Public Assessment Report

Decentralised Procedure

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

Ropinirole hydrochloride

UK/H/3489/001-5/DC

UK licence no: PL 29831/0412-4 and 0416-7

Wockhardt UK Limited
Lay Summary

On 20th January 2011, the Concerned Member States (CMSs) and the Reference Member State (RMS) agreed to grant Marketing Authorisations to Wockhardt UK Ltd for the medicinal products Ropinirole 0.25, 0.5, 1, 2, and 5mg Film-coated Tablets. The marketing authorisations were granted via the Decentralised Procedure (DCP), with the UK as Reference Member State (RMS). After the national phase, a licence was granted in the UK on 10th February 2011. These medicines are only available on prescription from your doctor.

The active ingredient in Ropinirole Tablets is ropinirole which belongs to a group of medicines called dopamine agonists. Dopamine agonists affect the brain in a similar way to natural substance called dopamine.

Ropinirole Tablets are used to treat:

- Parkinson’s disease. People with Parkinson’s disease have low levels of dopamine in some parts of their brains. Ropinirole has effects similar to those of natural dopamine, so it helps to reduce the symptoms of Parkinson’s disease.
- Moderate to severe Restless Legs Syndrome. People with Restless Legs Syndrome have an irresistible urge to move their legs, and sometimes their arms and other parts of their body. Usually, they have unpleasant sensations in their limbs-sometimes described as ‘crawling’ or ‘bubbling’-which can begin as soon as they sit or lie down, and are relieved only by movement. So they often have problems with sitting still, and especially with sleeping. Ropinirole relieves the unpleasant sensations, and so reduces the urge to move the legs and the limbs.

No new or unexpected safety concerns arose from these applications and it was, therefore, judged that the benefits of taking Ropinirole 0.25, 0.5, 1, 2, and 5mg Film-coated Tablets outweigh the risks, hence Marketing Authorisations have been granted.
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V. Overall conclusion and Benefit-Risk Assessment

Module 6  Steps taken after initial procedure
# Module 1

<table>
<thead>
<tr>
<th><strong>Product Name</strong></th>
<th>Ropinirole 0.25, 0.5mg, 1mg, 2mg and 5 mg 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>0.25, 0.5, 1, 2 and 5 mg, Film-coated Tablets</td>
</tr>
</tbody>
</table>
| **MA Holder** | Wockhardt UK Ltd  
Ash Road North, Wrexham Industrial Estate, Wrexham, LL13 9UF. United Kingdom |
| **RMS** | UK                                                           |
| **CMS** | Cyprus, Germany and Malta                                     |
| **Procedure Numbers** | UK/H/3489/001-5/DC                                             |
| **Timetable** | Day 210 – 20\textsuperscript{th} January 2011               |
Module 2
SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT
Ropinirole 0.25mg Film-Coated Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
One film-coated tablet contains 0.285mg ropinirole hydrochloride, equivalent to 0.25mg ropinirole.

Excipients: Lactose monohydrate – 118.6mg
For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Film-coated tablet.

White, irregular hexagonal shape film-coated tablets, debossed with ‘W’ on one side and ‘154’ on the other side.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications
Treatment of Parkinson's Disease under the following conditions:

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

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

4.2 Posology and method of administration

Route of administration
Oral use.

Treatment of idiopathic Parkinson’s Disease

Adults
Individual dose titration against efficacy and tolerability is recommended.

Ropinirole should be taken three times a day (t.i.d.), preferably with meals to improve gastrointestinal tolerance.

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

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

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

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

Doses of ropinirole above 24 mg/day have not been studied.
If treatment is interrupted for one day or more, re-initiation by dose titration should be considered (see above).

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

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

As with other dopamine agonists, it is necessary to discontinue ropinirole treatment gradually by reducing the number of daily doses over the period of one week.

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

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

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

A study into the use of ropinirole in patients with end stage renal disease (patients on haemodialysis) has shown that a dose adjustment in these patients is required as follows: the initial dose of Ropinirole Tablets should be 0.25 mg three times a day. Further dose escalations should be based on tolerability and efficacy. The recommended maximum dose of Ropinirole Tablets is 18 mg/day in patients receiving regular haemodialysis. Supplemental doses after haemodialysis are not required (see section 5.2).

The use of ropinirole in patients with severe renal (creatinine clearance <30ml/min) or hepatic impairment impairment has not been studied.

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

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

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

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

The dose may be increased to 1 mg once a day at week 2. The dose may then be increased by 0.5 mg per week over the next two weeks to a dose of 2 mg once a day. In some patients, to achieve optimal improvement, the dose may be increased gradually up to a maximum of 4 mg once a day. In clinical trials the dose was increased by 0.5 mg each week to 3 mg once a day and then by 1 mg up to the maximum recommended dose of 4 mg once a day as shown in 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 adolescents
Ropinirole is not recommended for use in children below 18 years of age due to a lack of data on safety
and efficacy.

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

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

A study into the use of ropinirole in patients with end stage renal disease (patients on haemodialysis)
has shown that a dose adjustment in these patients is required as follows: the recommended initial dose
of Ropinirole Tablets is 0.25 mg once daily. Further dose escalations should be based on tolerability and
efficacy. The recommended maximum dose of Ropinirole Tablets is 3 mg/day in patients receiving
regular haemodialysis. Supplemental doses after haemodialysis are not required (see section 5.2).

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

4.3 Contraindications
Hypersensitivity to the active substance or to any of the excipients.
Severe renal impairment (creatinine clearance <30ml/min) without regular haemodialysis.

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).

Paradoxical worsening of Restless Legs Syndrome symptoms described as augmentation (either earlier
onset, increased intensity, or spread of symptoms to previously unaffected limbs), or early morning
rebound, (reoccurrence of symptoms in the early morning hours) have been observed during treatment
with ropinirole. If this occurs, the adequacy of ropinirole treatment should be reviewed and dosage
adjustment or discontinuation of treatment may be considered (see section 4.8).

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

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

Impulse control disorders including pathological gambling, increased libido and hypersexuality have
been reported in patients treated with dopamine agonists, including ropinirole, principally for
Parkinson’s disease. These 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).
Due to the risk of hypotension, blood pressure monitoring is recommended, particularly at the beginning of treatment, in patients with severe cardiovascular disease (in particular coronary insufficiency).

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

Excipients:
The tablets contain lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

There is no pharmacokinetic interaction between ropinirole and levodopa or domperidone which would necessitate dosage adjustment of this 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 drugs with ropinirole should be avoided.

Increased plasma concentrations of ropinirole have been observed in patients treated with high doses of oestrogens. In patients already receiving hormone replacement therapy (HRT), ropinirole treatment may be initiated in the normal manner. However, it may be necessary to adjust the ropinirole dose, in accordance with clinical response, if HRT is stopped or introduced during treatment with ropinirole.

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 in patients with Parkinson’s disease 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.

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.

No information is available on the potential for interaction between ropinirole and alcohol. As with other centrally active medications, patients should be cautioned against taking ropinirole with alcohol.

4.6 Pregnancy and lactation

Pregnancy
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 fetus.

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

4.7 Effects on ability to drive and use machines

Patients should be warned about the possibility of dizziness (including vertigo). Patients being treated with ropinirole and presenting with somnolence and/or sudden sleep episodes must be informed to refrain from driving or engaging in activities where impaired alertness may put themselves or others at
risk of serious injury or death (e.g. operating machines) until such recurrent episodes and somnolence have resolved (see also Section 4.4).

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

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

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

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

<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>Frequency</th>
<th>Adverse Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Immune System Disorders</strong></td>
<td>not known</td>
<td>Hypersensitivity reactions (including urticaria, angioedema, rash, pruritis)</td>
</tr>
<tr>
<td><strong>Psychiatric disorders</strong></td>
<td>common</td>
<td>confusion¹, hallucinations</td>
</tr>
<tr>
<td></td>
<td>uncommon</td>
<td>Psychotic reactions (other than hallucinations), including delusion, paranoia, delirium. Impulse control disorders including pathological gambling and hypersexuality, and increased libido, have been reported in post-marketing reports (see section 4.4)</td>
</tr>
<tr>
<td><strong>Nervous system disorders</strong></td>
<td>very common</td>
<td>Syncope², somnolence, dyskinesia¹¹</td>
</tr>
<tr>
<td></td>
<td>common</td>
<td>dizziness (including vertigo),</td>
</tr>
<tr>
<td></td>
<td>uncommon</td>
<td>extreme daytime somnolence, sudden onset of sleep.</td>
</tr>
<tr>
<td><strong>Vascular disorders</strong></td>
<td>Uncommon</td>
<td>hypotension, postural hypotension</td>
</tr>
<tr>
<td></td>
<td></td>
<td>postural hypotension or hypotension is rarely severe</td>
</tr>
<tr>
<td><strong>Gastrointestinal disorders</strong></td>
<td>very common</td>
<td>nausea</td>
</tr>
<tr>
<td></td>
<td>common</td>
<td>abdominal pain¹, vomiting², heartburn</td>
</tr>
<tr>
<td><strong>Hepatobiliary disorders</strong></td>
<td>not known</td>
<td>hepatic reactions, hepatic enzymes increased</td>
</tr>
<tr>
<td><strong>General disorders and administrative site conditions</strong></td>
<td>common</td>
<td>leg oedema¹</td>
</tr>
</tbody>
</table>

**Adjunct therapy studies**
**Monotherapy studies**
* In patients with advanced Parkinson’s disease, dyskinesias can occur during the initial titration of ropinirole. In clinical trials it was shown that a reduction of the L-dopa dose may ameliorate dyskinesia (see also section 4.2)

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

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

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

<table>
<thead>
<tr>
<th>Nervous system disorders</th>
<th>Syncope, somnolence, dizziness (including vertigo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Common</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Vascular disorders</th>
<th>Postural hypotension, hypotension</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uncommon</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Gastrointestinal disorders</th>
<th>Vomiting, nausea</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very common</td>
<td></td>
</tr>
<tr>
<td>Common</td>
<td>Abdominal pain</td>
</tr>
</tbody>
</table>

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

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

**5 PHARMACOLOGICAL PROPERTIES**

**5.1 Pharmacodynamic properties**
Pharmacotherapeutic group: Dopaminergic agents, dopamine agonists, ATC code: N04BC04

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

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

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

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

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

Although sufficient data are not available to adequately demonstrate the long term efficacy of ropinirole in Restless Legs Syndrome (see section 4.2), in a 36-week study, patients who continued on ropinirole demonstrated a significantly lower relapse rate compared with patients randomised to placebo (33% versus 58%, p=0.0156).

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

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

In clinical studies most patients were of Caucasian origin.

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

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

5.2 Pharmacokinetic properties
Absorption
The bioavailability of ropinirole is about 50% (36% to 57%). Oral absorption of ropinirole film-coated (immediate-release) tablets is rapid with peak concentrations of ropinirole achieved at a median time of 1.5 hours post-dose. A high fat meal decreases the rate of absorption of ropinirole, as shown by a delay in median T_{max} by 2.6 hours and an average 25% decrease in C_{max}.

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

Metabolism
Ropinirole is primarily cleared by the cytochrome P450 enzyme, CYP1A2, and its metabolites are mainly excreted in the urine. The major metabolite is at least 100 times less potent than ropinirole in animal models of dopaminergic function.

Elimination
Ropinirole is cleared from the systemic circulation with an average elimination half-life of approximately 6 hours. No change in the oral clearance of ropinirole is observed following single and repeated oral administration. Wide inter-individual variability in the pharmacokinetic parameters has been observed.

Renal Impairment
There was no change observed in the pharmacokinetics of ropinirole in Parkinson’s disease patients with mild to moderate renal impairment.
In patients with end stage renal disease receiving regular haemodialysis, oral clearance of ropinirole is reduced by approximately 30%. Oral clearance of the metabolites SKF-104557 and SKF-89124 were also reduced by approximately 80% and 60%, respectively. Therefore, the recommended maximum dose is limited to 18 mg/day in these patients with Parkinson’s disease (see section 4.2).

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

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

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

### 5.3 Preclinical safety data

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

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

**Carcinogenicity**
From two-year studies conducted in the mouse and rat at dosages up to 50 mg/kg/day there was no evidence of any carcinogenic effect in the mouse. In the rat, the only ropinirole-related lesions were Leydig cell hyperplasia and testicular adenoma resulting from the hypoprolactinaemic effect of ropinirole. These lesions are considered to be a species specific phenomenon and do not constitute a hazard with regard to the clinical use of ropinirole.

**Reproductive Toxicity**
Administration of ropinirole to pregnant rats at maternally toxic doses resulted in decreased fetal body weight at 60 mg/kg/day (approximately twice the AUC at the maximum dose in humans), increased fetal death at 90 mg/kg/day (approximately 3 times the AUC at the maximum dose in humans) and digit malformations at 150 mg/kg/day (approximately 5 times the AUC at the maximum dose in humans). There were no teratogenic effects in the rat at 120 mg/kg/day (approximately 4 times the AUC at the maximum dose in humans) and no indication of an effect on development in the rabbit.

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

### 6 PHARMACEUTICAL PARTICULARS

#### 6.1 List of excipients

**Tablet core:**
- Lactose monohydrate
- Microcrystalline cellulose
- Croscarmellose sodium
- Hypromellose (6cps)
- Magnesium stearate

**Film coat (opadry white 03B28796):**
- Hypromellose 6cps
- Titanium dioxide (E171)
- Macrogol

#### 6.2 Incompatibilities

Not applicable.
6.3 **Shelf life**
Blisters: 18 months
HDPE bottles: 18 months. After first opening of the bottle use the medicinal product within one month.

6.4 **Special precautions for storage**
Blisters: Store below 25°C. Store in the original package (blister) in order to protect from moisture.
HDPE bottles: Store below 25°C. Keep the bottle tightly closed in order to protect from moisture.

6.5 **Nature and contents of container**
ALU/ALU blister packs of 12, 28 or 100 tablets
HDPE container with child resistant closure of 30 or 84 tablets.
Not all pack sizes may be marketed

6.6 **Special precautions for disposal**
No special requirements.

7 **MARKETING AUTHORISATION HOLDER**
Wockhardt UK Ltd
Ash Road North
Wrexham
LL13 9UF
UK

8 **MARKETING AUTHORISATION NUMBER(S)**
PL 29831/0412

9 **DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**
10/02/2011

10 **DATE OF REVISION OF THE TEXT**
10/02/2011
1 NAME OF THE MEDICINAL PRODUCT
Ropinirole 0.5mg Film-Coated Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
One film-coated tablet contains 0.57mg ropinirole hydrochloride, equivalent to 0.5mg ropinirole.

Excipients:
Lactose monohydrate – 118.3mg
For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Film-coated tablet.

Yellow, irregular hexagonal shape film-coated tablets, debossed with ‘W’ on one side and ‘155’ on the other side.

4 CLINICAL PARTICULARS
4.1 Therapeutic indications
Treatment of Parkinson’s Disease under the following conditions:

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

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

4.2 Posology and method of administration
Route of administration
Oral use.

Treatment of idiopathic Parkinson’s Disease
Adults
Individual dose titration against efficacy and tolerability is recommended.

Ropinirole should be taken three times a day (t.i.d.), preferably with meals to improve gastrointestinal tolerance.

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

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

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

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

Doses of ropinirole above 24 mg/day have not been studied.

If treatment is interrupted for one day or more, re-initiation by dose titration should be considered (see above).
When ropinirole is administered as adjunct therapy to L-dopa, the concurrent dose of L-dopa may be reduced gradually according to the symptomatic response. In clinical trials, the levodopa dose was reduced gradually by around 20% in patients treated with ropinirole as adjunct therapy. In patients with advanced Parkinson’s disease receiving ropinirole in combination with L-dopa, dyskinesias can occur during the initial titration of ropinirole. In clinical trials it was shown that a reduction of the levodopa dose may ameliorate dyskinesia (see section 4.8).

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

As with other dopamine agonists, it is necessary to discontinue ropinirole treatment gradually by reducing the number of daily doses over the period of one week.

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

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

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

A study into the use of ropinirole in patients with end stage renal disease (patients on haemodialysis) has shown that a dose adjustment in these patients is required as follows: the initial dose of Ropinirole Tablets should be 0.25 mg three times a day. Further dose escalations should be based on tolerability and efficacy. The recommended maximum dose of Ropinirole Tablets is 18 mg/day in patients receiving regular haemodialysis. Supplemental doses after haemodialysis are not required (see section 5.2).

The use of ropinirole in patients with severe renal (creatinine clearance <30ml/min) or hepatic impairment has not been studied.

Symptomatic treatment of moderate to severe idiopathic Restless Legs Syndrome

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

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

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

The dose may be increased to 1 mg once a day at week 2. The dose may then be increased by 0.5 mg per week over the next two weeks to a dose of 2 mg once a day. In some patients, to achieve optimal improvement, the dose may be increased gradually up to a maximum of 4 mg once a day. In clinical trials the dose was increased by 0.5 mg each week to 3 mg once a day and then by 1 mg up to the maximum recommended dose of 4 mg once a day as shown in 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 adolescents**
Ropinirole is not recommended for use in children below 18 years of age due to a lack of data on safety and efficacy.

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

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

A study into the use of ropinirole in patients with end stage renal disease (patients on haemodialysis) has shown that a dose adjustment in these patients is required as follows: the recommended initial dose of Ropinirole Tablets is 0.25 mg once daily. Further dose escalations should be based on tolerability and efficacy. The recommended maximum dose of Ropinirole Tablets is 3 mg/day in patients receiving regular haemodialysis. Supplemental doses after haemodialysis are not required (see section 5.2).

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

### 4.3 Contraindications
Hypersensitivity to the active substance or to any of the excipients.

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

Hepatic impairment.

### 4.4 Special warnings and precautions for use
Ropinirole should not be used to treat neuroleptic akathisia, tics, or secondary Restless Legs Syndrome (e.g. caused by renal failure, iron deficiency anaemia or pregnancy).

Paradoxical worsening of Restless Legs Syndrome symptoms described as augmentation (either earlier onset, increased intensity, or spread of symptoms to previously unaffected limbs), or early morning rebound, (reoccurrence of symptoms in the early morning hours) have been observed during treatment with ropinirole. If this occurs, the adequacy of ropinirole treatment should be reviewed and dosage adjustment or discontinuation of treatment may be considered (see section 4.8).

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

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

Impulse control disorders including pathological gambling, increased libido and hypersexuality have been reported in patients treated with dopamine agonists, including ropinirole, principally for Parkinson’s disease. These 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).

Due to the risk of hypotension, blood pressure monitoring is recommended, particularly at the beginning of treatment, in patients with severe cardiovascular disease (in particular coronary insufficiency).
Co-administration of ropinirole with anti-hypertensive and anti-arrhythmic agents has not been studied. Caution should be exercised when these compounds are given concomitantly with ropinirole because of the unknown potential for the occurrence of hypotension, bradycardias or other arrhythmias.

Excipients:
The tablets contain lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

There is no pharmacokinetic interaction between ropinirole and levodopa or domperidone which would necessitate dosage adjustment of this 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 drugs with ropinirole should be avoided.

Increased plasma concentrations of ropinirole have been observed in patients treated with high doses of oestrogens. In patients already receiving hormone replacement therapy (HRT), ropinirole treatment may be initiated in the normal manner. However, it may be necessary to adjust the ropinirole dose, in accordance with clinical response, if HRT is stopped or introduced during treatment with ropinirole.

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 in patients with Parkinson’s disease 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.

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.

No information is available on the potential for interaction between ropinirole and alcohol. As with other centrally active medications, patients should be cautioned against taking ropinirole with alcohol.

4.6 Pregnancy and lactation

Pregnancy

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 fetus.

Lactation

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

4.7 Effects on ability to drive and use machines

Patients should be warned about the possibility of dizziness (including vertigo). Patients being treated with ropinirole and presenting with somnolence and/or sudden sleep episodes must be informed to refrain from driving or engaging in activities where impaired alertness may put themselves or others at risk of serious injury or death (e.g. operating machines) until such recurrent episodes and somnolence have resolved (see also Section 4.4).
4.8 Undesirable effects

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

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

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

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

<table>
<thead>
<tr>
<th>Immune System Disorders</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>not known</td>
<td>Hypersensitivity reactions (including urticaria, angioedema, rash, pruritis)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Psychiatric disorders</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>common</td>
<td>confusion¹, hallucinations</td>
</tr>
<tr>
<td>uncommon</td>
<td>Psychotic reactions (other than hallucinations), including delusion, paranoia, delirium. Impulse control disorders including pathological gambling and hypersexuality, and increased libido, have been reported in post-marketing reports (see section 4.4)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Nervous system disorders</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>very common</td>
<td>Syncope², somnolence, dyskinesia¹*</td>
</tr>
<tr>
<td>common</td>
<td>dizziness (including vertigo),</td>
</tr>
<tr>
<td>uncommon</td>
<td>extreme daytime somnolence, sudden onset of sleep,</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Vascular disorders</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Uncommon</td>
<td>hypotension, postural hypotension</td>
</tr>
<tr>
<td></td>
<td>postural hypotension or hypotension is rarely severe</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Gastrointestinal disorders</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>very common</td>
<td>nausea</td>
</tr>
<tr>
<td>common</td>
<td>abdominal pain¹, vomiting², heartburn</td>
</tr>
</tbody>
</table>

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

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

Adjunct therapy studies
Monotherapy studies
* In patients with advanced Parkinson’s disease, dyskinesias can occur during the initial titration of ropinirole. In clinical trials it was shown that a reduction of the L-dopa dose may ameliorate dyskinesia (see also section 4.2)

**Use of ropinirole in Restless Legs Syndrome**

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

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

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

### 4.9 Overdose

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

### 5 PHARMACOLOGICAL PROPERTIES

#### 5.1 Pharmacodynamic properties

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

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

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

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

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

A 12-week placebo-controlled polysomnography study in Restless Legs Syndrome patients examined the effect of treatment with ropinirole on periodic leg movements of sleep. A statistically significant
A 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.

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

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

5.2 Pharmacokinetic properties
Absorption
The bioavailability of ropinirole is about 50% (36% to 57%). Oral absorption of ropinirole film-coated (immediate-release) tablets is rapid with peak concentrations of ropinirole achieved at a median time of 1.5 hours post-dose. A high fat meal decreases the rate of absorption of ropinirole, as shown by a delay in median T\text{max} by 2.6 hours and an average 25% decrease in C\text{max}.

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

Metabolism
Ropinirole is primarily cleared by the cytochrome P450 enzyme, CYP1A2, and its metabolites are mainly excreted in the urine. The major metabolite is at least 100 times less potent than ropinirole in animal models of dopaminergic function.

Elimination
Ropinirole is cleared from the systemic circulation with an average elimination half-life of approximately 6 hours. No change in the oral clearance of ropinirole is observed following single and repeated oral administration. Wide inter-individual variability in the pharmacokinetic parameters has been observed.

Renal Impairment
There was no change observed in the pharmacokinetics of ropinirole in Parkinson’s disease patients with mild to moderate renal impairment.

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

**Linearity**
The pharmacokinetics of ropinirole are linear overall (C<sub>max</sub> 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 ropinirole: behavioural changes, hypoprolactinaemia, decrease in blood pressure and heart rate, ptosis and salivation. In the albino rat only, retinal degeneration was observed in a long term study at the highest dose (50 mg/kg/day), and was probably associated with an increased exposure to light.

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

#### Carcinogenicity
From two-year studies conducted in the mouse and rat at dosages up to 50 mg/kg/day there was no evidence of any carcinogenic effect in the mouse. In the rat, the only ropinirole-related lesions were Leydig cell hyperplasia and testicular adenoma resulting from the hypoprolactinaemic effect of ropinirole. These lesions are considered to be a species specific phenomenon and do not constitute a hazard with regard to the clinical use of ropinirole.

#### Reproductive Toxicity
Administration of ropinirole to pregnant rats at maternally toxic doses resulted in decreased fetal body weight at 60 mg/kg/day (approximately twice the AUC at the maximum dose in humans), increased fetal death at 90 mg/kg/day (approximately 3 times the AUC at the maximum dose in humans) and digit malformations at 150 mg/kg/day (approximately 5 times the AUC at the maximum dose in humans). There were no teratogenic effects in the rat at 120 mg/kg/day (approximately 4 times the AUC at the maximum dose in humans) and no indication of an effect on development in the rabbit.

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

### 6 PHARMACEUTICAL PARTICULARS

#### 6.1 List of excipients
**Tablet core:**
- Lactose monohydrate
- Microcrystalline cellulose
- Croscarmellose sodium
- Hypromellose (6cps)
- Magnesium stearate

**Film coat (opadry yellow 03B52117)**
- Hypromellose 6cps
- Titanium dioxide (E171)
- Macrogol
- Iron oxide yellow (E172)

#### 6.2 Incompatibilities
Not applicable.
6.3 **Shelf life**
Blisters: 18 months

HDPE bottles: 18 months. After first opening of the bottle use the medicinal product within one month.

6.4 **Special precautions for storage**
Blisters: Store below 25°C. Store in the original package (blister) in order to protect from moisture.

HDPE bottles: Store below 25°C. Keep the bottle tightly closed in order to protect from moisture.

6.5 **Nature and contents of container**
ALU/ALU blister packs of 12, 28 or 100 tablets

HDPE container with child resistant closure of 30 or 84 tablets.

Not all pack sizes may be marketed.

6.6 **Special precautions for disposal**
No special requirements.

7 **MARKETING AUTHORISATION HOLDER**
Wockhardt UK Ltd
Ash Road North
Wrexham
LL13 9UF
UK

8 **MARKETING AUTHORISATION NUMBER(S)**
PL 29831/0413

9 **DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**
10/02/2011

10 **DATE OF REVISION OF THE TEXT**
10/02/2011
1 NAME OF THE MEDICINAL PRODUCT
Ropinirole 1mg Film-Coated Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
One film-coated tablet contains 1.14mg ropinirole hydrochloride, equivalent to 1mg ropinirole.

Excipients: Lactose monohydrate – 117.7mg
For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Film-coated tablet.

Green, irregular hexagonal shape film-coated tablets, debossed with ‘W’ on one side and ‘171’ on the other side.

4 CLINICAL PARTICULARS
4.1 Therapeutic indications
Treatment of Parkinson’s Disease under the following conditions:

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

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

4.2 Posology and method of administration

Route of administration
Oral use.

Treatment of idiopathic Parkinson’s Disease
Adults
Individual dose titration against efficacy and tolerability is recommended.

Ropinirole should be taken three times a day (t.i.d.), preferably with meals to improve gastrointestinal tolerance.

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

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

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

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

Doses of ropinirole above 24 mg/day have not been studied.

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

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

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

As with other dopamine agonists, it is necessary to discontinue ropinirole treatment gradually by reducing the number of daily doses over the period of one week.

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

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

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

A study into the use of ropinirole in patients with end stage renal disease (patients on haemodialysis) has shown that a dose adjustment in these patients is required as follows: the initial dose of Ropinirole Tablets should be 0.25 mg three times a day. Further dose escalations should be based on tolerability and efficacy. The recommended maximum dose of Ropinirole Tablets is 18 mg/day in patients receiving regular haemodialysis. Supplemental doses after haemodialysis are not required (see section 5.2).

The use of ropinirole in patients with severe renal (creatinine clearance <30ml/min) or hepatic impairment impairment has not been studied.

Symptomatic treatment of moderate to severe idiopathic Restless Legs Syndrome

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

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

Therapeutic regimen (week 2 onwards)
Following treatment initiation, the daily dose should be increased until optimal therapeutic response is achieved. The average dose in clinical trials, in patients with moderate to severe Restless Legs Syndrome, was 2 mg once a day. The dose may be increased to 1 mg once a day at week 2. The dose may then be increased by 0.5 mg per week over the next two weeks to a dose of 2 mg once a day. In some patients, to achieve optimal improvement, the dose may be increased gradually up to a maximum of 4 mg once a day. In clinical trials the dose was increased by 0.5 mg each week to 3 mg once a day and then by 1 mg up to the maximum recommended dose of 4 mg once a day as shown in 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 adolescents
Ropinirole is not recommended for use in children below 18 years of age due to a lack of data on safety and efficacy.

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

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

A study into the use of ropinirole in patients with end stage renal disease (patients on haemodialysis) has shown that a dose adjustment in these patients is required as follows: the recommended initial dose of Ropinirole Tablets is 0.25 mg once daily. Further dose escalations should be based on tolerability and efficacy. The recommended maximum dose of Ropinirole Tablets is 3 mg/day in patients receiving regular haemodialysis. Supplemental doses after haemodialysis are not required (see section 5.2).

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

4.3 Contraindications
Hypersensitivity to the active substance or to any of the excipients.

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

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).

Paradoxical worsening of Restless Legs Syndrome symptoms described as augmentation (either earlier onset, increased intensity, or spread of symptoms to previously unaffected limbs), or early morning rebound, (reoccurrence of symptoms in the early morning hours) have been observed during treatment with ropinirole. If this occurs, the adequacy of ropinirole treatment should be reviewed and dosage adjustment or discontinuation of treatment may be considered (see section 4.8).

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

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

Impulse control disorders including pathological gambling, increased libido and hypersexuality have been reported in patients treated with dopamine agonists, including ropinirole, principally for Parkinson’s disease. These 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).

Due to the risk of hypotension, blood pressure monitoring is recommended, particularly at the beginning of treatment, in patients with severe cardiovascular disease (in particular coronary insufficiency).
Co-administration of ropinirole with anti-hypertensive and anti-arrhythmic agents has not been studied. Caution should be exercised when these compounds are given concomitantly with ropinirole because of the unknown potential for the occurrence of hypotension, bradycardias or other arrhythmias.

Excipients:
The tablets contain lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

There is no pharmacokinetic interaction between ropinirole and levodopa or domperidone which would necessitate dosage adjustment of this 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 drugs with ropinirole should be avoided.

Increased plasma concentrations of ropinirole have been observed in patients treated with high doses of oestrogens. In patients already receiving hormone replacement therapy (HRT), ropinirole treatment may be initiated in the normal manner. However, it may be necessary to adjust the ropinirole dose, in accordance with clinical response, if HRT is stopped or introduced during treatment with ropinirole.

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 $C_{\text{max}}$ and AUC of ropinirole by 60% and 84% respectively, with a potential risk of adverse events. Hence, in patients already receiving ropinirole, the dose of ropinirole may need to be adjusted when medicinal products known to inhibit CYP1A2, e.g. ciprofloxacin, enoxacin or fluvoxamine, are introduced or withdrawn.

A pharmacokinetic interaction study in patients with Parkinson’s disease between ropinirole (at a dose of 2 mg, three times a day) and theophylline, a substrate of CYP1A2, revealed no change in the pharmacokinetics of either ropinirole or theophylline.

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.

No information is available on the potential for interaction between ropinirole and alcohol. As with other centrally active medications, patients should be cautioned against taking ropinirole with alcohol.

4.6 Pregnancy and lactation

Pregnancy
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 fetus.

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

4.7 Effects on ability to drive and use machines

Patients should be warned about the possibility of dizziness (including vertigo). Patients being treated with ropinirole and presenting with somnolence and/or sudden sleep episodes must be informed to refrain from driving or engaging in activities where impaired alertness may put themselves or others at risk of serious injury or death (e.g. operating machines) until such recurrent episodes and somnolence have resolved (see also Section 4.4).
4.8 Undesirable effects

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

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

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

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

<table>
<thead>
<tr>
<th>Immune System Disorders</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>not known</td>
<td>Hypersensitivity reactions (including urticaria, angioedema, rash, pruritis)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Psychiatric disorders</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>common</td>
<td>confusion¹, hallucinations</td>
</tr>
<tr>
<td>uncommon</td>
<td>Psychotic reactions (other than hallucinations), including delusion, paranoia, delirium. Impulse control disorders including pathological gambling and hypersexuality, and increased libido, have been reported in post-marketing reports (see section 4.4)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Nervous system disorders</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>very common</td>
<td>Syncope², somnolence, dyskinesia¹*</td>
</tr>
<tr>
<td>common</td>
<td>dizziness (including vertigo),</td>
</tr>
<tr>
<td>uncommon</td>
<td>extreme daytime somnolence, sudden onset of sleep.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Vascular disorders</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Uncommon</td>
<td>hypotension, postural hypotension, postural hypotension or hypotension is rarely severe</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Gastrointestinal disorders</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>very common</td>
<td>nausea</td>
</tr>
<tr>
<td>common</td>
<td>abdominal pain¹, vomiting⁴, heartburn</td>
</tr>
</tbody>
</table>

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

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

Adjunct therapy studies
Monotherapy studies

* In patients with advanced Parkinson’s disease, dyskinesias can occur during the initial titration of ropinirole. In clinical trials it was shown that a reduction of the L-dopa dose may ameliorate dyskinesia (see also section 4.2)

**Use of ropinirole in Restless Legs Syndrome**

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

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

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

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

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

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

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

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

5 PHARMACOLOGICAL PROPERTIES
5.1 Pharmacodynamic properties
Pharmacotherapeutic group: Dopaminergic agents, dopamine agonists, ATC code: N04BC04

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

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

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

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

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

A 12-week placebo-controlled polysomnography study in Restless Legs Syndrome patients examined the effect of treatment with ropinirole on periodic leg movements of sleep. A statistically significant
difference in the periodic leg movements of sleep was seen between ropinirole and placebo from baseline to week 12.

Although sufficient data are not available to adequately demonstrate the long term efficacy of ropinirole in Restless Legs Syndrome (see section 4.2), in a 36-week study, patients who continued on ropinirole demonstrated a significantly lower relapse rate compared with patients randomised to placebo (33% versus 58%, p=0.0156).

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

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

In clinical studies most patients were of Caucasian origin.

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

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

5.2 Pharmacokinetic properties

Absorption
The bioavailability of ropinirole is about 50% (36% to 57%). Oral absorption of ropinirole film-coated (immediate-release) tablets is rapid with peak concentrations of ropinirole achieved at a median time of 1.5 hours post-dose. A high fat meal decreases the rate of absorption of ropinirole, as shown by a delay in median T\text{max}\text{ by 2.6 hours} and an average 25% decrease in C\text{max}.

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

Metabolism
Ropinirole is primarily cleared by the cytochrome P450 enzyme, CYP1A2, and its metabolites are mainly excreted in the urine. The major metabolite is at least 100 times less potent than ropinirole in animal models of dopaminergic function.

Elimination
Ropinirole is cleared from the systemic circulation with an average elimination half-life of approximately 6 hours. No change in the oral clearance of ropinirole is observed following single and repeated oral administration. Wide inter-individual variability in the pharmacokinetic parameters has been observed.

Renal Impairment
There was no change observed in the pharmacokinetics of ropinirole in Parkinson’s disease patients with mild to moderate renal impairment.

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

**Linearity**
The pharmacokinetics of ropinirole are linear overall (C<sub>max</sub> 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 ropinirole;
behavioural changes, hypoprolactinaemia, decrease in blood pressure and heart rate, ptosis and
salivation. In the albino rat only, retinal degeneration was observed in a long term study at the highest
dose (50 mg/kg/day), and was probably associated with an increased exposure to light.

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

**Carcinogenicity**
From two-year studies conducted in the mouse and rat at dosages up to 50 mg/kg/day there was no
evidence of any carcinogenic effect in the mouse. In the rat, the only ropinirole-related lesions were
Leydig cell hyperplasia and testicular adenoma resulting from the hypoprolactinaemic effect of
ropinirole. These lesions are considered to be a species specific phenomenon and do not constitute a
hazard with regard to the clinical use of ropinirole.

**Reproductive Toxicity**
Administration of ropinirole to pregnant rats at maternally toxic doses resulted in decreased fetal body
weight at 60 mg/kg/day (approximately twice the AUC at the maximum dose in humans), increased
fetal death at 90 mg/kg/day (approximately 3 times the AUC at the maximum dose in humans) and
digit malformations at 150 mg/kg/day (approximately 5 times the AUC at the maximum dose in
humans). There were no teratogenic effects in the rat at 120 mg/kg/day (approximately 4 times the
AUC at the maximum dose in humans) and no indication of an effect on development in the rabbit.

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

### 6 PHARMACEUTICAL PARTICULARS

#### 6.1 List of excipients

**Tablet core:**
Lactose monohydrate  
Microcrystalline cellulose  
Crocarmellose sodium  
Hypermellose (6cps)  
Magnesium stearate

**Film coat (opadry green 03B21595):**
Hypermellose 6cps  
Titanium dioxide (E171)  
Macrogol  
Iron oxide yellow (E172)  
Indigo carmine aluminium lake (E132)

#### 6.2 Incompatibilities
Not applicable.
6.3 **Shelf life**
Blisters: 18 months
HDPE bottles: 18 months. After first opening of the bottle use the medicinal product within one month.

6.4 **Special precautions for storage**
Blisters: Store below 25°C. Store in the original package (blister) in order to protect from moisture.
HDPE bottles: Store below 25°C. Keep the bottle tightly closed in order to protect from moisture.

6.5 **Nature and contents of container**
ALU/ALU blister packs of 12, 28 or 100 tablets
HDPE container with child resistant closure of 30 or 84 tablets.
Not all pack sizes may be marketed.

6.6 **Special precautions for disposal**
No special requirements.

7 **MARKETING AUTHORISATION HOLDER**
Wockhardt UK Ltd
Ash Road North
Wrexham
LL13 9UF
UK

8 **MARKETING AUTHORISATION NUMBER(S)**
PL 29831/0414

9 **DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**
10/02/2011

10 **DATE OF REVISION OF THE TEXT**
10/02/2011
1 NAME OF THE MEDICINAL PRODUCT
Ropinirole 2mg Film-Coated Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
One film-coated tablet contains 2.28mg ropinirole hydrochloride, equivalent to 2mg ropinirole.

Excipients: Lactose monohydrate – 116.6mg
For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Film-coated tablet.
Pale yellowish pink, irregular hexagonal shape film-coated tablets, debossed with ‘W’ on one side and ‘172’ on the other side.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications
Treatment of Parkinson's Disease under the following conditions:

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

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

4.2 Posology and method of administration

Route of administration
Oral use.

Treatment of idiopathic Parkinson’s Disease

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

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

<table>
<thead>
<tr>
<th>Unit dose (mg)</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.25</td>
<td>0.25</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.25</td>
<td>0.25</td>
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<td>0.25</td>
<td>0.25</td>
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<td></td>
</tr>
<tr>
<td>0.75</td>
<td>0.75</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.75</td>
<td>1.0</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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

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

Doses of ropinirole above 24 mg/day have not been studied.

If treatment is interrupted for one day or more, re-initiation by dose titration should be considered (see above).
When ropinirole is administered as adjunct therapy to L-dopa, the concurrent dose of L-dopa may be reduced gradually according to the symptomatic response. In clinical trials, the levodopa dose was reduced gradually by around 20% in patients treated with ropinirole as adjunct therapy. In patients with advanced Parkinson’s disease receiving ropinirole in combination with L-dopa, dyskinesias can occur during the initial titration of ropinirole. In clinical trials it was shown that a reduction of the levodopa dose may ameliorate dyskinesia (see section 4.8).

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

As with other dopamine agonists, it is necessary to discontinue ropinirole treatment gradually by reducing the number of daily doses over the period of one week.

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

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

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

A study into the use of ropinirole in patients with end stage renal disease (patients on haemodialysis) has shown that a dose adjustment in these patients is required as follows: the initial dose of Ropinirole Tablets should be 0.25 mg three times a day. Further dose escalations should be based on tolerability and efficacy. The recommended maximum dose of Ropinirole Tablets is 18 mg/day in patients receiving regular haemodialysis. Supplemental doses after haemodialysis are not required (see section 5.2).

The use of ropinirole in patients with severe renal (creatinine clearance <30ml/min) or hepatic impairment has not been studied.

Symptomatic treatment of moderate to severe idiopathic Restless Legs Syndrome

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

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

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

The dose may be increased to 1 mg once a day at week 2. The dose may then be increased by 0.5 mg per week over the next two weeks to a dose of 2 mg once a day. In some patients, to achieve optimal improvement, the dose may be increased gradually up to a maximum of 4 mg once a day. In clinical trials the dose was increased by 0.5 mg each week to 3 mg once a day and then by 1 mg up to the maximum recommended dose of 4 mg once a day as shown in 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 adolescents
Ropinirole is not recommended for use in children below 18 years of age due to a lack of data on safety and efficacy.

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

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

A study into the use of ropinirole in patients with end stage renal disease (patients on haemodialysis) has shown that a dose adjustment in these patients is required as follows: the recommended initial dose of Ropinirole Tablets is 0.25 mg once daily. Further dose escalations should be based on tolerability and efficacy. The recommended maximum dose of Ropinirole Tablets is 3 mg/day in patients receiving regular haemodialysis. Supplemental doses after haemodialysis are not required (see section 5.2).

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

4.3 Contraindications
Hypersensitivity to the active substance or to any of the excipients.

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

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).

Paradoxical worsening of Restless Legs Syndrome symptoms described as augmentation (either earlier onset, increased intensity, or spread of symptoms to previously unaffected limbs), or early morning rebound, (reocurrence of symptoms in the early morning hours) have been observed during treatment with ropinirole. If this occurs, the adequacy of ropinirole treatment should be reviewed and dosage adjustment or discontinuation of treatment may be considered (see section 4.8).

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

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

Impulse control disorders including pathological gambling, increased libido and hypersexuality have been reported in patients treated with dopamine agonists, including ropinirole, principally for Parkinson’s disease. These 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).

Due to the risk of hypotension, blood pressure monitoring is recommended, particularly at the beginning of treatment, in patients with severe cardiovascular disease (in particular coronary insufficiency).
Co-administration of ropinirole with anti-hypertensive and anti-arrhythmic agents has not been studied. Caution should be exercised when these compounds are given concomitantly with ropinirole because of the unknown potential for the occurrence of hypotension, bradycardias or other arrhythmias.

Excipients:
The tablets contain lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction
There is no pharmacokinetic interaction between ropinirole and levodopa or domperidone which would necessitate dosage adjustment of this 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 sulphiride or metoclopramide, may diminish the effectiveness of ropinirole and, therefore, concomitant use of these drugs with ropinirole should be avoided.

Increased plasma concentrations of ropinirole have been observed in patients treated with high doses of oestrogens. In patients already receiving hormone replacement therapy (HRT), ropinirole treatment may be initiated in the normal manner. However, it may be necessary to adjust the ropinirole dose, in accordance with clinical response, if HRT is stopped or introduced during treatment with ropinirole.

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 in patients with Parkinson’s disease 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.

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.

No information is available on the potential for interaction between ropinirole and alcohol. As with other centrally active medications, patients should be cautioned against taking ropinirole with alcohol.

4.6 Pregnancy and lactation

Pregnancy
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 fetus.

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

4.7 Effects on ability to drive and use machines

Patients should be warned about the possibility of dizziness (including vertigo). Patients being treated with ropinirole and presenting with somnolence and/or sudden sleep episodes must be informed to refrain from driving or engaging in activities where impaired alertness may put themselves or others at risk of serious injury or death (e.g. operating machines) until such recurrent episodes and somnolence have resolved (see also Section 4.4 ).
4.8 Undesirable effects

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

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

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

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

<table>
<thead>
<tr>
<th>Immune System Disorders</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>not known</td>
<td>Hypersensitivity reactions (including urticaria, angioedema, rash, pruritis)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Psychiatric disorders</th>
</tr>
</thead>
<tbody>
<tr>
<td>common</td>
</tr>
<tr>
<td>uncommon</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Nervous system disorders</th>
</tr>
</thead>
<tbody>
<tr>
<td>very common</td>
</tr>
<tr>
<td>common</td>
</tr>
<tr>
<td>uncommon</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Gastrointestinal disorders</th>
</tr>
</thead>
<tbody>
<tr>
<td>very common</td>
</tr>
<tr>
<td>common</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Hepatobiliary disorders</th>
</tr>
</thead>
<tbody>
<tr>
<td>not known</td>
</tr>
</tbody>
</table>

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

Adjucent therapy studies

Monotherapy studies

* In patients with advanced Parkinson’s disease, dyskinesias can occur during the initial titration of ropinirole. In clinical trials it was shown that a reduction of the L-dopa dose may ameliorate dyskinesia (see also section 4.2)

**Use of ropinirole in Restless Legs Syndrome**

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

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

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

<table>
<thead>
<tr>
<th>Nervous system disorders</th>
<th>Syncope, somnolence, dizziness (including vertigo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Common</td>
<td>Syncope, somnolence, dizziness (including vertigo)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Vascular disorders</th>
<th>Postural hypotension, hypotension</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uncommon</td>
<td>Postural hypotension, hypotension</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Gastrointestinal disorders</th>
<th>Vomiting, nausea</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very common</td>
<td>Vomiting, nausea</td>
</tr>
<tr>
<td>Common</td>
<td>Abdominal pain</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>General disorders and administration site conditions</th>
<th>Fatigue</th>
</tr>
</thead>
<tbody>
<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.

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

**5 PHARMACOLOGICAL PROPERTIES**

**5.1 Pharmacodynamic properties**
Pharmacotherapeutic group: Dopaminergic agents, dopamine agonists, ATC code: N04BC04

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

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

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

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

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

A 12-week placebo-controlled polysomnography study in Restless Legs Syndrome patients examined the effect of treatment with ropinirole on periodic leg movements of sleep. A statistically significant
difference in the periodic leg movements of sleep was seen between ropinirole and placebo from baseline to week 12.

Although sufficient data are not available to adequately demonstrate the long term efficacy of ropinirole in Restless Legs Syndrome (see section 4.2), in a 36-week study, patients who continued on ropinirole demonstrated a significantly lower relapse rate compared with patients randomised to placebo (33% versus 58%, p=0.0156).

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

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

In clinical studies most patients were of Caucasian origin.

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

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

5.2 Pharmacokinetic properties

Absorption
The bioavailability of ropinirole is about 50% (36% to 57%). Oral absorption of ropinirole film-coated (immediate-release) tablets is rapid with peak concentrations of ropinirole achieved at a median time of 1.5 hours post-dose. A high fat meal decreases the rate of absorption of ropinirole, as shown by a delay in median T_max by 2.6 hours and an average 25% decrease in C_max.

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

Metabolism
Ropinirole is primarily cleared by the cytochrome P450 enzyme, CYP1A2, and its metabolites are mainly excreted in the urine. The major metabolite is at least 100 times less potent than ropinirole in animal models of dopaminergic function.

Elimination
Ropinirole is cleared from the systemic circulation with an average elimination half-life of approximately 6 hours. No change in the oral clearance of ropinirole is observed following single and repeated oral administration. Wide inter-individual variability in the pharmacokinetic parameters has been observed.

Renal Impairment
There was no change observed in the pharmacokinetics of ropinirole in Parkinson’s disease patients with mild to moderate renal impairment.

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

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

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

In patients with mild to moderate renal impairment (creatinine clearance between 30 and 50 ml/min),
o 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 ropinirole;
behavioural changes, hypoprolactinaemia, decrease in blood pressure and heart rate, ptosis and
salivation. In the albino rat only, retinal degeneration was observed in a long term study at the highest
dose (50 mg/kg/day), and was probably associated with an increased exposure to light.

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

##### Carcinogenicity
From two-year studies conducted in the mouse and rat at dosages up to 50 mg/kg/day there was no
evidence of any carcinogenic effect in the mouse. In the rat, the only ropinirole-related lesions were
Leydig cell hyperplasia and testicular adenoma resulting from the hypoprolactinaemic effect of
ropinirole. These lesions are considered to be a species specific phenomenon and do not constitute a
hazard with regard to the clinical use of ropinirole.

##### Reproductive Toxicity
Administration of ropinirole to pregnant rats at maternally toxic doses resulted in decreased fetal body
weight at 60 mg/kg/day (approximately twice the AUC at the maximum dose in humans), increased
fetal death at 90 mg/kg/day (approximately 3 times the AUC at the maximum dose in humans) and
digit malformations at 150 mg/kg/day (approximately 5 times the AUC at the maximum dose in
humans). There were no teratogenic effects in the rat at 120 mg/kg/day (approximately 4 times the
AUC at the maximum dose in humans) and no indication of an effect on development in the rabbit.

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

### 6 PHARMACEUTICAL PARTICULARS

#### 6.1 List of excipients
**Tablet core:**
- Lactose monohydrate
- Microcrystalline cellulose
- Croscarmellose sodium
- Hypromellose (6cps)
- Magnesium stearate

**Film coat (opadry pink 03B84727):**
- Hypromellose 6cps
- Titanium dioxide (E171)
- Macrogol
- Iron oxide red (E172)
- Iron oxide yellow (E172)

#### 6.2 Incompatibilities
Not applicable.
6.3 **Shelf life**
Blisters: 18 months
HDPE bottles: 18 months. After first opening of the bottle use the medicinal product within one month.

6.4 **Special precautions for storage**
Blisters: Store below 25°C. Store in the original package (blister) in order to protect from moisture.
HDPE bottles: Store below 25°C. Keep the bottle tightly closed in order to protect from moisture.

6.5 **Nature and contents of container**
ALU/ALU blister packs of 12, 28 or 100 tablets
HDPE container with child resistant closure of 30 or 84 tablets.
Not all pack sizes may be marketed.

6.6 **Special precautions for disposal**
No special requirements.

7 **MARKETING AUTHORISATION HOLDER**
Wockhardt UK Ltd
Ash Road North
Wrexham
LL13 9UF
UK

8 **MARKETING AUTHORISATION NUMBER(S)**
PL 29831/0416

9 **DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**
10/02/2011

10 **DATE OF REVISION OF THE TEXT**
10/02/2011
1 NAME OF THE MEDICINAL PRODUCT
Ropinirole 5mg Film-Coated Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
One film-coated tablet contains 5.7mg ropinirole hydrochloride, equivalent to 5mg ropinirole.

Excipients:Lactose monohydrate – 113.2mg
For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Film-coated tablet.

Blue, irregular hexagonal shape film-coated tablets, debossed with ‘W’ on one side and ‘177’ on the other side.

4 CLINICAL PARTICULARS
4.1 Therapeutic indications
Treatment of Parkinson's Disease under the following conditions:

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

4.2 Posology and method of administration
Route of administration
Oral use.

Adults
Individual dose titration against efficacy and tolerability is recommended.

Ropinirole should be taken three times a day (t.i.d.), preferably with meals to improve gastrointestinal tolerance.

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

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

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

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

Doses of ropinirole above 24 mg/day have not been studied.

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

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

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

As with other dopamine agonists, it is necessary to discontinue ropinirole treatment gradually by reducing the number of daily doses over the period of one week.

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

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

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

A study into the use of ropinirole in patients with end stage renal disease (patients on haemodialysis) has shown that a dose adjustment in these patients is required as follows: the initial dose of Ropinirole Tablets should be 0.25 mg three times a day. Further dose escalations should be based on tolerability and efficacy. The recommended maximum dose of Ropinirole Tablets is 18 mg/day in patients receiving regular haemodialysis. Supplemental doses after haemodialysis are not required (see section 5.2).

The use of ropinirole in patients with severe renal (creatinine clearance <30ml/min) or hepatic impairment impairment has not been studied.

4.3 Contraindications
Hypersensitivity to the active substance or to any of the excipients.

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

Hepatic impairment.

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

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

Impulse control disorders including pathological gambling, increased libido and hypersexuality have been reported in patients treated with dopamine agonists, including ropinirole, principally for Parkinson’s disease. These 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).

Due to the risk of hypotension, blood pressure monitoring is recommended, particularly at the beginning of treatment, in patients with severe cardiovascular disease (in particular coronary insufficiency).
Co-administration of ropinirole with anti-hypertensive and anti-arrhythmic agents has not been studied. Caution should be exercised when these compounds are given concomitantly with ropinirole because of the unknown potential for the occurrence of hypotension, bradycardias or other arrhythmias.

Excipients:
The tablets contain lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

There is no pharmacokinetic interaction between ropinirole and levodopa or domperidone would necessitate dosage adjustment of these medicinal products. 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 drugs with ropinirole should be avoided.

Increased plasma concentrations of ropinirole have been observed in patients treated with high doses of oestrogens. In patients already receiving hormone replacement therapy (HRT), ropinirole treatment may be initiated in the normal manner. However, it may be necessary to adjust the ropinirole dose, in accordance with clinical response, if HRT is stopped or introduced during treatment with ropinirole.

Ropinirole is principally metabolised by the cytochrome P450 isoenzyme CYP1A2. A pharmacokinetic study (with a ropinirole dose of 2 mg, three times a day in patients with Parkinson’s disease) revealed that ciprofloxacin increased the \( C_{\text{max}} \) and AUC of ropinirole by 60% and 84% respectively, with a potential risk of adverse events. Hence, in patients already receiving ropinirole, the dose of ropinirole may need to be adjusted when medicinal products known to inhibit CYP1A2, e.g. ciprofloxacin, enoxacin or fluvoxamine, are introduced or withdrawn.

A pharmacokinetic interaction study in patients with Parkinson’s disease between ropinirole (at a dose of 2 mg, three times a day) and theophylline, a substrate of CYP1A2, revealed no change in the pharmacokinetics of either ropinirole or theophylline.

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

No information is available on the potential for interaction between ropinirole and alcohol. As with other centrally active medications, patients should be cautioned against taking ropinirole with alcohol.

4.6 Pregnancy and lactation

Pregnancy

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 fetus.

Lactation

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

4.7 Effects on ability to drive and use machines

Patients should be warned about the possibility of dizziness (including vertigo). Patients being treated with ropinirole and presenting with somnolence and/or sudden sleep episodes must be informed to refrain from driving or engaging in activities where impaired alertness may put themselves or others at risk of serious injury or death (e.g. operating machines) until such recurrent episodes and somnolence have resolved (see also Section 4.4 ).
4.8 Undesirable effects
Undesirable effects are listed below by system organ class and frequency. It is noted if these undesirable effects were reported in clinical trials as monotherapy or adjunct therapy to levodopa.

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

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

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

<table>
<thead>
<tr>
<th>Immune System Disorders</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>not known</td>
<td>Hypersensitivity reactions (including urticaria, angioedema, rash, pruritis)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Psychiatric disorders</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>common</td>
<td>confusion¹, hallucinations</td>
</tr>
<tr>
<td>uncommon</td>
<td>Psychotic reactions (other than hallucinations), including delusion, paranoia, delirium. Impulse control disorders including pathological gambling and hypersexuality, and increased libido, have been reported in post-marketing reports (see section 4.4)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Nervous system disorders</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>very common</td>
<td>Syncope², somnolence, dyskinesia³ ³</td>
</tr>
<tr>
<td>common</td>
<td>dizziness (including vertigo)</td>
</tr>
<tr>
<td>uncommon</td>
<td>extreme daytime somnolence, sudden onset of sleep.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Vascular disorders</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Uncommon</td>
<td>hypotension, postural hypotension</td>
</tr>
<tr>
<td></td>
<td>postural hypotension or hypotension is rarely severe</td>
</tr>
</tbody>
</table>

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

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

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

Adjunct therapy studies
Monotherapy studies
*In patients with advanced Parkinson’s disease, dyskinesias can occur during the initial titration of ropinirole. In clinical trials it was shown that a reduction of the levodopa dose may ameliorate dyskinesia (see also section 4.2)

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

5 PHARMACOLOGICAL PROPERTIES
5.1 Pharmacodynamic properties
Pharmacotherapeutic group: Dopaminergic agents, dopamine agonists, ATC code: N04BC04

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

Ropinirole alleviates the dopamine deficiency which characterises Parkinson’s disease by stimulating striatal dopamine receptors.
Ropinirole acts in the hypothalamus and pituitary to inhibit the secretion of prolactin.

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

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

5.2 Pharmacokinetic properties

Absorption
The bioavailability of ropinirole is about 50% (36% to 57%). Oral absorption of ropinirole film-coated (immediate-release) tablets is rapid with peak concentrations of ropinirole achieved at a median time of 1.5 hours post-dose. A high fat meal decreases the rate of absorption of ropinirole, as shown by a delay in median T_max by 2.6 hours and an average 25% decrease in C_max.

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

Metabolism
Ropinirole is primarily cleared by the cytochrome P450 enzyme, CYP1A2, and its metabolites are mainly excreted in the urine. The major metabolite is at least 100 times less potent than ropinirole in animal models of dopaminergic function.

Elimination
Ropinirole is cleared from the systemic circulation with an average elimination half-life of approximately six hours. No change in the oral clearance of ropinirole is observed following single and repeated oral administration. Wide inter-individual variability in the pharmacokinetic parameters has been observed.

Renal Impairment
There was no change observed in the pharmacokinetics of ropinirole in Parkinson’s disease patients with mild to moderate renal impairment.

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

5.3 Preclinical safety data

Reproductive Toxicity
Administration of ropinirole to pregnant rats at maternally toxic doses resulted in decreased fetal body weight at 60 mg/kg/day (approximately twice the AUC at the maximum dose in humans), increased fetal death at 90 mg/kg/day (approximately 3 times the AUC at the maximum dose in humans) and digit malformations at 150 mg/kg/day (approximately 5 times the AUC at the maximum dose in humans). There were no teratogenic effects in the rat at 120 mg/kg/day (approximately 4 times 30 times the AUC at the maximum dose in humans) and no indication of an effect on development in the rabbit.

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

Genotoxicity
Genotoxicity was not observed in the usual battery of in vitro and in vivo tests.
Carcinogenicity
From two-year studies conducted in the mouse and rat at dosages up to 50 mg/kg/day there was no evidence of any carcinogenic effect in the mouse. In the rat, the only ropinirole-related lesions were Leydig cell hyperplasia and testicular adenoma resulting from the hypoprolactinaemic effect of ropinirole. These lesions are considered to be a species specific phenomenon and do not constitute a hazard with regard to the clinical use of ropinirole.

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

6 PHARMACEUTICAL PARTICULARS
6.1 List of excipients
Tablet core:
- Lactose monohydrate
- Microcrystalline cellulose
- Croscarmellose sodium
- Hypermellose (6cps)
- Magnesium stearate

Film coat (opadry pink 03B84727):
- Hypermellose 6cps
- Titanium dioxide (E171)
- Macrogol
- Indigo carmine aluminium lake (E132)

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
Blisters: 18 months.

HDPE bottles: 18 months. After first opening of the bottle use the medicinal product within one month.

6.4 Special precautions for storage
Blisters: Store below 25°C. Store in the original package (blister) in order to protect from moisture.

HDPE bottles: Store below 25°C. Keep the bottle tightly closed in order to protect from moisture.

6.5 Nature and contents of container
ALU/ALU blister packs of 12, 28 or 100 tablets

HDPE container with child resistant closure of 30 or 84 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal
No special requirements.

7 MARKETING AUTHORISATION HOLDER
Wockhardt UK Ltd
Ash Road North
Wrexham
LL13 9UF
UK

8 MARKETING AUTHORISATION NUMBER(S)
PL 29831/0417
<table>
<thead>
<tr>
<th></th>
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<td>9</td>
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</tr>
<tr>
<td>10</td>
<td>10/02/2011</td>
</tr>
</tbody>
</table>
Module 3

Read all of this leaflet carefully before you start to take this medicine.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, please 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 get 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 Tablets are and what they are used for
2. Before you take Ropinirole Tablets
3. How to take Ropinirole Tablets
4. Possible side effects
5. How to store Ropinirole Tablets
6. Further information

1. What Ropinirole Tablets are and what they are used for

The active ingredient in Ropinirole Tablets is ropinirole, which belongs to a group of medicines called dopamine agonists. Dopamine agonists affect the brain in a similar way to a natural substance called dopamine.

Ropinirole Tablets are used to treat:
- Parkinson's disease. People with Parkinson's disease have low levels of dopamine in some parts of their brains. Ropinirole has effects similar to those of natural dopamine, so it helps to reduce the symptoms of Parkinson's disease.
- moderate to severe Restless Legs Syndrome. People with Restless Legs Syndrome have an irresistible urge to move their legs, and sometimes their arms and other parts of their body. Usually, they have unpleasant sensations in their limbs — sometimes described as 'crawling' or 'bubbling' — which can begin as soon as they sit or lie down, and are relieved only by movement. So they often have problems with sitting still, and especially with sleeping. Ropinirole relieves the unpleasant sensations, and so reduces the urge to move the legs and other limbs.

breastfeeding, as it can affect your milk production.
Tell your doctor immediately if you are pregnant, if you think you might be pregnant or if you are planning to become pregnant. Your doctor will also advise you if you are breast feeding or planning to do so. Your doctor may advise you to stop taking Ropinirole Tablets.

While you are taking Ropinirole Tablets
Tell your doctor if you or your family notices that you are developing any unusual behaviours (such as an unusual urge to gamble or increased sexual urges and/or behaviours) while you are taking Ropinirole Tablets. Your doctor may need to adjust or stop your dose.

Driving and using machines
Ropinirole Tablets can make you feel drowsy. In very rare cases, Ropinirole Tablets can make people feel extremely sleepy, and it sometimes makes people fall asleep very suddenly without warning.

If you could be affected; do not drive, do not operate machines and do not put yourself in any situation where feeling sleepy or falling asleep could put you (or other people) at risk of serious injury or death. Do not take part in these activities until you are no longer affected.

Talk to your doctor if this causes problems for you.

Smoking and Ropinirole Tablets
Tell your doctor if you start smoking, or give up smoking, while you are taking Ropinirole Tablets. Your doctor may need to adjust your dose.

If your symptoms get worse
Some people taking Ropinirole Tablets find that their Restless Leg Syndrome symptoms get worse — for example, symptoms may start earlier than usual or be more intense, or affect other previously unaffected limbs, such as the arms or return in the early morning. Tell your doctor as soon as possible if you get any of these symptoms.

Important information about some of the ingredients of Ropinirole Tablets
This medicine contains lactose (a type of sugar). If you have been told by your doctor that you cannot tolerate certain sugars, contact your doctor before taking this medicine.

3. How to take Ropinirole Tablets

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

This medicine is to be swallowed whole with water and preferably with food.
2. Before you take Ropinirole Tablets

Do not take Ropinirole Tablets:

- If you are allergic (hypersensitive) to ropinirole or to any of the other ingredients in this medicine (see Section 4 and/or)
- If you have serious kidney disease
- If you have liver disease

Tell your doctor if you think any of these may apply to you.

Take special care with Ropinirole Tablets:

Your doctor needs to know before you take Ropinirole Tablets:

- If you are pregnant or think you may be pregnant
- If you are breast feeding
- If you are under 16 years old
- If you have a serious heart complaint
- If you have a serious mental health problem
- If you have experienced any unusual urges and/or behaviours (such as excessive gambling or excessive sexual behaviour)
- If you are taking medicines to treat high blood pressure
- If you are taking medicines to control your heartbeat

Tell your doctor if you think any of these may apply to you. Your doctor may decide that Ropinirole Tablets are not suitable for you, or that you need extra check-ups while you are taking them.

Taking other medicines

Please tell your doctor or pharmacist if you are taking, have recently taken, any other medicines, including any herbal medicines or other medicines you have obtained without a prescription. Remember to tell your doctor or pharmacist if you begin taking a new medicine while you are taking Ropinirole Tablets.

Some medicines can affect the way Ropinirole Tablets work, or make it more likely that you will have side effects. Ropinirole Tablets can also affect the way some other medicines work.

These include:
- the anti-depressant fluvoxamine
- medicines for other mental health problems, for example sulpiride
- hormone replacement therapy (HRT)
- metoclopramide, which is used to treat nausea and heartburn
- the antibiotics ciprofloxacin or enrofloxacin
- any other medicine for Parkinson's disease
- any other drug which blocks the action of dopamine in the brain

Taking with food and drink

If you take Ropinirole Tablets with food, you may be less likely to feel sick (nauseous) or be sick (Vomiti). So it's best to take it with food if you can.

Pregnancy and Breastfeeding

Ropinirole Tablets are not recommended if you are pregnant unless your doctor advises that the benefit to you of taking Ropinirole Tablets is greater than the risk to your unborn baby. Ropinirole Tablets are not recommended if you are

Do not give Ropinirole Tablets to children. Ropinirole Tablets are not normally prescribed for people under 18 years of age.

When you begin taking Ropinirole Tablets your dose will be increased gradually. It may take a while to find the right dose for you.

Treatment of Parkinson's disease:

Adults

The usual starting dose is 0.25mg three times a day. After one week your doctor may increase your dose to 0.25mg three times a day. Then your doctor may increase your dose gradually over the next two weeks, up to a daily dose of 3mg per day.

If a 3mg daily dose does not improve your symptoms enough, your doctor may gradually increase your dose to a maximum of 6mg per day.

If you are also taking other medicines for Parkinson's disease, your doctor may advise you to gradually reduce the dose of the other medicine. If you are taking L-Dopa you may experience some uncontrollable movements (dyskinesias) when you first start taking Ropinirole Tablets. Tell your doctor if this happens, as your doctor may need to adjust the doses of the medicines you are taking.

Treatment of Restless Legs Syndrome:

Adults

Take Ropinirole Tablets once a day, usually just before bedtime, but you can take it up to 3 hours before you go to bed. After two days your doctor may increase your dose to 0.5mg once a day for the remainder of the week. Then your doctor may gradually increase your dose to 3mg once a day over the next three weeks. In some patients, a 2mg daily dose may not improve Restless Legs Syndrome enough and your doctor may increase the dose up to a maximum of 4mg daily to improve your symptoms.

After three months of taking Ropinirole Tablets, your doctor may adjust your dose or advise you to stop taking this medicine, depending on your symptoms and how you feel.

If you take more Ropinirole Tablets than you should

Contact a doctor or pharmacist or go to your nearest hospital casualty department immediately. Take this leaflet and any unused tablets with you to show the doctor.

The symptoms of overdose include feeling sick (nausea), being sick (vomiting), dizziness, feeling drowsy, mental or physical tiredness, fainting, hallucinations.

If you forget to take Ropinirole Tablets

If you forget to take your medicine take it as soon as you remember. If it is almost time for your next dose, then do not take the missed dose at all. NEVER take a double dose to make up for the one missed. If you have missed taking Ropinirole Tablets for one day or more, ask your doctor for advice on how to start taking it again.

105293/1
PAR Ropinirole 0.25, 0.5, 1, 2 and 5mg Film-coated Tablets

UK/H/3489/001-5/DC

Do not stop taking this medicine suddenly without consulting 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 Tablets can cause side effects, although not everybody gets them. The side effects of Ropinirole Tablets are more likely to happen when you first start taking it, or when your dose has just been increased. They are usually mild, and may become less troublesome after you have taken the dose for a while. If you’re worried about side effects, talk to your doctor.

If you have an allergic reaction to Ropinirole Tablets, tell your doctor straight away. The signs of an allergic reaction include:

- swelling of your face
- low blood pressure (feeling faint, dizzy or light headed)
- difficulty breathing
- itchy lumpy rash.

Treatment of Parkinson’s disease:
The following side-effects may be experienced when taking Ropinirole Tablets:

Very common (affects more than 1 in 10 people):
- feeling drowsy or sleepy (somnolence)
- feeling sick (nausea)
- fainting.

Common (affects up to 10 users in 100):
- feeling or hearing things that are not there (hallucinations)
- dizziness (or a spinning sensation)
- stomach pains
- being sick (vomiting)
- indigestion or heartburn
- swelling of your legs

Uncommon (affects up to 10 users in 1,000):
- feeling dizzy or faint, especially when standing up from a sitting down or lying position (this is caused by a drop in blood pressure)
- feeling very sleepy during the day (extreme somnolence)
- falling asleep very suddenly without feeling sleepy first (sudden sleep onset episodes)
- mental problems such as delirium (severe confusion), delusions (unreasonable ideas) or paranoia (unreasonable suspicions).

Very rare (affects up to one in 10,000):
- a very small number of people taking Ropinirole Tablets have had changes in liver function, which have shown up in blood tests

Some patients may have the following side effects:

- allergic reactions such as rash, itchy swellings on the skin (hives), swelling of the face, lips, mouth, tongue or throat which may cause difficulty in swallowing or breathing, rash or intense itching (see Section 2);
- urge to behave in a way unusual for them such as an unusual urge to gamble or increased sexual urges and/or behaviours

an unusual urge to gamble or increased sexual urges and/or behaviours

You should seek advice from your doctor if you notice that your symptoms become worse, start earlier in the day or after less time at rest whilst taking Ropinirole Tablets.

Your doctor may adjust your dose.

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

5. How to store Ropinirole Tablets

Keep out of the reach and sight of children.

Do not use Ropinirole Tablets after the expiry date stated on the blister or carton. The expiry date refers to the last day of that month.

For tablets packed in plastic bottles: Ropinirole Tablets can be used for one month after first opening of the container.

Blister packs: Store below 25°C. Store in the original package (blister) in order to protect from moisture.

HDPE bottles: Store below 25°C. Keep the bottle tightly closed in order to protect from moisture.

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

6. Further information

What Ropinirole tablets contain

The active ingredient is ropinirole hydrochloride.

The other ingredients are lactose monohydrate, microcrystalline cellulose, croscarmellose sodium, hypromellose (E463), magnesium stearate.

Film coating:
Ropinirole 0.25mg Film-Coated tablets: opadry white 03828796 (hypromellose 6cps, titanium dioxide (E171), macrogol).
Ropinirole 0.5mg Film-Coated tablets: opadry yellow 03822117 (hypromellose 6cps, titanium dioxide (E171), macrogol, iron oxide yellow (E172)).
Ropinirole 1mg Film-Coated tablets: opadry green 03821595 (hypromellose 6cps, titanium dioxide (E171), macrogol, iron oxide yellow (E172), indigo carmine aluminium lake (E132)).
Ropinirole 2mg Film-Coated tablets: opadry pink 03884737 (hypromellose 6cps, titanium dioxide (E171), macrogol, iron oxide red (E172), iron oxide yellow (E172)).
Ropinirole 5mg Film-Coated tablets: are yellow irregular hexagonal shape film-coated tablets.

What Ropinirole Film-coated tablets look like and the contents of the pack
Ropinirole 0.25mg Film-coated tablets are white irregular hexagonal shape film-coated tablets, debossed ‘W’ on one side and ‘154’ on the other.
Ropinirole 0.5mg Film-coated tablets are yellow irregular hexagonal shape film-coated tablets.
If you are taking Ropinirole Tablets with L-dopa
People who are taking Ropinirole Tablets with
L-dopa may develop other side effects over time.
• uncontrollable movements (dyskinesias) are a very
common side effect. If you are taking L-dopa you
may experience some uncontrollable movements
(dyskinesias) when you first start taking Ropinirole
Tablets. Tell your doctor if this happens, as your
doctor may need to adjust the doses of the
medicines you are taking.
• feeling confused is a common side effect

Restless Legs Syndrome
The following side effects may be experienced when
taking Ropinirole Tablets:
Very common (affects more than 1 in 10 people):
• being sick (vomiting)
• feeling sick (nausea)

Common (affects up to 10 users in 100):
• feeling nervous
• fainting
• feeling drowsy
• fatigue (mental or physical tiredness)
• dizziness
• stomach pain
• worsening of RLS (symptoms may start earlier
than usual or be more intense, or affect other
parts of the body, such as the arms or return in
the early morning)

Uncommon (affects up to 10 users in 1000):
• feeling confused
• hallucinations (‘seeing’ things that are not really
there)
• low blood pressure which can make you feel dizzy
or faint especially when standing up from a sitting
down or lying position.

Very rare side effects (affects up to one in 10,000)
A very small number of people taking Ropinirole
Tablets have had:
• changes in liver function, which have shown up in
blood tests
• feeling very sleepy during the day (extreme
somnolence)
• falling asleep very suddenly without feeling sleepy
first (sudden sleep onset episodes)

Some patients may have the following side
effects:
• allergic reactions such as rash, itchy swellings on
the skin (hives), swelling of the face, lips, mouth,
tongue or throat which may cause difficulty in
swallowing or breathing, rash or intense itching
(see Section 2).
• other psychotic reactions in addition to
hallucinations, such as severe confusion (delirium),
irrational ideas (delusions) and irrational
suspiciousness (paranoia)
• urge to behave in a way unusual for them such as
debossed ‘W’ on one side and ‘155’ on the other.
Ropinirole 1mg Film-coated tablets: are green
irregular hexagonal shape film-coated tablets,
debossed ‘W’ on one side and ‘171’ on the other.
Ropinirole 2mg Film-coated tablets: are pale
yellowish pink irregular hexagonal shape
film-coated tablets, debossed ‘W’ on one side and
‘172’ on the other.

These tablets are available in:
• blister packs of 12, 28 or 100 tablets
• HDPE container with child resistant cap of 30 or 94
   tablets
Not all pack sizes may be marketed.

Marketing Authorisation Holder: Wockhardt UK Ltd,
Ash Road North, Wrexham, LL13 0UF, UK
Manufacturer: CP Pharmaceuticals Ltd.
Ash Road North, Wrexham, LL13 0UF, UK

These medicinal products are authorised in the
Member States of the EEA under the following
names:
UK: Ropinirole 0.25, 0.5, 1 and 2mg Film-Coated
Tablets
Germany: Ropinirole Wockhardt 0.25/0.5/1/2mg
Filmtabletten
Cyprus: Ropinirole 0.25, 0.5, 1 and 2mg Film-Coated
Tablets
Malta: Ropinirole 0.25, 0.5, 1 and 2mg Film-Coated
Tablets

Other formats:
To obtain or request a copy of this leaflet in Braille,
large print or audio please call, free of charge:
0800 198 5000 (UK Only).

Please be ready to give the following information:

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</tr>
<tr>
<td>Ropinirole 2mg Film-coated tablets</td>
<td>29831/0416</td>
</tr>
</tbody>
</table>

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Institute of Blind People
For the Republic of Ireland please call +353 32 01 8000
Leaflet prepared: January 2011

WOCHKARHD
Read all of this leaflet carefully before you start to take this medicine.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, please 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 get 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 Tablets are and what they are used for
2. Before you take Ropinirole Tablets
3. How to take Ropinirole Tablets
4. Possible side effects
5. How to store Ropinirole Tablets
6. Further information

1. What Ropinirole Tablets are and what they are used for

The active ingredient in Ropinirole Tablets is ropinirole which belongs to a group of medicines called dopamine agonists. Dopamine agonists affect the brain in a similar way to a natural substance called dopamine.

Ropinirole Tablets are used to treat Parkinson's disease. People with Parkinson's disease have low levels of dopamine in some parts of their brains. Ropinirole has effects similar to those of natural dopamine, so it helps to reduce the symptoms of Parkinson's disease.

2. Before you take Ropinirole Tablets

Do not take Ropinirole Tablets:
- if you are allergic (hypersensitive) to ropinirole or to any of the other ingredients in this medicine (see Section 4 and 6)
- if you have a serious kidney disease
- if you have a liver disease

pregnant, unless your doctor advises that the benefit to you of taking Ropinirole Tablets is greater than the risk to your unborn baby. Ropinirole Tablets are not recommended if you are breastfeeding, as it can affect your milk production.

Tell your doctor immediately if you are pregnant, if you think you might be pregnant, or if you are planning to become pregnant. Your doctor will also advise you if you are breast feeding or planning to do so. Your doctor may advise you to stop taking Ropinirole Tablets.

While you are taking Ropinirole Tablets

Tell your doctor if you or your family notices that you are developing any unusual behaviours (such as an unusual urge to gamble or increased sexual urges and/or behaviours) while you are taking Ropinirole Tablets. Your doctor may need to adjust or stop your dose.

Driving and using machines

Ropinirole Tablets can make you feel drowsy. In very rare cases, Ropinirole Tablets can make people feel extremely sleepy, and it sometimes makes people fall asleep very suddenly without warning.

If you could be affected: do not drive, do not operate machines and do not put yourself in any situation where feeling sleepy or falling asleep could put you (or other people) at risk of serious injury or death. Do not take part in these activities until you are no longer affected.

Talk to your doctor if this causes problems for you.

Smoking and Ropinirole Tablets

Tell your doctor if you start smoking, or give up smoking, while you are taking Ropinirole Tablets. Your doctor may need to adjust your dose.

Important Information about some of the ingredients of Ropinirole Tablets

This medicine contains lactose (a type of sugar). If you have been told by your doctor that you tolerate certain sugars, contact your doctor before taking this medicine.

3. How to take Ropinirole Tablets

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

This medicine is to be swallowed whole with water and preferably with food.
Tell your doctor if you think any of these may apply to you.

Take special care with Ropinirole Tablets:
Your doctor needs to know before you take Ropinirole Tablets:
• if you are pregnant or think you may be pregnant
• if you are breast feeding
• if you are under 18 years old
• if you have a serious heart complaint
• if you have a serious mental health problem
• if you have experienced any unusual urges and/or behaviours (such as excessive gambling or excessive sexual behaviour)
• are taking medicines to treat high blood pressure
• are taking medicines to control your heart beat

Tell your doctor if you think any of these may apply to you. Your doctor may decide that Ropinirole Tablets aren't suitable for you, or that you need extra check-ups while you are taking them.

Taking other medicines
Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including any herbal medicines or other medicines you have obtained without a prescription.
Remember to tell your doctor or pharmacist if you begin taking a new medicine while you are taking Ropinirole Tablets.

Some medicines can affect the way Ropinirole Tablets work, or make it more likely that you will have side effects. Ropinirole Tablets can also affect the way some other medicines work.

These include:
• the anti-depressant fluoxetine
• medications for other mental health problems, for example sulpiride
• hormone replacement therapy (HRT)
• metoclopramide, which is used to treat nausea and heartburn
• the antibiotics ciprofloxacin or enoxacin
• any other medicine for Parkinson's disease
• any other drug which blocks the action of dopamine in the brain

Taking with food and drink
If you take Ropinirole tablets with food, you may be less likely to feel sick (nauseous) or be sick (vomit). So it's best to take it with food if you can.

Pregnancy and Breastfeeding
Ropinirole Tablets are not recommended if you are pregnant.

Do not give Ropinirole Tablets to children.
Ropinirole Tablets are not normally prescribed for people under 18 years of age.

When you begin taking Ropinirole Tablets your dose will be increased gradually. It may take a while to find the right dose for you.

Adults
The usual starting dose is 0.25 mg three times a day. After one week your doctor may increase your dose to 0.5 mg three times a day. Then your doctor may increase your dose gradually over the next two weeks, up to a daily dose of 2 mg per day.

If a 3 mg daily dose does not improve your symptoms enough, your doctor may gradually increase your dose to a maximum of 5 mg per day.

If you are also taking other medicines for Parkinson's disease, your doctor may advise you to gradually reduce the dose of the other medicine. If you are taking L-dopa you may experience some uncontrollable movements (dyskinesia) when you first start taking Ropinirole Tablets. Tell your doctor if this happens, as your doctor may need to adjust the doses of the medicines you are taking.

If you take more Ropinirole Tablets than you should
Contact a doctor or pharmacist or go to your nearest hospital casualty department immediately. Take this leaflet and any unused tablets with you to show the doctor.
The symptoms of overdosage includes feeling sick (nausea), being sick (vomiting), dizziness, feeling drowsy, mental or physical tiredness, fainting, hallucinations.

If you forget to take Ropinirole Tablets
If you forget to take your medicine take it as soon as you remember. If it is almost time for your next dose, then do not take the missed dose at all. NEVER take a double dose to make up for the one missed. If you have missed taking Ropinirole Tablets for one day or more, ask your doctor for advice on how to start taking it again.

Do not stop taking this medicine suddenly without consulting 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 Tablets can cause side effects, although not everybody gets them. The side effects of Ropinirole Tablets are more likely to happen when you first start taking it, or when your dose has just been increased. They are usually mild, and may become less troublesome after you have taken the dose for a while. If you’re worried about side effects, talk to your doctor.

If you have an allergic reaction to Ropinirole Tablets, tell your doctor straight away. The signs of an allergic reaction include:
- swelling of your face
- low blood pressure (feeling faint, dizzy or light headed)
- difficulty breathing
- itchy, lumpy rash.

The following side effects may be experienced when taking Ropinirole Tablets:

Very common (affects more than 1 in 10 people):
- feeling drowsy or sleepy (somnolence)
- feeling sick (nausea)
- fainting.

Common (affects up to 10 users in 100):
- seeing or hearing things that are not there (hallucinations)
- dizziness (a spinning sensation)
- stomach pains
- being sick (vomiting)
- indigestion or heartburn
- swelling of your legs

Uncommon (affects up to 10 users in 1000):
- feeling dizzy or faint, especially when standing up from a sitting down or lying position (this is caused by a drop in blood pressure)
- feeling very sleepy during the day (extreme somnolence)
- falling asleep very suddenly without feeling sleepy first (sudden sleep onset episodes)
- mental problems such as delirium (severe confusion), delusions (unreasonable ideas) or paranoia (unreasonable suspicions).

Very rare (affects up to one in 10,000):
- a very small number of people taking Ropinirole Tablets have had changes in liver function, which have shown up in blood tests.

What Ropinirole Film-coated tablets look like and the contents of the pack

Ropinirole 5mg Film-coated tablets are blue irregular hexagonal shape film-coated tablets, debossed 'W' on one side and '177' on the other side.

These tablets are available in:
- blister packs of 12, 28 or 100 tablets
- HDPE container with child resistant cap of 30 or 84 tablets

Not all pack sizes may be marketed.

Marketing Authorisation Holder: Wockhardt UK Ltd, Ash Road North, Wrexham, LL13 9UF, UK
Manufacturer: CP Pharmaceuticals Ltd, Ash Road North, Wrexham, LL13 9UF, UK

These medicinal products are authorised in the Member States of the EEA under the following names:

UK: Ropinirole 5mg Film-Coated Tablets
Germany: Ropinirole Wockhardt 5mg Filmtabletten
Cyprus: Ropinirole 5mg Film-Coated Tablets
Malta: Ropinirole 5mg Film-Coated Tablets

Other formats:
To listen to or request a copy of this leaflet in Braille, large print or audio please call, free of charge: 0800 198 5000 (UK Only).

Please be ready to give the following information:

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<td>Film-coated tablets</td>
<td></td>
</tr>
</tbody>
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Leaflet prepared: January 2011
Some patients may have the following side effects:

- allergic reactions such as red, itchy swellings on the skin (hives), swelling of the face, lips, mouth, tongue or throat which may cause difficulty in swallowing or breathing, rash or intense itching (see Section 4).
- urges to behave in a way unusual for them such as an unusual urge to gamble or increased sexual urges and/or behaviours

If you are taking Ropinirole Tablets with L-dopa:

People who are taking Ropinirole Tablets with L-dopa may develop other side effects over time:

- uncontrollable movements (dyskinesias) are a very common side effect. If you are taking L-dopa you may experience some uncontrollable movements (dyskinesias) when you first start taking Ropinirole Tablets. Tell your doctor if this happens, as your doctor may need to adjust the doses of the medicines you are taking.
- feeling confused is a common side effect.

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

5. How to store Ropinirole Tablets

Keep out of the reach and sight of children.

Do not use Ropinirole Tablets after the expiry date stated on the blister or carton. The expiry date refers to the last day of that month.

For tablets packed in plastic bottles: Ropinirole Tablets can be used for one month after first opening of the container.

Blisters: Store below 25°C. Store in the original package (blister) in order to protect from moisture.

HDPE bottles: Store below 25°C. Keep the bottle tightly closed in order to protect from moisture.

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

6. Further information

What Ropinirole Tablets contain

The active ingredient is: ropinirole hydrochloride.

The other ingredients are: lactose monohydrate, microcrystalline cellulose, croscarmellose sodium, hypromellose (6cPs), magnesium stearate.

Film coating: opadry pink (B844727) (hypromellose 6cPs, titanium dioxide (E 171), macrogol, indigo carmine aluminium lake (E132)).
Module 4
Labelling
Each film-coated tablet contains 1 mg of ropinirole.

Dose: As directed by your doctor

Read the package leaflet before use

Contains lactose. Read the package leaflet for further information

Store below 25°C. Keep the bottle tightly closed in order to protect from moisture

Discard any unused tablets one month after first opening

Keep out of the reach and sight of children

Marketing Authorisation Holder:

Wockhardt UK Ltd, Ash Road North, Wixham, Ll15 9UF, UK

PL 29631/0414
MA 154/6503
Each film-coated tablet contains 2mg of ropinirole.

Dose: As directed by your doctor.
Read the package leaflet before use.
Contains lactose. Read the package leaflet for further information.

Store below 25°C. Keep the bottle tightly closed in order to protect from moisture.
Discard any unused tablets one month after first opening.

Keep out of the reach and sight of children.

Marketing Authorisation Holder: Wockhardt UK Ltd, Ash Road North, Wrexham, LL13 9UF, UK.

PL 29631/0416
PA 1239/2984
MA 154/08304
Each film-coated tablet contains 5mg of ropinirole.

Dose: As directed by your doctor.
Read the package leaflet before use.
Contains lactose. Read the package leaflet for further information.
Store below 25°C. Keep the bottle tightly closed in order to protect from moisture.
Discard any unused tablets one month after first opening.
Keep out of the reach and sight of children.

Marketing Authorisation Holder:
Wockhardt UK Ltd, Ash Road North, Wrexham, LL13 9UF, UK

Marketing Authorisation Reference:
PL 29831/0417
PA 1336/20/S
MA 154/06/005

84 film-coated tablets
Module 5
Scientific discussion during initial procedure

I  INTRODUCTION
Based on the review of the data on quality, safety and efficacy, the Reference Member State (RMS) and Concerned Member States (CMSs) consider that the applications for Ropinirole 0.25, 0.5, 1, 2 and 5 mg Film-coated Tablets in the treatment of idiopathic Parkinson’s Disease and for the symptomatic treatment of moderate to severe idiopathic Restless Legs Syndrome, could be approved.

The applications for the 0.25, 0.5, 1, 2 and 5 mg strengths have been submitted as ‘generic applications’ under Article 10.1 of Directive 2001/83/EC, as amended. The two brand leader products are Requip 0.25, 0.5, 1, 2 and 5 mg tablets, PL 10592/0085-89, authorised as the innovator products in the UK on 2nd July 1996; and Adartrel 0.25, 0.5, 1 and 2 mg film-coated tablets (PL 19494/0033-6), authorised in the UK as incoming Mutual Recognition applications (FR/H/0258/001-4) on 10th May 2006; both of these are marketed by GlaxoSmithKline UK. The innovator products, Requip 0.25, 0.5, 1, 2 and 5 mg tablets; have been authorised in the UK for more than 10 years, so the period of data exclusivity has expired.

Separate brand leader presentations are marketed for different indications – Requip is indicated for the treatment of Parkinson’s disease, while Adartrel is for the treatment of Restless Legs Syndrome (RLS). Both indications are being proposed for these applications for Ropinirole film-coated tablets.

For the 0.25, 0.5, 1, and 2mg tablet strengths, both indications Parkinson’s disease and RLS are proposed, whereas for the 5mg strength the proposed indication is for Parkinson’s disease only.

With the UK as the RMS in these Decentralised Procedures (UK/H/3489/001-5/DC), Wockhardt UK Ltd applied for the Marketing Authorisations for Ropinirole 0.25, 0.5, 1, 2 and 5 mg Film-coated Tablets in Cyprus, Germany and Malta.

Ropinirole hydrochloride is an orally administered anti-parkinsonian drug, is a non-ergoline dopamine agonist which stimulates striatal dopamine receptors. It is the hydrochloride salt of 2 (H)- Indol-2-one, 4-[2-(dipropylamino)ethyl]-1,3-dihydro-monohydrochloride and has an empirical formula of C_{16}H_{24}N_{2}O•HCl. Parkinson’s disease is characterised by a marked dopamine deficiency in the nigral striatal system. Ropinirole alleviates this deficiency by stimulating striatal dopamine receptors. Ropinirole acts in the hypothalamus and pituitary to inhibit the secretion of prolactin.

No new preclinical and clinical studies were conducted, which is acceptable given that the applications were based on being generic medicinal products of originator products that have been licensed for over 10 years. A bioequivalence study was carried out in accordance with Good Clinical Practice (GCP).

The RMS has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place for these product types at all sites responsible for the manufacture and assembly of these products.
The RMS considers that the Pharmacovigilance System as described by the applicant fulfils the requirements and provides adequate evidence that the applicant has the services of a qualified person responsible for pharmacovigilance and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country. A suitable justification has been provided for non-submission of a Risk Management Plan.

All member states agreed to grant a licence for the above products at the end of procedure (Day 210 – 20th January 2011). After a subsequent national phase, the UK granted a licence for these products on 10th February 2011 (PL 29831/0412-4, 0416-7).
II. ABOUT THE PRODUCT

<table>
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<td>Name(s) of the active substance(s) (INN)</td>
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<td>Pharmacotherapeutic classification (ATC code)</td>
<td>N04BC04 - Dopamine agonist</td>
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<td>Ash Road North, Wrexham Industrial Estate,</td>
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<td>Wrexham, LL13 9UF. United Kingdom</td>
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III  SCIENTIFIC OVERVIEW AND DISCUSSION

III.1  QUALITY ASPECTS

DRUG SUBSTANCE

INN: Ropinirole hydrochloride
Chemical Name: 4-[2-(Dipropylamino)-ethyl]-1,3-dihydro-2H-imdol-2-one hydrochloride
Structure:

Molecular Formula: C16H24N2OHCl
Molecular Weight: 296.84
Appearance: White to cream coloured crystalline powder.
Solubility: Soluble in water and methanol, very slightly soluble in ethyl alcohol.

Synthesis of the drug substance from the designated starting material 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. Appropriate proof-of-structure data have been supplied. All potential known impurities have been identified and characterised.

An appropriate specification is provided for the drug substance. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications. Certificates of Analysis for all working standards have been provided.

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

Satisfactory specifications and Certificates of Analysis have been provided for all packaging used to store the drug substance. Confirmation has been provided that the primary packaging complies with current guidelines concerning materials in contact with food.

Appropriate stability data have been generated, supporting a suitable retest period when the drug substance is stored in the packaging proposed.

DRUG PRODUCT

Other Ingredients
Other ingredients consist of the pharmaceutical excipients lactose monohydrate, microcrystalline cellulose, croscarmellose sodium, hypromellose (6cps), magnesium stearate and Opadry white 03B28796 consists of hypromellose 6cps, titanium dioxide (E171) and macrogol.

All excipients comply with their respective European Pharmacopoeia monographs except Opadry II White 85F18422, which complies with an in-house specification. Satisfactory Certificates of Analysis have been provided for all excipients.
The excipients derived from animal source are lactose monohydrate and magnesium stearate and satisfactory TSE declarations/certificate are provided.

**Pharmaceutical Development**
The objective of the development programme was to formulate robust, stable tablets that contain the same active ingredient as Requip 0.25, 0.5, 1, 2mg and 5mg tablets, which were first granted in the UK to GlaxoSmithKline UK, on 2nd July 1996.

Comparative impurity and dissolution profiles have been presented for test and reference products.

**Manufacture**
A satisfactory batch formula has 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 pilot-scale batches have been provided. The results are satisfactory. The applicant has committed to perform process validation on future production full-scale batches before marketing the product.

**Finished Product Specification**
The finished product specification is satisfactory. Test methods have been described and adequately validated, as appropriate. Batch data have been provided and comply with the release specification. Certificates of Analysis have been provided for any working standards used.

**Container-Closure System**
The finished product is packed in ALU/ALU blister packs of 12, 28 or 100 tablets. And HDPE container with child resistant closure, pack sizes of 30 or 84 tablets.

Specifications and Certificates of Analysis for all packaging materials have been provided. These are satisfactory. All primary packaging complies with EU legislation regarding contact with food.

**Stability**
Finished product stability studies have been conducted in accordance with current guidelines and in the packaging proposed for marketing.

Based on the results, a shelf-life of 18 months for blisters with storage conditions “Store below 25°C” and “Store in the original package (blister) in order to protect from moisture” are set.
For HDPE bottles a shelf-life of 18 months with storage conditions of ‘Store below 25°C’ and ‘Keep the bottle tightly closed in order to protect from moisture’ are set. After first opening of the bottle use the medicinal product within one month.

**Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and Labelling**
The SmPC, PIL and labels are pharmaceutically acceptable.

A package leaflet has been submitted to the MHRA together with results of consultations with target patient groups (“user testing”), in accordance with Article 59 of Council Directive
2001/83/EC. The results indicate that the package leaflet is 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 it contains.

The proposed artwork complies with the relevant statutory requirements. In line with current legislation the applicant has also included the name of the product in Braille on the outer packaging and has included sufficient space for a standard UK pharmacy dispensing label.

The MAH has stated that not all licensed pack sizes may be marketed. They have committed to submitting mock-ups for unmarketed pack sizes to the relevant regulatory authorities for approval before those packs are commercially marketed.

**Marketing Authorisation Application (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 aspects of the dossier.

**Conclusion**
There are no objections to the approval of these products from a pharmaceutical point of view.

**III.2 PRE-CLINICAL ASPECTS**
Pharmacodynamic, pharmacokinetic and toxicological properties of ropinirole hydrochloride are well known. As ropinirole is widely used and well-known, the applicant has not provided additional studies in support of their application. Overview based on literature review is, thus, appropriate.

No new preclinical data have been supplied with these applications and none are required for applications of this type. 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.

A suitable justification has been provided for non-submission of environmental risk assessment.

There are no objections to the approval of these products from a preclinical point of view.

**III.3 CLINICAL ASPECTS**

**Clinical Pharmacology**

**Pharmacokinetics**

In support of this application, the marketing authorisation holder has submitted the following bioequivalence study:

**Study 1**
This is a comparative, randomised, two-way, two-period, single dose crossover bioavailability study of Requip 0.25mg Tablets (GlaxoSmithKline, UK) and Ropinirole HCl 0.25mg Tablets (Wockhardt Limited, India) in healthy, male adult subjects under fasting conditions.

Serum drug levels were followed for 24 hours following dosing and the schedule was appropriate for accurate determination of $AUC_{inf}$ and $C_{max}$. The washout period between
phases was sufficiently long at 9 days, supported through Period II pre-dose plasma concentrations of ropinirole below the LLoQ in all subjects.

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

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Test</th>
<th>Reference</th>
<th>Ratio</th>
<th>90 % C.I.</th>
</tr>
</thead>
<tbody>
<tr>
<td>C\text{max} (pg/mL)</td>
<td>439.3711</td>
<td>453.9860</td>
<td>96.78%</td>
<td>87.12 % - 107.51 %</td>
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<tr>
<td>AUC\text{0-+} (pg.hr/mL)</td>
<td>2731.0031</td>
<td>2700.7259</td>
<td>101.12%</td>
<td>93.23 % - 109.68 %</td>
</tr>
<tr>
<td>AUC\text{0-∞} (pg.hr/mL)</td>
<td>2898.0605</td>
<td>2881.3955</td>
<td>100.58%</td>
<td>92.82 % - 108.98 %</td>
</tr>
</tbody>
</table>

The 90% confidence intervals for C\text{max} and AUC were within the pre-defined limits (80-125%). Bioequivalence has been shown for the test formulation (Ropinirole HCl 0.25mg Tablets) and the reference formulation (Requip 0.25mg Tablets). Satisfactory justification is provided for a bio-waiver according to the Committee for Proprietary Medicinal Products Notes for Guidance on “Guideline on the Investigation of Bioequivalence” (CPMP/EWP/QWP/1401/98 Rev.1 Corr**). The results of the study for 0.25mg formulation can therefore be extrapolated to the other strengths i.e 0.5, 1, 2 and 5mg Film-coated Tablets.

Pharmacodynamics
No new data have been submitted and none are required for these generic applications.

Clinical Efficacy
No new data have been submitted and none are required.

Clinical Safety
No new data have been submitted and none are required.

Expert Report
A clinical overall summary, written by an appropriately qualified physician, has been provided. This is a satisfactory, non-critical summary of Module 5.

Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and labelling
The SmPCs, PIL and labelling are medically satisfactory and consistent with those for the reference products.

Clinical Expert Report
The clinical expert report is written by an appropriately qualified physician and is a suitable summary of the clinical aspects of the dossier.

Marketing Authorisation Application (MAA) Forms
The MAA forms are medically satisfactory.

Clinical Conclusion
There are no objections to the approval of these products from a clinical point of view.
IV. OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

QUALITY
The important quality characteristics of Ropinirole 0.25, 0.5, 1, 2 and 5 mg 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 applications of this type.

EFFICACY
Bioequivalence have been demonstrated between the applicant’s Ropinirole HCl 0.25mg Tablets and the reference product, Requip 0.25mg Tablets and can be extrapolated to the 0.5 mg, 1 mg, 2 mg and 5 mg strength tablets.

No new or unexpected safety concerns arise from these applications.

The SmPC and PIL are satisfactory and consistent with that of the reference product. Satisfactory labelling has also been submitted.

RISK-BENEFIT ASSESSMENT
The quality of the product is acceptable and no new preclinical or clinical safety concerns have been identified. Extensive clinical experience with ropinirole hydrochloride is considered to have demonstrated the therapeutic value of the compound. The risk-benefit is, therefore, considered to be positive.
Module 6

STEPS TAKEN AFTER INITIAL PROCEDURE - SUMMARY

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<tr>
<th>Date submitted</th>
<th>Application type</th>
<th>Scope</th>
<th>Outcome</th>
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