Public Assessment Report

Decentralised

Ropinirole 0.25mg Film-coated Tablets
Ropinirole 0.5mg Film-coated Tablets
Ropinirole 1mg Film-coated Tablets
Ropinirole 2mg Film-coated Tablets
Ropinirole 5mg Film-coated Tablets

UK/H/1192/01-5/DC

Pliva Pharma Ltd
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<td>79</td>
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# Module 1

| **Product Name** | Ropinirole 0.25mg Film-coated Tablets  
|                 | Ropinirole 0.5mg Film-coated Tablets  
|                 | Ropinirole 1mg Film-coated Tablets  
|                 | Ropinirole 2mg Film-coated Tablets  
|                 | Ropinirole 5mg Film-coated Tablets  |
| **Type of Application** | Standard Complex Decentralised (Article 10.1)  |
| **Active Substance (INN)** | Ropinirole hydrochloride  |
| **Pharmacotherapeutic Classification (ATC)** | N04BC04  |
| **Pharmaceutical Form and Strength** | Powder for solution for injection or infusion  
|                                           | 25mg/ml  |
| **Procedure Numbers** | UK/H/1196/01-05/DC  |
| **RMS** | UK  |
| **CMS** | DE, EE, ES, IT, LT, LV, PL, RO, SK  |
| **Start Date** | 22/08/2007  |
| **End Date** | 18/11/2008  |
| **MA Number** | PL 10622/0319  
|               | PL 10622/0320  
|               | PL 10622/0321  
|               | PL 10622/0322  
|               | PL 10622/0323  |
| **Name and address of MA holder** | PLIVA Pharma Limited  
|                               | Vision house, Bedford Road  
|                               | Petersfield, Hampshire  
|                               | GU32 3QB  
|                               | UK  |
**Lay Summary**

The MHRA granted market authorisations to Pliva Pharma Ltd for the medicinal products Ropinirole 0.25-5mg Film-coated Tablets on 18/11/2008. These are prescription only medicines.

Ropinirole activates dopamine receptors in the brain and is used in the treatment of Parkinson’s Disease. Ropinirole is also used in the treatment of restless legs syndrome.

The originator products are Requip 0.25, 0.5, 1, 3, and 5mg film coated tablets (SmithKline Beecham PLC, UK), registered since 02/07/1996.
Module 2

Summary of Product Characteristics

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Ropinirole 0.25 mg Film-coated Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 0.25 mg film-coated tablet contains 0.25 mg of ropinirole (as hydrochloride).

Excipient(s):
Each 0.25 mg film-coated tablet contains 63.743 mg of lactose (as monohydrate)

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet.

Ropinirole 0.25 mg Film-coated Tablets are blue, round, biconvex tablets embossed with "RO" on one side and "025" on the other side.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

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).

Ropinirole is also indicated for the symptomatic treatment of moderate to severe idiopathic Restless Legs Syndrome (see section 5.1).
4.2 Posology and method of administration

Oral use.

The tablets should be swallowed whole with fluid and preferably taken with meals.

Different strengths of this medicinal product are available in order to allow dosing according to the recommended treatment initiation and therapeutic regimens below. When the available range of strengths does not permit dose titration according to the treatment initiation regimen, Ropinirole should not be used in ropinirole naïve patients.

Treatment of idiopathic Parkinson's Disease:

Adults
Individual dose titration against efficacy and tolerability is recommended. Ropinirole should be taken three times a day (t.i.d.), preferably with meals to improve gastrointestinal tolerance.

Treatment initiation: The initial dose should be 0.25 mg t.i.d. A guide for the titration regimen for the first four weeks of treatment is given in the table below:

<table>
<thead>
<tr>
<th>Ropinirole</th>
<th>Week 1</th>
<th>Week 2</th>
<th>Week 3</th>
<th>Week 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unit dose (mg)</td>
<td>0.25</td>
<td>0.5</td>
<td>0.75</td>
<td>1.0</td>
</tr>
<tr>
<td>Total daily dose (mg)</td>
<td>0.75</td>
<td>1.5</td>
<td>2.25</td>
<td>3.0</td>
</tr>
</tbody>
</table>

Therapeutic regimen: After the initial titration, weekly increments of up to 3 mg/day may be given. Ropinirole is usually given in divided doses three times per day.

The proposed titration regime is as follows:

<table>
<thead>
<tr>
<th>Ropinirole</th>
<th>Week 5</th>
<th>Week 6</th>
<th>Week 7</th>
<th>Week 8</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unit dose (mg)</td>
<td>1.5</td>
<td>2.0</td>
<td>2.5</td>
<td>3.0</td>
</tr>
<tr>
<td>Total daily dose (mg)</td>
<td>4.5</td>
<td>6.0</td>
<td>7.5</td>
<td>9.0</td>
</tr>
</tbody>
</table>

A therapeutic response may be seen between 3 and 9 mg/day, although adjunct therapy patients may require higher doses. 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 24 mg/day have not been investigated in clinical trials and this dose should not be exceeded.

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 by around 20% in total.
When switching treatment from another dopamine agonist to ropinirole, the manufacturer's guidance on discontinuation should be followed before initiating ropinirole.

Ropinirole should be discontinued gradually by reducing the number of daily doses over the period of one week.

*Renal impairment:* In parkinsonian 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.

*Elderly:* The clearance of ropinirole is decreased in patients over 65 years of age, but the dose of ropinirole for elderly patients can be titrated in the normal manner.

*Children and adolescents:* Parkinson's disease does not occur in children and adolescents. The use of ropinirole in this population has therefore not been studied and it should not be given to children.

**Symptomatic treatment of moderate to severe idiopathic Restless Legs Syndrome.**

*Adults*
Individual dose titration against efficacy and tolerability is recommended. Ropinirole should be taken just before bed time, however the dose can be taken up to 3 hours before retiring. Ropinirole may be taken with food, to improve gastrointestinal tolerance.

*Treatment initiation (week 1)*
The recommended initial dose is 0.25 mg once daily (administered as above) for 2 days. If this dose is well tolerated the dose should be increased to 0.5 mg once daily for the remainder of week 1.

*Therapeutic regimen (week 2 onwards)*
Following treatment initiation, the daily dose should be increased until optimal therapeutic response is achieved. The average dose in clinical trials, in patients with moderate to severe Restless Legs Syndrome, was 2 mg once a day.

The dose may be increased to 1 mg once a day at week 2. The dose may then be increased by 0.5 mg per week over the next two weeks to a dose of 2 mg once a day.

In some patients, to achieve optimal improvement, the dose may be increased gradually up to a maximum of 4 mg once a day. In clinical trials the dose was increased by 0.5 mg each week to 3 mg once a day and then by 1 mg up to the maximum recommended dose of 4 mg once a day as shown in the table below.

Doses above 4 mg once daily have not been investigated in Restless Legs Syndrome patients.

**Dose titration**

<table>
<thead>
<tr>
<th>Week</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5*</th>
<th>6*</th>
<th>7*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose (mg)/once</td>
<td>1</td>
<td>1.5</td>
<td>2</td>
<td>2.5</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>
The patient’s response to ropinirole should be evaluated after 3 months treatment (see section 5.1). At this time the dose prescribed and the need for continued treatment should be considered. If treatment is interrupted for more than a few days it should be re-initiated by dose titration carried out as above.

Renal impairment: No dosage adjustment is necessary in patients with mild to moderate renal impairment (creatinine clearance between 30 and 50 ml/min).

Elderly: The clearance of ropinirole is decreased in patients over 65 years of age. The increase in dosage should be gradual and titrated against the symptomatic response.

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

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients
- Severe renal impairment (creatinine clearance <30 ml/min)
- Severe hepatic impairment

4.4 Special warnings and precautions for use

Due to the pharmacological action of ropinirole, patients with severe cardiovascular disease (in particular coronary insufficiency) should be treated with caution due to the risk of hypotension; blood pressure monitoring is recommended, particularly at the beginning of treatment.

Co-administration of ropinirole with anti-hypertensive and anti-arrhythmic agents has not been studied. Caution should be exercised when these compounds are given concomitantly with ropinirole because of the unknown potential for the occurrence of hypotension, bradycardias or other arrhythmias.

Patients with a history or presence of psychiatric or psychotic disorders should only be treated with dopamine agonists if the potential benefits outweigh the risks (see also Section 4.5).

Pathological gambling, increased libido and hypersexuality have been reported in patients treated with dopamine agonists for Parkinson's disease, including ropinirole.

Ropinirole has been associated with somnolence and episodes of sudden sleep onset (see section 4.8), 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.

Ropinirole should not be used to treat neuroleptic akathisia, tasikinesia (neuroleptic-induced compulsive tendency to walk), or secondary Restless Legs Syndrome (e.g. caused by renal failure, iron deficiency anaemia or pregnancy).

During treatment with ropinirole, paradoxical worsening of Restless Legs Syndrome symptoms occurring with earlier onset (augmentation), and reoccurrence of symptoms in the early morning hours (early morning rebound), may be observed. If this occurs, treatment should be reviewed and dosage adjustment or discontinuation of treatment may be considered.

This medicinal product contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

Ropinirole is principally metabolized by the cytochrome P450 isoenzyme CYP1A2. A pharmacokinetic study (with a ropinirole dose of 2 mg, three times a day) revealed that ciprofloxacin increased the Cmax 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, fluvoxamine or cimetidine, are introduced or withdrawn.

A pharmacokinetic interaction study between ropinirole (at a 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. Therefore, it is not expected that ropinirole will compete with the metabolism of other medicinal products which are metabolised by CYP1A2.

Based on in-vitro data, ropinirole has little potential to inhibit cytochrome P450 at therapeutic doses. Hence, ropinirole is unlikely to affect the pharmacokinetics of other medicinal products, via a cytochrome P450 mechanism.

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

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, it may be necessary to adjust the ropinirole dose, in accordance with clinical response, if hormone replacement therapy is stopped or introduced during treatment with ropinirole.

No pharmacokinetic interaction has been seen between ropinirole and levodopa or domperidone (a medicinal product used to treat nausea and vomiting) which would necessitate dosage adjustment of either medicinal product. Domperidone antagonises
the dopaminergic actions of ropinirole peripherally and does not cross the blood-brain barrier. Hence its value as an anti-emetic in patients treated with centrally acting dopamine agonists.

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 with ropinirole should be avoided.

4.6 Pregnancy and lactation

There are no adequate data from the use of ropinirole in pregnant women.

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.

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

4.7 Effects on ability to drive and use machines

Ropinirole has major influence on the ability to drive and use machines.

Patients should be warned about the possibility of dizziness (including vertigo). Patients being treated with ropinirole and presenting with 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 effects have resolved (see also Section 4.4).

4.8 Undesirable effects

Undesirable effects are listed below by system organ class and frequency. 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).

Common and uncommon undesirable effects were generally determined from pooled safety data from clinical trial populations of ropinirole and are quoted as excess incidence over placebo. Rare and very rare undesirable effects were generally determined from post-marketing data and refer to reporting rate rather than true frequency.

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

**Adverse Drug Reactions Reported from Patients taking ropinirole in Parkinson’s Disease:**
The adverse drug reactions reported in patients with Parkinson’s disease on ropinirole monotherapy and adjunct therapy at doses up to 24mg/day at an excess incidence over placebo are described below.

The most commonly reported undesirable effects are nausea, somnolence, dyskinesia and syncope.

<table>
<thead>
<tr>
<th>Psychiatric disorders</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>common</strong></td>
</tr>
<tr>
<td>confusion¹, hallucinations</td>
</tr>
<tr>
<td><strong>uncommon</strong></td>
</tr>
<tr>
<td>Psychotic reactions (other than hallucinations), including delusion, paranoia, delirium.</td>
</tr>
</tbody>
</table>

Patients treated with dopamine agonists for treatment of Parkinson's disease, including ropinirole, especially at high doses, have been reported as exhibiting signs of pathological gambling, increased libido and hypersexuality, generally reversible upon reduction of the dose or treatment discontinuation³.

<table>
<thead>
<tr>
<th>Nervous system disorders</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>very common</strong></td>
</tr>
<tr>
<td>Syncope², dyskinesia¹, somnolence²</td>
</tr>
<tr>
<td><strong>common</strong></td>
</tr>
<tr>
<td>dizziness (including vertigo)¹,²</td>
</tr>
<tr>
<td><strong>uncommon</strong></td>
</tr>
<tr>
<td>extreme daytime somnolence³, sudden onset of sleep³</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Vascular disorders</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>uncommon</strong></td>
</tr>
<tr>
<td>hypotension, postural hypotension</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Gastrointestinal disorders</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>very common</strong></td>
</tr>
<tr>
<td>nausea</td>
</tr>
<tr>
<td><strong>common</strong></td>
</tr>
<tr>
<td>vomiting², abdominal pain², heartburn²</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>General disorders and administrative site conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>common</strong></td>
</tr>
<tr>
<td>leg oedema²</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Hepatobiliary disorders</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>not known</strong></td>
</tr>
<tr>
<td>hepatic reactions, hepatic enzymes increased³</td>
</tr>
</tbody>
</table>

¹ Adjunct therapy studies  
² Monotherapy studies  
³ Post-marketing data (see Section 4.4)

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**Use of ropinirole in Restless Legs Syndrome**

In Restless Legs Syndrome clinical trials the most common adverse drug reaction was nausea (approximately 30% of patients). Undesirable effects were normally mild to moderate and experienced at the start of therapy or on increase of dose and few patients withdrew from the clinical studies due to undesirable effects.
The table below lists the adverse drug reactions reported for ropinirole in the 12-week clinical trials at $\geq 1.0\%$ above the placebo rate or those reported uncommonly but known to be associated with ropinirole.

**Adverse drug reactions reported in 12-week Restless Legs Syndrome clinical trials**

(ropinirole n=309, placebo n=307)

<table>
<thead>
<tr>
<th><strong>Psychiatric disorders</strong></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Common</td>
<td>Nervousness</td>
</tr>
<tr>
<td>Uncommon</td>
<td>Confusion</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Nervous system disorders</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Common</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Vascular disorders</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Uncommon</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Gastrointestinal disorders</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Very common</td>
</tr>
<tr>
<td>Common</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>General disorders and administration site conditions</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Common</td>
</tr>
</tbody>
</table>

Hallucinations were reported uncommonly in the open label long-term studies.

In post-marketing reports, extreme daytime somnolence and sudden onset of sleep have been reported very rarely in Restless Legs Syndrome.

Paradoxical worsening of Restless Legs Syndrome symptoms occurring with earlier onset (augmentation), and reoccurrence of symptoms in the early morning hours (early morning rebound), may be observed during treatment with ropinirole.

**Management of undesirable effects**

Dose reduction should be considered if patients experience significant undesirable effects. If the undesirable effect abates, gradual up-titration can be re-instituted. Anti-nausea medicinal products that are not centrally active dopamine antagonists, such as domperidone, may be used, if required.

**4.9 Overdose**

There have been no incidences of intentional overdose with ropinirole in clinical trials. 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.

**5 PHARMACOLOGICAL PROPERTIES**

**5.1 Pharmacodynamic properties**

Pharmacotherapeutic group: Dopamine agonist, ATC code: N04BC04.
Mechanism of action
Ropinirole is a non ergoline D2/D3 dopamine agonist which stimulates striatal dopamine receptors.

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.

Clinical efficacy in Restless Legs Syndrome
Ropinirole should only be prescribed to patients with moderate to severe idiopathic Restless Legs Syndrome. Moderate to severe idiopathic Restless Legs Syndrome is typically represented by patients who suffer with insomnia or severe discomfort in the limbs.

In the four 12-week efficacy studies, patients with Restless Legs Syndrome were randomised to ropinirole or placebo, and the effects on the IRLS scale scores at week 12 were compared to baseline. The mean dose of ropinirole for the moderate to severe patients was 2.0 mg/day. In a combined analysis of moderate to severe Restless Legs Syndrome patients from the four 12-week studies, the adjusted treatment difference for the change from baseline in IRLS scale total score at week 12 Last Observation Carried Forward (LOCF) Intention To Treat population was -4.0 points (95% CI -5.6, -2.4, p<0.0001; baseline and week 12 LOCF mean IRLS points: ropinirole 28.4 and 13.5; placebo 28.2 and 17.4).

A 12-week placebo-controlled polysomnography study in Restless Legs Syndrome patients examined the effect of treatment with ropinirole on periodic leg movements of sleep. A statistically significant difference in the periodic leg movements of sleep was seen between ropinirole and placebo from baseline to week 12. Although sufficient data are not available to adequately demonstrate the long term efficacy of ropinirole in Restless Legs Syndrome (see section 4.2), in a 36-week study, patients who continued on ropinirole demonstrated a significantly lower relapse rate compared with patients randomised to placebo (33% versus 58%, p=0.0156).

A combined analysis of data from moderate to severe Restless Legs Syndrome patients, in the four 12-week placebo-controlled studies, indicated that ropinirole-treated patients reported significant improvements over placebo on the parameters of the Medical Outcome Study Sleep Scale (scores on 0-100 range except sleep quantity). The adjusted treatment differences between ropinirole and placebo were: sleep disturbance (-15.2, 95% CI -19.37, -10.94; p<0.0001), sleep quantity (0.7 hours, 95% CI 0.49, 0.94; p<0.0001), sleep adequacy (18.6, 95% CI 13.77, 23.45; p<0.0001) and daytime somnolence (-7.5, 95% CI -10.86, -4.23; p<0.0001).

A rebound phenomenon following discontinuation of ropinirole treatment (end of treatment rebound) cannot be excluded. In clinical trials, although the average IRLS total scores 7-10 days after withdrawal of therapy were higher in ropinirole-treated patients than in placebo-treated patients, the severity of symptoms following withdrawal of therapy generally did not exceed the baseline assessment in ropinirole-treated patients.

In clinical studies most patients were of Caucasian origin.
5.2 Pharmacokinetic properties

Absorption
The bioavailability of ropinirole is about 50% (36% to 57%), with $C_{\text{max}}$ reached on average 1.5 hours after the dose. In the presence of food, $C_{\text{max}}$ is delayed by about 2.6 hours and the peak plasma level is reduced by 25%, with no effect on the bioavailable quantity. The bioavailability of ropinirole varies greatly between individuals.

Distribution
The binding of ropinirole to plasma proteins is not high (<40%), with no effect on the distribution which is very extensive (volume of distribution in the order of 7 l/kg).

Metabolism
Ropinirole is mainly metabolised by the isoform CYP1A2 of cytochrome P450. None of the many metabolites formed are involved in the resulting activity of the product and the main metabolite is 100 times less potent than ropinirole in animal models examining dopaminergic function.

Elimination
Unchanged ropinirole and the metabolites are mainly excreted through the kidneys. The elimination half-life of ropinirole is 6 hours on average.

Linearity
The pharmacokinetics of ropinirole are linear overall ($C_{\text{max}}$ and AUC) in the therapeutic range between 0.25 mg and 4 mg, after a single dose and after repeated dosing.

Population-related characteristics
In patients over 65 years of age, a reduction in the systemic clearance of ropinirole by about 30% is possible.

In patients with mild to moderate renal impairment (creatinine clearance between 30 and 50 ml/min), no change in the pharmacokinetics of ropinirole is observed. No data are available in patients with severe renal impairment.

5.3 Preclinical safety data

Toxicology: The toxicology profile is principally determined by the pharmacological activity of the drug (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 a high dose (50 mg/kg), 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 drug-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.

Reproductive Toxicity: Administration of ropinirole to pregnant rats at maternally toxic doses resulted in decreased foetal body weight at 60 mg/kg/day (approximately equivalent to the AUC at the maximum dose in humans), increased foetal death at 90 mg/kg/day (approximately 2 times the AUC at the maximum dose in humans) and digit malformations at 150 mg/kg/day (approximately 3 times the AUC at the maximum dose in humans). There were no teratogenic effects in the rat at 120 mg/kg/day (approximately 2.5 times the AUC at the maximum dose in humans) and no indication of an effect on development in the rabbit.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

**Tablet core:**
- Lactose monohydrate
- Cellulose, microcrystalline
- Maize starch
- Silica colloidal anhydrous
- Magnesium stearate

**Film coating:**
- Opadry II 33G20418 Blue consisting of:
  - Hypromellose 6 cp (E464)
  - Lactose monohydrate
  - Titanium dioxide (E171)
  - Macrogol 3350
  - Triacetin
  - Indigo carmine aluminium lake (E132)
  - Quinoline yellow aluminium lake (E104)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

1 year.

6.4 Special precautions for storage
Do not store above 25 °C. Store in the original package in order to protect from moisture.

6.5 Nature and contents of container

Al//PVC/Al/oPA foil blisters
Packs of 2, 12, 21, 84, 126 and 210 film-coated tablets
Not all pack sizes may be marketed.

6.6 Special precautions for disposal <and other handling>

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Pliva Pharma Limited.
Vision House
Bedford Road
Petersfield
Hampshire
GU32 3QB

8 MARKETING AUTHORISATION NUMBER(S)

PL 10622/0319

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORIZATION

18/11/2008

10 DATE OF REVISION OF THE TEXT

18/11/2008
SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Ropinirole 0.5 mg Film-coated Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 0.5 mg film-coated tablet contains 0.5 mg of ropinirole (as hydrochloride).

Excipient(s):
Each 0.5 mg film-coated tablet contains 63.472 mg of lactose (as monohydrate)
For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet.
Ropinirole 0.5 mg Film-coated Tablets are green, round, biconvex tablets embossed with "RO" on one side and "05" on the other side.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

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).
Ropinirole is also indicated for the symptomatic treatment of moderate to severe idiopathic Restless Legs Syndrome (see section 5.1).

4.2 Posology and method of administration

Oral use.
The tablets should be swallowed whole with fluid and preferably taken with meals.
Different strengths of this medicinal product are available in order to allow dosing according to the recommended treatment initiation and therapeutic regimens below. When the available range of strengths does not permit dose titration according to the treatment initiation regimen, Ropinirole should not be used in ropinirole naïve patients.
Treatment of idiopathic Parkinson's Disease:

Adults
Individual dose titration against efficacy and tolerability is recommended. Ropinirole should be taken three times a day (t.i.d.), preferably with meals to improve gastrointestinal tolerance.

Treatment initiation: The initial dose should be 0.25 mg t.i.d. A guide for the titration regimen for the first four weeks of treatment is given in the table below:

<table>
<thead>
<tr>
<th>Ropinirole</th>
<th>Week 1</th>
<th>Week 2</th>
<th>Week 3</th>
<th>Week 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unit dose (mg)</td>
<td>0.25</td>
<td>0.5</td>
<td>0.75</td>
<td>1.0</td>
</tr>
<tr>
<td>Total daily dose (mg)</td>
<td>0.75</td>
<td>1.5</td>
<td>2.25</td>
<td>3.0</td>
</tr>
</tbody>
</table>

Therapeutic regimen: After the initial titration, weekly increments of up to 3 mg/day may be given. Ropinirole is usually given in divided doses three times per day.

The proposed titration regime is as follows:

<table>
<thead>
<tr>
<th>Ropinirole</th>
<th>Week 5</th>
<th>Week 6</th>
<th>Week 7</th>
<th>Week 8</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unit dose (mg)</td>
<td>1.5</td>
<td>2.0</td>
<td>2.5</td>
<td>3.0</td>
</tr>
<tr>
<td>Total daily dose (mg)</td>
<td>4.5</td>
<td>6.0</td>
<td>7.5</td>
<td>9.0</td>
</tr>
</tbody>
</table>

A therapeutic response may be seen between 3 and 9 mg/day, although adjunct therapy patients may require higher doses. 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 24 mg/day have not been investigated in clinical trials and this dose should not be exceeded.

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 by around 20% in total.

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

Ropinirole should be discontinued gradually by reducing the number of daily doses over the period of one week.

Renal impairment: In parkinsonian 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.

Elderly: The clearance of ropinirole is decreased in patients over 65 years of age, but the dose of ropinirole for elderly patients can be titrated in the normal manner.
Children and adolescents: Parkinson's disease does not occur in children and adolescents. The use of ropinirole in this population has therefore not been studied and it should not be given to children.

Symptomatic treatment of moderate to severe idiopathic Restless Legs Syndrome.

Adults
Individual dose titration against efficacy and tolerability is recommended. Ropinirole should be taken just before bed time, however the dose can be taken up to 3 hours before retiring. Ropinirole may be taken with food, to improve gastrointestinal tolerance.

Treatment initiation (week 1)
The recommended initial dose is 0.25 mg once daily (administered as above) for 2 days. If this dose is well tolerated the dose should be increased to 0.5 mg once daily for the remainder of week 1.

Therapeutic regimen (week 2 onwards)
Following treatment initiation, the daily dose should be increased until optimal therapeutic response is achieved. The average dose in clinical trials, in patients with moderate to severe Restless Legs Syndrome, was 2 mg once a day.

The dose may be increased to 1 mg once a day at week 2. The dose may then be increased by 0.5 mg per week over the next two weeks to a dose of 2 mg once a day. In some patients, to achieve optimal improvement, the dose may be increased gradually up to a maximum of 4 mg once a day. In clinical trials the dose was increased by 0.5 mg each week to 3 mg once a day and then by 1 mg up to the maximum recommended dose of 4 mg once a day as shown in the table below.

Doses above 4 mg once daily have not been investigated in Restless Legs Syndrome patients.

Dose titration

<table>
<thead>
<tr>
<th>Week</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5*</th>
<th>6*</th>
<th>7*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose (mg)/once daily</td>
<td>1</td>
<td>1.5</td>
<td>2</td>
<td>2.5</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>

* To achieve optimal improvement in some patients.

The patient’s response to ropinirole should be evaluated after 3 months treatment (see section 5.1). At this time the dose prescribed and the need for continued treatment should be considered. If treatment is interrupted for more than a few days it should be re-initiated by dose titration carried out as above.

Renal impairment: No dosage adjustment is necessary in patients with mild to moderate renal impairment (creatinine clearance between 30 and 50 ml/min).

Elderly: The clearance of ropinirole is decreased in patients over 65 years of age. The increase in dosage should be gradual and titrated against the symptomatic
response.

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

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients
- Severe renal impairment (creatinine clearance <30 ml/min)
- Hepatic impairment

4.4 Special warnings and precautions for use

Due to the pharmacological action of ropinirole, patients with severe cardiovascular disease (in particular coronary insufficiency) should be treated with caution due to the risk of hypotension; blood pressure monitoring is recommended, particularly at the beginning of treatment.

Co-administration of ropinirole with anti-hypertensive and anti-arrhythmic agents has not been studied. Caution should be exercised when these compounds are given concomitantly with ropinirole because of the unknown potential for the occurrence of hypotension, bradycardias or other arrhythmias.

Patients with a history or presence of psychiatric or psychotic disorders should only be treated with dopamine agonists if the potential benefits outweigh the risks (see also section 4.5).

Pathological gambling, increased libido and hypersexuality have been reported in patients treated with dopamine agonists for Parkinson's disease, including ropinirole.

Ropinirole has been associated with somnolence and episodes of sudden sleep onset (see section 4.8), 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.

Ropinirole should not be used to treat neuroleptic akathisia, tasikinesia (neuroleptic-induced compulsive tendency to walk), or secondary Restless Legs Syndrome (e.g. caused by renal failure, iron deficiency anaemia or pregnancy).

During treatment with ropinirole, paradoxical worsening of Restless Legs Syndrome symptoms occurring with earlier onset (augmentation), and reoccurrence of symptoms in the early morning hours (early morning rebound), may be observed. If this occurs, treatment should be reviewed and dosage adjustment or discontinuation of treatment may be considered.
This medicinal product contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

Ropinirole is principally metabolized by the cytochrome P450 isoenzyme CYP1A2. A pharmacokinetic study (with a ropinirole dose of 2 mg, three times a day) revealed that ciprofloxacin increased the C<sub>max</sub> 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, fluvoxamine or cimetidine, are introduced or withdrawn.

A pharmacokinetic interaction study between ropinirole (at a 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. Therefore, it is not expected that ropinirole will compete with the metabolism of other medicinal products which are metabolised by CYP1A2.

Based on in-vitro data, ropinirole has little potential to inhibit cytochrome P450 at therapeutic doses. Hence, ropinirole is unlikely to affect the pharmacokinetics of other medicinal products, via a cytochrome P450 mechanism.

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

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, it may be necessary to adjust the ropinirole dose, in accordance with clinical response, if hormone replacement therapy is stopped or introduced during treatment with ropinirole.

No pharmacokinetic interaction has been seen between ropinirole and levodopa or domperidone (a medicinal product used to treat nausea and vomiting) which would necessitate dosage adjustment of either medicinal product. Domperidone antagonises the dopaminergic actions of ropinirole peripherally and does not cross the blood-brain barrier. Hence its value as an anti-emetic in patients treated with centrally acting dopamine agonists.

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 with ropinirole should be avoided.

4.6 Pregnancy and lactation

There are no adequate data from the use of ropinirole in pregnant women.
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.

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

4.7 Effects on ability to drive and use machines

Ropinirole has major influence on the ability to drive and use machines.

Patients should be warned about the possibility of dizziness (including vertigo). Patients being treated with ropinirole and presenting with 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 effects have resolved (see also Section 4.4).

4.8 Undesirable effects

Undesirable effects are listed below by system organ class and frequency. 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).

Common and uncommon undesirable effects were generally determined from pooled safety data from clinical trial populations of ropinirole and are quoted as excess incidence over placebo. Rare and very rare undesirable effects were generally determined from post-marketing data and refer to reporting rate rather than true frequency.

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

Adverse Drug Reactions Reported from Patients taking ropinirole in Parkinson’s Disease:
The adverse drug reactions reported in patients with Parkinson’s disease on ropinirole monotherapy and adjunct therapy at doses up to 24mg/day at an excess incidence over placebo are described below.

The most commonly reported undesirable effects are nausea, somnolence, dyskinesia and syncope.

<table>
<thead>
<tr>
<th>Psychiatric disorders</th>
</tr>
</thead>
<tbody>
<tr>
<td>common</td>
</tr>
<tr>
<td>uncommon</td>
</tr>
</tbody>
</table>
including delusion, paranoia, delirium.

Patients treated with dopamine agonists for treatment of Parkinson's disease, including ropinirole, especially at high doses, have been reported as exhibiting signs of pathological gambling, increased libido and hypersexuality, generally reversible upon reduction of the dose or treatment discontinuation³.

**Nervous system disorders**

<table>
<thead>
<tr>
<th>Common</th>
<th>Syncope², dyskinesia¹, somnolence²</th>
</tr>
</thead>
<tbody>
<tr>
<td>Common</td>
<td>dizziness (including vertigo)¹,²</td>
</tr>
<tr>
<td>Uncommon</td>
<td>extreme daytime somnolence³, sudden onset of sleep³</td>
</tr>
</tbody>
</table>

**Vascular disorders**

| Uncommon        | hypotension, postural hypotension |

**Gastrointestinal disorders**

<table>
<thead>
<tr>
<th>Very common</th>
<th>Nausea</th>
</tr>
</thead>
<tbody>
<tr>
<td>Common</td>
<td>Vomiting², abdominal pain², heartburn²</td>
</tr>
</tbody>
</table>

**General disorders and administrative site conditions**

| Common          | Leg oedema²                        |

**Hepatobiliary disorders**

| Not known       | Hepatic reactions, hepatic enzymes increased³ |

1 Adjunct therapy studies
2 Monotherapy studies
3 Post-marketing data (see Section 4.4)

**Use of ropinirole in Restless Legs Syndrome**

In Restless Legs Syndrome clinical trials the most common adverse drug reaction was nausea (approximately 30% of patients). Undesirable effects were normally mild to moderate and experienced at the start of therapy or on increase of dose and few patients withdrew from the clinical studies due to undesirable effects.

The table below lists the adverse drug reactions reported for ropinirole in the 12-week clinical trials at ≥1.0% above the placebo rate or those reported uncommonly but known to be associated with ropinirole.

**Adverse drug reactions reported in 12-week Restless Legs Syndrome clinical trials (ropinirole n=309, placebo n=307)**

<table>
<thead>
<tr>
<th>Psychiatric disorders</th>
</tr>
</thead>
<tbody>
<tr>
<td>Common</td>
</tr>
<tr>
<td>Uncommon</td>
</tr>
<tr>
<td><strong>Nervous system disorders</strong></td>
</tr>
<tr>
<td>Common</td>
</tr>
<tr>
<td><strong>Vascular disorders</strong></td>
</tr>
</tbody>
</table>

Pliva Pharma Ltd, Ropinirole 0.25-5mg Film-coated Tablets 23
<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Uncommon</strong></td>
<td><strong>Postural hypotension, hypotension</strong></td>
</tr>
<tr>
<td><strong>Gastrointestinal disorders</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Very common</strong></td>
<td><strong>Vomiting, nausea</strong></td>
</tr>
<tr>
<td><strong>Common</strong></td>
<td><strong>Abdominal pain</strong></td>
</tr>
<tr>
<td><strong>General disorders and administration site conditions</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Common</strong></td>
<td><strong>Fatigue</strong></td>
</tr>
</tbody>
</table>

Hallucinations were reported uncommonly in the open label long-term studies.

In post-marketing reports, extreme daytime somnolence and sudden onset of sleep have been reported very rarely in Restless Legs Syndrome.

Paradoxical worsening of Restless Legs Syndrome symptoms occurring with earlier onset (augmentation), and reoccurrence of symptoms in the early morning hours (early morning rebound), may be observed during treatment with ropinirole.

**Management of undesirable effects**
Dose reduction should be considered if patients experience significant undesirable effects. If the undesirable effect abates, gradual up-titration can be re-instituted. Anti-nausea medicinal products that are not centrally active dopamine antagonists, such as domperidone, may be used, if required.

**4.9 Overdose**

There have been no incidences of intentional overdose with ropinirole in clinical trials. 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.

**5 PHARMACOLOGICAL PROPERTIES**

**5.1 Pharmacodynamic properties**

Pharmacotherapeutic group: Dopamine agonist, ATC code: N04BC04.

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

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.

**Clinical efficacy in Restless Legs Syndrome**
Ropinirole should only be prescribed to patients with moderate to severe idiopathic Restless Legs Syndrome. Moderate to severe idiopathic Restless Legs Syndrome is
typically represented by patients who suffer with insomnia or severe discomfort in the limbs.

In the four 12-week efficacy studies, patients with Restless Legs Syndrome were randomised to ropinirole or placebo, and the effects on the IRLS scale scores at week 12 were compared to baseline. The mean dose of ropinirole for the moderate to severe patients was 2.0 mg/day. In a combined analysis of moderate to severe Restless Legs Syndrome patients from the four 12-week studies, the adjusted treatment difference for the change from baseline in IRLS scale total score at week 12 Last Observation Carried Forward (LOCF) Intention To Treat population was -4.0 points (95% CI -5.6, -2.4, p<0.0001; baseline and week 12 LOCF mean IRLS points: ropinirole 28.4 and 13.5; placebo 28.2 and 17.4).

A 12-week placebo-controlled polysomnography study in Restless Legs Syndrome patients examined the effect of treatment with ropinirole on periodic leg movements of sleep. A statistically significant difference in the periodic leg movements of sleep was seen between ropinirole and placebo from baseline to week 12. Although sufficient data are not available to adequately demonstrate the long term efficacy of ropinirole in Restless Legs Syndrome (see section 4.2), in a 36-week study, patients who continued on ropinirole demonstrated a significantly lower relapse rate compared with patients randomised to placebo (33% versus 58%, p=0.0156).

A combined analysis of data from moderate to severe Restless Legs Syndrome patients, in the four 12-week placebo-controlled studies, indicated that ropinirole-treated patients reported significant improvements over placebo on the parameters of the Medical Outcome Study Sleep Scale (scores on 0-100 range except sleep quantity). The adjusted treatment differences between ropinirole and placebo were: sleep disturbance (-15.2, 95% CI -19.37, -10.94; p<0.0001), sleep quantity (0.7 hours, 95% CI 0.49, 0.94); p<0.0001), sleep adequacy (18.6, 95% CI 13.77, 23.45; p<0.0001) and daytime somnolence (-7.5, 95% CI -10.86, -4.23; p<0.0001).

A rebound phenomenon following discontinuation of ropinirole treatment (end of treatment rebound) cannot be excluded. In clinical trials, although the average IRLS total scores 7-10 days after withdrawal of therapy were higher in ropinirole-treated patients than in placebo-treated patients, the severity of symptoms following withdrawal of therapy generally did not exceed the baseline assessment in ropinirole-treated patients.

In clinical studies most patients were of Caucasian origin.

### 5.2 Pharmacokinetic properties

**Absorption**

The bioavailability of ropinirole is about 50% (36% to 57%), with $C_{\text{max}}$ reached on average 1.5 hours after the dose. In the presence of food, $C_{\text{max}}$ is delayed by about 2.6 hours and the peak plasma level is reduced by 25%, with no effect on the bioavailable quantity. The bioavailability of ropinirole varies greatly between individuals.

**Distribution**
The binding of ropinirole to plasma proteins is not high (<40%), with no effect on the distribution which is very extensive (volume of distribution in the order of 7 l/kg).

Metabolism
Ropinirole is mainly metabolised by the isoform CYP1A2 of cytochrome P450. None of the many metabolites formed are involved in the resulting activity of the product and the main metabolite is 100 times less potent than ropinirole in animal models examining dopaminergic function.

Elimination
Unchanged ropinirole and the metabolites are mainly excreted through the kidneys. The elimination half-life of ropinirole is 6 hours on average.

Linearity
The pharmacokinetics of ropinirole are linear overall (C_{max} and AUC) in the therapeutic range between 0.25 mg and 4 mg, after a single dose and after repeated dosing.

Population-related characteristics
In patients over 65 years of age, a reduction in the systemic clearance of ropinirole by about 30% is possible.

In patients with mild to moderate renal impairment (creatinine clearance between 30 and 50 ml/min), no change in the pharmacokinetics of ropinirole is observed. No data are available in patients with severe renal impairment.

5.3 Preclinical safety data

Toxicology: The toxicology profile is principally determined by the pharmacological activity of the drug (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 a high dose (50 mg/kg), 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 drug-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.

Reproductive Toxicity: Administration of ropinirole to pregnant rats at maternally toxic doses resulted in decreased foetal body weight at 60 mg/kg/day (approximately equivalent to the AUC at the maximum dose in humans), increased foetal death at 90 mg/kg/day (approximately 2 times the AUC at the maximum dose in humans) and digit malformations at 150 mg/kg/day (approximately 3 times the AUC at the maximum dose in humans). There were no teratogenic effects in the rat at
120 mg/kg/day (approximately 2.5 times the AUC at the maximum dose in humans) and no indication of an effect on development in the rabbit.

6 PHARMACEUTICAL PARTICULARS
6.1 List of excipients

**Tablet core:**
- Lactose monohydrate
- Cellulose, microcrystalline
- Maize starch
- Silica colloidal anhydrous
- Magnesium stearate

**Film coating:**
- Opadry II 33G21673 Green consisting of:
  - Hypromellose 6 cp (E464)
  - Lactose monohydrate
  - Titanium dioxide (E171)
  - Macrogol 3350
  - Triacetin
  - Iron oxide yellow (E172)
  - Iron oxide black (E172)
  - Quinoline yellow aluminium lake (E104)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

1 year.

6.4 Special precautions for storage

Do not store above 25 °C. Store in the original package in order to protect from moisture.

6.5 Nature and contents of container

AL/PVC/Al/oPA foil blisters
Packs of 21, 28 and 84 film-coated tablets

Not all pack sizes may be marketed.

6.6 Special precautions for disposal <and other handling>

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Pliva Pharma Limited.
Vision House
Bedford Road
Petersfield
Hampshire
GU32 3QB

8 MARKETING AUTHORISATION NUMBER(S)

PL 10622/0320

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHOURISATION

18/11/2008

10 DATE OF REVISION OF THE TEXT

18/11/2008
SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Ropinirole 1 mg Film-coated Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 1 mg film-coated tablet contains 1.0 mg of ropinirole (as hydrochloride).

Excipient(s): Each 1.0 mg film-coated tablet contains 63.501 mg of lactose (as monohydrate) and 0.0048mg of allura red AC (E129)

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet.

Ropinirole 1 mg Film-coated Tablets are pink, round, biconvex tablets embossed with „RO” on one side and “1” on the other side.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

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).

Ropinirole is also indicated for the symptomatic treatment of moderate to severe idiopathic Restless Legs Syndrome (see section 5.1).

4.2 Posology and method of administration

Oral use.

The tablets should be swallowed whole with fluid and preferably taken with meals.
Different strengths of this medicinal product are available in order to allow dosing according to the recommended treatment initiation and therapeutic regimens below. When the available range of strengths does not permit dose titration according to the treatment initiation regimen, Ropinirole Tablets should not be used in ropinirole naïve patients.

**Treatment of idiopathic Parkinson's Disease:**

**Adults**
Individual dose titration against efficacy and tolerability is recommended. Ropinirole should be taken three times a day (t.i.d.), preferably with meals to improve gastrointestinal tolerance.

**Treatment initiation:** The initial dose should be 0.25 mg t.i.d. A guide for the titration regimen for the first four weeks of treatment is given in the table below:

<table>
<thead>
<tr>
<th>Ropinirole</th>
<th>Week 1</th>
<th>Week 2</th>
<th>Week 3</th>
<th>Week 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unit dose (mg)</td>
<td>0.25</td>
<td>0.5</td>
<td>0.75</td>
<td>1.0</td>
</tr>
<tr>
<td>Total daily dose (mg)</td>
<td>0.75</td>
<td>1.5</td>
<td>2.25</td>
<td>3.0</td>
</tr>
</tbody>
</table>

**Therapeutic regimen:** After the initial titration, weekly increments of up to 3 mg/day may be given. Ropinirole is usually given in divided doses three times per day.

The proposed titration regime is as follows:

<table>
<thead>
<tr>
<th>Ropinirole</th>
<th>Week 5</th>
<th>Week 6</th>
<th>Week 7</th>
<th>Week 8</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unit dose (mg)</td>
<td>1.5</td>
<td>2.0</td>
<td>2.5</td>
<td>3.0</td>
</tr>
<tr>
<td>Total daily dose (mg)</td>
<td>4.5</td>
<td>6.0</td>
<td>7.5</td>
<td>9.0</td>
</tr>
</tbody>
</table>

A therapeutic response may be seen between 3 and 9 mg/day, although adjunct therapy patients may require higher doses. 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 24 mg/day have not been investigated in clinical trials and this dose should not be exceeded.

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 by around 20% in total.

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

Ropinirole should be discontinued gradually by reducing the number of daily doses over the period of one week.
Renal impairment: In parkinsonian 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.

Elderly: The clearance of ropinirole is decreased in patients over 65 years of age, but the dose of ropinirole for elderly patients can be titrated in the normal manner.

Children and adolescents: Parkinson's disease does not occur in children and adolescents. The use of ropinirole in this population has therefore not been studied and it should not be given to children.

Symptomatic treatment of moderate to severe idiopathic Restless Legs Syndrome.

Adults
Individual dose titration against efficacy and tolerability is recommended. Ropinirole should be taken just before bed time, however the dose can be taken up to 3 hours before retiring. Ropinirole may be taken with food, to improve gastrointestinal tolerance.

Treatment initiation (week 1)
The recommended initial dose is 0.25 mg once daily (administered as above) for 2 days. If this dose is well tolerated the dose should be increased to 0.5 mg once daily for the remainder of week 1.

Therapeutic regimen (week 2 onwards)
Following treatment initiation, the daily dose should be increased until optimal therapeutic response is achieved. The average dose in clinical trials, in patients with moderate to severe Restless Legs Syndrome, was 2 mg once a day.

The dose may be increased to 1 mg once a day at week 2. The dose may then be increased by 0.5 mg per week over the next two weeks to a dose of 2 mg once a day. In some patients, to achieve optimal improvement, the dose may be increased gradually up to a maximum of 4 mg once a day. In clinical trials the dose was increased by 0.5 mg each week to 3 mg once a day and then by 1 mg up to the maximum recommended dose of 4 mg once a day as shown in the table below.

Doses above 4 mg once daily have not been investigated in Restless Legs Syndrome patients.

Dose titration

<table>
<thead>
<tr>
<th>Week</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5*</th>
<th>6*</th>
<th>7*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose (mg/once daily)</td>
<td>1</td>
<td>1.5</td>
<td>2</td>
<td>2.5</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>

* To achieve optimal improvement in some patients.

The patient’s response to ropinirole should be evaluated after 3 months treatment (see section 5.1). At this time the dose prescribed and the need for continued treatment should be considered. If treatment is interrupted for more than a few days it should be re-initiated by dose titration carried out as above.
Renal impairment: No dosage adjustment is necessary in patients with mild to moderate renal impairment (creatinine clearance between 30 and 50 ml/min).

Elderly: The clearance of ropinirole is decreased in patients over 65 years of age. The increase in dosage should be gradual and titrated against the symptomatic response.

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

4.3 Contraindications

- Hypersensitivity to the active substance, allura red AC, or to any of the excipients
- Severe renal impairment (creatinine clearance <30 ml/min)
- Hepatic impairment

4.4 Special warnings and precautions for use

Due to the pharmacological action of ropinirole, patients with severe cardiovascular disease (in particular coronary insufficiency) should be treated with caution due to the risk of hypotension; blood pressure monitoring is recommended, particularly at the beginning of treatment.

Co-administration of ropinirole with anti-hypertensive and anti-arrhythmic agents has not been studied. Caution should be exercised when these compounds are given concomitantly with ropinirole because of the unknown potential for the occurrence of hypotension, bradycardias or other arrhythmias.

Patients with a history or presence of psychiatric or psychotic disorders should only be treated with dopamine agonists if the potential benefits outweigh the risks (see also Section 4.5).

Pathological gambling, increased libido and hypersexuality have been reported in patients treated with dopamine agonists for Parkinson's disease, including ropinirole.

Ropinirole has been associated with somnolence and episodes of sudden sleep onset (see section 4.8), 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.

Ropinirole should not be used to treat neuroleptic akathisia, tasikinesia (neuroleptic-induced compulsive tendency to walk), or secondary Restless Legs Syndrome (e.g. caused by renal failure, iron deficiency anaemia or pregnancy).
During treatment with ropinirole, paradoxical worsening of Restless Legs Syndrome symptoms occurring with earlier onset (augmentation), and reoccurrence of symptoms in the early morning hours (early morning rebound), may be observed. If this occurs, treatment should be reviewed and dosage adjustment or discontinuation of treatment may be considered.

This medicinal product contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Ropinirole 1 mg Film-coated Tablets also contain allura red AC azo dye. Allura red AC may cause allergic reactions.

4.5 Interaction with other medicinal products and other forms of interaction

Ropinirole is principally metabolized by the cytochrome P450 isoenzyme CYP1A2. A pharmacokinetic study (with a ropinirole dose of 2 mg, three times a day) 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, fluvoxamine or cimetidine, are introduced or withdrawn.

A pharmacokinetic interaction study between ropinirole (at a 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. Therefore, it is not expected that ropinirole will compete with the metabolism of other medicinal products which are metabolised by CYP1A2.

Based on in-vitro data, ropinirole has little potential to inhibit cytochrome P450 at therapeutic doses. Hence, ropinirole is unlikely to affect the pharmacokinetics of other medicinal products, via a cytochrome P450 mechanism.

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

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, it may be necessary to adjust the ropinirole dose, in accordance with clinical response, if hormone replacement therapy is stopped or introduced during treatment with ropinirole.

No pharmacokinetic interaction has been seen between ropinirole and levodopa or domperidone (a medicinal product used to treat nausea and vomiting) which would necessitate dosage adjustment of either medicinal product. Domperidone antagonises the dopaminergic actions of ropinirole peripherally and does not cross the blood-brain barrier. Hence its value as an anti-emetic in patients treated with centrally acting dopamine agonists.
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 with ropinirole should be avoided.

4.6 Pregnancy and lactation

There are no adequate data from the use of ropinirole in pregnant women.

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.

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

4.7 Effects on ability to drive and use machines

Ropinirole has major influence on the ability to drive and use machines.

Patients should be warned about the possibility of dizziness (including vertigo). Patients being treated with ropinirole and presenting with 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 effects have resolved (see also Section 4.4).

4.8 Undesirable effects

Undesirable effects are listed below by system organ class and frequency. 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).

Common and uncommon undesirable effects were generally determined from pooled safety data from clinical trial populations of ropinirole and are quoted as excess incidence over placebo. Rare and very rare undesirable effects were generally determined from post-marketing data and refer to reporting rate rather than true frequency.

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

**Adverse Drug Reactions Reported from Patients taking ropinirole in Parkinson’s Disease:**

The adverse drug reactions reported in patients with Parkinson’s disease on ropinirole monotherapy and adjunct therapy at doses up to 24mg/day at an excess incidence over placebo are described below.
The most commonly reported undesirable effects are nausea, somnolence, dyskinesia and syncope.

### Psychiatric disorders

<table>
<thead>
<tr>
<th>Common</th>
<th>confusion¹, hallucinations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uncommon</td>
<td>Psychotic reactions (other than hallucinations), including delusion, paranoia, delirium.</td>
</tr>
</tbody>
</table>

Patients treated with dopamine agonists for treatment of Parkinson's disease, including ropinirole, especially at high doses, have been reported as exhibiting signs of pathological gambling, increased libido and hypersexuality, generally reversible upon reduction of the dose or treatment discontinuation³.

### Nervous system disorders

<table>
<thead>
<tr>
<th>Very common</th>
<th>Syncope², dyskinesia¹, somnolence²</th>
</tr>
</thead>
<tbody>
<tr>
<td>Common</td>
<td>Dizziness (including vertigo)¹,²</td>
</tr>
<tr>
<td>Uncommon</td>
<td>Extreme daytime somnolence³, sudden onset of sleep³</td>
</tr>
</tbody>
</table>

### Vascular disorders

| Uncommon        | Hypotension, postural hypotension |

### Gastrointestinal disorders

<table>
<thead>
<tr>
<th>Very common</th>
<th>Nausea</th>
</tr>
</thead>
<tbody>
<tr>
<td>Common</td>
<td>Vomiting³, abdominal pain², heartburn²</td>
</tr>
</tbody>
</table>

### General disorders and administrative site conditions

| Common          | Leg oedema² |

### Hepatobiliary disorders

| Not known       | Hepatic reactions, hepatic enzymes increased³ |

1 Adjunct therapy studies  
2 Monotherapy studies  
3 Post-marketing data (see Section 4.4)

#### Use of ropinirole in Restless Legs Syndrome

In Restless Legs Syndrome clinical trials the most common adverse drug reaction was nausea (approximately 30% of patients). Undesirable effects were normally mild to moderate and experienced at the start of therapy or on increase of dose and few patients withdrew from the clinical studies due to undesirable effects.

The table below lists the adverse drug reactions reported for ropinirole in the 12-week clinical trials at ≥1.0% above the placebo rate or those reported uncommonly but known to be associated with ropinirole.

**Adverse drug reactions reported in 12-week Restless Legs Syndrome clinical trials**  
(ropinirole n=309, placebo n=307)
Hallucinations were reported uncommonly in the open label long-term studies.

In post-marketing reports, extreme daytime somnolence and sudden onset of sleep have been reported very rarely in Restless Legs Syndrome.

Paradoxical worsening of Restless Legs Syndrome symptoms occurring with earlier onset (augmentation), and reoccurrence of symptoms in the early morning hours (early morning rebound), may be observed during treatment with ropinirole.

Management of undesirable effects
Dose reduction should be considered if patients experience significant undesirable effects. If the undesirable effect abates, gradual up-titration can be re-instituted.
Anti-nausea medicinal products that are not centrally active dopamine antagonists, such as domperidone, may be used, if required.
Allura red AC may cause allergic reactions.

4.9 Overdose

There have been no incidences of intentional overdose with ropinirole in clinical trials. 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.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties
Pharmacotherapeutic group: Dopamine agonist, ATC code: N04BC04.

Mechanism of action
Ropinirole is a non ergoline D2/D3 dopamine agonist which stimulates striatal dopamine receptors.
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.

**Clinical efficacy in Restless Legs Syndrome**

Ropinirole should only be prescribed to patients with moderate to severe idiopathic Restless Legs Syndrome. Moderate to severe idiopathic Restless Legs Syndrome is typically represented by patients who suffer with insomnia or severe discomfort in the limbs.

In the four 12-week efficacy studies, patients with Restless Legs Syndrome were randomised to ropinirole or placebo, and the effects on the IRLS scale scores at week 12 were compared to baseline. The mean dose of ropinirole for the moderate to severe patients was 2.0 mg/day. In a combined analysis of moderate to severe Restless Legs Syndrome patients from the four 12-week studies, the adjusted treatment difference for the change from baseline in IRLS scale total score at week 12 Last Observation Carried Forward (LOCF) Intention To Treat population was -4.0 points (95% CI -5.6, -2.4, p<0.0001; baseline and week 12 LOCF mean IRLS points: ropinirole 28.4 and 13.5; placebo 28.2 and 17.4).

A 12-week placebo-controlled polysomnography study in Restless Legs Syndrome patients examined the effect of treatment with ropinirole on periodic leg movements of sleep. A statistically significant difference in the periodic leg movements of sleep was seen between ropinirole and placebo from baseline to week 12. Although sufficient data are not available to adequately demonstrate the long term efficacy of ropinirole in Restless Legs Syndrome (see section 4.2), in a 36-week study, patients who continued on ropinirole demonstrated a significantly lower relapse rate compared with patients randomised to placebo (33% versus 58%, p=0.0156).

A combined analysis of data from moderate to severe Restless Legs Syndrome patients, in the four 12-week placebo-controlled studies, indicated that ropinirole-treated patients reported significant improvements over placebo on the parameters of the Medical Outcome Study Sleep Scale (scores on 0-100 range except sleep quantity). The adjusted treatment differences between ropinirole and placebo were: sleep disturbance (-15.2, 95% CI -19.37, -10.94; p<0.0001), sleep quantity (0.7 hours, 95% CI 0.49, 0.94); p<0.0001), sleep adequacy (18.6, 95% CI 13.77, 23.45; p<0.0001) and daytime somnolence (-7.5, 95% CI -10.86, -4.23; p<0.0001).

A rebound phenomenon following discontinuation of ropinirole treatment (end of treatment rebound) cannot be excluded. In clinical trials, although the average IRLS total scores 7-10 days after withdrawal of therapy were higher in ropinirole-treated patients than in placebo-treated patients, the severity of symptoms following withdrawal of therapy generally did not exceed the baseline assessment in ropinirole-treated patients.

In clinical studies most patients were of Caucasian origin.

### 5.2 Pharmacokinetic properties

**Absorption**

The bioavailability of ropinirole is about 50% (36% to 57%), with $C_{max}$ reached on average 1.5 hours after the dose. In the presence of food, $C_{max}$ is delayed by about 2.6 hours and the peak plasma level is reduced by 25%, with no effect on the
bioavailable quantity. The bioavailability of ropinirole varies greatly between individuals.

**Distribution**
The binding of ropinirole to plasma proteins is not high (<40%), with no effect on the distribution which is very extensive (volume of distribution in the order of 7 l/kg).

**Metabolism**
Ropinirole is mainly metabolised by the isoform CYP1A2 of cytochrome P450. None of the many metabolites formed are involved in the resulting activity of the product and the main metabolite is 100 times less potent than ropinirole in animal models examining dopaminergic function.

**Elimination**
Unchanged ropinirole and the metabolites are mainly excreted through the kidneys. The elimination half-life of ropinirole is 6 hours on average.

**Linearity**
The pharmacokinetics of ropinirole are linear overall (Cmax and AUC) in the therapeutic range between 0.25 mg and 4 mg, after a single dose and after repeated dosing.

**Population-related characteristics**
In patients over 65 years of age, a reduction in the systemic clearance of ropinirole by about 30% is possible. In patients with mild to moderate renal impairment (creatinine clearance between 30 and 50 ml/min), no change in the pharmacokinetics of ropinirole is observed. No data are available in patients with severe renal impairment.

5.3 **Preclinical safety data**

*Toxicology:* The toxicology profile is principally determined by the pharmacological activity of the drug (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 a high dose (50 mg/kg), 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 drug-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.

*Reproductive Toxicity:* Administration of ropinirole to pregnant rats at maternally toxic doses resulted in decreased foetal body weight at 60 mg/kg/day (approximately equivalent to the AUC at the maximum dose in humans), increased foetal death at
90 mg/kg/day (approximately 2 times the AUC at the maximum dose in humans) and digit malformations at 150 mg/kg/day (approximately 3 times the AUC at the maximum dose in humans). There were no teratogenic effects in the rat at 120 mg/kg/day (approximately 2.5 times the AUC at the maximum dose in humans) and no indication of an effect on development in the rabbit.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

**Tablet core:**
- Lactose monohydrate
- Cellulose, microcrystalline
- Maize starch
- Silica colloidal anhydrous
- Magnesium stearate

**Film coating:**
- Opadry II 31F24239 Pink consisting of:
  - Hypromellose 15 cp (E464)
  - Lactose monohydrate
  - Titanium dioxide (E171)
  - Macrogol 4000
  - Iron oxide red (E172)
  - Allura red AC aluminium lake (E129)
  - Indigo carmine aluminium lake (E132)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

18 months.

6.4 Special precautions for storage

Do not store above 25 °C. Store in the original package in order to protect from moisture.

6.5 Nature and contents of container

AL/PVC/AL/oPA foil blisters
Packs of 21, 28 and 84 film-coated tablets
6.6 Special precautions for disposal <and other handling>

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Pliva Pharma Limited.
Vision House
Bedford Road
Petersfield
Hampshire
GU32 3QB

8 MARKETING AUTHORISATION NUMBER(S)

PL 10622/0321

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

18/11/2008

10 DATE OF REVISION OF THE TEXT

18/11/2008

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Ropinirole 2 mg Film-coated Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 2 mg film-coated tablet contains 2.0 mg of ropinirole (as hydrochloride).

Excipient(s):
Each 2.0 mg tablet contains 62.083 mg of lactose (as monohydrate)

For a full list of excipients, see section 6.1.
3 PHARMACEUTICAL FORM

Film-coated tablet.
Ropinirole 2 mg Film-coated Tablets are white, round, biconvex tablets embossed with "RO" on one side and "2" on the other side.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

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).

Ropinirole is also indicated for the symptomatic treatment of moderate to severe idiopathic Restless Legs Syndrome (see section 5.1).

4.2 Posology and method of administration

Oral use.

The tablets should be swallowed whole with fluid and preferably taken with meals.

Different strengths of this medicinal product are available in order to allow dosing according to the recommended treatment initiation and therapeutic regimens below.

When the available range of strengths does not permit dose titration according to the treatment initiation regimen, Ropinirole should not be used in ropinirole naïve patients.

Treatment of idiopathic Parkinson's Disease:

Adults
Individual dose titration against efficacy and tolerability is recommended. Ropinirole should be taken three times a day (t.i.d.), preferably with meals to improve gastrointestinal tolerance.

Treatment initiation: The initial dose should be 0.25 mg t.i.d. A guide for the titration regimen for the first four weeks of treatment is given in the table below:

<table>
<thead>
<tr>
<th>Ropinirole</th>
<th>Week 1</th>
<th>Week 2</th>
<th>Week 3</th>
<th>Week 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.25 mg</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.5 mg</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 mg</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 mg</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3 mg</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4 mg</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5 mg</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
**Therapeutic regimen:** After the initial titration, weekly increments of up to 3 mg/day may be given. Ropinirole is usually given in divided doses three times per day.

The proposed titration regime is as follows:

<table>
<thead>
<tr>
<th>Ropinirole</th>
<th>Week 5</th>
<th>Week 6</th>
<th>Week 7</th>
<th>Week 8</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unit dose (mg)</td>
<td>1.5</td>
<td>2.0</td>
<td>2.5</td>
<td>3.0</td>
</tr>
<tr>
<td>Total daily dose (mg)</td>
<td>4.5</td>
<td>6.0</td>
<td>7.5</td>
<td>9.0</td>
</tr>
</tbody>
</table>

A therapeutic response may be seen between 3 and 9 mg/day, although adjunct therapy patients may require higher doses. 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 24 mg/day have not been investigated in clinical trials and this dose should not be exceeded.

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 by around 20% in total.

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

Ropinirole should be discontinued gradually by reducing the number of daily doses over the period of one week.

**Renal impairment:** In parkinsonian 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.

**Elderly:** The clearance of ropinirole is decreased in patients over 65 years of age, but the dose of ropinirole for elderly patients can be titrated in the normal manner.

**Children and adolescents:** Parkinson's disease does not occur in children and adolescents. The use of ropinirole in this population has therefore not been studied and it should not be given to children.

**Symptomatic treatment of moderate to severe idiopathic Restless Legs Syndrome.**

**Adults**

Individual dose titration against efficacy and tolerability is recommended. Ropinirole should be taken just before bed time, however the dose can be taken up to 3 hours
before retiring. Ropinirole may be taken with food, to improve gastrointestinal tolerance.

**Treatment initiation (week 1)**
The recommended initial dose is 0.25 mg once daily (administered as above) for 2 days. If this dose is well tolerated the dose should be increased to 0.5 mg once daily for the remainder of week 1.

**Therapeutic regimen (week 2 onwards)**
Following treatment initiation, the daily dose should be increased until optimal therapeutic response is achieved. The average dose in clinical trials, in patients with moderate to severe Restless Legs Syndrome, was 2 mg once a day.

The dose may be increased to 1 mg once a day at week 2. The dose may then be increased by 0.5 mg per week over the next two weeks to a dose of 2 mg once a day. In some patients, to achieve optimal improvement, the dose may be increased gradually up to a maximum of 4 mg once a day. In clinical trials the dose was increased by 0.5 mg each week to 3 mg once a day and then by 1 mg up to the maximum recommended dose of 4 mg once a day as shown in the table below.

Doses above 4 mg once daily have not been investigated in Restless Legs Syndrome patients.

**Dose titration**

<table>
<thead>
<tr>
<th>Week</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5*</th>
<th>6*</th>
<th>7*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose (mg)/once daily</td>
<td>1</td>
<td>1.5</td>
<td>2</td>
<td>2.5</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>

* To achieve optimal improvement in some patients.

The patient’s response to ropinirole should be evaluated after 3 months treatment (see section 5.1). At this time the dose prescribed and the need for continued treatment should be considered. If treatment is interrupted for more than a few days it should be re-initiated by dose titration carried out as above.

**Renal impairment:** No dosage adjustment is necessary in patients with mild to moderate renal impairment (creatinine clearance between 30 and 50 ml/min).

**Elderly:** The clearance of ropinirole is decreased in patients over 65 years of age. The increase in dosage should be gradual and titrated against the symptomatic response.

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

### 4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients
- Severe renal impairment (creatinine clearance <30 ml/min)
4.4 Special warnings and precautions for use

Due to the pharmacological action of ropinirole, patients with severe cardiovascular disease (in particular coronary insufficiency) should be treated with caution due to the risk of hypotension; blood pressure monitoring is recommended, particularly at the beginning of treatment.

Co-administration of ropinirole with anti-hypertensive and anti-arrhythmic agents has not been studied. Caution should be exercised when these compounds are given concomitantly with ropinirole because of the unknown potential for the occurrence of hypotension, bradycardias or other arrhythmias.

Patients with a history or presence of psychiatric or psychotic disorders should only be treated with dopamine agonists if the potential benefits outweigh the risks (see also Section 4.5).

Pathological gambling, increased libido and hypersexuality have been reported in patients treated with dopamine agonists for Parkinson's disease, including ropinirole.

Ropinirole has been associated with somnolence and episodes of sudden sleep onset (see section 4.8), 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.

Ropinirole should not be used to treat neuroleptic akathisia, tasikinesia (neuroleptic-induced compulsive tendency to walk), or secondary Restless Legs Syndrome (e.g. caused by renal failure, iron deficiency anaemia or pregnancy).

During treatment with ropinirole, paradoxical worsening of Restless Legs Syndrome symptoms occurring with earlier onset (augmentation), and reoccurrence of symptoms in the early morning hours (early morning rebound), may be observed. If this occurs, treatment should be reviewed and dosage adjustment or discontinuation of treatment may be considered.

This medicinal product contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

Ropinirole is principally metabolized by the cytochrome P450 isoenzyme CYP1A2. A pharmacokinetic study (with a ropinirole dose of 2 mg, three times a day) revealed that ciprofloxacin increased the $C_{\text{max}}$ 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, fluvoxamine or cimetidine, are introduced or withdrawn.

A pharmacokinetic interaction study between ropinirole (at a 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. Therefore, it is not expected that ropinirole will compete with the metabolism of other medicinal products which are metabolised by CYP1A2.

Based on in-vitro data, ropinirole has little potential to inhibit cytochrome P450 at therapeutic doses. Hence, ropinirole is unlikely to affect the pharmacokinetics of other medicinal products, via a cytochrome P450 mechanism.

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

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, it may be necessary to adjust the ropinirole dose, in accordance with clinical response, if hormone replacement therapy is stopped or introduced during treatment with ropinirole.

No pharmacokinetic interaction has been seen between ropinirole and levodopa or domperidone (a medicinal product used to treat nausea and vomiting) which would necessitate dosage adjustment of either medicinal product. Domperidone antagonises the dopaminergic actions of ropinirole peripherally and does not cross the blood-brain barrier. Hence its value as an anti-emetic in patients treated with centrally acting dopamine agonists.

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 with ropinirole should be avoided.

4.6 Pregnancy and lactation

There are no adequate data from the use of ropinirole in pregnant women.

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.

Ropinirole should not be used in nursing mothers as it may inhibit lactation.
4.7 Effects on ability to drive and use machines

Ropinirole has major influence on the ability to drive and use machines.

Patients should be warned about the possibility of dizziness (including vertigo). Patients being treated with ropinirole and presenting with 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 effects have resolved (see also Section 4.4).

4.8 Undesirable effects

Undesirable effects are listed below by system organ class and frequency. 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).

Common and uncommon undesirable effects were generally determined from pooled safety data from clinical trial populations of ropinirole and are quoted as excess incidence over placebo. Rare and very rare undesirable effects were generally determined from post-marketing data and refer to reporting rate rather than true frequency.

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

Adverse Drug Reactions Reported from Patients taking ropinirole in Parkinson’s Disease:

The adverse drug reactions reported in patients with Parkinson’s disease on ropinirole monotherapy and adjunct therapy at doses up to 24mg/day at an excess incidence over placebo are described below.

The most commonly reported undesirable effects are nausea, somnolence, dyskinesia and syncope.

<table>
<thead>
<tr>
<th>Psychiatric disorders</th>
</tr>
</thead>
<tbody>
<tr>
<td>common</td>
</tr>
<tr>
<td>confusion¹, hallucinations</td>
</tr>
<tr>
<td>uncommon</td>
</tr>
<tr>
<td>Psychotic reactions (other than hallucinations), including delusion, paranoia, delirium.</td>
</tr>
</tbody>
</table>

Patients treated with dopamine agonists for treatment of Parkinson's disease, including ropinirole, especially at high doses, have been reported as exhibiting signs of pathological gambling, increased libido and hypersexuality, generally reversible upon reduction of the dose or treatment discontinuation³.

<table>
<thead>
<tr>
<th>Nervous system disorders</th>
</tr>
</thead>
<tbody>
<tr>
<td>very common</td>
</tr>
<tr>
<td>Syncope², dyskinesia¹, somnolence²</td>
</tr>
</tbody>
</table>
common  dizziness (including vertigo)¹,²
uncommon  extreme daytime somnolence³, sudden onset of sleep³

**Vascular disorders**
uncommon  hypotension, postural hypotension

**Gastrointestinal disorders**
very common  nausea
common  vomiting², abdominal pain², heartburn²

**General disorders and administrative site conditions**
common  leg oedema²

**Hepatobiliary disorders**
not known  hepatic reactions, hepatic enzymes increased³

1 Adjunct therapy studies
2 Monotherapy studies
3 Post-marketing data (see Section 4.4)

**Use of ropinirole in Restless Legs Syndrome**
In Restless Legs Syndrome clinical trials the most common adverse drug reaction was nausea (approximately 30% of patients). Undesirable effects were normally mild to moderate and experienced at the start of therapy or on increase of dose and few patients withdrew from the clinical studies due to undesirable effects.

The table below lists the adverse drug reactions reported for ropinirole in the 12-week clinical trials at ≥1.0% above the placebo rate or those reported uncommonly but known to be associated with ropinirole.

<table>
<thead>
<tr>
<th>Adverse drug reactions reported in 12-week Restless Legs Syndrome clinical trials (ropinirole n=309, placebo n=307)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Psychiatric disorders</strong></td>
</tr>
<tr>
<td>Common  Nervousness</td>
</tr>
<tr>
<td>Uncommon  Confusion</td>
</tr>
<tr>
<td><strong>Nervous system disorders</strong></td>
</tr>
<tr>
<td>Common  Syncope, somnolence, dizziness (including vertigo)</td>
</tr>
<tr>
<td><strong>Vascular disorders</strong></td>
</tr>
<tr>
<td>Uncommon  Postural hypotension, hypotension</td>
</tr>
<tr>
<td><strong>Gastrointestinal disorders</strong></td>
</tr>
<tr>
<td>Very common  Vomiting, nausea</td>
</tr>
<tr>
<td>Common  Abdominal pain</td>
</tr>
<tr>
<td><strong>General disorders and administration site conditions</strong></td>
</tr>
<tr>
<td>Common  Fatigue</td>
</tr>
</tbody>
</table>

Hallucinations were reported uncommonly in the open label long-term studies.
In post-marketing reports, extreme daytime somnolence and sudden onset of sleep have been reported very rarely in Restless Legs Syndrome.

Paradoxical worsening of Restless Legs Syndrome symptoms occurring with earlier onset (augmentation), and reoccurrence of symptoms in the early morning hours (early morning rebound), may be observed during treatment with ropinirole.

Management of undesirable effects
Dose reduction should be considered if patients experience significant undesirable effects. If the undesirable effect abates, gradual up-titration can be re-instituted. Anti-nausea medicinal products that are not centrally active dopamine antagonists, such as domperidone, may be used, if required.

4.9 Overdose

There have been no incidences of intentional overdose with ropinirole in clinical trials. 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.

5 PHARMACOLOGICAL PROPERTIES
5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Dopamine agonist, ATC code: N04BC04.

Mechanism of action
Ropinirole is a non ergoline D2/D3 dopamine agonist which stimulates striatal dopamine receptors.

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.

Clinical efficacy in Restless Legs Syndrome
Ropinirole should only be prescribed to patients with moderate to severe idiopathic Restless Legs Syndrome. Moderate to severe idiopathic Restless Legs Syndrome is typically represented by patients who suffer with insomnia or severe discomfort in the limbs.

In the four 12-week efficacy studies, patients with Restless Legs Syndrome were randomised to ropinirole or placebo, and the effects on the IRLS scale scores at week 12 were compared to baseline. The mean dose of ropinirole for the moderate to severe patients was 2.0 mg/day. In a combined analysis of moderate to severe Restless Legs Syndrome patients from the four 12-week studies, the adjusted treatment difference for the change from baseline in IRLS scale total score at week 12 Last Observation Carried Forward (LOCF) Intention To Treat population was -4.0 points (95% CI -5.6,
A 12-week placebo-controlled polysomnography study in Restless Legs Syndrome patients examined the effect of treatment with ropinirole on periodic leg movements of sleep. A statistically significant difference in the periodic leg movements of sleep was seen between ropinirole and placebo from baseline to week 12. Although sufficient data are not available to adequately demonstrate the long term efficacy of ropinirole in Restless Legs Syndrome (see section 4.2), in a 36-week study, patients who continued on ropinirole demonstrated a significantly lower relapse rate compared with patients randomised to placebo (33% versus 58%, p=0.0156).

A combined analysis of data from moderate to severe Restless Legs Syndrome patients, in the four 12-week placebo-controlled studies, indicated that ropinirole-treated patients reported significant improvements over placebo on the parameters of the Medical Outcome Study Sleep Scale (scores on 0-100 range except sleep quantity). The adjusted treatment differences between ropinirole and placebo were: sleep disturbance (-15.2, 95% CI -19.37, -10.94; p<0.0001), sleep quantity (0.7 hours, 95% CI 0.49, 0.94; p=0.0001), sleep adequacy (18.6, 95% CI 13.77, 23.45; p<0.0001) and daytime somnolence (-7.5, 95% CI -10.86, -4.23; p<0.0001).

A rebound phenomenon following discontinuation of ropinirole treatment (end of treatment rebound) cannot be excluded. In clinical trials, although the average IRLS total scores 7-10 days after withdrawal of therapy were higher in ropinirole-treated patients than in placebo-treated patients, the severity of symptoms following withdrawal of therapy generally did not exceed the baseline assessment in ropinirole-treated patients.

In clinical studies most patients were of Caucasian origin.

**5.2 Pharmacokinetic properties**

**Absorption**

The bioavailability of ropinirole is about 50% (36% to 57%), with $C_{\text{max}}$ reached on average 1.5 hours after the dose. In the presence of food, $C_{\text{max}}$ is delayed by about 2.6 hours and the peak plasma level is reduced by 25%, with no effect on the bioavailable quantity. The bioavailability of ropinirole varies greatly between individuals.

**Distribution**

The binding of ropinirole to plasma proteins is not high (<40%), with no effect on the distribution which is very extensive (volume of distribution in the order of 7 l/kg).

**Metabolism**

Ropinirole is mainly metabolised by the isoform CYP1A2 of cytochrome P450. None of the many metabolites formed are involved in the resulting activity of the product and the main metabolite is 100 times less potent than ropinirole in animal models examining dopaminergic function.

**Elimination**
Unchanged ropinirole and the metabolites are mainly excreted through the kidneys. The elimination half-life of ropinirole is 6 hours on average.

**Linearity**

The pharmacokinetics of ropinirole are linear overall (C\text{max} and AUC) in the therapeutic range between 0.25 mg and 4 mg, after a single dose and after repeated dosing.

**Population-related characteristics**

In patients over 65 years of age, a reduction in the systemic clearance of ropinirole by about 30% is possible.

In patients with mild to moderate renal impairment (creatinine clearance between 30 and 50 ml/min), no change in the pharmacokinetics of ropinirole is observed. No data are available in patients with severe renal impairment.

### 5.3 Preclinical safety data

**Toxicology:** The toxicology profile is principally determined by the pharmacological activity of the drug (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 a high dose (50 mg/kg), 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 drug-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.

**Reproductive Toxicity:** Administration of ropinirole to pregnant rats at maternally toxic doses resulted in decreased foetal body weight at 60 mg/kg/day (approximately equivalent to the AUC at the maximum dose in humans), increased foetal death at 90 mg/kg/day (approximately 2 times the AUC at the maximum dose in humans) and digit malformations at 150 mg/kg/day (approximately 3 times the AUC at the maximum dose in humans). There were no teratogenic effects in the rat at 120 mg/kg/day (approximately 2.5 times the AUC at the maximum dose in humans) and no indication of an effect on development in the rabbit.

### 6 PHARMACEUTICAL PARTICULARS

#### 6.1 List of excipients

**Tablet core:**

- Lactose monohydrate
- Cellulose, microcrystalline
Maize starch  
Silica colloidal anhydrous  
Magnesium stearate  

**Film coating:**  
Opadry II 31F58914 White consisting of: 
Hypromellose 15 cp (E464)  
Lactose monohydrate  
Titanium dioxide (E171)  
Macrogol 4000  
Sodium citrate dihydrate (E331C)

6.2 **Incompatibilities**

Not applicable.

6.3 **Shelf life**

18 months.

6.4 **Special precautions for storage**

Do not store above 25 °C. Store in the original package in order to protect from moisture.

6.5 **Nature and contents of container**

Al//PVC/Al/oPA foil blisters  
Packs of 21, 28 and 84 film-coated tablets  
Not all pack sizes may be marketed.

6.6 **Special precautions for disposal <and other handling>**

No special requirements.

7 **MARKETING AUTHORISATION HOLDER**

Pliva Pharma Limited.  
Vision House  
Bedford Road  
Petersfield  
Hampshire  
GU32 3QB
8  MARKETING AUTHORISATION NUMBER(S)

PL 10622/0322

9  DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

18/11/2008

10  DATE OF REVISION OF THE TEXT

18/11/2008
SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT
Ropinirole 5 mg Film-coated Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each 5 mg film-coated tablet contains 5.0 mg of ropinirole (as hydrochloride).

Excipient(s):
Each 5 mg film-coated tablet contains 59.168mg of lactose (as monohydrate)

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Film-coated tablet.

Ropinirole 5 mg Film-coated Tablets are yellow, round, biconvex tablets embossed with "RO" on one side and "5" on the other side.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

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

Oral use.

The tablets should be swallowed whole with fluid and preferably taken with meals.

Different strengths of this medicinal product are available in order to allow dosing according to the recommended treatment initiation and therapeutic regimens below. When the available range of strengths does not permit dose titration according to the
treatment initiation regimen, Ropinirole should not be used in ropinirole naïve patients.

**Treatment of idiopathic Parkinson's Disease:**

**Adults**

Individual dose titration against efficacy and tolerability is recommended. Ropinirole should be taken three times a day (t.i.d.), preferably with meals to improve gastrointestinal tolerance.

**Treatment initiation:** The initial dose should be 0.25 mg t.i.d. A guide for the titration regimen for the first four weeks of treatment is given in the table below:

<table>
<thead>
<tr>
<th>Ropinirole</th>
<th>Week 1</th>
<th>Week 2</th>
<th>Week 3</th>
<th>Week 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unit dose (mg)</td>
<td>0.25</td>
<td>0.5</td>
<td>0.75</td>
<td>1.0</td>
</tr>
<tr>
<td>Total daily dose (mg)</td>
<td>0.75</td>
<td>1.5</td>
<td>2.25</td>
<td>3.0</td>
</tr>
</tbody>
</table>

**Therapeutic regimen:** After the initial titration, weekly increments of up to 3 mg/day may be given. Ropinirole is usually given in divided doses three times per day.

The proposed titration regime is as follows:

<table>
<thead>
<tr>
<th>Ropinirole</th>
<th>Week 5</th>
<th>Week 6</th>
<th>Week 7</th>
<th>Week 8</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unit dose (mg)</td>
<td>1.5</td>
<td>2.0</td>
<td>2.5</td>
<td>3.0</td>
</tr>
<tr>
<td>Total daily dose (mg)</td>
<td>4.5</td>
<td>6.0</td>
<td>7.5</td>
<td>9.0</td>
</tr>
</tbody>
</table>

A therapeutic response may be seen between 3 and 9 mg/day, although adjunct therapy patients may require higher doses. 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 24 mg/day have not been investigated in clinical trials and this dose should not be exceeded.

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 by around 20% in total.

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

Ropinirole should be discontinued gradually by reducing the number of daily doses over the period of one week.

**Renal impairment:** In parkinsonian 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.
Elderly: The clearance of ropinirole is decreased in patients over 65 years of age, but the dose of ropinirole for elderly patients can be titrated in the normal manner.

Children and adolescents: Parkinson's disease does not occur in children and adolescents. The use of ropinirole in this population has therefore not been studied and it should not be given to children.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients
- Severe renal impairment (creatinine clearance <30 ml/min)
- Hepatic impairment

4.4 Special warnings and precautions for use

Due to the pharmacological action of ropinirole, patients with severe cardiovascular disease (in particular coronary insufficiency) should be treated with caution due to the risk of hypotension; blood pressure monitoring is recommended, particularly at the beginning of treatment.

Co-administration of ropinirole with anti-hypertensive and anti-arrhythmic agents has not been studied. Caution should be exercised when these compounds are given concomitantly with ropinirole because of the unknown potential for the occurrence of hypotension, bradycardias or other arrhythmias.

Patients with a history or presence of psychiatric or psychotic disorders should only be treated with dopamine agonists if the potential benefits outweigh the risks (see also section 4.5).

Pathological gambling, increased libido and hypersexuality have been reported in patients treated with dopamine agonists for Parkinson's disease, including ropinirole.

Ropinirole has been associated with somnolence and episodes of sudden sleep onset (see section 4.8), 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.

This medicinal product contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction
Ropinirole is principally metabolized by the cytochrome P450 isoenzyme CYP1A2. A pharmacokinetic study (with a ropinirole dose of 2 mg, three times a day) revealed that ciprofloxacin increased the Cmax 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, fluvoxamine or cimetidine, are introduced or withdrawn.

A pharmacokinetic interaction study between ropinirole (at a 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. Therefore, it is not expected that ropinirole will compete with the metabolism of other medicinal products which are metabolised by CYP1A2.

Based on in-vitro data, ropinirole has little potential to inhibit cytochrome P450 at therapeutic doses. Hence, ropinirole is unlikely to affect the pharmacokinetics of other medicinal products, via a cytochrome P450 mechanism.

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

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, it may be necessary to adjust the ropinirole dose, in accordance with clinical response, if hormone replacement therapy is stopped or introduced during treatment with ropinirole.

No pharmacokinetic interaction has been seen between ropinirole and levodopa or domperidone (a medicinal product used to treat nausea and vomiting) which would necessitate dosage adjustment of either medicinal product. Domperidone antagonises the dopaminergic actions of ropinirole peripherally and does not cross the blood-brain barrier. Hence its value as an anti-emetic in patients treated with centrally acting dopamine agonists.

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 with ropinirole should be avoided.

4.6 Pregnancy and lactation

There are no adequate data from the use of ropinirole in pregnant women. 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.

Ropinirole should not be used in nursing mothers as it may inhibit lactation.
4.7 Effects on ability to drive and use machines

Ropinirole has major influence on the ability to drive and use machines.

Patients should be warned about the possibility of dizziness (including vertigo). Patients being treated with ropinirole and presenting with 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 effects have resolved (see also Section 4.4).

4.8 Undesirable effects

Undesirable effects are listed below by system organ class and frequency. 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).

Common and uncommon undesirable effects were generally determined from pooled safety data from clinical trial populations of ropinirole and are quoted as excess incidence over placebo. Rare and very rare undesirable effects were generally determined from post-marketing data and refer to reporting rate rather than true frequency.

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

Adverse Drug Reactions Reported from Patients taking ropinirole in Parkinson’s Disease:
The adverse drug reactions reported in patients with Parkinson’s disease on ropinirole monotherapy and adjunct therapy at doses up to 24mg/day at an excess incidence over placebo are described below.

The most commonly reported undesirable effects are nausea, somnolence, dyskinesia and syncope.

<table>
<thead>
<tr>
<th>Psychiatric disorders</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>common</td>
<td>confusion(^1) , hallucinations</td>
</tr>
<tr>
<td>uncommon</td>
<td>Psychotic reactions (other than hallucinations), including delusion, paranoia, delirium.</td>
</tr>
</tbody>
</table>

Patients treated with dopamine agonists for treatment of Parkinson's disease, including ropinirole, especially at high doses, have been reported as exhibiting signs of pathological gambling, increased libido and hypersexuality, generally reversible upon reduction of the dose or treatment discontinuation\(^3\).

Nervous system disorders
very common Syncope\(^2\), dyskinesia\(^1\), somnolence\(^2\)
common dizziness (including vertigo)\(^1,2\)
uncommon extreme daytime somnolence\(^3\), sudden onset of sleep\(^3\)

**Vascular disorders**

uncommon hypotension, postural hypotension

**Gastrointestinal disorders**

very common nausea
common vomiting\(^2\), abdominal pain\(^2\), heartburn\(^2\)

**General disorders and administrative site conditions**

common leg oedema\(^2\)

**Hepatobiliary disorders**

not known hepatic reactions, hepatic enzymes increased\(^3\)

---

1 Adjunct therapy studies  
2 Monotherapy studies  
3 Post-marketing data (see Section 4.4)

**Management of undesirable effects**

Dose reduction should be considered if patients experience significant undesirable effects. If the undesirable effect abates, gradual up-titration can be re-instituted. Anti-nausea medicinal products that are not centrally active dopamine antagonists, such as domperidone, may be used, if required.

---

### 4.9 Overdose

There have been no incidences of intentional overdose with ropinirole in clinical trials. 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.

---

### 5 PHARMACOLOGICAL PROPERTIES

#### 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Dopamine agonist, ATC code: N04BC04.

**Mechanism of action**

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

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

Absorption
The bioavailability of ropinirole is about 50% (36% to 57%), with C_max reached on average 1.5 hours after the dose. In the presence of food, C_max is delayed by about 2.6 hours and the peak plasma level is reduced by 25%, with no effect on the bioavailable quantity. The bioavailability of ropinirole varies greatly between individuals.

Distribution
The binding of ropinirole to plasma proteins is not high (<40%), with no effect on the distribution which is very extensive (volume of distribution in the order of 7 l/kg).

Metabolism
Ropinirole is mainly metabolised by the isoform CYP1A2 of cytochrome P450. None of the many metabolites formed are involved in the resulting activity of the product and the main metabolite is 100 times less potent than ropinirole in animal models examining dopaminergic function.

Elimination
Unchanged ropinirole and the metabolites are mainly excreted through the kidneys. The elimination half-life of ropinirole is 6 hours on average.

Linearity
The pharmacokinetics of ropinirole are linear overall (C_max and AUC) in the therapeutic range between 0.25 mg and 4 mg, after a single dose and after repeated dosing.

Population-related characteristics
In patients over 65 years of age, a reduction in the systemic clearance of ropinirole by about 30% is possible.

In patients with mild to moderate renal impairment (creatinine clearance between 0 and 50 ml/min), no change in the pharmacokinetics of ropinirole is observed. No data are available in patients with severe renal impairment.

5.3 Preclinical safety data

Toxicology: The toxicology profile is principally determined by the pharmacological activity of the drug (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 a high dose (50 mg/kg), 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 drug-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.

Reproductive Toxicity: Administration of ropinirole to pregnant rats at maternally toxic doses resulted in decreased foetal body weight at 60 mg/kg/day (approximately equivalent to the AUC at the maximum dose in humans), increased foetal death at 90 mg/kg/day (approximately 2 times the AUC at the maximum dose in humans) and digit malformations at 150 mg/kg/day (approximately 3 times the AUC at the maximum dose in humans). There were no teratogenic effects in the rat at 120 mg/kg/day (approximately 2.5 times the AUC at the maximum dose in humans) and no indication of an effect on development in the rabbit.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

**Tablet core:**
- Lactose monohydrate
- Cellulose, microcrystalline
- Maize starch
- Silica colloidal anhydrous
- Magnesium stearate

**Film coating:**
- Opadry II 31F32601 Yellow consisting of:
  - Hypromellose 15 cp (E464)
  - Lactose monohydrate
  - Macrogol 4000
  - Titanium dioxide (E171)
  - Iron oxide yellow (E172)
  - Indigo carmine aluminum lake (E132)
  - Quinoline yellow aluminum lake (E104)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

18 months.
6.4 Special precautions for storage

Do not store above 25 °C. Store in the original package in order to protect from moisture.

6.5 Nature and contents of container

Al/PVC/Al/oPA foil blisters
Packs of 21, 28 and 84 film-coated tablets

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7 MARKETING AUTHORISATION HOLDER

PLIVA Pharma Limited.
Vision House
Bedford Road
Petersfield
Hampshire
GU32 3QB

8 MARKETING AUTHORISATION NUMBER(S)

PL 10622/0323

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

18/11/2008

10 DATE OF REVISION OF THE TEXT

18/11/2008
Module 3

Product Information Leaflet

**Ropinirole 0.25mg Film-coated Tablets**

**Ropinirole 0.5mg Film-coated Tablets**

**Ropinirole 1mg Film-coated Tablets**

**Ropinirole 2mg Film-coated Tablets**

**Ropinirole**

Read all of this leaflet carefully before you start taking this medicine.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.

This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.

- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:

1. What Ropinirole is and what it is used for
2. Before you take Ropinirole
3. How to take Ropinirole
4. Possible side effects
5. How to store Ropinirole
6. Further information

**What Ropinirole is and what it is used for**

Ropinirole belongs to a group of medicines called dopamine agonists. Dopamine agonists act like a naturally occurring chemical in your brain called dopamine.

Ropinirole is used to treat:

- Parkinson's disease. Ropinirole works by acting in a similar way to natural dopamine and helps to reduce the symptoms of Parkinson's disease. Parkinson's disease is caused by dopamine repairing to low levels in the brain.
- Restless Legs Syndrome. Ropinirole is used to treat the symptoms of severe or moderate Restless Legs Syndrome which often occurs as difficulty sleeping or severe discomfort in the legs or arms.

Restless Legs Syndrome is a condition characterised by an irresistible urge to move the legs and occasionally the arms, usually accompanied by uncomfortable sensations such as tugging, burning, or pricking. Those feelings occur during periods of rest or inactivity, such as sitting or lying down, especially in bed, and are worse in the evening or at night. Usually the only relief is obtained by walking about or moving the affected limb, which often leads to problems sleeping. Ropinirole relieves the discomfort and reduces the urge to move the limbs that disturbs night time sleep.

**Before you take Ropinirole**

Do not take Ropinirole 1mg Film-coated Tablets if you:

- Are allergic (hypersensitive) to ropinirole hydrochloride, Abbott Laboratories or any of the other ingredients of Ropinirole.

Do not take Ropinirole 0.25mg/0.5mg/1mg/2mg Film-coated Tablets if you:

- Are allergic (hypersensitive) to ropinirole hydrochloride or any of the other ingredients of Ropinirole.
- Have liver disease.
- Have serious kidney disease.

**Take special care with Ropinirole**

Tell your doctor before you start to take this medicine if any of the following apply to you. Your doctor may want to carefully supervise your treatment or may want to reduce your dose or stop your treatment.

- You have a serious heart complaint.
- You have, or have ever had, serious mental health problems.
- You have experienced any unusual urges and/or behaviours (such as excessive gambling or excessive sexual behaviour).

**Children and adolescents**

Ropinirole should not be given to children and adolescents under the age of 18 years.

**Taking other medicines**

Tell your doctor if you:

- Are already receiving any other medicines for Restless Legs Syndrome.
- Are taking other medicines for Parkinson's disease.
- Are going to start smoking whilst taking Ropinirole.

Your doctor may need to adjust your dose.

Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription. The effect of ropinirole may be increased or decreased by other medicines and vice versa.

These medicines include:

- Ciclosporin, or minocycline (types of antibiotics used to treat infections).
- Cimetidine (used to treat stomach ulcers).
- Fluoxetine (used to treat depression).
- Theophylline (used to treat asthma).
- Hormone replacement therapy (also called HRT, used to treat symptoms of the menopause).
- Drugs used to treat psychiatric conditions and other drugs that affect dopamine in the brain (e.g. sulpiride or metoclopramide).
- Drugs used to lower the blood pressure or to treat heart problems.

**Taking Ropinirole with food and drink**

Ropinirole should be taken with food as this may reduce the likelihood of you feeling or being sick. You should not drink alcohol whilst taking Ropinirole.

**Pregnancy and breastfeeding**

Ropinirole is not recommended if you are pregnant, unless your doctor advises that the benefit to you of taking ropinirole is greater than the risk to your unborn baby. Ropinirole is not recommended if you are breastfeeding, as it can affect your milk production.
Tell your doctor immediately if you are pregnant, if you think you might be pregnant, or if you are planning to become pregnant. Your doctor will also advise you if you are breastfeeding or planning to do so. Your doctor may advise you to stop taking Ropinirole.

Ask your doctor or pharmacist for advice before taking any medicine.

Driving and using machines
Ropinirole can cause dizziness, extreme sleepiness (somnolence) and sudden sleep onset episodes (suddenly falling asleep without apparently feeling sleepy). If you suffer from these effects you must not drive or put yourself in a situation where sleepiness or falling asleep may put you at risk of serious injury or death (for example using machinery) until these episodes have been resolved.

Important Information about some of the ingredients of Ropinirole
Ropinirole contains lactose monohydrate, a type of sugar. If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicinal product.

Ropinirole 1mg Film-coated Tablets also contain allura red AC, a type of dye. This may cause allergic reactions (see Section 4 Possible side effects).

How to take Ropinirole
Always take Ropinirole exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.

How to take Ropinirole for Parkinson’s Disease
You may be given Ropinirole on its own to treat the symptoms of your Parkinson’s disease. Or you may be given Ropinirole as well as another medicine called l-dopa (also called levodopa).

Ropinirole should be taken three times a day. The usual starting dose is 0.25mg ropinirole three times a day for the first week. Your doctor will then increase your dose gradually each week for the next three weeks. After that, your doctor will gradually increase the dose until you are taking the best dose for you. The usual dose is 1mg to 3mg three times a day (a total daily dose of 3mg to 9mg). Some people take up to 8mg three times a day (a total daily dose of 24mg).

How to take Ropinirole for Restless Legs Syndrome
Take Ropinirole once a day, every day at about the same time each day. Ropinirole is usually taken just before bedtime, but can be taken up to 3 hours before going to bed.

The usual starting dose is 0.25mg once daily. After two days your doctor will probably increase your dose to 0.5mg once daily for the remainder of your first week of treatment. Then your doctor may increase your dose by 0.5mg per week over three weeks to a dose of 2mg per day. In some patients with insufficient improvement, the dose may be increased gradually up to a maximum of 4mg daily.

Taking your dose of Ropinirole
You should swallow the film-coated tablet(s) whole with water and preferably with food. Taking Ropinirole with food may decrease the occurrence of nausea (feeling sick) which is a possible side effect of Ropinirole.

Do not chew the film-coated tablet(s).

After three months of treatment with Ropinirole, your doctor may adjust your dose or discontinue your treatment depending on your symptoms and how you feel.

You should continue to take your medicine even if you do not feel better, as it may take a number of weeks for your medicine to work for you. If you have the impression that the effect of Ropinirole is too strong or too weak, talk to your doctor or pharmacist. Do not take more tablets than your doctor has recommended.

If you take more Ropinirole than you should
You should never take more tablets than your doctor recommends. If you take more Ropinirole than you should, or if someone else has taken your medicine, tell a doctor or pharmacist immediately. Show them the package.

If you forget to take Ropinirole
Do not take a double dose to make up for a forgotten dose. If you find you have forgotten to take a dose of your Ropinirole, leave that dose out and take your next dose at the normal time. If you have missed taking Ropinirole for more than a few days consult your doctor for advice on restarting Ropinirole.
If you stop taking Ropinirole

You should not stop treatment with Ropinirole unless your doctor has told you to. If you are being treated for Parkinson’s disease, treatment should be stopped gradually by reducing the number of daily doses over a period of one week. If your symptoms worsen after you stop treatment with Ropinirole, you should contact your doctor.

If you have any further questions on the use of this product, ask your doctor or pharmacist.

Possible side effects

Like all medicines, Ropinirole can cause side effects, although not everybody gets them. Tell your doctor if you notice any side effects and they worry you. The more common side effects of Ropinirole are usually mild and usually occur when patients first start their therapy and/or when the dose is increased.

Tell your doctor if you experience:

Unusual worsening of symptoms (e.g. symptoms become worse, start earlier in the day or after less time at rest, or affect other parts of your body such as your arms) during treatment for restless legs syndrome. Your doctor may adjust the dose of Ropinirole that you are taking.

Very common side effects
(affecting more than 1 in 10 people)

- Fainting
- Unwanted jerky movements (particularly if you are also taking levodopa (L-Dopa))
- Feeling drowsy or sleepy
- Feeling or being sick. Taking Ropinirole with food may reduce the chance of this effect

Common side effects
(affecting less than 1 in 10 people)

- Feeling confused (particularly if you are also taking levodopa (L-Dopa))
- Hallucinations (seeing or hearing things)
- Dizziness (or spinning sensation)
- Stomach ache (abdominal pain) or upset stomach (with indigestion or bloating). Taking Ropinirole with food may reduce the chance of these effects
- Swelling of the legs (oedema)
- Nervousness
- Fatigue (mental or physical tiredness)

Uncommon side effects
(affecting less than 1 in 100 people)

- Psychotic reactions such as irrational ideas (delusion), irrational suspiciousness (paranoia) and severe confusion (delirium)
- Excessive daytime drowsiness (extreme somnolence)
- Sudden sleep onset episodes (suddenly falling asleep without feeling sleepy)
- Reduced blood pressure, which may make you feel dizzy or faint especially when standing up from a sitting or lying position

Very rare side effects
(affecting less than 1 in 10,000 people)

- Changes in your liver function (abnormal blood tests)
- Your doctor may want to monitor you

Some patients treated with dopamine agonists, including ropinirole, may also experience urges to behave in a way that is unusual for them such as an unusual urge to gamble or an increase in sexual urges and/or behaviors. These effects are more likely to occur at higher doses, however are generally reversible when the dose is reduced or treatment is stopped.

Ropinirole 1mg Film-coated Tablets contain Allura red AC, a type of dye. Allura red AC may cause allergic reactions. If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

How to store Ropinirole

Keep out of the reach and sight of children.

Do not use Ropinirole after the expiry date which is stated on the blister and the carton after EXP. The expiry date refers to the last day of that month.

Do not store above 25°C. Store in the original package in order to protect from moisture.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.
Further information

What Ropinirole contains
The active substance is ropinirole. Each film-coated tablet contains 0.25mg, 0.5mg, 1.0mg, 2.0mg of ropinirole (as hydrochloride).

The other ingredients of the tablet core are lactose monohydrate, cellulose, microcrystalline, maize starch, silica colloidal anhydrous, magnesium stearate. The film-coating contains:

0.25mg film-coated tablets: hypromellose 6 cp (E464), lactose monohydrate, titanium dioxide (E171), macrogel 3350, triacetin, indigo-carmine aluminium lake (E132), quinoline yellow aluminium lake (E104).

0.5mg film-coated tablets: hypromellose 6 cp (E464), lactose monohydrate, titanium dioxide (E171), macrogel 3350, triacetin, iron oxide yellow (E172), iron oxide black (E172), quinoline yellow aluminium lake (E104).

1mg film-coated tablets: hypromellose 15 cp (E464), lactose monohydrate, titanium dioxide (E171), macrogel 4000, iron oxide red (E172), allura red AC, aluminium lake (E129), indigo-carmine aluminium lake (E122).

2mg film-coated tablets: hypromellose 15 cp (E464), lactose monohydrate, titanium dioxide (E171), macrogel 4000, sodium citrate dihydrate (E331).

What Ropinirole looks like and contents of the pack
Ropinirole is supplied as film-coated tablets.

Ropinirole 0.25mg Film-coated Tablets are blue, round, biconvex tablets embossed with 'RO' on one side and '025' on the other side. They are available in blister packs of 2, 12, 21, 84, 126 and 210 tablets.

Ropinirole 0.5mg Film-coated Tablets are green, round, biconvex tablets embossed with 'RO' on one side and '05' on the other side. They are available in blister packs of 21, 28 and 84 tablets.

Ropinirole 1mg Film-coated Tablets are pink, round, biconvex tablets embossed with 'RO' on one side and '1' on the other side. They are available in blister packs of 21, 28 and 84 tablets.

Ropinirole 2mg Film-coated Tablets are white, round, biconvex tablets embossed with 'RO' on one side and '2' on the other side. They are available in blister packs of 21, 28 and 84 film-coated tablets.

Not all pack sizes may be marketed.

Marketing Authorisation Holder
Pliva Pharma Ltd
Vision House
Bedford Road
 Petersfield
Hampshire
GU32 3QB
United Kingdom.

Manufacturer
PLIVA Krakow Zakłady Farmaceutyczne S.A.
ul. Mogiliska 80
30-456 Krakow
Poland.

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Pliva Pharma Ltd, Ropinirole 0.25-5mg Film-coated Tablets 65
Module 4

Labelling
Ropinirole 0.5mg Film-coated Tablets

Ropinirole 0.5mg Film-coated Tablets

Ropinirole 0.5mg Film-coated Tablets

Ropinirole 0.5mg Film-coated Tablets
Module 5

Scientific discussion during initial procedure

Introduction

These are decentralised applications for Ropinirole 0.25, 0.5, 1, 2 and 5mg film coated tablets. These are abridged applications, submitted under article 10.1 of directive 2001/83/EC.

The originator products are Requip 0.25, 0.5, 1, 3, and 5mg film coated tablets (SmithKline Beecham PLC, UK), registered since 02/07/96. The UK reference products are Requip 0.25, 0.5, 1, 3, and 5mg film coated tablets (SmithKline Beecham PLC, UK).

Ropinirole is a non-ergoline 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.

The reference product has only one indication (Treatment of idiopathic Parkinson's Disease). The second indication (Symptomatic treatment of moderate to severe idiopathic Restless Legs Syndrome) was approved for the same product under a different name (Adartrel). However, based on the fact that both Requip and Adartrel contain the same active substance and the relationship between their MA Holders (Requip – SmithKline Beecham PLC; Adartrel – GlaxoSmithKline UK Ltd), both products are considered part of the same Global Manufacturing Authorisation and therefore it is acceptable for the product object of this report to have both indications.

General comments on compliance with GMP, GLP, GCP and agreed ethical principles.

The RMS has been assured that acceptable standards of GMP are in place for these product types at all sites responsible for the manufacture and assembly of this product.

For manufacturing sites within the Community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

SCIENTIFIC OVERVIEW AND DISCUSSION

Quality Aspects

Drug Substance

The active substance is ropinirole hydrochloride, an off-white to yellow coloured powder freely soluble in water, soluble in methanol, insoluble in acetone. The proposed re-test period is accepted as follows: 18 months / Store in well-closed container below 35°C.

An appropriate specification has been provided.
Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications.

Active ropinirole hydrochloride is stored in appropriate packaging. The specifications and typical analytical test reports are provided and are satisfactory.

Batch analysis data are provided and comply with the proposed specification.

Satisfactory certificates of analysis have been provided for working standards used by the active substance manufacturer and finished product manufacturer during validation studies.

Appropriate stability data have been generated supporting a retest period of 18 months, in well-closed container below 35°C.

**Drug Product**

**Other Ingredients**
The other ingredients of the drug product are:

**Tablet core:**
- Lactose monohydrate
- Cellulose, microcrystalline
- Maize starch
- Silica colloidal anhydrous
- Magnesium stearate

**Film coating: for 0.25mg Tablet**
- Opadry II 33G21673 Green consisting of:
  - Hypromellose 6 cp (E464)
  - Lactose monohydrate
  - Titanium dioxide (E171)
  - Macrogol 3350
  - Triacetin
  - Iron oxide yellow (E172)
  - Iron oxide black (E172)
  - Quinoline yellow aluminium lake (E104)

**Film coating: for 0.5mg Tablet**
- Opadry II 33G21673 Green consisting of:
  - Hypromellose 6 cp (E464)
  - Lactose monohydrate
  - Titanium dioxide (E171)
  - Macrogol 3350
  - Triacetin
  - Iron oxide yellow (E172)
  - Iron oxide black (E172)
  - Quinoline yellow aluminium lake (E104)
**Film coating: for 1mg Tablet**
Opadry II 31F24239 Pink consisting of:
Hypromellose 15 cp (E464)
Lactose monohydrate
Titanium dioxide (E171)
Macrogol 4000
Iron oxide red (E172)
Allura red AC aluminium lake (E129)
Indigo carmine aluminium lake (E132)

**Film coating: for 2mg Tablet**
Opadry II 31F58914 White consisting of:
Hypromellose 15 cp (E464)
Lactose monohydrate
Titanium dioxide (E171)
Macrogol 4000
Sodium citrate dihydrate (E331C)

**Film coating: for 5mg Tablet**
Opadry II 31F32601 Yellow consisting of:
Hypromellose 15 cp (E464)
Lactose monohydrate
Macrogol 4000
Titanium dioxide (E171)
Iron oxide yellow (E172)
Indigo carmine aluminum lake (E132)
Quinoline yellow aluminum lake (E104)

The excipients are appropriately controlled, using either Pharm. Eur. monographs or in-house specifications (coating materials – Opadry).

The ingredients and the manufacturing process of the drug product are considered suitable to produce a pharmaceutical product of the proposed quality. As required in Directive 2001/83/EC, the documentation provides an adequate synopsis of the method of preparation, mentioning the various stages of production, the in-process controls and batch formula. The manufacturing process demonstrated the consistency of the specifications. The process has been evaluated adequately by investigating the critical manufacturing steps.

The tablets are stored in a blister pack made of PVC, aluminium and QPA.
The proposed stability conditions for the 0.25mg and 0.5mg Tablets are accepted as follows:

12 months with the following storage conditions: “Store in the original package” and “Do not store above 25°C”

The proposed stability conditions for the 1, 2 and 5mg Tablets are accepted as follows:

18 months with the following storage conditions: “Store in the original package” and “Do not store above 25°C”

**Pre-Clinical Aspects**

Pharmacodynamic, pharmacokinetic and toxicological properties of ropinirole are well known. As ropinirole is a widely used, well-known active substance, no further studies are required and the applicant provides none. Overview based on literature review is, thus, appropriate.

The preclinical toxicology of ropinirole is well documented in the literature and no new data are supplied with the current application. Clinical experience and the availability of human data supplant the need for further preclinical data.

**Clinical Aspects**

Ropinirole is a non-ergoline 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.

Oral absorption of ropinirole is rapid and essentially complete. Bioavailability of ropinirole is approximately 50% and average peak concentrations of the drug are achieved at a median time of 1.5 hours post-dose. Wide inter-individual variability in the pharmacokinetic parameters has been seen but, overall, there is a proportional increase in the systemic exposure (Cmax and AUC) to the drug with an increase in dose, over the therapeutic dose range. Consistent with its high lipophilicity, ropinirole exhibits a large volume of distribution (approx. 8 l/kg) and is cleared from the systemic circulation with an average elimination half-life of about six hours. Plasma protein binding of the drug is low (10-40%). Ropinirole is metabolised primarily by oxidative metabolism and ropinirole 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.

Ropinirole is indicated for the treatment of idiopathic Parkinson's Disease. It may be used alone (without levodopa). The addition of ropinirole to levodopa may also be used to control "on-off" fluctuations and permit a reduction in the total daily dose of levodopa. Ropinirole is also indicated for the symptomatic treatment of moderate to severe idiopathic Restless Legs Syndrome.

**Bioequivalence Study**

**Biowaiver**
The company’s clinical expert has provided the following justification for studying the 1mg strength only, rather than all strengths:

1. The pharmaceutical products are manufactured by the same manufacturer and process
2. The drug input has been shown to be linear over the therapeutic dose range
3. The qualitative composition of the different strengths is the same
4. The ratio between the amounts of active substance and excipients is the same
5. The dissolution profile is similar under identical conditions for the additional strengths and the strength of the batch used in the bioequivalence study.

Study design
A comparative, randomised, two-way, two-period, single dose crossover study performed in fasting subjects.

26 (24 + 2 alternates) healthy fasting male volunteers, aged 18-39 years, were randomised to receive a single dose of 1mg orally of either the applicant's test product or the reference product ropinirole.

The randomisation scheme was balanced for sequence and appears random.

Serum drug levels were followed for 30 hours following dosing and the schedule was appropriate for accurate determination of AUC_{inf} and C_{max}. The washout period between phases was sufficiently long at 7 days.

**Assessor's comment**
Satisfactory study design

Test and reference products
Reference: Requip 1mg (Ropinirole Hydrochloride) (GlaxoSmithKline)
Test: Ropinirole 1mg Tablets (PLIVA-)

**Assessor's comment:**
The comparator product is the EEA product to which essential similarity is claimed and is therefore satisfactory.

Population(s) studied
26 healthy fasted state adult male volunteers were randomised and 24 completed the study. One subject dropped out for personal reasons. The reasons for this dropout are satisfactory and the data were handled appropriately according to the study protocol.

**Assessor's comment:**
No concerns raised.

Analytical methods
Plasma samples were analysed to quantify the concentration of ropinirole using a validated LC/MS/MS bioanalytical method. Linearity range for ropinirole was 3.000 - 3840.0 ng/ml and the lower limit of quantification was 3.000 ng/ml.

**Pharmacokinetic Variables**

**Assessor's comment:**
*Conventional bioequivalence criteria.*

Statistical methods
ANOVA for AUC, Cmax. Non-parametric for Tmax. Analysis of sequence/period effects.

**Assessor's comment:**
*Conventional statistical methods.*

**Results**
Table 1. Pharmacokinetic parameters for parent drug (non-transformed values; arithmetic mean ± SD, t\text{max} median, range)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>C\text{max} (pg/ml)</th>
<th>T\text{max} (hours)</th>
<th>AUC0-t (pg/ml*h)</th>
<th>AUC0-inf (pg/ml*h)</th>
<th>AUC%extra (%)</th>
<th>Thalf (hours)</th>
<th>MRT (hours)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>1684.788</td>
<td>1.260</td>
<td>9276.039</td>
<td>9537.314</td>
<td>3.019</td>
<td>4.086</td>
<td>5.969</td>
</tr>
<tr>
<td>SD</td>
<td>491.862</td>
<td>1.045</td>
<td>3562.471</td>
<td>3611.803</td>
<td>1.267</td>
<td>1.113</td>
<td>1.114</td>
</tr>
<tr>
<td>CV</td>
<td>29.194</td>
<td>82.899</td>
<td>38.405</td>
<td>37.870</td>
<td>41.948</td>
<td>27.269</td>
<td>18.656</td>
</tr>
</tbody>
</table>

Treatment = REFERENCE

<table>
<thead>
<tr>
<th>Test name</th>
<th>Parameter</th>
<th>Test value (test/reference)</th>
<th>Lower 90% CL</th>
<th>Upper 90% CL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Classic 90% CI</td>
<td>AUC0-t</td>
<td>103.232</td>
<td>93.192</td>
<td>114.354</td>
</tr>
<tr>
<td></td>
<td>C\text{max}</td>
<td>101.833</td>
<td>91.536</td>
<td>113.333</td>
</tr>
</tbody>
</table>

*If the lower and upper CL lie within accepted CL (80-125%) one can conclude equivalence.*

Table 2. Pharmacokinetic parameters for parent drug (log-transformed values)

<table>
<thead>
<tr>
<th>Test name</th>
<th>Parameter</th>
<th>Test value (test/reference)</th>
<th>Lower 90% CL</th>
<th>Upper 90% CL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Classic 90% CI</td>
<td>AUC0-inf</td>
<td>103.180</td>
<td>93.324</td>
<td>114.077</td>
</tr>
</tbody>
</table>

**Assessor's comment:**
*Within conventional bioequivalence criteria 80-125%.*
Pharmacokinetic conclusion

Based on the submitted bioequivalence study, Ropinorole 0.25, 0.5, 1, 2 and 5mg film coated tablets can be considered bioequivalent with Requip 0.25, 0.5, 1, 2 and 5mg tablets.

The results of the study with the 1mg formulation can be extrapolated to the other strengths, according to conditions in Note for Guidance on the Investigation of Bioavailability and Bioequivalence CPMP/EWP/QWP/1401/98, section 5.4.

Post marketing experience
Ropinorole 0.25, 0.5, 1, 2 and 5mg film coated tablets have a well-recognised efficacy and an acceptable level of safety in the indications approved for Ropinirole, and corresponding products have been widely used in many countries.

Summary of Product Characteristics (SPC), Patient Information Leaflet (PIL) and Labels.
The SPC, PIL and labels are satisfactory.

Benefit-Risk Assessment
The benefit risk assessment for this product is considered to be positive and market authorisations were granted.
Module 6

Steps taken after procedure

No non-confidential changes have been made to the market authorisations.