



## APO-ROPINIROLE

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### 1. PRODUCT NAME

APO-ROPINIROLE 0.25mg, 0.5mg, 1mg, 2mg, 3mg, 4mg and 5mg tablets

### 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Ropinirole hydrochloride 0.25mg  
Ropinirole hydrochloride 0.5mg  
Ropinirole hydrochloride 1mg  
Ropinirole hydrochloride 2mg  
Ropinirole hydrochloride 3mg  
Ropinirole hydrochloride 4mg  
Ropinirole hydrochloride 5mg

#### Excipient(s) with known effect

Contains lactose.

For the full list of excipients, see section 6.1

### 3. PHARMACEUTICAL FORM

APO-ROPINIROLE is available as oral, film coated tablets in the following strengths:

APO-ROPINIROLE 0.25mg tablets are white, pentagonal, biconvex film-coated tablet identified by an engraved "ROP" over ".25" on one side and "APO" on the other side. Each tablet typically weighs about 153mg.

APO-ROPINIROLE 0.5mg tablets are yellow, pentagonal, biconvex film-coated tablet identified by an engraved "ROP" over ".5" on one side and "APO" on the other side. Each tablet typically weighs about 153mg.

APO-ROPINIROLE 1mg tablets are green, pentagonal, biconvex film-coated tablet identified by an engraved "ROP" over "1" on one side and "APO" on the other side. Each tablet typically weighs about 153mg.

APO-ROPINIROLE 2mg tablets are pink, pentagonal, biconvex film-coated tablet identified by an engraved "ROP" over "2" on one side and "APO" on the other side. Each tablet typically weighs about 153mg.

APO-ROPINIROLE 3mg tablets are purple, pentagonal, biconvex film-coated tablet identified by an engraved "ROP" over "3" on one side and "APO" on the other side. Each tablet typically weighs about 153mg.

APO-ROPINIROLE 4mg tablets are pale brown, pentagonal, biconvex film-coated tablet identified by an engraved "ROP" over "4" on one side and "APO" on the other side. Each tablet typically weighs about 153mg.

APO-ROPINIROLE 5mg tablets are blue, pentagonal, biconvex film-coated tablet identified by an engraved "ROP" over "5" on one side and "APO" on the other side. Each tablet typically weighs about 153mg.

### 4. CLINICAL PARTICULARS

#### 4.1 Therapeutic indications

Ropinirole is indicated for the treatment of Parkinson's disease.



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Ropinirole is effective as early therapy in patients requiring dopaminergic therapy.

In a comparative study, ropinirole was superior to bromocriptine. When these two drugs were administered concomitantly with selegiline there was no difference between them.

Ropinirole delays the need for initiation of *L*-dopa therapy.

As adjunctive treatment of *L*-dopa, ropinirole enhances the efficacy of *L*-dopa, including control of "on-off" fluctuations and "end of dose" effects associated with chronic *L*-dopa therapy and permits reduction in daily *L*-dopa dose.

## 4.2 Dose and method of administration

### Dose

Individual dose titration against efficacy and tolerability is recommended.

Ropinirole should be taken three times a day and maybe taken with or without food (see section 5.2 Pharmacokinetic properties).

### Treatment Initiation

The initial dose of ropinirole should be 0.25mg three times daily. A guide for the titration regimen for the first four weeks of treatment is given in the table below:

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

### Therapeutic Regimen

After the initial titration, weekly increments of 0.5 to 1mg three times daily (1.5 to 3mg/day) may be given.

A therapeutic response can be expected between 3mg and 9mg/day. If sufficient symptomatic control is not achieved, or maintained, the dose of ropinirole may be increased until an acceptable therapeutic response is established. Doses above 24mg/day have not been investigated in clinical trials.

When ropinirole is administered as adjunct therapy to *L*-dopa, the concurrent dose of *L*-dopa may be reduced gradually by around 20% in total. In patients with advanced Parkinson's disease receiving ropinirole in combination with *L*-dopa, dyskinesias can occur during the initial titration of ropinirole. In clinical trials, it was shown that a reduction of the *L*-dopa dose may ameliorate dyskinesia.

When switching treatment from another dopamine agonist to ropinirole, the manufacturer's guidance on discontinuation should be followed before initiating ropinirole.

As with other dopamine agonists, ropinirole should be discontinued gradually by reducing the number of daily doses over the period of one week.

**ELDERLY:** Although the clearance of ropinirole is decreased in patients aged 65 years or above, the dose of ropinirole for elderly patients can be titrated in the normal manner.

**CHILDREN and ADOLESCENTS:** The safety and efficacy of ropinirole have not been established in patients under 18 years of age; therefore, ropinirole is not recommended for use in patients within this age group.

**RENAL IMPAIRMENT:** No dosage adjustment is necessary in patients with mild to moderate renal impairment (creatinine clearance 30-50mL/min).

A study into the use of ropinirole in patients with end stage renal disease (patients on haemodialysis) 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.

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

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

### 4.3 Contraindications

Hypersensitivity to ropinirole and excipients.

### 4.4 Special warnings and precautions for use

Due to the pharmacological action of ropinirole, patients with severe cardiovascular disease should be treated with caution.

Patients with a history or presence of major psychotic disorders should only be treated with dopamine agonists if the potential benefits outweigh the risks.

Patients should be regularly monitored for the development of impulse control disorders. Patients and carers should be made aware that behavioural symptoms of impulse control disorders including pathological gambling, increased libido, hypersexuality, compulsive spending or buying, binge eating, and compulsive eating can occur in patients treated with dopamine agonists including ropinirole. Dose reduction/tapered discontinuation should be considered if such symptoms develop.

Patients should be warned about the possibility of somnolence.

### 4.5 Interaction with other medicines and other forms of interaction

#### Pharmacokinetics Interactions

Neuroleptics and other centrally active dopamine antagonists, such as sulpiride or metoclopramide, may diminish the effectiveness of ropinirole and, therefore, concomitant use of these drugs with ropinirole should be avoided.

No pharmacokinetic interaction has been seen between ropinirole and *L*-dopa or domperidone which would necessitate dosage adjustment of either drug. No interaction has been seen between ropinirole and other drugs commonly used to treat Parkinson's Disease.

In a study in patients with Parkinson's Disease receiving concurrent digoxin, no interaction was seen which would require dosage adjustment.

Ropinirole is principally metabolised by the cytochrome P450 enzyme CYP1A2. A pharmacokinetic study in patients with Parkinson's Disease revealed that ciprofloxacin increased the C<sub>max</sub> and AUC of ropinirole. Hence, in patients already receiving ropinirole, the dose of ropinirole may need to be adjusted when drugs known to inhibit CYP1A2, e.g. ciprofloxacin, enoxacin or fluvoxamine, are introduced or withdrawn.

A pharmacokinetic interaction study in patients with Parkinson's Disease between ropinirole and theophylline, as representative of substrates of CYP1A2, revealed no change in the pharmacokinetics of either ropinirole or theophylline. Hence, changes in ropinirole pharmacokinetics following coadministration with other substrates of CYP1A2 are not expected.

Increased plasma concentrations of ropinirole have been observed in patients treated with high doses of oestrogens. In patients already receiving hormone replacement therapy (HRT), ropinirole treatment

maybe initiated in the normal manner. However, if HRT is stopped or introduced during treatment with ropinirole, dosage adjustment may be required.

### **Pharmacodynamic Interactions**

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.

Smoking is known to induce CYP1A2 metabolism, therefore if patients stop or start smoking during treatment with ropinirole, adjustment of the dose may be required.

Ropinirole may be taken with or without food.

## **4.6 Fertility, pregnancy and lactation**

### **Pregnancy**

Category B3

Ropinirole should not be used during pregnancy. In animal studies, administration of ropinirole to pregnant rats at maternally toxic doses resulted in decreased foetal body weight at 60 mg/kg, increased foetal death at 90 mg/kg and digit malformations at 150 mg/kg. There was no teratogenic effect in the rat at 120 mg/kg and no indication of an effect on development in the rabbit. There have been no studies of ropinirole in human pregnancy.

### **Breast-feeding**

Ropinirole should not be used in nursing mothers as it may inhibit lactation.

## **4.7 Effects on ability to drive and use machines**

Patients should be informed about very rare cases of sudden onset of sleep without any prior warning or apparent daytime somnolence and of dizziness (including vertigo) and should be cautioned that their safety and that of others is at risk if this happens whilst driving or operating dangerous machinery. If patients develop significant daytime sleepiness or episodes of falling asleep during activities that require active participation, patients should be told not to drive and to avoid other potentially dangerous activities.

## **4.8 Undesirable effects**

The most common adverse experiences reported by early therapy patients receiving ropinirole in clinical trials, and not seen at an equivalent or greater incidence on placebo, were; nausea, somnolence, leg oedema, abdominal pain, vomiting, syncope, dyspepsia, nervousness and hallucinations. An increased libido was reported uncommonly.

Similarly, the most common adverse experiences reported in adjunct therapy clinical trials were; dyskinesia, nausea, hallucinations and confusion.

As with other dopamine agonists, hypotension, including postural hypotension, has been observed with ropinirole treatment.

As with other dopaminergic therapies, extreme somnolence and/or sudden onset of sleep have been reported rarely during post-marketing experience, occasionally when the patient was driving. Patients experiencing this phenomenon cannot resist the urge to sleep, and on waking may be unaware of any tiredness prior to the sleep. Most patients were taking other medication with potentially sedating properties or alcohol in combination with ropinirole. There is no clear relationship between treatment dose or duration and the onset of symptoms.

*Psychiatric disorders* - uncommon

Psychotic reactions (other than hallucinations) including delusion, paranoia, delirium.

Pathological gambling, increased libido, hypersexuality, compulsive spending or buying, binge eating, and compulsive eating can occur in patients treated with dopamine agonists including ropinirole (see section 4.4).

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

### Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions <https://nzphvc.otago.ac.nz/reporting/>

### 4.9 Overdose

The symptoms of ropinirole overdose are related to its dopaminergic activity. These symptoms may be alleviated by appropriate treatment with dopamine antagonists such as neuroleptics or metoclopramide.

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

## 5. PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic Properties

**Pharmacotherapeutic group:** nervous system / anti-parkinson drugs / dopaminergic agents / dopamine agonists

**ATC code:** N04BC04

#### Mechanism of action

Ropinirole is a potent, non-ergoline D2/D3 dopamine agonist.

Parkinson's Disease is characterised by a marked dopamine deficiency in the nigral striatal system. Ropinirole alleviates this deficiency by stimulating striatal dopamine receptors.

Ropinirole acts in the hypothalamus and pituitary to inhibit the secretion of prolactin.

### 5.2 Pharmacokinetic properties

Oral absorption of ropinirole is rapid and essentially complete. Bioavailability of ropinirole is approximately 50% (36% to 57%) and average peak concentrations of the drug are achieved at a median time of 1.5 hours post dose. The bioavailability of ropinirole was similar in both the fed and fasted state. However, food decreases the rate of absorption of ropinirole, as shown by a delay in median  $T_{max}$  by 2.6 hours and an average 25% decrease in  $C_{max}$ . Wide inter-individual variability in the pharmacokinetic parameters has been seen and the increase in systemic exposure ( $C_{max}$  and AUC) to ropinirole is approximately proportional, over the therapeutic dose range. Consistent with its high lipophilicity, ropinirole exhibits a large volume of distribution (approx. 7 L/kg) and is cleared from the systemic circulation with an average elimination half-life of about 6 hours. Plasma protein binding of the drug is low (10-40%). Ropinirole is primarily cleared by CYP1A2 metabolism and its metabolites are mainly excreted in the urine. The major metabolite is at least 100 times less potent than ropinirole in animal models of dopaminergic function.

No change in the oral clearance of ropinirole is observed following single and repeated oral administration. As expected for a drug being administered approximately every half-life, there is, on average, 2-fold higher steady-state plasma concentrations of ropinirole following the recommended three times daily regimen compared to those observed following a single oral dose.



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## Special Patient Populations

**ELDERLY:** Oral clearance of ropinirole is reduced by approximately 15% in elderly patients (65 years or above) compared to younger patients. Dosing adjustment is not necessary in the elderly.

**RENAL IMPAIRMENT:** There was no change observed in the pharmacokinetics of ropinirole in Parkinson's disease patients with mild to moderate renal impairment.

In patients with end stage renal disease receiving regular dialysis, oral clearance of ropinirole is reduced by approximately 30%. The recommended maximum dose is limited to 18 mg/day in patients with Parkinson's disease (see section 4.2).

## 5.3 Preclinical safety data

**General Toxicology:** Ropinirole is well tolerated in laboratory animals in the dose range of 15 to 50 mg/kg. The toxicology profile is principally determined by the pharmacological activity of the drug (behavioural changes, hypoprolactinaemia, and decrease in blood pressure and heart rate, ptosis and salivation).

**Genotoxicity:** Genotoxicity was not observed in a battery of in vitro and in vivo tests.

**Carcinogenicity:** Two-year studies have been conducted in the mouse and rat at dosages up to 50 mg/kg. The mouse study did not reveal any carcinogenic effect. In the rat, the only drug-related lesions were Leydig cell hyperplasia/adenoma in the testis resulting from the hypoprolactinaemic effect of ropinirole. These lesions are considered to be a species-specific phenomenon and do not constitute a hazard with regard to the clinical use of ropinirole.

## 6. PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

APO-ROPINIROLE contains the following excipients:

Lactose, Citric Acid, Magnesium Stearate (vegetable source), Hypromellose, Hydroxypropylcellulose, Macrogol.

Colouring agents are also contained in the film coating as follows:

0.25mg tablets (white) contains titanium oxide.

0.5mg tablets (yellow) contains titanium dioxide and iron oxide yellow.

1.0mg tablets (green) contains titanium dioxide, iron oxide yellow and indigotine aluminium.

2.0mg tablets (pink) contains titanium dioxide and iron oxide red.

5.0mg tablets (blue) contains titanium dioxide and indigotine aluminium.

APO-ROPINIROLE tablets do not contain gluten, sucrose, tartrazine, or any other azo dyes.

APO-Ropinirole contains lactose.

### 6.2 Incompatibilities

Nil.

### 6.3 Shelf life

24 months.

### 6.4 Special precautions for storage

Store at or below 25°C. Protect from heat, light and moisture.

### 6.5 Nature and contents of container

APO-ROPINIROLE 0.25mg, 0.5mg, 1mg, 2mg and 5mg film-coated tablets are available as



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Bottle packs of 84 and 100 tablets.  
Blister packs of 84 and 100 tablets.

APO-ROPINIROLE 3mg and 4mg tablets are currently not marketed.

## 6.6 Special precautions for disposal

No special requirements for disposal.

Any unused medicine or waste material should be disposed of in accordance with local requirements.

## 7. MEDICINE SCHEDULE

Prescription Medicine

## 8. SPONSOR

Apotex NZ Ltd.  
32 Hillside Road  
Wairau Valley  
AUCKLAND 0627  
Telephone: (09) 444 2073  
Fax: (09) 444 2951  
E-mail: [NZcustomerservice@apotex.com](mailto:NZcustomerservice@apotex.com)

## 9. DATE OF FIRST APPROVAL

29 September 2011

## 10. DATE OF REVISION OF THE TEXT

21 March 2019

## SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
Whole data sheet	Reformatted as per Medsafe new guideline for data sheet.
8	Sponsor address updated, and email address added