SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Ropinirole SR 3mg prolonged release tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 3 mg ropinirole (as 3.42 mg ropinirole hydrochloride)

Excipients with known effect

Each tablet contains 0.321 mg lactose (as monohydrate) and 0.0040 mg sunset yellow aluminium lake (E110).

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Purple round biconvex tablets with approximately 8.1 mm in diameter and 4.7 mm in thickness.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Ropinirole SR is indicated in adults for

Treatment of Parkinson's disease under the following conditions:

- Initial treatment as monotherapy, in order to delay the introduction of levodopa
- In combination with levodopa, over the course of the disease, when the effect of levodopa wears off or becomes inconsistent and fluctuations in the therapeutic effect occur (“end of dose” or “on-off” type fluctuations).

4.2 Posology and method of administration

Posology

Adults

Individual dose titration against efficacy and tolerability is recommended.

Initial titration

The starting dose is 2 mg ropinirole once daily for the first week; this should be increased to 4 mg ropinirole once daily from the second week of treatment. A therapeutic response may be seen at a dose of 4 mg once daily of prolonged-release tablets.

The prolonged-release tablets should be taken once a day and at a similar time each day.

The tablets may be taken with or without food. A high fat meal may double the AUC and Cmax in some individuals (see section 5.2).

Patients who initiate treatment with a dose of 2 mg/day of ropinirole prolonged-release tablets and who experience undesirable effects that they cannot tolerate, may benefit from switching to treatment with ropinirole immediate release tablets at a lower daily dose, divided into three equal doses.

Therapeutic regimen

Patients should be maintained on the lowest dose of ropinirole prolonged-release tablets that achieves symptomatic control.

If sufficient symptomatic control is not achieved or maintained at a dose of 4 mg once daily of ropinirole prolonged release tablets, the daily dose may be increased by 2 mg at weekly or longer intervals up to a dose of 8 mg once daily of prolonged-release tablets.

If sufficient symptomatic control is still not achieved or maintained at a dose of 8 mg once daily of ropinirole prolonged-release tablets, the daily dose may be increased by

2 mg to 4 mg at two weekly or longer intervals. The maximum daily dose of ropinirole prolonged-release tablets is 24 mg.

It is recommended that patients are prescribed the minimum number of ropinirole prolonged-release tablets that are necessary to achieve the required dose by utilising the highest available strengths of ropinirole prolonged-release tablets.

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

When ropinirole prolonged-release tablets are administered as adjunct therapy to levodopa, it may be possible to gradually reduce the levodopa dose, depending on the clinical response. In clinical trials, the levodopa dose was reduced gradually by approximately 30% in patients receiving ropinirole prolonged-release tablets concurrently. In patients with advanced Parkinson's disease receiving ropinirole prolonged-release tablets in combination with L-dopa, dyskinesias can occur during the initial titration of ropinirole prolonged-release tablets. In clinical trials it was shown that a reduction of the L-dopa dose may ameliorate dyskinesia (see also section 4.8).

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

t is necessary to discontinue ropinirole treatment gradually by reducing the daily dose over the period of one week (see section 4.4).

Switching from ropinirole immediate release tablets to ropinirole prolonged-release tablets

Patients may be switched overnight from ropinirole immediate release tablets to ropinirole prolonged-release tablets.

The dose of ropinirole prolonged-release tablets should be based on the total daily dose of ropinirole immediate release tablets that the patient was taking.:

The table below shows the recommended dose of ropinirole prolonged-release tablets for patients switching from ropinirole immediate-release tablets:

Switching from ropinirole immediate-release tablets to ropinirole prolonged-release tablets

ropinirole immediate release tablets Total daily dose (mg)	ropinirole prolonged-release tablets Total daily dose (mg)
0.75 – 2.25	2
3 - 4.5	4
6	6
7.5 - 9	8
12	12
15 - 18	16
21	20
24	24

After switching to ropinirole prolonged-release tablets, the dose may be adjusted depending on the therapeutic response (see “Initial titration” and “Therapeutic regimen” above).

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. In patients aged 75 years and above, slower titration during treatment initiation may be considered.

Renal impairment

In patients with mild to moderate renal impairment (creatinine clearance between 30 and 50 ml/min) no change in the clearance of ropinirole was observed, indicating that no dose 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 recommended initial dose of ropinirole is 2 mg once daily. 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 dialysis 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 haemodialysis has not been studied.

Paediatric population

The safety and efficacy of Ropinirole SR in children and adolescents below 18 years of age have not been established.Ropinirole SR is not recommended for use in this age group.

Method of administration

For oral use.

The tablets must be swallowed whole and must not be chewed, crushed or divided.

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

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 (see section 4.8). 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. Reduction of dose or termination of therapy may be considered.

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

Impulse control disorders

Patients should be regularly monitored for the development of impulse control disorders. Patients and carers should be made aware that behavioral 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.

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).

Ropinirole SR prolonged released tablets are designed to release ropinirole over a 24hr period. If rapid gastrointestinal transit occurs, there may be risk of incomplete release of the active substance, and of residue of the medicinal product being passed in the stool.

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

To discontinue treatment in patients with Parkinson's disease, ropinirole should be tapered off (see section 4.2). Nonmotor adverse effects may occur when tapering or discontinuing dopamine agonists including ropinirole. Symptoms include apathy, anxiety, depression, fatigue, sweating and pain which may be severe. Patients should be informed about this before tapering the dopamine agonist, and monitored regularly thereafter. In case of persistent symptoms, it may be necessary to increase the ropinirole dose temporarily (see section 4.8).

Hallucinations

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

Ropinirole SR 2 mg and 3 mg prolonged release tablets

The prolonged-release tablets contain lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

Ropinirole SR 3 mg and 4 mg prolonged release tablets

The prolonged-release tablets contain the azo colouring agent sunset yellow (E110), which may cause allergic reactions.

4.5 Interaction with other medicinal products and other forms of interaction

There is no pharmacokinetic interaction between ropinirole and L-dopa or domperidone which would necessitate dose adjustment of these medicinal products.

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

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

ropinirole is principally metabolised by the cytochrome P450 enzyme CYP1A2. A pharmacokinetic study (with a ropinirole immediate-release tablet dose of 2 mg, three times a day) in Parkinson's disease patients, revealed that ciprofloxacin increased the Cmax and AUC of ropinirole by 60% an 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 know 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 (with a ropinirole immediate-release tablet dose of 2 mg, three times a day) and theophylline, a substrate of CYP1A2, revealed no change in the pharmacokinetics of either ropinirole or theophylline.

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

In patients receiving the combination of vitamin K antagonists and ropinirole, cases of unbalanced INR have been reported. Increased clinical and biological surveillance (INR) is warranted.

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 breast-feeding 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 also 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.

The following adverse drug reactions have been reported in either Parkinson's disease clinical trials with <Ropinirole SR prolonged-release or film-coated (immediate-release) tablets at doses up to 24 mg/day, or from post-marketing reports:

	In monotherapy	**In adjunct therapy**
Immune system disorders		
Not known	Hypersensitivity reactions (including urticaria, angioedema, rash,	

	pruritus).	
Psychiatric disorders		
Common	Hallucinations	Confusion
Uncommon	Psychotic reactions (other than hallucinations) including delirium, delusion, paranoia.	
Not known	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).	
	Aggression*	
	Dopamine dysregulation syndrome	
Nervous system disorders		
Very common	Somnolence	Somnolence**
	Syncope	Dyskinesia***
Common	Dizziness (including vertigo), sudden onset of sleep	
Uncommon	Excessive day time somnolence	
Vascular disorders		
Common		Postural hypotension, hypotension
Uncommon	Postural hypotension, hypotension	
Gastrointestinal disorders		
Very common	Nausea	Nausea ****
Common	Constipation, heartburn	
	Vomiting, abdominal pain	
Hepatobiliary disorders		
Not known	Hepatic reactions, mainly increased liver enzymes	
General disorders and administration site conditions		
Common	Oedema peripheral	
	Leg oedema	
Not known	Dopamine agonist withdrawal syndrome (including apathy, anxiety, depression, fatigue, sweating and pain)*****	
Reproductive system and breast disorders		
Not know	Spontaneous penile erection	
Respiratory, thoracic and mediastinal disorders		
Uncommon	Hiccups	

**Aggression has been associated with psychotic reactions as well as compulsivesymptoms.*

*** Somnolence has been reported very commonly in the adjunct therapy immediate - release clinical trials, and commonly in the*

adjunct therapy prolonged- release clinical trials.

**** 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).*

*****Nausea has been reported very commonly in the adjunct therapy immediate - release clinical trials, and commonly in the adjunct therapy prolonged- release clinical trials.*

****** 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 medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via Yellow Card Scheme at: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

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

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Anti-Parkinson drugs; dopaminergic agents; Dopamine agonist.

ATC code: N04BC04

Mechanism of action

Ropinirole is a non-ergoline D2/D3 dopamine agonist that alleviates this deficiency by stimulating striatal dopamine receptors.

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

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

Clinical efficacy

A 36-week, double-blind, three-period crossover study, in monotherapy with a primary end point of change from period baseline in Unified Parkinson's

Disease Rating Scale (UPDRS) total motor score was conducted in 161 patients with early phase Parkinson's disease. A subgroup analysis of patients initiated on monotherapy treatment with ropinirole immediate release tablets and switched overnight to the nearest equivalent dose of ropinirole prolonged-release tablets was consistent with similar efficacy from equivalent mg for mg doses. The adjusted mean difference between ropinirole prolonged-release tablets and ropinirole immediate-release tablets at studyendpoint was 0.7 points (95% CI: [-1.51, 0.10], p=0.0842).

Following the overnight switch to a similar dose of the alternative tablet formulation, there was no difference in the adverse event profile and less than 3% of patients required a dose adjustment (all dose adjustments were increases by one dose level. No patients required a dose increase).

A 24-week, double-blind, placebo-controlled, parallel group study in patients with Parkinson's disease who were not optimally controlled on levodopa demonstrated that adjunctive therapy of ropinirole prolonged-release tablets results in clinically relevant and statistically significant superiority over placebo in a change from baseline in awake time “off” (adjusted mean treatment difference -1.7 hours (95% CI: [-2.34, -1.09], p<0.0001). This was supported by secondary efficacy parameters of change from baseline in total awake time “on” (+1.7 hours (95% CI [1.06, 2.33], p<0.0001) and total awake time “on” without troublesome dyskinesias (+1.5 hours (95% CI: [0.85, 2.13], p<0.0001). Importantly, there was no indication of an increase from baseline in awake time “on” with troublesome dyskinesias, either from diary card data or from the UPDRS items.

Study of 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 (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% (36–57%). Following oral administration of ropinirole prolonged release tablets, plasma concentrations increase slowly, with a median time to Cmax generally achieved between 6 and 10 hours.

In a steady-state study in 25 Parkinson's disease patients receiving 12 mg of ropinirole prolonged release tablets once daily, a high fat meal increased the systemic exposure to ropinirole as shown by an average 20% increase in AUC and an average 44% increase in Cmax . Tmax was delayed by 3.0 hours. However, these changes are unlikely to be clinically relevant (e.g. Increased incidence of adverse events).

The systemic exposure to ropinirole is comparable for ropinirole prolonged-release tablets and ropinirole immediate-release tablets based on the same daily dose.

Distribution

Plasma protein binding of the active substance is low (10–40%). Consistent with its high lipophilicity, ropinirole exhibits a large volume of distribution (approximately 7 l/kg).

Biotransformation

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.

Elimination

Ropinirole is cleared from the systemic circulation with an average elimination half-life of about 6 hours. The increase in systemic exposure (Cmax 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. Following steady-state administration of ropinirole prolonged-release tablets, the inter-individual variability of Cmax was between 30% and 55% and for AUC was between 40% and 70%.

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 dialysis, 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 also 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 (approximately twice the highest AUC at the Maximum Recommended Human Dose (MRHD)), increased foetal death at 90 mg/kg/day (mean AUC in rats is 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 Cmax at the MRHD). However, ropinirole at 10 mg/kg (4.8 times the mean human Cmax at the MRHD) administered to rabbits in combination with oral L-dopa produced a higher incidence and severity of digit malformations than L-dopa 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 a battery of in vitro and in vivo tests.

Carcinogenicity

From two-year studies conducted in the mouse and rat at doses 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 IC50 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

Tablet core

Ammonio Methacrylate Copolymer, Type B

Hydroxypropylmethyl cellulose

Sodium Lauryl Sulfate

Copovidone K25.2 -30.8

Magnesium stearate

Film coating

Lactose monohydrate, Titanium dioxide (E171), Hypromellose, Macrogol 4000, Carmine (E120), Indigo carmine aluminium lake (E132), Sunset yellow aluminium lake (E110)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

Store below 25°C.

6.5 Nature and contents of container

White opaque PVC/PCTFE blisters with Aluminum foil

White opaque HDPE bottle with white cylindrical caps of polypropylene with three break points on the tamper-evident ring and aperture of desiccant (Silica Gel) insert.

Pack sizes: 28 or 84 prolonged-release tablets

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements for disposal.

7 MARKETING AUTHORISATION HOLDER

Crescent Pharma
Ltd., Key House,
Sarum Hill,
Basingstoke, RG21
8SR, United
Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PLGB 20416/0871

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

28/09/2020

10 DATE OF REVISION OF THE TEXT

18/06/2024