkinson's disease with concomitant L-dopa.

Among these 11 studies, 3 placebo-controlled studies provide the most persuasive evidence of ropinirole's effectiveness in the management of patients with Parkinson's disease. 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 III of the UPDRS contains 14 items 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. Responders were defined as patients with at least a 30% reduction in the Part III RLS Scale at the week 12 endpoint as the primary efficacy outcome.

In this study of advanced Parkinson's disease (with L-dopa) patients, both reduction in percent awake time spent "off" and the ability to reduce the daily use of L-dopa were assessed as a combined endpoint and individually.

Studies in Patients with Early Parkinson's Disease (Without L-dopa):
One early therapy study was a 12-week multicenter study in which 63 patients (41 on ropinirole hydrochloride) with idiopathic Parkinson's disease receiving concomitant anti-Parkinson medication (but not L-dopa) were randomized to either ropinirole hydrochloride or placebo. Patients had a mean disease duration of approximately 2 years. Patients were eligible for enrollment if they presented with bradykinesia and at least tremor, rigidity, or postural instability. In addition, they must not have been classified as Hoehn & Yahr Stage I-V. This scale, ranging from 1 = unilateral involvement with minimal impairment to 5 = confined to wheelchair or bed, is a standard instrument used for staging patients with Parkinson's disease. The primary outcome measure in this trial was the proportion of patients experiencing a decrease (compared to baseline) of at least 30% in the UPDRS motor score.

Patients were titrated for up to 10 weeks, starting at 0.5 mg twice daily, with weekly increments of 0.5 mg twice daily to a maximum of 5 mg twice daily. Once patients reached their maximally tolerated dose (or 5 mg twice daily), they were maintained on that dose through 12 weeks. The mean dose achieved by patients at study endpoint was 7.4 mg/day. At the end of 12 weeks, 71% of patients treated with ropinirole hydrochloride were responders, compared with 41% of patients in the placebo group (p = 0.021).

Statistically significant differences between the percentage of responders on ropinirole hydrochloride compared to placebo were seen after 8 weeks of treatment. In addition, the mean percentage improvement from baseline in the Total Motor Score was 43% in patients treated with ropinirole hydrochloride compared with 21% in patients treated with placebo (p = 0.018).

Statistically significant differences in UPDRS motor score between ropinirole hydrochloride and placebo were seen after 2 weeks of treatment. The median daily dose at which a 30% reduction in UPDRS motor score was sustained was 4 mg.

The second trial in early Parkinson's disease (without L-dopa) patients was a double-blind, randomized, placebo-controlled, 6-month study. Patients were essentially similar to those in the study described above; concomitant use of selegiline was allowed, but patients were not permitted to use anticholinergics or amantadine during the study. Patients had a mean disease duration of 2 years and limited (not more than a 6-week period) or no prior exposure to L-dopa. The starting dose of ropinirole hydrochloride in this trial was 0.25 mg 3 times daily. The dose was titrated at weekly intervals by increments of 0.25 mg 3 times daily to a dose of 1 mg 3 times daily. Further titrations at weekly intervals were made at increments of 1.5 mg 3 times daily up to a dose of 5 mg 3 times daily, and then weekly at increments of 1 mg 3 times daily. Patients were to be titrated to a dose of at least 1.5 mg 3 times daily and then to their maximally tolerated dose, up to a maximum of 8 mg 3 times daily. The mean dose attained in patients at study endpoint was 15.7 mg/day.

The primary measure of effectiveness was the mean percent reduction (improvement) from baseline in the UPDRS Motor Score. In this study 24 patients were enrolled. At the end of the 6-month study, patients treated with ropinirole hydrochloride had 22% improvement in motor score, compared with a 4% worsening in the placebo group (p < 0.001).

Statistically significant differences in UPDRS motor score improvement between ropinirole hydrochloride and placebo were seen after 12 weeks of treatment.

Study in Patients with Advanced Parkinson's Disease (With L-dopa):
This double-blind, placebo-controlled, 6-month trial evaluated 148 patients (Hoehn & Yahr II-IV) who were not adequately controlled on L-dopa. Patients in this study had a mean disease duration of approximately 9 years, had been exposed to L-dopa for approximately 7 years, and had experienced "on-off" periods with L-dopa therapy. Patients previously receiving stable doses of selegiline, amantadine, and/or anticholinergic agents could continue on these agents during the study. Patients were started at a dose of 0.25 mg 3 times daily, and the dose was titrated at weekly intervals up to a maximum of 5 mg 3 times daily, and then weekly at increments of 1 mg 3 times daily. The maximum dose of study medication was 8 mg 3 times daily. All patients had to be titrated to at least a dose of 2.5 mg 3 times daily. Patients could then be maintained on this dose level or higher for the remainder of the study. Once a dose of 2.5 mg 3 times daily was achieved, patients underwent a mandatory reduction in their L-dopa dose, to be followed by additional mandatory reductions with concomitant escalation of the dose of ropinirole hydrochloride. Reductions in the dosage of L-dopa were also allowed if patients experienced adverse events that the investigator considered related to dopaminergic therapy. The mean dose attained at study endpoint was 16.3 mg/day. The primary outcome was the proportion of responders, defined as patients who were able both to achieve a decrease (compared to baseline) of at least 20% in L-dopa dose and to maintain this reduction for at least 4 weeks. The primary efficacy outcome was the proportion of responders among the day when patients are particularly immobile), as determined by patient diary. In addition, the mean percent change from baseline in L-dopa dose was examined.

At the end of 6 months, 28% of patients treated with ropinirole hydrochloride were classified as responders (based on combined endpoint) and 11% of patients treated with placebo were responders (p = 0.02). Based on an protocol-mandated reduction in L-dopa dosage with escalating doses of ropinirole hydrochloride, patients treated with ropinirole hydrochloride had a 19.4% mean reduction in L-dopa dose while patients treated with placebo had a 3% reduction (p < 0.001). L-dopa dosage reduction was also allowed during the study if dyskinesias or other dopaminergic effects occurred. Overall, reduction of L-dopa dose was sustained in 87% of patients treated with ropinirole hydrochloride and in 57% of patients on placebo. On average, the L-dopa dose was reduced by 31% in patients treated with ropinirole hydrochloride.

The mean number of "off" hours per day during baseline was 6.4 hours for patients treated with ropinirole hydrochloride and 7.3 hours for patients treated with placebo. At the end of the 6-month study, patients treated with ropinirole hydrochloride had a mean of 4.9 hours per day "off" time, while placebo-treated patients had a mean of 6.4 hours per day of "off" time.

Restless Legs Syndrome (RLS):
The effectiveness of ropinirole hydrochloride in the treatment of RLS was demonstrated in randomized, double-blind, placebo-controlled studies in adults diagnosed with RLS using the International Restless Legs Syndrome Study diagnostic criteria (see **INDICATIONS AND USAGE**). Patients were required to have a history of a minimum of 15 RLS episodes/month during the previous month and a total score of ≥ 15 on the International RLS Rating Scale (RLS scale) at baseline. Patients with RLS secondary to other conditions (e.g., pregnancy, renal failure, and anemia) were excluded. All studies employed flexible dosing, with patients initiating therapy at 0.25 mg ropinirole hydrochloride once daily. Patients were titrated based on clinical response and tolerability over 7 weeks to a maximum of 4 mg once daily. All studies were taken between 1 and 3 hours before bedtime.

A variety of measures were used to assess the effects of treatment, including the IRLS Scale and Clinical Global Impression-Global Improvement (CGI-I) scores. 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. Three of the controlled studies utilized the change from baseline in the IRLS Scale at the week 12 endpoint as the primary efficacy outcome.

Three hundred eighty-eight patients were randomized to receive ropinirole hydrochloride (n = 187) or placebo (n = 193) in a US study. 284 were randomized to receive either ropinirole hydrochloride (n = 146) or placebo (n = 138) in a multinational study (excluding US); and 267 patients were randomized to ropinirole hydrochloride (n = 131) or placebo (n = 136) in a multinational study (including US). Across the 3 studies, the mean duration of RLS was 22 years (range 0 to 65 years), mean age was approximately 54 years (range 18 to 79 years), and approximately 61% were women. The mean dose at week 12 was approximately 2 mg/day for the 3 studies.

In all 3 studies, a statistically significant difference between the treatment group receiving ropinirole hydrochloride and the treatment group receiving placebo was observed at week 12 for both the mean change from baseline in the IRLS Scale total score and the percentage of patients rated as responders (much improved or very much improved) on the CGI-I (see Table 1).

Table 1
Mean Change in IRLS Score and Percent Responders on CGI-I

	Ropinirole Hydrochloride	Placebo	p-value
Mean Change in IRLS Score at Week 12			
US study	-13.5	-9.8	p<0.0001
Multinational study (excluding US)	-11.0	-8.0	p=0.0036
Multinational study (including US)	-11.2	-8.7	p=0.0197
Percent responders on CGI-I at Week 12			
US study	73.3%	56.5%	p=0.0006
Multinational study (excluding US)	53.4%	40.9%	p=0.0416
Multinational study (including US)	59.5%	39.6%	p=0.0010

Long-term maintenance of efficacy in the treatment of RLS was demonstrated in a 36-week study. Following a 24-week single-blind treatment phase (flexible doses of ropinirole hydrochloride 0.25 to 4 mg once daily), patients who were responders (defined as a decrease in IRLS score of ≥ 10 points relative to baseline) were randomized in double-blind fashion to placebo or continuation of ropinirole hydrochloride for an additional 12 weeks. Relapse was defined as an increase of at least 8 points on the IRLS Scale total score to a total score of at least 15, or withdrawal due to lack of efficacy. For patients who were responders at week 24, the mean dose of ropinirole was 2 mg (range 0.25 to 4 mg). Patients continued on ropinirole hydrochloride demonstrated a significantly lower relapse rate compared with patients randomized to placebo (32.6% vs. 57.8%, p = 0.0156).

INDICATIONS AND USAGE
Parkinson's Disease:
Ropinirole hydrochloride tablets are indicated for the treatment of the signs and symptoms of idiopathic Parkinson's disease. The effectiveness of ropinirole hydrochloride tablets were demonstrated in randomized, controlled trials in patients with early Parkinson's disease who were not receiving concomitant L-dopa therapy as well as in patients with advanced disease on concomitant L-dopa (see **CLINICAL PHARMACOLOGY: Clinical Trials**).

Restless Legs Syndrome:
Ropinirole hydrochloride 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 that are worse 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 moderate-to-severe RLS.

CONTRAINDICATIONS
Ropinirole hydrochloride tablets are contraindicated for patients known to have hypersensitivity to the product.
WARNINGS
Falling Asleep During Activities of Daily Living:
Patients treated with ropinirole hydrochloride have reported falling asleep while engaged in activities of daily living, including the operation of motor vehicles, resulting in accidents. Although many of these patients reported some time while on ropinirole hydrochloride, some perceived that they had no warning signs such as excessive drowsiness, and believed that they were alert immediately prior to the event. Some of these events have been reported as late as 1 year after initiation of treatment.

In controlled clinical trials, somnolence was a common occurrence in patients receiving ropinirole hydrochloride and is more frequent in Parkinson's disease (up to 40% ropinirole hydrochloride, 6% placebo) than in Restless Legs Syndrome (12% ropinirole hydrochloride, 6% placebo). Many clinical experts believe that falling asleep while engaged in activities of daily living always occurs in a setting of preexisting somnolence, although patients may not give such a history. For this reason, prescribers should carefully monitor 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 ropinirole hydrochloride, patients should be advised of the potential to develop drowsiness and specifically asked about factors that may increase the risk with ropinirole hydrochloride such as concomitant sedating medications, the presence of sleep disorders (other than Restless Legs Syndrome), and concomitant medications that increase ropinirole plasma levels (e.g., ciprofloxacin—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.), ropinirole hydrochloride should be discontinued (see **DOSE AND ADMINISTRATION** for guidance in discontinuing ropinirole hydrochloride). If a decision is made to continue ropinirole hydrochloride, patients should be advised to not drive and to avoid other potentially dangerous activities. There is insufficient information to establish that dose reduction will eliminate episodes of falling asleep while engaged in activities of daily living.

Syncope:
Syncope, sometimes associated with bradycardia, was observed in association with ropinirole in both Parkinson's disease patients and RLS patients. In the 2 double-blind, placebo-controlled studies of ropinirole hydrochloride in patients with Parkinson's disease who were not being treated with L-dopa, 11.5% (18 of 157) of patients on ropinirole hydrochloride had syncope compared to 1.4% (2 of 147) of patients on placebo. Most of these events occurred more than 4 weeks after initiation of therapy with ropinirole hydrochloride, and were usually associated with a recent increase in dose.

Of 208 patients being treated with both L-dopa and ropinirole hydrochloride in placebo-controlled advanced Parkinson's disease trials, there were reports of syncope in 6 (2.9%) compared to 2 of 120 (1.7%) of placebo-L-dopa patients.

In patients with RLS, 3 (2.3%) of 129 patients treated with ropinirole hydrochloride and 2 (1.5%) of 132 patients treated with placebo had syncope. Because the studies of ropinirole hydrochloride excluded patients with significant cardiovascular disease, it is not known to what extent the estimated incidence figures apply to either Parkinson's disease or RLS patients in clinical practice. Therefore, patients with severe cardiovascular disease should be treated with caution.

Two of 47 Parkinson's disease patients enrolled in phase 1 studies had syncope following a 1-mg dose. In 2 studies in RLS patients that used a forced titration regimen and orthostatic challenge with intensive blood pressure monitoring, 1 of 55 RLS patients treated with ropinirole hydrochloride compared with 0 of 27 patients receiving placebo reported syncope. In phase 1 studies including 110 healthy volunteers, 1 patient developed hypotension, bradycardia, and sinus arrest of 26 seconds accompanied by syncope; the patient recovered spontaneously without intervention. One other healthy volunteer reported syncope.

Symptomatic Hypotension:
Dopamine agonists, in clinical studies and clinical experience, appear to impair the systemic regulation of blood pressure, with resulting postural hypotension, especially during dose escalation. Parkinson's disease patients, in addition, appear to have an impaired capacity to compensate for orthostatic hypotension. The frequency of hypotension associated with dopaminergic agonists ordinarily (1) require careful monitoring for signs and symptoms of postural hypotension, especially during dose escalation, and (2) should be informed of this risk (see **PRECAUTIONS: Information for Patients**).

Although the clinical trials were not designed to systematically monitor blood pressure, there were individual reported cases of postural hypotension in patients treated with ropinirole hydrochloride. Most of these cases occurred more than 4 weeks after initiation of therapy with ropinirole hydrochloride and were usually associated with a recent increase in dose. In 12-week placebo-controlled trials of patients with RLS, the adverse event orthostatic hypotension was reported by 0 of 496 patients (0.6%) treated with ropinirole hydrochloride compared with 2 of 500 patients (0.4%) receiving placebo.

In two phase 2 studies in patients with RLS that used a forced-titration regimen and orthostatic challenges with intensive blood pressure monitoring, 1 of 55 ropinirole hydrochloride patients who had post-dose blood pressure assessments following placebo experienced an orthostatic blood pressure decrease of at least 20 mm Hg systolic and/or at least 20 mm Hg diastolic; not all of these changes were associated with clinical symptoms. Except for its forced nature these studies used a similar titration schedule as those in the phase 3 efficacy trials.

In phase 3 studies of ropinirole hydrochloride that included 110 healthy volunteers, 9 subjects had documented symptomatic postural hypotension. These episodes appeared mainly at doses above 0.5 mg and these doses are higher than the starting doses recommended for either Parkinson's disease patients or RLS patients. In 8 of these 9 individuals, the hypotension was accompanied by bradycardia, but did not develop into syncope (see **Syncope** subsection). None of these events resulted in death or hospitalization.

One of 47 Parkinson's disease patient volunteers enrolled in phase 1 studies had documented hypotension following a 2-mg dose on 2 occasions.

Hallucinations:
In double-blind, placebo-controlled, early-therapy studies in patients with Parkinson's disease who were not treated with L-dopa, 5.2% (8 of 157) of patients treated with ropinirole hydrochloride reported hallucinations, compared to 1.4% of patients on placebo (2 of 147). Among these patients receiving ropinirole hydrochloride, 4.2% (6 of 143) of patients treated with L-dopa also reported hallucinations. 10% (11 of 2108) were reported to experience hallucinations, compared to 4.2% (5 of 120) of patients treated with placebo and L-dopa.

Hallucinations were of sufficient severity to cause discontinuation of treatment in 1.3% of the early Parkinson's disease (without L-dopa) patients and 1.9% of the advanced Parkinson's disease (with L-dopa) patients, compared to 0% and 1.7% of placebo patients, respectively. In patients with RLS, hallucinations were reported by 0% of patients treated with ropinirole hydrochloride (0 of 496) compared with 0.2% of patients treated with placebo (1 of 500) in the 12-week placebo-controlled trials; in marketing long-term open-label studies, 0.5% of patients reported hallucinations during therapy with ropinirole hydrochloride (2 of 390) but did not discontinue treatment and symptoms resolved.

PRECAUTIONS
General:
Dyskinesia:
Ropinirole hydrochloride may potentiate the dopaminergic side effects of L-dopa and may cause and/or exacerbate preexisting dyskinesia in patients treated with L-dopa for Parkinson's disease. Decreasing the dose of L-dopa may ameliorate this side effect.

Renal Impairment:
No dosage adjustment is needed in patients with mild to moderate renal impairment (creatinine clearance of 30 to 50 mL/min). The use of ropinirole hydrochloride in patients with severe renal impairment has not been studied.

Hepatic Impairment:
The pharmacokinetics of ropinirole have not been studied in patients with hepatic impairment. Since patients with hepatic impairment may have higher plasma levels and lower clearance, ropinirole hydrochloride should be titrated with caution in these patients.

Events Reported with Dopaminergic Therapy:
Withdrawal-Emergent Hyperpyrexia and Confusion:
Although not reported with ropinirole hydrochloride, 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 anti-Parkinsonian therapy.

Fibrotic Complications:
The use of retropirone hydrochloride, pulmonary infiltrates, pleural effusion, pleuritic/pleurisy, 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 pleural effusion, pleural fibrosis, interstitial lung disease, and cardiac valvulopathy, in the development program and postmarketing experience for ropinirole hydrochloride. While the evidence is not sufficient to establish a causal relationship between ropinirole hydrochloride and these fibrotic complications, a contribution of ropinirole hydrochloride cannot be completely ruled out in rare cases.

Metabolic Studies:
Epidemiologic 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.

Patients who are treated with ropinirole, patients and providers are advised to monitor for melanomas frequently and on a regular basis when using ropinirole hydrochloride for any indication. Ideally, periodic skin examinations should be performed by appropriately qualified individuals (e.g., dermatologists).

Augmentation and Rebound in RLS:
Reports in the literature indicate treatment of RLS with dopaminergic medications can result in a worsening of symptoms in the early morning hours, referred to as rebound. 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. The controlled trials of ropinirole hydrochloride in patients with RLS excluded patients with augmentation and rebound and were generally not of sufficient duration to evaluate the frequency of augmentation and rebound. In marketing long-term open-label studies, 0.5% of patients reported augmentation and rebound, but cannot be disregarded because of disruption of a mechanism that is universally present in vertebrates (e.g., disk shedding) may be involved.

Human:
In order to evaluate the effect of ropinirole hydrochloride in humans, ocular electroretinogram (ERG) assessments were conducted during a 2-year, double-blind, multicenter, flexible dose, L-dopa controlled study of ropinirole hydrochloride in patients with Parkinson's disease. The frequency of abnormal ERG findings in patients on ropinirole hydrochloride (78 on L-dopa; mean dose 55.2 mg/day) were evaluated for evidence of retinal dysfunction through electroretinograms. There was no clinically meaningful difference between the treatment groups in retinal function over the duration of the study.

Binding to Melanin:
Ropinirole hydrochloride binds to melanin-containing tissues (i.e., eyes, skin) in pigmented rats. After a single dose, long-term retention of drug was demonstrated, with a half-life in the eye of 20 days. It is not known if ropinirole hydrochloride accumulates in these tissues over time.

Information for Patients:
Physicians should instruct their patients to read the Patient Information Leaflet before starting therapy with ropinirole hydrochloride and to read it upon prescription renewal for new information regarding the use of ropinirole hydrochloride.

Patients should be instructed to take ropinirole hydrochloride only as prescribed. If a dose is missed, patients should be advised not to double their next dose.

Ropinirole hydrochloride can be taken with or without food. Patients may be advised that taking ropinirole hydrochloride with food may reduce the occurrence of nausea. However, this has not been established in controlled clinical trials.

Patients should be advised that they may develop postural (orthostatic) hypotension with or without symptoms such as dizziness, nausea, syncope, and sometimes sweating. Hypotension and/or orthostatic symptoms may occur more frequently during initial therapy or with an increase in dose at any time (cases have been seen after weeks of treatment). 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 ropinirole hydrochloride.

Patients should be alerted to the potential sedating effects associated with ropinirole hydrochloride, including somnolence and the possibility of falling asleep while engaged in activities of daily living. Since somnolence is a frequent adverse event with potentially serious consequences, patients should be advised to avoid driving or operating potentially dangerous activities until they have gained sufficient experience with ropinirole hydrochloride to gauge whether or not it affects their mental and/or motor performance adversely. Patients should be advised that if increased somnolence or 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 ropinirole hydrochloride and when taking concomitant medications that increase plasma levels of ropinirole (e.g., ciprofloxacin).

Because of the possible additive sedative effects, caution should also be used when patients are taking alcohol or other CNS depressants (e.g., benzodiazepines, antipsychotics, antiexpressants, etc.) in combination with ropinirole hydrochloride.

Patients should be informed they may experience hallucinations (unreal visions, sounds, or sensations

