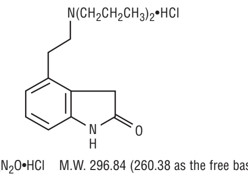
DESCRIPTION

Ropinirole hydrochloride is an orally administered non-ergoline dopamine agonist. It is the hydrochloride salt of 4-[2-(dipropylamino)ethyl]-1,3-dihydro-2*H*-indol-2-one monohydrochloride. The structural formula is:



$C_{16}H_{24}N_2O•HCl$ M.W. 296.84 (260.38 as the free base)

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

Each convex, round film-coated tablet contains ropinirole hydrochloride equivalent to ropinirole, 0.25 mg, 0.5 mg, 1 mg, 2 mg, 3 mg, 4 mg, or 5 mg and the following inactive ingredients: croscarmellose sodium, hydroxypropyl cellulose, lactose monohydrate, magnesium stearate, microcrystalline cellulose, polyethylene glycol, polyvinyl alcohol-part hydrolyzed, talc, and titanium dioxide. In addition, the 0.5 mg, 1 mg, 2 mg, 3 mg, and 4 mg tablets contain lecithin; the 0.5 mg, 1 mg, and 4 mg tablets contain iron oxide yellow; the 1 mg, 3 mg, and 5 mg tablets contain FD&C Blue #2/Indigo Carmine Aluminum Lake; the 0.5 mg, 2 mg, and 4 mg tablets contain iron oxide red; and the 2 mg and 4 mg tablets contain iron oxide black; the 3 mg tablet contains FD&C Blue #1/Brilliant Blue Aluminum Lake and D&C Red #30/Helendon Pink Aluminum Lake.

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 D_2 and D_3 dopamine receptor subtypes, binding with higher affinity to D_3 than to D_2 or D_4 receptor subtypes.

Ropinirole has moderate *in vitro* affinity for opioid receptors. Ropinirole and its metabolites have negligible *in vitro* affinity for dopamine D_1, 5-HT_1, 5-HT_2, benzodiazepine, GABA, muscarinic, alpha$_1$-, alpha$_2$-, and beta-adrenoreceptors.

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. 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 postural hypotension induced by ropinirole hydrochloride is presumed to be due to a D_2-mediated blunting of the noradrenergic response to standing and subsequent decrease in peripheral vascular resistance. Nausea is a common concomitant 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 due to drug interactions has not been systematically evaluated.

Pharmacokinetics

Absorption, Distribution, Metabolism, and Elimination

Ropinirole is rapidly absorbed after oral administration, reaching peak concentration in approximately 1 to 2 hours. In clinical studies, over 88% of a radio labeled 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 47 L/hr (cv = 45%) and its elimination half-life is approximately 6 hours. Ropinirole is extensively metabolized by 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 P_{450} 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 hydroxyl metabolites. The hydroxy metabolite of ropinirole is rapidly glucuronidated. 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 hydroxyl metabolite (10%).

P_{450} Interaction

In vitro metabolism studies showed that CYP1A2 was the major enzyme responsible for the metabolism of ropinirole. Inhibitors or inducers of the enzyme have been shown to alter its 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 between 30 to 50 mL/min.) compared to an 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.

Clinical Trials

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 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, 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 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 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 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	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 who were responders (defined as 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

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; symptoms begin or worsen during periods of rest or inactivity such as lying or sitting; symptoms are partially or totally relieved by movement such as walking or stretching at least as long as the activity continues; and symptoms are worse or occur only in the evening or night. Difficulty falling asleep may frequently be associated with 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, 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 (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 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 ordinarily be discontinued. (See DOSAGE 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 RLS 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 RLS patients in clinical practice. Therefore, patients with severe cardiovascular disease should be treated with caution.

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.

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 force-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 a similar adverse event. 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 that included 110 healthy 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 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.

Hallucinations

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 premarketing 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. 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.

Fibrotic complications

Cases of retroperitoneal fibrosis, pulmonary infiltrates, pleural effusion, pleural thickening, pericarditis, and cardiac valvulopathy have been reported in some patients treated with ergot-derived dopaminergic agents. While these complications may resolve when the drug is discontinued, complete resolution does not always occur.

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

A small number of reports have been received of possible fibrotic complications, including 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

Although ropinirole hydrochloride has not been associated with an increased risk of melanoma specifically, its potential role as a risk factor has not been systemically studied. Patients using ropinirole hydrochloride for any indication should undergo periodic dermatologic screening.

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 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.

Retinal Pathology

Albino rats

Retinal degeneration was observed in albino rats in the 2 year carcinogenicity study at all doses tested (equivalent to 0.6 to 20 times the maximum recommended human dose on a mg/m^2 basis), but was statistically significant at the highest dose (50 mg/kg/day). Additional studies to further evaluate the specific pathology (e.g., loss of photoreceptor cells) have not been performed. Similar changes were not observed in a 2 year carcinogenicity study in albino mice or in rats or monkeys treated for 1 year. The potential significance of this effect in humans has not been established, but cannot be disregarded because disruption of a mechanism that is universally present in vertebrates (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 clinical study. A total of 156 patients (78 on ropinirole, mean dose 11.9 mg/day and 78 on L-dopa, mean dose 555.2 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 reread 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 tablets can be taken with or without food. Patients may be advised that taking ropinirole hydrochloride tablets 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 neither drive a car nor engage in other 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, antidepressants, etc.) in combination with ropinirole hydrochloride.

Patients should be informed they may experience hallucinations (unreal visions, sounds, or sensations) while taking ropinirole hydrochloride. These were uncommon in patients taking ropinirole hydrochloride for Restless Legs Syndrome. The risk is greater in patients who are taking ropinirole hydrochloride with L-dopa, or taking higher doses of ropinirole hydrochloride.

Because of the possibility that ropinirole may be excreted in breast milk, patients should be advised to notify their physicians if they intend to breastfeed or are breastfeeding an infant.

Because ropinirole has been shown to have adverse effects on embryo-fetal development, including teratogenic effects, in animals, and because experience in humans is limited, patients should be advised to notify their physician if they become pregnant or intend to become pregnant during therapy (see **PRECAUTIONS**, **Pregnancy**).

Drug Interactions

P_{450} Interaction

In vitro metabolism studies showed that CYP1A2 was the major enzyme responsible for the metabolism of ropinirole. There is thus the potential for substrates or inhibitors of this enzyme when coadministered with ropinirole to alter its clearance. 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.

L-dopa

Coadministration of carbidopa + L-dopa (10/100 mg twice daily) with ropinirole (2 mg 3 times daily) had no effect on the steady-state pharmacokinetics of ropinirole (n = 28 patients). Oral administration of ropinirole hydrochloride 2 mg 3 times daily increased mean steady state C_{max} of L-dopa by 20%, but its AUC was unaffected (n = 23 patients).

Digoxin

Coadministration of ropinirole hydrochloride (2 mg 3 times daily) with digoxin (0.125 to 0.25 mg once daily) did not alter the steady-state pharmacokinetics of digoxin in 10 patients.

Theophylline

Administration of theophylline (300 mg twice daily, a substrate of CYP1A2) did not alter the steady-state pharmacokinetics of ropinirole (2 mg 3 times daily). Ropinirole (2 mg 3 times daily) did not alter the pharmacokinetics of theophylline (5 mg/kg IV).

Ciprofloxacin

Coadministration of ciprofloxacin (500 mg twice daily), an inhibitor of CYP1A2, with ropinirole (2 mg 3 times daily) increased ropinirole AUC by 84% on average and C_{max} by 60% (n = 12 patients).

Estrogens

Population pharmacokinetic analysis revealed that estrogens (mainly ethinylestradiol: intake 0.6 to 3 mg over 4 month to 23 year period) reduced the oral clearance of ropinirole by 36% in 16 patients. Dosage adjustment may not be needed for ropinirole hydrochloride in patients on estrogen therapy because patients must be carefully titrated with ropinirole to tolerance or adequate effect. However, if estrogen therapy is stopped or started during treatment with ropinirole hydrochloride, then adjustment of the dose of ropinirole hydrochloride may be required.

Dopamine Antagonists

Since ropinirole is a dopamine agonist, it is possible that dopamine antagonists such as neuroleptics (phenothiazines, butyrophenones, thioxanthenes) or metoclopramide may diminish the effectiveness of ropinirole hydrochloride. Patients with major psychotic disorders treated with neuroleptics should only be treated with dopamine agonists if the potential benefits outweigh the risks.

Population analysis showed that commonly administered drugs, e.g., selegiline, amantadine, tricyclic antidepressants, benzodiazepines, ibuprofen, thiazides, antihistamines, and anticholinergics, did not affect the oral clearance of ropinirole.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Two-year carcinogenicity studies were conducted in Charles River CD-1 mice at doses of 5, 15, and 50 mg/kg/day and in Sprague-Dawley rats at doses of 1.5, 15, and 50 mg/kg/day (top doses equivalent to 10 and 20 times, respectively, the maximum recommended human dose of 24 mg/day on a mg/m^2 basis). In the male rat, there was a significant increase in testicular Leydig cell adenomas at all doses tested, i.e., ≥ 1.5 mg/kg (0.6 times the maximum recommended human dose on a mg/m^2 basis). This finding is of questionable significance because the endocrine mechanisms believed to be involved in the production of Leydig cell hyperplasia and adenomas in rats are not relevant to humans. In the female mouse, there was an increase in benign uterine endometrial polyps at a dose of 50 mg/kg/day (10 times the maximum recommended human dose on a mg/m^2 basis).

Ropinirole was not mutagenic or clastogenic in the *in vitro* Ames test, the *in vitro* chromosome aberration test in human lymphocytes, the *in vitro* mouse lymphoma (L1578Y cells) assay, and the *in vivo* mouse micronucleus test.

When administered to female rats prior to and during mating and throughout pregnancy, ropinirole caused disruption of implantation at doses of 20 mg/kg/day (8 times the maximum recommended human dose on a mg/m^2 basis) or greater. This effect is thought to be due to the prolactin-lowering effect of ropinirole. In humans, chorionic gonadotropin, not prolactin, is essential for implantation. In rat studies using low doses (5 mg/kg) during the prolactin-dependent phase of early pregnancy (gestation days 0 to 8), ropinirole did not affect female fertility at dosages up to 100 mg/kg/day (40 times the maximum recommended human dose on a mg/m^2 basis). No effect on male fertility was observed in rats at dosages up to 125 mg/kg/day (50 times the maximum recommended human dose on a mg/m^2 basis).

Pregnancy

Teratogenic Effects

Pregnancy category C

In animal reproduction studies, ropinirole has been shown to have adverse effects on embryo-fetal development, including teratogenic effects. Ropinirole given to pregnant rats during organogenesis (20 mg/kg on gestation days 6 and 7 followed by 20, 60, 90, 120, or 150 mg/kg on gestation days 8 through 15) resulted in decreased fetal body weight at 60 mg/kg/day, increased fetal death at 90 mg/kg/day, and digital malformations at 150 mg/kg/day (24, 36, and 60 times the maximum recommended clinical dose on a mg/m^2 basis, respectively). The combined administration of ropinirole (10 mg/kg/day, 8 times the maximum recommended human dose on a mg/m^2 basis) and L-dopa (250 mg/kg/day) to pregnant rabbits during organogenesis produced a greater incidence and severity of fetal malformations (primarily digit defects) than were seen in the offspring of rabbits treated with L-dopa alone. No indication of an effect on development of the conceptus was observed in rabbits when a maternally toxic dose of ropinirole was administered alone (20 mg/kg/day, 16 times the maximum recommended human dose on a mg/m^2 basis). In a perinatal-postnatal study in rats, 10 mg/kg/day (4 times the maximum recommended human dose on a mg/m^2 basis) of ropinirole impaired growth and development of nursing offspring and altered neurological development of female offspring.

There are no adequate and well-controlled studies using ropinirole hydrochloride in pregnant women. Ropinirole hydrochloride should be used during pregnancy only if the potential benefit outweighs the potential risk to the fetus.

Nursing Mothers

Ropinirole hydrochloride inhibits prolactin secretion in humans and could potentially inhibit lactation.

Studies in rats have shown that ropinirole hydrochloride and/or its metabolite(s) is excreted in breast milk. It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from ropinirole hydrochloride, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use

Safety and effectiveness in the pediatric population have not been established.

ADVERSE REACTIONS

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

Adverse Experience	Ropinirole n = 496 (%)	Placebo n = 500 (%)
Ear and labyrinth disorders		
Vertigo	2	1
Gastrointestinal disorders		
Nausea	40	8
Vomiting	11	2
Diarrhea	5	3
Dyspepsia	4	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	3	2
Nasal congestion	2	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 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 Disorder: 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.

Congenital, Familial, and Genetic Disorders: Infrequent: Pigmented nevus.

Ear and Labyrinth Disorder: 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 distension, abdominal pain lower, duodenal ulcer, dysphagia, eructation, flatulence, gastric disorder, gastric hemorrhage, gastric polyps, gastric ulcer, gastritis, gastrointestinal pain, hematemesis, hemorrhoids, hiatus 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, chest pain, influenza-like illness, rigors. ***Infrequent:*** Chest discomfort, feeling cold, feeling hot, hunger, lethargy, malaise, edema, pain, pyrexia.

Hepatobiliary Disorders: Infrequent: Cholecystitis, cholelithiasis, ischemic hepatitis.

Immune System Disorders: Infrequent: Hypersensitivity.

Infections and Infestations: Frequent: Bronchitis, gastroenteritis, gastroenteritis viral, lower respiratory tract infection, rhinitis, tooth abscess, urinary tract infection. ***Infrequent:*** Appendicitis, bacterial infection, bladder infection, bronchitis acute, candidiasis, cellulitis, cystitis, diarrhea infectious, diverticulitis, ear infection, folliculitis, fungal infection, gastrointestinal infection, herpes simplex, infected cyst, laryngitis, localized infection, mastitis, otitis externa, otitis media, pharyngitis,

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What is the most important information I should know about ropinirole hydrochloride?

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- There are known side effects of ropinirole hydrochloride. If you fall asleep or feel very sleepy while doing normal activities such as driving, faint, feel dizzy, nauseated, or sweaty when you stand up from sitting or lying down, you should talk with your doctor (see **What are the possible side effects of ropinirole hydrochloride?**).
- Before starting ropinirole hydrochloride tablet, be sure to tell your doctor if you are taking any medicines that make you drowsy.

Who should not take ropinirole hydrochloride?

You should not take ropinirole hydrochloride tablets if you are allergic to the active ingredient ropinirole or to any of the inactive ingredients. Your doctor and pharmacist have a list of the inactive ingredients.

What should I tell my doctor?

Be sure to tell your doctor if:

- you are pregnant or plan to become pregnant.
- you are breast-feeding.
- you have daytime sleepiness from a sleep disorder other than RLS or have unexpected sleepiness or periods of sleep while taking ropinirole hydrochloride.
- you are taking any other prescription or over-the-counter medicines. Some of these medicines may increase your chances of getting side effects while taking ropinirole hydrochloride.
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- Most people who take ropinirole hydrochloride tolerate it well. The most commonly reported side effects in people taking ropinirole hydrochloride for RLS are nausea, vomiting, dizziness, and drowsiness or sleepiness. You should be careful until you know if ropinirole hydrochloride affects 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 hydrochloride. Your chances of falling asleep while doing normal activities while taking ropinirole hydrochloride are greater if you are taking other medicines that cause drowsiness.
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Other information about ropinirole hydrochloride

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pneumonia, postoperative infection, respiratory tract infection, tonsillitis, tooth infection, vaginal candidiasis, vaginal infection, vaginal mycosis, viral infection, viral upper respiratory tract infection, wound infection.

Injury, Poisoning, and Procedural Complications: Infrequent: Concussion, lower limb fracture, post procedural hemorrhage, road traffic accident.

Investigations: Infrequent: Blood cholesterol increased, blood iron decreased, blood pressure increased, blood urine present, hemoglobin decreased, heart rate increased, protein urine present, weight decreased, weight increased.

Metabolism and Nutrition Disorders: Infrequent: Anorexia, decreased appetite, diabetes mellitus non-insulin-dependent, fluid retention, gout, hypercholesterolemia.

Musculoskeletal and Connective Tissue Disorders: Frequent: Muscle spasms, musculoskeletal stiffness, myalgia, neck pain, osteoarthritis, tendonitis. ***Infrequent:*** Arthritis, aseptic necrosis bone, bone pain, bone spur, bursitis, groin pain, intervertebral disc degeneration, intervertebral disc protrusion, joint stiffness, joint swelling, localized osteoarthritis, monoarthritis, muscle contracture, muscle tightness, muscle twitching, osteoporosis, rotator cuff syndrome, sacroiliitis, synovitis.

Neoplasms Benign, Malignant, and Unspecified: Infrequent: Anaplastic thyroid cancer, angiomyolipoma, basal cell carcinoma, breast cancer, gastric cancer, gastrointestinal stromal tumor, malignant melanoma, prostate cancer, skin papilloma, squamous cell carcinoma, uterine leiomyoma.

Nervous System Disorders: Frequent: Hypoesthesia, migraine. ***Infrequent:*** Amnesia, aphasia, ataxia, balance disorder, benign intracranial hypertension, burning sensation, carpal tunnel syndrome, disturbance in attention, dizziness postural, dysgeusia, dyskinesia, head discomfort, hyperesthesia, hypersomnia, lethargy, loss of consciousness, memory impairment, migraine with aura, migraine without aura, neuralgia, sciatica, sinus headache, sleep apnea syndrome, syncope vasovagal, tension headache, transient ischemic attack, tremor.

Psychiatric Disorders: Frequent: Anxiety, depression, irritability, sleep disorder. ***Infrequent:*** Abnormal dreams, agitation, bruxism, confusional state, depressed mood, disorientation, early morning awakening, libido decreased, loss of libido, mood swings, nervousness, nightmare, panic attack, stress symptoms, tension.

Renal and Urinary Disorders: Infrequent: Dysuria, hematuria, hypertonic bladder, micturition disorder, nephrolithiasis, nocturia, pollakiuria, proteinuria, urinary retention.

Reproductive System and Breast Disorders: Frequent: Erectile dysfunction. ***Infrequent:*** Breast cyst, dysmenorrhea, menorrhagia, pelvic peritoneal adhesions, postmenopausal hemorrhage, premenstrual syndrome, prostatitis.

Respiratory, Thoracic and Mediastinal Disorders: Frequent: Asthma, pharyngolaryngeal pain. ***Infrequent:*** Dry throat, dyspnea, epistaxis, hemoptysis, hoarseness, interstitial lung disease, nasal mucosal disorder, nasal polyps, respiratory tract congestion, rhinorrhea, sinus congestion, sneezing, wheezing, yawning.

Skin and Subcutaneous Tissue Disorders: Frequent: Night sweats, rash. ***Infrequent:*** Acne, actinic keratosis, alopecia, cold sweat, dermatitis, dermatitis allergic, dermatitis contact, eczema, exanthem, face edema, photosensitivity reaction, pruritus, psoriasis, rash pruritic, skin lesion, urticaria.

Vascular Disorders: Frequent: Hot flush, hypertension, hypotension. ***Infrequent:*** Atherosclerosis, circulatory collapse, flushing, hematoma, thrombosis, varicose vein.

DRUG ABUSE AND DEPENDENCE

Controlled Substance Class

Ropinirole hydrochloride is not a controlled substance.

Physical and Psychological Dependence

Animal studies and human clinical trials with ropinirole hydrochloride did not reveal any potential for drug-seeking behavior or physical dependence.

OVERDOSAGE

Of patients who received a dose greater than 24 mg/day, reported symptoms included adverse events commonly reported during dopaminergic therapy (nausea, dizziness), as well as visual hallucinations, hyperhidrosis, claustrophobia, chorea, palpitations, asthenia, and nightmares. Additional symptoms reported for doses of 24 mg or less or for overdoses of unknown amount included vomiting, increased coughing, fatigue, syncope, vasovagal syncope, dyskinesia, agitation, chest pain, orthostatic hypotension, somnolence, and confusional state.

Overdose Management

It is anticipated that the symptoms of overdose with ropinirole hydrochloride will be related to its dopaminergic activity. General supportive measures are recommended. Vital signs should be maintained, if necessary. Removal of any unabsorbed material (e.g., by gastric lavage) should be considered.

DOSAGE AND ADMINISTRATION

General Dosing Considerations for RLS

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

If a significant interruption in therapy with ropinirole hydrochloride has occurred, retitration of therapy may be warranted.

Geriatric Use

Pharmacokinetic studies demonstrated a reduced clearance of ropinirole in the elderly (see **CLINICAL PHARMACOLOGY**). Dose adjustment is not necessary since the dose is individually titrated to clinical response.

Renal Impairment

The pharmacokinetics of ropinirole were not altered in patients with moderate renal impairment (see **CLINICAL PHARMACOLOGY**). Therefore, no dosage adjustment is necessary in patients with moderate renal impairment. 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.

Dosing for Restless Legs Syndrome

In all clinical trials, the dose for ropinirole hydrochloride was initiated at 0.25 mg once daily, 1 to 3 hours before bedtime. Patients were titrated based on clinical response and tolerability.

The recommended adult starting dosage for RLS is 0.25 mg once daily, 1 to 3 hours before bedtime. After 2 days, the dosage can be increased to 0.5 mg once daily and to 1 mg once daily at the end of the first week of dosing, then as shown in **Table 3** as needed to achieve efficacy. For RLS, the safety and effectiveness of doses greater than 4 mg once daily have not been established.

Table 3. Dose Titration Schedule for RLS

Day/Week	Dosage to be taken once daily, 1 to 3 hours before bedtime
Days 1 and 2	0.25 mg
Days 3 to 7	0.5 mg
Week 2	1 mg
Week 3	1.5 mg
Week 4	2 mg
Week 5	2.5 mg
Week 6	3 mg
Week 7	4 mg

In clinical trials of patients being treated for RLS with doses up to 4 mg once daily, ropinirole hydrochloride was discontinued without a taper.

HOW SUPPLIED

Ropinirole hydrochloride tablets are supplied as follows:

0.25 mg are white, film-coated, convex, round tablets, debossed with “93” on one side and “5282” on the other side in bottles of 100 and 1000.

0.5 mg are yellow, film-coated, convex, round tablets, debossed with “93” on one side and “5283” on the other side in bottles of 100 and 1000.

1 mg are green, film-coated, convex, round tablets, debossed with “93” on one side and “5284” on the other side in bottles of 100 and 1000.

2 mg are pink, film-coated, convex, round tablets, debossed with “93” on one side and “5285” on the other side in bottles of 100 and 1000.

3 mg are purple, film-coated, convex, round tablets, debossed with “93” on one side and “5286” on the other side in bottles of 100.

4 mg are beige, film-coated, convex, round tablets, debossed with “93” on one side and “5287” on the other side in bottles of 100.

5 mg are blue, film-coated, convex, round tablets, debossed with “93” on one side and “5288” on the other side in bottles of 100.

STORAGE

Protect from light and moisture. Close container tightly after each use.

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

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

Manufactured By:
TEVA PHARMACEUTICALS USA
Sellersville, PA 18960

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PATIENT INFORMATION
ROPINIROLE HYDROCHLORIDE TABLETS

℞ only

Read this information completely before you start taking ropinirole hydrochloride. Read the information each time you get more medicine. There may be new information. This leaflet provides a summary about ropinirole hydrochloride. It does not include everything there is to know about your medicine. This information should not take the place of discussions with your doctor about your medical condition or ropinirole hydrochloride.

What is ropinirole hydrochloride?

Ropinirole hydrochloride tablet is a prescription medicine to treat primary moderate-to-severe Restless Legs Syndrome.

What is the most important information I should know about ropinirole hydrochloride?

- A lower dose of ropinirole hydrochloride is generally needed for patients with RLS, and is taken once daily before bedtime (see **How should I take ropinirole hydrochloride tablets for RLS?** for the recommended dosing).
- There are known side effects of ropinirole hydrochloride. If you fall asleep or feel very sleepy while doing normal activities such as driving, faint, feel dizzy, nauseated, or sweaty when you stand up from sitting or lying down, you should talk with your doctor (see **What are the possible side effects of ropinirole hydrochloride?**).
- Before starting ropinirole hydrochloride tablet, be sure to tell your doctor if you are taking any medicines that make you drowsy.

Who should not take ropinirole hydrochloride?

You should not take ropinirole hydrochloride tablets if you are allergic to the active ingredient ropinirole or to any of the inactive ingredients. Your doctor and pharmacist have a list of the inactive ingredients.

What should I tell my doctor?

Be sure to tell your doctor if:

- you are pregnant or plan to become pregnant.
- you are breast-feeding.
- you have daytime sleepiness from a sleep disorder other than RLS or have unexpected sleepiness or periods of sleep while taking ropinirole hydrochloride.
- you are taking any other prescription or over-the-counter medicines. Some of these medicines may increase your chances of getting side effects while taking ropinirole hydrochloride.
- you start or stop taking other medicines while you are taking ropinirole hydrochloride. This may increase your chances of getting side effects.
- you start or stop smoking while you are taking ropinirole hydrochloride. Smoking may decrease the treatment effect of ropinirole hydrochloride.
- you feel dizzy, nauseated, sweaty, or faint when you stand up from sitting or lying down.
- you drink alcoholic beverages. This may increase your chances of becoming drowsy or sleepy while taking ropinirole hydrochloride.

How should I take ropinirole hydrochloride tablets for RLS?

- Be sure to take ropinirole hydrochloride tablets exactly as directed by your doctor or healthcare provider.
- The usual way to take ropinirole hydrochloride tablets is once in the evening, 1 to 3 hours before bedtime.
- Your doctor will start you on a low dose of ropinirole hydrochloride tablets. Your doctor may change the dose until you are taking the amount of medicine that is right for you to control your symptoms.
- **If you miss your dose, do not double your next dose.** Take only your usual dose 1 to 3 hours before your next bedtime.
- Contact your doctor, if you stop taking ropinirole hydrochloride tablets for any reason. Do not restart without consulting your doctor.
- You can take ropinirole hydrochloride tablets with or without food. Taking ropinirole hydrochloride with food may decrease the chances of feeling nauseated.

What are the possible side effects of ropinirole hydrochloride?

- Most people who take ropinirole hydrochloride tolerate it well. The most commonly reported side effects in people taking ropinirole hydrochloride for RLS are nausea, vomiting, dizziness, and drowsiness or sleepiness. You should be careful until you know if ropinirole hydrochloride affects 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 hydrochloride. Your chances of falling asleep while doing normal activities while taking ropinirole hydrochloride are greater if you are taking other medicines that cause drowsiness.
- When you start taking ropinirole hydrochloride 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.
- Hallucinations (unreal sounds, visions, or sensations) have been reported in patients taking ropinirole hydrochloride. These were uncommon in patients taking ropinirole hydrochloride for RLS. The risk is greater in patients taking ropinirole hydrochloride with L-dopa, or taking higher doses of ropinirole hydrochloride 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 hydrochloride

Patients being treated with ropinirole hydrochloride should have periodic skin examinations for melanoma.

- Take ropinirole hydrochloride exactly as your doctor prescribes it.
- Do not share ropinirole hydrochloride with other people, even if they have the same symptoms you have.
- Keep ropinirole hydrochloride out of the reach of children.
- Store ropinirole hydrochloride at room temperature out of direct sunlight.
- Keep ropinirole hydrochloride in a tightly closed container.

This leaflet summarizes important information about ropinirole hydrochloride. Medicines are sometimes prescribed for purposes other than those listed in this leaflet. Do not take ropinirole hydrochloride 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 hydrochloride that is written for healthcare professionals.

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