PRODUCT MONOGRAPH

Pr ROPINIROLE

Ropinirole Tablets, USP
0.25 mg and 1 mg ropinirole (as ropinirole hydrochloride)

Antiparkinsonian Agent / Dopamine Agonist

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Table of Contents

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PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	All Nonmedicinal Ingredients
Oral	Tablets 0.25 mg, 1 mg	Croscarmellose sodium, lactose monohydrate, magnesium stearate and microcrystalline cellulose. Tablet coatings contain the following ingredients: polyvinyl alcohol (part hydrolyzed), titanium dioxide, polyethylene glycol, talc, FD&C Blue #2 (1 mg), iron oxide yellow (1 mg).

INDICATIONS AND CLINICAL USE

Adults:
ROPINIROLE (ropinirole hydrochloride) is indicated in the treatment of the signs and symptoms of idiopathic Parkinson's disease.

ROPINIROLE can be used both as early therapy without concomitant levodopa and as an adjunct to levodopa.

Geriatrics (> 65 years of age):
Oral clearance of ropinirole is reduced in patients older than 65 years of age, however the dosing of ROPINIROLE for elderly patients can be titrated in the normal manner. (see ACTION AND CLINICAL PHARMACOLOGY, Special Populations and Conditions, Geriatrics).

Pediatrics (≤ 18 years of age):
The safety and efficacy of ropinirole have not been established in children under 18 years of age, therefore ROPINIROLE is not recommended in this patient population.

CONTRAINDICATIONS

ROPINIROLE is contraindicated in patients with a known hypersensitivity to ropinirole hydrochloride or the excipients of the drug product. For a complete listing of excipients, see DOSAGE FORMS, COMPOSITION AND PACKAGING.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

Sudden Onset of Sleep

Patients receiving treatment with ropinirole and other dopaminergic agents have reported suddenly falling asleep while engaged in activities of daily living, including operating a motor vehicle, which has sometimes resulted in accidents. Although some of the patients reported somnolence while on ropinirole, others perceived that they had no warning signs, such as excessive drowsiness, and believed that they were alert immediately prior to the event.

Physicians should alert patients of the reported cases of sudden onset of sleep, bearing in mind that these events are NOT limited to initiation of therapy. Patients should also be advised that sudden onset of sleep has occurred without warning signs. If drowsiness or sudden onset of sleep should occur, patients should immediately contact their physician.

Until further information is available on the management of this unpredictable and serious adverse event, patients should be warned not to drive or engage in other activities where impaired alertness could put themselves and others at risk of serious injury or death (e.g., operating machines). Episodes of falling asleep while engaged in activities of daily living have also been reported in patients taking other dopaminergic agents, therefore, symptoms may not be alleviated by substituting these products.

Presently, the precise cause of this event is unknown. It is known that many Parkinson's disease patients experience alterations in sleep architecture, which results in excessive daytime sleepiness or spontaneous dozing, and that dopaminergic agents can also induce sleepiness. There is insufficient information to determine whether this event is associated with ropinirole, all dopaminergic agents or Parkinson's disease itself.

The following Warnings and Precautions are listed in alphabetical order.

Carcinogenesis and Mutagenesis

See PART II: TOXICOLOGY, Carcinogenicity and Mutagenicity for discussion on animal data.

Cardiovascular

Patients with pre-existing cardiovascular conditions

Since ropinirole has not been studied in patients with a history or evidence of significant

cardiovascular disease including myocardial infarction, unstable angina, cardiac decompensation, cardiac arrhythmias, vaso-occlusive disease (including cerebral) or cardiomyopathy, it should be used with caution in such patients.

There is limited experience with ropinirole in patients treated with antihypertensive and antiarrhythmic agents. Consequently, in such patients, the dose of ROPINIROLE should be titrated with caution.

Orthostatic hypotension
Dopamine agonists appear to impair the systemic regulation of blood pressure with resulting orthostatic symptoms of dizziness or light-headedness, with or without documented hypotension. These symptoms appear to occur especially during dose initiation and escalation. Therefore, patients treated with ROPINIROLE and other dopamine agonists should be carefully monitored for signs and symptoms of orthostatic hypotension, especially during dose initiation and escalation (see DOSAGE AND ADMINISTRATION) and should be informed of this risk (see PART III: CONSUMER INFORMATION).

Connective Tissue

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

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

A small number of reports have been received of possible fibrotic complications, including pleural effusion, pleural fibrosis, interstitial lung diseases, and cardiac valvulopathy, 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 completely ruled out in rare cases.

Neurologic

Neuroleptic Malignant Syndrome
A symptom complex resembling the neuroleptic malignant syndrome (characterized by elevated temperature, muscular rigidity, altered consciousness, and autonomic instability), with no other obvious aetiology, has been reported in association with rapid dose reduction, withdrawal of, or changes in antiparkinsonian therapy.

A single spontaneous report of a symptom complex resembling the neuroleptic malignant syndrome has been observed in a 66 year old diabetic male patient with Parkinson's disease, who

developed fever, muscle stiffness, and drowsiness 8 days after beginning ropinirole treatment. The patient also experienced acute bronchitis, which did not respond to antibiotic treatment. Ropinirole was discontinued three days before the patient died. The reporting physician considered these events to be possibly related to ropinirole treatment. (see DOSAGE AND ADMINISTRATION).

A single spontaneous report of severe muscle pain has been reported in a 66 year old male patient around his thigh. The reporting physician considered the event to be probably related to ropinirole treatment.

Dyskinesia with Adjunctive Levodopa
ROPINIROLE may potentiate the dopaminergic side effects of levodopa and may cause or exacerbate pre-existing dyskinesia. Decreasing the dose of levodopa may ameliorate this side effect.

Ophthalmologic

Retinal Pathology in Rats
In a two year carcinogenicity study in albino Sprague-Dawley rats, retinal atrophy was observed at incidences of 0%, 1.4%, 1.4% and 10% of male rats and 0%, 4.4%, 2.9% and 12.9% of female rats dosed at 0, 1.5, 15 and 50 mg/kg/day respectively. The incidence was statistically significant at 50 mg/kg/day. This dose represents a 2.8 fold (AUC) and 13.1 fold (C_{max}) greater exposure to ropinirole in rats than the exposure in humans at the maximum recommended dose of ropinirole of 24 mg/day.

While the potential significance of this effect on humans has not been established, it cannot be excluded that human albinos (or people who suffer from albinismus oculi) might have an increased susceptibility to ropinirole compared to normally pigmented people. Therefore, such patients should take ropinirole only under ophthalmological control.

Psychiatric

Compulsive Behaviours
Impulse control symptoms including compulsive behaviours (including pathological gambling, hypersexuality, compulsive shopping and binge eating) have been reported in patients treated with dopaminergic agents, including ropinirole (see ADVERSE REACTIONS). These were generally reversible upon dose reduction or treatment discontinuation. In some ropinirole cases, other factors were present such as a history of compulsive behaviours or concurrent dopaminergic treatment.

Aggression has been associated with psychotic reactions as well as compulsive symptoms.

Hallucinations

Early Therapy: In placebo-controlled trials, ropinirole caused hallucinations in 5.1% of patients during early therapy (1.4% in the placebo group). Hallucinations were of sufficient severity to result in that it led to discontinuation in 1.3% of patients. The incidence of hallucinations was dose-dependent.

In a 5-year study comparing ropinirole with levodopa in early Parkinson's patients, the overall incidence of hallucinations was 17.3% (31/179) for patients treated with ropinirole and 5.6% (5/89) for levodopa patients. Hallucinations led to discontinuation of the study treatment in 5.0% of ropinirole and 2.2% of levodopa patients. In a 3-year study comparing ropinirole with another dopamine agonist, the overall incidence of hallucinations was 9.5% (16/168) for patients treated with ropinirole and 9.0% (15/167) for patients receiving active comparator. Hallucinations led to discontinuation of the study treatment in 2.4% of ropinirole patients and 3.0% of comparator patients.

Concomitant Selegiline: In a 5-year study, ropinirole patients receiving concomitant selegiline reported a higher incidence of hallucinations (23.5%) than did those without (12.2%); this subpopulation effect was not seen in the L-dopa arm (hallucinations with concomitant selegiline = 2.0% vs. hallucinations without selegiline = 8.0%).

Adjunct Therapy: Hallucinations were experienced by 10.1% of patients receiving ropinirole and levodopa, compared to 4.2% receiving placebo and levodopa. Hallucinations were of sufficient severity that it led to discontinuation in 1.9% of patients. The incidence of hallucinations was dose dependent.

Skin

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 healthcare 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).

Special Populations

Pregnant Women: The use of ROPINIROLE during pregnancy is not recommended unless the potential benefit to the mother justifies the potential risk to the fetus. There are no adequate and well-controlled studies of ropinirole in pregnant women.

Teratogenic effects:

Since ropinirole has been shown to have developmental and teratogenic effects in animals, advise patients to notify their physician if they become pregnant or intend to become pregnant during therapy (see TOXICOLOGY).

Ropinirole given to pregnant rats during organogenesis (gestation days 8 through 15) resulted in decreased fetal body weight at 60 mg/kg/day (approximately 3.4 times the AUC at the maximum recommended human dose, MRHD, of 8 mg t.i.d), increased fetal death at 90 mg/kg/day (5.1 times the AUC at the MRHD) and malformations at 120 mg/kg/day (6.8 times the AUC at the MRHD). These effects occurred at maternally toxic doses. There was no indication of an effect during organogenesis at a maternally toxic dose of 20 mg/kg/day (9.5 times the mean human C_{max} at the MRHD) in the rabbit. However, ropinirole at 10 mg/kg (4.8 times the mean human C_{max} at the MRHD) administered to rabbits in combination with oral L-dopa produced a higher incidence and severity of malformations (particularly digits) than L-dopa alone.

In a perinatal-postnatal study in rats, 10 mg/kg/day of ropinirole (approximately 0.5 - 0.6 times the AUC at the maximal human dose of 8 mg t.i.d.) impaired growth and development of nursing offspring and altered neurological development of female offspring.

Nursing Women: Since ropinirole suppresses lactation, it should not be administered to mothers who wish to breast-feed infants.

There are no data regarding the excretion of ropinirole in human milk. Studies in rats have shown that ropinirole and/or its metabolites cross the placenta and are excreted in breast milk. Consequently, the human foetus and/or neonate may be exposed to dopamine agonist activity.

Use in Women receiving Oestrogen Replacement Therapy: In female patients on long-term treatment with conjugated oestrogens, oral clearance was reduced and elimination half-life prolonged compared to patients not receiving oestrogens (see ACTION AND CLINICAL PHARMACOLOGY, Special Populations and Conditions). In patients, already receiving oestrogen replacement therapy, ROPINIROLE may be titrated in the recommended manner according to clinical response. However, if oestrogen replacement therapy is stopped or introduced during treatment with ROPINIROLE, adjustment of the ROPINIROLE dosage may be required.

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

Renal Impairment: No dosage adjustment is needed in patients with mild to moderate renal impairment (creatinine clearance between 30 to 50 mL/min; see ACTION AND CLINICAL PHARMACOLOGY).

Because the use of ropinirole in patients with severe renal impairment (creatinine clearance less than 30 mL/min without regular dialysis) has not been studied, administration of ROPINIROLE to such patients is not recommended.

In patients with end stage renal disease (ESRD), a lower maximum dose is recommended which, compared to the maximum exposure evaluated in clinical trials, results in similar exposure to ropinirole, and to a 4.5-fold increased exposure to the N-despropyl inactive metabolite (see

DOSAGE AND ADMINISTRATION and ACTION AND CLINICAL PHARMACOLOGY, Special Populations and Conditions). Caution should be taken with the use of concomitant CYP1A2 inhibitors in these patients.

Hepatic Impairment: The use of ropinirole in patients with hepatic impairment has not been studied. Administration of ropinirole to such patients is not recommended.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

Most Frequent Adverse Events
Adverse events occurring with an incidence of greater than, or equal to, 10% were as follows: ***Early therapy:*** nausea, dizziness, somnolence, headache, peripheral oedema, vomiting, syncope, fatigue and viral infection. ***Adjunct therapy:*** dyskinesia, nausea, dizziness, somnolence and headache.

Adverse Reactions Associated with Discontinuation of Treatment
Of 1599 patients who received ropinirole during the premarketing clinical trials, 17.1% in early-therapy studies and 17.3% in adjunct-therapy studies discontinued treatment due to adverse reactions. The events resulting in discontinuation of ropinirole in 1% or more of patients were as follows: ***Early therapy:*** nausea (6.4%), dizziness (3.8%), aggravated Parkinson's disease (1.3%), hallucination (1.3%), headache (1.3%), somnolence (1.3%) and vomiting (1.3%). ***Adjunct therapy:*** dizziness (2.9%), dyskinesia (2.4%), confusion (2.4%), vomiting (2.4%), hallucination (1.9%), nausea (1.9%), anxiety (1.9%), and increased sweating (1.4%). Patients over 75 years of age (n=130) showed slightly higher incidences of withdrawal due to hallucination, confusion and dizziness than patients less than 75 years of age.

Clinical Trial Adverse Drug Reactions

> *Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates*.

Incidence of Adverse Events in Placebo Controlled Trials
The incidence of postural hypotension, an event commonly associated with initiation of dopamine agonist therapy, was not notably different from placebo in clinical trials. However, decreases in systolic blood pressure to <90 mmHg have been observed in 13% (< 65 years), 16% (65-75 years) and 7.6% (> 75 years) of patients treated with ropinirole.

The following table lists adverse events that occurred at an incidence of 1% or more among

ropinirole-treated patients who participated in placebo-controlled trials for up to one year. Patients were dosed in a range of 0.75 mg to 24 mg/day. Reported adverse events were classified using a standard World Health Organization Reaction Term Thesaurus (WHO-ART).

Table 1 Adverse events with incidence > 1% from all placebo-controlled early and adjunct therapy studies

	Early Therapy		Adjunct Therapy	
	Ropinirole N = 157 % occurrence	**Placebo N = 147 % occurrence**	**Ropinirole N = 208 % occurrence**	**Placebo N = 120 % occurrence**
Autonomic Nervous System				
Sweating Increased	6.4	4.1	7.2	1.7
Mouth Dry	5.1	3.4	5.3	0.8
Flushing	3.2	0.7	1.4	0.8
Body as a Whole General				
Peripheral Edema	13.4	4.1	3.9	2.5
Fatigue	10.8	4.1	-	-
Injury	-	-	10.6	9.2
Pain	7.6	4.1	5.3	3.3
Asthenia	6.4	1.4	-	-
Drug Level Increased	4.5	2.7	6.7	3.3
Chest Pain	3.8	2.0	-	-
Malaise	3.2	0.7	1.4	0.8
Therapeutic Response Decreased	1.9	0.7	-	-
Cellulitis	1.3	0.0	-	-
Influenza-Like Symptoms	-	-	1.0	0.0
Fever	-	-	1.4	0.0
Cardiovascular General				
Syncope	11.5	1.4	2.9	1.7
Hypotension Postural	6.4	4.8	-	-
Hypertension	4.5	3.4	3.4	3.3
Hypotension	1.9	0.0	2.4	0.8
Cardiac Failure	-	-	1.0	0.0
Central and Peripheral Nervous System				
Dizziness	40.1	21.8	26.0	15.8
Dyskinesia	-	-	33.7	12.5
Headache	17.2	17.0	16.8	11.7
Ataxia (Falls)	-	-	9.6	6.7
Tremor	-	-	6.3	2.5
Paresthesia	-	-	5.3	2.5
Hyperesthesia	3.8	2.0	-	-
Dystonia	-	-	4.3	4.2
Hypokinesia	-	-	5.3	4.2
Paresis	-	-	2.9	0.0
Speech disorder	-	-	1.0	0.0
Vertigo	1.9	0.0	-	-
Carpal Tunnel Syndrome	1.3	0.7	-	-

Table 1 (continued) **Adverse events with incidence > 1% from all placebo-controlled early and adjunct therapy studies**

	Early Therapy		Adjunct Therapy	
	Ropinirole N = 157 % occurrence	**Placebo N = 147 % occurrence**	**Ropinirole N = 208 % occurrence**	**Placebo N = 120 % occurrence**
Gastrointestinal System				
Nausea	59.9	21.8	29.8	18.3
Vomiting	12.1	6.8	7.2	4.2
Dyspepsia	9.6	4.8	-	-
Constipation	8.3	7.5	5.8	3.3
Abdominal Pain	6.4	2.7	8.7	7.5
Diarrhea	-	-	4.8	2.5
Anorexia	3.8	1.4	-	-
Flatulence	2.5	1.4	1.9	0.8
Tooth Disorder	1.9	0.7	1.0	0.8
Saliva Increased	-	-	2.4	0.8
Colitis	1.3	0.0	-	-
Dysphagia	1.3	0.0	2.4	0.8
Periodontitis	1.3	0.0	1.4	0.8
Eructation	-	-	1.4	0.0
Fecal Incontinence	-	-	1.0	0.0
Hemorrhoids	-	-	1.0	0.0
Gastroesophageal Reflux	-	-	1.0	0.0
Gastrointestinal Disorder (NOS)	-	-	1.0	0.0
Tooth Ache	-	-	1.0	0.0
Hearing and Vestibular				
Tinnitus	1.3	0.0	-	-
Heart Rate and Rhythm				
Palpitation	3.2	2.0	2.9	2.5
Extrasystoles	1.9	0.7	-	-
Tachycardia	1.9	0.0	1.0	0.0
Fibrillation Atrial	1.9	0.0	-	-
Tachycardia Supraventricular	1.3	0.0	-	-
Bradycardia	-	-	1.0	0.0
Liver and Biliary System				
Gamma – GT Increased	1.3	0.7	1.0	0.0
Hepatic Enzymes Increased	1.3	0.0	-	-
Metabolic and Nutritional				
Alkaline Phosphate Increased	2.5	1.4	1.0	0.0
Weight Decrease	-	-	2.4	0.8
Hypoglycemia	1.3	0.0	-	-
Musculoskeletal System				
Arthralgia	-	-	6.7	5.0
Arthritis	-	-	2.9	0.8
Arthritis Aggravated	1.3	0.0	1.4	0.0

Table 1 (continued) **Adverse events with incidence > 1% from all placebo-controlled early and adjunct therapy studies**

	Early Therapy		Adjunct Therapy	
	Ropinirole N = 157 % occurrence	**Placebo N = 147 % occurrence**	**Ropinirole N = 208 % occurrence**	**Placebo N = 120 % occurrence**
Myocardial, Endocardial, Pericardial Valve				
Myocardial Ischemia	1.3	0.7	-	-
Psychiatric				
Somnolence	40.1	6.1	20.2	8.3
Anxiety	-	-	6.3	3.3
Confusion	5.1	1.4	8.7	1.7
Hallucination	5.1	1.4	10.1	4.2
Nervousness	-	-	4.8	2.5
Yawning	3.2	0.0	-	-
Amnesia	2.5	1.4	4.8	0.8
Dreaming Abnormal	-	-	2.9	1.7
Depersonalization	-	-	1.4	0.0
Paranoid Reaction	-	-	1.4	0.0
Agitation	1.3	0.7	1.0	0.0
Concentration Impaired	1.9	0.0	1.0	0.0
Illusion	1.3	0.0	-	-
Thinking Abnormal	-	-	1.4	0.8
Apathy	-	-	1.0	0.0
Personality Disorder	-	-	1.0	0.0
Red Blood Cell				
Anemia	-	-	2.4	0.0
Reproductive Male				
Impotence	2.5	1.4	-	-
Prostatic Disorder	-	-	1.0	0.0
Penis Disorder	-	-	1.3	0.0
Resistance Mechanism				
Upper Respiratory Tract Infection	-	-	8.7	8.3
Infection Viral	10.8	3.4	7.2	6.7
Respiratory System				
Pharyngitis	6.4	4.1	-	-
Rhinitis	3.8	2.7	-	-
Sinusitis	3.8	2.7	-	-
Dyspnea	3.2	0.0	2.9	1.7
Bronchitis	2.5	1.4	-	-
Respiratory Disorder	1.9	1.4	1.9	0.0
Pneumonia	1.3	0.7	1.0	0.8
Coughing	-	-	1.4	0.8
Skin/Appendages				
Pruritis	-	-	1.0	0.0

Table 1 (continued) **Adverse events with incidence > 1% from all placebo-controlled early and adjunct therapy studies**

	Early Therapy		Adjunct Therapy	
	Ropinirole N = 157 % occurrence	**Placebo N = 147 % occurrence**	**Ropinirole N = 208 % occurrence**	**Placebo N = 120 % occurrence**
Urinary System				
Urinary Tract Infection	5.1	4.1	6.3	2.5
Cystitis	1.3	0.7	-	-
Micturition Frequency	-	-	1.4	0.0
Pyuria	-	-	1.9	0.8
Urinary Incontinence	-	-	1.9	0.8
Urinary Retention	1.3	0.7	-	-
Dysuria	-	-	1.0	0.0
Vascular Extracardiac				
Peripheral Ischemia	2.5	0.0	-	-
Vision				
Vision Abnormal	5.7	3.4	-	-
Eye Abnormality	3.2	1.4	-	-
Diplopia	-	-	1.9	0.8
Xerophthalmia	1.9	0.0	1.4	0.8
Cataract	-	-	1.4	0.8
Lacrimation Abnormal	-	-	1.4	0.0
White Cell and Reticuloendothelial System				
Eosinophilia	-	-	1.4	0.0

- Incidence of adverse event <1%

In addition to the events listed in Table 1, the following adverse events were recorded with rates equal to, or more common in, placebo-treated patients:

Early therapy: fever, hot flushes, injury, rigors, ataxia, dyskinesia, dystonia, hyperkinesia, involuntary muscle contractions, paresthesia, aggravated Parkinsonism, tremor, diarrhea, gingivitis, increased saliva, bradycardia, gout, hyperglycemia, decreased weight, arthralgia, arthritis, back pain, myalgia, basal cell carcinoma, anxiety, depression, abnormal dreaming, insomnia, nervousness, prostatic disorder, upper respiratory tract infection, coughing, rash, hematuria and leg cramps.

Adjunct therapy: asthenia, chest pain, fatigue, hot flushes, postural hypotension, abnormal gait, hyperkinesia, aggravated Parkinsonism, vertigo, abdominal pain, constipation, back pain, myalgia, depression, insomnia, paroniria (WHO dictionary term for nightmares), viral infection, upper respiratory tract infection, pharyngitis, rhinitis, rash, rash erythematous, taste perversion, hematuria, leg cramps and diplopia, myocardial infarction, extrasystoles supraventricular.

Events Observed During the Premarketing Evaluation of Ropinirole

Of the 1,599 patients who received ropinirole in therapeutic studies, the following adverse events, which are not included in Table 1 or in the listing above, have been noted up to May

1996. In the absence of appropriate controls in some of the studies, a causal relationship between these events and treatment with ropinirole cannot be determined.

Events are categorized by body system and listed in order of decreasing frequency according to the following definitions: "*frequent*" adverse events are those occurring on one or more occasions in at least 1/100 patients; "*infrequent*" adverse events are those occurring in 1/100 to 1/1,000 patients; "*rare*" events are those occurring in fewer than 1/1,000 patients.

Table 2 Adverse Events Observed During the Premarketing Evaluation of Ropinirole

Frequency	**Frequent**	**Infrequent**	**Rare**
	< 10% and ≥ 1%	**< 1% and ≥ 0.1%**	**< 0.1% and ≥ 0.01%**
Body System			
Autonomic Nervous System			cold, clammy hands
Body as a Whole		pallor, allergy, enlarged abdomen, substernal chest pain, oedema allergic reaction, ascites, precordial chest pain, therapeutic response increased, ischemic necrosis, oedema generalised	periorbital oedema, face oedema, halitosis
Cardiovascular System		cardiac failure, heart disorder, specific abnormal ECG, aneurysm, cardiomegaly, abnormal ECG, aggravated hypertension	cyanosis, fluid overload, heart valve disorder
Central and Peripheral Nervous System	neuralgia	hypertonia, speech disorder, choreoathetosis, abnormal coordination, dysphonia, extrapyramidal disorder, migraine, aphasia, coma, convulsions, hypotonia, nerve root lesion, peripheral neuropathy, paralysis, stupor	cerebral atrophy, grand mal convulsions, hemiparesis, hemiplegia, hyperreflexia, neuropathy, ptosis, sensory disturbance, hydrocephaly
Collagen			rheumatoid arthritis
Endocrine System		gynaecomastia, hypothyroidism	SIADH (syndrome of inappropriate antidiuretic hormone secretion), increased thyroxine, goiter, hyperthyroid

Table 2 (continued) Adverse Events Observed During the Premarketing Evaluation of Ropinirole

Frequency	Frequent	Infrequent	Rare
	< 10% and ≥ 1%	**< 1% and ≥ 0.1%**	**< 0.1% and ≥ 0.01%**
Body System			
Gastrointestinal System	gastrointestinal disorder (NOS)	gastritis, gastroenteritis, gastroesophageal reflux, increased appetite, oesophagitis, peptic ulcer, diverticulitis, haemorrhoids, hiccup, tooth caries, increased amylase, duodenal ulcer, duodenitis, fecal incontinence, GI hemorrhage, glossitis, rectal hemorrhage, melena, pancreatitis, rectal disorder, altered saliva, stomatitis, ulcerative stomatitis, tongue oedema, gastric ulcer, tooth disorder	oesophageal stricture, oesophageal ulceration, hemorrhagic gastritis, gingival bleeding, haematemesis, lactose intolerance, salivary duct obstruction, tenesmus, tongue disorder, hemorrhagic duodenal ulcer, aggravated tooth caries
Hearing		earache, decreased hearing, vestibular disorder, ear disorder (NOS)	hyperacusis, deafness
Heart Rate and Rhythm		arrhythmia, bundle branch block, cardiac arrest, supraventricular extrasystoles, ventricular tachycardia	atrioventricular block
Liver and Biliary System		abnormal hepatic function, increased SGPT, bilirubinemia, cholecystitis, cholelithiasis, hepatocellular damage, increased SGOT	biliary pain, aggravated bilirubinemia, gall bladder disorder
Metabolic and Nutritional System	increased blood urea nitrogen	increased LDH, increased NPN, hyperuricemia, increased weight, hyperphosphatemia, diabetes mellitus, glycosuria, hypercholesterolemia, acidosis, hypokalemia, hyponatremia, thirst, increased creatine phosphokinase, dehydration, aggravated diabetes mellitus, hyperkalemia	electrolyte abnormality, enzyme abnormality, hypochloremia, obesity, increased phosphatase acid, decreased serum iron
Musculoskeletal System	arthrosis	arthropathy, osteoporosis, tendonitis, bone disorder, bursitis, muscle weakness, polymyalgia rheumatica, skeletal pain, torticollis	muscle atrophy, myositis, Dupuytren's contracture, spine malformation.

Table 2 (continued) Adverse Events Observed During the Premarketing Evaluation of Ropinirole

Frequency	Frequent	Infrequent	Rare
	< 10% and ≥ 1%	**< 1% and ≥ 0.1%**	**< 0.1% and ≥ 0.01%**
Body System			
Myocardial, Endocardial, Pericardial Valve	angina pectoris	myocardial infarction, aggravated angina pectoris	mitral insufficiency
Neoplasm		carcinoma, malignant female breast neoplasm, dermoid cyst, malignant skin neoplasm, prostate adenocarcinoma, adenocarcinoma, neoplasm (NOS)	bladder carcinoma, benign brain neoplasm, breast fibroadenosis, malignant endometrial neoplasm, oesophageal carcinoma, malignant larynx neoplasm, malignant lymphoma, malignant neoplasm, neuroma, lipoma, rectal carcinoma, uterine neoplasm
Platelet Bleeding and Clotting		purpura, thrombocytopenia, haematoma	
Psychiatric	aggravated depression, agitation	sleep disorder, apathy, dementia, delirium, emotional lability, psychosis, aggressive reaction, delusion, psychotic depression, euphoria, decreased libido, manic reaction, neurosis, personality disorder, somnambulism	suicide attempt
Red Blood Cell		hypochromic anaemia, anaemia B12 deficiency	polycythemia
Female Reproductive		amenorrhea, menstrual disorder, vaginal haemorrhage, uterine disorders (NOS)	female breast enlargement, inter-menstrual bleeding, mastitis, uterine haemorrhage, dysmenorrhoea
Male Reproductive		epididymitis, balanoposthitis, ejaculation failure, penis disorder, perineal pain	Peyronie's disease, ejaculation disorder, testicular disorder
Resistance Mechanism	infection	herpes zoster, moniliasis, otitis media, sepsis, herpes simplex, fungal infection, abscess, bacterial infection, genital moniliasis	poliomyelitis
Respiratory System	pneumonia	asthma, epistaxis, laryngitis, pleurisy, increased sputum, pulmonary oedema	hypoxia, respiratory insufficiency, vocal cord paralysis

Table 2 (continued) Adverse Events Observed During the Premarketing Evaluation of Ropinirole

Frequency	Frequent	Infrequent	Rare
	< 10% and ≥ 1%	**< 1% and ≥ 0.1%**	**< 0.1% and ≥ 0.01%**
Body System			
Skin and Appendages		dermatitis, alopecia, skin discolouration, dry skin, skin hypertrophy, skin ulceration, fungal dermatitis, eczema, hyperkeratosis, photosensitivity reaction, psoriasis, maculopapular rash, psoriaform rash, seborrhoea, skin disorder, urticaria, furunculosis	bullous eruption, nail disorder, nevus, photosensitivity allergic reaction, aggravated psoriasis, skin exfoliation, abnormal skin odour
Other Special Senses			parosmia
Urinary		albuminuria, dysuria, nocturia, polyuria, renal calculus, abnormal urine, micturition disorder	oliguria, pyelonephritis, renal cyst, acute renal failure, renal pain, uremia, urethral disorder, urinary casts, bladder calculus, nephritis
Vascular Extracardiac		cerebrovascular disorder, vein disorder, varicose vein, peripheral gangrene, phlebitis, vascular disorder	atherosclerosis, limb embolism, pulmonary embolism, gangrene, superficial phlebitis, subarachnoid hemorrhage, deep thrombophlebitis, leg thrombophlebitis, thrombosis, arteritis
Vision		conjunctivitis, blepharitis, abnormal accommodation, blepharospasm, eye pain, glaucoma, photophobia, scotoma	blindness, blindness temporary, hemianopia, keratitis, photopsia, macula lutea degeneration, vitreous detachment, retinal disorder
White Cell and Reticuloendothelial System		leukocytosis, leukopenia, lymphopenia, lymphedema, lymphocytosis	lymphadenopathy, granulocytopenia

Events Observed During Long-Term Therapy with Ropinirole

In two long-term, comparator-controlled studies of early therapy (durations of three and five years), patients with mild to moderate Parkinson's disease initiated treatment on ropinirole alone, with open L-dopa available as supplementary medication.

The overall rates of withdrawal due to adverse events were 27% for the five year study and 20% for the three year one.

Table 3 lists the adverse events that occurred at an incidence of 5% or more in these two studies.

Concomitant Selegiline and associated Hallucination rates

In the five year study, ropinirole patients receiving concomitant selegiline reported a higher incidence of hallucination (23.5%) than did those without (12.2%); this subpopulation effect was not seen in the L-dopa arm (hallucination with concomitant selegiline = 2.0% vs. hallucination without selegiline = 8.0%).

Table 3 Adverse events with incidence of > 5% from two long-term comparator-controlled early therapy studies (regardless of the presence or absence of concomitant L-dopa):

	Three-year study		Five-year study	
	Ropinirole (N=168) % occurrence	**Dopamine Agonist (N=167) % occurrence**	**Ropinirole (N=179) % occurrence**	**L-Dopa (N=89) % occurrence**
Autonomic Nervous System				
Mouth Dry	5.4	4.8	6.1	5.6
Sweating Increased	-	-	6.1	10.1
Body as a Whole General				
Asthenia	8.9	3.0	7.8	5.6
Chest Pain	-	-	8.4	9.0
Edema Dependent	6.0	6.6	-	-
Edema Legs	6.5	5.4	14.0	5.6
Fatigue	8.9	4.8	7.3	5.6
Injury	7.1	11.4	19.0	19.1
Pain	11.3	3.6	11.7	15.7
Cardiovascular General				
Hypertension	5.4	6.0	7.8	4.5
Hypotension Postural	9.5	13.2	11.2	12.4
Syncope	6.5	4.2	7.8	6.7
Central and Peripheral Nervous System				
Ataxia	5.4	4.2	14.0	9.0
Dizziness	22.6	19.8	20.1	19.1
Dyskinesia*	-	-	8.9	25.8
Dystonia	-	-	6.7	12.4
Headache	10.7	15.6	14.0	18.0
Hyperkinesia	-	-	0.0	5.6
Hypokinesia	-	-	8.4	9.0
Paresthesia	-	-	3.4	6.7
Parkinsonism Aggravated	8.9	12.0	22.3	20.2
Tremor	-	-	16.2	12.4
Vertigo	7.1	7.8	-	-
Gastrointestinal System				
Abdominal Pain	10.7	15.6	15.1	14.6
Anorexia	-	-	8.9	9.0
Constipation	7.7	12.0	9.5	12.4
Diarrhea	5.4	4.8	4.5	10.1
Dyspepsia	5.4	7.8	20.7	16.9
Nausea	40.5	25.1	48.6	49.4
Vomiting	14.9	7.2	16.2	11.2

Table 3 (continued) **Adverse events with incidence of > 5% from two long-term comparator-controlled early therapy studies (regardless of the presence or absence of concomitant L-dopa):**

	Three-year study		Five-year study	
	Ropinirole (N=168) % occurrence	**Dopamine Agonist (N=167) % occurrence**	**Ropinirole (N=179) % occurrence**	**L-Dopa (N=89) % occurrence**
Heart Rate and Rhythm				
Palpitation	-	-	5.0	3.4
Liver and Biliary System				
Hepatic Enzymes Increased	-	-	6.1	5.6
Musculoskeletal System				
Arthralgia	7.1	8.4	15.1	13.5
Arthritis	-	-	7.8	7.9
Arthrosis	-	-	3.9	5.6
Back Pain	11.9	11.4	17.9	16.9
Myalgia	-	-	4.5	6.7
Psychiatric				
Amnesia	-	-	3.4	9.0
Anxiety	4.8	9.0	11.7	9.0
Confusion	7.7	5.4	7.3	9.0
Depression	11.3	10.2	14.5	22.5
Dreaming Abnormal	-	-	5.0	3.4
Hallucination	9.5	9.0	17.3	5.6
Insomnia	12.5	10.8	25.1	23.6
Nervousness	6.0	2.4	-	-
Paroniria	-	-	4.5	7.9
Somnolence	8.9	7.8	27.4	19.1
Yawning	-	-	5.0	1.1
Red Blood Cell				
Anemia	1.8	6.6	5.6	4.5
Resistance Mechanism				
Infection	-	-	5.6	0.0
Infection Viral	14.3	14.4	8.4	13.5
Upper Resp Tract Infection	-	-	7.3	7.9
Respiratory System				
Bronchitis	4.8	7.2	4.5	7.9
Coughing	-	-	6.1	4.5
Dyspnea	6.5	3.0	7.3	10.1
Respiratory Disorder	-	-	7.8	5.6
Skin and Appendages				
Rash	-	-	7.8	6.7
Urinary System				
Urinary Incontinence	-	-	5.6	1.1
Urinary Tract Infection	-	-	10.6	12.4
Vision				
Vision Abnormal	-	-	3.9	5.6

* In the 5-year study, it was shown that initial treatment of early Parkinson's disease with ropinirole (without concomitant L-dopa) reduces the risk of developing abnormal involuntary movements (i.e. dyskinesias), compared to that associated with the administration of levodopa as initial therapy.

Adverse Drug Reactions from Post-Market Experience and Post-Launch Clinical Trials

The following section enumerates potentially important adverse drug reactions that have been reported spontaneously to various surveillance systems and have also occurred in post-launch clinical trials. The events enumerated represent reports arising from both domestic and nondomestic use of ropinirole. These events do not include those already listed in the ADVERSE REACTIONS section above.

Patients treated with ropinirole have rarely reported suddenly falling asleep while engaged in activities of daily living, including operation of motor vehicles which has sometimes resulted in accidents (see WARNINGS AND PRECAUTIONS).

Pathological (compulsive) gambling has been reported in post-market data, including those in the literature, for antiparkinson drugs. Sporatic cases of pathological (compulsive) gambling have been reported in patients treated with ropinirole. Dosage adjustment should be considered in the management of this behaviour.

Impulse control symptoms, increased libido including hypersexuality, compulsive shopping and binge eating have been reported (see WARNINGS AND PRECAUTIONS).

Psychotic reactions (other than hallucinations) including delusion, paranoia, and delirium have been reported.

Aggressive behaviour has been reported. Aggression has been associated with psychotic reactions as well as compulsive symptoms (see WARNINGS AND PRECAUTIONS).

Hypersensitivity reactions (including urticaria, angioedema, rash, pruritus) have been very rarely reported.

DRUG INTERACTIONS

Overview

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

Drug-Drug Interactions

Psychotropic Drugs: Neuroleptics and other centrally active dopamine antagonists may diminish the effectiveness of ropinirole. Therefore, concomitant use of these products is not recommended.

Based on population pharmacokinetic assessment, no interaction was seen between ropinirole and tricyclic antidepressants or benzodiazepines.
Anti-Parkinson Drugs: Based on population pharmacokinetic assessment, there were no interactions between ropinirole and drugs commonly used to treat Parkinson's disease, i.e., selegiline, amantadine, and anticholinergics.

Levodopa: The potential pharmacokinetic interaction of levodopa/carbidopa (100 mg/10 mg b.i.d.) and ropinirole (2 mg t.i.d.) was assessed in levodopa naive (*de novo*) male and female patients with Parkinson's disease (n=30, mean age 64 years). The rate and extent of availability of ropinirole at steady state were essentially the same with or without levodopa. Similarly, the rate and extent of availability of levodopa, as well as its elimination half-life, were essentially the same in the presence and absence of ropinirole.

Inhibitors of CYP1A2: Ciprofloxacin
The effect of ciprofloxacin (500 mg b.i.d.) on the pharmacokinetics of ropinirole (2 mg t.i.d.) was studied in male and female patients with Parkinson's disease (n=12, mean age 55 years). The extent of systemic availability of ropinirole was significantly increased when co-administered with ciprofloxacin (AUC increased by 1.84 fold). Thus, in patients already receiving CYP1A2 inhibitors such as ciprofloxacin, ROPINIROLE therapy may be instituted in the recommended manner and the dose titrated according to clinical response. However, if therapy with a drug known to be an inhibitor of CYP1A2 is stopped or introduced during treatment with ROPINIROLE, adjustment of the ROPINIROLE dosage will be required.

Substrates of CYP1A2: Theophylline
The effect of oral theophylline (300 mg b.i.d.) on the pharmacokinetics of ropinirole (2 mg t.i.d.) was studied in male and female patients with Parkinson's disease (n=12, mean age 59 years). There was no marked change in the rate or extent of availability of ropinirole when co-administered with theophylline. Similarly, coadministration of ropinirole with intravenous theophylline (5 mg/kg) did not result in any marked change in the pharmacokinetics of theophylline. It is therefore unlikely that substrates of CYP1A2 would significantly alter the pharmacokinetics of ropinirole, and vice-versa.

Digoxin: The effect of ropinirole (2 mg t.i.d.) on the pharmacokinetics of digoxin (0.125 - 0.25 mg o.d.) was studied in male and female patients with Parkinson's disease (n=10, mean age 72 years). Co-administration at steady state with ropinirole resulted in a 10% decrease in digoxin AUC although mean trough digoxin plasma concentrations were unaltered. However, the effect of higher recommended doses of ropinirole on the pharmacokinetics of digoxin is not known.

Alcohol: No information is available on the potential for interaction between ropinirole and alcohol. As with other centrally active medications, patients should be cautioned against taking ROPINIROLE with alcohol.

Drug-Lifestyle Interactions

Psycho-Motor Performance
(See WARNINGS AND PRECAUTIONS – Sudden Onset of Sleep).

DOSAGE AND ADMINISTRATION

Dosing Considerations

Renal Impairment: In patients with mild to moderate renal impairment, ROPINIROLE may be titrated in the recommended manner according to clinical response. A study into the use of ropinirole in patients with end stage renal disease (patients on hemodialysis) has shown that a dose adjustment in these patients is required as follows:

The initial dose of ROPINIROLE should be 0.25 mg three times a day. Further dose escalations should be based on tolerability and efficacy. The recommended maximum dose is 18 mg/day in patients receiving regular dialysis. Supplemental doses after dialysis are not required.

Patients with severe renal impairment (creatinine clearance less than 30 mL/min without regular dialysis) have not been studied and administration of ROPINIROLE to such patients is not recommended.

Hepatic Impairment: Patients with hepatic impairment have not been studied and administration of ROPINIROLE to such patients is not recommended.

Oestrogen Replacement Therapy: In patients already receiving oestrogen replacement therapy, ROPINIROLE may be titrated in the recommended manner according to clinical response. However, if oestrogen replacement therapy is stopped or started during treatment with ROPINIROLE adjustment of the ROPINIROLE dosage may be required.

Recommended Dose and Dosage Adjustment
ROPINIROLE should be taken three times daily and may be taken with or without food (see ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics).

The recommended starting dosage is 0.25 mg three times daily. Based on individual patient response, dosage should then be titrated by weekly increments of 0.25 mg per dose as described in the table below. After week 4, daily dosage may be increased by 0.5 to 1 mg per dose on a weekly basis until an optimal therapeutic response is established. Smaller dose increments are recommended for patients who may be at risk for orthostatic symptoms.

	Week			
	1	2	3	4
Unit Dose (mg)	0.25	0.5	0.75	1
Total Daily Dose (mg)	0.75	1.5	2.25	3

In clinical trials, initial benefits were observed with 3 mg/day and higher doses. Doses greater than 24 mg/day have not been included in clinical trials.

In a 5-year, double-blind study of early therapy in Parkinson's disease patients, the average daily dose of ropinirole (based on the observed data set) was 10.1 mg at 6 months (median dose = 9 mg), 14.4 mg at 3 years (median dose = 15 mg), and 16.6 mg at 5 years (median dose = 18 mg), regardless of levodopa supplementation.

When ROPINIROLE is administered as adjunct therapy to levodopa, the dose of levodopa may be decreased gradually as tolerated once a therapeutic effect with ROPINIROLE has been observed (see CLINICAL TRIALS). A decrease in levodopa dosage may be necessary in order to avoid excessive dopamine stimulation.

ROPINIROLE should be discontinued gradually over a 7-day period. 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.

Missed Dose

Patients should be instructed that, if they miss a dose of ROPINIROLE, they should wait and take the next dose as scheduled. There is no need to make up for the missed dose. Patients should not take two doses at once. If treatment is interrupted for one day or more, re-initiation by dose titration should be considered (see DOSAGE AND ADMINISTRATION).

OVERDOSAGE

Symptoms and Signs

There were no reports of intentional overdose of ropinirole in the premarketing clinical trials. A total of 27 patients accidentally took more than their prescribed dose of ropinirole, with 10 patients ingesting more than 24 mg/day. The largest overdose reported in premarketing 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, one experienced mild oro-facial dyskinesia, another patient experienced intermittent nausea. Other symptoms reported with accidental overdoses were: agitation, increased dyskinesia, grogginess, sedation, orthostatic hypotension, chest pain, confusion, vomiting and nausea.

Recommended Management
It is anticipated that the symptoms of ropinirole overdose will be related to its dopaminergic activity. These symptoms may be alleviated by appropriate treatment with dopamine antagonists such as neuroleptics or metoclopramide. The efficacy of such drugs in reversing the effects of overdosage however, has not been assessed. General supportive measures are recommended. Vital signs should be maintained, if necessary.

For management of a suspected drug overdose, contact your regional Poison Control Centre immediately.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action
Ropinirole is a non-ergoline dopamine agonist, which activates post-synaptic dopamine receptors.

In vitro studies have shown that ropinirole binds with high affinity to cloned human D_2, D_3 and D_4 receptors. The antiparkinson activity of ropinirole is believed to be due to its stimulatory effects on central post-synaptic dopamine D_2 receptors within the caudate-putamen.

Ropinirole is a potent agonist both *in vitro* and *in vivo* and restores motor function in animal models of Parkinson's disease. Ropinirole has been shown to reverse the motor deficits induced by the neurotoxin 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) in primates.

Neither ropinirole nor its metabolites bind with high affinity to dopamine D_1 receptors. Ropinirole also has very low affinity for 5-HT_1, 5-HT_2, benzodiazepine, $GABA_A$, muscarinic, alpha- or beta-adrenoreceptors. Ropinirole binds to opiate receptors with low affinity, however, studies show that this weak opiate activity has no consequences at pharmacological doses *in vivo*.

In rats, ropinirole binds to melanin-containing tissues (e.g. the eye) to a greater degree than non-pigmented tissues, and tissue levels decline with a half-life of 16-20 days. It is unknown whether or not ropinirole accumulates in these tissues over time.

Pharmacodynamics
In healthy normotensive subjects, single oral doses of ropinirole, in the range of 0.01 to 2.5 mg, had little or no effect on supine blood pressure and pulse rate. Upon standing, ropinirole caused decreases in systolic and mainly diastolic blood pressure at doses above 0.25 mg. In some subjects, these changes were associated with the emergence of orthostatic symptoms, bradycardia, and, in one case, transient sinus arrest in the context of a severe vasovagal syncope.

The effect of repeat dosing and slow titration of ropinirole was not studied in healthy volunteers.

The mechanism of ropinirole-induced orthostatic symptoms probably relates to its dopamine D_2-mediated blunting of the noradrenergic response to standing and subsequent decrease in peripheral vascular resistance. Orthostatic signs and symptoms were often accompanied by nausea.

Ropinirole had no dose-related effect on ECG wave form and rhythm in young healthy male volunteers.

At doses ≥ 0.8 mg ropinirole suppressed serum prolactin concentrations in healthy male volunteers.

Pharmacokinetics

Absorption, Bioavailability and Distribution

Ropinirole is rapidly absorbed with median peak concentrations occurring within 1.5 hours after oral dosing. Despite complete absorption, absolute bioavailability of ropinirole is reduced to approximately 50% as a result of first-pass metabolism. Relative bioavailability from a tablet compared to an oral solution is 85%. Over the therapeutic dose range, C_{max} and AUC values increase in proportion to the increase in dose (see Table 4).

The average oral clearance is approximately 47 L/h (range 17-113 L/h) and is constant over the entire dosage range. The terminal elimination half-life is approximately 6 h (range 2-27 h) and the volume of distribution at steady state is approximately 480 L (range 216-891 L) or 7.0 L/kg (range 3.1-12.9 L/kg).

Table 4 Steady state pharmacokinetic parameters (mean and range) of ropinirole in patients with Parkinson's disease administered ropinirole in a t.i.d. regimen

Unit Dose	C_{max}	C_{min}	T_{max}*	AUC_{0-8}
mg	ng/mL	ng/mL	h	ng.h/mL
1	5.3	2.6	2.0	27.5
	(3.1-9.0)	(0.9-4.2)	(0.5-7.0)	(14.9-46.5)
2	9.8	4.8	1.0	53.8
	(5.0-18.0)	(2.3-10.0)	(0.6-4.0)	(23.9-108)
4	23.7	13.1	1.0	136
	(14.2-40.9)	(4.8-23.9)	(1.0-3.0)	(66.1-241)

*median

Steady state concentrations are expected to be achieved within 2 days of dosing. There is, on average, a two-fold higher steady-state plasma concentration of ropinirole following the recommended t.i.d. regimen compared to those observed following a single oral dose.

A high fat meal delayed the rate of absorption of ropinirole (median T_{max} was increased by 2.6 hours and C_{max} was decreased by 25%) in Parkinsonian patients. However, there was no marked change in the overall systemic availability of the drug. Ropinirole may be given with or without food. While administration of the drug with food may improve gastrointestinal tolerance, in severely fluctuating patients, the morning dose may be given without food in order to avoid a delay in time to switch "ON".

Population pharmacokinetic analyses have shown that frequently co-administered medications, such as levodopa, selegiline, amantadine, anticholinergic drugs, ibuprofen, benzodiazepines and antidepressants did not alter the pharmacokinetics of ropinirole.

Plasma protein binding is low (10 to 40%).

Ropinirole has a blood to plasma ratio of 1.2.

***Metabolism*:** Ropinirole is extensively metabolized by the liver. The N-despropyl metabolite is the major metabolite circulating in the plasma. Based on AUC data, the plasma levels of the metabolite were consistently higher than those of the parent drug suggesting a nonsaturable conversion of ropinirole to the N-despropyl metabolite. The affinity of the N-despropyl metabolite for human cloned D_2 receptors is lower than the affinity of ropinirole. In addition the metabolite does not cross the blood-brain barrier; thus, it is unlikely to contribute to the therapeutic effects of ropinirole. The plasma concentrations of the hydroxylated metabolite are low and account for about 1-5% of the ropinirole concentrations. Although the hydroxylated metabolite was more active than ropinirole in *in vitro* D_2 receptor binding studies, at therapeutic doses it is not expected to contribute to the activity of ropinirole.

In vitro studies indicate that the major cytochrome P450 isozyme involved in the metabolism of ropinirole is CYP1A2. In patients with Parkinson's disease, ciprofloxacin, an inhibitor of CYP1A2, significantly increased the systemic availability of ropinirole, while theophylline, a substrate of CYP1A2, was devoid of such activity (see DRUG INTERACTIONS).

***Excretion*:** Recovery of radioactivity after oral and intravenous administration of ^{14}C-ropinirole was approximately 88% and 90% of the dose, respectively. Urinary excretion of unchanged ropinirole is low and represents approximately 5 to 10% of the dose. N-despropyl ropinirole is the predominant metabolite found in the urine (40%), followed by the glucuronide of the hydroxy metabolite (10%), and the carboxylic acid metabolite (10%) formed from N-despropyl ropinirole.

Special Populations and Conditions

Geriatrics: Population pharmacokinetic analysis revealed that the oral clearance of ropinirole, seen in patients under the age of 65 years (n=97), was reduced from 62.1 L/h to 45.5 L/h in patients between the ages of 65 and 75 years (n=63). In patients older than 75 years (n=11), oral clearance was similar to that seen in the 65 to 75 year age group (41.7 L/h). Dosage adjustment is not necessary in the elderly (65 years or above).

Gender: Population pharmacokinetic analysis indicated that the oral clearance and volume of distribution of ropinirole at steady state were similar in male patients (n=99, mean age 60 years) and female patients who were not taking concomitant estrogens (n=56, mean age 65 years).

Oestrogen Replacement Therapy: In women, on long-term treatment with conjugated estrogens (n=16, mean age 63 years), the oral clearance of ropinirole was decreased by an average of 36% compared to the oral clearance in women not receiving supplemental oestrogens (n=56, mean age 65 years). The average terminal elimination half-life was 9.0 hours in the oestrogen group and 6.5 hours in patients not taking oestrogens (see WARNINGS AND PRECAUTIONS and DOSAGE AND ADMINISTRATION).

Renal/Hepatic Insufficiency: Based on population pharmacokinetics, no clinically significant differences were observed in the pharmacokinetics of ropinirole in Parkinsonian patients with mild to moderate renal impairment (creatinine clearance between 30 to 50 mL/min; n=18, mean age 74 years) compared to age-matched patients with creatinine clearance above 50 mL/min (n=44, mean age 70 years). Therefore, no dosage adjustment is necessary in Parkinsonian patients with mild to moderate renal impairment (see WARNINGS AND PRECAUTIONS and DOSAGE AND ADMINISTRATION).

The use of ropinirole in patients with severe renal impairment (creatinine clearance less than 30 mL/min) without regular dialysis or with hepatic impairment has not been studied. Administration of ROPINIROLE to such patients is not recommended (see WARNINGS AND PRECAUTIONS and DOSAGE AND ADMINISTRATION).

In patients with end stage renal disease receiving regular dialysis, oral clearance of ropinirole is reduced by approximately 30%. Exposure to the N-despropyl inactive metabolite is increased 4.5-fold; there is no clinical experience with long-term exposure to high levels of this metabolite although exposure which is several-fold the maximum exposure in humans has been evaluated in toxicology studies with no apparent toxicity observed. The clinical relevance of these findings is unknown. The recommended maximum dose is limited to 18 mg/day in patients with Parkinson's disease (see DOSAGE AND ADMINISTRATION, Renal Impairment).

STORAGE AND STABILITY

ROPINIROLE tablets should be stored between 15º to 30ºC. Protect from light and moisture. Close container tightly after each use.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Dosage Forms:

ROPINIROLE is available as 0.25 mg and 1 mg tablets with the following descriptions.

0.25 mg:	White to off white, film-coated, raised pentagon-shaped tablet with "RI" on one side and "ᘐ" on the other side. 25
1 mg:	Green, film-coated, raised pentagon-shaped tablet with "RI" on one side and "ᘐ" on the other side. 1

Composition:

ROPINIROLE tablets contain 0.25 mg or 1 mg of ropinirole as ropinirole hydrochloride as the active ingredient, and the following non medicinal ingredients: croscarmellose sodium, lactose monohydrate, magnesium stearate and microcrystalline cellulose.

Tablet coatings contain the following ingredients

0.25 mg:	polyvinyl alcohol (part hydrolyzed), titanium dioxide, polyethylene glycol, talc
1 mg:	polyvinyl alcohol (part hydrolyzed), titanium dioxide, polyethylene glycol, talc, FD&C Blue #2, iron oxide yellow

Packaging:

ROPINIROLE is available in HDPE bottles of 100's.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

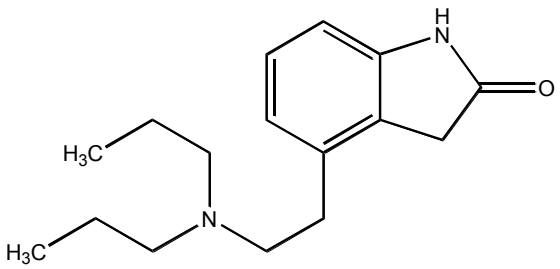
Drug Substance

Common name: ropinirole hydrochloride

Chemical name: 4-[2-(Dipropylamino)ethyl]-2-indolinone monohydrochloride

Molecular formula and molecular mass: $C_{16}H_{25}N_2OCl$
296.84 g/mol (260.38 g/mol as the free base)

Structural formula:



, HCl

Description: Ropinirole hydrochloride is a white or yellowish powder.

Physicochemical properties: Ropinirole hydrochloride has a melting range of 239° to 245°C and a solubility of 133 mg/mL in water. The pKa is 9.5 and the pH is approximately 5.0 to 6.5

CLINICAL TRIALS

Comparative Bioavialability Trials

A blinded, randomized, two-treatment, two-period, two-sequence, single-dose, two-way crossover comparative bioavailability study of ROPINIROLE 0.25 mg (ropinirole hydrochloride, Sanis Health Inc.) versus Requip® 0.25 mg (ropinirole hydrochloride, GlaxoSmithKline Inc., Canada) was performed in 22 healthy subjects under fasting conditions. A summary of the bioavailability data is presented in the table below.

Ropinirole (1 x 0.25 mg) From measured data (uncorrected for potency) Geometric Mean Arithmetic Mean (CV %)				
Parameter	**ROPINIROLE 0.25 mg Tablets***	**Requip® 0.25 mg Tablets†**	**% Ratio of Geometric Means**	**90% Confidence Interval**
AUC_{0-t} (pg·hr/mL)	4525.88 4992.29 (49.16)	4341.84 4824.98 (56.83)	104.24	97.81 – 111.09
AUC_{0-inf} (pg·hr/mL)	4774.71 5366.32 (54.67)	4592.13 5238.18 (66.51)	103.98	96.82 – 111.66
C_{max} (pg /mL)	629.75 653.26 (28.93)	580.80 605.97 (31.95)	108.43	99.01 – 118.74
T_{max}§ (h)	1.57 (41.01)	1.74 (68.75)		
$T_{½}$§ (h)	5.35 (23.83)	5.33 (27.94)		

* Ropinirole 0.25 mg Tablets (manufactured for Sanis Health Inc.)

† Requip® 0.25 mg Tablets (manufactured by GlaxoSmithKline Inc.), was purchased in Canada.

§ Expressed as the arithmetic mean (CV%) only

Safety and Efficacy Trials

In pre-marketing clinical trials, 1599 patients have been exposed to ropinirole, with 481 patients being exposed for over one year and 241 patients being exposed for over two years.

Evidence to support the efficacy of ropinirole in treating the signs and symptoms of Parkinson's disease was obtained in multicentre, double-blind, studies. These studies included either patients who had minimal or no prior dopaminergic therapy, or patients who were not optimally controlled with current levodopa-decarboxylase inhibitor therapy. In patients with early disease, ropinirole improved motor function (assessed by the motor component of the UPDRS [Unified Parkinson's Disease Rating Scale]) and delayed the need to initiate treatment with levodopa. In patients with more advanced disease, ropinirole reduced "off" time (based upon patient diaries recording time "on" and "off") and permitted a reduction in levodopa dose. The subsequent section describes some of the studies in which ropinirole was titrated (see DOSAGE AND ADMINISTRATION) to the maximal dose of 8 mg t.i.d.

In clinical trials where dosing was titrated to optimal clinical effect, the mean daily dose of ropinirole at 24 weeks was 9.5 mg in early therapy (n=282) and was 13.5 mg in adjunct therapy (n=303).

In the pivotal clinical trials, including studies where the dose was titrated to the target maximum of 24 mg per day, the mean daily dose of ropinirole at a 6 month study endpoint was 10.7 mg in early therapy (n=458) and 12.5 mg in adjunct therapy (n=456). At the end of a 3-year double-blind study in early Parkinson's patients, the average dose of ropinirole for those patients remaining in the trial (n=102) was 11.9 mg/day, regardless of levodopa supplementation; at the 3-year point of a similar 5-year study, the corresponding mean dose (n=103) was 14.4 mg. At the completion of the 5-year study, the corresponding mean dose (n=85) of ropinirole was 16.6 mg/day.

In the premarketing clinical trial patient database (n=1599) over 50% of patients were dosed between 6 and 15 mg of ropinirole per day in both early and adjunct therapy. Less than 22% of patients exceeded a total daily dose of 15 mg.

During the clinical trials, the dose of ropinirole was titrated to optimal clinical response and tolerance. Retrospective analysis showed that female patients required lower doses than male patients but were exposed to ropinirole for similar periods of time.

Early Therapy

Placebo-Controlled Studies

In a double-blind, randomized, placebo-controlled, 6-month study, ropinirole-treated patients (n=116) demonstrated a 24% improvement in UPDRS motor scores from baseline, compared to placebo-treated patients (n=125), who demonstrated a 3% worsening in motor scores. On the Clinical Global Impression (CGI) scale, 33% of ropinirole-treated patients and 12% of placebo-treated patients were rated as "very much improved" and "much improved". "Rescue levodopa" was needed by 11% of ropinirole-treated and 29% of placebo-treated patients. All differences were statistically significant.

Comparator-Controlled Studies

Five-Year Study

In a 5-year multi-centre, double-blind, flexible dose study, 268 patients were randomized to either ropinirole (n=179) or levodopa-benserazide (n=89), with open-label L-dopa available as supplementary medication. Patients were classified between Hoehn and Yahr (H&Y) stage I and stage III, and had a mean disease duration of approximately 2.5 years and a mean age of approximately 63 years.

Six Month Interim Findings

The decrease in UPDRS motor scores vs. baseline was greater with L-dopa than with ropinirole. However, the proportion of "responders" (UPDRS improvement of at least 30%) did not differ between L-dopa and ropinirole. Results on the CGI indicated that there was no difference between ropinirole and L-dopa for the less severely afflicted patients (Hoehn and Yahr stage I to II) but L-dopa was more efficacious in patients with more severe disease.

Five Year Endpoint Findings

It should be noted that the interpretability of these data is limited with regard to the relative clinical efficacy of the two drugs beyond the six month point considering the progressive degenerative nature of the disease, the lack of a placebo control arm and that the minimal change associated with clinical relevance for efficacy was not defined in this study for the five year endpoint analysis.

Safety

Dyskinesia: In this 5-year study, the risk of patients developing involuntary movements (i.e. dyskinesias) was shown to be reduced with initial treatment with ropinirole (without concomitant L-dopa) compared to that associated with the administration of levodopa as initial therapy.

The primary endpoint of the 5-year study was dyskinesia, defined as UPDRS Part IV Item 32 (duration of abnormal movement), plus related adverse event reports. A significantly smaller proportion of patients developed dyskinesias in the ropinirole arm (20%, 36/177) compared to the L-dopa arm (45%, 40/88).

This treatment difference becomes larger if the factor of supplementary L-dopa is taken into account; due to methodological issues, this comparison is most appropriately done through survival analysis. Figure 1, (below) displays the survival curves for time to dyskinesia regardless of supplementary L-dopa for both treatment groups. The vertical axis represents the proportion of individuals who remained free from dyskinesia at various times following the initiation of treatment, with the horizontal axis indicating time. The two survival curves were demonstrated to be statistically different by Cox regression analysis, such that the overall risk of dyskinesia onset was 2.82 times higher in the L-dopa arm than in the ropinirole arm (hazard ratio of 2.82).

Figure 2 (below) displays the survival curves for time to dyskinesia onset before receipt of supplementary L-dopa (thus, any dyskinesia-free patients who received supplementary L-dopa were removed from the analysis at the time the supplementary medication was initiated). The treatment difference between these subgroup survival curves was larger than that between the overall survival curves, such that the risk of dyskinesia onset prior to the initiation of any

supplemental L-dopa was seven times higher in the L-dopa treatment arm than in the ropinirole arm (hazard ratio of 7.00).

Figure 1 **Kaplan-Meier survival plot for the time to onset of dyskinesias in those patients remaining in the study over time**

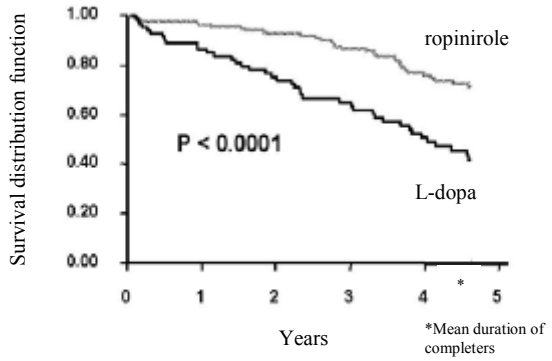
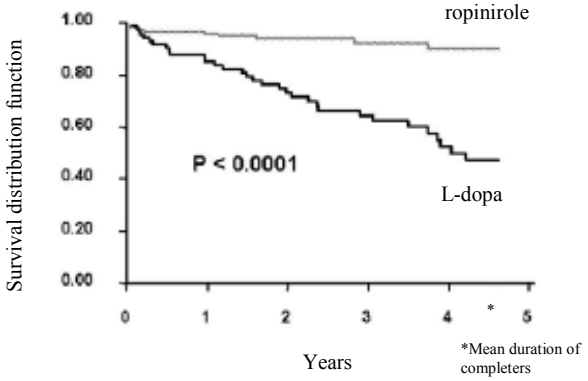


Figure 2 **Kaplan-Meier survival plot for the time to onset of dyskinesias (prior to supplementary L-dopa) in those patients remaining in the study over time**



Dystonias: Dystonias were identified using Item 34 (painful dyskinesias) plus any adverse events coding to dystonia (including blepharospasm and torticollis). Dystonia was experienced by 48 (27%) ropinirole patients and 42 (49%) L-dopa patients. Of the patients in the study that remained dyskinesia-free, dystonia was experienced by 12/140 patients on ropinirole and 2/46 patients on L-dopa.

General: The proportion of patients who completed the study was not different between treatment arms (47% ropinirole vs. 51% L-dopa), nor did the overall rate of withdrawal due to adverse events differ between the two treatments (27% for ropinirole vs. 33% for L-dopa). Ropinirole patients receiving concomitant selegiline reported a higher incidence of hallucination (23.5%) than did those without (12.2%); this subpopulation effect was not seen in the L-dopa

arm (hallucination with concomitant selegiline = 2.0% vs. hallucination without selegiline = 8.0%).

Efficacy

Overall, in both the ropinirole and L-dopa arms, improvements in efficacy outcomes were seen for the first six months, with gradual deterioration back towards baseline over the remainder of the trial.

For the observed-cases data set, mean change from baseline scores for Activities of Daily Living (ADL, UPDRS part II) indicated that L-dopa patients showed consistently better improvement than did ropinirole patients, by a margin of approximately 0.5 to 1.5 points. At completion, ropinirole patients showed a mean deterioration of 1.6 ± 5.4 points from baseline, compared to 0.0 ± 4.7 points for L-dopa patients. This difference is not statistically significant.

Within the ropinirole arm there was a subpopulation effect in the ADL scores, in that ropinirole patients with less severe status at baseline (H&Y stages I - II) showed a significantly better response than did patients with more severe status at baseline (H&Y stages II.5 - III); in contrast, the L-dopa arm showed no subpopulation effect in the ADL scores. (Mean change from baseline in ADL scores at completion, for ropinirole: less severe patients = 0.18 vs. more severe patients = 3.61; for L-dopa: less severe patients = -0.18 vs. more severe patients = -0.61).

For the observed-cases data set, the mean change from baseline motor scores (UPDRS part III) show a consistent difference throughout the study of approximately 2 to 4 points in favour of L-dopa. At completion, was a statistically significant difference between the treatment arms in favour of L-dopa (mean change from baseline: ropinirole = -0.8 ± 10.1 vs. L-dopa = ± -4.8 ± 8.3).

Of the Intent-to-Treat patient set, supplemental L-dopa was given to 51% of ropinirole-treated and 35% of levodopa-treated patients. Of the subset of patients who completed the study, 66% in the ropinirole arm received supplemental L-dopa, compared to 36% in the L-dopa arm.

Three-year Study

In a 3-year multi-centre, double-blind study, 355 patients were randomized to receive either ropinirole (n=168) or another dopamine agonist (n=167), with open-label L-dopa available as supplementary medication. Patients were classified between Hoehn and Yahr (H&Y) stage I and stage III, had a mean disease duration of approximately 2 years and a mean age of approximately 63 years.

It should be noted that the interpretability of these data is limited with regard to the relative clinical efficacy of the two drugs considering the progressive degenerative nature of the disease,

the lack of a placebo control arm and that the minimal change associated with clinical relevance for efficacy was not defined in this study for the three year end point analysis.

Safety

Dyskinesias were defined by UPDRS Part IV Items 32 (duration of abnormal movement), 33 (disability), and 34 (painful dyskinesia), plus all related adverse events. A total of 8% of ropinirole-treated patients and 7% of comparator-treated patients had developed dyskinesias by the 3 years end point. The proportion of patients who completed the study did not differ between treatment arms (61% ropinirole vs. 67% active comparator), nor did the overall rate of withdrawal due to adverse events (20.2% for ropinirole vs. 19.8% for the active control).

Efficacy

Overall, in both the ropinirole and dopamine agonist comparator arms, improvements in efficacy outcomes were seen for the first six months, with gradual deterioration back towards baseline over the remainder of the trial.

For the observed-cases data set, mean change from baseline scores for Activities of Daily Living (ADL, UPDRS part II) for both treatment groups were within 0 to 0.5 points of each other until Week 120 (2.5 years). During the final six months, the ropinirole scores remained relatively stable in contrast to those of the treatment group, such that at study endpoint, ropinirole patients showed statistically more improvement than did the patients receiving the comparator agonist (mean change from baseline 1.9 ± 0.6 vs. 0.4 ± 0.6, respectively).

For the observed-cases dataset, the mean change from baseline motor scores (UPDRS part III) show a consistent difference throughout the study of approximately 1 to 3 points in favour of ropinirole. At completion, ropinirole patients showed a mean improvement of -6.5 ± 10.0 points from baseline, compared to -4.1 ± 10.6 for comparator patients. This difference is not statistically significant. The proportion of "responders" (UPDRS improvement of at least 30%) did not differ statistically between the two treatment arms (ropinirole = 53%; comparator = 42.5%). Supplemental levodopa was given to 34% of ropinirole-treated and 42% of active comparator-treated patients.

Adjunct Therapy

In a double-blind, randomized, clinical trial of 6-month duration, ropinirole (n=94) was compared to placebo (n=54) as adjunct therapy to levodopa. The primary efficacy parameter, defined as both a 20% or greater reduction in levodopa dose and a 20% or greater reduction in "off" time, was achieved by 28% of ropinirole-treated patients and 11% of placebo-treated patients. This difference was statistically significant. The daily dose of levodopa was reduced by 19% and 2.8% in the ropinirole and placebo-treated patients, respectively.

Therapeutic Effect – Plasma Concentration
The relationship between efficacy and plasma concentrations of ropinirole was assessed from population pharmacokinetic data obtained in 141 male and female patients who participated in two prospective studies.

In general, the average plasma concentrations of ropinirole at steady-state (C_{ss}) were higher in patients classified as responders versus non-responders, although considerable overlap in the range of C_{ss} between the two groups was noted. Mean (± SD) ropinirole C_{ss} for responders and non-responders were 22.8 ± 10.8 ng/mL and 15.1 ± 9.7 ng/mL, respectively.

DETAILED PHARMACOLOGY

***In vitro* receptor binding studies**
Ropinirole has high affinity for the D_2 family of dopamine receptors (which comprises the D_2, D_3 and D_4 receptors) as established in radioligand binding studies using cloned human and rat receptors.

	D_2 Ki^1 (nM)	**D_3 Ki^1 (nM)**	**D_4 Ki (nM)**
Human Cloned Receptors	1380	69.1	1130
Rat Cloned Receptors	948	98.6	NT

NT Not tested
Ki^1 represents the high affinity binding site

Ropinirole has negligible activity as a dopamine D_1 receptor agonist, shown by both very weak ability to bind to the D_1 receptor or to stimulate adenylyl cyclase activity.

Ropinirole did not bind with high affinity to a number of non-dopaminergic receptor sites, namely 5-HT_1, 5-HT_2, muscarinic cholinergic, $GABA_A$, alpha-adrenergic, beta-adrenergic receptors, and peripheral benzodiazepine receptors. Ropinirole bound with moderate affinity to opiate receptors in guinea-pig cerebellum, labelled by the non-selective opiate antagonist ^{3}H-naloxone. The rank order of potency of ropinirole at the opiate receptor subtypes was kappa>mu>sigma.

The N-despropyl metabolite of ropinirole had lower affinity than ropinirole at both the D_2 and D_3 receptor sites. The hydroxy metabolite of ropinirole had a 50 fold greater affinity than ropinirole at the cloned human D_2 receptors.

Behavioural studies in rodent and primate models
The doses refer to the hydrochloride salt. Ropinirole has a biphasic effect on locomotor activity which is characteristic of centrally active dopamine agonists. Low doses inhibit spontaneous

locomotion, while higher doses cause locomotor stimulation. In mice, 10 and 100 mg/kg ip doses brought about inhibition and stimulation, respectively. In rats, considerably lower doses produced these effects, namely hypoactivity was observed at 0.3 mg/kg and hyperactivity in the 1-30 mg/kg dose range.

In mice, ropinirole caused sniffing which, however, did not develop into full stereotypy over a 1 to 100 mg/kg ip dose range. In rats, ropinirole caused stereotyped behaviour. However, the intensity of this stereotypy, seen at the maximally effective dose of 3 mg/kg sc, was less than that seen with apomorphine.

Ropinirole was also active in 6-OHDA (hydroxydopamine)-lesioned animals. In mice, ropinirole caused contralateral asymmetry in the dose range of 0.01-100 mg/kg ip, while in rats, the drug induced contralateral circling in a dose range of 0.05-3.2 mg/kg sc. The hydroxy metabolite of ropinirole was equipotent to the parent drug in inducing rotational behaviour, while the N-despropyl metabolite was approximately 100 fold less potent.

The neurotoxin, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) produces bradykinesia, rigidity of the limbs and trunk and immobility of the neck and head in marmosets, symptoms which resemble those of Parkinson's disease. Ropinirole antagonized the effects of MPTP. At the threshold dose of 0.05 mg/kg sc, only some of the animals responded. However, in the 0.1 to 1.0 mg/kg sc dose range, ropinirole reversed completely the MPTP-induced motor deficits. At the 0.1 and 1.0 mg/kg doses, ropinirole also caused some dose-related emesis.

There was no evidence that repeated dosing led to the development of tolerance to the CNS effects of ropinirole.

Cardiovascular effects

Ropinirole induced a dose-related fall in blood pressure and reduced heart rate in anaesthetised rats. In conscious spontaneously hypertensive rats, iv doses of 0.5, 2.5 and 5.0 mg/kg produced falls of 11.5, 24.5 and 28.0 mmHg while oral doses of 10, 15, 20 and 40 mg/kg caused falls of 4.0, 12, 19 and 25 mmHg. The fall in blood pressure was generally accompanied by bradycardia. The ropinirole-induced hypotension was reversed by sulpiride or domperidone, two dopamine antagonists, confirming that ropinirole exerts its pharmacological effects via activation of D_2-dopamine receptors. When administering ropinirole up to 14 days to spontaneously hypertensive rats, at doses of 10, 20 and 40 mg/kg/day, tolerance developed rapidly to the hypotensive effect of the drug.

Falls in blood pressure and heart rate were also demonstrated in mongrel dogs (10 mcg/kg/min iv). In beagle dogs, a 100 mcg/kg bolus dose caused sustained decreases in blood pressure and total peripheral resistance without compensatory tachycardia, attesting to the sympatholytic activity of ropinirole.

In cynomolgous monkeys, 0.1 mg/kg iv ropinirole caused hypotension. Following repeated administration of ropinirole (5 mg/kg p.o., bid for up to 35 days) tolerance developed to the hypotensive effect of not only the 0.1 mg/kg iv dose, but to the 10 times larger iv dose as well. In addition, cross-tolerance to the cardiovascular effect of bromocriptine was demonstrated in this paradigm.

TOXICOLOGY

Single Dose Studies

Swiss Mice: the approximate median lethal dose was 657 mg/kg p.o. and 46 mg/kg iv

Wistar Rats: the approximate median lethal dose was 862 mg/kg p.o. and 66 mg/kg iv

Clinical signs: The clinical signs, that were similar in both species, were characteristic of central D_2 stimulatory activity and at higher doses of general CNS stimulation. They were clearly dose-related and included hyperactivity, abnormal locomotion, stereotypy, tremors, convulsions and finally death.

Repeat Dose Studies

The studies were carried out in mice, rats, and cynomolgous monkeys. The dog could not be used since dopamine agonists act as potent emetics in this species.

Mice

The studies included a 7-day, 60-day and 90-day study. The clinical observations, which were clearly dose-related, included ptosis, hyperactivity, vocalization, aggression, tremors, convulsions, rapid/laboured respiration and in a few animals death. In all three studies, the maximal no effect dose was 25 mg/kg.

Rats

30-day study: the maximal no effect dose was <10 mg/kg. BUN, ALT and AP were increased in a few mid- and high-dose animals. At necropsy, the relative weights of the liver, adrenals and ovaries were increased in mid- and high-dose females. In the adrenals, the zona fasciculata and the zona reticularis were somewhat increased. In the ovaries, the number of corpora lutea was increased. In the liver, 'ground glass' appearance of the centrilobular hepatocytes, due to moderate proliferation of the smooth endoplasmic reticulum, were noted in both sexes at the high dose (250 mg/kg).

6-month study: the maximal no effect dose was 10 mg/kg. ALT and AP were increased in a few mid- and high-dose animals. Ropinirole reduced serum prolactin levels in both sexes at all doses. In most of the animals, the levels were below the limit of detection; however, following a 6-week recovery period, they returned to control values. There were a number of histological abnormalities that could be related to reduced prolactin levels, namely changes in the ovaries, vagina, and mammary glands, in the hypophysis of male rats and adrenocortical hypertrophy in females. Except for the ovarian changes, the abnormalities were not present after the 6-week recovery period. In addition, the following changes were observed: centrilobular hepatocyte hypertrophy in some of the high-dose animals (200 mg/kg reduced to 125 mg/kg/day on day 57), and epithelial hyperplasia of the urinary bladder in 3 high-dose animals. Leydig cell hyperplasia, observed in the 1-year toxicology and 2-year carcinogenicity studies, was not observed in this study.

1-year study: mortality was higher in the high dose group (100 mg/kg) than at the lower doses (5 and 50 mg/kg), and it was often preceded by convulsions. Weight gain was decreased in both sexes at the mid- and high-doses, although in females the decreased weight gain was preceded by an actual weight gain during the first month of the study. In contrast to the observed decreased weight gain, food intake was increased in both sexes, although it was more marked in female rats. Prolactin levels were markedly decreased in male but not in female rats. Both plasma estrogen and progesterone levels were increased, but the former to a greater extent, thus, there was an absolute increase in the ratio of estrogen to progesterone. There was also a slight increase in BUN. Absolute adrenal weights were increased in mid- and high-dose males and females and absolute liver weights in females. Histopathology revealed the following changes – with most of the changes affecting animals in the mid- and high-dose groups: erosion or ulceration of the glandular mucosa of the stomach; hepatocellular alterations and centrilobular hypertrophy of the liver; a decrease in proliferative pituitary lesions at the high dose of both sexes; an increase in the incidence of Leydig cell hyperplasia in the testes. Other changes included increased incidence of endometrial hyperplasia of the uterus, and changes in the ovaries and vagina.

Cynomolgous monkeys

30-day study: the maximal no effect dose was 5 mg/kg (high dose: 15 mg/kg). At lower doses, the animals showed slight nervousness, lip smacking and piloerection, while at higher doses they showed ptosis, salivation, hyperactivity and self-inflicted wounds. Pathological examination revealed no drug-related lesions either macroscopically or microscopically.

34-week study: the maximal no effect dose was 15 mg/kg. Originally, the highest dose was 15 mg/kg. Since no behavioural changes were noted, the dose was increased after 8 weeks to 30 mg/kg and treatment was continued for an additional 26 weeks. Decreased weight gain was noted in some high-dose males but not in females. Plasma ALT was increased and plasma sodium decreased in some high-dose males. Serum prolactin was decreased. No ocular changes

were seen by ophthalmoscopy. Adrenal weights were increased in mid- and high-dose males and liver weights in high-dose females. No drug-related changes were observed in macroscopic or microscopic examinations. Toxicokinetic analysis indicated that the levels of the N-despropyl metabolite were considerably higher than those of the parent drug or the hydroxy metabolite. Accumulation of the N-despropyl metabolite was noted.

***1-year study*:** the maximal no effect dose was 5 mg/kg (high dose: 15 mg/kg). Clinical signs included stereotyped locomotion and excessive grooming in some high-dose monkeys. Decreased weight gain was noted in some high-dose males but not in females. No ocular changes were seen by ophthalmoscopic exams. Adrenal weights were increased in high-dose animals of both sexes; increased weights were also noted for testes and ovaries. No drug-related changes were observed in macroscopic or microscopic examinations. Toxicokinetic analysis showed that systemic exposure to ropinirole and the N-despropyl metabolite increased non-proportionally with increasing doses, indicating saturable first pass metabolism. The concentration of the N-despropyl metabolite was considerably higher than that of ropinirole.

Carcinogenicity

Mice

Charles River mice received ropinirole by gavage at doses of 5, 15 and 50 mg/kg/day for 104 weeks. There were two control groups. Mortality was similar in all groups. Mean weight gain was less in mid- and high-dose males than among controls; the weight of females was not affected. Dose-dependent alopecia and/or thinning of fur was noted in ropinirole-treated females. WBC was lower at the end of the study in high-dose males.
Histopathological examination revealed an increased incidence of benign uterine endometrial stromal polyps in high dose females.

Rats

Sprague-Dawley rats received ropinirole by gavage at doses of 1.5, 15 and 50 mg/kg/day for approximately 23 months. There were two control groups. Mortality was similar in all groups. Increased incidences of aggression, foot pad lesions and alopecia were noted in animals of both sexes at the mid- and high-doses. At necropsy, urinary bladder distension was noted more frequently among high-dose animals than controls. Enlargement of the pituitary was less frequent in treated animals than in controls. *Histology*: increased incidence of testicular Leydig cell adenomas at doses > 1.5 mg/kg; *pituitary gland*: increased incidence of hyperplasia in females and increased cytoplasmic vacuolation in males; *ovary*: decreased incidence of ovarian quiescence and sertoliform hyperplasia with increased incidence of abnormal corpora lutea; *mammary glands*: decreased incidence of fibroadenomas and adenocarcinomas at the high dose; *liver*: increased incidence of centrilobular hepatocellular hypertrophy in mid- and high-dose animals, but decreased incidence of vacuolation and biliary hyperplasia. Retinal atrophy was

seen only in ropinirole but not in control rats. The incidence was 1.4%, 1.4% and 10% in male rats and 1.4%, 2.9% and 12.9% in female rats. Results from a subsequent 3 month investigative study, suggested that in albino rats there was an association between retinal degeneration and exposure of the retina to a higher light level. Ropinirole 100 mg/kg/day had no significant effect on the severity of light-induced retinal degeneration. Retinal degeneration was not observed in normal (pigmented) rats after 3 months, in a 2 year carcinogenicity study in albino mice, or in 1 year studies in monkeys or albino rats.

Mutagenicity

Ropinirole did not cause gene mutation or chromosome damage in a battery of genotoxicity assays, including the bacterial mutagenicity tests (*Salmonella typhimurium* and *Escherichia coli*), *in vitro* chromosome aberration test in human lymphocytes, *in vitro* mouse lymphoma (L5178Y cells) assay and *in vivo* mouse micronucleus test.

Reproductive Studies

Pregnant Rats

^{14}C-ropinirole was given to pregnant rats from day 11 to day 16 of pregnancy. Radioactivity was detectable in maternal plasma, amniotic fluid and foetuses.

Lactating Rats

^{14}C-ropinirole was given to lactating Wistar rats. Radioactivity was detectable in the milk, albeit at lower concentrations than in plasma.

Fertility Study in Male Rats

Animals were treated for 107 days, the maximal dose being 125 mg/kg/day. At this dose, clinical signs, including tremors, stereotypy, convulsions, and deaths have occurred, and the incidence of pregnancy was slightly decreased (72% versus 86% in the control group). At lower doses there was no effect on mating or fertility.

Fertility Study in Female Rats

Reproduction in the rat is prolactin-dependent during early pregnancy and throughout lactation. In studies, in which sub- or low-pharmacological doses were administered (pregnancy days 0 to 8 [5 mg/kg] and lactation [5, 10, or 20 mg/kg]), ropinirole did not affect mating performance, fertility rate or pregnancy outcome. If doses were not lowered, a dose-related decrease in fertility was seen at doses > 10 mg/kg. Ropinirole, when given at 50 mg/kg, markedly decreased serum levels of prolactin and progesterone, and prevented the establishment of pregnancy or

caused abortion.

Teratology Study in Rats

Ropinirole was given to mated Wistar female rats at 20 mg/kg, from day 7 to day 8 of pregnancy. From days 9 to 16, the daily dose either remained 20 mg/kg, or was increased to 60, 90, 120, or 150 mg/kg. There were no maternal deaths or abortions. A dose-related increase in post-implantation loss (up to 43%) and a decrease in mean fetal weight were noted in groups which received ropinirole at 20/120 and 20/150 mg/kg/day. Retarded ossification of hindlimb metatarsals was seen in the 20/150 mg/kg group. Malformations, including abnormal digits, neural tube defects and cardiovascular abnormalities were observed in the fetuses of dams dosed with 20/120 and 20/150 mg/kg/day.

Teratology Study in Rabbits

Ropinirole was given to mated New Zealand White female rabbits at doses of 1, 5, and 20 mg/kg from day 6 to day 18 of pregnancy. At the high-dose, two females died after receiving 2-3 doses. Of three females who had vaginal bleeding, one rabbit had no fetuses. Thus, although there was maternal toxicity, development of the fetuses (weight, sex ratio, skeletal and visceral development) was not affected.

Mated New Zealand White rabbits were orally given ropinirole alone (10 mg/kg/day), L-dopa alone (250 mg/kg/day) or ropinirole combined with L-dopa, from day 6 to 20 of pregnancy. There was a greater incidence and severity of fetal malformations (primarily digit defects) when ropinirole was given in combination with L-dopa than when L-dopa was given alone. This drug combination was also associated with maternal toxicity.

Peri-/Post-Natal Study in Rats

Ropinirole was given at 0.1, 1.0 and 10 mg/kg/day to pregnant Sprague-Dawley rats from day 15 of pregnancy to weaning. No maternal deaths or abortions were observed. While the weights of the high-dose pups was higher than that of the controls at age 1-2 days, their weight subsequently decreased and by day 14, they weighed 18% less than controls. The retardation of the growth of the offsprings was due to maternal hypoprolactinemia and reduced lactation. The startle response to auditory and tactile stimulation was reduced in female, but not male offsprings, by age 29 days at the 1 and 10 mg/kg doses and at sexual maturity at the high dose.

Table 5 Comparative pharmacokinetic data at steady-state for ropinirole and its metabolites following oral administration of ropinirole to mice, rats, cynomolgus monkeys and Parkinson's disease patients

Compound	Dose (mg/kg/day)	C_{max} (ng/mL)	T_{max} (h)	AUC (ng.h/mL)[B]
Ropinirole				
Man	0.48[A]	36.7	0.5 – 7	557
Mouse	43.8	430 (11.7)*	0.5	325(0.6)*
Rat	50	479 (13.1)*	1.5 – 4	1580 (2.8)*
Monkey	15	184 (5.0)*	1 – 2	511 (0.9)*
SK&F 89124 (7-hydroxy ropinirole)				
Man	0.48 [A]	1.3	0.5 – 1	19.2
Rat	50	55.1 (42.4)*	4 – 8	198 (10.3)*
SK&F 104557 (N-despropyl ropinirole)				
Man	0.48 [A]	33.0	1 – 8	605
Rat	50	281 (8.5)*	3 – 4	1320 (2.2)*
Monkey	15	2930 (88.8)*	1 – 2	11500 (19.0)*

Data presented are for male and female animals.

[A] Data for man are at a maximal daily dose of 24 mg given as 8 mg t.i.d. (equivalent to 0.48 mg/kg/day assuming a body weight of 50 kg). C_{max} and AUC values for man were derived by extrapolation from dose normalised data obtained in male and female patients (C_{max} and AUC per mg multiplied by 24).

[B] AUC_{0-t} where t is the time of the last data point (6, 8 and up to 24 h in mouse, rat and monkey, respectively, and 24 h in man). A dose of 50 mg/kg/day was the highest dose tested in the 2-year oral carcinogenicity studies in the mouse and in the rat. A dose of 15 mg/kg/day was the highest dose tested in the 1-year oral toxicity study in the monkey.

ND- SK&F 89124 was not detected in monkey plasma. Pharmacokinetic data for SK&F 89124 and SK&F 104557 have not been determined in the mouse.

* Numbers in parentheses represent ratios of exposure in animals to those in Parkinsonian patients at 0.48 mg/kg/day.

REFERENCES

Preclinical References

1. Freedman SB, Patel S, Marwood R, Emms F, Seabrook GR, Knowles MR et al. Expression and pharmacological characterization of the human D3 dopamine receptor. J Pharm Exp Ther 1994; 268(1): 417-426.

2. Griffith RW, Grauwiler J, Hodel C, Leist KH and Matter B. Toxicologic Considerations. Ergot Alkaloids and Related Compounds. Handbook of Experimental Pharmacology, 1978; 49:805-851.

3. Haseman JK, Arnold JaES. Tumour incidences in Fischer 344 rats: NTP historical data. Pathology of the Fischer rat Boorman GA et al (eds), Academic Press, Inc, San Diego, CA, 1990; 555-564.

4. Hernandez DE, Adcock JW, Orlando RC, Patrick KS, Nemeroff CB and Prange AJ, Jr. Prevention of stress-induced gastric ulcers by dopamine agonists in the rat. Life Sci 1984; 35(24):2453-2458.

5. Huhtaniemi IT, Catt KJ. Induction and maintenance of gonadotropin and lactogen receptors in hypoprolactinemic rats. Endocrinology 1981; 109(2):483-490.

6. Huhtaniemi IT, Stewart JM, Channabasavaiah K, Fraser HM, Clayton RN. Effect of treatment with GnRH antagonist, GnRH antiserum and bromocriptine on pituitary-testicular function in adult rats. Mol Cell Endocrinol 1984; 34(2):127-135.

7. Mackenzie RG, VanLeeuwen D, Pugsley TA, Shih YH, Demattos S, Tang L et al. Characterization of the human dopamine D3 receptor expressed in transfected cell lines. Eur J Pharmacol 1994; 266(1):79-85.

8. McMartin DN, Sahota PS, Gunson DE, Hsu HH, Spaet RH. Neoplasms and related proliferative lesions in control Sprague-Dawley rats from carcinogenicity studies. Historical data and diagnostic considerations. Toxicol Pathol 1992; 20(2):212-225.

9. McNeilly AS, Glasier A, Jonassen J and Howie PW. Evidence for direct inhibition of ovarian function by prolactin. J Reprod Fertil 1982; 65(2):559-569.

10. Prentice D, Siegel RA, Donatsch P, Qureshi S and Ettlin RA. Mesulergine induced leydig cell tumors, a syndrome involving the pituitary-testicular axis of the rat. Medical Toxicology Proceeding of the 1991 EUROTOX Congress 1992;197-204.

11. Purvis K, Clausen O-PF, Hansson V. Regulation of Leydig cell sensitivity and responsiveness to LH/hCG. International Journal of Andrology {INT J ANDROL} 1978; 1(SUPP.2):247-263.

12. Purvis K, Clausen OP, Olsen A, Haug E, Hansson V. Prolactin and Leydig cell responsiveness to LH/hCG in the rat. Arch Androl 1979; 3(3):219-230.

13. Roberts SA, Nett TM, Hartman HA, Adams TE, Stoll RE. SDZ-200-110 induces Leydig cell tumors by increasing gonadotropins in rats. Journal of the American College of Toxicology 1989; 8(3):487-505.

14. Seeman P, Van Tol HH. Dopamine receptor pharmacology. Trends Pharmacol Sci 1994; 15(7):264-270.

15. Sharpe RM, McNeilly AS. The effect of induced hyperprolactinaemia on Leydig cell function and LH-induced loss of LH-receptors in the rat testis. Mol Cell Endocrinol 1979; 16(1):19-27.

16. Sokoloff P, Giros B, Martres MP, Bouthenet ML, Schwartz JC. Molecular cloning and characterisation of a novel dopamine receptor (D3) as a target for neuroleptics. Nature 1990; 347(6289):146-151.

17. Stahle L. Do autoreceptors mediate dopamine agonist--induced yawning and suppression of exploration? A critical review. Psychopharmacology (Berl) 1992; 106(1):1-13.

18. Waeber C, Reymond O, Reymond M, Lemarchand-Beraud T. Effects of hyper- and hypoprolactinemia on gonadotropin secretion, rat testicular luteinizing hormone/human chorionic gonadotropin receptors and testosterone production by isolated Leydig cells. Biol Reprod 1983; 28(1):167-177.

19. Wahlström T, Huhtaniemi I, Hovatta O, Seppälä M. Localization of luteinising hormone, follicle-stimulating hormone, prolactin, and their receptors in human and rat testis using immunohistochemistry and radioreceptor assay. J Clin Endocrinol Metab 1983; 57(4): 825-830.

20. Watts VJ, Lawler CP, Knoerzer T, Mayleben MA, Neve KA, Nichols DE et al. Hexahydrobenzo[a]phenanthridines: novel dopamine D3 receptor ligands. Eur J Pharmacol 1993; 239(1-3):271-273.

Clinical References

21. Calne DB, Teychenne PF, Claveria LE, Eastman R, Greenacre JK, Petrie A. Bromocriptine in Parkinsonism. Br Med J 1974; 4(5942):442-444.

22. Comella CL, Stebbins GT, Brown-Toms N, Goetz CG. Physical therapy and Parkinson's disease: a controlled clinical trial. Neurology 1994; 44(3 Pt 1):376-378.

23. De Jong GJ, Meerwaldt JD, Schmitz PI. Factors that influence the occurrence of response variations in Parkinson's disease. Ann Neurol 1987; 22(1):4-7.

24. Fabbrini G, Mouradian MM, Juncos JL, Schlegel J, Mohr E, Chase TN. Motor fluctuations in Parkinson's disease: central pathophysiological mechanisms – Part I. Ann Neurol 1988; 24(3):366-371.

25. Fahn S, Elton RL UPDRS Development Committee. Unified Parkinson`s Disease Rating Scale. Recent Developments in Parkinson`s Disease MacMillan Healthcare Information, Florham park NJ USA 1987; 2:153-163.

26. Fahn S. Is levodopa toxic? Neurology 1996; 47(6 Suppl 3):S184-S195.

27. Gasser T, Schwarz J, Arnold G, Trenkwalder C, Oertel WH. Apomorphine test for dopaminergic responsiveness in patients with previously untreated Parkinson's disease. Arch Neuro 1992; 49(11):1131-1134.

28. Hefti F, Melamed E, Bhawan J, Wurtman RJ. Long-term adminisration of L DOPA does not damage Dopaminergic Neurons in the mouse. Neurology, 1981; 31(0028-3878):1194-1195.

29. Hely MA, Morris JG, Reid WG, O'Sullivan DJ, Williamson PM, Rail D et al. The Sydney Multicentre Study of Parkinson's Disease: a randomized, prospective five year study comparing low dose bromocriptine and low dose levodopa-carbidopa. J Neurol Neurosurg Psychiatry 1994; 57(8):903-910.

30. Hoehn MM, Yahr MD. Parkinsonism: onset, progression and mortality. Neurology 1967; 17(5):427-442.

31. Hubble JP, Pahwa R, Michalek DK, Thomas C, Koller WC. Interactive video conferencing: a means of providing interim care to Parkinson's disease patients. Mov Disord 1993; 8(3):380-382.

32. Hughes AJ, Ben Shlomo Y, Daniel SE, Lees AJ. What features improve the accuracy of clinical diagnosis in Parkinson's disease: a clinicopathologic study. Neurology 1992; 42(6):1142-1146.

33. Jankovic J. Long-term study of pergolide in Parkinson's disease. Neurology 1985; 35(3):296-299.

34. Korczyn AD, Rascol O, Adler CH. Dosing with Ropinirole in a clinical setting. Poster Presentation from the XIII International Congress on Parkinson's Disease, Vancouver, Canada 1999.

35. Lees AJ. L-dopa treatment and Parkinson's disease. Q J Med 1986; 59(230):535-547.

36. Lieberman A, Imke S, Muenter M, Wheeler K, Ahlskog JE, Matsumoto JY et al. Multicenter study of cabergoline, a long-acting dopamine receptor agonist, in Parkinson's disease patients with fluctuating responses to levodopa/carbidopa. Neurology 1993; 43(10):1981-1984.

37. Martinez-Martin P, Gil-Nagel A, Gracia LM, Gomez JB, Martinez-Sarries J, Bermejo F. Unified Parkinson's Disease Rating Scale characteristics and structure. The Cooperative Multicentric Group. Mov Disord 1994; 9(1):76-83.

38. Marttila RJ, Rinne UK. Changing epidemiology of Parkinson's disease: predicted effects of levodopa treatment. Acta Neurol Scand 1979; 59(2-3):80-87.

39. Montastruc JL, Rascol O, Senard JM, Rascol A. A randomized controlled study comparing bromocriptine to which levodopa was later added, with levodopa alone in previously untreated patients with Parkinson's disease: a five year follow up. J Neurol Neurosurg Psychiatry 1994; 57(9):1034-1038.

40. Mouradian MM, Juncos JL, Fabbrini G, Schlegel J, Bartko JJ, Chase TN. Motor fluctuations in Parkinson's disease: central pathophysiological mechanisms, Part II. Ann Neurol 1988; 24(3):372-378.

41. Ogawa N. Levodopa and dopamine agonists in the treatment of Parkinson's disease: advantages and disadvantages. Eur Neurol 1994; 34 Suppl 3:20-28.

42. Olanow CW. An introduction to the free radical hypothesis in Parkinson's Disease. Ann Neurol 1992; 32 Suppl:S2- S9.

43. Olanow CW, Fahn S, Muenter M, Klawans H, Hurtig H, Stern M et al. A multicenter double-blind placebo-controlled trial of pergolide as an adjunct to Sinemet in Parkinson's disease. Mov Disord 1994; 9(1):40-47.

44. Pallis CA. Parkinsonism--Natural history and clinical features. British medical journal 1971; 18:683-690.

45. Peppe A, Dambrosia JM, Chase TN. Risk factors for motor response complications in L-dopa-treated parkinsonian patients. Adv Neurol 1993; 60:698-702.

46. Rascol O, Brooks DJ, Korczyn AD. Ropinirole reduces the risk of dyskinesia compared to L-dopa when used in early PD. Poster.

47. Rascol O, Brooks DJ, Korczyn AD, De Deyn PP, Clarke CE, Lang AE. A five-year study of the Incidence of dyskinesia in patients with early Parkinson's disease who were treated with ropinirole or levodopa. 056 Study Group. N Engl J Med 2000; 342(20):1484-1491.

48. Rasmussen C, Brownell J, Bergh T. Clinical response and prolactin concentration in hyperprolactinemic women during and after treatment for 24 months with the new dopamine agonist, CV 205-502. Acta Endocrinol (Copenh) 1991; 125(2):170-176.

49. Richards M, Marder K, Cote L, Mayeux R. Interrater reliability of the Unified Parkinson's Disease Rating Scale motor examination. Mov Disord 1994; 9(1):89-91.

50. Richardson BP, Turkalj I, Flueckinger E. Bromocriptine. Safety Testing of New Drugs 1984;19-63.

51. Rinne UK. Dopamine agonists in the treatment of Parkinson's Disease. Controversies in treatment of Parkinson's Disease Rinne UK & Yanagisawa eds PMSI Japan, Tokyo 1992;49-60.

52. Schapira AH, Advances in the understanding of the cause of Parkinson's disease, J R Soc Med 1994; 87(7):373-375.

53. Shaw KM, Lees AJ, Stern GM. The impact of treatment with levodopa on Parkinson's disease. Q J Med 1980; 49(195):283-293.

54. The Parkinson Study Group. Effect of deprenyl on the progression of disability in early Parkinson's disease. N Engl J Med 1989; 321(20):1364-1371.

55. The Parkinson Study Group. Effects of tocopherol and deprenyl on the progression of disability in early Parkinson's disease. N Engl J Med 1993; 328(3):176-183.

56. Uitti RJ, Ahlskog JE. Comparative review of dopamine receptor agonists in Parkinson's disease. CNS 1996; 5(1172-7047):369-388.

57. Yahr MD, Wolf A, Antunes JL, MiyoshiI K, Duffy P. Autopsy findings in Parkinsonism following treatment with Levo Dopa. Neurology, 1972; 22(0028-3878): 56-71.

58. Product Monograph for REQUIP®. Manufactured by GlaxoSmithKline Inc. Date of Revision: April 4, 2017; Submission Control No. 202058.

PART III: CONSUMER INFORMATION

Pr ROPINIROLE

Ropinirole Tablets, USP

0.25 mg & 1 mg ropinirole
(as ropinirole hydrochloride)

This leaflet is part III of a three-part "Product Monograph" published when ROPINIROLE was approved for sale in Canada and is designed specifically for Consumers.

Please read this information before you start to take your medicine. Keep this leaflet until you have finished all your tablets as you may need to read it again. If you are helping someone else to take ROPINIROLE, read this leaflet before you give the first tablet.

This leaflet is a summary and will not tell you everything about ROPINIROLE. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:
ROPINIROLE, also known as ropinirole is used to treat the signs and symptoms of Parkinson's disease.

You may receive ROPINIROLE on its own, but it may also be given with another drug used to treat Parkinson's disease.

What it does:
ROPINIROLE belongs to the family of medicines called dopamine agonists. ROPINIROLE improves some of the chemical imbalance in the part of the brain affected by Parkinson's disease.

When it should not be used:
Do not use ROPINIROLE if you are allergic to it or any of the components of its formulation (see list below). ROPINIROLE is not recommended for children under 18 years of age.

What the medicinal ingredient is:
Ropinirole hydrochloride

What the nonmedicinal ingredients are:
Non-medicinal ingredients include: croscarmellose sodium, lactose monohydrate, magnesium stearate, microcrystalline cellulose, polyvinyl alcohol, titanium dioxide, polyethylene glycol, talc, FD&C Blue #2 (1mg), iron oxide yellow (1mg).

What dosage forms it comes in:
ROPINIROLE is available as 0.25 mg (white) and 1 mg (green) tablets.

WARNINGS AND PRECAUTIONS

You are warned of a sudden onset of sleep condition which may occur without warning, while taking ROPINIROLE. You should not operate machinery or engage in activities that require alertness, as you may put yourself and others at risk of serious injury or death. This sudden onset of sleep condition has also been reported in patients taking other similar anti-Parkinson drugs.

What should I know before taking ROPINIROLE:
Studies of people with Parkinson's disease show that they may be at an increased risk of developing melanoma, a form of skin cancer, when compared to people without Parkinson's disease. It is not known if this problem is associated with Parkinson's disease or the drugs used to treat Parkinson's disease. ROPINIROLE is one of the drugs used to treat Parkinson's disease, therefore, patients treated with ROPINIROLE should have periodic skin examinations.

Drop in Blood Pressure
While taking ROPINIROLE you may experience a drop in blood pressure that may make you feel dizzy or faint especially when standing up from a sitting or lying position.

Neurological Disorder
Symptoms resembling a neurological disorder (Neuroleptic Malignant Syndrome) characterized by fever, muscle stiffness, stupor and unstable involuntary actions have been reported in relation to changes in treatment, reduction of treatment dose and stopping treatment,

ROPINIROLE taken with L-dopa
ROPINIROLE may amplify the side effects of L-dopa (also called levodopa) and may cause or worsen pre-existing uncontrolled jerky movements (dyskinesia).Tell your doctor if this happens as the dose of your medicines may need adjusting.

Eye Disorders
If you have albinism (lack of pigmentation in skin or hair), you may have an increased risk of eye disorders while taking ROPINIROLE compared to people without albinism. Therefore, you should take ROPINIROLE only under an ophthalmologist's (doctor who specializes in eye disorders) care.

Hallucinations
While taking ROPINIROLE, you may experience hallucinations, such as seeing or hearing things that aren't really there.

Psychiatric Disorders
Impulse control symptoms including compulsive behaviours, e.g. feeling an urge to gamble, hypersexuality, compulsive shopping,

or binge eating, as well as aggression have been reported with the use of ROPINIROLE.

BEFORE you use ROPINIROLE talk to your doctor or pharmacist if you:

- **have any health problem, especially any heart, liver or kidney condition.**
- **have previously taken ropinirole and became unwell.**
- **have any allergies or reactions to foods or drugs.**
- **are pregnant or think you may be pregnant, or if you are breast feeding. You should not be taking ROPINIROLE if you are pregnant or breast feeding.**
- **are taking any other medications, including any drugs you can buy without a prescription.**
- **have experienced any unusual urges and/or behaviours (such as excessive gambling or excessive sexual behaviour). (See SIDE EFFECTS AND WHAT TO DO ABOUT THEM)**

INTERACTIONS WITH THIS MEDICATION

Other medications may be affected by ROPINIROLE or may affect how ROPINIROLE works. Do not take any other medication, including any drugs or herbal products you can buy without a prescription. Tell any other doctor, dentist or pharmacist that you talk to that you are taking ROPINIROLE.

Drug-drug Interaction:
Drugs that may interact with ROPINIROLE include:

- a drug used to help with breathing difficulties called theophylline
- an antibiotic called ciprofloxacin
- any hormone replacement therapy (HRT)
- other dopamine agonists, e.g. L-dopa: ROPINIROLE may make some of the side effects of L-dopa worse, e.g. jerky movement.
- certain medicines called neuroleptics used to treat schizophrenia and other serious mental illnesses
- digoxin, a heart medicine that is used to treat congestive heart failure or certain heartbeat irregularities

Drug-lifestyle Interaction:

- ROPINIROLE may affect your ability to remain alert while doing normal daily activities. You should refrain yourself from doing activities such as driving a car doing physical tasks or using hazardous machinery until you know how ROPINIROLE affects you.
- Because ROPINIROLE can make you feel sleepy, tell your doctor or pharmacist if you are planning to drink alcohol.

Before making any change to other medications you are taking, or stopping them, talk to your doctor first.

PROPER USE OF THIS MEDICATION

Usual dose:
Follow the doctor's instructions about how and when you should take your tablets. Your doctor will decide how many tablets you need to take each day and you should always follow his/her instructions. When you first start taking ROPINIROLE, the amount you take will be increased gradually.

Your doctor may adjust the amount that you are taking. You will usually be told to take ROPINIROLE three times a day. You should not change the dose or discontinue treatment with ROPINIROLE without the recommendation of your doctor.

If you are taking other medicines for Parkinson's disease, the doctor may adjust the dose of these medicines while you are taking ROPINIROLE.

You should swallow the tablets whole with water. Do not chew. ROPINIROLE can be taken with or without food.

You should continue to take your medicine even if you do not feel better, as it may take a number of weeks for the medicine to work.

REMEMBER: THIS MEDICINE IS FOR THE PERSON NAMED BY THE DOCTOR. DO NOT GIVE IT TO ANYBODY ELSE.

Overdose:

If you think you have taken too much ROPINIROLE, contact your healthcare professional, hospital emergency department or regional poison control centre immediately, even if there are no symptoms.

If you or someone you know have taken too many tablets all at once, you should get medical help immediately, either by calling your doctor, the Regional Poison Control Centre, or the nearest hospital (do not drive yourself). Always take the labelled medicine container with you even if there are no tablets left.

Missed Dose:
If you have forgotten to take ROPINIROLE, do not take extra doses to make up for the forgotten individual doses. When you do remember to take ROPINIROLE, take your next dose of ROPINIROLE at the usual time. If you have missed taking ROPINIROLE for one day or more consult your doctor for advice on restarting ROPINIROLE.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Like all medications, ROPINIROLE tablets can cause some side effects. You may not experience any of them. For most patients these side effects are likely to be minor and temporary. However, some may be serious. Consult your doctor if you experience these or other side effects.

Some of the most commonly reported side effects of ropinirole tablets are:

- Feeling or being sick
- Stomach ache
- Dizziness or light-headedness, fainting
- Sleepiness
- Headache
- Some leg swelling
- Tiredness
- Viral infection
- Feeling full and bloated or experiencing heartburn

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect		Talk with your doctor or pharmacist right away		Stop taking drug and seek immediate emergency assistance
		Only if severe	In all cases	
Very Common	Uncontrollable movements (dyskinesias)		✓	
Common	Hallucinations, feeling confused		✓	
Uncommon	Having severe confusion, irrational ideas or feeling irrational suspiciousness, other psychotic reactions, impulse control (symptoms like increased libido, feeling the urge to gamble, to shop or eat, acting in an aggressive manner)		✓	
Very rare	Allergic reactions (symptoms like red, itchy swellings on the skin, swelling of the face, lips, mouth, tongue or throat, difficulty swallowing or breathing, rash or intense itching)			✓
	Extreme sleepiness, falling asleep without warning		✓	

This is not a complete list of side effects. For any unexpected effects while taking ROPINIROLE, contact your doctor or pharmacist.

HOW TO STORE IT

The expiry date of this medicine is printed on the label. Do not use the medicine after this date.

Keep your tablets in their original pack in a dry place away from light and moisture. They should be kept at room temperature (between 15 to 30°C). Close container tightly after each use.

Keep out of the reach and sight of children.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

If you want more information about ROPINIROLE:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Consumer Information by visiting the Health Canada website (https://health-products.canada.ca/dpd-bdpp/index-eng.jsp); the manufacturer's website (www.sanis.com), or by contacting Sanis Health Inc. at:

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