ROPINIROLE- ropinirole tablet
Carilion Materials Management

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use rOPINIRole Tablets USP safely and effectively. See full prescribing information for rOPINIRole Tablets USP.
rOPINIRole Tablets USP, for oral use
Initial U.S. Approval: 1997

RECENT MAJOR CHANGES

Dosage and Administration (2.2, 2.3) 8/2014
Warnings and Precautions (5.4, 5.6, 5.9) 8/2014

INDICATIONS AND USAGE

Ropinirole Tablets USP are a non-ergoline dopamine agonist indicated for the treatment of Parkinson's disease (PD) and moderate-to-severe primary Restless Legs Syndrome (RLS) (1.1, 1.2) (1)

DOSAGE AND ADMINISTRATION

- Ropinirole Tablets USP can be taken with or without food (2.1)
- Retitration of ropinirole may be warranted if therapy is interrupted (2.1)

Parkinson's Disease: (2)

- The recommended starting dose is 0.25 mg taken three times daily; titrate to maximum daily dose of 24 mg (2.2)
- Renal Impairment: The maximum recommended dose is 18 mg/day in patients with end-stage renal disease on hemodialysis (2.2)

Restless Legs Syndrome: (2)

- The recommended starting dose is 0.25 mg once daily, 1 to 3 hours before bedtime, titrate to maximum recommended dose of 4 mg daily (2.3)
- Renal Impairment: The maximum recommended dose is 3 mg/day in patients with end-stage renal disease on hemodialysis (2.3)

DOSAGE FORMS AND STRENGTHS

Tablets: 0.25 mg, 0.5 mg, 1 mg, 2 mg, 3 mg, 4 mg, and 5 mg (3) (3)

CONTRAINDICATIONS

History of hypersensitivity/allergic reaction (including urticaria, angioedema, rash, pruritus) to ropinirole or to any of the excipients (4) (4)

WARNINGS AND PRECAUTIONS

- Sudden onset of sleep and somnolence may occur (5.1)
- Syncope may occur (5.2)
- Hypotension, including orthostatic hypotension may occur (5.3)
- May cause hallucinations and psychotic-like behaviors (5.4)
- May cause or exacerbate dyskinesia (5.5)
- May cause problems with impulse control or compulsive behaviors (5.6)

ADVERSE REACTIONS

Most common adverse reactions (incidence with ropinirole at least 5% greater than placebo) in the respective indications were:

- Early PD: Nausea, somnolence, dizziness, syncope, asthenic condition, viral infection, leg edema, vomiting, and dyspepsia (6.1)
- Advanced PD: Dyskinesia, somnolence, nausea, dizziness, confusion, hallucinations, sweating, and headache (6.1)
- RLS: Nausea, vomiting, somnolence, dizziness, and asthenic condition (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Roxane Laboratories, Inc. at 1-800-962-8364 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- Inhibitors or inducers of CYP1A2: May alter the clearance of ropinirole; dose adjustment may be required (7.1, 12.3)
- Hormone replacement therapy (HRT): Starting or stopping HRT may require dose adjustment of ropinirole (7.2, 12.3)
- Dopamine antagonists (e.g., neuroleptics, metoclopramide): May reduce efficacy of ropinirole (7.3)

USE IN SPECIFIC POPULATIONS

Pregnancy: Based on animal data, may cause fetal harm (8.1) (8)

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 12/2017

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1Parkinson's Disease

Ropinirole Tablets USP are indicated for the treatment of Parkinson's disease.

1.2Restless Legs Syndrome

Ropinirole Tablets USP are indicated for the treatment of moderate-to-severe primary Restless Legs Syndrome (RLS).

2 DOSAGE AND ADMINISTRATION

2.1General Dosing Recommendations

Ropinirole can be taken with or without food *[see Clinical Pharmacology (12.3)]*.

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

2.2Dosing for Parkinson's Disease

The recommended starting dose for Parkinson's disease is 0.25 mg three times daily. Based on individual patient therapeutic response and tolerability, if necessary, the dose should then be titrated with weekly increments as described in Table 1. After week 4, if necessary, the daily dose may be increased by 1.5 mg/day on a weekly basis up to a dose of 9 mg/day, and then by up to 3 mg/day weekly to a maximum recommended total daily dose of 24 mg/day (8 mg three time daily). Doses greater than 24 mg/day have not been tested in clinical trials.

Table 1: Ascending-Dose Schedule of Ropinirole for Parkinson's Disease

Week	Dosage	Total Daily Dose
1	0.25 mg 3 times daily	0.75 mg
2	0.5 mg 3 times daily	1.5 mg
3	0.75 mg 3 times daily	2.25 mg
4	1 mg 3 times daily	3 mg

Ropinirole should be discontinued gradually over a 7-day period in patients with Parkinson's disease. The frequency of administration should be reduced from three times daily to twice daily for 4 days. For the remaining 3 days, the frequency should be reduced to once daily prior to complete withdrawal of ropinirole.

Renal Impairment

No dose adjustment is necessary in patients with moderate renal impairment (creatinine clearance of 30 to 50 mL/min). The recommended initial dose of ropinirole for patients with end-stage renal disease on hemodialysis is 0.25 mg three times a day. Further dose escalations should be based on tolerability and need for efficacy. The recommended maximum total daily dose is 18 mg/day in patients receiving regular dialysis. Supplemental doses after dialysis are not required. The use of ropinirole in patients with severe renal impairment without regular dialysis has not been studied.

2.3Dosing for Restless Legs Syndrome

The recommended adult starting dose for RLS is 0.25 mg once daily 1 to 3 hours before bedtime. After 2 days, if necessary, the dose 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 2 as needed to achieve efficacy. Titration should be based on individual patient therapeutic response and tolerability, up to a maximum recommended dose of 4 mg daily. For RLS, the safety and effectiveness of doses greater than 4 mg once daily have not been established.

Table 2: Dose Titration Schedule of Ropinirole for Restless Legs Syndrome

Day/Week	Dosage to Be Taken Once Daily, 1 to 3 Hours Before Bedtime
Days 1 and 2	0.25 mg
Days 3-7	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 treated for RLS with doses up to 4 mg once daily, ropinirole was discontinued without a taper.

Renal Impairment

No dose adjustment is necessary in patients with moderate renal impairment (creatinine clearance of 30 to 50 mL/min). The recommended initial dose of ropinirole for patients with end-stage renal disease on hemodialysis is 0.25 mg once daily. Further dose escalations should be based on tolerability and need for efficacy. The recommended maximum total daily dose is 3 mg/day in patients receiving regular dialysis. Supplemental doses after dialysis are not required. The use of ropinirole in patients with severe renal impairment without regular dialysis has not been studied.

3 DOSAGE FORMS AND STRENGTHS

- 0.25 mg, white tablet debossed with "54 511" on one side and plain on the other side
- 0.5 mg, yellow tablet debossed with "54 337" on one side and plain on the other side
- 1 mg, green tablet debossed with "54 751" on one side and plain on the other side

- 2 mg, orange tablet debossed with “54 231” on one side and plain on the other side
- 3 mg, red tablet debossed with “54 575” on one side and plain on the other side
- 4 mg, brown tablet debossed with “54 273” on one side and plain on the other side
- 5 mg, blue tablet debossed with “54 722” on one side and plain on the other side

4 CONTRAINDICATIONS

Ropinirole Tablets USP are contraindicated in patients known to have hypersensitivity/allergic reaction (including urticaria, angioedema, rash, pruritus) to ropinirole or to any of the excipients.

5 WARNINGS AND PRECAUTIONS

5.1 Falling Asleep During Activities of Daily Living and Somnolence

Patients treated with ropinirole have reported falling asleep while engaged in activities of daily living, including driving or operating machinery, which sometimes resulted in accidents. Although many of these patients reported somnolence while on ropinirole, some perceived that they had no warning signs, such as excessive drowsiness, and believed that they were alert immediately prior to the event. Some have reported these events more than 1 year after initiation of treatment.

In controlled clinical trials, somnolence was commonly reported in patients receiving ropinirole and was more frequent in Parkinson's disease (up to 40% ropinirole, 6% placebo) than in Restless Legs Syndrome (12% ropinirole, 6% placebo) *[see Adverse Reactions (6.1)]*.

It has been reported that falling asleep while engaged in activities of daily living usually occurs in a setting of preexisting somnolence, although patients may not give such a history. For this reason, prescribers should 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, patients should be advised of the potential to develop drowsiness and specifically asked about factors that may increase the risk with ropinirole such as concomitant sedating medications, the presence of sleep disorders (other than RLS), and concomitant medications that increase ropinirole plasma levels (e.g., ciprofloxacin) *[see Drug Interactions (7.1)]*. If a patient develops significant daytime sleepiness or episodes of falling asleep during activities that require active participation (e.g., driving a motor vehicle, conversations, eating), ropinirole should ordinarily be discontinued *[see Dosage and Administration (2.2, 2.3)]*. If a decision is made to continue ropinirole, 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.

5.2 Syncope

Syncope, sometimes associated with bradycardia, was observed in association with ropinirole in both patients with Parkinson’s disease and patients with RLS. In controlled clinical trials in patients with Parkinson’s disease, syncope was observed more frequently in patients receiving ropinirole than in patients receiving placebo (early Parkinson’s disease without L-dopa: ropinirole 12%, placebo 1%; advanced Parkinson’s disease: ropinirole 3%, placebo 2%). Syncope was reported in 1% of patients treated with ropinirole for RLS in 12-week, placebo-controlled clinical trials compared with 0.2% of patients treated with placebo *[see Adverse Reactions (6.1)]*. Most cases occurred more than 4 weeks after initiation of therapy with ropinirole, and were usually associated with a recent increase in dose.

Because the trials of ropinirole excluded patients with significant cardiovascular disease, patients with significant cardiovascular disease should be treated with caution.

Approximately 4% of patients with Parkinson's disease enrolled in Phase 1 trials had syncope following a 1-mg dose of ropinirole. In two trials in patients with RLS that used a forced-titration regimen and orthostatic challenge with intensive blood pressure monitoring, 2% of RLS patients treated with ropinirole compared with 0% of patients receiving placebo reported syncope.

In Phase 1 trials including healthy volunteers, the incidence of syncope was 2%. Of note, 1 subject with syncope developed hypotension, bradycardia, and sinus arrest; the subject recovered spontaneously without intervention.

5.3 Hypotension/Orthostatic Hypotension

Dopamine agonists in clinical trials and clinical experience appear to impair the systemic regulation of blood pressure, with resulting orthostatic hypotension, especially during dose escalation. In addition, patients with Parkinson's disease appear to have an impaired capacity to respond to a postural challenge. For these reasons, patients should be monitored for signs and symptoms of orthostatic hypotension, especially during dose escalation, and patients should be informed of the risk for syncope and hypotension *[see Patient Counseling Information (17)]*.

Although the clinical trials were not designed to systematically monitor blood pressure, there were individual reported cases of orthostatic hypotension in early Parkinson's disease (without L-dopa) in patients treated with ropinirole. Most of these cases occurred more than 4 weeks after initiation of therapy with ropinirole 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 compared with 2 of 500 patients (0.4%) receiving placebo.

In two Phase 2 studies in patients with RLS, 14 of 55 patients (25%) receiving ropinirole experienced an adverse event of hypotension or orthostatic hypotension compared with none of the 27 patients receiving placebo. In these studies, 11 of the 55 patients (20%) receiving ropinirole 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.

In Phase 1 trials of ropinirole with healthy volunteers who received single doses on more than one occasion without titration, 7% had documented symptomatic orthostatic hypotension. These episodes appeared mainly at doses above 0.8 mg and these doses are higher than the starting doses recommended for patients with either Parkinson's disease or with RLS. In most of these individuals, the hypotension was accompanied by bradycardia but did not develop into syncope *[see Warnings and Precautions (5.2)]*.

Although dizziness is not a specific manifestation of hypotension or orthostatic hypotension, patients with hypotension or orthostatic hypotension frequently reported dizziness. In controlled clinical trials, dizziness was a common adverse reaction in patients receiving ropinirole and was more frequent in patients with Parkinson's disease or with RLS receiving ropinirole than in patients receiving placebo (early Parkinson's disease without L-dopa: ropinirole 40%, placebo 22%; advanced Parkinson's disease: ropinirole 26%, placebo 16%; RLS: ropinirole 11%, placebo 5%). Dizziness of sufficient severity to cause trial discontinuation of ropinirole was 4% in patients with early Parkinson's disease without L-dopa, 3% in patients with advanced Parkinson's disease, and 1% in patients with RLS *[See Adverse Reactions (6.1)]*.

5.4 Hallucinations/Psychotic-Like Behavior

In double-blind, placebo-controlled, early-therapy trials in patients with Parkinson's disease who were not treated with L-dopa, 5.2% (8 of 157) of patients treated with ropinirole reported hallucinations, compared with 1.4% of patients on placebo (2 of 147). Among those patients receiving both ropinirole and L-dopa in advanced Parkinson's disease studies, 10.1% (21 of 208) were reported to experience hallucinations, compared with 4.2% (5 of 120) of patients treated with placebo and L-dopa.

The incidence of hallucination was increased in elderly patients (i.e., older than 65 years) treated with

extended-release ropinirole *[see Use in Specific Populations (8.5)]*.

Postmarketing reports indicate that patients may experience new or worsening mental status and behavioral changes, which may be severe, including psychotic-like behavior during treatment with ropinirole or after starting or increasing the dose of ropinirole. Other drugs prescribed to improve the symptoms of Parkinson's disease can have similar effects on thinking and behavior. This abnormal thinking and behavior can consist of one or more of a variety of manifestations including paranoid ideation, delusions, hallucinations, confusion, psychotic-like behavior, disorientation, aggressive behavior, agitation, and delirium.

Patients with a major psychotic disorder should ordinarily not be treated with ropinirole because of the risk of exacerbating the psychosis. In addition, certain medications used to treat psychosis may exacerbate the symptoms of Parkinson's disease and may decrease the effectiveness of ropinirole *[see Drug Interactions (7.3)]*.

5.5 Dyskinesia

Ropinirole may potentiate the dopaminergic side effects of L-dopa and may cause and/or exacerbate pre-existing dyskinesia in patients treated with L-dopa for Parkinson's disease. In double-blind, placebo-controlled trials in advanced Parkinson's disease, dyskinesia was much more common in patients treated with ropinirole than in those treated with placebo. Among those patients receiving both ropinirole and L-dopa in advanced Parkinson's disease trials, 34% were reported to experience dyskinesia, compared with 13% of patients treated with placebo *[see Adverse Reactions (6.1)]*. Decreasing the dose of dopaminergic drug may ameliorate this adverse reaction.

5.6 Impulse Control/Compulsive Behaviors

Case reports suggest that patients can experience intense urges to gamble, increased sexual urges, intense urges to spend money, binge or compulsive eating, and/or other intense urges, and the inability to control these urges while taking one or more of the medications, including ropinirole, that increase central dopaminergic tone and that are generally used for the treatment of Parkinson's disease and RLS. In some cases, although not all, these urges were reported to have stopped when the dose was reduced or the medication was discontinued. Because patients may not recognize these behaviors as abnormal, it is important for prescribers to specifically ask patients or their caregivers about the development of new or increased gambling urges, sexual urges, uncontrolled spending, binge or compulsive eating, or other urges while being treated with ropinirole. Physicians should consider dose reduction or stopping the medication if a patient develops such urges while taking ropinirole.

5.7 Withdrawal-Emergent Hyperpyrexia and Confusion

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 dopaminergic therapy. Therefore, it is recommended that the dose be tapered at the end of treatment with ropinirole for Parkinson's disease as a prophylactic measure *[see Dosage and Administration (2.2)]*.

5.8 Melanoma

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

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

5.9 Augmentation and Early-Morning Rebound in Restless Legs Syndrome

Reports in the literature indicate treatment of RLS with dopaminergic medications can result in recurrence 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. Rebound refers to new onset of symptoms in the early morning hours. Augmentation and/or early-morning rebound have been observed in a postmarketing trial. If augmentation or early-morning rebound occurs, the use of ropinirole should be reviewed and dosage adjustment or discontinuation of treatment should be considered.

5.10 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 reactions are believed to be related to the ergoline structure of these compounds, whether other, non-ergot-derived dopamine agonists such as ropinirole can cause them is unknown.

Cases of possible fibrotic complications, including pleural effusion, pleural fibrosis, interstitial lung disease, and cardiac valvulopathy, have been reported in the development program and postmarketing experience for ropinirole. While the evidence is not sufficient to establish a causal relationship between ropinirole and these fibrotic complications, a contribution of ropinirole cannot be excluded.

5.11 Retinal Pathology

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 [MRHD] for Parkinson’s disease [24 mg/day] on a mg/m^2 basis), but was statistically significant at the highest dose (50 mg/kg/day). Retinal degeneration was not observed in a 3-month study in pigmented rats, in a 2-year carcinogenicity study in albino mice, or in 1-year studies in monkeys or albino rats. The significance of this effect for humans has not been established, but involves disruption of a mechanism that is universally present in vertebrates (e.g., disk shedding).

Ocular electroretinogram (ERG) assessments were conducted during a 2-year, double-blind, multicenter, flexible dose, L-dopa-controlled clinical study of ropinirole in patients with Parkinson's diseas; 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 trial.

5.12 Binding to Melanin

Ropinirole 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.

6 ADVERSE REACTIONS

Adverse Reactions

The following adverse reactions are described in more detail in other sections of the label:

- Hypersensitivity *[see Contraindications (4)]*
- Falling Asleep during Activities of Daily Living and Somnolence *[see Warnings and Precautions (5.1)]*

- Syncope *[see Warnings and Precautions (5.2)]*
- Hypotension/Orthostatic Hypotension *[see Warnings and Precautions (5.3)]*
- Hallucinations/Psychotic-like Behavior *[see Warnings and Precautions (5.4)]*
- Dyskinesia *[see Warnings and Precautions (5.5)]*
- Impulse Control/Compulsive Behaviors *[see Warnings and Precautions (5.6)]*
- Withdrawal-emergent Hyperpyrexia and Confusion *[see Warnings and Precautions (5.7)]*
- Melanoma *[see Warnings and Precautions (5.8)]*
- Augmentation and Early-morning rebound in RLS *[see Warnings and Precautions (5.9)]*
- Fibrotic Complications *[see Warnings and Precautions (5.10)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared with rates in the clinical trials of another drug (or of another development program of a different formulation of the same drug) and may not reflect the rates observed in practice.

Parkinson's Disease

During the premarketing development of ropinirole, patients received ropinirole either without L-dopa (early Parkinson's disease trials) or as concomitant therapy with L-dopa (advanced Parkinson's disease trials). Because these two populations may have differential risks for various adverse reactions, this section will in general present adverse reaction data for these two populations separately.

Early Parkinson's Disease (Without L-dopa)

In the double-blind, placebo-controlled trials in patients with early-stage Parkinson's disease, the most commonly observed adverse reactions in patients treated with ropinirole (incidence at least 5% greater than placebo) were nausea, somnolence, dizziness, syncope, asthenic condition (i.e., asthenia, fatigue, and/or malaise), viral infection, leg edema, vomiting, and dyspepsia.

Approximately 24% of patients treated with ropinirole who participated in the double-blind, placebo-controlled early Parkinson's disease (without L-dopa) trials discontinued treatment due to adverse reactions compared with 13% of patients who received placebo. The most common adverse reactions in patients treated with ropinirole (incidence at least 2% greater than placebo) of sufficient severity to cause discontinuation were nausea and dizziness.

Table 3 lists treatment-emergent adverse reactions that occurred in at least 2% of patients with early Parkinson's disease (without L-dopa) treated with ropinirole participating in the double-blind, placebo-controlled trials and were numerically more common than the incidence for placebo-treated patients. In these trials, either ropinirole or placebo was used as early therapy (i.e., without L-dopa).

Table 3: Treatment-Emergent Adverse Reaction Incidence in Double-Blind, Placebo-Controlled Early Parkinson's Disease (without L-dopa) Trials (Events ≥2% of Patients Treated with Ropinirole and Numerically More Frequent than the Placebo Group)[*]

Body System/Adverse Reaction	Ropinirole (n=157) (%)	Placebo (n=147) (%)
Autonomic Nervous System		
Flushing	3	1
Dry Mouth	5	3
Increased Sweating	6	4
Body as a Whole		
Asthenic Condition[†]	16	5

Chest Pain	4	2
Dependent Edema	6	3
Leg Edema	7	1
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
Hypesthesia	4	2
Vertigo	2	0
Gastrointestinal		
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	2	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		
Bronchitis	3	1
Dyspnea	3	0
Pharyngitis	6	4
Rhinitis	4	3
Sinusitis	4	3
Urinary		
Urinary Tract Infection	5	4
Vascular Extracardiac		

Peripheral Ischemia	3	0
Vision		
Eye Abnormality	3	1
Abnormal Vision	6	3
Xerophthalmia	2	0

* Patients may have reported multiple adverse reactions during the trial or at discontinuation; thus, patients may be included in more than one category.

† Asthenic condition (i.e., asthenia, fatigue, and/or malaise).

Advanced Parkinson's Disease (with L-dopa)

In the double-blind, placebo-controlled trials in patients with advanced-stage Parkinson's disease, the most commonly observed adverse reactions in patients treated with ropinirole (incidence at least 5% greater than placebo) were dyskinesia, somnolence, nausea, dizziness, confusion, hallucinations, increased sweating, and headache.

Approximately 24% of patients who received ropinirole in the double-blind, placebo-controlled advanced Parkinson's disease (with L-dopa) trials discontinued treatment due to adverse reactions compared with 18% of patients who received placebo. The most common adverse reaction in patients treated with ropinirole (incidence at least 2% greater than placebo) of sufficient severity to cause discontinuation was dizziness.

Table 4 lists treatment-emergent adverse reactions that occurred in at least 2% of patients with advanced Parkinson's disease (with L-dopa) treated with ropinirole who participated in the double-blind, placebo-controlled trials and were numerically more common than the incidence for placebo-treated patients. In these trials, either ropinirole or placebo was used as an adjunct to L-dopa.

Table 4: Treatment-Emergent Adverse Reaction Incidence in Double-Blind, Placebo-Controlled Advanced Parkinson's Disease (with L-dopa) Trials (Events ≥2% of Patients Treated with Ropinirole and Numerically More Frequent than the Placebo Group)*

Body System/Adverse Reaction	**Ropinirole (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		
Hypotension	2	1
Syncope	3	2
Central/Peripheral Nervous System		
Dizziness	26	16
Dyskinesia	34	13
Falls	10	7
Headache	17	12
Hypokinesia	5	4
Paresis	3	0
Paresthesia	5	3
Tremor	6	3
Gastrointestinal		

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		
Arthralgia	7	5
Arthritis	3	1
Psychiatric		
Amnesia	5	1
Anxiety	6	3
Confusion	9	2
Abnormal Dreaming	3	2
Hallucination	10	4
Nervousness	5	3
Somnolence	20	8
Red Blood Cell		
Anemia	2	0
Resistance Mechanism		
Upper Respiratory Tract Infection	9	8
Respiratory		
Dyspnea	3	2
Urinary		
Pyuria	2	1
Urinary Incontinence	2	1
Urinary Tract Infection	6	3
Vision		
Diplopia	2	1

* Patients may have reported multiple adverse reactions during the trial or at discontinuation; thus, patients may be included in more than one category.

Restless Legs Syndrome

In the double-blind, placebo-controlled trials in patients with RLS, the most commonly observed adverse reactions in patients treated with ropinirole (incidence at least 5% greater than placebo) were nausea, vomiting, somnolence, dizziness, and asthenic condition (i.e., asthenia, fatigue, and/or malaise).

Approximately 5% of patients treated with ropinirole who participated in the double-blind, placebo-controlled trials in the treatment of RLS discontinued treatment due to adverse reactions compared with 4% of patients who received placebo. The most common adverse reaction in patients treated with ropinirole (incidence at least 2% greater than placebo) of sufficient severity to cause discontinuation was nausea.

Table 5 lists treatment-emergent adverse reactions that occurred in at least 2% of patients with RLS treated with ropinirole participating in the 12-week, double-blind, placebo-controlled trials and were numerically more common than the incidence for placebo-treated patients.

Table 5: Treatment-Emergent Adverse Reaction Incidence in Double-Blind, Placebo-Controlled RLS Trials (Events ≥2% of Patients Treated with Ropinirole and Numerically More Frequent than the Placebo Group)[*]

Body System/Adverse Reaction	Ropinirole (n=496) (%)	Placebo (n=500) (%)
Ear and Labyrinth		
Vertigo	2	1
Gastrointestinal		
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		
Asthenic Condition[*]	9	4
Edema Peripheral	2	1
Infections and Infestations		
Nasopharyngitis	9	8
Influenza	3	2
Musculoskeletal and Connective Tissue		
Arthralgia	4	3
Muscle Cramps	3	2
Pain in Extremity	3	2
Nervous System		
Somnolence	12	6
Dizziness	11	5
Paresthesia	3	1
Respiratory, Thoracic, and Mediastinal		
Cough	3	2
Nasal Congestion	2	1
Skin and Subcutaneous Tissue		
Hyperhidrosis	3	1

[*] Asthenic condition (i.e., asthenia, fatigue, and/or malaise).

7 DRUG INTERACTIONS

7.1 CYP1A2 Inhibitors and Inducers

In vitro metabolism studies showed that CYP1A2 was the major enzyme responsible for the metabolism of ropinirole. There is thus the potential for inducers or inhibitors of this enzyme to alter the clearance of ropinirole. Therefore, if therapy with a drug known to be a potent inducer or inhibitor of CYP1A2 is stopped or started during treatment with ropinirole, adjustment of the dose of ropinirole may be required. Coadministration of ciprofloxacin, an inhibitor of CYP1A2, increases the AUC and C_{max} of ropinirole *[see Clinical Pharmacology (12.3)]*. Cigarette smoking is expected to increase the clearance of ropinirole since CYP1A2 is known to be induced by smoking *[see Clinical Pharmacology (12.3)]*.

7.2 Estrogens

Population pharmacokinetic analysis revealed that higher doses of estrogens (usually associated with hormone replacement therapy [HRT]) reduced the clearance of ropinirole. Starting or stopping HRT may require adjustment of dosage of ropinirole *[see Clinical Pharmacology (12.3)]*.

7.3 DopamineAntagonists

Because ropinirole is a dopamine agonist, it is possible that dopamine antagonists such as neuroleptics (e.g., phenothiazines, butyrophenones, thioxanthenes) or metoclopramide may reduce the efficacy of ropinirole.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C. There are no adequate and well-controlled studies in pregnant women. In animal reproduction studies, ropinirole has been shown to have adverse effects on embryo-fetal development, including teratogenic effects. Ropinirole should be used during pregnancy only if the potential benefit outweighs the potential risk to the fetus.

Oral treatment of pregnant rats with ropinirole during organogenesis resulted in decreased fetal body weight, increased fetal death, and digital malformations at 24, 36, and 60 times, respectively, the maximum recommended human dose (MRHD) for Parkinson's disease (24 mg/day) on a mg/m^2basis. The combined oral administration of ropinirole at 8 times the MRHD and a clinically relevant dose of L-dopa 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 effect on fetal development was observed in rabbits when ropinirole was administered alone at an oral dose 16 times the MRHD on a mg/m^2basis. In a perinatal-postnatal study in rats, impaired growth and development of nursing offspring and altered neurological development of female offspring were observed when dams were treated with 4 times the MRHD on a mg/m^2basis.

8.3 Nursing Mothers

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

Ropinirole has been detected in rat milk. It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when ropinirole is administered to a nursing woman.

8.4 Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

8.5 Geriatric Use

Dose adjustment is not necessary in elderly (65 years and older) patients, as the dose of ropinirole is individually titrated to clinical therapeutic response and tolerability. Pharmacokinetic trials conducted in patients demonstrated that oral clearance of ropinirole is reduced by 15% in patients older than 65 years compared with younger patients *[see Clinical Pharmacology (12.3)]*.

In clinical trials of extended-release ropinirole for Parkinson's disease, 387 patients were 65 years and older and 107 patients were 75 years and older. Among patients receiving extended-release ropinirole, hallucination was more common in elderly patients (10%) compared with non-elderly patients (2%). The incidence of overall adverse reactions increased with increasing age for both patients receiving extended-release ropinirole and placebo.

8.6 Renal Impairment

No dose adjustment is necessary in patients with moderate renal impairment (creatinine clearance of 30

to 50 mL/min). For patients with end-stage renal disease on hemodialysis, a reduced maximum dose is recommended *[see Dosage and Administration (2.2, 2.3), Clinical Pharmacology (12.3)]*.

The use of ropinirole in patients with severe renal impairment (creatinine clearance less than 30 mL/min) without regular dialysis has not been studied.

8.7 Hepatic Impairment

The pharmacokinetics of ropinirole have not been studied in patients with hepatic impairment.

10 OVERDOSAGE

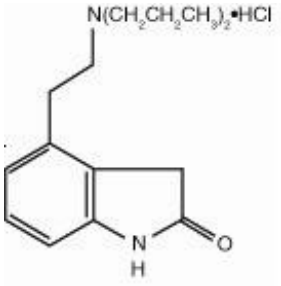
The symptoms of overdose with ropinirole are generally related to its dopaminergic activity. General supportive measures are recommended. Vital signs should be maintained, if necessary.

In the Parkinson's disease program, there have been patients who accidentally or intentionally took more than their prescribed dose of ropinirole. The largest overdose reported with ropinirole in clinical trials was 435 mg taken over a 7-day period (62.1 mg/day). 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.

11 DESCRIPTION

Ropinirole Tablets USP contains ropinirole, a non-ergoline dopamine agonist, as the hydrochloride salt. The chemical name of ropinirole hydrochloride is 4-[2-(dipropylamino)ethyl]-1,3-dihydro-2H-indol-2-one and the molecular formula is $C_{16}H_{24}N_2O$•HCl. The molecular weight is 296.84 (260.38 as the free base).

The structural formula is:



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

Each round, biconvex tablet contains ropinirole hydrochloride equivalent to ropinirole, 0.25 mg, 0.5 mg, 1 mg, 2 mg, 3 mg, 4 mg, or 5 mg. Inactive ingredients consist of: colloidal silicon dioxide, croscarmellose sodium, lactose (anhydrous), magnesium stearate, microcrystalline cellulose, and one or more of the following: D&C Yellow #10 aluminum lake, FD&C Blue # 2 aluminum lake, FD&C Yellow # 6 aluminum lake, FD&C Red #40 aluminum lake, FD&C Lime Green lake blend, and FD&C brown lake blend.

USP dissolution test is pending.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Ropinirole is a non-ergoline dopamine agonist. The precise mechanism of action of ropinirole as a treatment for Parkinson's disease is unknown, although it is thought to be related to its ability to stimulate dopamine D_2 receptors within the caudate-putamen in the brain. The precise mechanism of action of ropinirole as a treatment for Restless Legs Syndrome is unknown, although it is thought to be related to its ability to stimulate dopamine receptors.

12.2 Pharmacodynamics

Clinical experience with dopamine agonists, including ropinirole, suggests an association with impaired ability to regulate blood pressure with resulting orthostatic hypotension, especially during dose escalation. In some patients in clinical trials, blood pressure changes were associated with the emergence of orthostatic symptoms, bradycardia, and, in one case in a healthy volunteer, transient sinus arrest with syncope *[see Warnings and Precautions (5.2, 5.3)]*.

The mechanism of orthostatic hypotension induced by ropinirole 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 symptom of orthostatic signs and symptoms.

At oral doses as low as 0.2 mg, ropinirole suppressed serum prolactin concentrations in healthy male volunteers.

Ropinirole 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 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 on QTc intervals at higher exposures achieved either due to drug interactions, hepatic impairment, or at higher doses has not been systematically evaluated.

12.3 Pharmacokinetics

Ropinirole displayed linear kinetics over the dosing range of 1 to 8 mg three times daily. Steady-state concentrations are expected to be achieved within 2 days of dosing. Accumulation upon multiple dosing is predictive from single dosing.

Absorption

Ropinirole is rapidly absorbed after oral administration, reaching peak concentration in approximately 1 to 2 hours. In clinical trials, more than 88% of a radiolabeled dose was recovered in urine and the absolute bioavailability was 45% to 55%, indicating approximately 50% first-pass effect.

Relative bioavailability from a tablet compared with 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.

Distribution

Ropinirole is widely distributed throughout the body, with an apparent volume of distribution of 7.5 L/kg. It is up to 40% bound to plasma proteins and has a blood-to-plasma ratio of 1:1.

Metabolism

Ropinirole is extensively metabolized by the liver. The major metabolic pathways are N-despropylation and hydroxylation to form the inactive N-despropyl metabolite and hydroxy metabolites. The N-despropyl metabolite is converted to carbamyl glucuronide, carboxylic acid, and N-despropyl hydroxy metabolites. The hydroxy metabolite of ropinirole is rapidly glucuronidated.

In vitro studies indicate that the major cytochrome P450 enzyme involved in the metabolism of

ropinirole is CYP1A2, an enzyme known to be induced by smoking and omeprazole and inhibited by, for example, fluvoxamine, mexiletine, and the older fluoroquinolones such as ciprofloxacin and norfloxacin.

Elimination

The clearance of ropinirole after oral administration is 47 L/h and its elimination half-life is approximately 6 hours. 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%).

Drug Interactions

Digoxin

Coadministration of ropinirole (2 mg three 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 three times daily) in 12 patients with Parkinson's disease. Ropinirole (2 mg three times daily) did not alter the pharmacokinetics of theophylline (5 mg/kg IV) in 12 patients with Parkinson's disease.

Ciprofloxacin

Coadministration of ciprofloxacin (500 mg twice daily), an inhibitor of CYP1A2, with ropinirole (2 mg three 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.

L-dopa

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

Commonly Administered Drugs

Population analysis showed that commonly administered drugs, e.g., selegiline, amantadine, tricyclic antidepressants, benzodiazepines, ibuprofen, thiazides, antihistamines, and anticholinergics, did not affect the clearance of ropinirole. An *in vitro* study indicates that ropinirole is not a substrate for P-gp. Ropinirole and its circulating metabolites do not inhibit or induce P450 enzymes; therefore, ropinirole is unlikely to affect the pharmacokinetics of other drugs by a P450 mechanism.

Population Subgroups

Because therapy with ropinirole 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 15% in patients older than 65 years compared with younger

patients. Dosage adjustment is not necessary in the elderly (older than 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.

CigaretteSmoking

Smoking is expected to increase the clearance of ropinirole since CYP1A2 is known to be induced by smoking. In a trial in patients with RLS, smokers (n=7) had an approximately 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 with an age-matched population with creatinine clearance above 50 mL/min. 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.

A trial of ropinirole in subjects with end-stage renal disease on hemodialysis has shown that clearance of ropinirole was reduced by approximately 30%. The recommended maximum dose should be lower in these patients *[see Dosage and Administration (2.2, 2.3)]*.

The use of ropinirole in subjects with severe renal impairment (creatinine clearance less than 30 mL/min) without regular dialysis has not been studied.

HepaticImpairment

The pharmacokinetics of ropinirole have not been studied in patients with hepatic impairment. Because ropinirole is extensively metabolized by the liver, these patients may have higher plasma levels and lower clearance of ropinirole than patients with normal hepatic function.

OtherDiseases

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

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Two-year carcinogenicity studies of ropinirole were conducted in mice at doses of 5, 15, and 50 mg/kg/day and in rats at doses of 1.5, 15, and 50 mg/kg/day.

In rats, there was an increase in testicular Leydig cell adenomas at all doses tested. The lowest dose tested (1.5 mg/kg/day) is less than the MRHD for Parkinson's disease (24 mg/day) on a mg/m^2basis. The endocrine mechanisms believed to be involved in the production of these tumors in rats are not considered relevant to humans.

In mice, there was an increase in benign uterine endometrial polyps at a dose of 50 mg/kg/day. The highest dose not associated with this finding (15 mg/kg/day) is three times the MRHD on a mg/m^2 basis.

Mutagenesis

Ropinirole was not mutagenic or clastogenic in *in vitro* (Ames, chromosomal aberration in human lymphocytes, mouse lymphoma *tk*) assays, and in the *in vivo* mouse micronucleus test.

Impairment of Fertility

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 MRHD on a mg/m^2 basis) or greater. This effect is thought to be due to the prolactin-lowering effect of ropinirole. In rats using a low oral dose (5 mg/kg) during the prolactin-dependent phase of early pregnancy (gestation days 0 to 8), ropinirole did not affect female fertility at oral doses up to 100 mg/kg/day (40 times the MRHD on a mg/m^2 basis). No effect on male fertility was observed in rats at doses up to 125 mg/kg/day (50 times the MRHD on a mg/m^2 basis).

14 CLINICAL STUDIES

14.1 Parkinson's Disease

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

Three placebo-controlled trials provide evidence of effectiveness of ropinirole in the management of patients with Parkinson's disease who were and were not receiving concomitant L-dopa. Two of these three trials enrolled patients with early Parkinson's disease (without L-dopa) and one enrolled patients receiving L-dopa.

In these trials a variety of measures were used to assess the effects of treatment (e.g., the Unified Parkinson's Disease Rating Scale [UPDRS], Clinical Global Impression [CGI] scores, patient diaries recording time "on" and "off," tolerability of L-dopa dose reductions).

In both trials of patients with early Parkinson's disease (without L-dopa), the motor component (Part III) of the UPDRS was the primary outcome assessment. The UPDRS is a multi-item rating scale intended to evaluate mentation (Part I), activities of daily living (Part II), motor performance (Part III), and complications of therapy (Part IV). Part III of the UPDRS contains 14 items designed to assess the severity of the cardinal motor findings in patients with Parkinson's disease (e.g., tremor, rigidity, bradykinesia, postural instability) scored for different body regions and has a maximum (worst) score of 108. In the trial of patients with advanced Parkinson's disease (with L-dopa), both reduction in percent awake time spent "off" and the ability to reduce the daily use of L-dopa were assessed as a combined endpoint and individually.

Trials in Patients with Early Parkinson's Disease (without L-dopa)

Trial 1 was a 12-week multicenter trial in which 63 patients with idiopathic Parkinson's disease receiving concomitant anti-Parkinson medication (but not L-dopa) were enrolled and 41 were randomized to ropinirole and 22 to 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-IV. 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 with baseline) of at least 30% in the UPDRS motor score.

Patients were titrated for up to 10 weeks, starting at 0.5 mg twice daily, with weekly increments of 0.5

mg twice daily to a maximum of 5 mg twice daily. Once patients reached their maximally tolerated dose (or 5 mg twice daily), they were maintained on that dose through 12 weeks. The mean dose achieved by patients at trial endpoint was 7.4 mg/day. Mean baseline UPDRS motor score was 18.6 for patients treated with ropinirole and 19.9 for patients treated with placebo. At the end of 12 weeks, the percentage of responders was greater on ropinirole than on placebo and the difference was statistically significant (Table 6).

Table 6: Percent Responders for UPDRS Motor Score in Trial 1 (Intent-to-Treat Population)

	% Responders	Difference from Placebo
Placebo	41%	NA
Ropinirole	71%	30%

Trial 2 in patients with early Parkinson's disease (without L-dopa) was a double-blind, randomized, placebo-controlled, 6-month trial. In this trial, 241 patients were enrolled and 116 were randomized to ropinirole and 125 to placebo. Patients were essentially similar to those in the trial described above; concomitant use of selegiline was allowed, but patients were not permitted to use anticholinergics or amantadine during the trial. Patients had a mean disease duration of 2 years and limited (not more than a 6-week period) or no prior exposure to L-dopa. The starting dosage of ropinirole in this trial was 0.25 mg three times daily. The dosage was titrated at weekly intervals by increments of 0.25 mg three times daily to a dosage of 1 mg three times daily. Further titrations at weekly intervals were at increments of 0.5 mg three times daily up to a dosage of 3 mg three times daily, and then weekly at increments of 1 mg three times daily. Patients were to be titrated to a dosage of at least 1.5 mg three times daily and then to their maximally tolerated dosage, up to a maximum of 8 mg three times daily. The mean dose attained in patients at trial endpoint was 15.7 mg/day.

The primary measure of effectiveness was the mean percent reduction (improvement) from baseline in the UPDRS motor score. At the end of the 6-month trial, patients treated with ropinirole showed improvement in motor score compared with placebo and the difference was statistically significant (Table 7).

Table 7: Mean Percentage Change from Baseline in UPDRS Motor Score at End of Treatment in Trial 2 (Intent-to-Treat Population)

Treatment	Baseline UPDRS Motor Score	Mean Change From Baseline	Difference from Placebo
Placebo	17.7	+4%	NA
Ropinirole	17.9	-22%	-26%

Trial in Patients with Advanced Parkinson's Disease (with L-dopa)

Trial 3 was a double-blind, randomized, placebo-controlled, 6-month trial that randomized 149 patients (Hoehn & Yahr II-IV) who were not adequately controlled on L-dopa. Ninety-five patients were randomized to ropinirole and 54 were randomized to placebo. Patients in this trial had a mean disease duration of approximately 9 years, had been exposed to L-dopa for approximately 7 years, and had experienced "on-off" periods with L-dopa therapy. Patients previously receiving stable doses of selegiline, amantadine, and/or anticholinergic agents could continue on these agents during the trial. Patients were started at a dosage of 0.25 mg three times daily of ropinirole and titrated upward by weekly intervals until an optimal therapeutic response was achieved. The maximum dosage of trial medication was 8 mg three times daily. All patients had to be titrated to at least a dosage of 2.5 mg three times daily. Patients could then be maintained on this dosage level or higher for the remainder of the trial. Once a dosage of 2.5 mg three times daily was achieved, patients underwent a mandatory reduction in their L-dopa dosage, to be followed by additional mandatory reductions with continued escalation of

the dosage of ropinirole. Reductions in the dosage of L-dopa were also allowed if patients experienced adverse reactions that the investigator considered related to dopaminergic therapy. The mean dose attained at trial 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 with baseline) of at least 20% in their L-dopa dosage and a decrease of at least 20% in the proportion of the time awake in the "off" condition (a period of time during the day when patients are particularly immobile), as determined by subject diary. In addition, the mean change in "off" time from baseline and the percent change from baseline in daily L-dopa dosage were examined.

At the end of 6 months, the percentage of responders was greater on ropinirole than on placebo and the difference was statistically significant (Table 8).

Based on the protocol-mandated reductions in L-dopa dosage with escalating doses of ropinirole, patients treated with ropinirole had a 19.4% mean reduction in L-dopa dosage while patients treated with placebo had a 3% reduction. Mean daily L-dopa dosage at baseline was 759 mg for patients treated with ropinirole and 843 mg for patients treated with placebo.

The mean number of daily "off" hours at baseline was 6.4 hours for patients treated with ropinirole and 7.3 hours for patients treated with placebo. At the end of the 6-month trial, there was a mean reduction of 1.5 hours of "off" time in patients treated with ropinirole and a mean reduction of 0.9 hours of "off" time in patients treated with placebo, resulting in a treatment difference of 0.6 hours of "off" time.

Table 8: Mean Responder Percentage of Patients Reducing Daily L-Dopa Dosage by at Least 20% and Daily Proportion of "Off" Time by at Least 20% at End of Treatment in Trial 3 (Intent-to-Treat Population)

Treatment	% Responders	Difference from Placebo
Placebo	11%	NA
Ropinirole	28%	17%

14.2 Restless Legs Syndrome

The effectiveness of ropinirole in the treatment of RLS was demonstrated in randomized, double-blind, placebo-controlled trials in adults diagnosed with RLS using the International Restless Legs Syndrome Study Group diagnostic criteria. 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, anemia) were excluded. All trials employed flexible dosing, with patients initiating therapy at 0.25 mg ropinirole 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 trials 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 (n=187) or placebo (n=193) in a US trial (RLS-1); 284 were randomized to receive either ropinirole (n=146) or placebo (n=138) in a multinational trial (excluding US) (RLS-2); and 267 patients were randomized to ropinirole (n=131) or placebo (n=136) in a multinational trial (including US) (RLS-3). Across the three trials, the mean duration of RLS was 16 to 22 years (range: 0 to 65 years), mean age was approximately 54 years (range: 18 to 79 years), and approximately 61% were women. The mean dose at Week 12 was approximately 2 mg/day for the three trials.

At baseline, mean total IRLS score was 22.0 for ropinirole and 21.6 for placebo in RLS-1, was 24.4 for ropinirole and 25.2 for placebo in RLS-2, and was 23.6 for ropinirole and 24.8 for placebo in RLS-3. In all three trials, a statistically significant difference between the treatment group receiving ropinirole 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 9).

Table 9: Mean Change in Total IRLS Score and Percent Responders on CGI-I

	Ropinirole	**Placebo**	**Difference from Placebo**
Mean change in total IRLS score at Week 12			
RLS-1	-13.5	-9.8	-3.7
RLS-2	-11.0	-8.0	-3.0
RLS-3	-11.2	-8.7	-2.5
Percent responders on CGI-I at Week 12			
RLS-1	73.3%	56.5%	16.8%
RLS-2	53.4%	40.9%	12.5%
RLS-3	59.5%	39.6%	19.9%

Long-term maintenance of efficacy in the treatment of RLS was demonstrated in a 36-week trial. Following a 24-week, single-blind treatment phase (flexible dosages of ropinirole 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 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 demonstrated a significantly lower relapse rate compared with patients randomized to placebo (32.6% versus 57.8%, P = 0.0156).

15 REFERENCES

1. Sinemet® is a registered trademark of Bristol Myers Squibb.

16 HOW SUPPLIED/STORAGE AND HANDLING

Product: 68151-4071

NDC: 68151-4071-2 1 TABLET in a PACKAGE

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information).

Dosing Instructions

Instruct patients to take ropinirole only as prescribed. If a dose is missed, advise patients not to double their next dose. Ropinirole can be taken with or without food *[see Dosage and Administration (2.1)]*.

Ropinirole is the active ingredient in ropinirole tablets. Ask your patients if they are taking another medication containing ropinirole.

Hypersensitivity/Allergic Reactions

Advise patients about the potential for developing a hypersensitivity/allergic reaction including manifestations such as urticaria, angioedema, rash, and pruritus when taking any ropinirole product.

Inform patients who experience these or similar reactions to immediately contact their healthcare professional *[see Contraindications (4)]*.

Falling Asleep During Activities of Daily Living and Somnolence

Alert patients to the potential sedating effects caused by ropinirole, including somnolence and the possibility of falling asleep while engaged in activities of daily living. Because somnolence is a frequent adverse reaction with potentially serious consequences, patients should not drive a car, operate machinery, or engage in other potentially dangerous activities until they have gained sufficient experience with ropinirole to gauge whether or not it affects their mental and/or motor performance adversely. Advise patients that if increased somnolence or episodes of falling asleep during activities of daily living (e.g., conversations, eating, driving a motor vehicle, etc.) are experienced at any time during treatment, they should not drive or participate in potentially dangerous activities until they have contacted their physician.

Advise patients of possible additive effects when patients are taking other sedating medications, alcohol, or other central nervous system depressants (e.g., benzodiazepines, antipsychotics, antidepressants, etc.) in combination with ropinirole or when taking a concomitant medication (e.g., ciprofloxacin) that increases plasma levels of ropinirole *[see Warnings and Precautions (5.1)]*.

Syncope and Hypotension/Orthostatic Hypotension

Advise patients that they may experience syncope and may develop hypotension with or without symptoms such as dizziness, nausea, syncope, and sometimes sweating while taking ropinirole, especially if they are elderly. 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). Postural/orthostatic symptoms may be related to sitting up or standing. Accordingly, caution patients against standing 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 *[see Warnings and Precautions (5.2, 5.3)]*.

Hallucinations/Psychotic-like Behavior

Inform patients that they may experience hallucinations (unreal visions, sounds, or sensations), and that other psychotic-like behavior can occur while taking ropinirole. The elderly are at greater risk than younger patients with Parkinson’s disease. This risk is greater in patients who are taking ropinirole with L-dopa or taking higher doses of ropinirole and may also be further increased in patients taking any other drugs that increase dopaminergic tone. Tell patients to report hallucinations or psychotic-like behavior to their healthcare provider promptly should they develop *[see Warnings and Precautions (5.4)]*.

Dyskinesia

Inform patients that ropinirole may cause and/or exacerbate pre-existing dyskinesias *[see Warnings and Precautions (5.5)]*.

Impulse Control/Compulsive Behaviors

Advise patients that they may experience impulse control and/or compulsive behaviors while taking one or more of the medications (including ropinirole) that increase central dopaminergic tone, that are generally used for the treatment of Parkinson’s disease. Advise patients to inform their physician or healthcare provider if they develop new or increased gambling urges, sexual urges, uncontrolled spending, binge or compulsive eating, or other urges while being treated with ropinirole. Physicians should consider dose reduction or stopping the medication if a patient develops such urges while taking ropinirole *[see Warnings and Precautions (5.6)]*.

Withdrawal-Emergent Hyperpyrexia and Confusion

Advise patients to contact their healthcare provider if they wish to discontinue ropinirole or decrease the dose of ropinirole *[see Warnings and Precautions (5.7)]*.

Melanoma

Advise patients with Parkinson's disease that they have a higher risk of developing melanoma. Advise patients to have their skin examined on a regular basis by a qualified healthcare provider (e.g., dermatologist) when using ropinirole for any indication *[see Warnings and Precautions (5.8)]*.

Augmentation and Rebound

Inform patients with RLS that augmentation and/or rebound may occur after starting treatment with ropinirole *[see Warnings and Precautions (5.9)]*.

Nursing Mothers

Because of the possibility that ropinirole may be excreted in breast milk, 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 *[see Use in Specific Populations (8.3)]*. Advise patients that ropinirole could inhibit lactation because ropinirole inhibits prolactin secretion.

Pregnancy

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, advise patients to notify their physician if they become pregnant or intend to become pregnant during therapy *[see Use in Specific Populations (8.1)]*.

Patient Information

If you have Parkinson's disease, read this side.

If you have Restless Legs Syndrome (RLS), read the other side.

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

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

Ropinirole can cause serious side effects, including:

- **Hypersensitivity/allergic reactions.** You may experience a hypersensitivity/allergic reaction characterized by hives, rash, itching, and/or swelling of the face, lips, mouth, tongue, or throat, which may cause problems in swallowing or breathing. **If you experience any of these reactions**, you should not take ropinirole again until you talk to a healthcare provider and seek their advice.
- **Falling asleep during normal activities.** You may fall asleep while doing normal activities such as driving a car, doing physical tasks, or using hazardous machinery while taking ropinirole. You may suddenly fall asleep without being drowsy or without warning. This may result in having accidents. Your chances of falling asleep while doing normal activities while taking ropinirole are greater if you take other medicines that cause drowsiness. Tell your healthcare provider right away if this happens. Before starting ropinirole, be sure to tell your healthcare provider if you take any medicines that make you drowsy.
- **Fainting.** Fainting can happen, and sometimes your heart rate may be decreased. This can happen especially when you start taking ropinirole or your dose is increased. Tell your healthcare provider if you faint or feel dizzy or light-headed.
- **Decrease in blood pressure.** Ropinirole can decrease your blood pressure. Decreases in your blood pressure (hypotension) can happen, especially when you start taking ropinirole or when

your dose is changed. If you faint or feel dizzy, nauseated, or sweaty when you stand up from sitting or lying down (orthostatic hypotension), this may mean that your blood pressure is decreased. When you change position from lying down or sitting to standing up, you should do it carefully and slowly. Call your healthcare provider if you have any of the symptoms of decreased blood pressure listed above.

- **Increase in blood pressure.** Ropinirole may increase your blood pressure.
- **Changes in heart rate (decrease or increase).** Ropinirole can decrease or increase your heart rate.
- **Hallucinations and other psychotic-like behavior.** Ropinirole can cause or worsen psychotic-like behavior including hallucinations (seeing or hearing things that are not real), confusion, excessive suspicion, aggressive behavior, agitation, delusional beliefs (believing things that are not real), and disorganized thinking. The chances of having hallucinations or these other psychotic-like changes are higher in people with Parkinson's disease who are taking ropinirole or taking higher doses of these drugs. If you have hallucinations or any of these other psychotic-like changes, talk with your healthcare provider.
- **Uncontrolled sudden movements.** Ropinirole may cause uncontrolled sudden movements or make such movements you already have worse or more frequent. Tell your healthcare provider if this happens. The doses of your anti-Parkinson's medicine may need to be changed.
- **Unusual urges.** Some patients taking ropinirole get urges to behave in a way unusual for them. Examples of this are an unusual urge to gamble, increased sexual urges and behaviors, or an uncontrollable urge to shop, spend money, or eat. If you notice or your family notices that you are developing any unusual behaviors, talk to your healthcare provider.
- **Increased chance of skin cancer (melanoma).** People with Parkinson's disease may have a higher chance of getting melanoma. It is not known if ropinirole increases your chances of getting melanoma. You and your healthcare provider should check your skin on a regular basis. Tell your healthcare provider right away if you notice any changes in your skin such as a change in the size, shape, or color of moles on your skin.

What is ropinirole?

- Ropinirole is a short-acting prescription medicine containing ropinirole (usually taken 3 times a day) that is used to treat Parkinson's disease. It is also used to treat a condition called Restless Legs Syndrome (RLS).

Having one of these conditions does not mean you have or will develop the other condition.

You should not be taking more than 1 medicine containing ropinirole. Tell your healthcare provider if you are taking any other medicine containing ropinirole.

It is not known if ropinirole is safe and effective for use in children younger than 18 years of age.

Who should not take ropinirole?

Do not take ropinirole if you:

- are allergic to ropinirole or any of the ingredients in ropinirole. See the end of this page for a complete list of the ingredients in ropinirole.

Call your healthcare provider and get help right away if you have any of the following symptoms of an allergic reaction. Symptoms of an allergic reaction may include:

- **hives**
- **rash**
- **swelling of the face, lips, mouth, tongue, or throat**

- **itching**

What should I tell my healthcare provider before taking ropinirole?

Before you take ropinirole, tell your healthcare provider if you:

- have daytime sleepiness from a sleep disorder or have unexpected or unpredictable sleepiness or periods of sleep.
- 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.
- start or stop taking other medicines while you are taking ropinirole. This may increase your chances of getting side effects.
- start or stop smoking while you are taking ropinirole. Smoking may decrease the treatment effect of ropinirole.
- feel dizzy, nauseated, sweaty, or faint when you stand up from sitting or lying down.
- drink alcoholic beverages. This may increase your chances of becoming drowsy or sleepy while taking ropinirole.
- have high or low blood pressure.
- have or have had heart problems.
- are pregnant or plan to become pregnant. Ropinirole should only be used during pregnancy if needed.
- are breastfeeding. It is not known if ropinirole passes into your breast milk. Talk to your healthcare provider to decide whether you will breastfeed or take ropinirole.
- have any other medical conditions.

How should I take ropinirole for Parkinson's disease?

- Take ropinirole exactly as directed by your healthcare provider.
- **Do not** suddenly stop taking ropinirole without talking to your healthcare provider. If you stop this medicine suddenly, you may develop fever, confusion, or severe muscle stiffness.
- Before starting ropinirole, you should talk to your healthcare provider about what to do if you miss a dose. If you have missed the previous dose and it is time for your next dose, **do not double the dose.**
- Your healthcare provider will start you on a low dose of ropinirole. Your healthcare provider will change the dose until you are taking the right amount of medicine to control your symptoms. **It may take several weeks before you reach a dose that controls your symptoms.**

If you are taking ropinirole:

- Ropinirole tablets are usually taken 3 times a day for Parkinson's disease.
- Contact your healthcare provider if you stop taking ropinirole for any reason. Do not restart without talking with your healthcare provider.
- Your healthcare provider may prescribe ropinirole alone, or add ropinirole to medicine that you are already taking for Parkinson's disease.
- You should not substitute ropinirole without talking with your healthcare provider.
- You can take ropinirole with or without food.

What are the possible side effects of ropinirole?

Ropinirole can cause serious side effects, including:

- **See "What is the most important information I should know about ropinirole?"**

The most common side effects of ropinirole include:

- fainting
- sleepiness or drowsiness
- hallucinations (seeing or hearing things that are not real)
- dizziness
- nausea or vomiting
- uncontrolled sudden movements
- leg swelling
- fatigue, tiredness, or weakness
- confusion
- headache
- upset stomach, abdominal pain or discomfort
- increased sweating

Tell your healthcare provider if you have any side effect that bothers you or does not go away.

This is not a complete list of side effects and should not take the place of talking with your healthcare provider. Your healthcare provider or pharmacist can give you a more complete list of possible side effects.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store ropinirole?

- Store ropinirole at room temperature between 68°F to 77°F (20°C to 25°C).
- Keep ropinirole in a tightly closed container and out of direct sunlight.

Keep ropinirole and all medicines out of the reach of children.

General information about the safe and effective use of ropinirole.

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not take ropinirole for a condition for which it was not prescribed. Do not give ropinirole to other people, even if they have the same symptoms you have. It may harm them.

This side of the patient information leaflet summarizes the most important information about ropinirole for Parkinson's disease. If you would like more information, talk with your healthcare provider or pharmacist. You can ask your healthcare provider or pharmacist for information about ropinirole that is written for healthcare professionals. For more information go to www.Roxane.com or call 1-800-962-8364 (toll-free).

What are the ingredients in ropinirole?

The following ingredients are in ropinirole:

Active ingredient: ropinirole (as ropinirole hydrochloride)

Inactive ingredients: colloidal silicon dioxide, croscarmellose sodium, lactose (anhydrous), magnesium stearate, microcrystalline cellulose, and one or more of the following: D&C Yellow #10 aluminum lake, FD&C Blue # 2 aluminum lake, FD&C Yellow # 6 aluminum lake, FD&C Red #40 aluminum lake, FD&C Lime Green lake blend, and FD&C brown lake blend.

Patient Information

If you have Restless Legs Syndrome (RLS), read this side.

If you have Parkinson's disease, read the other side.

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

People with RLS should take ropinirole differently than people with Parkinson's disease (see **"How should I take ropinirole for RLS?"** for the recommended dosing for RLS). A lower dose is generally needed for people with RLS, and is taken once daily before bedtime.

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

Ropinirole can cause serious side effects, including:

- **Hypersensitivity/allergic reactions.** You may experience a hypersensitivity/allergic reaction characterized by hives, rash, itching, and/or swelling of the face, lips, mouth, tongue, or throat, which may cause problems in swallowing or breathing. **If you experience any of these reactions** after starting ropinirole, you should not take ropinirole again until you talk to a healthcare provider and seek their advice.
- **Falling asleep during normal activities.** You may fall asleep while doing normal activities such as driving a car, doing physical tasks, or using hazardous machinery while taking ropinirole. You may suddenly fall asleep without being drowsy or without warning. This may result in having accidents. Your chances of falling asleep while doing normal activities while taking ropinirole are greater if you take other medicines that cause drowsiness. Tell your healthcare provider right away if this happens. Before starting ropinirole, be sure to tell your healthcare provider if you take any medicines that make you drowsy.
- **Fainting.** Fainting can occur, and sometimes your heart rate may be decreased. This can happen especially when you start taking ropinirole or your dose is increased. Tell your healthcare provider if you faint or feel dizzy or light-headed.
- **Decrease in blood pressure.** Ropinirole can decrease your blood pressure (hypotension), especially when you start taking ropinirole or when your dose is changed. If you faint or feel dizzy, nauseated, or sweaty when you stand up from sitting or lying down (orthostatic hypotension), this may mean that your blood pressure is decreased. When you change position from lying down or sitting to standing up, you should do it carefully and slowly. Call your healthcare provider if you have any of the symptoms of decreased blood pressure listed above.
- **Changes in heart rate (decrease or increase).** Ropinirole can decrease or increase your heart rate.
- **Unusual urges.** Some patients taking ropinirole get urges to behave in a way unusual for them. Examples of this are an unusual urge to gamble, increased sexual urges and behaviors, or an uncontrollable urge to shop, spend money, or eat. If you notice or your family notices that you are developing any unusual behaviors, talk to your healthcare provider.
- **Increased chance of skin cancer (melanoma).** It is not known if ropinirole increases your chances of getting melanoma. You and your healthcare provider should check your skin on a regular basis. Tell your healthcare provider right away if you notice any changes in your skin such as a change in the size, shape, or color of moles on your skin.
- **Changes in Restless Legs Syndrome symptoms.** Ropinirole may cause Restless Legs symptoms to come back in the morning (rebound), happen earlier in the evening, or even happen in the afternoon.

What is ropinirole?

- Ropinirole is a prescription medicine containing ropinirole used to treat moderate-to-severe primary Restless Legs Syndrome (RLS). It is also used to treat Parkinson's disease.

Having one of these conditions does not mean you have or will develop the other condition.

You should not be taking more than 1 medicine containing ropinirole. Tell your healthcare provider if you are taking any other medicine containing ropinirole.

It is not known if ropinirole is safe and effective for use in children younger than 18 years of age.

Who should not take ropinirole?

Do not take ropinirole if you:

- are allergic to ropinirole or any of the ingredients in ropinirole. See the end of this leaflet for a complete list of the ingredients in ropinirole.

Call your healthcare provider and get help right away if you have any of the following symptoms of an allergic reaction. Symptoms of an allergic reaction may include:

- **hives**
- **rash**
- **swelling of the face, lips, mouth, tongue, or throat**
- **itching**

What should I tell my healthcare provider before taking ropinirole?

Before you take ropinirole, tell your healthcare provider if you:

- have daytime sleepiness from a sleep disorder or have unexpected or unpredictable sleepiness or periods of sleep.
- 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.
- start or stop taking other medicines while you are taking ropinirole. This may increase your chances of getting side effects.
- start or stop smoking while you are taking ropinirole. Smoking may decrease the treatment effect of ropinirole.
- feel dizzy, nauseated, sweaty, or faint when you stand up from sitting or lying down.
- drink alcoholic beverages. This may increase your chances of becoming drowsy or sleepy while taking ropinirole.
- have high or low blood pressure.
- have or have had heart problems.
- are pregnant or plan to become pregnant. Ropinirole should only be used during pregnancy if needed.
- are breastfeeding. It is not known if ropinirole passes into your breast milk. Talk to your healthcare provider to decide whether you will breastfeed or take ropinirole.
- have any other medical conditions.

How should I take ropinirole for RLS?

- Take ropinirole exactly as directed by your healthcare provider.

- The usual way to take ropinirole is once in the evening, 1 to 3 hours before bedtime.
- Your healthcare provider will start you on a low dose of ropinirole. Your healthcare provider may change the dose until you are taking the right amount of medicine 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 healthcare provider if you stop taking ropinirole for any reason. Do not restart without consulting your healthcare provider.
- You can take ropinirole with or without food.

What are the possible side effects of ropinirole?

Ropinirole can cause serious side effects, including:

- **See "What is the most important information I should know about ropinirole?"**

The most common side effects of ropinirole include:

- nausea or vomiting
- drowsiness or sleepiness
- dizziness
- fatigue, tiredness, or weakness

Tell your healthcare provider if you have any side effect that bothers you or does not go away.

This is not a complete list of side effects and should not take the place of talking with your healthcare provider. Your healthcare provider or pharmacist can give you a more complete list of possible side effects.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store ropinirole?

- Store ropinirole at room temperature between 68°F to 77°F (20°C to 25°C).
- Keep ropinirole in a tightly closed container and out of direct sunlight.

Keep ropinirole and all medicines out of the reach of children.

General information about the safe and effective use of ropinirole.

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not take ropinirole for a condition for which it was not prescribed. Do not give ropinirole to other people, even if they have the same symptoms you have. It may harm them.

This side of the patient information leaflet summarizes the most important information about ropinirole for Restless Legs Syndrome (RLS). If you would like more information, talk with your healthcare provider or pharmacist. You can ask your healthcare provider or pharmacist for information about ropinirole that is written for healthcare professionals. For more information go to www.Roxane.com or call 1-800-962-8364 (toll-free).

What are the ingredients in ropinirole?

The following ingredients are in ropinirole:

Active ingredient: ropinirole (as ropinirole hydrochloride)

Inactive ingredients: colloidal silicon dioxide, croscarmellose sodium, lactose (anhydrous), magnesium stearate, microcrystalline cellulose, and one or more of the following: D&C Yellow #10

aluminum lake, FD&C Blue # 2 aluminum lake, FD&C Yellow # 6 aluminum lake, FD&C Red #40 aluminum lake, FD&C Lime Green lake blend, and FD&C brown lake blend.

This Patient Information has been approved by the U.S. Food and Drug Administration.

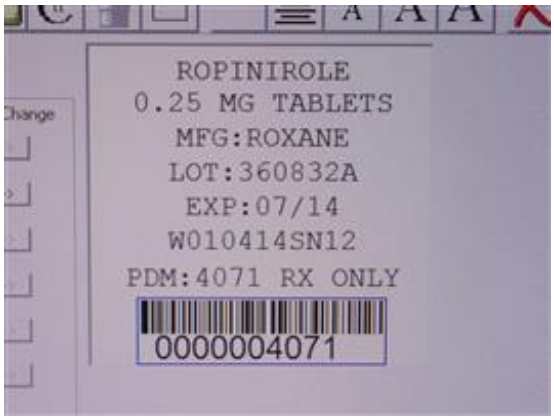
Roxane Laboratories, Inc.

Columbus, Ohio 43216

10004278/07

Revised October 2014

Ropinirole HCL 0.25 mg tabs



ROPINIROLE

ropinirole tablet

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:68151-4071(NDC:0054-0116)
Route of Administration	ORAL		

Active Ingredient/Active Moiety		
Ingredient Name	**Basis of Strength**	**Strength**
ROPINIROLE HYDROCHLORIDE (UNII: D7ZD41RZI9) (ROPINIROLE - UNII:030PYR8953)	ROPINIROLE	0.25 mg

Inactive Ingredients	
Ingredient Name	**Strength**
SILICON DIOXIDE (UNII: ETJ7Z6XBU4)	
CROSCARMELLOSE SODIUM (UNII: M28OL1HH48)	
D&C YELLOW NO. 10 (UNII: 35SW5USQ3G)	
FD&C BLUE NO. 2 (UNII: L06K8R7DQK)	
FD&C RED NO. 40 (UNII: WZB9127XOA)	
FD&C YELLOW NO. 6 (UNII: H77VEI93A8)	
LACTOSE, UNSPECIFIED FORM (UNII: J2B2A4N98G)	

MAGNESIUM STEARATE (UNII: 70097M6I30)	
MICROCRYSTALLINE CELLULOSE (UNII: OP1R32D61U)	

Product Characteristics			
Color	WHITE	**Score**	no score
Shape	ROUND (biconvex)	**Size**	1mm
Flavor		**Imprint Code**	54;511
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:68151-4071-2	1 in 1 PACKAGE; Type 0: Not a Combination Product	05/05/2008	

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA077852	05/05/2008	

Labeler - Carilion Materials Management (079239644)

Establishment

Name	Address	ID/FEI	Business Operations
Carilion Materials Management		079239644	REPACK(68151-4071)

Revised: 12/2017 Carilion Materials Management