
Data Sheet

ROPACCORD

Ropinirole hydrochloride 0.25mg, 0.5mg, 1mg and 2mg tablets

Presentation

Ropaccord Tablets are presented as round, biconvex, film coated tablets plain on both sides containing ropinirole hydrochloride equivalent to 0.25, 0.5, 1.0 or 2.0mg ropinirole (as hydrochloride).

Ropaccord tablets contain lactose, cellulose microcrystalline, croscarmellose sodium, magnesium stearate, hypromellose, macrogol as excipients. The 0.25mg tablets also contain polysorbate. Colouring agents are also contained in the film coating as follows:

- 0.25mg tablets (White to off white) contains titanium dioxide.
- 0.5mg tablets (yellow) contains titanium dioxide, iron oxide yellow, iron oxide red, indigo carmine aluminium lake.
- 1.0mg tablets (green) contains titanium dioxide, iron oxide yellow, indigo carmine aluminium lake.
- 2.0mg tablets (pink) contains titanium dioxide, iron oxide yellow, iron oxide red.

Ropaccord Tablets are presented in Alu/Alu blister pack and HDPE bottle.

Clinical Particulars

Therapeutic indications

Ropaccord Tablets is indicated for the treatment of Parkinson's disease.

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.

Ropaccord Tablets delays the need for initiation of L-dopa therapy.

As adjunctive treatment of *L*-dopa, Ropaccord Tablets 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.

Posology and method of administration

Individual dose titration against efficacy and tolerability is recommended.

Ropaccord Tablets should be taken three times a day and maybe taken with or without food (see Pharmacokinetics).

Treatment Initiation

The initial dose of Ropaccord Tablets should be 0.25mg tid. A guide for the titration regimen for the first four weeks of treatment is given in the table below

	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

The Ropaccord Tablets Starter Pack contains the necessary tablets to achieve the titration regimen shown above, and may be used to minimise patient confusion.

Therapeutic Regimen

After the initial titration, weekly increments of 0.5 to 1mg tid (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 Ropaccord Tablets may be increased until an acceptable therapeutic response is established. Doses above 24mg/day have not been investigated in clinical trials.

The Ropaccord Tablets Follow-on Pack contains the necessary tablets to achieve a dose titration from 4.5mg/day up to 9mg/day, and can be used to minimise patient confusion.

When Ropaccord Tablets 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 Ropaccord Tablets in combination with *L*-dopa, dyskinesias can occur during the initial titration of

Ropaccord Tablets. 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 Ropaccord Tablets, the manufacturer's guidance on discontinuation should be followed before initiating Ropaccord Tablets.

As with other dopamine agonists, Ropaccord Tablets 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: The use of Ropaccord Tablets in children is not recommended as safety and efficacy have not been established in this population.

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 Ropaccord Tablets 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.

Contraindications

Hypersensitivity to ropinirole and excipients.

Special warnings and special 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.

Impulsive control symptoms, including compulsive behaviours such as pathological gambling and hypersexuality, have been reported in patients treated with dopaminergic agents, including ropinirole. As described in the literature, such behaviours have been reported principally in Parkinson's disease patients treated with dopaminergic agents, especially at higher doses, and were generally reversible upon dose reduction or treatment discontinuation. In some ropinirole cases, other factors were present such as a history of compulsive behaviour or concurrent dopaminergic treatment. Healthcare professionals are advised to warn patients about these possible side-effects, and to inform patients to seek help from their doctor if they, their family or their carer notice that their behaviour is unusual.

Patients should be warned about the possibility of somnolence.

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_{max} 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.

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.

Pregnancy and lactation

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.

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

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.

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, impulse control symptoms, increased libido including hypersexuality, pathological gambling.

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

Overdose

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

Pharmacological Properties

Pharmacodynamic properties

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.

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 Tmax by 2.6 hours and an average 25% decrease in Cmax. Wide inter-individual variability in the pharmacokinetic parameters has been seen and the increase in systemic exposure (Cmax 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 t.i.d. regimen compared to those observed following a single oral dose.

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 Posology and method of administration, Renal Impairment).

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.

Pharmaceutical Particulars

Incompatibilities

None known.

Shelf life

24 months

For HDPE container: Shelf-life after date of first opening is 6 months

Special precautions for storage

“Store in a dry place, away from direct light at room temperature (25°C or below)”.

Medicine Classification

Prescription Only Medicine

Package Quantities

Ropaccord 0.25 mg tablets, blister pack 42 tablets

Ropaccord 0.5 mg tablets, blister pack 42 tablets

Ropaccord 1 mg tablets, blister pack 21 and 42 tablets

Ropaccord 2 mg tablets, blister pack 63 tablets

Ropaccord 0.25/0.5/1/2 mg tablets, HDPE bottle pack 84 tablets

Name and address

Distributed in New Zealand by:

Douglas Pharmaceuticals Ltd
Central Park Drive
Lincoln

Auckland 0610

Date of preparation

29th September 2009