Public Assessment Report

Decentralised Procedure

ROPINIROLE 0.25MG, 0.5MG, 1MG AND 2MG
FILM-COATED TABLETS

UK/H/1094/001-4/DC
UK Licence No: PL 30139/0001-4

INTAS PHARMACEUTICALS LIMITED
LAY SUMMARY

On 27th January 2009, the UK granted Intas Pharmaceuticals Limited Marketing Authorisations (licences) for the prescription only medicinal products Ropinirole 0.25mg, 0.5mg, 1mg and 2mg Film-Coated Tablets (PL 30139/0001-4; UK/H/1094/001-4/DC).

Ropinirole hydrochloride tablets belong to a group of medicines called dopamine agonists. Dopamine agonists act like a naturally occurring chemical in your brain called dopamine. Ropinirole hydrochloride tablets are used to treat the symptoms of moderate to severe idiopathic Restless Legs Syndrome. Moderate to severe Restless Legs Syndrome is typically represented by patients who have difficulty sleeping and severe discomfort in their legs or arms. Ropinirole hydrochloride tablets relieve the discomfort and reduce the urge to move the limbs that disturb night time sleep.

No new or unexpected safety concerns arose from these applications and it was, therefore, judged that the benefits of taking Ropinirole 0.25mg, 0.5mg, 1mg and 2 mg Film-Coated Tablets outweigh the risks; hence these Marketing Authorisations have been granted.
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### Module 1

<table>
<thead>
<tr>
<th><strong>Product Name</strong></th>
<th>Ropinirole 0.25mg, 0.5mg, 1mg and 2mg Film-Coated Tablets</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Type of Application</strong></td>
<td>Generic, Article 10.1</td>
</tr>
<tr>
<td><strong>Active Substance</strong></td>
<td>Ropinirole Hydrochloride</td>
</tr>
<tr>
<td><strong>Form</strong></td>
<td>Film-Coated Tablets</td>
</tr>
<tr>
<td><strong>Strength</strong></td>
<td>0.25mg, 0.5mg, 1mg and 2mg</td>
</tr>
<tr>
<td><strong>MA Holder</strong></td>
<td>Intas Pharmaceuticals Limited</td>
</tr>
<tr>
<td></td>
<td>Sage House, 319 Pinner Road, Harrow, Middlesex, HA1 4HG</td>
</tr>
<tr>
<td><strong>Reference Member State (RMS)</strong></td>
<td>UK</td>
</tr>
<tr>
<td><strong>CMS</strong></td>
<td>Germany and Spain</td>
</tr>
<tr>
<td><strong>Procedure Number</strong></td>
<td>UK/H/1094/001-4/DC</td>
</tr>
<tr>
<td><strong>End of Procedure</strong></td>
<td>Day 210 – 23\textsuperscript{rd} December 2008</td>
</tr>
</tbody>
</table>
Module 2
Summary of Product Characteristics

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT
Ropinirole 0.25mg Film coated Tablets.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each film-coated tablet contains 0.25 mg, ropinirole (as hydrochloride).
Excipient(s): Each film-coated tablet contains 46.276 mg of lactose.
For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Film-coated tablet.
White to off white, round biconvex, film-coated tablets plain on both sides.

4 CLINICAL PARTICULARS
4.1 Therapeutic indications
Ropinirole is 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
Adults
Individual dose titration against efficacy and tolerability is recommended. Ropinirole should be taken just before bedtime, however it 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 table 1.

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

Table 1 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.

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

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

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

4.4 Special warnings and precautions for use
Ropinirole should not be used to treat neuroleptic akathisia, tiasikinesia (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.

In Parkinson's disease, ropinirole has been associated uncommonly with somnolence and episodes of sudden sleep onset (see section 4.8) however, in Restless Legs Syndrome, this phenomenon is very rare. Nevertheless, patients must be informed of this phenomenon 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.

Patients with major psychotic disorders should not be treated with dopamine agonists unless the potential benefits outweigh the risks.

Pathological gambling, increased libido and hypersexuality have been reported in patients treated with dopamine agonists for Parkinson’s disease, including Ropinirole tablets. Those disorders were reported especially at high doses and were generally reversible upon reduction of the dose or treatment discontinuation. Risk factors such as a history of compulsive behaviours were present in some cases (see section 4.8).

Ropinirole should be administered with caution to patients with moderate hepatic impairment. Undesirable effects should be closely monitored.

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.

Due to the risk of hypotension, patients with severe cardiovascular disease (in particular coronary insufficiency) should be treated with caution.

4.5 Interaction with other medicinal products and other forms of interaction
Ropinirole is principally metabolised 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 or fluvoxamine, 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 hormone replacement therapy. In patients already receiving hormone replacement therapy, ropinirole treatment may be initiated in the usual 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 domperidone (a medicinal product used to treat nausea and vomiting) that 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

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 recurrent episodes and somnolence have resolved (see also Section 4.4).

4.8 Undesirable effects

Adverse drug reactions are listed below by system organ class and frequency. Frequencies from the clinical trials are determined as excess incidence over placebo and are classified as very common (>1/10) or common (>1/100, <1/10) or uncommon (>1/1000, <1/100), rare (>1/10,000, <1/100) and very rare (<1/10,000), including isolated reports. Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Use of ropinirole in Restless Legs Syndrome

In Restless Legs Syndrome clinical trials the most common adverse drug reaction is 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.

Table 2 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>Table 2 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</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>
<tr>
<td>Uncommon</td>
</tr>
<tr>
<td><strong>Gastrointestinal disorders</strong></td>
</tr>
</tbody>
</table>

7
Hallucinations were reported uncommonly in the open label long-term studies. 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.

Other experience with ropinirole
Ropinirole is also indicated for the treatment of Parkinson’s disease. The adverse drug reactions reported in patients with Parkinson’s disease on ropinirole monotherapy and adjunct therapy at doses up to 24 mg/day at an excess incidence over placebo are described below.

Table 3 Adverse drug reactions reported in Parkinson’s disease clinical trials at doses up to 24 mg/day

<table>
<thead>
<tr>
<th>Psychiatric disorders</th>
<th>Nervous system disorders</th>
<th>Gastrointestinal disorders</th>
</tr>
</thead>
<tbody>
<tr>
<td>Common</td>
<td>Very common</td>
<td>Very common</td>
</tr>
<tr>
<td>Hallucinations, confusion</td>
<td>Syncope, dyskinesia, somnolence</td>
<td>Nausea</td>
</tr>
<tr>
<td>Uncommon</td>
<td></td>
<td>Common</td>
</tr>
<tr>
<td>Increased libido</td>
<td></td>
<td>Vomiting, abdominal pain, heartburn</td>
</tr>
</tbody>
</table>

Post marketing reports
Psychotic reactions (other than hallucinations) including delirium, delusion, paranoia have been reported.

Patients treated with dopamine agonists for treatment of Parkinson’s disease, including (Ropinirole tablets), 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.

In Parkinson's disease, ropinirole is associated with somnolence and has been associated uncommonly (>1/1,000, <1/100) with excessive daytime somnolence and sudden sleep onset episodes, however, in Restless Legs Syndrome, this phenomenon is very rare (<1/10,000).

Following ropinirole therapy, postural hypotension or hypotension has been reported uncommonly (>1/1,000, <1/100), rarely severe.
Very rare cases of hepatic reactions (<1/10,000), mainly increase of liver enzymes, have been reported.

4.9 Overdose
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 antagonist 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.
Clinical efficacy
Ropinirole tablets 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 Cmax reached on average 1.5 hours after the dose. In the presence of food, Cmax 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 isoenzyme 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 (approximately 15 times the AUC at the maximum dose in humans), increased foetal death at 90 mg/kg (approximately 25 times the AUC at the maximum dose in humans), and digit malformations at 150 mg/kg (approximately 40 times the AUC at the maximum dose in humans). There were no teratogenic effects in the rat at 120 mg/kg (approximately 30 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
Core Tablet:
Lactose monohydrate
Cellulose microcrystalline
Crocarmellose sodium
Magnesium stearate

Film coating:
Hypromellose 6cp (E464)
Titanium dioxide (E171)
Macrogol 400
Polysorbate 80 (E433)

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
2 years.
For HDPE container:
Shelf-life after date of first opening is 6 months.

6.4 Special precautions for storage
Do not store above 25°C.

6.5 Nature and contents of container
Tablets are in Alu-Alu blister and packed in final carton along with package insert in 42’s counts. Ropinirole 0.25 mg tablets are in HDPE bottles of 84’s counts along with silica gel canister which acts as a desiccant and packed in a carton with a package insert.

6.6 Special precautions for disposal
Any unused product or waste material should be disposed of in accordance with local requirements.
<p>| | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
</table>
| 7 | **MARKETING AUTHORIZATION HOLDER**  
Intas Pharmaceuticals Limited  
Sage House 319 Pinner Road  
North Harrow  
Middlesex HA1 4HF  
UK |   |   |
| 8 | **MARKETING AUTHORIZATION NUMBER(S)**  
PL 30139/0001 |   |   |
| 9 | **DATE OF FIRST AUTHORIZATION/RENEWAL OF THE AUTHORIZATION**  
27/01/2009 |   |   |
| 10 | **DATE OF REVISION OF THE TEXT**  
27/01/2009 |   |   |
1 **NAME OF THE MEDICINAL PRODUCT**
Ropinirole 0.5mg Film coated Tablets

2 **QUALITATIVE AND QUANTITATIVE COMPOSITION**
Each film-coated tablet contains 0.5 mg, ropinirole (as hydrochloride).
Excipient (s): Each film-coated tablet contains 46.010 mg of lactose.
For a full list of excipients, see section 6.1.

3 **PHARMACEUTICAL FORM**
Film-coated Tablet.
Yellow, round, biconvex, film-coated tablets plain on both sides.

4 **CLINICAL PARTICULARS**
4.1 Therapeutic indications
Ropinirole is 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**
**Adults**
Individual dose titration against efficacy and tolerability is recommended. Ropinirole should be taken just before bedtime, however it 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 table 1.

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

<table>
<thead>
<tr>
<th>Table 1 Dose titration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Week</td>
</tr>
<tr>
<td>Dose (mg)</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.

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

**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.

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

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

4.4 **Special warnings and precautions for use**

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.

In Parkinson's disease, ropinirole has been associated uncommonly with somnolence and episodes of sudden sleep onset (see section 4.8) however, in Restless Legs Syndrome, this phenomenon is very rare. Nevertheless, patients must be informed of this phenomenon 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.

Patients with major psychotic disorders should not be treated with dopamine agonists unless the potential benefits outweigh the risks.

Pathological gambling, increased libido and hypersexuality have been reported in patients treated with dopamine agonists for Parkinson’s disease, including Ropinirole tablets. Those disorders were reported especially at high doses and were generally reversible upon reduction of the dose or treatment discontinuation. Risk factors such as a history of compulsive behaviours were present in some cases (see section 4.8).

Ropinirole should be administered with caution to patients with moderate hepatic impairment. Undesirable effects should be closely monitored.

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.

Due to the risk of hypotension, patients with severe cardiovascular disease (in particular coronary insufficiency) should be treated with caution.

4.5 **Interaction with other medicinal products and other forms of interaction**

Ropinirole is principally metabolised 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 or fluvoxamine, 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 hormone replacement therapy. In patients already receiving hormone replacement therapy, ropinirole treatment may be initiated in the usual 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 domperidone (a medicinal product used to treat nausea and vomiting) that 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

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 recurrent episodes and somnolence have resolved (see also Section 4.4).

4.8 Undesirable effects

Adverse drug reactions are listed below by system organ class and frequency. Frequencies from the clinical trials are determined as excess incidence over placebo and are classified as very common (>1/10) or common (>1/100, <1/10) or uncommon (>1/1000, <1/100), rare (>1/10,000, <1/100) and very rare (<1/10,000), including isolated reports. Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Use of ropinirole in Restless Legs Syndrome

In Restless Legs Syndrome clinical trials the most common adverse drug reaction is 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.

Table 2 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>Table 2 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</td>
</tr>
<tr>
<td>Nervousness</td>
</tr>
<tr>
<td>Uncommon</td>
</tr>
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<td><strong>Nervous system disorders</strong></td>
</tr>
<tr>
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</tr>
<tr>
<td><strong>Vascular disorders</strong></td>
</tr>
<tr>
<td>Uncommon</td>
</tr>
<tr>
<td>Postural hypotension, hypotension</td>
</tr>
<tr>
<td><strong>Gastrointestinal disorders</strong></td>
</tr>
<tr>
<td>Very common</td>
</tr>
<tr>
<td>Vomiting, nausea</td>
</tr>
<tr>
<td>Common</td>
</tr>
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</tr>
<tr>
<td>Common</td>
</tr>
<tr>
<td>Fatigue</td>
</tr>
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Hallucinations were reported uncommonly in the open label long-term studies.
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.

Other experience with ropinirole
Ropinirole is also indicated for the treatment of Parkinson’s disease. The adverse drug reactions reported in patients with Parkinson's disease on ropinirole monotherapy and adjunct therapy at doses up to 24 mg/day at an excess incidence over placebo are described below.

Table 3 Adverse drug reactions reported in Parkinson's disease clinical trials at doses up to 24 mg/day

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</tr>
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</tr>
<tr>
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<td>Common Leg oedema</td>
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Post marketing reports
Psychotic reactions (other than hallucinations) including delirium, delusion, paranoia have been reported.

Patients treated with dopamine agonists for treatment of Parkinson’s disease, including (Ropinirole tablets), 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.

In Parkinson's disease, ropinirole is associated with somnolence and has been associated uncommonly (>1/1,000, <1/100) with excessive daytime somnolence and sudden sleep onset episodes, however, in Restless Legs Syndrome, this phenomenon is very rare (<1/10,000).

Following ropinirole therapy, postural hypotension or hypotension has been reported uncommonly (>1/1,000, <1/100), rarely severe. Very rare cases of hepatic reactions (<1/10,000), mainly increase of liver enzymes, have been reported.

4.9 Overdose
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 antagonist 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.

Clinical efficacy
Ropinirole tablets 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 Cmax reached on average 1.5 hours after the dose. In the presence of food, Cmax 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 (approximately 15 times the AUC at the maximum dose in humans), increased foetal death at 90 mg/kg (approximately 25 times the AUC at the maximum dose in humans), and digit malformations at 150 mg/kg (approximately 40 times the AUC at the maximum dose in humans). There were no teratogenic effects in the rat at 120 mg/kg (approximately 30 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

Core Tablet:
Lactose monohydrate
Cellulose microcrystalline
Crocarmellose sodium
Magnesium stearate

Film coating:
Hypromellose 6cp (E464)
Macrogol 400
Titanium dioxide (E171)
Iron oxide yellow (E172)
Iron oxide red (E172)
Indigo carmine aluminum lake (E132)

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
2 years.
For HDPE container:
Shelf-life after date of first opening is 6 months.

6.4 Special precautions for storage
Do not store above 25°C.

6.5 Nature and contents of container
Tablets are in Alu-Alu blister and packed in final carton along with package insert in 42’s counts.
Ropinirole 0.5 mg tablets are in HDPE bottles of 84’s counts along with silica gel canister which acts as a desiccant and packed in a carton with a package insert.

6.6 Special precautions for disposal
Any unused product or waste material should be disposed of in accordance with local requirements
MARKETING AUTHORIZATION HOLDER
Intas Pharmaceuticals Limited
Sage House 319 Pinner Road
North Harrow
Middlesex HA1 4HF
UK

MARKETING AUTHORIZATION NUMBER(S)
PL 30139/0002

DATE OF FIRST AUTHORIZATION/RENEWAL OF THE AUTHORIZATION
27/01/2009

DATE OF REVISION OF THE TEXT
27/01/2009
1 NAME OF THE MEDICINAL PRODUCT
Ropinirole 1mg Film coated Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each film-coated tablet contains 1 mg, ropinirole (as hydrochloride).
Excipient(s): Each film-coated tablet contains 45.468 mg of lactose.
For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Film-coated Tablet.
Green, round, biconvex, film-coated tablets plain on both sides.

4 CLINICAL PARTICULARS
4.1 Therapeutic indications
Ropinirole is 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
Adults
Individual dose titration against efficacy and tolerability is recommended. Ropinirole should be taken just before bedtime, however it 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 table 1.

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

<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.

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

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.

Renal impairment
No dosage adjustment is necessary in patients with mild to moderate renal impairment (creatinine clearance between 30 and 50 ml/min).
4.3 Contraindications
Hypersensitivity to the active substance or to any of the excipients.
Severe renal impairment (creatinine clearance < 30ml/min).
Severe hepatic impairment.

4.4 Special warnings and precautions for use
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.

In Parkinson's disease, ropinirole has been associated uncommonly with somnolence and episodes of sudden sleep onset (see section 4.8) however, in Restless Legs Syndrome, this phenomenon is very rare. Nevertheless, patients must be informed of this phenomenon 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.

Patients with major psychotic disorders should not be treated with dopamine agonists unless the potential benefits outweigh the risks.

Pathological gambling, increased libido and hypersexuality have been reported in patients treated with dopamine agonists for Parkinson’s disease, including Ropinirole tablets. Those disorders were reported especially at high doses and were generally reversible upon reduction of the dose or treatment discontinuation. Risk factors such as a history of compulsive behaviours were present in some cases (see section 4.8).

Ropinirole should be administered with caution to patients with moderate hepatic impairment. Undesirable effects should be closely monitored.

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.

Due to the risk of hypotension, patients with severe cardiovascular disease (in particular coronary insufficiency) should be treated with caution.

4.5 Interaction with other medicinal products and other forms of interaction
Ropinirole is principally metabolised 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 or fluvoxamine, 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 hormone replacement therapy. In patients already receiving hormone replacement therapy, ropinirole treatment may be initiated in the usual 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 domperidone (a medicinal product used to treat nausea and vomiting) that 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
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 recurrent episodes and somnolence have resolved (see also Section 4.4).

4.8 Undesirable effects
Adverse drug reactions are listed below by system organ class and frequency. Frequencies from the clinical trials are determined as excess incidence over placebo and are classified as very common (>1/10) or common (>1/100, <1/10) or uncommon (>1/1000, <1/100), rare (>1/10,000, <1/100) and very rare (<1/10,000), including isolated reports. Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Use of ropinirole in Restless Legs Syndrome
In Restless Legs Syndrome clinical trials the most common adverse drug reaction is 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.

Table 2 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.

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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.

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Other experience with ropinirole
Ropinirole is also indicated for the treatment of Parkinson's disease. The adverse drug reactions reported in patients with Parkinson's disease on ropinirole monotherapy and adjunct therapy at doses up to 24 mg/day at an excess incidence over placebo are described below.

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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 antagonist such as neuroleptics or metoclopramide.

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5.1 Pharmacodynamic properties
Pharmacotherapeutic group: Dopamine agonist, ATC code: N04BC04.
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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 (approximately 15 times the AUC at the maximum dose in humans), increased foetal death at 90 mg/kg (approximately 25 times the AUC at the maximum dose in humans), and digit malformations at 150 mg/kg (approximately 40 times the AUC at the maximum dose in humans). There were no teratogenic effects in the rat at 120 mg/kg (approximately 30 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

Core Tablet:
- Lactose monohydrate
- Cellulose microcrystalline
- Croscarmellose sodium
- Magnesium stearate

Tablet coating:
- Hypromellose 6cp (E464)
- Macrogol 400
- Titanium dioxide (E171)
- Iron oxide yellow (E172)
- Indigo carmine aluminum lake (E132)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.

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

6.4 Special precautions for storage

Do not store above 25°C.

6.5 Nature and contents of container

Tablets are in Alu-Alu blister and packed in final carton along with package insert in 21’s counts and 42’s counts.

Not all pack sizes may be marketed.

Ropinirole 1 mg tablets are in HDPE bottles of 84’s counts along with silica gel canister which acts as a desiccant and packed in a carton with a package insert.

6.6 Special precautions for disposal

Any unused product or waste material should be disposed of in accordance with local requirements.
MARKETING AUTHORISATION HOLDER
Intas Pharmaceuticals Limited
Sage House 319 Pinner Road
North Harrow
Middlesex HA1 4HF
UK

MARKETING AUTHORISATION NUMBER(S)
PL 30139/0003

DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
27/01/2009

DATE OF REVISION OF THE TEXT
27/01/2009
**1 NAME OF THE MEDICINAL PRODUCT**
Ropinirole 2mg Film coated Tablets

**2 QUALITATIVE AND QUANTITATIVE COMPOSITION**
Each film-coated tablet contains 2 mg, ropinirole (as hydrochloride).
Excipient(s): Each film-coated tablet contains 44.384 mg of lactose.
For a full list of excipients, see section 6.1.

**3 PHARMACEUTICAL FORM**
Film-coated Tablet.
Pink, round, biconvex, film-coated tablets plain on both sides.

**4 CLINICAL PARTICULARS**

**4.1 Therapeutic indications**
Ropinirole is 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
Adults
Individual dose titration against efficacy and tolerability is recommended. Ropinirole should be taken just before bedtime, however it 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 table 1.

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

<table>
<thead>
<tr>
<th>Table 1 Dose titration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Week</td>
</tr>
<tr>
<td>Dose (mg)/once daily</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.

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

**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.

**Renal impairment**
No dosage adjustment is necessary in patients with mild to moderate renal impairment (creatinine clearance between 30 and 50 ml/min).
4.3 Contraindications
Hypersensitivity to the active substance or to any of the excipients.
Severe renal impairment (creatinine clearance < 30ml/min).
Severe hepatic impairment.

4.4 Special warnings and precautions for use
Ropinirole should not be used to treat neuroleptic akathisia, tardive dyskinesia (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 recurrence 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.

In Parkinson's disease, ropinirole has been associated uncommonly with somnolence and episodes of sudden sleep onset (see section 4.8) however, in Restless Legs Syndrome, this phenomenon is very rare. Nevertheless, patients must be informed of this phenomenon 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.

Patients with major psychotic disorders should not be treated with dopamine agonists unless the potential benefits outweigh the risks.

Pathological gambling, increased libido and hypersexuality have been reported in patients treated with dopamine agonists for Parkinson's disease, including Ropinirole tablets. Those disorders were reported especially at high doses and were generally reversible upon reduction of the dose or treatment discontinuation. Risk factors such as a history of compulsive behaviours were present in some cases (see section 4.8).

Ropinirole should be administered with caution to patients with moderate hepatic impairment. Undesirable effects should be closely monitored.

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.

Due to the risk of hypotension, patients with severe cardiovascular disease (in particular coronary insufficiency) should be treated with caution.

4.5 Interaction with other medicinal products and other forms of interaction
Ropinirole is principally metabolised 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 or fluvoxamine, 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 hormone replacement therapy. In patients already receiving hormone replacement therapy, ropinirole treatment may be initiated in the usual 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 domperidone (a medicinal product used to treat nausea and vomiting) that 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
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 recurrent episodes and somnolence have resolved (see also Section 4.4).

4.8 Undesirable effects
Adverse drug reactions are listed below by system organ class and frequency. Frequencies from the clinical trials are determined as excess incidence over placebo and are classified as very common (>1/10) or common (>1/100, <1/10) or uncommon (>1/1000, <1/100), rare (>1/10,000, <1/100) and very rare (<1/10,000), including isolated reports. Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Use of ropinirole in Restless Legs Syndrome
In Restless Legs Syndrome clinical trials the most common adverse drug reaction is 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.

Table 2 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>Table 2</th>
<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>
<td></td>
</tr>
<tr>
<td>Common</td>
<td>Nervousness</td>
</tr>
<tr>
<td>Uncommon</td>
<td>Confusion</td>
</tr>
<tr>
<td><strong>Nervous system disorders</strong></td>
<td></td>
</tr>
<tr>
<td>Common</td>
<td>Syncope, somnolence, dizziness (including vertigo)</td>
</tr>
<tr>
<td><strong>Vascular disorders</strong></td>
<td></td>
</tr>
<tr>
<td>Uncommon</td>
<td>Postural hypotension, hypotension</td>
</tr>
<tr>
<td><strong>Gastrointestinal disorders</strong></td>
<td></td>
</tr>
<tr>
<td>Very common</td>
<td>Vomiting, nausea</td>
</tr>
<tr>
<td>Common</td>
<td>Abdominal pain</td>
</tr>
<tr>
<td><strong>General disorders and administration site conditions</strong></td>
<td></td>
</tr>
<tr>
<td>Common</td>
<td>Fatigue</td>
</tr>
</tbody>
</table>

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

Other experience with ropinirole
Ropinirole is also indicated for the treatment of Parkinson's disease. The adverse drug reactions reported in patients with Parkinson's disease on ropinirole monotherapy and adjunct therapy at doses up to 24 mg/day at an excess incidence over placebo are described below.

Table 3 Adverse drug reactions reported in Parkinson's disease clinical trials at doses up to 24 mg/day

<table>
<thead>
<tr>
<th>Psychiatric disorders</th>
<th>Common</th>
<th>Uncommon</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hallucinations, confusion</td>
<td>Increased libido</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Nervous system disorders</th>
<th>Very common</th>
<th>Common</th>
</tr>
</thead>
<tbody>
<tr>
<td>Syncope, dyskinesia, somnolence</td>
<td>Nausea</td>
<td>Vomiting, abdominal pain, heartburn</td>
</tr>
</tbody>
</table>

Post marketing reports
Psychotic reactions (other than hallucinations) including delirium, delusion, paranoia have been reported.

Patients treated with dopamine agonists for treatment of Parkinson’s disease, including (Ropinirole tablets), 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.

In Parkinson's disease, ropinirole is associated with somnolence and has been associated uncommonly (>1/1,000, <1/100) with excessive daytime somnolence and sudden sleep onset episodes, however, in Restless Legs Syndrome, this phenomenon is very rare (<1/10,000).

Following ropinirole therapy, postural hypotension or hypotension has been reported uncommonly (>1/1,000, <1/100), rarely severe.
Very rare cases of hepatic reactions (<1/10,000), mainly increase of liver enzymes, have been reported.

4.9 Overdose
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 antagonist 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.

Clinical efficacy
Ropinirole tablets 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
PAR Ropinirole 0.25mg, 0.5mg, 1mg and 2mg Film-Coated Tablets

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 Cmax reached on average 1.5 hours after the dose. In the presence of food, Cmax 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 (approximately 15 times the AUC at the maximum dose in humans), increased foetal death at 90 mg/kg (approximately 25 times the AUC at the maximum dose in humans), and digit malformations at 150 mg/kg (approximately 40 times the AUC at the maximum dose in humans). There were no teratogenic effects in the rat at 120 mg/kg (approximately 30 times the AUC at the maximum dose in humans) and no indication of an effect on development in the rabbit.

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- Macrogol 400
- Titanium dioxide (E171)
- Iron oxide yellow (E172)
- Iron oxide red (E172)

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Not applicable.

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2 years.
For HDPE container:
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Do not store above 25°C.

6.5 Nature and contents of container
Tablets are in Alu-Alu blister and packed in final carton along with package insert in 63’s counts.
Ropinirole 2 mg tablets are in HDPE bottles of 84’s counts along with a silica gel canister which acts as a desiccant and packed in a carton with a package insert.

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

7 MARKETING AUTHORISATION HOLDER
Intas Pharmaceuticals Limited
Sage House 319 Pinner Road
North Harrow
Middlesex HA1 4HF
UK
8 MARKETING AUTHORISATION NUMBER(S)
PL 30139/0004

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
27/01/2009

10 DATE OF REVISION OF THE TEXT
27/01/2009
Module 3

The Patient Information Leaflet (PIL) below is the leaflet agreed at the end of the decentralised procedure. The marketing authorisation holder has stated that it is not intending to market either product and, thus, no UK-specific documents have been submitted. The marketing authorisation holder has committed to submit the UK PIL and labelling for review to the regulatory authority before marketing either product.

PACKAGE LEAFLET: INFORMATION FOR USER
ROPINIROLE 0.25MG 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 Hydrochloride Tablets is and what it is used for
2. Before you take Ropinirole Hydrochloride Tablets
3. How to take Ropinirole Hydrochloride Tablets
4. Possible side effects
5. How to store Ropinirole Hydrochloride Tablets
6. Further information

1. What Ropinirole Hydrochloride Tablets is and what it is used for

Ropinirole Hydrochloride Tablets belong to a group of medicines called dopamine agonists. Dopamine agonists act like a naturally occurring chemical in your brain called dopamine. Ropinirole Hydrochloride Tablets is used to treat the symptoms of moderate to severe idiopathic Restless Legs Syndrome. Moderate to severe Restless Legs Syndrome is typically represented by patients who have difficulty sleeping and severe discomfort in their legs or arms.

Restless Legs Syndrome is a condition characterized by an irresistible urge to move the legs and occasionally the arms, usually accompanied by uncomfortable sensations such as tingling, burning or pricking. These 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 limbs, which often leads to problems sleeping. Ropinirole Hydrochloride Tablets relieves the discomfort and reduces the urge to move the limbs that disturb night time sleep.

2. Before you take Ropinirole Hydrochloride Tablets

Do not take Ropinirole Hydrochloride Tablets:
- If you are allergic (hypersensitive) to the active ingredient, Ropinirole or any other ingredients of Ropinirole Hydrochloride Tablets.
- If you have serious liver disease.
- If you have serious kidney disease.
- If you are unsure, it is essential to talk to your doctor.

Take special care with Ropinirole Hydrochloride Tablets:
- If you are pregnant or think you are pregnant.
- If you are breast-feeding.
- If you are intolerant to some sugars (e.g. lactose).
- If you have liver disease.
- If you are under 18 years of age.
- If you have serious heart complaint.
- If you have serious mental health problem.
- If you have experienced any unusual urges and/or behaviours (such as excessive gambling or excessive sexual behaviour).

In these situations tell your doctor before you start to take this medicine, your doctor should carefully supervise your treatment. If during treatment your symptoms become worse, start earlier in the day or after less time at rest, or affect other parts of your body such as arms, you should see your doctor who may adjust the dose of Ropinirole Hydrochloride Tablets that you are taking.

Taking other medicines:
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 Hydrochloride Tablets may be increased or decreased by other medicines and vice versa. These medicines include:
- Ciprofloxacin (an antibiotic).
- Ibuprofen (an antibiotic).
- Flavoxate (a drug used to treat depression).
- Theophylline (a drug used to treat asthma).
- Hormone replacement therapy (also called HRT).
- Anti-psychotics and other drugs that block dopamine in the brain (e.g. sulpiride or metoclopramide).

Tell your doctor if:
- You are already receiving any other medicines for Restless Legs Syndrome.
- You give up or start smoking while taking Ropinirole Hydrochloride Tablets. Your doctor may need to adjust your dose.
- You are taking Ropinirole Hydrochloride Tablets and the doctor is going to prescribe you any other medicine.

Taking Ropinirole Hydrochloride Tablets with food and drink:
Taking Ropinirole Hydrochloride Tablets with food may reduce the likelihood of you feeling or being sick.

Pregnancy and breast-feeding:
Tell your doctor immediately if:
- You are pregnant.
PAR Ropinirole 0.25mg, 0.5mg, 1mg and 2mg Film-Coated Tablets

- You think you might be or are planning to become pregnant.
- You are breast-feeding.

Ropinirole Hydrochloride Tablets should not be used during breast-feeding as milk production may be affected. Ropinirole Hydrochloride Tablets should only be used during pregnancy after your doctor has considered the benefit to you and the potential risk of harm to your unborn child. Your doctor will advise you to discontinue this medicine.

Driving and using machines:
This medicine does not usually affect people’s normal activities. However, ropinirole hydrochloride tablets can cause extreme sleepiness (somnolence) and sudden sleep onset episodes. If you do 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 hydrochloride tablets
This medicinal product contains lactose. If you have been told by your doctor that you have intolerance to lactose or any sugars, contact your doctor before taking this medicinal product.

3. How to take Ropinirole Hydrochloride Tablets

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

- The starting dose is 0.25 mg once daily. After two days your doctor will probably increase your dose to 0.5 mg once daily for the remainder of your first week of treatment. Then your doctor may increase your dose to 1 mg once a day at week 2. The dose may 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 with insufficient improvement, the dose may be increased gradually up to a maximum of 4 mg daily. After three months of treatment with Ropinirole Hydrochloride Tablets, your doctor may adjust your dose or discontinue your treatment depending on your symptoms and how you feel.
- Take Ropinirole Hydrochloride Tablets once a day by mouth, every day at about the same time each day. Ropinirole Hydrochloride Tablets is usually taken just before bedtime, but can be taken up to 3 hours before going to bed.
- Swallow the Ropinirole Hydrochloride Tablets whole with water. Taking Ropinirole Hydrochloride Tablets with food may decrease the occurrence of nausea (feeling sick), which is a possible side effect of Ropinirole Hydrochloride Tablets. Do not chew the tablets.
- 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 Hydrochloride Tablets 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 Hydrochloride Tablets than you should:
If you have taken more Ropinirole Hydrochloride Tablets than you were told to, or if someone else has taken any Ropinirole Hydrochloride Tablets contact accident and emergency department of your nearest hospital. Take any left over tablets or empty box with you for easier identification.

If you forget to take Ropinirole Hydrochloride Tablets:
Do not take a double dose to make up for the forgotten dose, take your next dose as usual and continue you course. If you have missed taking Ropinirole Hydrochloride Tablets for more than a few days you should contact your doctor for advice on restarting Ropinirole Hydrochloride Tablets.

If you stop taking Ropinirole Hydrochloride Tablets:
If your symptoms worsen after you stop treatment with Ropinirole Hydrochloride Tablets, you should contact your doctor. If you have any further questions on the use of this product, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, Ropinirole Hydrochloride Tablets can cause side effects, although not everybody gets them. Possible side effects are listed under headings of frequency, using the following categories: very common: affects more than 1 in 10, common: affects 1 to 10 users in 100, uncommon: affects 1 to 10 users in 1,000, rare: affects 1 to 10 users in 10,000, very rare: affects less than 1 user in 10,000, not known: frequency cannot be estimated from the available data.

Very common side effects (affects more than 1 user in 10):
- Vomiting
- Nausea (feeling or being sick)

Common side effects (affects 1 to 10 users in 100):
- Fatigue (tiredness, weakness)
- Feeling drowsy
- Stomach pain
- Nervousness
- Fainting
- Dizziness (including vertigo)

Uncommon side effects (affects 1 to 10 users in 1,000):
- Hypotension (Decrease in blood pressure)
- Postural hypotension (Decrease in blood pressure while sitting or standing)
- Feeling confused
- Hallucinations (Emergence of surprising or warded-off memory or fantasy images)

Very rare side effects (affects less than 1 user in 10,000):
- Altered liver function
- Excessive daytime somnolence (excessive drowsiness)
- Insomnia (false ideas)
- Sudden sleep onset episodes
- Delirium (severe confusion)
- Paranoia (excessive anxiety or fear)

There are some reports of patients treated for Parkinson’s disease with medicinal products of this group of substance (dopamine agonists) who showed pathological compulsive gambling or compulsive and excessive sexual drive. These adverse effects were reversible when doses were reduced or treatment was stopped.
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.

5. How to store Ropinirole Hydrochloride Tablets

- Keep out of the reach and sight of children.
- Do not use Ropinirole Hydrochloride Tablets after the expiry date which is stated on the carton or bottle after (exp). The expiry date refers to last day of that month.
- Do not store above 25°C.
- For HDPE container: Shelf-life after date of first opening is 6 months.
- 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.

6. Further Information

What Ropinirole Hydrochloride Tablets contain:

The active substance is Ropinirole. Each film-coated tablet contains 0.25mg ropinirole (as hydrochloride).

Core Tablets: Lactose monohydrate, cellulose microcrystalline, crescarmellose sodium, magnesium stearate.

Film coat:
Hypromellose 6cp (E464), titanium dioxide (E171), macrogol 400, polysorbate 60 (E433).

What Ropinirole Hydrochloride Tablets looks like and content of the pack:

0.25 mg tablets are white to off white, round, biconvex, film coated tablets plain on both sides.

Ropinirole Hydrochloride Tablets are packed in blister packs and in bottle packs as follows:

The tablets are packed in blisters of 42’s counts packed in a carton with package leaflet.

Ropinirole 0.25 mg Tablets are packed in HDPE bottles of 84’s counts with silica gel container and packed in a carton with a package insert.

Marketing Authorisation Holder and Manufacturer

Marketing Authorisation Holder:
Intas Pharmaceuticals Limited, Sage House 319 Pinner Road, North Harrow, Middlesex, HA1 4HF UK

Manufacturer:
Accord Healthcare Limited, Sage House 319 Pinner Road, North Harrow, Middlesex, HA1 4HF UK

This medicinal product is authorized in the Member States of the EEA under the following names:

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<tr>
<td>UK</td>
<td>Ropinirole 0.25mg Film coated Tablets</td>
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<tr>
<td>Germany</td>
<td>Ropinirol Intas 0.25mg Filmtabletten</td>
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<td>Spain</td>
<td>Ropinirol Intas 0.25mg Comprimidos EFG</td>
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The leaflet was last approved in.

To be completed nationally.
PAR Ropinirole 0.25mg, 0.5mg, 1mg and 2mg Film-Coated Tablets

UK/H/1094/001-4/DC

PACKAGE LEAFLET: INFORMATION FOR USER
ROPINIROLE 0.5MG 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 Hydrochloride Tablets is and what it is used for
2. Before you take Ropinirole Hydrochloride Tablets
3. How to take Ropinirole Hydrochloride Tablets
4. Possible side effects
5. How to store Ropinirole Hydrochloride Tablets
6. Further information

1. What Ropinirole Hydrochloride Tablets is and what it is used for

Ropinirole Hydrochloride Tablets belong to a group of medicines called dopamine agonists. Dopamine agonists act like a naturally occurring chemical in your brain called dopamine. Ropinirole Hydrochloride Tablets is used to treat the symptoms of moderate to severe idiopathic Restless Legs Syndrome. Moderate to severe Restless Legs Syndrome is typically represented by patients who have difficulty sleeping and severe discomfort in their legs or arms.

Restless Legs Syndrome is a condition characterized by an irreversible urge to move the legs and occasionally the arms, usually accompanied by uncomfortable sensations such as tingling, burning or pricking. These 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 limbs, which often leads to problems sleeping. Ropinirole Hydrochloride Tablets relieves the discomfort and reduces the urge to move the limbs that disturb night time sleep.

2. Before you take Ropinirole Hydrochloride Tablets

Do not take Ropinirole Hydrochloride Tablets:
- If you are allergic (hypersensitive) to the active ingredient, Ropinirole or any other ingredients of Ropinirole Hydrochloride Tablets.
- If you have serious liver disease.
- If you have serious kidney disease.
- If you are unsure, it is essential to talk to your doctor.

Take special care with Ropinirole Hydrochloride Tablets:
- If you are pregnant or think you are pregnant.
- If you are breast-feeding.
- If you are intolerant to some sugars (e.g. lactose).
- If you have liver disease.
- If you are under 18 years of age.
- If you have serious heart complaint.
- If you have serious mental health problem.
- If you have experienced any unusual urges and/or behaviours (such as excessive gambling or excessive sexual behaviour).

In these situations tell your doctor before you start to take this medicine, your doctor should carefully supervise your treatment. If during treatment your symptoms become worse, start earlier in the day or after less time at rest, or affect other parts of your body such as arms, you should see your doctor who may adjust the dose of Ropinirole Hydrochloride Tablets that you are taking.

Taking other medicines:
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 Hydrochloride Tablets may be increased or decreased by other medicines and vice versa. These medicines include:
- Ciprofloxacin (an antibiotic).
- Enoxacin (an antibiotic).
- Fluvoxamine (a drug used to treat depression).
- Theophylline (a drug used to treat asthma).
- Hormone replacement therapy (also called HRT).
- Anti-psychotics and other drugs that block dopamine in the brain (e.g. sulphride or metoclopramide).

Tell your doctor if:
- You are already receiving any other medicines for Restless Legs Syndrome.
- You give up or start smoking while taking Ropinirole Hydrochloride Tablets. Your doctor may need to adjust your dose.
- You are taking Ropinirole Hydrochloride Tablets and the doctor is going to prescribe you any other medicine.

Taking Ropinirole Hydrochloride Tablets with food and drink:
Taking Ropinirole Hydrochloride Tablets with food may reduce the likelihood of you feeling or being sick.

Pregnancy and breast-feeding:
Tell your doctor immediately if:
- You are pregnant.
You think you might be or are planning to become pregnant.
- You are breast-feeding.

Ropinirole Hydrochloride Tablets should not be used during breast-feeding as milk production may be affected. Ropinirole Hydrochloride Tablets should only be used during pregnancy after your doctor has considered the benefit to you and the potential risk of harm to your unborn child. Your doctor will advise you to discontinue this medicine.

Driving and using machines:
This medicine does not usually affect people’s normal activities. However, ropinirole hydrochloride tablets can cause extreme sleepiness (somnolence) and sudden sleep onset episodes. If you do 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 hydrochloride tablets
This medicinal product contains lactose. If you have been told by your doctor that you have intolerance to lactose or any sugars, contact your doctor before taking this medicinal product.

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

- The starting dose is 0.25 mg once daily. After two days your doctor will probably increase your dose to 0.5 mg once daily for the remainder of your first week of treatment. Then your doctor may increase your dose to 1 mg once a day at week 2. The dose may be increased by 0.8 mg per week over the next two weeks to a dose of 2 mg once a day.
- Take Ropinirole Hydrochloride Tablets once a day by mouth, every day at about the same time each day.
- Swallow the Ropinirole Hydrochloride Tablets whole with water.
- Do not chew the tablet(s).

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 Hydrochloride Tablets 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 Hydrochloride Tablets than you should:
If you have taken more Ropinirole Hydrochloride Tablets than you were told to, or if someone else has taken any Ropinirole Hydrochloride Tablets contact accident and emergency department of your nearest hospital. Take any left over tablets or empty box with you for easier identification.

If you forget to take Ropinirole Hydrochloride Tablets:
Do not take a double dose to make up for the forgotten dose, take you next dose as usual and continue you course. If you have missed taking Ropinirole Hydrochloride Tablets for more than a few days consult your doctor for advice on restarting Ropinirole Hydrochloride Tablets.

If you stop taking Ropinirole Hydrochloride Tablets:
If your symptoms worsen after you stop treatment with Ropinirole Hydrochloride Tablets, you should contact your doctor. If you have any further questions on the use of this product, ask your doctor or pharmacist.

4. Possible side effects
Like all medicines, Ropinirole Hydrochloride Tablets can cause side effects, although not everybody gets them. Possible side effects are listed under headings of frequency, using the following categories: very common: affects more than 1 user in 10, common: affects 1 to 10 users in 100, uncommon: affects 1 to 10 users in 1,000, rare: affects 1 to 10 users in 10,000, very rare: affects less than 1 user in 10,000, not known: frequency cannot be estimated from the available data.

Very common side effects (affects more than 1 user in 10):
- Nausea (feeling sick)
- Vomiting
- Dizziness (including vertigo)
- Fatigue (tiredness, weakness)
- Feeling drowsy
- Feeling confusion
- Hallucinations ( Emergence of surprising or warded-off memory or fantasy images)
- Postural hypotension (Decrease in blood pressure while sitting or standing)
- Stomach pain
- Nervousness
- Feeling faint

Common side effects (affects 1 to 10 users in 100):

Uncommon side effects (affects 1 to 10 users in 1,000):

- Sudden sleep onset episodes
- Paranoia (excessive anxiety or fear)
- Excessive daytime somnolence (excessive drowsiness)
- Illusions (false ideas)
- Stomach pain
- Nervousness
- Feeling confusion
- Fatigue (tiredness, weakness)
- Dizziness (including vertigo)
- Feeling drowsy
- Feeling faint
- Vomiting
- Nausea (feeling sick)
- Postural hypotension (Decrease in blood pressure while sitting or standing)
- Feeling faint
- Stomach pain
- Nervousness
- Feeling confusion
- Fatigue (tiredness, weakness)
- Dizziness (including vertigo)
- Feeling drowsy
- Feeling faint
- Vomiting
- Nausea (feeling sick)
- Postural hypotension (Decrease in blood pressure while sitting or standing)

There are some reports of patient treated for Parkinson’s disease with medicinal products of this group of substance (dopamine agonists) who showed pathological compulsive gambling or compulsive and excessive sexual drive. These adverse effects were reversible when doses were reduced or treatment was stopped.
5. How to store Ropinirole Hydrochloride Tablets

- Keep out of the reach and sight of children.
- Do not use Ropinirole Hydrochloride Tablets after the expiry date which is stated on the carton or bottle after (exp). The expiry date refers to last day of that month.
- Do not store above 25°C.
- For HDPE container: Shelf-life after date of first opening is 6 months.
- 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.

6. Further information

What Ropinirole Hydrochloride Tablets contain:

The active substance is Ropinirole. Each film-coated tablet contains 0.5 mg ropinirole (as hydrochloride).

Core Tablets: Lactose monohydrate, cellulose microcrystalline, croscarmellose sodium, magnesium stearate.

Film coat:

Hypermellose 6cp (E464), macrogol 400, titanium dioxide (E171), iron oxide yellow (E172), iron oxide red (E172), indigo carmine aluminum lake (E132).

What Ropinirole Hydrochloride Tablets looks like and content of the pack:

Ropinirole 0.5 mg tablets are yellow, round, biconvex, film coated tablets plain on both sides.

Ropinirole Hydrochloride Tablets are packed in blister packs and in bottle packs as follows:

The tablets are packed in blisters of 42's counts packed in a carton with package leaflet

Ropinirole 0.5 mg Tablets are packed in HDPE bottles of 84's counts with silica gel canister and packed in a carton with a package insert.

Marketing Authorisation Holder and Manufacturer

Marketing Authorisation Holder:
Intas Pharmaceuticals Limited, Sage House 319 Pinner Road, North Harrow, Middlesex, HA1 4HF UK

Manufacturer:
Accord Healthcare Limited, Sage House 319 Pinner Road, North Harrow, Middlesex, HA1 4HF UK

This medicinal product is authorized in the Member States of the EEA under the following names:

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<td>Ropinirole 0.5 mg Film coated Tablets</td>
</tr>
<tr>
<td>Germany</td>
<td>Ropiklor Intas 0.5mg Filmtabletten</td>
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<td>Spain</td>
<td>Ropinirole Intas 0.5mg Comprimidos BP</td>
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The leaflet was last approved in.

To be completed nationally.
PAR Ropinirole 0.25mg, 0.5mg, 1mg and 2mg Film-Coated Tablets  UK/H/1094/001-4/DC

PACKAGE LEAFLET: INFORMATION FOR USER
ROPINIROLE 1MG 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 Hydrochloride Tablets is and what it is used for
2. Before you take Ropinirole Hydrochloride Tablets
3. How to take Ropinirole Hydrochloride Tablets
4. Possible side effects
5. How to store Ropinirole Hydrochloride Tablets
6. Further information

1. What Ropinirole Hydrochloride Tablets is and what it is used for
Ropinirole Hydrochloride Tablets belong to a group of medicines called dopamine agonists. Dopamine agonists act like a naturally occurring chemical in your brain called dopamine. Ropinirole Hydrochloride Tablets is used to treat the symptoms of moderate to severe idiopathic Restless Legs Syndrome. Moderate to severe Restless Legs Syndrome is typically represented by patients who have difficulty sleeping and severe discomfort in their limbs or arms.

Restless Legs Syndrome is a condition characterized by an irresistible urge to move the legs and occasionally the arms, usually accompanied by uncomfortable sensations such as tugging, burning or pricking. These 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 limbs, which often leads to problems sleeping. Ropinirole Hydrochloride Tablets relieve the discomfort and reduces the urge to move the limbs that disturb night time sleep.

2. Before you take Ropinirole Hydrochloride Tablets
Do not take Ropinirole Hydrochloride Tablets;
- If you are allergic (hypersensitive) to the active ingredient, Ropinirole or any other ingredients of Ropinirole Hydrochloride Tablets.
- If you have serious liver disease.
- If you have serious kidney disease.
- If you are unsure, it is essential to talk to your doctor.

Take special care with Ropinirole Hydrochloride Tablets;
- If you are pregnant or think you are pregnant.
- If you are breast-feeding.
- If you are intolerant to some sugars (e.g. lactose).
- If you have liver disease.
- If you are under 18 years of age.
- If you have serious heart complaint.
- If you have serious mental health problem.
- If you have experienced any unusual urges and/or behaviours (such as excessive gambling or excessive sexual behaviour).

In these situations tell your doctor before you start taking this medicine, your doctor should carefully supervise your treatment. If during treatment your symptoms become worse, start earlier in the day or after less time at rest, or affect other parts of your body such as arms, you should see your doctor who may adjust the dose of Ropinirole Hydrochloride Tablets that you are taking.

Taking other medicines;
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 Hydrochloride Tablets may be increased or decreased by other medicines and vice versa. These medicines include:
- Ciprofloxacin (an antibiotic).
- Enoxacin (an antibiotic).
- Fluoxetine (a drug used to treat depression).
- Theophylline (a drug used to treat asthma).
- Hormone replacement therapy (also called HRT).
- Anti-psychotics and other drugs that block dopamine in the brain (e.g. sulphuride or metoclopramide).

Tell your doctor if;
- You are already receiving any other medicines for Restless Legs Syndrome.
- You give up or start smoking while taking Ropinirole Hydrochloride Tablets, your doctor may need to adjust your dose.
- You are taking Ropinirole Hydrochloride Tablets and the doctor is going to prescribe you any other medicine.

Taking Ropinirole Hydrochloride Tablets with food and drink;
Taking Ropinirole Hydrochloride Tablets with food may reduce the likelihood of you feeling or being sick.

Pregnancy and breast-feeding;
Tell your doctor immediately if;
- You are pregnant.
You think you might be or are planning to become pregnant.
You are breast-feeding.

Ropinirole Hydrochloride Tablets should not be used during breast-feeding as milk production may be affected. Ropinirole Hydrochloride Tablets should only be used during pregnancy after your doctor has considered the benefit to you and the potential risk of harm to your unborn child. Your doctor will advise you to discontinue this medicine.

Driving and using machines:
This medicine does not usually affect people's normal activities. However, ropinirole hydrochloride tablets can cause extreme sleepiness (somnialess) and sudden sleep onset episodes. If you do 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 Hydrochloride tablets
This medicinal product contains lactose. If you have been told by your doctor that you have intolerance to lactose or any sugars, contact your doctor before taking this medicinal product.

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

The starting dose is 0.25 mg once daily. After two days your doctor will probably increase your dose to 0.5 mg once daily for the remainder of your first week of treatment. Then your doctor may increase your dose to 1 mg once a day at week 2. The dose may 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 with insufficient improvement, the dose may be increased gradually up to a maximum of 4 mg daily. After three months of treatment with Ropinirole Hydrochloride Tablets, your doctor may adjust your dose or discontinue your treatment depending on your symptoms and how you feel.

Take Ropinirole Hydrochloride Tablets once a day by mouth, every day at about the same time each day. Ropinirole Hydrochloride Tablets is usually taken just before bedtime, but can be taken up to 2 hours before going to bed.

Swallow the Ropinirole Hydrochloride Tablets whole with water. Taking Ropinirole Hydrochloride Tablets with food may decrease the occurrence of nausea (feeling sick), which is a possible side effect of Ropinirole Hydrochloride Tablets. Do not chew the tablets.

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 Hydrochloride Tablets 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 Hydrochloride Tablets than you should:
If you have taken more Ropinirole Hydrochloride Tablets than you were told to, or if someone else has taken any Ropinirole Hydrochloride Tablets contact accident and emergency department of your nearest hospital. Take any left over tablets or empty box with you for easier identification.

If you forget to take Ropinirole Hydrochloride Tablets:
Do not take a double dose to make up for the forgotten dose, take your next dose as usual and continue your course. If you have missed taking Ropinirole Hydrochloride Tablets for more than a few days consult your doctor for advice on restarting Ropinirole Hydrochloride Tablets.

If you stop taking Ropinirole Hydrochloride Tablets:
If your symptoms worsen after you stop treatment with Ropinirole Hydrochloride Tablets, you should contact your doctor. If you have any further questions on the use of this product ask your doctor or pharmacist.

4. Possible side effects
Like all medicines, Ropinirole Hydrochloride Tablets can cause side effects, although not everybody gets them. Possible side effects are listed under headings of frequency, using the following categories: very common: affects more than 1 in 10; common: affects 1 to 10 in 100, uncommon: affects 1 to 10 in 1,000; rare: affects 1 to 10 in 10,000, very rare: affects less than 1 in 10,000, not known: frequency cannot be estimated from the available data.

Very common side effects (affects more than 1 user in 10):
- Vomiting
- Nausea (feeling or being sick)

Common side effects (affects 1 to 10 users in 100):
- Fatigue (tiredness, weakness)
- Feeling dizzy
- Stomach pain
- Dizziness (including vertigo)
- Feeling or being sick

Uncommon side effects (affects 1 to 10 users in 1,000):
- Hypotension (Reduce in blood pressure)
- Postural hypotension (Decrease in blood pressure while sitting or standing)
- Feeling or being sick
- Hallucinations (Emergence of surprising or warded-off memory or fantasy images)

Very rare side effects (affects less than 1 user in 10,000):
- Altered liver function
- Delirious (severe confusion)
- Illusions (false ideas)
- Paranoia (excessive anxiety or fear)
- Sudden sleep onset episodes
- Excessive daytime somnolence (excessive drowsiness)
- Other side effects

There are some reports of patients treated for Parkinson's disease with medicinal products of this group of substance ( dopamin agonists) who showed pathological compulsive gambling or compulsive and excessive sexual drive. These adverse effects were reversible when doses were reduced or treatment was stopped.
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.

5. How to store Ropinirole Hydrochloride Tablets
- Keep out of the reach and sight of children.
- Do not use Ropinirole Hydrochloride Tablets after the expiry date which is stated on the carton or bottle after (exp). The expiry date refers to last day of that month.
- Do not store above 35°C.
- For HDPE container: Shelf-life after date of first opening is 6 months.
- 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.

6. Further Information
What Ropinirole Hydrochloride Tablets contain:
The active substance is Ropinirole. Each film-coated tablet contains 1mg ropinirole (as hydrochloride).
Core Tablets: Lactose monohydrate, cellulose microcrystalline, croscarmellose sodium, magnesium stearate.
Film coat:
Hyprimellose 6cp (E464), macrogol 400, titanium dioxide (E171), iron oxide yellow (E172), indigo carmine aluminum lake (E132).

What Ropinirole Hydrochloride Tablets looks like and content of the pack:
1 mg tablets are green, round, biconvex, film coated tablets plain on both sides.
Ropinirole Hydrochloride Tablets are packed in blister packs and in bottle packs as follows:
The tablets are packed in blisters of 21’s counts and 42’s counts packed in a carton with package leaflet. Not all pack sizes may be marketed.
Ropinirole 1 mg Tablets are packed in HDPE bottles of 84’s counts with silica gel canister and packed in a carton with a package insert.

Marketing Authorisation Holder and Manufacturer
Marketing Authorisation Holder:
Intas Pharmaceuticals Limited, Sage House 219 Pinner Road, North Harrow, Middlesex, HA1 4HF UK
Manufacturer:
Accord Healthcare Limited, Sage House 319 Pinner Road, North Harrow, Middlesex, HA1 4HF UK

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<tr>
<td>Germany</td>
<td>Ropinirol Intas 1mg Filmtabletten</td>
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The leaflet was last approved in.
To be completed nationally.
PAR Ropinirole 0.25mg, 0.5mg, 1mg and 2mg Film-Coated Tablets

UK/H/1094/001-4/DC

PACKAGE LEAFLET: INFORMATION FOR USER
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 Hydrochloride Tablets is and what it is used for
2. Before you take Ropinirole Hydrochloride Tablets
3. How to take Ropinirole Hydrochloride Tablets
4. Possible side effects
5. How to store Ropinirole Hydrochloride Tablets
6. Further information

1. What Ropinirole Hydrochloride Tablets is and what it is used for

Ropinirole Hydrochloride Tablets belongs to a group of medicines called dopamine agonists. Dopamine agonists act like a naturally occurring chemical in your brain called dopamine. Ropinirole Hydrochloride Tablets is used to treat the symptoms of moderate to severe idiopathic Restless Legs Syndrome. Moderate to severe Restless Legs Syndrome is typically represented by patients who have difficulty sleeping and severe discomfort in their legs or arms.

Restless Legs Syndrome is a condition characterized by an irreversible urge to move the legs and occasionally the arms, usually accompanied by uncomfortable sensations such as tingling, burning or prickling. These 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 limbs, which often leads to problems sleeping. Ropinirole Hydrochloride Tablets relieves the discomfort and reduces the urge to move the limbs that disturb night time sleep.

2. Before you take Ropinirole Hydrochloride Tablets

Do not take Ropinirole Hydrochloride Tablets:
- If you are allergic (hypersensitive) to the active ingredient, Ropinirole or any other ingredients of Ropinirole Hydrochloride Tablets.
- If you have serious liver disease.
- If you have serious kidney disease.
- If you are unsure, it is essential to talk to your doctor.

Take special care with Ropinirole Hydrochloride Tablets:
- If you are pregnant or think you are pregnant.
- If you are breast-feeding.
- If you are intolerant to some sugars (e.g. lactose).
- If you have liver disease.
- If you are under 18 years of age.
- If you have serious heart complaint.
- If you have serious mental health problem.
- If you have experienced any unusual urges and/or behaviours (such as excessive gambling or excessive sexual behaviour).

In these situations tell your doctor before you start to take this medicine, your doctor should carefully supervise your treatment. If during treatment your symptoms become worse, start earlier in the day or after less time at rest, or affect other parts of your body such as arms, you should see your doctor who may adjust the dose of Ropinirole Hydrochloride Tablets that you are taking.

Taking other medicines:
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 Hydrochloride Tablets may be increased or decreased by other medicines and vice versa. These medicines include:
- Ciproflaxacin (an antibiotic).
- Enoxacin (an antibiotic).
- Fluoxetine (a drug used to treat depression).
- Theophylline (a drug used to treat asthma).
- Hormone replacement therapy (also called HRT).
- Antipsychotics and other drugs that block dopamine in the brain (e.g. sulpiride or metoclopramide).

Tell your doctor if:
- You are already receiving any other medicines for Restless Legs Syndrome.
- You give up or start smoking while taking Ropinirole Hydrochloride Tablets. Your doctor may need to adjust your dose.
- You are taking Ropinirole Hydrochloride Tablets and the doctor is going to prescribe you any other medicine.

Taking Ropinirole Hydrochloride Tablets with food and drink:
Taking Ropinirole Hydrochloride Tablets with food may reduce the likelihood of you feeling or being sick.

Pregnancy and breast-feeding:
Tell your doctor immediately if;
- You are pregnant.
PAR Ropinirole 0.25mg, 0.5mg, 1mg and 2mg Film-Coated Tablets

- You think you might be or are planning to become pregnant.
- You are breast-feeding.

Ropinirole Hydrochloride Tablets should not be used during breast-feeding as milk production may be affected. Ropinirole Hydrochloride Tablets should only be used during pregnancy after your doctor has considered the benefit to you and the potential risk of harm to your unborn child. Your doctor will advise you to discontinue this medicine.

Driving and using machines:
This medicine does not usually affect people’s normal activities. However, ropinirole hydrochloride tablets can cause extreme sleepiness (somnolence) and sudden sleep onset episodes. If you do 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 hydrochloride tablets
This medicinal product contains lactose. If you have been told by your doctor that you have intolerance to lactose or any sugars, contact your doctor before taking this medicinal product.

3. How to take Ropinirole Hydrochloride Tablets
Always take Ropinirole Hydrochloride Tablets exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.
- The starting dose is 0.25 mg once daily. After two days your doctor will probably increase your dose to 0.5 mg once daily for the remainder of your first week of treatment. Then your doctor may increase your dose to 1 mg once a day at week 2. The dose may 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 with insufficient improvement, the dose may be increased gradually up to a maximum of 4 mg daily. After three months of treatment with Ropinirole Hydrochloride Tablets, your doctor may adjust your dose or discontinue your treatment depending on your symptoms and how you feel.
- Take Ropinirole Hydrochloride Tablets once a day by mouth, every day at about the same time each day. Ropinirole Hydrochloride Tablets is usually taken just before bedtime, but can be taken up to 3 hours before going to bed.
- Swallow the Ropinirole Hydrochloride Tablets whole with water. Taking Ropinirole Hydrochloride Tablets with food may decrease the occurrence of nausea (feeling sick), which is a possible side effect of Ropinirole Hydrochloride Tablets. Do not chew the tablet(s).
- 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 Hydrochloride Tablets 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 Hydrochloride Tablets than you should:
If you have taken more Ropinirole Hydrochloride Tablets than you were told to, or if someone else has taken any Ropinirole Hydrochloride Tablets contact accident and emergency department of your nearest hospital. Take any left over tablets or empty box with you for further identification.

If you forget to take Ropinirole Hydrochloride Tablets:
Do not take a double dose to make up for the forgotten dose, take you next dose as usual and continue you course. If you have missed taking Ropinirole Hydrochloride Tablets for more than a few days consult your doctor for advice on restarting Ropinirole Hydrochloride Tablets.

If you stop taking Ropinirole Hydrochloride Tablets:
If your symptoms worsen after you stop treatment with Ropinirole Hydrochloride Tablets, you should contact your doctor. If you have any further questions on the use of this product, ask your doctor or pharmacist.

4. Possible side effects
Like all medicines, Ropinirole Hydrochloride Tablets can cause side effects, although not everybody gets them. Possible side effects are listed under headings of frequency, using the following categories: very common: affects more than 1 user in 10, common: affects 1 to 10 users in 100, uncommon: affects 1 to 10 users in 1,000, rare: affects 1 to 10 users in 10,000, very rare: affects less than 1 user in 10,000, not known: frequency cannot be estimated from the available data.

Very common side effects (affects more than 1 user in 10):
- Vomiting
- Nausea (feeling or being sick)

Common side effects (affects 1 to 10 users in 100):
- Fatigue (tiredness, weakness)
- Dizziness (including vertigo)
- Feeling drowsy
- Stomach pain
- Nervousness
- Fainting

Uncommon side effects (affects 1 to 10 users in 1,000):
- Hypotension (Reduce the blood pressure)
- Postural hypotension (Decrease in blood pressure while sitting or standing)
- Feeling confused
- Hallucinations (Emergence of surprising or warded-off memory or fantasy images)

Very rare side effects (affects less than 1 user in 10,000):
- Altered liver function
- Delirious (severe confusion)
- Excessive daytime somnolence (excessive drowsiness)
- Illusions (false ideas)
- Sudden sleep onset episodes
- Paranoid (excessive anxiety or fear)

There are some reports of patients treated for Parkinson’s disease with medicinal products of this group of substance (dopamine agonists) who showed pathological compulsive gambling or compulsive and excessive sexual drive. These adverse effects were reversible when doses were reduced or treatment was stopped.
PAR Ropinirole 0.25mg, 0.5mg, 1mg and 2mg Film-Coated Tablets

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.

5. How to store Ropinirole Hydrochloride Tablets

- Keep out of the reach and sight of children.
- Do not use Ropinirole Hydrochloride Tablets after the expiry date which is stated on the carton or bottle after (exp). The expiry date refers to last day of that month.
- Do not store above 25°C.
- For HDPE container: Shelf-life after date of first opening is 6 months.
- 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.

6. Further information

What Ropinirole Hydrochloride Tablets contain:

The active substance is Ropinirole. Each film-coated tablet contains 2mg ropinirole (as hydrochloride).

Core Tablets: Lactose monohydrate, cellulose microcrystalline, croscarmellose sodium, magnesium stearate.

Film coat:
Hypromellose 6cp (E464), macrogol 400, titanium dioxide (E171), iron oxide yellow (E172), iron oxide red (E172),

What Ropinirole Hydrochloride Tablets looks like and content of the pack:

2 mg tablets are pink, round, biconvex, film coated tablets plain on both sides.

Ropinirole Hydrochloride Tablets are packed in blister packs and in bottle packs as follows:

The tablets are packed in blisters of 63’s counts packed in a carton with package leaflet

Ropinirole 2 mg Tablets are packed in HDPE bottles of 84’s counts with silica gel canister and packed in a carton with a package insert.

Marketing Authorisation Holder and Manufacturer

Marketing Authorisation Holder:
Intas Pharmaceuticals Limited, Sage House 319 Pinner Road, North Harrow, Middlesex, HA1 4HF UK

Manufacturer:
Accord Healthcare Limited, Sage House 319 Pinner Road, North Harrow, Middlesex, HA1 4HF UK

This medicinal product is authorized in the Member States of the EEA under the following names:

<table>
<thead>
<tr>
<th>Name of the member state</th>
<th>Name of the medicinal product</th>
</tr>
</thead>
<tbody>
<tr>
<td>UK</td>
<td>Ropinirole 2mg Film coated Tablets</td>
</tr>
<tr>
<td>Germany</td>
<td>Ropinirol Intas 2mg Filmtabletten</td>
</tr>
<tr>
<td>Spain</td>
<td>Ropinirole Intas 2mg Comprimidos EFG</td>
</tr>
</tbody>
</table>

The leaflet was last approved in.

To be completed nationally.
Module 4
Labelling

The labelling below is the label agreed at the end of the decentralised procedure. The marketing authorisation holder has stated that it is not intending to market either product and, thus, no UK-specific documents have been submitted. The marketing authorisation holder has committed to submit the UK PIL and labelling for review to the regulatory authority before marketing either product.

Blister:

MINIMUM PARTICULARS TO APPEAR ON BLISTERS [PVC/PVdC-Al Blister]

1. **NAME OF THE MEDICINAL PRODUCT**
   
   Ropinirole 0.25mg Film coated Tablets
   Ropinirole

2. **NAME OF THE MARKETING AUTHORISATION HOLDER**
   
   Intas Pharmaceuticals Limited

3. **EXPIRY DATE**
   
   EXP:

4. **BATCH NUMBER**
   
   LOT:

5. **OTHER**
PARTICULARS TO APPEAR ON <THE OUTER PACKAGING>{Carton}

1. **NAME OF THE MEDICINAL PRODUCT**
   Ropinirole 0.25mg Film coated Tablets
   Ropinirole

2. **STATEMENT OF ACTIVE SUBSTANCE (S)**
   Each film-coated tablet contains 0.25 mg ropinirole (as hydrochloride).

3. **LIST OF EXCIPIENTS**
   Contains lactose
   
   See the package leaflet for further information.

4. **PHARMACEUTICAL FORM AND CONTENTS**
   Film-coated tablet.
   
   42’s counts

5. **METHOD AND ROUTE (S) OF ADMINISTRATION**
   Oral use.
   
   Read the package leaflet before use.

6. **SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN**
   Keep out of the reach and sight of children.

7. **OTHER SPECIAL WARNING (S), IF NECESSARY**

8. **EXPIRY DATE**
   EXP:

9. **SPECIAL STORAGE CONDITIONS**
   Do not store above 25° C.
10. **SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCT OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**

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

11. **NAME AND ADDRESS OF MARKETING AUTHORISATION HOLDER**

Intas Pharmaceuticals Limited  
Sage House 319 Pinner Road  
North Harrow  
Middlesex HA1 4HF  
UK

12. **MARKETING AUTHORISATION NUMBER (S)**

PL 30139/0001

13. **BATCH NUMBER**

LOT:

14. **GENERAL CLASSIFICATION FOR SUPPLY**

POM

15. **INSTRUCTION ON USE**

16. **INFORMATION IN BRAILLE**

<Invented Name>
Labeling:

PARTICULARS TO APPEAR ON <THE IMMEDIATE PACKING> {HDPE BOTTLE}

1. **NAME OF THE MEDICINAL PRODUCT**
   Ropinirole 0.25mg Film coated Tablets
   Ropinirole

2. **STATEMENT OF ACTIVE SUBSTANCE (S)**
   Each film-coated tablet contains 0.25 mg ropinirole (as hydrochloride).

3. **LIST OF EXCIPIENTS**
   Contains lactose.
   See the package leaflet for further information.

4. **PHARMACEUTICAL FORM AND CONTENT**
   Film-coated tablet.
   84’s counts

5. **METHOD AND ROUTE(S) OF ADMINISTRATION**
   Oral use.
   Read the package leaflet before use.

6. **SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN**
   Keep out of the reach and sight of children.

7. **OTHER SPECIAL WARNING(S), IF NECESSARY**

8. **EXPIRY DATE**
   EXP:
   Shelf-life after date of first opening: 6 months.

9. **SPECIAL STORAGE CONDITIONS**
   Do not store above 25°C.
10. **SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**

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

11. **NAME AND ADDRESS OF MARKETING AUTHORIZATION HOLDER**

Intas Pharmaceuticals Limited  
Sage House 319 Pinner Road  
North Harrow  
Middlesex HA1 4HF  
UK

12. **MARKETING AUTHORIZATION NUMBER(S)**

PL 30139/0001

13. **BATCH NUMBER**

LOT:

14. **GENERAL CLASSIFICATION FOR SUPPLY**

POM

15. **INSTRUCTION ON USE**

16. **INFORMATION IN BRAILLE**

<Invented Name>
Labelling:

**PARTICULARS TO APPEAR ON <THE IMMEDIATE PACKING>**

| Outer carton |

1. **NAME OF THE MEDICINAL PRODUCT**
   Ropinirole 0.25mg Film coated Tablets
   Ropinirole

2. **STATEMENT OF ACTIVE SUBSTANCE (S)**
   Each film-coated tablet contains 0.25 mg ropinirole (as hydrochloride).

3. **LIST OF EXCIPIENTS**
   Contains Lactose.
   See the package leaflet for further information.

4. **PHARMACEUTICAL FORM AND CONTENT**
   Film-coated tablet.
   84’s counts

5. **METHOD AND ROUTE(S) OF ADMINISTRATION**
   Oral use.
   Read the package leaflet before use.

6. **SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN**
   Keep out of the reach and sight of children.

7. **OTHER SPECIAL WARNING(S), IF NECESSARY**

8. **EXPIRY DATE**
   EXP:
   Shelf-life after date of first opening: 6 months.

9. **SPECIAL STORAGE CONDITIONS**
   Do not store above 25° C.
10. **SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**

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

11. **NAME AND ADDRESS OF MARKETING AUTHORISATION HOLDER**

Intas Pharmaceuticals Limited  
Sage House 319 Pinner Road  
North Harrow  
Middlesex HA1 4HF  
UK

12. **MARKETING AUTHORISATION NUMBER(S)**

PL 30139/0001

13. **BATCH NUMBER**

LOT:

14. **GENERAL CLASSIFICATION FOR SUPPLY**

POM

15. **INSTRUCTION ON USE**

16. **INFORMATION IN BRAILLE**

< Invented Name>
Blister:

MINIMUM PARTICULARS TO APPEAR ON BLISTERS {PVC/PVdC-Al Blister}:

1. **NAME OF THE MEDICINAL PRODUCT**
   - Ropinirole 0.5mg Film coated Tablets
   - Ropinirole

2. **NAME OF THE MARKETING AUTHORISATION HOLDER**
   - Intas Pharmaceuticals Limited

3. **EXPIRY DATE**
   - EXP:

4. **BATCH NUMBER**
   - LOT:

5. **OTHER**
PARTICULARS TO APPEAR ON <THE OUTER PACKAGING>[Carton]

1. **NAME OF THE MEDICINAL PRODUCT**
   
   Ropinirole 0.5mg Film coated Tablets  
   Ropinirole

2. **STATEMENT OF ACTIVE SUBSTANCE (S)**
   
   Each film-coated tablet contains 0.5 mg ropinirole (as hydrochloride).

3. **LIST OF EXCIPIENTS**
   
   Contains lactose  
   
   See the package leaflet for further information.

4. **PHARMACEUTICAL FORM AND CONTENTS**
   
   Film-coated tablet.  
   
   Count’s 42 tablets

5. **METHOD AND ROUTE (S) OF ADMINISTRATION**
   
   Oral use.  
   
   Read the package leaflet before use.

6. **SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN**
   
   Keep out of the reach and sight of children.

7. **OTHER SPECIAL WARNING (S), IF NECESSARY**

8. **EXPIRY DATE**
   
   EXP:

9. **SPECIAL STORAGE CONDITIONS**
   
   Do not store above 25° C.
10. **SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCT OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**

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

11. **NAME AND ADDRESS OF MARKETING AUTHORISATION HOLDER**

Intas Pharmaceuticals Limited  
Sage House 319 Pinner Road  
North Harrow  
Middlesex HA1 4HF  
UK

12. **MARKETING AUTHORISATION NUMBER(S)**

PL 30139/0002

13. **BATCH NUMBER**

LOT:

14. **GENERAL CLASSIFICATION FOR SUPPLY**

POM

15. **INSTRUCTION ON USE**

16. **INFORMATION IN BRAILLE**

<Invented Name>
**Labeling:**

<table>
<thead>
<tr>
<th>PARTICULARS TO APPEAR ON &lt;THE IMMEDIATE PACKING&gt; [HDPE BOTTLE]</th>
</tr>
</thead>
</table>

1. **NAME OF THE MEDICINAL PRODUCT**
   Ropinirole 0.5mg Film coated Tablets
   Ropinirole

2. **STATEMENT OF ACTIVE SUBSTANCE (S)**
   Each film-coated tablet contains 0.5 mg ropinirole (as hydrochloride).

3. **LIST OF EXCIPIENTS**
   Contains lactose.
   See the package leaflet for further information.

4. **PHARMACEUTICAL FORM AND CONTENT**
   Film-coated tablet.
   84’s counts

5. **METHOD AND ROUTE(S) OF ADMINISTRATION**
   Oral use.
   Read the package leaflet before use.

6. **SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN**
   Keep out of the reach and sight of children.

7. **OTHER SPECIAL WARNING(S), IF NECESSARY**

8. **EXPIRY DATE**
   EXP.
   Shelf-life after date of first opening: 6 months.

9. **SPECIAL STORAGE CONDITIONS**
   Do not store above 25° C.
10. **SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**

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

11. **NAME AND ADDRESS OF MARKETING AUTHORISATION HOLDER**

Intas Pharmaceuticals Limited
Sage House 319 Pinner Road
North Harrow
Middlesex HA1 4HF
UK

12. **MARKETING AUTHORISATION NUMBER(S)**

PL 30139/0002

13. **BATCH NUMBER**

LOT:

14. **GENERAL CLASSIFICATION FOR SUPPLY**

POM

15. **INSTRUCTION ON USE**

16. **INFORMATION IN BRAILLE**

<Invented name>
**Labeling:**

<table>
<thead>
<tr>
<th>PARTICULARS TO APPEAR ON &lt;THE IMMEDIATE PACKING&gt; {Outer carton}</th>
</tr>
</thead>
</table>

1. **NAME OF THE MEDICINAL PRODUCT**
   - Ropinirole 0.5mg Film coated Tablets
   - Ropinirole

2. **STATEMENT OF ACTIVE SUBSTANCE(S)**
   - Each film-coated tablet contains 0.5 mg ropinirole (as hydrochloride).

3. **LIST OF EXCPIENTS**
   - Contains lactose.
   - See the package leaflet for further information.

4. **PHARMACEUTICAL FORM AND CONTENT**
   - Film-coated tablet.
   - 84's counts

5. **METHOD AND ROUTE(S) OF ADMINISTRATION**
   - Oral use.
   - Read the package leaflet before use.

6. **SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN**
   - Keep out of the reach and sight of children.

7. **OTHER SPECIAL WARNING(S), IF NECESSARY**

8. **EXPIRY DATE**
   - EXP:
   - Shelf-life after date of first opening: 6 months.

9. **SPECIAL STORAGE CONDITIONS**
   - Do not store above 25° C.
10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

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

11. NAME AND ADDRESS OF MARKETING AUTHORISATION HOLDER

Intas Pharmaceuticals Limited
Sage House 319 Pinner Road
North Harrow
Middlesex HA1 4HF
UK

12. MARKETING AUTHORISATION NUMBER(S)

PL 30139/0002

13. BATCH NUMBER

LOT:

14. GENERAL CLASSIFICATION FOR SUPPLY

POM

15. INSTRUCTION ON USE

16. INFORMATION IN BRAILLE

<Invented name>
Blister:

**MINIMUM PARTICULARS TO APPEAR ON BLISTERS {PVC/PVdC-Al Blister}**

1. **NAME OF THE MEDICINAL PRODUCT**
   
   Ropinirole 1mg Film coated Tablets
   Ropinirole

2. **NAME OF THE MARKETING AUTHORISATION HOLDER**
   
   Intas Pharmaceuticals Limited

3. **EXPIRY DATE**
   
   EXP:

4. **BATCH NUMBER**
   
   LOT:

5. **OTHER**
PARTICULARS TO APPEAR ON <THE OUTER PACKAGING> [Carton]

1. **NAME OF THE MEDICINAL PRODUCT**
   
   Ropinirole 1mg Film coated Tablets
   Ropinirole

2. **STATEMENT OF ACTIVE SUBSTANCE (S)**
   
   Each film-coated tablet contains 1 mg ropinirole (as hydrochloride).

3. **LIST OF EXCIPIENTS**
   
   Contains lactose

   See the package leaflet for further information.

4. **PHARMACEUTICAL FORM AND CONTENTS**

   Film-coated tablet.

   21’s counts
   42’s counts

   Not all pack sizes may be marketed.

5. **METHOD AND ROUTE(S) OF ADMINISTRATION**

   Oral use.

   Read the package leaflet before use.

6. **SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN**

   Keep out of the reach and sight of children.

7. **OTHER SPECIAL WARNING (S), IF NECESSARY**

8. **EXPIRY DATE**

   EXP:

9. **SPECIAL STORAGE CONDITIONS**

   Do not store above 25°C.
10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCT OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

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

11. NAME AND ADDRESS OF MARKETING AUTHORISATION HOLDER

Intas Pharmaceuticals Limited
Sage House 319 Pinner Road
North Harrow
Middlesex HA1 4HF
UK

12. MARKETING AUTHORISATION NUMBER (S)

PL 30139/0003

13. BATCH NUMBER

LOT:

14. GENERAL CLASSIFICATION FOR SUPPLY

POM

15. INSTRUCTION ON USE

16. INFORMATION IN BRAILLE

<Invented Name>
Labeling:

PARTICULARS TO APPEAR ON <THE IMMEDIATE PACKING>{HDPE BOTTLE}

1. NAME OF THE MEDICINAL PRODUCT

Ropinirole 1mg Film coated Tablets
Ropinirole

2. STATEMENT OF ACTIVE SUBSTANCE (S)

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

3. LIST OF EXCIPIENTS

Contains lactose.

See the package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENT

Film-coated tablet.

84’s counts

5. METHOD AND ROUTE (S) OF ADMINISTRATION

Oral use.

Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING (S), IF NECESSARY

8. EXPIRY DATE

EXP:
Shelf-life after date of first opening: 6 months.

9. SPECIAL STORAGE CONDITIONS

Do not store above 25° C.
10. **SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**

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

11. **NAME AND ADDRESS OF MARKETING AUTHORISATION HOLDER**

Intas Pharmaceuticals Limited
Sage House 319 Pinner Road
North Harrow
Middlesex HA1 4HF
UK

12. **MARKETING AUTHORISATION NUMBER(S)**

PL 30139/0003

13. **BATCH NUMBER**

LOT:

14. **GENERAL CLASSIFICATION FOR SUPPLY**

POM

15. **INSTRUCTION ON USE**

16. **INFORMATION IN BRAILLE**

<Invented name>
Labeling:

PARTICULARS TO APPEAR ON <THE IMMEDIATE PACKING>{Outer carton}

1. **NAME OF THE MEDICINAL PRODUCT**
   
   Ropinirole 1mg Film coated Tablets
   
   Ropinirole

2. **STATEMENT OF ACTIVE SUBSTANCE (S)**
   
   Each film-coated tablet contains 1 mg ropinirole (as hydrochloride).

3. **LIST OF EXCIPIENTS**
   
   Contains lactose.
   
   See the package leaflet for further information.

4. **PHARMACEUTICAL FORM AND CONTENT**
   
   Film-coated tablet.
   
   84's counts

5. **METHOD AND ROUTE (S) OF ADMINISTRATION**
   
   Oral use.
   
   Read the package leaflet before use.

6. **SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN**
   
   Keep out of the reach and sight of children.

7. **OTHER SPECIAL WARNING (S), IF NECESSARY**

8. **EXPIRY DATE**
   
   EXP:
   
   Shelf-life after date of first opening: 6 months.

9. **SPECIAL STORAGE CONDITIONS**
   
   Do not store above 25° C.
10. **SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**

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

11. **NAME AND ADDRESS OF MARKETING AUTHORISATION HOLDER**

Intas Pharmaceuticals Limited  
Sage House 319 Pinner Road  
North Harrow  
Middlesex HA1 4HF  
UK

12. **MARKETING AUTHORISATION NUMBER(S)**

PL 30139/0003

13. **BATCH NUMBER**

LOT:

14. **GENERAL CLASSIFICATION FOR SUPPLY**

POM

15. **INSTRUCTION ON USE**

16. **INFORMATION IN BRAILLE**

<i>Invented name></i>
Blister:

MINIMUM PARTICULARS TO APPEAR ON BLISTERS (PVC/PVdC-Al Blister)

1. NAME OF THE MEDICINAL PRODUCT
   Ropinirole 2mg Film coated Tablets
   Ropinirole

2. NAME OF THE MARKETING AUTHORISATION HOLDER
   Intas Pharmaceuticals Limited

3. EXPIRY DATE
   EXP:

4. BATCH NUMBER
   LOT:

5. OTHER
Par Ropinirole 0.25mg, 0.5mg, 1mg and 2mg Film-Coated Tablets

Carton:

PARTICULARS TO APPEAR ON <THE OUTER PACKAGING> {Carton}

1. **NAME OF THE MEDICINAL PRODUCT**
   
   Ropinirole 2mg Film coated Tablets
   
   Ropinirole

2. **STATEMENT OF ACTIVE SUBSTANCE(S)**
   
   Each film-coated tablet contains 2 mg of ropinirole hydrochloride.

3. **LIST OF EXCIPIENTS**
   
   Contains lactose
   
   See the package leaflet for further information.

4. **PHARMACEUTICAL FORM AND CONTENTS**
   
   Film-coated tablet.
   
   63's counts

5. **METHOD AND ROUTE(S) OF ADMINISTRATION**
   
   Oral use.
   
   Read the package leaflet before use.

6. **SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN**
   
   Keep out of the reach and sight of children.

7. **OTHER SPECIAL WARNING(S), IF NECESSARY**

8. **EXPIRY DATE**
   
   EXP:

9. **SPECIAL STORAGE CONDITIONS**
   
   Do not store above 25° C.
10. **SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCT OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**

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

11. **NAME AND ADDRESS OF MARKETING AUTHORISATION HOLDER**

Intas Pharmaceuticals Limited  
Sage House 319 Pinner Road  
North Harrow  
Middlesex HA1 4HF  
UK

12. **MARKETING AUTHORISATION NUMBER(S)**

PL 30139/0004

13. **BATCH NUMBER**

LOT:

14. **GENERAL CLASSIFICATION FOR SUPPLY**

POM

15. **INSTRUCTION ON USE**

16. **INFORMATION IN BRAILLE**

<Invented Name>
Labeling:

**PARTICULARS TO APPEAR ON THE IMMEDIATE PACKING (HDPE BOTTLE)**

1. **NAME OF THE MEDICINAL PRODUCT**
   Ropinirole 2mg Film coated Tablets
   Ropinirole

2. **STATEMENT OF ACTIVE SUBSTANCE(S)**
   Each film-coated tablet contains 2 mg ropinirole (as hydrochloride).

3. **LIST OF EXCIPIENTS**
   Contains lactose.
   
   See the package leaflet for further information.

4. **PHARMACEUTICAL FORM AND CONTENT**
   Film-coated tablet.
   84's counts

5. **METHOD AND ROUTE(S) OF ADMINISTRATION**
   Oral use.
   
   Read the package leaflet before use.

6. **SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN**
   Keep out of the reach and sight of children.

7. **OTHER SPECIAL WARNING(S), IF NECESSARY**

8. **EXPIRY DATE**
   EXP:
   Shelf-life after date of first opening: 6 months.

9. **SPECIAL STORAGE CONDITIONS**
   Do not store above 25° C.
10. **SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**

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

11. **NAME AND ADDRESS OF MARKETING AUTHORISATION HOLDER**

Intas Pharmaceuticals Limited
Sage House 319 Pinner Road
North Harrow
Middlesex HA1 4HF
UK

12. **MARKETING AUTHORISATION NUMBER(S)**

PL 30139/0004

13. **BATCH NUMBER**

LOT:

14. **GENERAL CLASSIFICATION FOR SUPPLY**

POM

15. **INSTRUCTION ON USE**

16. **INFORMATION IN BRAILLE**

<Invented name>
Labeling:

PARTICULARS TO APPEAR ON <THE IMMEDIATE PACKING>{Outer carton}

1. **NAME OF THE MEDICINAL PRODUCT**
   
   Ropinirole 2mg Film coated Tablets
   Ropinirole

2. **STATEMENT OF ACTIVE SUBSTANCE (S)**
   
   Each film-coated tablet contains 2 mg ropinirole (as hydrochloride).

3. **LIST OF EXCIPIENTS**
   
   Contains lactose.

   See the package leaflet for further information.

4. **PHARMACEUTICAL FORM AND CONTENT**
   
   Film-coated tablet.

   84's counts

5. **METHOD AND ROUTE(S) OF ADMINISTRATION**
   
   Oral use.

   Read the package leaflet before use.

6. **SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN**
   
   Keep out of the reach and sight of children.

7. **OTHER SPECIAL WARNING(S), IF NECESSARY**

8. **EXPIRY DATE**
   
   EXP:
   Shelf-life after date of first opening: 6 months.

9. **SPECIAL STORAGE CONDITIONS**
   
   Do not store above 25°C.
10. **SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**

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

11. **NAME AND ADDRESS OF MARKETING AUTHORISATION HOLDER**

Intas Pharmaceuticals Limited  
Sage House 319 Pinner Road  
North Harrow  
Middlesex HA1 4HF  
UK

12. **MARKETING AUTHORISATION NUMBER(S)**

PL 30139/0004

13. **BATCH NUMBER**

LOT:

14. **GENERAL CLASSIFICATION FOR SUPPLY**

POM

15. **INSTRUCTION ON USE**

16. **INFORMATION IN BRAILLE**

<Invented name>
Module 5
Scientific discussion during initial procedure

I  INTRODUCTION

Based on the review of the data on quality, safety and efficacy, Germany, Spain and the UK considered that the applications for Ropinirole 0.25mg, 0.5mg, 1mg and 2mg Film-Coated Tablets could be approved. These products are prescription only medicines (POM) for the symptomatic treatment of moderate to severe idiopathic Restless Legs Syndrome.

These applications for Ropinirole 0.25mg, 0.5mg, 1mg and 2mg Film-Coated Tablets are submitted as abridged applications according to Article 10.1 of Directive 2001/83/EC, claiming to be generic medicinal products to Adartrel 0.25mg, 0.5mg, 1mg and 2mg Film-Coated Tablets, first authorised in the UK to GlaxoSmithKline UK Limited since May 2006.

These products contain the active substance ropinirole (as hydrochloride), a non-ergoline dopamine agonist. Ropinirole stimulates striatal dopamine receptors. Ropinirole acts in the hypothalamus and pituitary to inhibit the secretion of prolactin.

No new preclinical studies were conducted, which is acceptable given that the products contain a widely-used, well-known active substance. No clinical studies with the exception of the bioequivalence study have been performed and none are required for these applications as the pharmacology of ropinirole is well-established.

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.

For manufacturing sites outside the community, the RMS has accepted copies of current GMP Certificates or satisfactory inspection summary reports, ‘close-out letters’ or ‘exchange of information’ issued by the inspection services of the competent authorities (or those countries with which the EEA has a Mutual Recognition Agreement for their own territories) as certification that acceptable standards of GMP are in place at those non-Community sites.
## II. ABOUT THE PRODUCT

<table>
<thead>
<tr>
<th>Name of the product in the Reference Member State</th>
<th>Ropinirole 0.25mg, 0.5mg, 1mg and 2mg Film-Coated Tablets</th>
</tr>
</thead>
<tbody>
<tr>
<td>Name(s) of the active substance(s) (INN)</td>
<td>Ropinirole hydrochloride</td>
</tr>
<tr>
<td>Pharmacotherapeutic classification (ATC code)</td>
<td>Dopamine agonist (N04BC04)</td>
</tr>
<tr>
<td>Pharmaceutical form and strength(s)</td>
<td>0.25mg, 0.5mg, 1mg and 2mg Film-Coated Tablets</td>
</tr>
<tr>
<td>Reference numbers for the Decentralised Procedure</td>
<td>UK/H/1094/001-4/DC</td>
</tr>
<tr>
<td>Reference Member State</td>
<td>United Kingdom</td>
</tr>
<tr>
<td>Member States concerned</td>
<td>Germany and Spain</td>
</tr>
<tr>
<td>Marketing Authorisation Number(s)</td>
<td>PL 30139/0001-4</td>
</tr>
<tr>
<td>Name and address of the authorisation holder</td>
<td>Intas Pharmaceuticals Limited</td>
</tr>
<tr>
<td></td>
<td>Sage House, 319 Pinner Road, Harrow, Middlesex, HA1 4HG</td>
</tr>
</tbody>
</table>
III SCIENTIFIC OVERVIEW AND DISCUSSION

III.1 QUALITY ASPECTS

S. Active substance

INN/Ph.Eur name: Ropinirole
Chemical name: 4-[2-(dipropylamino)ethyl]-1,3-dihydro-2H-indol-2-one hydrochloride
2H-Indol-2-one, 4-[2-(dipropylamino)ethyl]-1,3-dihydro-, monohydrochloride

Structural formula:

\[
\text{\textbf{\begin{figure}[h]
\centering
\includegraphics[width=0.5\textwidth]{structured_formula.png}
\end{figure}}}
\]

Molecular formula: \( \text{C}_{16}\text{H}_{24}\text{N}_2\text{OHCl} \)

Appearance: Pale yellow or greenish powder.
Freely soluble in water, soluble in methanol, slightly soluble in ethanol and very slightly soluble in acetone.

Molecular formula: \( \text{C}_{16}\text{H}_{24}\text{N}_2\text{OHCl} \)
Molecular weight: 296.84
Chirality: This structure does not have a chiral centre.

Ropinirole hydrochloride complies with in-house specifications.

Synthesis of the drug substance from the designated starting materials has been adequately described, and appropriate in-process controls and intermediate specifications are applied.

Satisfactory specification tests are in place for all starting materials and reagents, and these are supported by relevant certificates of analysis.

All potential known impurities have been identified and characterised. Appropriate proof of structure data has been supplied for the active pharmaceutical ingredient.

An appropriate specification is provided for the active substance ropinirole, with suitable test methods and limits. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications. Batch analysis data are provided and comply with the proposed specification.

Satisfactory specifications and certificates of analysis have been provided all aspects of the container-closure system. A declaration has been provided that the primary packaging complies with current regulations concerning contact with foodstuff.

Appropriate proof-of-structure data have been supplied for the active pharmaceutical ingredient. All potential known impurities have been identified and characterised. Suitable certificates of analysis have been provided for all reference standards used.
Appropriate stability data have been generated showing the active substance to be a physically and chemically stable drug, and supporting an appropriate retest period.

P. Medicinal Product

Other Ingredients
Other ingredients consist of pharmaceutical excipients lactose monohydrate, croscarmellose sodium, microcrystalline cellulose, water purified, magnesium stearate. All excipients within the tablet comply with their relevant European Pharmacopoeia monographs. The tablet coating contains Opadry 13B58802 white, which complies with in-house specifications.

With the exception of lactose monohydrate, none of the excipients used contain material of animal or human origin. The applicant has provided a declaration that milk used in the production of lactose monohydrate is sourced from healthy animals under the same conditions as those intended for human consumption. No genetically modified organisms (GMO) have been used in the preparation of this product.

Magnesium stearate is sourced from vegetable origin and therefore a European Pharmacopoeia Certificate of suitability for TSE in not required.

Pharmaceutical Development
The objective of the development programme was to produce products that could be considered generic medicinal products of Requip 0.25mg, 0.5mg, 1mg and 2mg Film-Coated Tablets (GlaxoSmithKline Pharmaceuticals).

The reference product used in the bioequivalence study is qualitatively and quantitatively identical to the UK reference product.

The applicant has provided suitable product development sections. Justifications for the use and amounts of each excipient have been provided and are valid. Comparative impurity profiles have been provided for the finished products versus the reference products of Requip 0.25mg, 0.5mg, 1mg and 2mg Film-Coated Tablets (GlaxoSmithKline Pharmaceuticals).

Comparative in vitro dissolution profiles and impurity profiles have been provided for the proposed and originator products.

Manufacturing Process
Satisfactory batch formulae have been provided for the manufacture of the products, along with an appropriate account of the manufacturing process. The manufacturing process has been validated and has shown satisfactory results. Process validation data on three pilot scale batches per strength have been provided. The applicant has committed to perform process validation with the future commercial batches of the drug products.

Finished Product Specification
The finished product specification proposed for the products is acceptable. Test methods have been described and have been adequately validated, as appropriate. Batch data have been provided and comply with the release specifications. Certificates of analysis have been provided for any working standards used.
Container-Closure System
These products are packaged either in blister packs composed of aluminium or bottles composed of white high-density polyethylene (HDPE) with polypropylene (PP) closures and silica gel as desiccant.
For the 0.25mg and 0.5mg strength, the products are packaged in sizes of 42 tablets for the blister packs and 84 tablets for the bottles.
For the 1mg strength, the product is packaged in sizes of 21 and 42 tablets for the blister packs and 84 tablets for the bottles.
For the 2mg strength, the product is packaged in sizes of 63 tablets for the blister packs and 84 tablets for the bottles.

Satisfactory specifications and certificates of analysis have been provided for all packaging components. All primary product packaging complies with EU legislation regarding contact with food.

Stability of the product
Stability studies were performed on batches of the finished products in the packaging proposed for marketing and in accordance with current guidelines. These data support a shelf-life of two years for an unopened product with the storage conditions “Do not store above 25°C”.
There is a shelf-life of six months for the bottled product after first opening.

Summary of Product Characteristics (SPC), Patient Information Leaflet (PIL), Labels
The SPCs, PILs and labelling are pharmaceutically acceptable.
User testing results have been submitted for typical PILs for these products. The results indicate that the PILs are well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that the patients/users are able to act upon the information that they contain.

MAA forms
The MAA forms are pharmaceutically satisfactory.

Expert report
The pharmaceutical expert report has been written by an appropriately qualified person and is a suitable summary of the pharmaceutical dossier.

Conclusion
It is recommended that Marketing Authorisations are granted for these applications.

III.2 PRE-CLINICAL ASPECTS
The pharmacodynamics, pharmacokinetics and toxicological properties of ropinirole are well-known. As ropinirole is a widely used, well-known active substance, the applicant has not provided any additional studies and none are required.

The pre-clinical expert report has been written by an appropriately qualified person and is a suitable summary of the pre-clinical aspects of the dossier.
III.3 CLINICAL ASPECTS

1. Introduction
This assessment report represents an evaluation of the key elements of the information provided by the company in the dossier. For more details, the reader should refer to the company’s clinical overview and summary and to the clinical file.

The clinical overview has been written by an appropriately qualified physician. The clinical overview on the clinical pharmacology, efficacy and safety is adequate.

2. Clinical study reports
To support these applications, the marketing authorisation holder has submitted one single dose bioequivalence study.

Open-label, balanced, randomised, two- treatment, two-sequence, two-period, single-dose, crossover bioequivalence study of Ropinirole hydrochloride 0.25mg tablets versus Requip® 0.25mg Tablets, (GlaxoSmithKline GmbH, Germany) in healthy, adult, male, human subjects under fasting conditions.

All subjects were in a fasted state before dosing. Blood sampling was performed pre- and at 0.25, 0.5, 0.75, 1, 1.25, 1.5, 1.75, 2, 2.5, 3, 4, 5, 6, 7, 8, 10, 12, 16, 20 and 24 hours post dose in each treatment period. There was a washout period of 7 days. Pharmacokinetic parameters were measured from the plasma and statistically analysed.

Results from this study are presented below as log-transformed values:

<table>
<thead>
<tr>
<th>Treatment</th>
<th>AUC&lt;sub&gt;0-t&lt;/sub&gt; (ng/ml/h)</th>
<th>AUC&lt;sub&gt;0-∞&lt;/sub&gt; (ng/ml/h)</th>
<th>C&lt;sub&gt;max&lt;/sub&gt; (ng/ml)</th>
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<tbody>
<tr>
<td>Ropinirole:</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Test</td>
<td>4.6565</td>
<td>4.9207</td>
<td>0.6864</td>
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<tr>
<td>Reference</td>
<td>4.7761</td>
<td>5.0206</td>
<td>0.7111</td>
</tr>
<tr>
<td>Ratio (90% CI)</td>
<td>(91.42-103.98%)</td>
<td>(91.82-104.62%)</td>
<td>(91.60-101.74%)</td>
</tr>
</tbody>
</table>

The results for the primary variables indicated that the 90% confidence intervals test/reference ratio of geometric means for AUC<sub>0-t</sub> and C<sub>max</sub> for ropinirole lie within 80-125% boundaries. Thus, bioequivalence has been shown between the test and reference products in this study.

The MAH gave the following justification for the use of the lower dose strength of 0.25mg for the bioequivalence study:

According to the literatures the adverse effects of Ropinirole make even small doses of Ropinirole difficult to tolerate in healthy volunteers who have normal levels of dopamine. Therefore, the choice of the lowest strength (0.25mg) to be used in the bioequivalence study is justified on safety grounds.

Ropinirole has a broader therapeutic window than other dopamine agonists, so that an increase in dose is more likely to lead to an increase in the therapeutic response. Ropinirole is extensively metabolized by the liver to inactive metabolites and displays linear kinetics over the therapeutic dosing range of 0.25 to 24 mg/day.
The method used for the analysis of the samples was sensitive enough to quantify the plasma concentration of drug obtained for the samples in the study conducted using 0.25 mg dosage strength. The method was also validated for the concentration range (calibration curve) used for this study.

These justifications were considered satisfactory and the use of the 0.25mg dose strength for the bioequivalence study was accepted.

As 0.25mg, 0.5mg, 1mg and 2mg strength products meet all the criteria as specified in the Note for Guidance on the Investigation of Bioavailability and Bioequivalence (CPMP/EWP/QWP/1401/98), the results and conclusions of the bioequivalence study on the 0.25mg strength qualify for an extrapolation to the higher strengths.

3. **Post marketing experience**
Ropinirole has a well-recognised efficacy and an acceptable level of safety in the indications approved for Adartrel 0.25mg, 0.5mg, 1mg and 2mg Film-Coated Tablets and corresponding products have been widely used in many countries. Therefore, the submission of PSUR at the renewal of the marketing authorisations is supported.

4. **Benefit-Risk assessment**
The quality of the products is acceptable and no new preclinical or clinical safety concerns have been identified. The data supplied supports the claim that the applicant’s products and the innovator products are interchangeable. Extensive clinical experience with ropinirole is considered to have demonstrated the therapeutic value of the compound. The risk benefit is, therefore, considered to be positive.

5. **Conclusions**
The grant of marketing authorisations for Ropinirole 0.25mg, 0.5mg, 1mg and 2mg Film-Coated Tablets is recommended from a clinical viewpoint.
IV OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

QUALITY

The important quality characteristics of Ropinirole 0.25mg, 0.5mg, 1mg and 2mg Film-Coated Tablets are well-defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

PRECLINICAL

No new preclinical data were submitted and none are required for an application of this type.

EFFICACY

Bioequivalence has been demonstrated between the applicant’s Ropinirole 0.25mg, 0.5mg, 1mg and 2mg Film-Coated Tablets and the originator products Requip 0.25mg, 0.5mg, 1mg and 2mg Film-Coated Tablets (GlaxoSmithKline Pharmaceuticals).

No new or unexpected safety concerns arise from these applications.

The SPCs, PILs and labelling are satisfactory and consistent with that for the innovator products.

RISK-BENEFIT ASSESSMENT

The quality of the products is acceptable and no new preclinical or clinical safety concerns have been identified. Extensive clinical experience with ropinirole is considered to have demonstrated the therapeutic value of the compound. The risk benefit is, therefore, considered to be positive.
# Module 5

## STEPS TAKEN AFTER INITIAL PROCEDURE - SUMMARY

<table>
<thead>
<tr>
<th>Date submitted</th>
<th>Application type</th>
<th>Scope</th>
<th>Outcome</th>
</tr>
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<tbody>
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