ROPINIROLE - ropinirole tablet, film coated, extended release
Alembic Pharmaceuticals Limited

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use ROPINIROLE EXTENDED-RELEASE TABLETS safely and effectively. See full prescribing information for ROPINIROLE EXTENDED-RELEASE TABLETS.

ROPINIROLE extended-release tablets, for oral use

Initial U.S. Approval: 1997

RECENT MAJOR CHANGES

Dosage and Administration (2.2, 2.3)	8/2014
Contraindications (4)	8/2014
Warnings and Precautions (5.5, 5.7)	8/2014

INDICATIONS AND USAGE

Ropinirole extended-release tablets are non-ergoline dopamine agonist indicated for the treatment of Parkinson's disease (1.1) (1)

DOSAGE AND ADMINISTRATION

•Ropinirole extended-release tablets are taken once daily, with or without food; tablets must be swallowed whole and must not be chewed, crushed, or divided (2.1)
•The recommended starting dose is 2 mg taken once daily for 1 to 2 weeks; the dose should be increased by 2 mg/day at 1 week or longer intervals; the maximum dose is 24 mg/day (2.2, 14.2)
•Renal Impairment: In patients with end-stage renal disease on hemodialysis, the maximum recommended dose is 18 mg/day (2.2)
•If ropinirole extended-release tablets must be discontinued, it should be tapered gradually over a 7-day period; retitration of ropinirole extended-release tablets may be warranted if therapy is interrupted (2.1, 2.2)
•Patients may be switched directly from immediate-release ropinirole to ropinirole extended-release tablets; the initial switching dose of ropinirole extended-release tablets should most closely match the total daily dose of immediate-release ropinirole. (2.3) (2)

DOSAGE FORMS AND STRENGTHS

Tablets: 2 mg, 4 mg, 6 mg, 8 mg, and 12 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)
•Elevation of blood pressure and changes in heart rate may occur (5.4)
•May cause hallucinations and psychotic-like behaviors (5.5)
•May cause or exacerbate dyskinesia (5.6)
•May cause problems with impulse control or compulsive behaviors (5.7) (5)

ADVERSE REACTIONS

· Most common adverse reactions (incidence for ropinirole extended-release tablets at least 5% greater than placebo) in advanced Parkinson's disease with concomitant L-dopa were dyskinesia, nausea, dizziness, hallucination. (6.1)
· Most common adverse reactions (incidence incidence for ropinirole extended-release tablets at least 5%) in early Parkinson's disease without L-dopa were nausea, somnolence, abdominal pain/discomfort, dizziness, headache, and constipation (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact 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 treatment may require dose adjustment of ropinirole extended-release tablets (7.2, 12.3)
•Dopamine antagonists (e.g., neuroleptics metoclopramide): May reduce efficacy of ropinirole extended-release tablets (7.3) (7)

USE IN SPECIFIC POPULATIONS

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

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 9/2019

FULL PRESCRIBING INFORMATION: CONTENTS*

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

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Parkinson's Disease

Ropinirole extended-release tablets are indicated for the treatment of Parkinson’s disease.

2 DOSAGE AND ADMINISTRATION

2.1 General Dosing Recommendations

· Ropinirole extended-release tablets are taken once daily, with or without food *[see Clinical Pharmacology (12.3)]*.

· Tablets must be swallowed whole and must not be chewed, crushed, or divided.

· If a significant interruption in therapy with ropinirole extended-release tablets has occurred, retitration of therapy may be warranted.

2.2 Dosing for Parkinson's Disease

The starting dose is 2 mg taken once daily for 1 to 2 weeks, followed by increases of 2 mg/day at 1-week or longer intervals as appropriate, based on therapeutic response and tolerability. The maximum recommended dose of ropinirole extended-release tablets is 24 mg/day.

In clinical trials, dosage was initiated at 2 mg/day and gradually titrated based on individual patient therapeutic response and tolerability. Doses greater than 24 mg/day have not been studied in clinical trials. Patients should be assessed for therapeutic response and tolerability at a minimal interval of 1 week or longer after each dose increment. Monitor patients during dose titration because too rapid a rate of titration may lead to dose selection that may not provide additional benefit, but that may increase the risk of adverse reactions *[see Clinical Studies (14.2)]*. Due to the flexible dosing design used in clinical trials, specific dose-response information could not be determined.

Ropinirole extended-release tablets should be discontinued gradually over a 7-day period.

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 extended-release tablets for patients with end-stage renal disease on hemodialysis is 2 mg once daily. 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 extended-release tablets in patients with severe renal impairment without regular dialysis has not been studied.

2.3 Switching from Immediate-Release Ropinirole Tablets to Extended-Release Ropinirole Tablets

Patients may be switched directly from immediate-release ropinirole to extended-release ropinirole tablets. The initial dose of ropinirole extended-release tablets should most closely match the total daily dose of the immediate-release formulation of ropinirole tablets, as shown in Table 1.

Table 1. Conversion from Immediate-Release Ropinirole Tablets to Extended-Release Ropinirole Tablets

Immediate-Release Ropinirole Tablets Total Daily Dose (mg)	Extended-Release Ropinirole Tablets Total Daily Dose (mg)
0.75 to 2.25	2
3 to 4.5	4
6	6
7.5 to 9	8
12	12
15	16
18	18
21	20
24	24

Following conversion to ropinirole extended-release tablets, the dose may be adjusted depending on therapeutic response and tolerability [see Dosage and Administration (2.2)].

2.4 Effect of Gastrointestinal Transit Time on Medication Release

Ropinirole extended-release tablets are designed to release medication over a 24-hour period. If rapid gastrointestinal transit occurs, there may be risk of incomplete release of medication and medication residue being passed in the stool.

3 DOSAGE FORMS AND STRENGTHS

- 2 mg, pink, capsule shaped, film coated tablet, debossed with ‘L191’ on one side and plain on other side.
- 4 mg, light brown, capsule shaped, film coated tablet, debossed with ‘L193’ on one side and plain on other side.
- 6 mg, white to off white, capsule shaped, film coated tablet, debossed with ‘L321’ on one side and plain on other side.
- 8 mg, dark brown to red, capsule shaped, film coated tablet, debossed with ‘L194’ on one side and plain on other side.
- 12 mg, light green, capsule shaped, film coated tablet, debossed with ‘L195’ on one side and plain on other side.

4 CONTRAINDICATIONS

Ropinirole extended-release tablets are contraindicated in patients known to have a hypersensitivity/allergic reaction including urticaria, angioedema, rash, pruritus) to ropinirole or 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 machinary, 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.

Among the 613 patients who received ropinirole extended-release tablets in clinical trials, there were 5 cases of sudden onset of sleep and 2 cases of motor vehicle accident in which it is not known if falling asleep was a contributing factor.

During the 6-month trial in advanced Parkinson's disease, somnolence was reported in 7% of patients receiving ropinirole extended-release tablets compared with 4% of patients receiving placebo. During the 36-week trial in early Parkinson's disease, somnolence was reported in 11% of patients receiving ropinirole extended-release tablets compared with 15% of patients receiving the immediate-release formulation of ropinirole tablets*[see Adverse Reactions (6.1)]*. However, because dose-response was not systematically studied with ropinirole extended-release tablets, the occurrence of somnolence at the highest recommended doses may be higher than these reported frequencies *[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 extended-release tablets, patients should be advised of the potential to develop drowsiness and specifically asked about factors that may increase the risk with ropinirole extended-release tablets such as concomitant sedating medications, the presence of sleep disorders, 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 extended-release tablets should ordinarily be discontinued *[see Dosage and Administration (2.2)]*. If a decision is made to continue ropinirole extended-release tablets, 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 extended-release tablets in Parkinson's disease patients. In a placebo-controlled trial involving patients with advanced Parkinson's disease, syncope occurred in 2 of the 202 patients (1%) who received ropinirole extended-release tablets, and in none of the 191 patients who received placebo *[see Adverse Reactions (6.1)]*.

Because the trial of ropinirole extended-release tablets excluded patients with significant cardiovascular disease, patients with significant cardiovascular disease should be treated with caution.

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)]*.

In a placebo-controlled trial involving patients with advanced Parkinson's disease, hypotension was reported as an adverse event in 5 of 202 patients (2%) receiving ropinirole extended-release tablets and in none of the 191 patients receiving placebo. Orthostatic hypotension was reported as an adverse event in 5% of patients receiving ropinirole extended-release tablets, and in 1% of placebo recipients *[see Adverse Reactions (6.1)]*.

An analysis of the randomized, double-blinded, placebo-controlled trial in advanced Parkinson's disease was conducted using a variety of adverse event terms possibly suggestive of hypotension, including hypotension, orthostatic hypotension, dizziness, vertigo, and blood pressure decreased. This analysis showed a higher incidence of these events with ropinirole extended-release tablets (7%, 15 of 202) vs. placebo (3%, 6 of 191). The increased incidence with ropinirole extended-release tablets was observed in a setting in which patients were very carefully titrated, and patients with clinically relevant cardiovascular disease or symptomatic orthostatic hypotension at baseline had been excluded from this trial. Orthostatic vital signs (semi-supine to standing) were monitored throughout the advanced Parkinson's disease trial and changes related to ropinirole extended-release tablets (compared with placebo) from baseline were assessed.

The frequency of orthostatic hypotension at any time during the trial was 38% for ropinirole extended-release tablets vs. 31% for placebo for mild to moderate systolic blood pressure decrements (≥20 mm Hg), 63% for ropinirole extended-release tablets vs. 58% for placebo for mild-to-moderate diastolic blood pressure decrements (≥10 mm Hg), 10% for ropinirole extended-release tablets vs. 7% for placebo for severe diastolic blood pressure decrements (≥20 mm Hg), and 23% for ropinirole extended-release tablets vs. 19% for placebo for mild-to-moderate combined systolic and diastolic blood pressure decrements.

Significant decrements in blood pressure unrelated to standing were also reported in some patients taking ropinirole extended-release tablets. In the semi-supine position, the frequency was 10% for ropinirole extended-release tablets vs. 8% for placebo for severe systolic blood pressure decrease (≥40 mm Hg), and was 25% for ropinirole extended-release tablets vs. 21% for placebo for severe diastolic blood pressure decrease (≥20 mm Hg).

The increased incidence for hypotension and/or orthostatic hypotension was observed in both the titration and maintenance phases and in some cases persisted into the maintenance period after developing in the titration phase.

5.4 Elevation of Blood Pressure and Changes in Heart Rate

In the placebo-controlled trial in advanced Parkinson's disease, there were no clear effects of ropinirole extended-release tablets on average changes in blood pressure or heart rate compared with placebo.

In the semi-supine position, the frequency was 8% for ropinirole extended-release tablets vs. 5% for placebo for severe systolic blood pressure increase (≥40 mm Hg). In the standing position, the frequency was 9% for ropinirole extended-release tablets vs. 6% for placebo for severe systolic blood pressure increase ≥40 mm Hg). In the semi-supine position, the frequency was 23% for ropinirole extended-release tablets vs. 18% for placebo for moderate pulse increase (≥15 beats/minute), and 19% for ropinirole extended-release tablets vs. 17% for placebo for moderate pulse decrease (≥15 beats/minute). In the standing position, the frequency was 2% for ropinirole extended-release tablets vs. <1% for placebo for severe pulse increase (≥30 beats/minute), and 24% for ropinirole extended-release tablets vs. 19% for placebo for moderate pulse decrease (≥15 beats/minute).

The increased incidence for various elevations of systolic and/or diastolic blood pressure and/or changes in pulse was observed in both the titration and maintenance phases as well as persisting into the maintenance period after developing in the titration phase.

Elevation of blood pressure and/or changes in heart rate in patients taking ropinirole extended-release tablets should be considered when treating patients with cardiovascular disease.

5.5 Hallucinations/Psychotic-like Behavior

In the double-blind, placebo-controlled, advanced Parkinson's disease trial 8% (17 of 202) of patients receiving ropinirole extended-release tablets reported hallucination compared with 2% (4 of 191) patients receiving placebo *[see Adverse Reactions (6.1)]*. Hallucination led to discontinuation of treatment in 2% (4 of 202) of patients on ropinirole extended-release tablets and 1% (2 of 191) of patients on placebo.

The incidence of hallucination is increased in elderly patients (i.e., older than 65 years) treated with ropinirole extended-release tablets *[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 extended-release tablets 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 extended-release tablets *[see Drug Interactions (7.3)]*.

5.6 Dyskinesia

Ropinirole extended-release tablets 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 the double-blind, placebo-controlled trial in patients with advanced Parkinson's disease dyskinesia was reported as an adverse event in 13% of patients taking ropinirole extended-release tablets and 3% of patients on placebo *[see Adverse Reactions (6.1)]*. Decreasing the dose of a dopaminergic drug may ameliorate this side effect.

5.7 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 extended-release tablets, that increase central dopaminergic tone and that are generally used for the treatment of Parkinson's disease. 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 extended-release tablets. Physicians should consider dose reduction or stopping the medication if a patient develops such urges while taking ropinirole extended-release tablets.

5.8 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 extended-release tablets as a prophylactic measure *[see Dosage and Administration (2.2)]*.

5.9 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. In the clinical development program (N = 613), one patient treated with ropinirole extended-release tablets and also levodopa/carbidopa developed melanoma.

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

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. In the clinical development program (N = 613), 2 patients treated with ropinirole extended-release tablets had pleural effusion. 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) of 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 trial of immediate-release ropinirole in patients with Parkinson's disease; 156 patients (78 on immediate-release 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

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)]*
- Elevation of Blood Pressure and Changes in Heart Rate *[see Warnings and Precautions (5.4)]*
- Hallucinations/Psychotic-like Behavior *[see Warnings and Precautions (5.5)]*
- Dyskinesia *[see Warnings and Precautions (5.6)]*
- Impulse Control/Compulsive Behaviors *[see Warnings and Precautions (5.7)]*
- Withdrawal-emergent Hyperpyrexia and Confusion *[see Warnings and Precautions (5.8)]*
- Melanoma *[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.

During the premarketing development of ropinirole extended-release tablets, patients with advanced Parkinson's disease received ropinirole extended-release tablets or placebo as adjunctive therapy in 1 clinical trial. In a second trial, patients with early Parkinson's disease were treated with ropinirole extended-release tablets or the immediate-release formulation of ropinirole tablets without L-dopa.

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Advanced Parkinson's Disease (with L-dopa)

In the 24-week, double-blind, placebo-controlled trial for the treatment of advanced Parkinson's disease, the most commonly observed adverse reactions in patients treated with ropinirole extended-release tablets (incidence at least 5% greater than placebo) were dyskinesia, nausea, dizziness and hallucination.

Approximately 6% of patients treated with ropinirole extended-release tablets discontinued treatment due to adverse reactions compared with 5% of patients who received placebo. The most common adverse reaction in patients treated with ropinirole extended-release tablets causing discontinuation of treatment with ropinirole extended-release tablets was hallucination (2%)

Table 2 lists treatment-emergent adverse reactions that occurred in at least 2% (and were numerically greater than placebo) of patients with advanced Parkinson's disease treated with ropinirole extended-release tablets who participated in the 26-week, double-blind, placebo-controlled trial. In this trial, either ropinirole extended-release tablets or placebo was used as an adjunct to L-dopa.

Table 2. Treatment-Emergent Adverse Reaction Incidence in a Double-Blind, Placebo-Controlled Trial in Advanced Stage Parkinson's Disease (With L-dopa) (Events ≥2% of Patients Treated with Ropinirole Extended-Release Tabletsand >% with Placebo)[a]

Body System/Adverse Reaction	**Ropinirole Extended-Release Tablets (n = 202) %**	**Placebo (n = 191) %**
Ear and labyrinth disorders		
Vertigo	4	2
Gastrointestinal disorders		
Nausea	11	4
Constipation	4	2
Abdominal pain/discomfort	6	3
Diarrhea	3	2
Dry mouth	2	<1
General disorders		
Edema peripheral	4	1
Injury, poisoning, and procedural complication		
Fall*	2	1
Musculoskeletal and connective tissue disorders		
Back pain	3	2
Nervous system disorders		
Dyskinesia[b]	13	3

Dizziness	8	3
Somnolence	7	4
Psychiatric disorders		
Hallucination	8	2
Anxiety	2	1
Vascular disorders		
Orthostatic hypotension	5	1
Hypotension	2	0
Hypertension[b]	3	2

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

[b]Dose-related.

Although this trial was not designed for optimally characterizing dose-related adverse reactions, there was a suggestion (based upon comparison of incidence of adverse reactions across dose ranges for ropinirole extended-release tablets and placebo) that the incidence for dyskinesia, hypertension, and fall was dose-related to ropinirole extended-release tablets.

The incidence for many adverse reactions with ropinirole extended-release tablets treatment was increased relative to placebo (i.e., the incidence in the group receiving ropinirole extended-release tablets was 2% or greater than placebo in either the titration or maintenance phases of the trial. During the titration phase, an increased incidence (shown in descending order of % treatment difference) was observed for dyskinesia, nausea, abdominal pain/discomfort, orthostatic hypotension, dizziness, vertigo, hypertension, peripheral edema, and dry mouth. During the maintenance phase, an increased incidence was observed for dyskinesia, nausea, dizziness, hallucination, somnolence, fall, hypertension, abnormal dreams, constipation, chest pain, bronchitis, and nasopharyngitis. Some adverse reactions developing in the titration phase persisted

(³7 days) into the maintenance phase. These “persistent” adverse reactions included dyskinesia, hallucination, orthostatic hypotension, and dry mouth.

The incidence of adverse reactions was not clearly different between women and men.

Early Parkinson’s Disease (without L-dopa)

In the 36–week early Parkinson’s disease trial the most commonly observed adverse reactions in patients treated with ropinirole extended-release tablets (≥5%) were nausea (19%), somnolence (11%), abdominal pain/discomfort (7%), dizziness (6%), headache (6%), and constipation (5%). The type of adverse reactions and the frequency (i.e. incidence) with which they occurred were generally similar over the whole treatment period in this trial of early Parkinson’s disease patients who were initially treated with ropinirole extended-release tablets or the immediate-release formulation of ropinirole tablets and subsequently crossed over to treatment with the other formulation.

During the titration phase, an increased incidence with ropinirole extended-release tablets compared with the immediate-release formulation of ropinirole tablets (i.e., the incidence in ropinirole extended-release tablets was 2% or greater than immediate-release ropinirole tablets), shown in descending order of % treatment difference, was observed for: constipation, hallucination, vertigo, abdominal pain/discomfort, nausea, vomiting, fall, headache, diarrhea, pyrexia, and flatulence. During the maintenance phase, an increased incidence was observed for fall, myalgia, and sleep disorder. Several adverse reactions developing in the titration phase persisted (³7 days) into the maintenance phase. These “persistent” adverse reactions included: constipation, hallucination, muscle spasms, flatulence, insomnia,

sleep disorder, abdominal pain/discomfort, cough, and nasopharyngitis.

6.2 Adverse Reactions Observed during the Clinical Development of the Immediate-release Formulation of Ropinirole Tablets for Parkinson's Disease (Advanced and Early)

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.

In patients with advanced Parkinson's disease who were treated with the immediate-release formulation of ropinirole tablets, the most common adverse reactions (³5% treatment difference from placebo; presented in order of decreasing treatment difference frequency) were dyskinesia (21%), somnolence (12%), nausea (12%), dizziness (10%), confusion (7%), hallucinations (6%), headache (5%), and increased sweating (5%). In patients with early Parkinson's disease who were treated with the immediate-release formulation of ropinirole tablets, the most common adverse reactions (³5% treatment difference from placebo; presented in order of decreasing treatment difference frequency) were nausea (38%), somnolence (34%), dizziness (18%), syncope (11%), asthenic condition (11%), viral infection (8%), leg edema (6%), vomiting (5%), and dyspepsia (5%).

7 DRUG INTERACTIONS

7.1 CYP1A2 Inhibitors and Inducers

In vitro metabolism studies showed that CYP1A2 is 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 extended-release tablets, adjustment of the dose of ropinirole extended-release tablets may be required. Coadministration of ciprofloxacin, an inhibitor of CYP1A2, with immediate-release ropinirole 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 extended-release tablets *[see Clinical Pharmacology (12.3)]*.

7.3 Dopamine Antagonists

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 extended-release tablets.

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 extended-release tablets 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^2 basis.

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^2 basis. 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^2 basis.

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 the pediatric population 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 extended-release tablets 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 above 65 years compared with younger patients *[see Clinical Pharmacology (12.3)]*.

In clinical trials of ropinirole extended-release tablets for Parkinson's disease, 387 patients were 65 years and older and 107 were 75 and older. Among patients receiving ropinirole extended-release tablets, 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 ropinirole extended-release tablets 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), Clinical Pharmacology (12.3)]*. The use of ropinirole extended-release tablets 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.

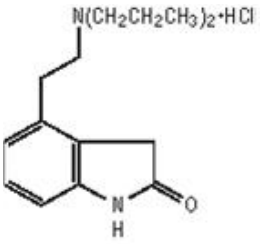
10 OVERDOSAGE

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 immediate-release 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 extended-release tablets 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 empirical 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 capsule shaped, film coated tablet contains 2.28 mg, 4.56 mg, 6.84 mg, 9.12 mg, or 13.68 mg ropinirole hydrochloride equivalent to ropinirole 2 mg, 4 mg, 6 mg, 8 mg, or 12 mg, respectively. Inactive ingredients consist of carboxymethylcellulose sodium, colloidal silicon dioxide, hydrogenated castor oil, hypromellose, magnesium stearate, povidone, pregelatinized starch, ethylcellulose and one or more of the following: FD&C Blue No. 2 aluminum lake, ferric oxides (black, red, yellow), polyethylene glycol 6000, polyethylene glycol 8000, titanium dioxide, talc.

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-type receptors within the caudate-putamen in the brain.

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 subjects 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.

Immediate-release 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.

Immediate-release ropinirole had no dose- or exposure-related effect on mean QTc 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

Increase in systemic exposure of ropinirole following oral administration of 2 to 12 mg of ropinirole extended-release tablets was approximately dose-proportional. For ropinirole extended-release tablets, steady-state concentrations of ropinirole are expected to be achieved within 4 days of dosing.

Absorption

In clinical trials with immediate-release ropinirole, over 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 of ropinirole extended-release tablets compared with immediate-release tablets was approximately 100%. In a repeat-dose trial in subjects with Parkinson's disease using ropinirole extended-release tablets 8 mg, the dose-normalized $AUC_{(0-24)}$ and C_{min} for ropinirole extended-release tablets and immediate-release ropinirole were similar. Dose-normalized C_{max} was, on average, 12% lower for ropinirole extended-release tablets than for the immediate-release formulation and the median time-to-peak concentration was 6 to 10 hours. In a single-dose trial, administration of ropinirole extended-release tablets to healthy volunteers with food (i.e., high-fat meal) increased AUC by approximately 30% and C_{max} by approximately 44%, compared with dosing under fasted conditions. In a repeat-dose trial in patients with Parkinson's disease, food (i.e., high-fat meal) increased AUC by approximately 20% and C_{max} by approximately 44%; T_{max} was prolonged by 3 hours (median prolongation) compared with dosing under fasted conditions *[see Dosage and Administration (2)]*.

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 to patients is 47 L/hr 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 immediate-release 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 immediate-release ropinirole (2 mg three times daily) in 12 patients with Parkinson's disease. Immediate-release 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 immediate-release 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 immediate-release ropinirole (2 mg three times daily) had no effect on the steady-state pharmacokinetics of ropinirole (n = 28 patients). Oral administration of immediate-release 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.

Specific Populations

Because therapy with ropinirole extended-release tablets is initiated at a low dose and gradually titrated upward according to clinical tolerability to obtain the optimum therapeutic effect, adjustment of the initial dose based on gender, weight, or age is not necessary.

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 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 trial in patients with Restless Legs Syndrome, 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 subjects 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.

A trial of immediate-release 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)]*.

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

Hepatic Impairment: 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.

Other Diseases: 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 with 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 oral doses of 5, 15, and 50

mg/kg/day and rats at oral 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^2 basis. 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, or 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 oral doses of 20 mg/kg/day (8 times the MRHD on a mg/m^2 basis) or greater. This effect in rats is thought to be due to the prolactin-lowering effect of ropinirole. In rat studies 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 oral doses up to 125 mg/kg/day (50 times the MRHD on a mg/m^2 basis).

14 CLINICAL STUDIES

The effectiveness of ropinirole was initially established with the immediate-release formulation (ropinirole tablets) for the treatment of early and advanced Parkinson's disease in three randomized, double-blind, placebo-controlled trials.

The effectiveness of ropinirole extended-release tablets in the treatment of Parkinson's disease was supported by two randomized, double-blind, multicenter clinical trials and clinical pharmacokinetic considerations. One trial conducted in patients with advanced Parkinson's disease compared ropinirole extended-release tablets with placebo as adjunctive therapy to L-dopa. A second trial compared ropinirole extended-release tablets with ropinirole tablets in patients with early phase Parkinson's disease not receiving L-dopa.

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

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

The effectiveness of ropinirole extended-release tablets as adjunctive therapy to L-dopa in patients with Parkinson's disease was established in a randomized, double-blind, placebo-controlled, parallel group, 24-week clinical trial in 393 patients (Hoehn & Yahr criteria Stages II-IV) who were not adequately controlled by L-dopa therapy. Patients were allowed to be on concomitant selegiline, amantadine, anticholinergics, and catechol-O-methyltransferase (COMT) inhibitors provided the doses were stable for at least 4 weeks prior to screening and throughout the trial. The primary efficacy endpoint evaluated was the mean change from baseline in total awake time spent "off".

Patients in this trial had a mean disease duration of 8.6 years, a mean duration of exposure to L-dopa of 6.5 years, had experienced a minimum of 3 hours awake time "off" with a baseline average of approximately 7 hours awake time "off", and had a mean baseline UPDRS motor score of approximately 30 points with similar mean data in each treatment group. The mean baseline dose of L-dopa in the group

receiving ropinirole extended-release tablets was 824 mg/day and 776 mg/day for the placebo group. Patients initiated treatment at 2 mg/day for 1 week followed by increases of 2 mg/day at weekly intervals to a minimum dose of 6 mg/day. The following week, the total daily dose of ropinirole extended-release tablets could be further increased (based upon therapeutic response and tolerability) to 8 mg/day. Once a daily dose of 8 mg/day was reached, the background L-dopa dosage was reduced. Thereafter, the daily dose could be increased by up to 4 mg/day approximately every 2 weeks until an optimal dose was achieved (based upon therapeutic response and tolerability). The mean dose of ropinirole extended-release tablets at the end of Week 24 was 18.8 mg/day. Dose titrations were based upon the degree of symptom control, planned L-dopa dosage reduction, and/or tolerability. The maximum allowed daily dosage for ropinirole extended-release tablets was 24 mg/day.

The primary efficacy endpoint was mean change from baseline in total awake time spent “off” at Week 24. At baseline the mean total awake time spent “off” was approximately 7 hours in each treatment group. At Week 24, the total awake time spent “off”, on average, had decreased by approximately 2 hours in the group receiving ropinirole extended-release tablets and by approximately half an hour in the placebo group. The adjusted mean difference in total awake time spent “off” between ropinirole extended-release tablets and placebo was -1.7 hours, which was statistically significant (ANCOVA, $P<0.0001$). Results for this endpoint showing the statistical superiority of ropinirole extended-release tablets over placebo are presented in Table 3.

Table 3. Change from Baseline in Total Awake Time Spent “Off” at Week 24

	Ropinirole Extended-Release Tablets (n = 201)	**Placebo (n = 190)**
Mean “off” time at baseline (hours)	7	7
Mean change from baseline in “off” time (hours)	-2.1	-0.4

The difference between groups in favor of ropinirole extended-release tablets, with regard to a decrease in total “off” hours, was primarily related to an increase in total “on” hours without troublesome dyskinesia. Patients treated with ropinirole extended-release tabletshad a mean reduction in L-dopa dose of 278 mg/day (34%) while patients treated with placebo had a mean reduction of 164 mg/day (21%). In patients who reduced their L-dopa dose, reduction was sustained in 93% of patients treated with ropinirole extended-release tabletsand in 72% of patients treated with placebo ($P<0.001$).

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

A 36-week multicenter, double-blind, titration/3-period maintenance, cross-over study compared the efficacy of ropinirole extended-release tabletswith the immediate-release formulation of ropinirole tablets(IR) in 161 patients with early phase Parkinson’s disease (Hoehn & Yahr Stages I-III) with limited prior exposure to L-dopa or dopamine agonists. Eligible subjects were randomized (1:1:1:1) to 4 treatment sequences (2 were titrated on ropinirole tabletsIR and 2 on ropinirole extended-release tablets). Titration rate of ropinirole tablets IR was slower than that of the ropinirole extended-release tablets. Patients were titrated, during the 12-week titration period, to their optimal dosage, based upon tolerance and therapeutic response. This was followed by three consecutive 8-week maintenance periods, during which patients were either maintained on the prior formulation or switched to the alternative formulation. All switches were performed overnight by using the approximately equivalent doses of ropinirole. The primary efficacy endpoint was the change of UPDRS motor score within each maintenance period.

Patients in all four groups started out with similar UPDRS motor scores (about 21) at baseline. All 4 groups exhibited similar improvement in UPDRS total motor scores from baseline until the completion of the titration phase, with a change in score of about -9 observed for the groups started on ropinirole tabletsIR and of about -10 for the groups started on ropinirole extended-release tablets. No difference

was observed between groups when switches were made between identical formulations or between different formulations. This suggests therapeutic dosage equivalence betweenformulations of ropinirole tabletsIR and ropinirole extended-release tabletsformulations.

The optimal daily dose at the end of the titration period for patients on ropinirole tabletsIR was substantially lower (mean 7 mg) compared with the dose at the end of the titration period for patients on ropinirole extended-release tablets(mean 18 mg). In this trial, the marked difference in the final optimal dosages suggests that the higher doses afforded no additional benefit when compared with the lower doses *[see Dosage and Administration (2.2)]*.

16 HOW SUPPLIED/STORAGE AND HANDLING

Each capsule shaped, film coated tablet contains ropinirole hydrochloride equivalent to the labeled amount of ropinirole as follows:

2 mg: pink tablets debossed with 'L191'

NDC 46708-262-30 bottle of 30 tablets

NDC 46708-262-90 bottle of 90 tablets

NDC 46708-262-31 bottle of 100 tablets
NDC 46708-262-71 bottle of 500 tablets
NDC 46708-262-91 bottle of 1000 tablets

NDC 46708-262-10 carton of 100 (10X10) unit dose tablets

4 mg: light brown tablets debossed with 'L193'

NDC 46708-263-30 bottle of 30 tablets

NDC 46708-263-90 bottle of 90 tablets

NDC 46708-263-31 bottle of 100 tablets
NDC 46708-263-71 bottle of 500 tablets
NDC 46708-263-91 bottle of 1000 tablets

NDC 46708-263-10 carton of 100 (10X10) unit dose tablets

6 mg: white to off white tablets debossed with 'L321'

NDC 46708-264-30 bottle of 30 tablets

NDC 46708-264-90 bottle of 90 tablets

NDC 46708-264-31 bottle of 100 tablets
NDC 46708-264-71 bottle of 500 tablets
NDC 46708-264-91 bottle of 1000 tablets

NDC 46708-264-10 carton of 100 (10X10) unit dose tablets

8 mg: dark brown to red tablets debossed with 'L194'

NDC 46708-265-30 bottle of 30 tablets

NDC 46708-265-90 bottle of 90 tablets

NDC 46708-265-31 bottle of 100 tablets
NDC 46708-265-71 bottle of 500 tablets
NDC 46708-265-91 bottle of 1000 tablets

NDC 46708-265-10 carton of 100 (10X10) unit dose tablets

12 mg: light green tablets debossed with 'L195'

NDC 46708-266-30 bottle of 30 tablets

NDC 46708-266-90 bottle of 90 tablets

NDC 46708-266-31 bottle of 100 tablets
NDC 46708-266-71 bottle of 500 tablets
NDC 46708-266-91 bottle of 1000 tablets

NDC 46708-266-10 carton of 100 (10X10) unit dose tablets

Storage

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.

17 PATIENT COUNSELING INFORMATION

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

Dosing Instructions

- Instruct patients to take ropinirole extended-release tablets only as prescribed. If a dose is missed, advise patients not to double their next dose. Ropinirole extended-release tablets can be taken with or without food. Inform patients to swallow ropinirole extended-release tablets whole and not to chew, crush, or divide the tablets *[see Dosage and Administration (2.1)]*.
- Ropinirole is the active ingredient in both ropinirole extended-release tablets and ropinirole tablets (the immediate-release formulation). 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 after starting ropinirole tablets or ropinirole extended-release tablets, 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 extended-release tablets, 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 extended-release tablets 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 extended-release tablets 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 extended-release tablets, 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 extended-release tablets*[see Warnings and Precautions (5.2, 5.3)]*.

Elevation of Blood Pressure and Changes in Heart Rate

Alert patients to the possibility of increases in blood pressure during treatment with ropinirole extended-release tablets. Exacerbation of hypertension may occur. Medication dose adjustment may be necessary if elevation of blood pressure is sustained over multiple evaluations. Alert patients with cardiovascular disease, who may not tolerate marked changes in heart rate, to the possibility that they may experience significant increases or decreases in heart rate during treatment with ropinirole extended-release tablets*[see Warnings and Precautions (5.4)]*.

Hallucinations/Psychotic-like Behavior

Inform patients that they may experience hallucinations (unreal visions, sounds, or sensations) and 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 (5.5)]*.

Dyskinesia

Inform patients that ropinirole extended-release tablets may cause and/or exacerbate pre-existing dyskinesias *[see Warnings and Precautions (5.6)]*.

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 extended-release tablets) 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 extended-release tablets. Physicians should consider dose reduction or stopping the medication if a patient develops such urges while taking ropinirole extended-release tablets*[see Warnings and Precautions (5.7)]*.

Withdrawal-emergent Hyperpyrexia and Confusion

Advise patients to contact their healthcare provider if they wish to discontinue ropinirole extended-release tablets or decrease the dose of ropinirole extended-release tablets *[see Warnings and Precautions (5.8)]*.

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 extended-release tablets*[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 extended-release tablets 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, advice 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

Ropinirole Extended-Release Tablets

Important Note: Ropinirole extended-release tablets have not been studied in Restless Legs Syndrome (RLS) and are not approved for the treatment of RLS. However, an immediate-release form of ropinirole is approved for the treatment of moderate to severe primary RLS.

Read this information completely before you start taking ropinirole extended-release tablets.
Read the information each time you get more medicine. There may be new information. This leaflet provides a summary about ropinirole extended-release tablets. 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 extended-release tablets.

What is the most important information I should know about ropinirole extended-release tablets?
Ropinirole extended-release tablets 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 extended-release tablets 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 extended-release tablets. 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 extended-release tablets are greater if you take other medicines that cause drowsiness. Tell your healthcare provider right away if this happens. Before starting ropinirole extended-release tablets, 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 extended-release tablets or your dose is increased. Tell your healthcare provider if you faint or feel dizzy or light-headed.
• **Decrease in blood pressure.** Ropinirole extended-release tablets can decrease your blood pressure. Decreases in your blood pressure (hypotension) can happen, especially when you start taking ropinirole extended-release tablets 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 extended-release tablets may increase your blood pressure.
• **Changes in heart rate (decrease or increase).** Ropinirole extended-release tablets can decrease or increase your heart rate.
• **Hallucinations and other psychotic-like behavior.** Ropinirole extended-release tablets 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 extended-release tablets 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 extended-release tablets 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 medicines may need to be changed.
•**Unusual urges.** Some patients taking ropinirole extended-release tablets 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 extended-release tablets increase 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 are ropinirole extended-release tablets?
Ropinirole extended-release tablets are long-acting prescription medicine containing ropinirole (taken 1

time a day) that is used only to treat Parkinson's disease but not to treat 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 extended-release tablets are safe and effective for use in children younger than 18 years of age.

Who should not take ropinirole extended-release tablets?
Do not take ropinirole extended-release tablets if you:
• are allergic to ropinirole or any of the ingredients in ropinirole extended-release tablets. See the end of this page for a complete list of the ingredients in ropinirole extended-release tablets.
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 extended-release tablets?
Before you take ropinirole extended-release tablets, 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 extended-release tablets.
• start or stop taking other medicines while you are taking ropinirole extended-release tablets. This may increase your chances of getting side effects.
• start or stop smoking while you are taking ropinirole extended-release tablets. Smoking may decrease the treatment effect of ropinirole extended-release tablets.
• feel dizzy, nauseated, sweaty, or faint when you first stand up from sitting or lying down.
• drink alcoholic beverages. This may increase your chances of becoming drowsy or sleepy while taking ropinirole extended-release tablets.
• have high or low blood pressure.
• have or have had heart problems.
• are pregnant or plan to become pregnant. Ropinirole extended-release tablets should only be used during pregnancy if needed.
• are breastfeeding. It is not known if ropinirole extended-release tablets passes into your breast milk. Talk to your healthcare provider to decide whether you will breastfeed or take ropinirole extended-release tablets.
• have any other medical conditions.

How should I take ropinirole extended-release tablets for Parkinson's disease?
• Take ropinirole extended-release tablets exactly as directed by your healthcare provider.
• **Do not** suddenly stop taking ropinirole extended-release tablets without talking to your healthcare provider. If you stop this medicine suddenly, you may develop fever, confusion, or severe muscle stiffness.
• Before starting ropinirole extended-release tablets, 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 extended-release tablets. 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 extended-release tablets:
• Take ropinirole extended-release tablets 1 time each day for Parkinson's disease, preferably at or around the same time of day.
• Swallow ropinirole extended-release tablets whole. Do not chew, crush, or split ropinirole extended-release tablets.
• Ropinirole extended-release tablets release drug over a 24-hour period. If you have a condition where medicine passes through your body too quickly, such as diarrhea, the tablet(s) may not dissolve completely and you may see tablet residue in your stool. If this happens, let your healthcare provider know as soon as possible.
• Contact your healthcare provider if you stop taking ropinirole extended-release tablets for any reason.

Do not restart without talking with your healthcare provider.
• Your healthcare provider may prescribe ropinirole extended-release tablets alone, or add ropinirole extended-release tablets to medicine that you are already taking for Parkinson's disease.
• You should not substitute ropinirole extended-release tablets for ropinirole tablets without talking with your healthcare provider.
• You can take ropinirole extended-release tablets with or without food.

What are the possible side effects of ropinirole extended-release tablets?
Ropinirole extended-release tablets can cause serious side effects including:
See "What is the most important information I should know about ropinirole extended-release tablets?"
The most common side effects of ropinirole extended-release tablets 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 extended-release tablets?

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

Keep ropinirole extended-release tablets and all medications out of reach of children.

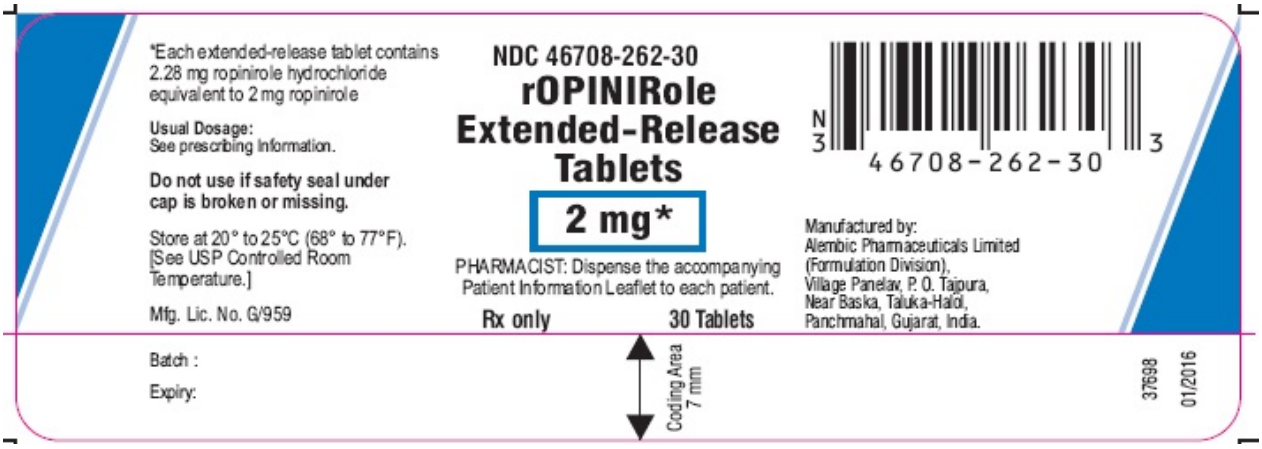
General information about the safe and effective use of ropinirole extended-release tablets:
Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not take ropinirole extended-release tablets for a condition for which it was not prescribed. Do not give ropinirole extended-release tablets 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 extended-release tablets 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 extended-release tablets that is written for healthcare professionals.

What are the ingredients in ropinirole extended-release tablets?
Active ingredient: ropinirole (as ropinirole hydrochloride)
Inactive ingredients: carboxymethylcellulose sodium, colloidal silicon dioxide, hydrogenated castor oil, hypromellose, magnesium stearate, povidone, pregelatinized starch, ethylcellulose and one or more of the following: FD&C Blue No. 2 aluminum lake, ferric oxides (black, red, yellow), polyethylene glycol 6000, polyethylene glycol 8000, titanium dioxide, talc.
This Patient Information has been approved by the U.S. Food and Drug Administration.

Manufactured by:
Alembic Pharmaceuticals Limited (Formulation Division),
Village Panelav, P. O. Tajpura, Near Baska,
Taluka-Halol, Panchmahal, Gujarat, India.
Revised: 01/2016

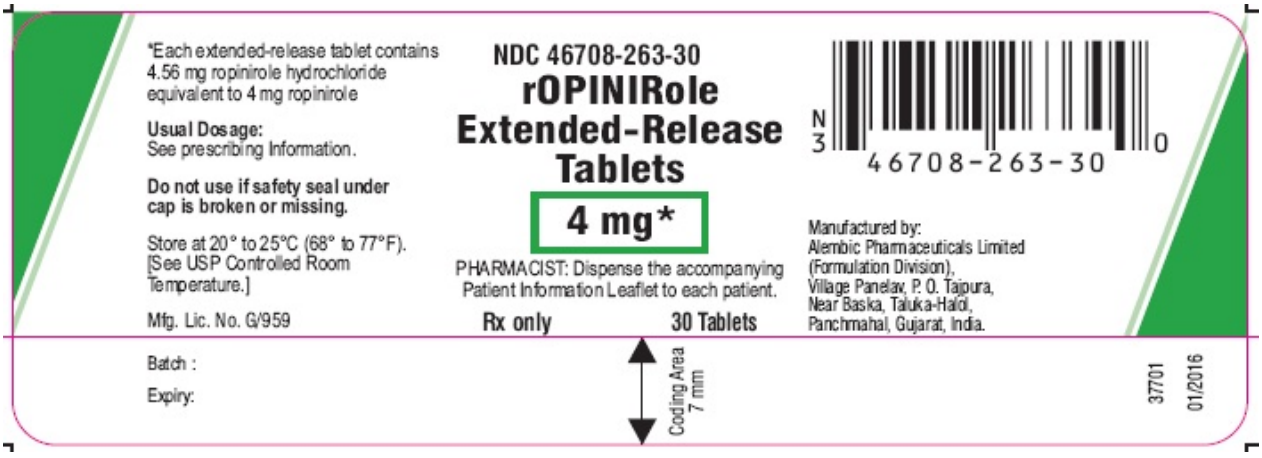
PACKAGE LABEL.PRINCIPAL DISPLAY PANEL - 2mg

rOPINIRole Extended-Release Tablets 2 mg* (30 Tablets in 1 Bottle)
*Each extended-release tablet contains 2.28 mg ropinirole hydrochloride equivalent to 2 mg ropinirole
46708-262-30



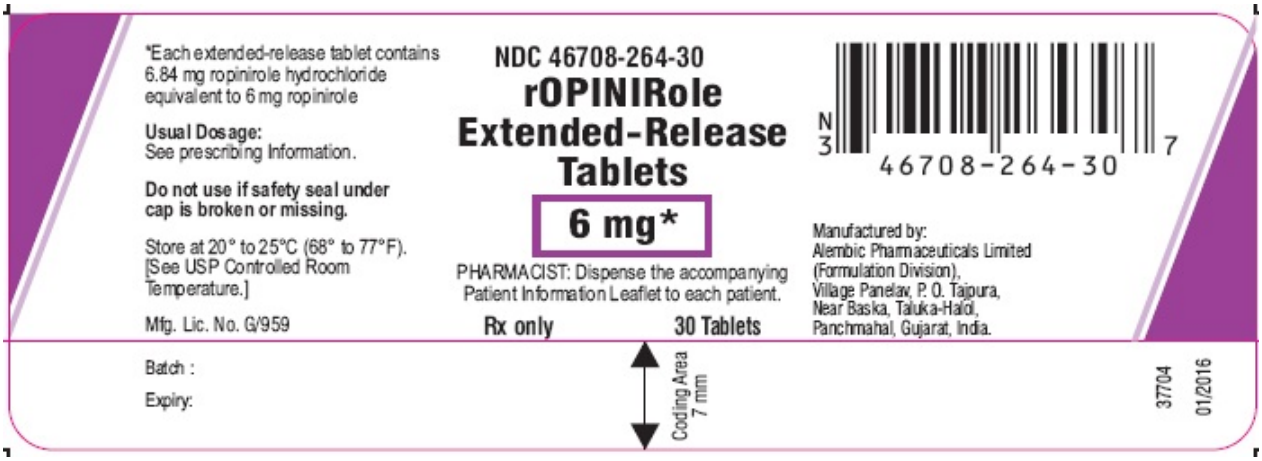
PACKAGE LABEL.PRINCIPAL DISPLAY PANEL - 4mg

rOPINIRole Extended-Release Tablets 4 mg* (30 Tablets in 1 Bottle)
*Each extended-release tablet contains 4.56 mg ropinirole hydrochloride equivalent to 4 mg ropinirole
46708-263-30



PACKAGE LABEL.PRINCIPAL DISPLAY PANEL - 6mg

rOPINIRole Extended-Release Tablets 6 mg* (30 Tablets in 1 Bottle)
*Each extended-release tablet contains 6.84 mg ropinirole hydrochloride equivalent to 6 mg ropinirole
46708-264-30

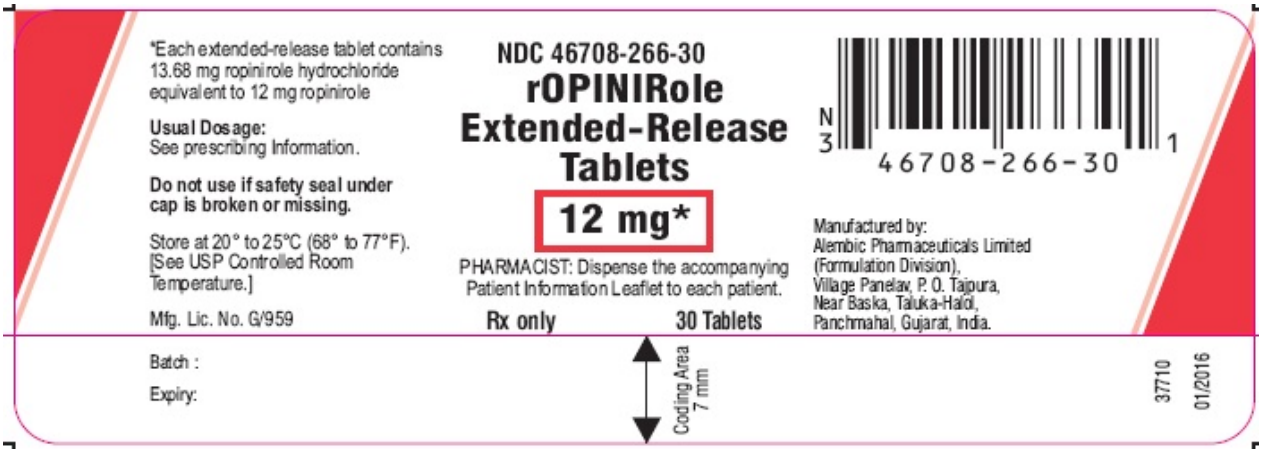


PACKAGE LABEL.PRINCIPAL DISPLAY PANEL - 8mg

rOPINIRole Extended-Release Tablets 8 mg* (30 Tablets in 1 Bottle)
*Each extended-release tablet contains 9.12 mg ropinirole hydrochloride equivalent to 8 mg ropinirole
46708-265-30

PACKAGE LABEL.PRINCIPAL DISPLAY PANEL - 12mg

rOPINIRole Extended-Release Tablets 12 mg* (30 Tablets in 1 Bottle)
*Each extended-release tablet contains 13.68 mg ropinirole hydrochloride equivalent to 12 mg ropinirole
46708-266-30



ROPINIROLE

ropinirole tablet, film coated, extended release

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:46708-262
Route of Administration	ORAL		

Active Ingredient/Active Moiety		
Ingredient Name	**Basis of Strength**	**Strength**
ROPINIROLE HYDROCHLORIDE (UNII: D7ZD41RZI9) (ROPINIROLE - UNII:030PYR8953)	ROPINIROLE	2 mg

Inactive Ingredients	
Ingredient Name	**Strength**
HYPROMELLOSE, UNSPECIFIED (UNII: 3NXW29V3WO)	
HYDROGENATED CASTOR OIL (UNII: ZF94AP8MEY)	
CARBOXYMETHYLCELLULOSE SODIUM (UNII: K679OBS311)	
STARCH, CORN (UNII: O8232NY3SJ)	
POVIDONE, UNSPECIFIED (UNII: FZ989GH94E)	
SILICON DIOXIDE (UNII: ETJ7Z6XBU4)	
MAGNESIUM STEARATE (UNII: 70097M6I30)	
ETHYLCELLULOSE (7 MPA.S) (UNII: H3UP11403C)	
TITANIUM DIOXIDE (UNII: 15FIX9V2JP)	
POLYETHYLENE GLYCOL 6000 (UNII: 30IQX730WE)	
TALC (UNII: 7SEV7J4R1U)	
FERRIC OXIDE RED (UNII: 1K09F3G675)	

Product Characteristics			
Color	PINK	**Score**	no score
Shape	CAPSULE	**Size**	12mm
Flavor		**Imprint Code**	L191
Contains			

Packaging				
#	**Item Code**	**Package Description**	**Marketing Start Date**	**Marketing End Date**
1	NDC:46708-262-30	30 in 1 BOTTLE; Type 0: Not a Combination Product	03/14/2013	
2	NDC:46708-262-90	90 in 1 BOTTLE; Type 0: Not a Combination Product	03/14/2013	
3	NDC:46708-262-31	100 in 1 BOTTLE; Type 0: Not a Combination Product	03/14/2013	
4	NDC:46708-262-91	1000 in 1 BOTTLE; Type 0: Not a Combination Product	03/14/2013	
5	NDC:46708-262-10	100 in 1 CARTON; Type 0: Not a Combination Product	03/14/2013	
6	NDC:46708-262-71	500 in 1 BOTTLE; Type 0: Not a Combination Product	03/14/2013	

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA202786	03/14/2013	

ROPINIROLE

ropinirole tablet, film coated, extended release

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:46708-263
Route of Administration	ORAL		

Active Ingredient/Active Moiety		
Ingredient Name	**Basis of Strength**	**Strength**
ROPINIROLE HYDROCHLORIDE (UNII: D7ZD41RZI9) (ROPINIROLE - UNII:030PYR8953)	ROPINIROLE	4 mg

Inactive Ingredients	
Ingredient Name	**Strength**
HYPROMELLOSE, UNSPECIFIED (UNII: 3NXW29V3WO)	
HYDROGENATED CASTOR OIL (UNII: ZF94AP8MEY)	
CARBOXYMETHYLCELLULOSE SODIUM (UNII: K679OBS311)	
STARCH, CORN (UNII: O8232NY3SJ)	
POVIDONE, UNSPECIFIED (UNII: FZ989GH94E)	
SILICON DIOXIDE (UNII: ETJ7Z6XBU4)	
MAGNESIUM STEARATE (UNII: 70097M6I30)	
ETHYLCELLULOSE (7 MPA.S) (UNII: H3UP11403C)	
TITANIUM DIOXIDE (UNII: 15FIX9V2JP)	
POLYETHYLENE GLYCOL 8000 (UNII: Q662QK8M3B)	
FERRIC OXIDE YELLOW (UNII: EX438O2MRT)	
FERRIC OXIDE RED (UNII: 1K09F3G675)	

Product Characteristics			
Color	BROWN (Light Brown)	**Score**	no score
Shape	CAPSULE	**Size**	12mm
Flavor		**Imprint Code**	L193
Contains			

Packaging				
#	**Item Code**	**Package Description**	**Marketing Start Date**	**Marketing End Date**
1	NDC:46708-263-30	30 in 1 BOTTLE; Type 0: Not a Combination Product	03/14/2013	
2	NDC:46708-263-90	90 in 1 BOTTLE; Type 0: Not a Combination Product	03/14/2013	
3	NDC:46708-263-31	100 in 1 BOTTLE; Type 0: Not a Combination Product	03/14/2013	
4	NDC:46708-263-91	1000 in 1 BOTTLE; Type 0: Not a Combination Product	03/14/2013	
5	NDC:46708-263-10	100 in 1 CARTON; Type 0: Not a Combination Product	03/14/2013	
6	NDC:46708-263-71	500 in 1 BOTTLE; Type 0: Not a Combination Product	03/14/2013	

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA202786	03/14/2013	

ROPINIROLE

ropinirole tablet, film coated, extended release

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:46708-264
Route of Administration	ORAL		

Active Ingredient/Active Moiety		
Ingredient Name	**Basis of Strength**	**Strength**
ROPINIROLE HYDROCHLORIDE (UNII: D7ZD41RZI9) (ROPINIROLE - UNII:030PYR8953)	ROPINIROLE	6 mg

Inactive Ingredients	
Ingredient Name	**Strength**
MAGNESIUM STEARATE (UNII: 70097M6I30)	
ETHYLCELLULOSE (7 MPA.S) (UNII: H3UP11403C)	
TITANIUM DIOXIDE (UNII: 15FIX9V2JP)	
POLYETHYLENE GLYCOL 8000 (UNII: Q662QK8M3B)	
HYPROMELLOSE, UNSPECIFIED (UNII: 3NXW29V3WO)	
HYDROGENATED CASTOR OIL (UNII: ZF94AP8MEY)	
CARBOXYMETHYLCELLULOSE SODIUM (UNII: K679OBS311)	
STARCH, CORN (UNII: O8232NY3SJ)	
POVIDONE, UNSPECIFIED (UNII: FZ989GH94E)	
SILICON DIOXIDE (UNII: ETJ7Z6XBU4)	

Product Characteristics			
Color	WHITE (White to off-White)	**Score**	no score
Shape	CAPSULE	**Size**	12mm
Flavor		**Imprint Code**	L321
Contains			

Packaging				
#	**Item Code**	**Package Description**	**Marketing Start Date**	**Marketing End Date**
1	NDC:46708-264-30	30 in 1 BOTTLE; Type 0: Not a Combination Product	03/14/2013	
2	NDC:46708-264-90	90 in 1 BOTTLE; Type 0: Not a Combination Product	03/14/2013	
3	NDC:46708-264-31	100 in 1 BOTTLE; Type 0: Not a Combination Product	03/14/2013	
4	NDC:46708-264-91	1000 in 1 BOTTLE; Type 0: Not a Combination Product	03/14/2013	
5	NDC:46708-264-10	100 in 1 CARTON; Type 0: Not a Combination Product	03/14/2013	
6	NDC:46708-264-71	500 in 1 BOTTLE; Type 0: Not a Combination Product	03/14/2013	

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA202786	03/14/2013	

ROPINIROLE

ropinirole tablet, film coated, extended release

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:46708-265

Route of Administration	ORAL

Active Ingredient/Active Moiety		
Ingredient Name	**Basis of Strength**	**Strength**
ROPINIROLE HYDROCHLORIDE (UNII: D7ZD41RZI9) (ROPINIROLE - UNII:030PYR8953)	ROPINIROLE	8 mg

Inactive Ingredients	
Ingredient Name	**Strength**
HYPROMELLOSE, UNSPECIFIED (UNII: 3NXW29V3WO)	
HYDROGENATED CASTOR OIL (UNII: ZF94AP8MEY)	
CARBOXYMETHYLCELLULOSE SODIUM (UNII: K679OBS311)	
STARCH, CORN (UNII: O8232NY3SJ)	
POVIDONE, UNSPECIFIED (UNII: FZ989GH94E)	
SILICON DIOXIDE (UNII: ETJ7Z6XBU4)	
MAGNESIUM STEARATE (UNII: 70097M6I30)	
ETHYLCELLULOSE (7 MPA.S) (UNII: H3UP11403C)	
TITANIUM DIOXIDE (UNII: 15FIX9V2JP)	
POLYETHYLENE GLYCOL 8000 (UNII: Q662QK8M3B)	
FERRIC OXIDE RED (UNII: 1K09F3G675)	
FERROSOFERRIC OXIDE (UNII: XM0M87F357)	

Product Characteristics			
Color	BROWN (Dark Brown to Red)	**Score**	no score
Shape	CAPSULE	**Size**	12mm
Flavor		**Imprint Code**	L194
Contains			

Packaging				
#	**Item Code**	**Package Description**	**Marketing Start Date**	**Marketing End Date**
1	NDC:46708-265-30	30 in 1 BOTTLE; Type 0: Not a Combination Product	03/14/2013	
2	NDC:46708-265-90	90 in 1 BOTTLE; Type 0: Not a Combination Product	03/14/2013	
3	NDC:46708-265-31	100 in 1 BOTTLE; Type 0: Not a Combination Product	03/14/2013	
4	NDC:46708-265-91	1000 in 1 BOTTLE; Type 0: Not a Combination Product	03/14/2013	
5	NDC:46708-265-10	100 in 1 CARTON; Type 0: Not a Combination Product	03/14/2013	
6	NDC:46708-265-71	500 in 1 BOTTLE; Type 0: Not a Combination Product	03/14/2013	

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA202786	03/14/2013	

ROPINIROLE

ropinirole tablet, film coated, extended release

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:46708-266
Route of Administration	ORAL		

Active Ingredient/Active Moiety		
Ingredient Name	**Basis of Strength**	**Strength**
ROPINIROLE HYDROCHLORIDE (UNII: D7ZD41RZI9) (ROPINIROLE - UNII:030PYR8953)	ROPINIROLE	12 mg

Inactive Ingredients	
Ingredient Name	**Strength**
HYPROMELLOSE, UNSPECIFIED (UNII: 3NXW29V3WO)	
HYDROGENATED CASTOR OIL (UNII: ZF94AP8MEY)	
CARBOXYMETHYLCELLULOSE SODIUM (UNII: K679OBS311)	
STARCH, CORN (UNII: O8232NY3SJ)	
POVIDONE, UNSPECIFIED (UNII: FZ989GH94E)	
SILICON DIOXIDE (UNII: ETJ7Z6XBU4)	
MAGNESIUM STEARATE (UNII: 70097M6I30)	
ETHYLCELLULOSE (7 MPA.S) (UNII: H3UP11403C)	
TITANIUM DIOXIDE (UNII: 15FIX9V2JP)	
POLYETHYLENE GLYCOL 6000 (UNII: 30IQX730WE)	
FERRIC OXIDE YELLOW (UNII: EX438O2MRT)	
FD&C BLUE NO. 2 (UNII: L06K8R7DQK)	

Product Characteristics			
Color	GREEN (Light Green)	**Score**	no score
Shape	CAPSULE	**Size**	12mm
Flavor		**Imprint Code**	L195
Contains			

Packaging				
#	**Item Code**	**Package Description**	**Marketing Start Date**	**Marketing End Date**
1	NDC:46708-266-30	30 in 1 BOTTLE; Type 0: Not a Combination Product	03/14/2013	
2	NDC:46708-266-90	90 in 1 BOTTLE; Type 0: Not a Combination Product	03/14/2013	
3	NDC:46708-266-31	100 in 1 BOTTLE; Type 0: Not a Combination Product	03/14/2013	
4	NDC:46708-266-91	1000 in 1 BOTTLE; Type 0: Not a Combination Product	03/14/2013	
5	NDC:46708-266-10	100 in 1 CARTON; Type 0: Not a Combination Product	03/14/2013	
6	NDC:46708-266-71	500 in 1 BOTTLE; Type 0: Not a Combination Product	03/14/2013	

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA202786	03/14/2013	

Labeler - Alembic Pharmaceuticals Limited (650574663)

Establishment

Name	Address	ID/FEI	Business Operations
Alembic Pharmaceuticals Limited		650574671	MANUFACTURE(46708-262, 46708-263, 46708-264, 46708-265, 46708-266)