

PRESCRIBING INFORMATION

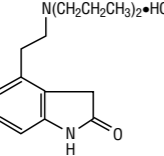
Ropinirole Tablets USP

Patient Information Included

DESCRIPTION

Ropinirole hydrochloride USP is an orally administered non-ergoline dopamine agonist. It is the hydrochloride salt of 4-[2-(dipropylamino)ethyl]-1,3-dihydro-2H-imidolo-2-one monohydrochloride and has an empirical formula of C₁₂H₁₆N₂O•HCl. The molecular weight is 296.84 (260.38 as the free base).

The structural formula is:



Ropinirole hydrochloride USP is a pale cream to yellow powder with a melting range of 243° to 250°C and a solubility of 133 mg/mL in water.

Each circular unit-dose tablet contains ropinirole hydrochloride USP equivalent to ropinirole, 0.25 mg, 0.5 mg, 1 mg, 3 mg, 4 mg, or 5 mg. Inactive ingredients consist of: citric acid anhydrous powder, croscarmellose sodium, lactose anhydrous, lactose monohydrate, magnesium stearate, microcrystalline cellulose, and one or more of the following: carmine, FD&C Blue No. 1, ferrous lactate, FD&C Blue No. 2, aluminum lake, FD&C Yellow No. 6, aluminum lake, hypromellose, ferric oxide black, ferric oxide red, ferric oxide yellow, polyethylene glycol, talc and titanium dioxide. The product meets USP Dissolution test 2.

CLINICAL PHARMACOLOGY

Mechanism of Action: Ropinirole hydrochloride is a non-ergoline dopamine agonist with high relative in vivo 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 affinity for opiate receptors. Ropinirole and its metabolites have negligible in vivo affinity for dopamine D₁, 5-HT₁, 5-HT₂, benzodiazepine, GABA, muscarinic, alpha₁, alpha₂, 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 deficits in various animal models of Parkinson's disease. In particular, ropinirole attenuates the motor deficits induced by lesioning the ascending nigrostriatal dopaminergic pathway with the neurotoxin 1-methyl-4-phenyl-1,2,3,6-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 Ekbohm Syndrome) 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.

Clinical Pharmacology Studies: In healthy normotensive 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 pulse rates. 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 the hypotensive effect of 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 ECG 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, approximately 88% of the dose was recovered in urine and the absolute bioavailability was 55%, indicating 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 4.7 L/hr (cv = 45%) and its terminal half-life is approximately 7 hours. Ropinirole is extensively metabolized in the liver 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 fluoroquinolones such as ciprofloxacin and norfloxacin. The N-despropyl metabolite is converted to carbamyl glucuronide, carboxylic acid, and N-despropyl hydroxy metabolites. The hydroxy metabolite is rapidly converted to a glucuronide. Less than 10% of the administered dose is excreted as unchanged drug in urine. N-despropyl ropinirole is 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 alter clearance when coadministered 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: Female and male 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 of 30 to 50 mL/min) compared to those with normal renal function with creatinine clearance above 50 mL/min. Therefore, no dosage adjustment is necessary in moderately renal 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.

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 who were and were not receiving concomitant L-dopa. Two of these 3 trials enrolled patients with early Parkinson's disease (without L-dopa) and 1 enrolled patients receiving L-dopa. In these studies a variety of measures were used to assess the effects of treatment (e.g., the Unified Parkinson's Disease Rating Scale [UPDRS], motor sub-score, depression [CGI] scores, patient diaries recording time "on" and "off," and tolerability of L-dopa dose reductions).

In both studies of early Parkinson's disease (without L-dopa) patients, the motor component (Part III) of the UPDRS was the primary outcome assessment. 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 gait and posture (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 (worse) score of 108. Responders were defined as patients with at least a 30% reduction in the Part III score.

In the 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 primary endpoint.

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 have been classified as Hoehn & Yahr Stage I-V. This scale, ranging from I = unilateral involvement with minimal impairment to V = 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 treated up to 2 hours 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 disease was 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 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 have been classified as Hoehn & Yahr Stage I-V. This scale, ranging from I = unilateral involvement with minimal impairment to V = 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 treated up to 2 hours 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. 71% of patients treated with ropinirole hydrochloride were responders, compared with 41% of patients in the placebo group (p = 0.021).

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Study in Patients With Advanced Parkinson's Disease (With L-dopa): This double-blind, randomized, 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 anticholinergic agents could continue on these agents during the study. Patients were started at a dose of 0.25 mg 3 times daily of ropinirole hydrochloride and titrated upward by weekly intervals until an optimal therapeutic response was achieved. 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 continued 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 their L-dopa dose and a decrease of at least 20% in the proportion of time spent "off" during the study when patients are particularly immobile), as determined by patient diary. In addition, the mean percent change from baseline in daily 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) while 11% of patients treated with placebo were responders (p = 0.02). Based on the protocol-mandated reductions in L-dopa dose, the mean percentage change from baseline in L-dopa dose was 25% in 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 of "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 two placebo-controlled studies in adults diagnosed with RLS using the International Restless Legs Syndrome Study Group 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 (IRLS scale) at baseline. Patients with RLS secondary to other conditions (e.g., pregnancy, renal failure, and anemia) were excluded. All studies employed flexible dosing regimens with a maximum of 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 doses 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 consists of 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 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 16 to 22 years (range of 0 to 65 years), mean age was approximately 54 years (range of 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 of 0.25 to 4 mg once daily), patients in a multinational study (excluding US) who had a decrease of ≥6 points on the IRLS Scale total score 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 6 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 tablets USP are indicated for the treatment of the signs and symptoms of idiopathic Parkinson's disease.

The effectiveness of ropinirole hydrochloride 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 tablets USP 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 restless symptoms, especially at rest or 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 is 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, which sometimes resulted in accidents. Although many of these patients reported somnolence 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 continually reassess patients for drowsiness or sleepiness, especially since some of the events occur well after the start of therapy. Patients should be alert 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, 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 continually reassess patients for drowsiness or sleepiness, especially since some of the events occur well after the start of therapy. Patients should be alert aware that patients may not acknowledge drowsiness or sleepiness until directly questioned about drowsiness or sleepiness during specific activities.

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(See DOSAGE AND ADMINISTRATION for guidance in discontinuing ropinirole hydrochloride.) It is advised to discontinue ropinirole hydrochloride therapy and to 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 cases occurred more than 4 weeks after the start 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, of 496 patients treated with ropinirole hydrochloride in 12-week placebo-controlled trials, there were reports of syncope in 5 (1.0%) compared with 1 of 500 (0.2%) patients treated with placebo.

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 patient volunteers enrolled in phase 1 studies had syncope following a 1 mg oral dose. In 2 studies, patients were given a forced titration protocol and orthostatic challenge with intensive blood pressure monitoring. 1 of 155 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 and associated symptoms. In 2 studies in which patients were given a forced titration appear to have an impaired capacity to respond to a postural challenge. For these reasons, Parkinson's patients being treated 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 early Parkinson's disease (without L-dopa) 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 4 of 496 patients (0.8%) 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, 14 of 55 patients (25%) receiving ropinirole hydrochloride experienced an adverse event of hypotension or postural hypotension. As described above, one additional patient was noted to have an episode of vasovagal syncope (although no blood pressure recording was documented). None of the 27 patients receiving placebo had orthostatic hypotension. In these studies, 11 of the 55 patients (20%) receiving ropinirole hydrochloride and 3 of the 26 patients (12%) who had post-dose blood pressure assessments following placebo, experienced an orthostatic blood pressure decrease of at least 40 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 1 studies of ropinirole hydrochloride in healthy young, fit, open-label volunteers, 9 subjects had documented symptomatic postural hypotension. These episodes appeared mainly at doses above 0.8 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 orthostatic hypotension following a 1 mg oral dose.

Hallucinations: In double-blind, placebo-controlled, early-therapy studies in patients with Parkinson's disease, 11% of patients on ropinirole hydrochloride (n = 15) and 15% of patients on placebo (n = 22) reported hallucinations, compared to 1.4% of patients on placebo (2 of 147). Among those patients receiving both ropinirole hydrochloride and L-dopa in advanced Parkinson's disease (with L-dopa) studies, 10.1% (21 of 208) 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 who received placebo (1 of 500) in the 12-week placebo-controlled trials. In long-term open-label studies, 0% 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 Rhabdomyolysis: 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: Cases of retroperitoneal fibrosis, pulmonary infiltrates, pleural effusions, pleural thickening, pericarditis, and cardiac valvulopathy have been reported in some patients treated with dopamine-derivative 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.

Melanoma: Epidemiologic studies have shown that patients with Parkinson's disease have an increased risk to develop melanoma, a type of skin cancer, compared to the general population. Whether the increased risk 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 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 clinical risk of ropinirole hydrochloride in patients with RLS who are treated with augmentation and rebound is not clear. The potential of sufficient duration to capture these phenomena. The frequency of augmentation and/or rebound after longer use of ropinirole hydrochloride and the appropriate management of these events, have not been evaluated in controlled clinical trials.

nausea, headache, dizziness, drowsiness or sleepiness.

- You should be careful until you know if ropinirole tablets affect your ability to remain alert while doing normal daily activities, and you should watch for the development of significant daytime sleepiness or episodes of falling asleep. It is possible that you could fall asleep while doing normal activities such as driving a car, doing physical tasks, or using hazardous machinery while taking ropinirole tablets. Your chances of falling asleep while doing normal activities are greater if you are taking other medicines that cause drowsiness.

- When you start taking ropinirole tablets or when you increase your dose, you may feel dizzy, nauseated, sweaty or faint, when first standing up from sitting or lying down. Therefore, do not stand up quickly after sitting or lying down, particularly if you have been sitting or lying down for a long period of time. Take a minute sitting on the edge of the bed or chair before you get up.
- Some patients taking ropinirole have shown urges to behave in a way unusual for them. Examples of this are an unusual urge to gamble or increased sexual urges and/or behaviors. If you or your family notices that you are developing any unusual behaviors, talk to your doctor.

- Hallucinations (unreal visions, sounds, or sensations) have been reported in patients taking ropinirole tablets. The risk is greater in patients with Parkinson's disease who are elderly, taking ropinirole tablets with L-dopa, or taking higher amounts of ropinirole tablets.
- If you are taking L-dopa for Parkinson's disease, ropinirole tablets may make some of the side effects of L-dopa worse. Ropinirole tablets may cause uncontrolled sudden movements or make such movements you already have worse or more frequent.

This is not a complete list of side effects and should not take the place of discussions with your healthcare providers. Your doctor or pharmacist can give you a more complete list of possible side effects. Talk to your doctor about any side effects or problems you may have.

Other Information about ropinirole tablets

- 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 ropinirole tablets or the medicines used to treat Parkinson's disease. Therefore, patients being treated with ropinirole tablets should have periodic skin examinations.
- Take ropinirole tablets exactly as your doctor prescribes it.
- Do not share ropinirole tablets with other people, even if they have the same symptoms you have.
- Keep ropinirole tablets out of the reach of children.
- Store ropinirole tablets at room temperature out of direct sunlight.
- Keep ropinirole tablets in a tightly closed container.

This leaflet summarizes important information about ropinirole tablets. Medicines are sometimes prescribed for purposes other than those listed in this leaflet. Do not take ropinirole tablets for a condition for which it was not prescribed. For more information, talk with your doctor or pharmacist. They can give you information about ropinirole tablets that is written for healthcare professionals.

Manufactured by:
Glenmark Generics Ltd.
Colvale-Bardde, Goa 403 513, India

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hazardous machinery while taking ropinirole tablets. Your chances of falling asleep while doing normal activities are greater if you are taking other medicines that cause drowsiness.

- When you start taking ropinirole tablets or when you increase your dose, you may feel dizzy, nauseated, sweaty or faint, when first standing up from sitting or lying down. Therefore, do not stand up quickly after sitting or lying down, particularly if you have been sitting or lying down for a long period of time. Take a minute sitting on the edge of the bed or chair before you get up.
- Some patients taking ropinirole have shown urges to behave in a way unusual for them. Examples of this are an unusual urge to gamble or increased sexual urges and/or behaviors. If you or your family notices that you are developing any unusual behaviors, talk to your doctor.

- Hallucinations (unreal sounds, visions, or sensations) have been reported in patients taking ropinirole tablets. These were uncommon in patients taking ropinirole tablets for RLS. The risk is greater in patients with Parkinson's disease who are elderly, taking ropinirole tablets with L-dopa, or taking higher doses of ropinirole tablets than recommended for RLS.

This is not a complete list of side effects and should not take the place of discussions with your healthcare providers. Your doctor or pharmacist can give you a more complete list of possible side effects. Talk to your doctor about any side effects or problems you may have.

Other Information about ropinirole tablets

- 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 ropinirole tablets or the medicines used to treat Parkinson's disease. Therefore, patients being treated with ropinirole tablets should have periodic skin examinations.
- Take ropinirole tablets exactly as your doctor prescribes it.
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This leaflet summarizes important information about ropinirole tablets. Medicines are sometimes prescribed for purposes other than those listed in this leaflet. Do not take ropinirole tablets for a condition for which it was not prescribed. For more information, talk with your doctor or pharmacist. They can give you information about ropinirole tablets that is written for healthcare professionals.

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Early Parkinson's Disease (Without L-dopa): The most commonly observed adverse events (>5%) in the double-blind, placebo-controlled early Parkinson's disease trials associated with the use of ropinirole hydrochloride (n = 157) not seen at an equivalent frequency among the placebo-treated patients (n = 147) were, in order of decreasing incidence: nausea, dizziness, somnolence, headache, vomiting, syncope, fatigue, dyspepsia, viral infection, constipation, pain, increased sweating, asthenia, dependent leg edema, orthostatic symptoms, abdominal pain, pharyngitis, confusion, hallucinations, urinary tract infections, and abnormal vision.

Approximately 24% of 157 patients treated with ropinirole hydrochloride who participated in the double-blind, placebo-controlled early Parkinson's disease (without L-dopa) trials discontinued treatment due to adverse events compared to 13% of 147 patients who received placebo. The adverse events most commonly causing discontinuation of treatment by patients treated with ropinirole hydrochloride were: nausea (6.4%), dizziness (3.3%), aggravated Parkinson's disease (1.3%), hallucinations (1.3%), somnolence (1.3%), vomiting (1.3%), and headache (1.3%). Of these, hallucinations appear to be dose-related. While other adverse events leading to discontinuation may be dose-related, the titration design utilized in these trials precluded an adequate assessment of the dose response. For example, in the larger of the 2 trials described in CLINICAL PHARMACOLOGY: Clinical Trials, the difference in the rate of discontinuations emerged only after 10 weeks of treatment, suggesting, although not proving, that the effect could be related to dose.

Adverse Event Incidence in Controlled Clinical Studies: Table 2 lists treatment-emergent adverse events that occurred in ≥2% of patients with early Parkinson's disease (without L-dopa) treated with ropinirole hydrochloride participating in the double-blind, placebo-controlled studies and were numerically more common in the group treated with ropinirole hydrochloride. In these studies, either ropinirole hydrochloride or placebo was used as early therapy (i.e., without L-dopa).

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 non-drug factors to the adverse-events incidence rate in the population studied.

Table 2. Treatment-Emergent Adverse Event* Incidence in Double-Blind, Placebo-Controlled Early Parkinson's Disease (Without L-dopa) Trials (Events ≥2% of Patients Treated With Ropinirole Hydrochloride and Numerically More Frequent Than the Placebo Group)

Adverse Experience	Ropinirole Hydrochloride (n = 157) (%)	Placebo (n = 147) (%)
Autonomic nervous system		
Flushing	3	1
Dry mouth	5	3
Increased sweating	6	4
Body as a whole		
Asthenia	6	1
Chest pain	4	2
Dependent edema	6	3
Leg edema	7	1
Fatigue	11	4
Malaise	3	4
Pain	8	4
Cardiovascular general		
Hypertension	5	3
Hypotension	2	0
Orthostatic symptoms	6	5
Syncope	12	1
Central/peripheral nervous system		
Dizziness	40	22
Hyperkinesia	2	1
Hyposthesia	4	2
Vertigo	2	0
Gastrointestinal system		
Abdominal pain	6	3
Anorexia	4	1
Dyspepsia	10	5
Flatulence	3	1
Nausea	60	22
Vomiting	12	7
Heart rate/rhythm		
Extrasystoles	2	1
Atrial fibrillation	2	0
Palpitation	3	2
Tachycardia	2	0
Metabolic/nutritional		
Increased alkaline phosphatase	3	1
Psychiatric		
Amnesia	3	1
Impaired concentration	3	0
Confusion	5	1
Hallucination	5	1
Somnolence	40	6
Yawning	3	0
Reproductive male		
Impotence	3	1
Resistance mechanism		
Viral infection	11	3
Respiratory system		
Bronchitis	3	1
Dyspnea	3	0
Pharyngitis	6	4
Rhinitis	4	3
Sinusitis	4	3
Urinary system		
Urinary tract infection	5	4
Vascular/extracardiac		
Peripheral ischemia	3	0
Vision		
Eye abnormality	3	1
Abnormal vision	6	3
Xerophthalmia	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 1% or more of early Parkinson's disease (without L-dopa) patients treated with ropinirole hydrochloride, but that were equally or more frequent in the placebo group, were: headache, upper respiratory infection, insomnia, arthralgia, tremor, back pain, anxiety, dyskinesias, aggravated Parkinsonism, depression, falls, myalgia, leg cramps, paresthesias, nervousness, diarrhea, arthritis, hot flashes, weight loss, rash, cough, hyperglycemia, muscle spasm, arthralgia, abnormal dreams, dystonia, increased salivation, bradycardia, gout, basal cell carcinoma, gingivitis, hematuria, and rigors.

Among the treatment-emergent adverse events in patients treated with ropinirole hydrochloride, hallucinations appear to be dose-related.

The incidence of adverse events was not materially different between women and men.

Advanced Parkinson's Disease (With L-dopa): The most commonly observed adverse events (>5%), in the double-blind, placebo-controlled advanced Parkinson's disease (with L-dopa) trials associated with the use of ropinirole hydrochloride (n = 208) as an adjunct to L-dopa not seen at an equivalent frequency among the placebo-treated patients (n = 120) were, in order of decreasing incidence: dyskinesias, nausea, dizziness, aggravated Parkinsonism, somnolence, headache, insomnia, injury, hallucinations, falls, abdominal pain, upper respiratory infection, confusion, increased sweating, vomiting, viral infection, increased drug level, arthralgia, tremor, anxiety, urinary tract infection, constipation, dry mouth, pain, hypokinesia, and paresthesia.

Approximately 24% of 208 patients who received ropinirole hydrochloride in the double-blind, placebo-controlled advanced Parkinson's disease (with L-dopa) trials discontinued treatment due to adverse events compared to 18% of 120 patients who received placebo. The events most commonly (>1%) causing discontinuation of treatment by patients treated with ropinirole hydrochloride were: dizziness (2.9%), dyskinesias (2.4%), vomiting (2.4%), confusion (2.4%), nausea (1.9%), hallucinations (1.9%), anxiety (1.9%), and increased sweating (1.4%). Of these, hallucinations and dyskinesias appear to be dose-related.

Adverse Event Incidence in Controlled Clinical Studies: Table 3 lists treatment-emergent adverse events that occurred in ≥2% of patients with advanced Parkinson's disease (with L-dopa) treated with ropinirole hydrochloride who participated in the double-blind, placebo-controlled studies and were numerically more common in the group treated with ropinirole hydrochloride. In these studies, either ropinirole hydrochloride or placebo was used as an adjunct to L-dopa. 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 non-drug factors to the adverse-events incidence rate in the population studied.

Table 3. Treatment-Emergent Adverse Event* Incidence in Double-Blind, Placebo-Controlled Advanced Parkinson's Disease (With L-dopa) Trials (Events ≥2% of Patients Treated With Ropinirole Hydrochloride and Numerically More Frequent Than the Placebo Group)

Adverse Experience	Ropinirole Hydrochloride (n = 208) (%)	Placebo (n = 120) (%)
Autonomic nervous system		
Dry mouth	5	1
Increased sweating	7	2
Body as a whole		
Increased drug level	7	3
Pain	5	3
Cardiovascular general		
Hypertension	2	1
Syncope	3	2
Central/peripheral nervous system		
Dizziness	26	16
Dyskinesia	34	13
Falls	7	7
Headache	17	12
Hypokinesia	5	4
Paresis	3	0
Paresthesia	5	3
Tremor	6	3
Gastrointestinal system		
Abdominal pain	9	8
Constipation	6	3
Diarrhea	5	3
Dysphagia	2	1
Flatulence	2	1
Nausea	30	18
Increased saliva	2	1
Vomiting	7	4
Metabolic/nutritional		
Weight decrease	2	1
Musculoskeletal system		
Arthralgia	7	5
Arthritis	3	1
Psychiatric		
Amnesia	5	1
Anxiety	6	3
Confusion	9	2
Abnormal dreaming	3	2
Hallucinations	10	4
Nervousness	5	3
Somnolence	20	8
Red blood cell		
Anemia	2	0
Resistance mechanism		
Upper respiratory tract infection	9	8
Respiratory system		
Dyspnea	3	2
Urinary system		
Pyuria	2	1
Urinary incontinence	2	1
Urinary tract infection	6	3
Vision		
Diplopia	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 treated with both ropinirole hydrochloride and L-dopa, but equally or more frequent in the placebo/L-dopa group, were: myocardial infarction, orthostatic symptoms, virus infections, asthenia, dyspepsia, myalgia, back pain,

depression, leg cramps, fatigue, rhinitis, chest pain, hematuria, vertigo, tinnitus, leg edema, hot flashes, abnormal gait, hyperkinesia, and pharyngitis.

Among the treatment-emergent adverse events in patients treated with ropinirole hydrochloride, hallucinations and dyskinesias appear to be dose-related.

Restless Legs Syndrome: The most commonly observed adverse events (>5%) in the 12-week double-blind, placebo-controlled trials in the treatment of Restless Legs Syndrome with ropinirole hydrochloride (n = 496) and at least twice the rate for placebo-treated patients (n = 500) were, in order of decreasing incidence: nausea, somnolence, vomiting, dizziness, and fatigue (see Table 4). Occurrences of nausea in clinical trials were generally mild to moderate in intensity (see also DOSAGE AND ADMINISTRATION: General Dosing Considerations).

Approximately 5% of 496 patients treated with ropinirole hydrochloride who participated in the double-blind, placebo-controlled trials in the treatment of RLS discontinued treatment due to adverse events compared to 4% of 500 patients who received placebo. The adverse events most commonly causing discontinuation of treatment by patients treated with ropinirole hydrochloride were: nausea (1.6%), dizziness (0.8%), and headache (0.8%).

Adverse Event Incidence in Controlled Clinical Studies: Table 4 lists treatment-emergent adverse events that occurred in ≥2% of patients with RLS treated with ropinirole hydrochloride participating in the 12-week double-blind, placebo-controlled studies and were numerically more common in the group treated with ropinirole hydrochloride.

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 non-drug factors to the adverse-events incidence rate in the population studied.

Table 4. Treatment-Emergent Adverse Event Incidence in Double-Blind, Placebo-Controlled RLS Trials (Events ≥2% of Patients Treated With Ropinirole Hydrochloride and Numerically More Frequent Than the Placebo Group)

Adverse Experience	Ropinirole Hydrochloride n = 496 (%)	Placebo n = 500 (%)
Ear and labyrinth disorders		
Vertigo	2	1
Gastrointestinal disorders		
Nausea	40	8
Vomiting	11	2
Diarrhea	5	3
Dyspepsia	3	3
Dry mouth	3	2
Abdominal pain upper	3	1
General disorders and administration site conditions		
Fatigue	8	4
Edema peripheral	2	1
Infections and infestations		
Nasopharyngitis	9	8
Influenza	3	2
Musculoskeletal and connective tissue disorders		
Arthralgia	4	3
Muscle cramps	3	2
Pain in extremity	3	2
Nervous system disorders		
Somnolence	12	6
Dizziness	11	5
Paresthesia	3	1
Respiratory, thoracic, and mediastinal disorders		
Cough	2	2
Nasal congestion	3	1
Skin and subcutaneous tissue disorders		
Hyperhidrosis	3	1

Other events reported by 2% or more of patients treated with ropinirole hydrochloride, but equally or more frequent in the placebo group, were: headache, insomnia, restless legs syndrome, upper respiratory tract infection, back pain, and sinusitis.

Other Adverse Events Observed During All Phase 2/3 Clinical Trials for Parkinson's Disease: Ropinirole hydrochloride has been administered to 1,599 individuals in clinical trials. During these trials, all adverse events were recorded by the clinical investigators using terminology of their own choosing. To provide a meaningful estimate of the proportion of individuals having adverse events, similar types of events were grouped into a smaller number of standardized categories using modified WHOART dictionary terminology. These categories are used in the listing below. The frequencies presented represent the proportion of the 1,599 individuals exposed to ropinirole hydrochloride who experienced events of the type cited on at least 1 occasion while receiving ropinirole hydrochloride. All reported events that occurred at least twice (or once for serious or potentially serious events), except those already listed above, trivial events, and terms too vague to be meaningful, are included without regard to determination of a causal relationship to ropinirole hydrochloride, except that events very unlikely to be drug-related have been deleted.

Events are further classified within body system categories and enumerated in order of decreasing frequency using the following definitions: frequent adverse events are defined as those occurring in at least 1/100 patients and infrequent adverse events are those occurring in 1/100 to 1/1,000 patients and rare events are those occurring in fewer than 1/1,000 patients.

Body as a Whole: **Infrequent:** Cellulitis, peripheral edema, fever, influenza-like symptoms, enlarged abdomen, precordial chest pain, and generalized edema. **Rare:** Ascites.

Cardiovascular: **Infrequent:** Cardiac failure, bradycardia, tachycardia, supraventricular tachycardia, angina pectoris, bundle branch block, cardiac arrest, cardiomegaly, aneurysm, myocardial infarction. **Rare:** Ventricular tachycardia.

Central/Peripheral Nervous System: **Frequent:** Neuralgia. **Infrequent:** Involuntary muscle contractions, hypertonía, dysphonia, abnormal coordination, extrapyramidal disorder, migraine, choreoathetosis, coma, stupor, aphasia, convulsions, hypotonia, peripheral neuropathy, paralysis. **Rare:** Grand mal convulsions, hemiparesis, hemiplegia.

Endocrine: **Infrequent:** Hypothyroidism, gynecomastia, hyperthyroidism. **Rare:** Goiter, SIADH.

Gastrointestinal: **Infrequent:** Increased hepatic enzymes, bilirubinemia, cholecystitis, cholelithiasis colitis, dysphagia, peridontitis, fecal incontinence, gastroesophageal reflux, hemorrhoids, toothache, eructation, gastritis, esophagitis, hiccup, diverticulitis, duodenal ulcer, gastric ulcer, melena, duodenitis, gastrointestinal hemorrhage, glossitis, rectal hemorrhage, pancreatitis, stomatitis and ulcerative stomatitis, tongue edema. **Rare:** Biliary pain, hemorrhagic gastritis, hematemesis, salivary duct obstruction.

Hematologic: **Infrequent:** Purpura, thrombocytopenia, hematoma, Vitamin B12 deficiency, hypochromic anemia, eosinophilia, leukocytosis, leukopenia, lymphocytosis, lymphopenia, lymphedema.

Metabolic/Nutritional: **Frequent:** Increased BUN. **Infrequent:** Hypoglycemia, increased alkaline phosphatase, increased LDH, weight increase, hyperphosphatemia, hyperuricemia, diabetes mellitus, glycosuria, hypokalemia, hypercholesterolemia, hyperkalemia, acidosis, hypernatremia, hypocalcemia, hypomagnesemia, hypocalcemia.

Musculoskeletal: **Infrequent:** Aggravated arthritis, tendonitis, osteoporosis, bursitis, polyomyalgia rheumatica, muscle weakness, skeletal pain, torticollis. **Rare:** Dupuytren's contracture requiring surgery.

Neoplasms: **Infrequent:** Malignant breast neoplasm. **Rare:** Bladder carcinoma, benign brain neoplasm, esophageal carcinoma, malignant laryngeal neoplasm, lipoma, rectal carcinoma, uterine cancer.

Psychiatric: **Infrequent:** Increased libido, agitation, apathy, impaired concentration, depersonalization, paranoid reaction, personality disorder, euphoria, delirium, dementia, delusion, emotional lability, decreased libido, manic reaction, somnambulism, aggressive reaction, neurosis. **Rare:** Suicide attempt.

Genitourinary: **Infrequent:** Amenorrhea, vaginal hemorrhage, penile disorder, prostatic disorder, balanoposthitis, epididymitis, penile pain, dysuria, micturition frequency, albuminuria, polyuria, renal colic. **Rare:** Breast enlargement, mastitis, uterine hemorrhage, ejaculation disorder, Peyronie's disease, pyelonephritis, acute renal failure, uremia.

Resistance Mechanism: **Infrequent:** Herpes zoster, otitis media, sepsis, abscess, herpes simplex, fungal infection, genital moniliasis.

Respiratory: **Infrequent:** Asthma, epistaxis, laryngitis, pleurisy, pulmonary edema.

Skin/Appendages: **Infrequent:** Pruritus, dermatitis, eczema, skin ulceration, alopecia, skin hypertrophy, skin discoloration, urticaria, fungal dermatitis, furunculosis, hyperkeratosis, photosensitivity reaction, psoriasis, maculopapular rash, psoriasisform rash, seborrhea.

Special Senses: **Infrequent:** Tinnitus, earache, decreased hearing, abnormal lacrimation, conjunctivitis, blepharitis, glaucoma, abnormal accommodation, blepharospasm, eye pain, photophobia. **Rare:** Scotoma.

Vascular/Extracardiac: **Infrequent:** Varicose veins, phlebitis, peripheral gangrene. **Rare:** Limb embolism, pulmonary embolism, gangrene, subarachnoid hemorrhage, deep thrombophlebitis, leg thrombophlebitis, thrombosis.

Falling Asleep During Activities of Daily Living: Patients treated with ropinirole hydrochloride 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).

Other Adverse Events Observed During Phase 2/3 Clinical Trials for RLS: Ropinirole hydrochloride has been administered to 911 individuals in clinical trials. During these trials, all adverse events were recorded by the clinical investigators using terminology of their own choosing. To provide a meaningful estimate of the proportion of individuals having adverse events, similar types of events were grouped into a smaller number of standardized categories using MedDRA dictionary terminology. These categories are used in the listing below. The frequencies presented represent the proportion of the 911 individuals exposed to ropinirole hydrochloride who experienced events of the type cited on at least one occasion while receiving ropinirole hydrochloride. All reported events that occurred at least twice (or once for serious or potentially serious events), except those already listed, trivial events, and terms too vague to be meaningful, are included without regard to determination of a causal relationship to ropinirole hydrochloride, except that events very unlikely to be drug-related have been deleted.

Events are further classified within body system categories and enumerated in order of decreasing frequency using the following definitions: frequent adverse events are defined as those occurring in at least 1/100 patients and infrequent adverse events are those occurring in 1/100 to 1/1,000 patients.

Blood and Lymphatic System Disorders: **Infrequent:** Anemia, lymphadenopathy.

Cardiac Disorders: **Frequent:** Palpitations. **Infrequent:** Acute coronary syndrome, angina pectoris, angina unstable, bradycardia, cardiac failure, cardiovascular disorder, coronary artery disease, myocardial infarction, sick sinus syndrome, tachycardia.

Conjunctival, Familial, and Genetic Disorders: **Infrequent:** Pigmented nevus.

Ear and Labyrinth Disorders: **Infrequent:** Ear pain, middle ear effusion, tinnitus.

Endocrine Disorders: **Infrequent:** Goiter, hypothyroidism.

Eye Disorders: **Infrequent:** Blepharitis, conjunctival hemorrhage, conjunctivitis, eye irritation, eye pain, keratoconjunctivitis sicca, vision blurred, visual acuity reduced, visual disturbance.

Gastrointestinal Disorders: **Frequent:** Abdominal pain, constipation, gastroesophageal reflux disease, stomach discomfort, toothache. **Infrequent:** Abdominal adhesions, abdominal discomfort, abdominal distention, abdominal pain lower, duodenal ulcer, dysphagia, eructation, flatulence, gastric disorder, gastric hemorrhage, gastric polyps, gastric ulcer, gastritis, gastrointestinal pain, hematemesis, hemorrhoids, hiatal hernia, intestinal obstruction, irritable bowel syndrome, loose stools, mouth ulceration, pancreatitis acute, peptic ulcer, rectal hemorrhage, reflux esophagitis.

General Disorders and Administration Site Conditions: **Frequent:** Asthenia