ROPIN

1. Product Name

ROPIN, 0.25 mg, 0.5 mg, 1 mg, 2 mg, 5 mg, tablet.

2. Qualitative and Quantitative Composition

Each tablet contains 0.25 mg, 0.5 mg, 1 mg, 2 mg or 5 mg of ropinirole (as hydrochloride).

Excipient with known effect: lactose.

For the full list of excipients, see section 6.1.

3. Pharmaceutical Form

ROPIN Tablets 0.25mg: White to off white, capsule shaped, biconvex film-coated tablets, with breakline both sides.

ROPIN Tablets 0.5mg: Yellow coloured, capsule shaped, biconvex film-coated tablets, with breakline both sides.

ROPIN Tablets 1mg: Green coloured, capsule shaped, biconvex film-coated tablets, with breakline both sides.

ROPIN Tablets 2mg: Pink coloured, capsule shaped, biconvex film-coated tablets, with breakline both sides.

ROPIN Tablets 5mg: Blue coloured, capsule shaped, biconvex film-coated tablets, with breakline both sides.

All tablets can be divided into equal doses.

4. Clinical Particulars

4.1 Therapeutic indications

ROPIN is indicated for the treatment of Parkinson's Disease.

ROPIN 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.

ROPIN delays the need for initiation of levodopa therapy.

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

4.2 Dose and method of administration

Dose

Individual dose titration against efficacy and tolerability is recommended.

Patients should be down-titrated if they experience disabling somnolence at any dose level. For other adverse events, down-titration followed by more gradual up-titration has been shown to be beneficial.

Adults

ROPIN should be taken three times a day, preferably with meals to improve gastrointestinal tolerance.

Treatment initiation

The initial dose of ROPIN should be 0.25 mg three times daily for one week. Thereafter, the dose of ropinirole can be increased in 0.25 mg three times daily increments, according to the following regimen:

	Week			
	1	**2**	**3**	**4**
Unit dose (mg) of ropinirole	0.25	0.5	0.75	1.0
Total daily dose (mg) of ropinirole	0.75	1.5	2.25	3.0

Therapeutic regimen

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

A therapeutic response may be seen between 3 mg and 9 mg/day. If sufficient symptomatic control is not achieved, or maintained after the initial titration as described above, the dose of ROPIN may be increased until an acceptable therapeutic response is established (up to 24 mg/day).

Doses of ropinirole above 24 mg/day have not been investigated in clinical trials.

If treatment is interrupted for one day or more re-initiation by dose titration should be considered (see above).

When ropinirole is administered as adjunct therapy to levodopa, the concurrent dose of levodopa may be reduced gradually according to the symptomatic response. In clinical trials, the levodopa dose was reduced gradually by around 20% in patients treated with ropinirole as adjunct therapy. In patients with advanced Parkinson’s disease receiving ropinirole in combination with levodopa, dyskinesias can occur during the initial titration of ropinirole. In clinical trials, it was shown that a reduction of the levodopa dose may ameliorate dyskinesia (see section 4.8).

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, ROPIN should be discontinued gradually by reducing the number of daily doses over the period of one week (see section 4.4).

Special populations

Elderly

The clearance of ropinirole is decreased by approximately 15% in patients aged 65 years or above. Although a dose adjustment is not required, ropinirole dose should be individually titrated, with careful monitoring of tolerability, to the optimal clinical response.

Children and adolescents

Ropinirole is not recommended for use in children below 18 years of age due to a lack of data on safety and efficacy.

Renal Impairment

In patients with mild to moderate renal impairment (creatinine clearance 30 - 50 mL/min) no change in the clearance of ropinirole was observed, indicating that no dosage adjustment is necessary in this population.

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 haemodialysis. Supplemental doses after haemodialysis are not required (see section 5.2).

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

Method of administration

Oral use

4.3 Contraindications

Hypersensitivity to ropinirole or to any of the excipients listed in section 6.1.

Severe renal impairment (creatinine clearance < 30 mL/min) without regular haemodialysis.

Hepatic impairment.

4.4 Special warnings and precautions for use

Psychiatric or psychotic disorders

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

Somnolence and episodes of sudden sleep onset

Ropinirole has been associated with somnolence and episodes of sudden sleep onset, particularly in patients with Parkinson's disease. Sudden onset of sleep during daily activities, in some cases without awareness or warning signs, has been reported uncommonly. Patients must be informed of this and advised to exercise caution while driving or operating machines during treatment with ropinirole. Patients who have experienced somnolence and/or an episode of sudden sleep onset must refrain from driving or operating machines. Furthermore, a reduction of dosage or termination of therapy may be considered.

Impulse control disorders

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.

Impulse control disorders were reported especially at high doses and were generally reversible upon reduction of the dose or treatment discontinuation. Risk factors such as history of compulsive behaviours were present in some cases (see section 4.8).

Mania

Patients should be regularly monitored for the development of mania. Patients and carers should be made aware that symptoms of mania can occur with or without the symptoms of impulse control disorders in patients treated with ropinirole. Dose reduction/tapered discontinuation should be considered if such symptoms develop.

Neuroleptic malignant syndrome

Symptoms suggestive of neuroleptic malignant syndrome have been reported with abrupt withdrawal of dopaminergic therapy. Therefore, it is recommended to taper treatment (see section 4.2).

Hypotension

Due to the risk of hypotension, blood pressure monitoring is recommended, particularly at the start of treatment, in patients with severe cardiovascular disease (in particular coronary insufficiency).

Dopamine agonist withdrawal syndrome (DAWS)

DAWS has been reported with dopamine agonists, including ropinirole (see Section 4.8). To discontinue treatment in patients with Parkinson's disease, ropinirole should be tapered off (see Section 4.2). Limited data suggests that patients with impulse control disorders and those receiving high daily dose and/or high cumulative doses of dopamine agonists may be at higher risk for developing DAWS. Withdrawal symptoms may include apathy, anxiety, depression, fatigue, sweating and pain and not respond to levodopa. Prior to tapering off and discontinuing ropinirole, patients should be informed about potential withdrawal symptoms. Patients should be closely monitored during tapering and discontinuation. In case of severe and/or persistent withdrawal symptoms, temporary re-administration of ropinirole at the lowest effective dose may be considered.

Hallucinations

Hallucinations are known as a side effect of treatment with dopamine agonists and levodopa. Patients should be informed that hallucinations can occur.

Excipients

Lactose

This medicinal product also contains lactose

Patients with rare hereditary problems of galactose intolerance, total lactose deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicines and other forms of interaction

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

There is no pharmacokinetic interaction between ropinirole and levodopa or domperidone which would necessitate dosage adjustment of these medicinal products.

Ropinirole is principally metabolised by the cytochrome P450 enzyme CYP1A2. A pharmacokinetic study (with a ropinirole dose of 2 mg, three times a day in patients with Parkinson's disease) revealed that ciprofloxacin increased the C_{max} and AUC of ropinirole by 60% and 84% respectively, with a potential risk of adverse events. Hence, in patients already receiving ropinirole, the dose of ropinirole may need to be adjusted when medicinal products 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 (at a dose of 2 mg, three times a day) and theophylline, substrates of CYP1A2, revealed no change in the pharmacokinetics of either ropinirole or theophylline.

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, in accordance with clinical response.

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.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no adequate data from the use of ropinirole in pregnant women. Ropinirole concentrations may gradually increase during pregnancy (see section 5.2).

Studies in animals have shown reproductive toxicity (see section 5.3). As the potential risk for humans is unknown, it is recommended that ropinirole is not used during pregnancy unless the potential benefit to the patient outweighs the potential risk to the foetus.

Breast-feeding

Ropinirole-related material was shown to transfer into the milk of lactating rats. It is unknown whether ropinirole and its metabolites are excreted in human milk. A risk to the suckling child cannot be excluded.

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

Fertility

There are no data on the effects of ropinirole on human fertility.

In female fertility studies in rats, effects were seen on implantation but no effects were seen on male fertility (see Section 5.3).

4.7 Effects on ability to drive and use machines

Patients being treated with ropinirole and presenting with hallucinations, somnolence and/or sudden sleep episodes must be informed to refrain from driving or engaging in activities where impaired alertness may put themselves or others at risk of serious injury or death (e.g. operating machines) until such recurrent episodes and somnolence have resolved (see section 4.4).

4.8 Undesirable effects

Adverse events are listed below by system organ class and frequency. It is noted if these undesirable effects were reported in clinical trials as monotherapy or adjunct therapy to levodopa.

Frequencies are defined as: very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), rare (≥ 1/10,000 to < 1/1,000) very rare (< 1/10,000), not known (cannot be estimated from the available data).

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Immune system disorders

Not known: hypersensitivity reactions (including urticaria, angioedema, rash, pruritis)

Psychiatric disorders

Common: hallucinations,
Uncommon: psychotic reactions (other than hallucinations) including delirium, delusion, paranoia
Not known: aggression*, dopamine dysregulation syndrome, mania (see section 4.4), impulse control disorders** (see section 4.4)

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

** Impulse control disorders 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).

Use in adjunct therapy studies:

Common: confusion

Nervous system disorders

Very common: somnolence Common: dizziness (including vertigo)

Uncommon: sudden onset of sleep, excessive daytime somnolence.
Ropinirole is associated with somnolence and has been associated uncommonly with excessive daytime somnolence and sudden sleep onset episodes

Use in monotherapy studies:

Very Common: syncope

Use in adjunct therapy studies:

Very Common: dyskinesia in patients with advanced Parkinson's disease, dyskinesias can occur during the initial titration of ropinirole. In clinical trials it was shown that a reduction of the levodopa dose may ameliorate dyskinesia (see section 4.2).

Vascular disorder

Uncommon: postural hypotension, hypotension
Postural hypotension or hypotension is rarely severe.

Gastrointestinal disorders

Very common: nausea
Common: heartburn

Use in monotherapy studies

Common: vomiting, abdominal pain

Hepatobiliary disorders

Not known: hepatic reactions, mainly increased liver enzymes

General disorders

Use in monotherapy studies:

Common: oedema peripheral (including leg oedema)

Not Known: dopamine agonist withdrawal syndrome (including apathy, anxiety, depression, fatigue, sweating and pain).

Dopamine agonist withdrawal syndrome

Non-motor adverse effects may occur when tapering or discontinuing dopamine agonists including ropinirole (see section 4.4)

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

Symptoms and signs

The symptoms of ropinirole overdose are generally related to its dopaminergic activity.

Treatment

These symptoms may be alleviated by appropriate treatment with dopamine antagonists such as neuroleptics or metoclopramide.

For further advice on management of overdose please contact the National Poisons Information Centre (0800 POISON or 0800 764 766).

5. Pharmacological Properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Dopaminergic agents, dopamine agonists.

ATC code: N04BC04

Mechanism of action

Ropinirole is a non-ergoline D2/D3 dopamine agonist which stimulates striatal dopamine receptors.

Ropinirole alleviates the dopamine deficiency which characterizes Parkinson's disease by stimulating striatal dopamine receptors.

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

Study on the effect of ropinirole on cardiac repolarisation

A thorough QT study conducted in male and female healthy volunteers who received doses of 0.5, 1, 2 and 4 mg of ropinirole film-coated (immediate release) tablets once daily showed a maximum increase of the QT interval duration at the 1 mg dose of 3.46 milliseconds (point estimate) as compared to placebo. The upper bound of the one sided 95% confidence interval for the largest mean effect was less than 7.5 milliseconds. The effect of ropinirole at higher doses has not been systematically evaluated.

The available clinical data from a thorough QT study do not indicate a risk of QT prolongation at doses of ropinirole up to 4 mg/day. A risk of QT prolongation cannot be excluded as a thorough QT study at doses up to 24 mg/day has not been conducted.

5.2 Pharmacokinetic properties

Absorption

Bioavailability of ropinirole is approximately 50% (36% to 57%). Oral absorption of ropinirole film-coated (immediate release) tablets is rapid with peak concentrations achieved at a median time of

1.5 hours post dose. A high fat meal 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}.

Distribution

Consistent with its high lipophilicity, ropinirole exhibits a large volume of distribution (approx. 7 L/kg). Plasma protein binding of the drug is low (10-40%).

Biotransformation

Ropinirole is primarily cleared by the cytochrome P450 enzyme, CYP1A2, 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.

Elimination

Ropinirole is cleared from the systemic circulation with an average elimination half-life of about 6 hours. The increase in systemic exposure (C_{max} and AUC) to ropinirole is approximately proportional over the therapeutic dose range. No change in the oral clearance of ropinirole is observed following single and repeated oral administration. Wide inter-individual variability in the pharmacokinetic parameters has been observed.

Special populations

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 haemodialysis, oral clearance of ropinirole is reduced by approximately 30%. Oral clearance of the metabolites SKF-104557 and SKF-89124 were also reduced by approximately 80% and 60%, respectively. Therefore, the recommended maximum dose is limited to 18 mg/day in these patients with Parkinson's disease (see section 4.2).

Pregnancy

Physiological changes in pregnancy (including decreased CYP1A2 activity) are predicted to gradually lead to an increased maternal systemic exposure of ropinirole (see section 4.6).

5.3 Preclinical safety data

Reproductive toxicity

In fertility studies in female rats, effects were seen on implantation due to the prolactin-lowering effect of ropinirole. It should be noted that prolactin is not essential for implantation in humans.

Administration of ropinirole to pregnant rats at maternally toxic doses resulted in decreased foetal body weight at 60 mg/kg/day (mean AUC in rats approximately twice the highest AUC at the Maximum Recommended Human Dose (MRHD)), increased foetal death at 90 mg/kg/day (approximately 3 times the highest AUC at the MRHD) and digit malformations at 150 mg/kg/day (approximately 5 times the highest AUC at the MRHD). There were no teratogenic effects in the rat at 120 mg/kg/day (approximately 4 times the highest AUC at the MRHD) and no indication of an effect during organogenesis in the rabbit when given alone at 20 mg/kg (9.5 times the mean human C_{max} at the MRHD). However, ropinirole at 10 mg/kg (4.8 times the mean human C_{max} at the MRHD) administered to rabbits in combination with oral levodopa produced a higher incidence and severity of digit malformations than levodopa alone.

Toxicology

The toxicology profile is principally determined by the pharmacological activity of ropinirole: behavioural changes, hypoprolactinaemia, decrease in blood pressure and heart rate, ptosis and salivation. In the albino rat only, retinal degeneration was observed in a long term study at the highest dose (50 mg/kg/day), and was probably associated with an increased exposure to light.

Genotoxicity

Genotoxicity was not observed in the usual battery of *in vitro* and *in vivo* tests.

Carcinogenicity

From two-year studies conducted in the mouse and rat at dosages up to 50 mg/kg there was no evidence of any carcinogenic effect in the mouse. In the rat, the only ropinirole-related lesions were Leydig cell hyperplasia and testicular adenoma 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.

Safety pharmacology

In vitro studies have shown that ropinirole inhibits hERG-mediated currents. The IC_{50} is 5-fold higher than the expected maximum plasma concentration in patients treated at the highest recommended dose (24 mg/day), see section 5.1.

6. Pharmaceutical Particulars

6.1 List of excipients

ROPIN tablets also contain

- lactose monohydrate
- microcrystalline cellulose
- croscarmellose sodium
- hypromellose and
- magnesium stearate.

The film coat consists of

- hypromellose
- macrogol 400
- titanium dioxide
- polysorbate (0.25 mg and 5 mg tablets)
- ferric oxide yellow (0.5 mg, 1 mg and 2 mg tablets),
- ferric oxide red (2 mg tablets) and
- indigo carmine lake (1 mg and 5 mg tablets).

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

Store at or below 25°C.

6.5 Nature and contents of container

HDPE bottle with a child-resistant closure and a silica gel desiccant. Pack-size of 84 film-coated tablets.

Not all strengths may be marketed.

6.6 Special precautions for disposal

Not applicable.

7. Medicines Schedule

Prescription Medicine

8. Sponsor Details

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9. Date of First Approval

30 Oct 2008

10. Date of Revision of the Text

15 March 2022

Summary table of changes

Section	Summary of new information
4.2, 4.4, 4.7, 4.8, 5.1, 5.3	Minor editorial changes regarding format, spelling, subtitles, rearrangement of information for better flow and ease of use, removal of notes as information added into main text
4.4	Information added on Mania, Dopamine agonist withdrawal syndrome, hallucinations, lactose and rare hereditary problems
4.8	Undesirable effects added: mania, impulse control disorders
5.1	Update subsection heading to better describe associated information
10	Updated date of revision