

**Ropinirole 0.25 mg Film-Coated Tablets**  
**Ropinirole 0.5 mg Film-Coated Tablets**  
**Ropinirole 1 mg Film-Coated Tablets**  
**Ropinirole 2 mg Film-Coated Tablets**  
**Ropinirole 3 mg Film-Coated Tablets**  
**Ropinirole 4 mg Film-Coated Tablets**  
**Ropinirole 5 mg Film-Coated Tablets**

**(ropinirole hydrochloride)**

**PL 24668/0078-84**

**UK Public Assessment Report**

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**Ropinirole 0.25 mg, 0.5 mg, 1 mg, 2 mg, 3 mg,  
4 mg & 5 mg Film-Coated Tablets  
(ropinirole hydrochloride)**

**PL 24668/0078-84**

**LAY SUMMARY**

The Medicines and Healthcare products Regulatory Agency (MHRA) granted Caduceus Pharma Limited Marketing Authorisations (licences) for the medicinal products Ropinirole 0.25 mg, 0.5 mg, 1 mg, 2 mg, 3 mg, 4 mg and 5 mg Film-Coated Tablets (PL 24668/0078-84) on 21<sup>st</sup> January 2011. These are prescription-only medicines (POM).

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

Ropinirole 0.25 mg, 0.5 mg, 1 mg, 2 mg, 3 mg and 4 mg Film-Coated Tablets are used to treat the symptoms of moderate to severe idiopathic Restless Legs Syndrome. Moderate to severe Restless Legs Syndrome is typically represented by patients who have difficulty sleeping or severe discomfort in their legs or arms. It is a condition characterised by an irresistible urge to move the legs and occasionally the arms, usually accompanied by uncomfortable sensations such as tingling, burning or prickling. These feelings occur during periods of rest or inactivity such as sitting or lying down, especially in bed, and are worse in the evening or at night. Usually the only relief is obtained by walking about or moving the affected limbs, which often leads to problems sleeping. Ropinirole 0.25 mg, 0.5 mg, 1 mg, 2 mg, 3 mg and 4 mg Film-Coated Tablets relieve the discomfort and reduce the urge to move the limbs that disrupts night time sleep.

Ropinirole 5 mg Film-Coated Tablets are used to treat Parkinson's disease. The cause of Parkinson's disease is a lack of the substance dopamine in the brain. Ropinirole acts in a similar way to the natural dopamine, so helping the symptoms of Parkinson's disease. Ropinirole 5 mg Film-Coated Tablets may be used alone or in combination with other medicines against Parkinson's disease, to achieve a more effective treatment.

No new or unexpected safety concerns arose from these applications and it was therefore judged that the benefits of Ropinirole 0.25 mg, 0.5 mg, 1 mg, 2 mg, 3 mg, 4 mg and 5 mg Film-Coated Tablets outweigh the risks; hence Marketing Authorisations have been granted.

**Ropinirole 0.25 mg, 0.5 mg, 1 mg, 2 mg, 3 mg,  
4 mg & 5 mg Film-Coated Tablets**

**(ropinirole hydrochloride)**

**PL 24668/0078-84**

**SCIENTIFIC DISCUSSION**

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## INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the MHRA granted Caduceus Pharma Limited Marketing Authorisations for the medicinal products Ropinirole 0.25 mg, 0.5 mg, 1 mg, 2 mg, 3 mg, 4 mg and 5 mg Film-Coated Tablets (PL 24668/0078-84) on 21<sup>st</sup> January 2011. These are prescription-only medicines (POM).

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. Since the brand leader does not hold licences for the 3 mg and 4 mg strengths, the applications for these strengths have been made under Article 10.3 as ‘hybrid applications : different strength’, with the 2 mg strength of the brand leader as a cross reference product. 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 2<sup>nd</sup> July 1996; and Adartrel ▼ 0.25, 0.5, and 2 mg film-coated tablets (PL 19494/0033-34 and 0036), authorised in the UK as incoming Mutual Recognition applications (FR/H/0258/001-2 & 004) on 10<sup>th</sup> 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. Both indications are being proposed for these applications for Ropinirole film-coated tablets.

Ropinirole 0.25 mg, 0.5 mg, 1 mg, 2 mg, 3 mg and 4 mg Film-Coated Tablets are indicated for the symptomatic treatment of moderate to severe idiopathic Restless Legs Syndrome.

Ropinirole 5 mg Film-Coated Tablets may be used alone (without levodopa) in the treatment of idiopathic Parkinson’s disease. Addition of ropinirole to levodopa may be used to control “on-off” fluctuations and permit a reduction in the total daily dose of levodopa.

Ropinirole is a non-ergoline D2/D3 dopamine agonist (ATC code – N04B C04). Parkinson's disease is characterised by a marked dopamine deficiency in the nigral striatal system. Ropinirole alleviates this deficiency by stimulating striatal dopamine receptors. Ropinirole acts in the hypothalamus and pituitary to inhibit the secretion of prolactin.

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

protein binding of the drug is low (10-40%). Ropinirole is metabolised primarily by oxidative metabolism and ropinirole and its metabolites are mainly excreted in the urine. The major metabolite is at least 100 times less potent than ropinirole in animal models of dopaminergic function.

The MHRA has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place for this product type at all sites responsible for the manufacture and assembly of these products. Evidence of compliance with GMP has been provided for the named manufacturing and assembly sites

The applications are supported by the bioequivalence study presented by the applicant comparing the pharmacokinetic profile of the test product, Ropinirole 0.25 mg Film-Coated Tablets, to that of the reference product, Requip 0.25 mg Tablets. The bioequivalence study was carried out in accordance with Good Clinical Practice (GCP).

The Marketing Authorisation Holder has provided adequate justification for not submitting an Environmental Risk Assessment (ERA). These were applications for generic products and there is no reason to conclude that marketing of these products will change the overall use pattern of the existing market.

## PHARMACEUTICAL ASSESSMENT

### ACTIVE SUBSTANCE

#### Ropinirole hydrochloride

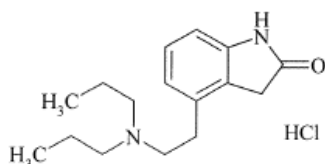
Nomenclature:

INN: Ropinirole hydrochloride

Chemical names:

- (i) 4-[2-(Dipropylamino)-ethyl]-1,3-dihydro-2H-indol-2-one Hydrochloride
- (ii) 4-[2-(Di-n-propylamino)-ethyl]-2(3H)-indolone Hydrochloride
- (iii) 4-[2-(Dipropylamino)ethyl]-2-indolinone Hydrochloride

Structure:



Molecular formula:  $C_{16}H_{24}N_2O \cdot HCl$

Molecular weight: 296.84 g/mol

CAS No: 91374-20-8

Physical form: White to off-white crystalline powder

Solubility: Soluble in water and methanol, very slightly soluble in ethyl alcohol

The active substance, ropinirole hydrochloride, is not the subject of a European Pharmacopoeia (Ph. Eur.) monograph.

Synthesis of the active substance from the designated starting materials has been adequately described and appropriate in-process controls and intermediate specifications are applied. Satisfactory specifications are in place for all starting materials and reagents and these are supported by relevant Certificates of Analysis. Confirmation has been provided that the raw materials, intermediates and auxiliary agents used in synthesis of the active are not of animal, biological or genetically modified origin.

Appropriate specifications have been provided for the active substance. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications. Batch analysis data are provided and comply with the proposed specifications. Satisfactory Certificates of Analysis have been provided for any reference standards used by the active substance manufacturers during validation studies.

The active substance is stored in appropriate packaging. Specifications and Certificates of Analysis have been provided for the packaging materials used. The primary packaging in direct contact with the active substance satisfies Directive 2002/72/EC (as amended) and is suitable for contact with foodstuffs.

Appropriate stability data have been generated by the active substance manufacturers for active substance stored in packaging representative of the proposed commercial packaging. These data demonstrate the stability of the active substance and appropriate retest periods have been applied.

## **MEDICINAL PRODUCT**

### **Description and Composition**

Ropinirole 0.25 mg, 0.5 mg, 1 mg, 2 mg, 3 mg, 4 mg and 5 mg Film-Coated Tablets are presented as round, biconvex, film-coated tablets containing ropinirole hydrochloride equivalent to 0.25, 0.5, 1, 2, 3, 4 and 5 mg ropinirole base (see SmPCs / patient information leaflet for full descriptions of individual tablets).

Other ingredients consist of pharmaceutical excipients, namely lactose monohydrate, microcrystalline cellulose, pregelatinised starch and magnesium stearate making up the tablet cores; and 'Opadry' film-coatings (see SmPCs for full details) – white 0.25 mg tablets - Opadry II 85F18378; yellow 0.5 mg tablets - Opadry II 85F32111; green 1 mg tablets - Opadry II 85F21676; pink 2 mg tablets - Opadry II 85F24026; purple 3 mg tablets - Opadry II 85F20157; orange 4 mg tablets - Opadry II 85F23579; and blue 5 mg tablets - Opadry II 85F20521. Appropriate justification for the inclusion of each excipient has been provided.

All excipients of the tablet cores comply with their respective European Pharmacopoeia monographs. The Opadry formulations used for film-coating are constituted from pharmacopoeial ingredients along with colourants that comply with Directive 95/45/EC. Suitable in-house specifications, accompanied by analytical methodology, are presented for each Opadry formulation. Satisfactory Certificates of Analysis have been provided for all excipients.

The magnesium stearate has been confirmed as being of vegetable origin. The only excipient used that contains material of animal or human origin is lactose. The applicant has provided a declaration that milk used in the production of lactose is sourced from healthy animals under the same conditions as that for human consumption. None of the excipients are sourced from genetically modified organisms.

There were no novel excipients used and no overages.

### **Pharmaceutical development**

Details of the pharmaceutical development of the medicinal products have been supplied and are satisfactory. The objective was to develop stable, generic formulations, bioequivalent to the reference products, Requip tablets, PL 10592/0085-89 (GlaxoSmithKline UK).

Comparative dissolution data were provided for batches of the test product and appropriate reference products. The dissolution profiles were satisfactory.

### **Manufacture**

A description and flow-chart of the manufacturing method has been provided.

In-process controls have been provided and are appropriate considering the nature of the products and the method of manufacture. Process validation studies were conducted and the results were satisfactory.

### **Finished product specification**

The finished product specifications are provided for both release and shelf-life and are satisfactory. Acceptance limits have been justified with respect to conventional pharmaceutical requirements and, where appropriate, safety. Test methods have been described and have been adequately validated, as appropriate. Satisfactory batch analysis data are provided and accepted. Certificates of Analysis have been provided for any reference standards used.

### **Container Closure System**

The tablets are licensed for marketing in aluminium / aluminium blister strips, or in High-Density Polyethylene (HDPE) containers, which are packaged with the Patient Information Leaflet (PIL) into cardboard outer cartons. The licensed pack sizes are 2, 5, 7, 10, 12, 14, 20, 21, 28, 30, 50, 56, 60, 84, 100, 126 and 210 film-coated tablets, although the MAH has stated that not all pack sizes may be marketed.

Satisfactory specifications and Certificates of Analysis for all packaging components used have been provided. All primary product packaging complies with EU legislation, Directive 2002/72/EC (as amended), and is suitable for contact with foodstuffs.

### **Stability**

Finished product stability studies have been conducted in accordance with current guidelines, using product stored in packaging representative of the packaging proposed for marketing. Based on the results, a shelf-life of 24 months has been set, which is satisfactory. Storage instructions are 'Do not store above 25°C. Store in the original package in order to protect from light'. Additional instructions for the HDPE containers only are 'Keep the container tightly closed in order to protect from moisture'.

### **Bioequivalence Study**

A bioequivalence study was submitted comparing the test product, Ropinirole 0.25 mg Film-Coated Tablets, to the reference product, Requip 0.25 mg Tablets.

An evaluation of the bioequivalence study is found in the Clinical Assessment section.

### **Quality Overall Summary**

A satisfactory quality overview is provided and has been prepared by an appropriately qualified expert. The CV of the expert has been supplied.

### **Product Information**

The approved Summaries of Product Characteristics (SmPCs), and Patient Information Leaflet (PIL) and labelling texts are satisfactory. Mock-up PILs have been provided. The labelling fulfils the statutory requirements for Braille.



The package leaflets are in line with the SmPCs and are satisfactory. The package leaflets have been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The results show that the package leaflets meet the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

For PL 24668/0078-81 and 0084, satisfactory mock-ups of the labelling have been provided.

For PL 24668/0082-83, the MAH has submitted text versions only and has committed to submitting mock-up labelling to the relevant regulatory authorities for approval before packs are marketed.

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.

### **Conclusion**

All pharmaceutical issues have been resolved and the quality grounds for these applications are considered adequate. There are no objections to approval of Ropinirole 0.25 mg, 0.5 mg, 1 mg, 2 mg, 3 mg, 4 mg and 5 mg Film-Coated Tablets from a pharmaceutical point of view.

## **PRE-CLINICAL ASSESSMENT**

These abridged applications, submitted under Articles 10.1 and 10.3 (for the 3 mg and 4 mg strengths) of Directive 2001/83/EC, as amended, are for Ropinirole 0.25 mg, 0.5 mg, 1 mg, 2 mg, 3 mg, 4 mg and 5 mg Film-Coated Tablets, products claiming to be generic medicinal products of Requip 0.25, 0.5, 1, 2 and 5 mg tablets (PL 10592/0085-89, GlaxoSmithKline UK).

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

A pre-clinical overview has been written by a suitably qualified person and is satisfactory. The CV of the expert has been supplied.

## **CLINICAL ASSESSMENT**

### **INDICATIONS**

Ropinirole 0.25 mg, 0.5 mg, 1 mg, 2 mg, 3 mg and 4 mg Film-Coated Tablets are indicated for the symptomatic treatment of moderate to severe idiopathic Restless Legs Syndrome.

Ropinirole 5 mg Film-Coated Tablets may be used alone (without levodopa) in the treatment of idiopathic Parkinson's disease. Addition of ropinirole to levodopa may be used to control "on-off" fluctuations and permit a reduction in the total daily dose of levodopa.

The indications are consistent with those for the reference products and are satisfactory.

### **POSOLGY AND METHOD OF ADMINISTRATION**

Full details concerning the posology are provided in the SmPCs. The posology is consistent with that for the reference products and is satisfactory.

### **TOXICOLOGY**

The toxicology of ropinirole is well known. No new data have been submitted and none are required for applications of this type.

### **CLINICAL PHARMACOLOGY**

#### **Pharmacodynamics**

The clinical pharmacology of ropinirole is well known. With the exception of the bioequivalence study, no new pharmacodynamic or pharmacokinetic data are supplied and none are required for these applications.

#### **Pharmacokinetics - Bioequivalence study**

The applications are supported by the bioequivalence study presented by the applicant comparing the pharmacokinetic profiles of Ropinirole 0.25 mg Film-Coated Tablets (test) and Requip 0.25 mg Tablets (reference). The study was of an appropriate design and was conducted to principles of Good Clinical Practice (GCP).

This was a randomised, two-treatment, two-period, two-sequence, single dose crossover bioequivalence study conducted in 30 healthy adult human male subjects under fasting conditions. Following a fast of at least 10 hours, a single dose of the investigational products was administered orally, with 240 ml of water, to each subject in each period. A satisfactory washout period of 7 days was maintained between the two dosing days in each group.

Blood samples were taken pre-dose (0.0) and at specified time points up to 24.0 hours after administration of test or reference product. Plasma levels of ropinirole were detected by a validated HPLC-MS / MS method.

The primary pharmacokinetic parameters for this study were  $C_{max}$ ,  $AUC_{0-t}$ , and  $AUC_{0-\infty}$ . Bioequivalence of the test product versus the reference product was concluded if the 90% Confidence Intervals (CI) fell within the acceptance range, 0.80-1.25 (80.00%-125.00%), for log-transformed  $C_{max}$ ,  $AUC_{0-t}$ , and  $AUC_{0-\infty}$ .

#### Results:

30 subjects were enrolled in the study; 29 of these completed the study and were included in the pharmacokinetic evaluation and statistical analysis. The discontinuation, and non-inclusion in the pharmacokinetic analysis, of one subject was satisfactorily justified.

*Safety* - There were no serious adverse events reported. There were no clinically significant changes in the post study evaluations of haematology and biochemistry.

The summary of the results of the bioequivalence study are tabulated below:

Pharmacokinetic results for ropinirole for a randomised, two-treatment, two-sequence, single-dose crossover study between the test and reference products. n=29 healthy subjects, dosed fasted; t=24 hours. Wash-out period: 7 days.

Ratio and 90% Confidence Intervals of Test Product versus Reference Product			
Pharmacokinetic Parameter	Ratio	90% Confidence Intervals	
		Lower 90% CI	Upper 90% CI
$AUC_{0-t}$	0.99	0.92	1.06
$AUC_{0-\infty}$	0.99	0.93	1.05
$C_{max}$	1.03	0.99	1.07

#### **Conclusion on Bioequivalence**

The results of the bioequivalence study show that the test and reference products are bioequivalent under fasting conditions, as the confidence intervals for  $C_{max}$ ,  $AUC_{0-t}$ , and  $AUC_{0-\infty}$  for ropinirole fall within the acceptance criteria ranges of 80.00-125.00%, in line with current CHMP guidelines.

Satisfactory justification is provided for a bio-waiver for Ropinirole 0.5 mg, 1 mg, 2 mg, 3 mg, 4 mg and 5 mg Film-Coated Tablets. As Ropinirole 0.25 mg, 0.5 mg, 1 mg, 2 mg, 3 mg, 4 mg and 5 mg Film-Coated Tablets meet the criteria specified in the "Guideline on the Investigation of Bioequivalence" (CPMP/EWP/QWP/1401/98 rev. 1/Corr), the results and conclusions of the bioequivalence study on the 0.25 mg strength can be extrapolated to the 0.5 mg, 1 mg, 2 mg, 3 mg, 4 mg and 5 mg strength tablets.

#### **EFFICACY**

No new data have been submitted and none are required. The reference products are established and the applications depend upon the ability to demonstrate bioequivalence. Efficacy is reviewed in the clinical overview. The efficacy of ropinirole is well-established from its extensive use in clinical practice.

#### **SAFETY**

No new data have been submitted and none are required for applications of this type. No new or unexpected safety concerns arose from these applications. Safety is reviewed in the clinical overview. The safety profile of ropinirole is well-known.

## **PRODUCT INFORMATION:**

### **Summary of Product Characteristics**

The approved SmPCs are consistent with those for the reference products and are acceptable.

### **Patient Information Leaflet**

The final PILs are in line with the approved SmPCs and are satisfactory. The PIL user testing has been evaluated and is accepted.

### **Labelling**

The labelling is satisfactory.

### **Clinical overview**

A satisfactory clinical overview is provided, and has been prepared by an appropriately qualified expert. The CV of the clinical expert has been supplied.

## **CONCLUSIONS**

All issues have been adequately addressed by the applicant. Sufficient clinical information has been submitted to support these applications. The risk-benefit of the products is considered favourable from a clinical perspective. The grant of Marketing Authorisations was, therefore, recommended on medical grounds.

## **OVERALL CONCLUSION AND BENEFIT- RISK ASSESSMENT**

### **QUALITY**

The important quality characteristics of Ropinirole 0.25 mg, 0.5 mg, 1 mg, 2 mg, 3 mg, 4 mg 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.

### **PRE-CLINICAL**

No new pre-clinical data were submitted and none are required for applications of this type.

### **CLINICAL**

Bioequivalence has been demonstrated between the applicant's Ropinirole 0.25 mg Film-Coated Tablets, and the reference product Requip 0.25 mg Tablets (sourced from Germany).

As the proposed products, Ropinirole 0.25 mg, 0.5 mg, 1 mg, 2 mg, 3 mg, 4 mg and 5 mg Film-Coated Tablets, meet the criteria specified in the "Guideline on the Investigation of Bioequivalence" (CPMP/EWP/QWP/1401/98 rev. 1/Corr), the results and conclusions of the bioequivalence study on the 0.25 mg strength were extrapolated to the 0.5 mg, 1 mg, 2 mg, 3 mg, 4 mg and 5 mg strength tablets, and omission of further bioequivalence studies on the other strengths can be accepted.

No new or unexpected safety concerns arise from these applications.

### **PRODUCT LITERATURE**

The approved SmPCs are consistent with those for the reference products and are satisfactory.

Mock-up PILs have been provided. The package leaflets are in line with the SmPCs and are satisfactory. The package leaflets have been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The results show that the package leaflets meet the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

For PL 24668/0078-81 and 0084, satisfactory mock-ups of the labelling have been provided. The approved labelling artwork complies with statutory requirements. In line with current legislation, the name of the product in Braille appears on the outer packaging and sufficient space has been included for a standard UK pharmacy dispensing label.

For PL 24668/0082-83, the MAH has submitted text versions only and has committed to submitting mock-up labelling to the relevant regulatory authorities for approval before packs are marketed.

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.

#### **BENEFIT- RISK ASSESSMENT**

The quality of the products is acceptable and no new pre-clinical or clinical safety concerns have been identified. The bioequivalence study and its conclusions support the claim that the applicant's Ropinirole 0.25 mg, 0.5 mg, 1 mg, 2 mg, 3 mg, 4 mg and 5 mg Film-Coated Tablets are generics of the reference products, Requip 0.25, 0.5, 1, 2 and 5 mg tablets (GlaxoSmithKline UK). Extensive clinical experience with ropinirole is considered to have demonstrated the therapeutic value of the active substance. The benefit: risk ratio is considered to be positive.

**Ropinirole 0.25 mg, 0.5 mg, 1 mg, 2 mg, 3 mg,  
4 mg & 5 mg Film-Coated Tablets  
(ropinirole hydrochloride)**

**PL 24668/0078-84**

**STEPS TAKEN FOR ASSESSMENT**

- 1 The MHRA received the marketing authorisation applications on 13<sup>th</sup> June 2007
- 2 Following standard checks and communication with the applicant the MHRA considered the applications valid on 28<sup>th</sup> August 2007
- 3 Following assessment of the applications the MHRA requested further information relating to the quality dossier on 12<sup>th</sup> March 2008, 23<sup>rd</sup> October 2008 and 25<sup>th</sup> June 2009; and further information relating to the clinical dossier on 17<sup>th</sup> November 2008
- 4 The applicant responded to the MHRA's requests, providing further information for the quality sections on 25<sup>th</sup> July 2008, 21<sup>st</sup> April 2009 and , 8<sup>th</sup> March 2010 respectively; and further information for the clinical sections on 14<sup>th</sup> May 2009
- 5 The applications were determined on 21<sup>st</sup> January 2011



**Ropinirole 0.25 mg, 0.5 mg, 1 mg, 2 mg, 3 mg,  
4 mg & 5 mg Film-Coated Tablets**

**(ropinirole hydrochloride)**

**PL 24668/0078-84**

**STEPS TAKEN AFTER AUTHORISATION**

Not applicable

## SUMMARY OF PRODUCT CHARACTERISTICS

The UK Summary of Product Characteristics (SmPC) for Ropinirole 0.25 mg, 0.5 mg, 1 mg, 2 mg, 3 mg and 4 mg Film-Coated Tablets (PL 24668/0078-83) is as follows. Differences between the individual SmPCs are highlighted:

### 1 NAME OF THE MEDICINAL PRODUCT

Ropinirole 0.25 mg Film-Coated Tablets

Ropinirole 0.5 mg Film-Coated Tablets

Ropinirole 1 mg Film-Coated Tablets

Ropinirole 2 mg Film-Coated Tablets

Ropinirole 3 mg Film-Coated Tablets

Ropinirole 4 mg Film-Coated Tablets

### 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains ropinirole hydrochloride equivalent to 0.25 / 0.5 / 1 / 2 / 3 / 4 mg ropinirole base.

For a full list of excipients, see section 6.1.

### 3 PHARMACEUTICAL FORM

Film-coated tablet.

Ropinirole 0.25 mg Film-Coated Tablets are white, round (7mm in diameter), biconvex, and embossed with R0.25 on one side.

Ropinirole 0.5 mg Film-Coated Tablets are yellow, round (7mm in diameter), biconvex, and embossed with R0.5 on one side.

Ropinirole 1 mg Film-Coated Tablets are green, round (7mm in diameter), biconvex, and embossed with R1 on one side.

Ropinirole 2 mg Film-Coated Tablets are pink, round (7mm in diameter), biconvex, and embossed with R2 on one side.

Ropinirole 3 mg Film-Coated Tablets are purple, round (8.5mm in diameter), biconvex, and embossed with R3 on one side.

Ropinirole 4 mg Film-Coated Tablets are orange, round (9.5mm in diameter), biconvex, and embossed with R4 on one side.

### 4 CLINICAL PARTICULARS

#### 4.1 Therapeutic indications

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

#### 4.2 Posology and method of administration

Oral use.

##### Adults

Individual dose titration against efficacy and tolerability is recommended.

Ropinirole should be taken just before bedtime, however 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 2.0 mg once a day.

The dose may be increased to 1.0 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 2.0 mg once a day. In some patients, to achieve optimal improvement, the dose may be increased gradually up to a maximum of 4.0 mg once a day. In clinical trials the dose was increased by 0.5 mg each week to 3.0 mg once a day and then by 1.0 mg up to the maximum recommended dose of 4.0 mg once a day as shown in Table 1.

Doses above 4.0 mg once daily have not been investigated in Restless Legs Syndrome patients.

Table 1 – Dose titration

Week	2	3	4	5*	6*	7*
*Dose (mg) / once daily	1.0	1.5	2.0	2.5	3.0	4.0

T

o\* 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 in patients over 65 years of age. Any increase in dosage should be gradual and titrated against the symptomatic response.

Renal impairment

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

**4.3 Contraindications**

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

Severe renal impairment (creatinine clearance < 30ml/min).

Severe hepatic impairment.

**4.4 Special warnings and precautions for use**

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

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

In Parkinson's disease, ropinirole has been associated uncommonly with somnolence and episodes of sudden sleep onset (see Section 4.8) however in Restless Legs Syndrome, this phenomenon is very rare. Nevertheless, patients must be informed of this phenomenon and advised to exercise caution while driving or operating machines during treatment with ropinirole. Patients who have experienced somnolence and/or an episode of sudden sleep onset must refrain from driving or operating machines. Furthermore, a reduction of dosage or termination of therapy may be considered.

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

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

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

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

Ropinirole Film-Coated Tablets contain lactose monohydrate. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

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

Ropinirole is principally 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  $C_{max}$  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 between ropinirole (at a dose of 2 mg, three times a day) and theophylline, a substrate of CYP1A2, revealed no change in the pharmacokinetics of either ropinirole or theophylline. Therefore, it is not expected that ropinirole will compete with the metabolism of other medicinal products which are metabolised by CYP1A2.

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

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

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

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

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

#### 4.6 Pregnancy and lactation

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

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

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

#### 4.7 Effects on ability to drive and use machines

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

#### 4.8 Undesirable effects

Adverse drug reactions are listed below by system organ class and frequency. Frequencies from clinical trials are determined as excess incidence over placebo and are classed as Very Common (> 1/10) or Common (> 1/100 to < 1/10) or uncommon (> 1/1000 to < 1/100).

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

##### Use of ropinirole in Restless Legs Syndrome

In Restless Legs Syndrome clinical trials the most common adverse drug reaction 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  $\geq 1.0\%$  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)

<b>Psychiatric Disorders</b>	
<i>Common:</i>	Nervousness
<i>Uncommon:</i>	Confusion
<b>Nervous System Disorders</b>	
<i>Common:</i>	Syncope, Somnolence, Dizziness (including vertigo)
<b>Vascular Disorders</b>	
<i>Uncommon:</i>	Postural hypotension, hypotension
<b>Gastrointestinal Disorders</b>	
<i>Very Common:</i>	Vomiting, Nausea
<i>Common:</i>	Abdominal pain
<b>General Disorders and Administration Site Conditions</b>	
<i>Common:</i>	Fatigue

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

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

Management of undesirable effects

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

Other experience with Ropinirole

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

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

<b>Psychiatric Disorders</b>	
<i>Common:</i>	Hallucinations, Confusion
<i>Uncommon:</i>	Increased libido
<b>Nervous System Disorders</b>	
<i>Very Common:</i>	Syncope, Dyskinesia, Somnolence
<b>Gastrointestinal Disorders</b>	
<i>Very Common:</i>	Nausea
<i>Common:</i>	Vomiting, Abdominal pain, Heartburn
<b>General Disorders and Administration Site Conditions</b>	
<i>Common:</i>	Leg oedema

Post marketing reports

Hypersensitivity reactions (including urticaria, angioedema, rash, pruritus)

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

Impulse control disorders including pathological gambling and hypersexuality, and increased libido, have been reported (see section 4.4).

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

Following ropinirole therapy, postural hypotension or hypotension has been reported uncommonly (>1/1,000, <1/100), rarely severe.

Very rare cases of hepatic reactions (<1/10,000), mainly increase of liver enzymes, have been reported.

**4.9 Overdose**

It is anticipated that the symptoms of ropinirole overdose will be related to its dopaminergic activity. These symptoms may be alleviated by appropriate treatment with dopamine antagonists such as neuroleptics or metoclopramide.

**5 PHARMACOLOGICAL PROPERTIES****5.1 Pharmacodynamic properties**

Pharmacotherapeutic Group: *Dopamine agonist*

ATC code: *N04BC04*

Mechanism of action

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

### Clinical efficacy

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

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

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

Although sufficient data is 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 1mg 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.

## **5.2 Pharmacokinetic properties**

### Absorption

The bioavailability of ropinirole is about 50% (36% to 57%), with  $C_{max}$  reached on average 1.5 hours after the dose. 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.

### Linearity

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

### Population-related characteristics

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

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

## **5.3 Preclinical safety data**

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

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

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

**Reproductive Toxicity:** Administration of ropinirole to pregnant rats at maternally toxic doses resulted in decreased foetal body weight at 60 mg/kg/day (approximately 15 times the AUC at the maximum dose in humans), increased foetal death at 90 mg/kg/day (approximately 25 times the AUC at the maximum dose in humans) and digit malformations at 150 mg/kg/day (approximately 40 times the AUC at the maximum dose in humans). There were no teratogenic effects in the rat at 120 mg/kg/day (approximately 30 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 (4 mg/day), see section 5.1.



## 6 PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

*Tablet core:*

Lactose monohydrate  
Microcrystalline cellulose  
Pregelatinised starch  
Magnesium stearate

*Film coating:*

0.25 mg - Opadry II 85F18378 (Polyvinyl alcohol, Titanium dioxide, Macrogl 3350, Talc)

0.5 mg - Opadry II 85F32111 (Polyvinyl alcohol, Titanium dioxide, Macrogl 3350, Talc, Iron oxide yellow)

1 mg - Opadry II 85F21676 (Polyvinyl alcohol, Titanium dioxide, Macrogl 3350, Talc, Iron oxide yellow, Brilliant blue aluminium lake, Iron oxide black)

2 mg - Opadry II 85F24026 (Polyvinyl alcohol, Titanium dioxide, Macrogl 3350, Talc, Iron oxide yellow, Iron oxide red)

3 mg - Opadry II 85F20157 (Polyvinyl alcohol, Macrogl 3350, Titanium dioxide, Talc, Carmine, Indigo carmine aluminium lake)

4 mg - Opadry II 85F23579 (Polyvinyl alcohol, Macrogl 3350, Titanium dioxide, Talc, Iron oxide yellow, Iron oxide red, Iron oxide black)

### 6.2 Incompatibilities

Not applicable

### 6.3 Shelf life

24 months

### 6.4 Special precautions for storage

Do not store above 25°C

Store in the original package in order to protect from light

*HDPE tablet containers only:*

Keep the container tightly closed in order to protect from moisture

### 6.5 Nature and contents of container

Aluminium/Aluminium blister or induction sealed HDPE tablet containers of 2, 5, 7, 10, 12, 14, 20, 21, 28, 30, 50, 56, 60, 84, 100, 126 and 210 tablets.

Not all pack sizes may be marketed.

### 6.6 Special precautions for disposal

No special requirements

## 7 MARKETING AUTHORISATION HOLDER

Caduceus Pharma Limited  
6<sup>th</sup> Floor,  
94 Wigmore Street,  
London  
W1U 3RF  
UK

**8      MARKETING AUTHORISATION NUMBER(S)**

PL 24668/0078  
PL 24668/0079  
PL 24668/0080  
PL 24668/0081  
PL 24668/0082  
PL 24668/0083

**9      DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

21/01/2011

**10     DATE OF REVISION OF THE TEXT**

21/01/2011

The UK Summary of Product Characteristics (SmPC) for Ropinirole 5 mg Film-Coated Tablets (PL 24668/0084) is as follows.

**1 NAME OF THE MEDICINAL PRODUCT**

Ropinirole 5 mg Film-Coated Tablets

**2 QUALITATIVE AND QUANTITATIVE COMPOSITION**

Each film-coated tablet contains ropinirole hydrochloride equivalent to 5.0 mg ropinirole base.

For a full list of excipients, see section 6.1.

**3 PHARMACEUTICAL FORM**

Film-coated tablet.

Ropinirole 5 mg Film-Coated Tablets are blue, round (10.5mm in diameter), biconvex, and embossed with R5 on one side.

**4 CLINICAL PARTICULARS**

**4.1 Therapeutic indications**

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

Ropinirole may be used alone (without levodopa) in the treatment of idiopathic Parkinson's disease.

Addition of ropinirole to levodopa may be used to control "on-off" fluctuations and permit a reduction in the total daily dose of levodopa.

**4.2 Posology and method of administration**

Oral use.

Individual dose titration against efficacy and tolerability is recommended.

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

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

	Week			
	1	2	3	4
Unit dose ( mg )	0.25	0.5	0.75	1.0
Unit dose presentation ( mg )	0.25	0.5	0.25, 0.5	1.0
Total daily dose ( mg )	0.75	1.5	2.25	3.0

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

A therapeutic response may be seen between 3 and 9 mg/day, although adjunct therapy patients may require higher doses. If sufficient symptomatic control is not achieved, or maintained, the dose of ropinirole may be increased until an acceptable therapeutic response is established. Doses above 24 mg/day have not been investigated in clinical trials and this dose should not be exceeded.

When ropinirole is administered as adjunct therapy to L-dopa, the concurrent dose of L-dopa may be reduced gradually by around 20% in total. 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 L-dopa dose may ameliorate dyskinesia (see also section 4.8).

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

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

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

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

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

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

#### **4.3 Contraindications**

Hypersensitivity to ropinirole or to any of the excipients.

In light of the results of animal studies and the lack of studies in human pregnancy, ropinirole is contra-indicated in pregnancy, lactation and in women of child-bearing potential unless adequate contraception is used.

#### **4.4 Special warnings and precautions for use**

Due to the pharmacological action of ropinirole, patients with severe cardiovascular disease should be treated with caution.

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

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

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

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

Ropinirole Film-Coated Tablets contain lactose monohydrate. 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

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

No pharmacokinetic interaction has been seen between ropinirole and L-dopa or domperidone which would necessitate dosage adjustment of either drug. No interaction has been seen between ropinirole and other drugs commonly used to treat Parkinson's Disease but, as is common practice, care should be taken when adding a new drug to a treatment regimen. Other dopamine agonists may be used with caution.

In a study of Parkinsonian patients receiving concurrent digoxin, no interaction was seen which would require dosage adjustment.

It has been established from in vitro experiments that ropinirole is metabolised by the cytochrome P450 enzyme CYP1A2. There is, therefore, the potential for an interaction between ropinirole and substrates (such as theophylline) or inhibitors (such as ciprofloxacin, fluvoxamine and cimetidine) of this enzyme. In patients already receiving ropinirole, the dose of ropinirole may need to be adjusted when these drugs are introduced or withdrawn.

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

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

#### 4.6 Pregnancy and lactation

Ropinirole should not be used during pregnancy. In animal studies, administration of ropinirole to pregnant rats at maternally toxic doses resulted in decreased foetal body weight at 60 mg/kg (approximately three times the AUC of the maximum dose in man), increased foetal death at 90 mg/kg (~x5) and digit malformations at 150 mg/kg (~x9).

There was no teratogenic effect in the rat at 120 mg/kg (~x7) and no indication of an effect on development in the rabbit. There have been no studies of ropinirole in human pregnancy. 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

Adverse drug reactions are listed below by system organ class and frequency. Frequencies are defined as: Very Common (> 1/10), Common (> 1/100, < 1/10), Uncommon (> 1/1000, < 1/100), Rare (> 1/10,000, < 1/1000), and Very Rare (<1/10,000), including isolated reports.

Common and uncommon events were generally determined from pooled safety data from clinical trial populations of ropinirole and are quoted as excess incidence over placebo.

Rare and Very Rare events were generally determined from post-marketing data and refer to reporting rate rather than the true frequency.

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

*Adverse drug reactions reported from patients taking ropinirole*

<b>Immune system disorders</b>	
<i>Very Rare:</i>	Hypersensitivity reactions (including urticaria, angioedema, rash, pruritis) <sup>3</sup>
<b>Psychiatric Disorders</b>	
<i>Common:</i>	Confusion <sup>1</sup> , Hallucinations
<i>Uncommon:</i>	Psychotic reactions (other than hallucinations) including delusion, and paranoia, delirium. Patients treated with dopamine agonists for treatment of Parkinson's disease, including ropinirole, especially at high doses, have been reported as exhibiting signs of pathological gambling, increased libido and hypersexuality, generally reversible upon reduction of the dose or treatment discontinuation <sup>3</sup> .
<b>Nervous System Disorders</b>	
<i>Very Common:</i>	Somnolence <sup>2</sup> , Dyskinesia <sup>1*</sup>
<i>Common:</i>	Dizziness (including vertigo) <sup>1,2</sup> , syncope <sup>2</sup>
<i>Uncommon:</i>	Extreme somnolence <sup>3</sup> , Sudden onset of sleep <sup>3</sup>
<b>Vascular Disorders</b>	
<i>Common:</i>	Hypotension, Postural hypotension
<b>Gastrointestinal Disorders</b>	
<i>Very Common:</i>	Nausea
<i>Common:</i>	Abdominal pain <sup>2</sup> , Vomiting <sup>2</sup> , Dyspepsia <sup>2</sup>
<b>General Disorders and Administration Site Conditions</b>	
<i>Common:</i>	Leg oedema <sup>2</sup>
<b>Hepatobiliary Disorders</b>	
<i>Very Rare:</i>	Hepatic enzymes increased <sup>3</sup>

1 Adjunct therapy studies

2 Monotherapy studies

3 Post-marketing data (see Section 4.4)

\* 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)

#### 4.9 Overdose

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

## 5 PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

Pharmacotherapeutic Group: *Dopamine agonist*

ATC code: *N04BC04*

#### Mechanism of action

Ropinirole is a non-ergoline dopamine agonist.

Parkinson's disease is characterised by a marked dopamine deficiency in the nigral striatal system. Ropinirole alleviates this deficiency by stimulating striatal dopamine receptors.

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

## 5.2 Pharmacokinetic properties

Oral absorption of ropinirole is rapid and essentially complete. Bioavailability of ropinirole is approximately 50% and average peak concentrations of the drug are achieved at a median time of 1.5 hours post-dose. Wide inter-individual variability in the pharmacokinetic parameters has been seen but, overall, there is a proportional increase in the systemic exposure (C<sub>max</sub> and AUC) to the drug with an increase in dose, over the therapeutic dose range. Consistent with its high lipophilicity, ropinirole exhibits a large volume of distribution (approx. 8 l/kg) and is cleared from the systemic circulation with an average elimination half-life of about six hours. Plasma protein binding of the drug is low (10-40%). Ropinirole is metabolised primarily by oxidative metabolism and ropinirole and its metabolites are mainly excreted in the urine. The major metabolite is at least 100 times less potent than ropinirole in animal models of dopaminergic function.

No change in the oral clearance of ropinirole is observed following single and repeated oral administration. As expected for a drug being administered approximately every half life, there is, on average, two-fold higher steady-state plasma concentrations of ropinirole following the recommended t.i.d. regimen compared to those observed following a single oral dose.

## 5.3 Preclinical safety data

*General toxicology:* Ropinirole caused no serious or irreversible toxicity in laboratory animals at 15mg/kg (monkey), 20mg/kg (mouse) or 50mg/kg (rat). The toxicology profile is principally determined by the pharmacological activity of the drug (behavioural changes, hypoprolactinaemia, decrease in blood pressure and heart rate, ptosis and salivation).

*Genotoxicity:* Genotoxicity was not observed in a battery of in vitro and in vivo tests.

*Carcinogenicity:* Two-year studies have been conducted in the mouse and rat at dosages up to 50 mg/kg. The mouse study did not reveal any carcinogenic effect. In the rat, the only drug-related lesions were Leydig cell hyperplasia/adenoma in the testis 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.

## 6 PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

#### Tablet core:

Lactose monohydrate  
Microcrystalline cellulose  
Pregelatinised starch  
Magnesium stearate

#### Film coating:

Opadry II 85F20521 (Polyvinyl alcohol, Titanium dioxide, Macrogol 3350, Talc, Indigo carmine aluminium lake)

### 6.2 Incompatibilities

Not applicable

### 6.3 Shelf life

24 months

### 6.4 Special precautions for storage

Do not store above 25°C

Store in the original package in order to protect from light

#### *HDPE tablet containers only:*

Keep the container tightly closed in order to protect from moisture

**6.5 Nature and contents of container**

Aluminium/Aluminium blister or induction sealed HDPE tablet containers of 2, 5, 7, 10, 12, 14, 20, 21, 28, 30, 50, 56, 60, 84, 100, 126 and 210 tablets.

Not all pack sizes may be marketed.

**6.6 Special precautions for disposal**

No special requirements

**7 MARKETING AUTHORISATION HOLDER**

Caduceus Pharma Limited  
6th Floor,  
94 Wigmore Street,  
London  
W1U 3RF  
UK

**8 MARKETING AUTHORISATION NUMBER(S)**

PL 24668/0084

**9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

21/01/2011

**10 DATE OF REVISION OF THE TEXT**

21/01/2011



## PATIENT INFORMATION LEAFLET

Combined PIL for PL 24668/0078-83 – 0.25, 0.5, 1, 2, 3 and 4 mg strengths



*(Only the marketed strengths will be stated on the printed leaflets)*

### Ropinirole (as hydrochloride)

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

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:

1. What Ropinirole Film-coated Tablets are and what they are used for
2. Before you take Ropinirole Film-coated Tablets
3. How to take Ropinirole Film-coated Tablets
4. Possible side effects
5. How to store Ropinirole Film-coated Tablets
6. Further information

#### 1. WHAT ROPINIROLE FILM-COATED TABLETS ARE AND WHAT THEY ARE USED FOR

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

Ropinirole Film-coated Tablets are used to treat the symptoms of moderate to severe idiopathic Restless Legs Syndrome.

Moderate to severe Restless Legs Syndrome is typically represented by patients who have difficulty sleeping or severe discomfort in their legs or arms. It is a condition characterised by an irresistible urge to move the legs and occasionally the arms, usually accompanied by uncomfortable sensations such as tingling, burning or prickling. These feelings occur during periods of rest or inactivity such as sitting or lying down, especially in bed, and are worse in the evening or at night. Usually the only relief is obtained by walking about or moving the affected limbs, which often leads to problems sleeping.

Tell your doctor if:

- you are taking medicines to treat high blood pressure, or for heart problems
- you give up or start smoking while taking Ropinirole Film-coated Tablets. Your doctor may need to adjust your dose.
- you are taking Ropinirole Film-coated Tablets and the doctor is going to prescribe you any other medicine.

#### Taking Ropinirole Film-coated Tablets with food and drink

Always swallow the tablets whole with water and preferably with food. Do not chew them.

Taking Ropinirole Film-coated Tablets with food may reduce the likelihood of you feeling or being sick.

You should not drink alcohol while you are taking this medicine.

#### Pregnancy and breast-feeding

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

Ropinirole is **not recommended** if you are breast feeding, as it can affect your milk production.

Talk to 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.

#### Driving and using machines

This medicine does not usually affect people's normal activities. However, Ropinirole Film-coated Tablets can cause extreme sleepiness (somnia) in some people and may cause them to fall asleep suddenly without any apparent warning. Contact your doctor if you experience either of these effects. If you do suffer from these effects then DO NOT drive or operate machinery, and do not put yourself in any situation where sleepiness or falling asleep may put you (or others) at risk of serious injury or death.

Ropinirole Film-coated Tablets relieve the discomfort and reduce the urge to move the limbs that disrupts night time sleep.

Ropinirole is also authorised to treat other conditions which are not mentioned in this leaflet. Ask your doctor or pharmacist if you have further questions.

## 2. BEFORE YOU TAKE ROPINIROLE FILM-COATED TABLETS

### Do not take Ropinirole Film-coated Tablets

- if you are allergic (hypersensitive) to ropinirole or any of the other ingredients of Ropinirole Film-coated Tablets
- if you have serious liver disease
- if you have serious kidney disease

If you are unsure, it is essential to talk to your doctor.

### Take special care with Ropinirole Film-coated Tablets

Tell your doctor before you start to take this medicine if you:

- are pregnant or think you may be pregnant
- are breast-feeding
- have liver disease
- have a serious heart complaint
- have a serious mental health problem
- have a history of any unusual urges and/or behaviours (such as 'excessive gambling or excessive sexual behaviour')

In these situations your doctor should carefully supervise your treatment.

During treatment with Ropinirole Film-coated Tablets take special care when you drive or operate machinery. If you suffer from extreme sleepiness or suddenly fall asleep without apparently feeling sleepy, do not drive or use machinery, and contact your doctor.

During treatment for Restless Legs Syndrome: If your symptoms become worse, start earlier in the day or after less time at rest, or affect other parts of your body such as your arms, you should see your doctor who may adjust the dose of ropinirole that you are taking.

### Taking other medicines

Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription. This applies also to herbal medicines as well as strong vitamins and minerals.

The effect of Ropinirole Film-coated Tablets may be increased or decreased by other medicines, and vice versa. These medicines include:

- ciprofloxacin (an antibiotic)
- enoxacin (an antibiotic)
- fluvoxamine (a drug used to treat depression)
- theophylline (a drug used to treat asthma)
- hormone replacement therapy (also called HRT)
- anti-psychotics and other drugs that block dopamine in the brain (e.g. sulphiride or metoclopramide)

ACTPL083

### Important information about some of the ingredients of Ropinirole Film-coated Tablets

Patients who are intolerant to lactose should note that each Ropinirole Film-coated Tablet contains a small amount of lactose. If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicinal product.

### Children

Ropinirole Film-coated Tablets are not recommended for use in children.

## 3. HOW TO TAKE ROPINIROLE FILM-COATED TABLETS

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

Swallow the Ropinirole Film-coated Tablet(s) whole with water. You can take the tablets with or without food. However, taking Ropinirole Film-coated Tablets with food may decrease the occurrence of nausea (feeling sick) which is a possible side-effect of the tablets. Do not chew the tablet(s). Do not take more than your doctor has recommended.

When you first start taking Ropinirole Film-coated Tablets, the amount you take will be increased gradually.

The exact dose of ropinirole that people take can be different. Your doctor will decide on the dose you need to take each day and you should follow the doctor's instructions.

When treating Restless Legs Syndrome, Ropinirole Film-coated Tablets should be taken once a day, at about the same time each day. They are usually taken just before bedtime, but can be taken up to 3 hours before going to bed.

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

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

Please read the pharmacist's label carefully. If you have any questions about Ropinirole Film-coated Tablets and how to take them, ask your doctor or pharmacist.

### If you take more Ropinirole Film-coated Tablets than you should

You should never take more tablets than your doctor recommends. Someone who has taken an overdose may experience; feeling or being sick, dizziness (or a spinning sensation), feeling drowsy, fatigue (mental or physical tiredness), stomach pain, fainting or nervousness. If you take too many tablets, or if someone else has taken your medicine, tell a doctor or pharmacist straight away. Show them your pack of tablets.

**If you forget to take Ropinirole Film-coated Tablets**

Remember to take your medicine. If you have trouble remembering when to take your medicine, ask your pharmacist for some hints.

If you do forget to take a dose, leave out that dose completely. Take your next dose at the normal time.  
Do not take a double dose to make up for a forgotten tablet.

If you have missed taking your tablets for more than a few days, consult your doctor for advice on restarting.

**If you stop taking Ropinirole Film-coated Tablets**

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

If you wish to stop the treatment, this has to be done gradually. You must not stop taking Ropinirole Film-coated Tablets without your doctor's advice. If your symptoms worsen after you stop treatment with Ropinirole Film-coated Tablets, you should contact your doctor.

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

**4. POSSIBLE SIDE EFFECTS**

Like all medicines, Ropinirole Film-coated Tablets can cause side effects, although not everybody gets them.

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

The more common side effects of Ropinirole Film-coated Tablets sometimes occur when patients first start their therapy and/or when the dose is increased. The side effects are generally mild and may become less after you have taken the medicine for a short time.

**Restless Legs Syndrome**

The side effects reported in people taking ropinirole for Restless Legs Syndrome are listed below:

**Very Common Side Effects (they occur in more than 1 per 10 patients who receive treatment)**

Vomiting, nausea (feeling sick)

**Common Side Effects (they occur in between 1 and 10 per 100 patients who receive treatment)**

Nervousness, fainting, drowsiness, dizziness (or a spinning sensation), stomach ache, fatigue (mental or physical tiredness)

**6. FURTHER INFORMATION**

*(Only the marketed strengths will be stated on the printed leaflets)*

**What Ropinirole Film-coated Tablets contain**

The active substance is ropinirole (as ropinirole hydrochloride).

The other ingredients are:

**Tablet Core**

- Lactose Monohydrate
- Microcrystalline cellulose
- Pregelatinised starch
- Magnesium stearate

**Film Coating**

- 0.25 mg:** Opadry II 85F18378 (Polyvinyl alcohol, Titanium dioxide (E171), Macrogol 3350, Talc)
- 0.5 mg:** Opadry II 85F32111 (Polyvinyl alcohol, Titanium dioxide (E171), Macrogol 3350, Talc, Iron oxide yellow (E172))
- 1 mg:** Opadry II 85F21676 (Polyvinyl alcohol, Titanium dioxide (E171), Macrogol 3350, Talc, Iron oxide yellow (E172), Brilliant blue aluminium lake (E133), Iron oxide black (E172))
- 2 mg:** Opadry II 85F24026 (Polyvinyl alcohol, Titanium dioxide (E171), Macrogol 3350, Talc, Iron oxide yellow (E172), Iron oxide red (E172))
- 3 mg:** Opadry II 85F20157 (Polyvinyl alcohol, Macrogol 3350, Titanium dioxide (E171), Talc, Carmine (E120), Indigo carmine aluminium lake (E132))
- 4 mg:** Opadry II 85F23579 (Polyvinyl alcohol, Macrogol 3350, Titanium dioxide (E171), Talc, Iron oxide yellow (E172), Iron oxide red (E172), Iron oxide black (E172))

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

The **0.25 mg** film-coated tablets are white, round, biconvex and 7 mm in diameter.

They are marked R0.25 on one side.

The **0.5 mg** film-coated tablets are yellow, round, biconvex and 7 mm in diameter.

They are marked R0.5 on one side.

The **1 mg** film-coated tablets are green, round, biconvex and 7 mm in diameter.

They are marked R1 on one side.

Uncommon Side Effects (they occur in between one and ten per 1000 patients who receive treatment)

Confusion, hallucinations, low blood pressure which may make you feel dizzy or faint especially when standing up from a sitting or lying position

Very rare (they occur in less than one per 10,000 patients who receive treatment)

Hepatic reactions (mainly increase of liver enzymes), extreme sleepiness or sudden sleep onset episodes (suddenly falling asleep without any apparent warning)

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 2)
- other psychotic reactions in addition to hallucinations, such as severe confusion (delirium), irrational ideas (delusions) and irrational suspiciousness (paranoia)
- urges to behave in a way unusual for them such as an unusual urge to gamble or increased sexual urges and/or behaviours

During treatment with Ropinirole Film-coated Tablets you may experience unusual worsening of symptoms (e.g. symptoms become worse, start earlier in the day or after less time at rest, or affect other parts of your body such as your arms). If this occurs, you should see your doctor.

**5. HOW TO STORE ROPINIROLE FILM-COATED TABLETS**

Keep out of the reach and sight of children.

Do not store above 25°C.

Store in the original package in order to protect from light.

HDPE containers only: Keep the container tightly closed in order to protect from moisture.

Do not take Ropinirole Film-coated Tablets after the expiry date which is stated on the carton and blister foil or bottle label. (*\* only the marketed pack types will be stated on the printed leaflets*)

The expiry date refers to the last day of that month.

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

The **2 mg** film-coated tablets are pink, round, biconvex and 7 mm in diameter.

They are marked R2 on one side.

The **3 mg** film-coated tablets are purple, round, biconvex and 8.5 mm in diameter.

They are marked R3 on one side.

The **4 mg** film-coated tablets are orange, round, biconvex and 9.5 mm in diameter.

They are marked R4 on one side.

**Pack sizes:**

*\*(only the actual marketed pack sizes will be stated on the leaflet)*  
All Strengths are available in blister packs or plastic containers of 2, 5, 7, 10, 12, 14, 20, 21, 28, 30, 50, 56, 60, 84, 100, 126 and 210 tablets.

**Marketing Authorisation Holder and Manufacturer**

Marketing Authorisation Holder:

CADUCEUS PHARMA LIMITED  
6th floor  
94 Wigmore Street  
London  
W1U 3RF  
UK

Distributed by:

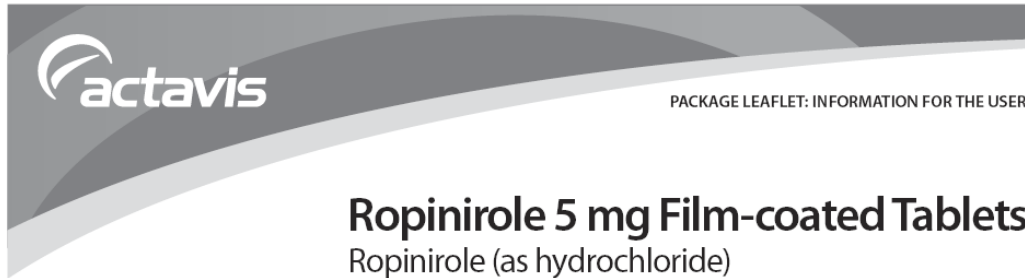
Actavis UK Ltd  
Barnstaple  
EX32 8NS  
UK

Manufacturer:

Actavis Ltd  
B16 Bulebel Industrial Estate  
Zejtun ZTN08  
Malta

This leaflet was last updated in 09/2010.

## Individual PIL for PL 24668/0084 – 5 mg strength



PACKAGE LEAFLET: INFORMATION FOR THE USER

## Ropinirole 5 mg Film-coated Tablets

### Ropinirole (as hydrochloride)

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

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

#### In this leaflet:

1. What Ropinirole Film-coated Tablets are and what they are used for
2. Before you take Ropinirole Film-coated Tablets
3. How to take Ropinirole Film-coated Tablets
4. Possible side effects
5. How to store Ropinirole Film-coated Tablets
6. Further information

#### 1. WHAT ROPINIROLE FILM-COATED TABLETS ARE AND WHAT THEY ARE USED FOR

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

Ropinirole Film-coated Tablets are used to treat Parkinson's Disease.

The cause of Parkinson's Disease is a lack of the substance dopamine in the brain. Ropinirole acts in a similar way to the natural dopamine, so helping the symptoms of Parkinson's Disease.

The effect of Ropinirole Film-coated Tablets may be increased or decreased by other medicines, and vice versa. These medicines include:

- ciprofloxacin (an antibiotic)
- fluvoxamine (a drug used to treat depression)
- cimetidine (a drug used to treat stomach ulcers)
- theophylline (a drug used to treat asthma)
- hormone replacement therapy (also called HRT)
- anti-psychotics and other drugs that block dopamine in the brain (e.g. sulpiride or metoclopramide)

Tell your doctor if:

- you are already receiving any other medicines for Parkinson's Disease
- you are taking medicines to treat high blood pressure, or for heart problems
- you give up or start smoking while taking Ropinirole Film-coated Tablets. Your doctor may need to adjust your dose.
- you are taking Ropinirole Film-coated Tablets and the doctor is going to prescribe you any other medicine.

#### Taking Ropinirole Film-coated Tablets with food and drink

Always swallow the tablets whole with water and preferably with food. Do not chew them.

Taking Ropinirole Film-coated Tablets with food may reduce the likelihood of you feeling or being sick.

You should not drink alcohol while you are taking this medicine.

#### Pregnancy and breast-feeding

Women who are pregnant or breast-feeding must not take Ropinirole Film-coated Tablets.

Tell your doctor immediately if you:

- are pregnant, if you think you might be pregnant or if you're planning to become pregnant
- are breast-feeding or planning to breast-feed.

Ropinirole Film-coated Tablets may be used alone or in combination with other medicines against Parkinson's disease, to achieve a more effective treatment.

## 2. BEFORE YOU TAKE ROPINIROLE FILM-COATED TABLETS

### Do not take Ropinirole Film-coated Tablets

- if you are allergic (hypersensitive) to ropinirole or any of the other ingredients of Ropinirole Film-coated Tablets
- if you are pregnant or think you may be pregnant
- if you are breast feeding

If you are unsure, it is essential to talk to your doctor.

### Take special care with Ropinirole Film-coated Tablets

Tell your doctor before you start to take this medicine if you:

- have serious kidney disease
- have liver disease
- have a serious heart complaint
- have a serious mental health problem
- have a history of any unusual urges and/or behaviours (such as excessive gambling or excessive sexual behaviour)
- have an intolerance to some sugars (such as lactose)

In these situations your doctor should carefully supervise your treatment.

During treatment with Ropinirole Film-coated Tablets take special care when you drive or operate machinery. If you suffer from extreme sleepiness or suddenly fall asleep without apparently feeling sleepy, do not drive or use machinery, and contact your doctor.

### Taking other medicines

Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription. This applies also to herbal medicines as well as strong vitamins and minerals.

Your doctor will advise you to stop taking Ropinirole Film-coated Tablets.

Women taking Ropinirole Film-coated Tablets should use adequate precautions to avoid becoming pregnant.

### Driving and using machines

This medicine does not usually affect people's normal activities. However, Ropinirole Film-coated Tablets can cause extreme sleepiness (somnolence) in some people and may cause them to fall asleep suddenly without any apparent warning. Contact your doctor if you experience either of these effects. If you do suffer from these effects then DO NOT drive or operate machinery, and do not put yourself in any situation where sleepiness or falling asleep may put you (or others) at risk of serious injury or death.

### Important information about some of the ingredients of Ropinirole Film-coated Tablets

Patients who are intolerant to lactose should note that each Ropinirole Film-coated Tablet contains a small amount of lactose. If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicinal product.

### Children

Ropinirole Film-coated Tablets are not recommended for use in children.

## 3. HOW TO TAKE ROPINIROLE FILM-COATED TABLETS

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

Swallow the Ropinirole Film-coated Tablet(s) whole with water. You can take the tablets with or without food. However, taking Ropinirole Film-coated Tablets with food may decrease the occurrence of nausea (feeling sick) which is a possible side-effect of the tablets. Do not chew the tablet(s). Do not take more than your doctor has recommended.

When you first start taking Ropinirole Film-coated Tablets, the amount you take will be increased gradually. The exact dose of ropinirole that people take can be different. Your doctor will decide on the dose you need to take each day and you should follow the doctor's instructions.



When treating Parkinson's Disease, the starting dose is 0.25 mg three times per day for one week. The dose is then gradually increased in accordance with the following:

1<sup>st</sup> Week: 0.25 mg three times daily  
 2<sup>nd</sup> Week: 0.5 mg three times daily  
 3<sup>rd</sup> Week: 0.75 mg three times daily  
 4<sup>th</sup> Week: 1 mg three times daily

Hereafter, your doctor may increase or decrease the dose that you are taking to get the best effect. The usual dose is between 1 mg and 3 mg taken three times daily (a total daily dose of 3 mg to 9 mg), but if sufficient effects are not achieved or maintained then the total daily dose may be gradually increased up to a maximum of 24 mg.

Ropinirole Film-coated Tablets may also be used in combination with other medicines that act against Parkinson's Disease.

Your doctor may then increase or decrease the amount of ropinirole that you are taking to get the best effect.

Please read the pharmacist's label carefully. If you have any questions about Ropinirole Film-coated Tablets and how to take them, ask your doctor or pharmacist.

**If you take more Ropinirole Film-coated Tablets than you should**

You should never take more tablets than your doctor recommends.

Someone who has taken an overdose may experience; feeling or being sick, dizziness (or a spinning sensation), feeling drowsy, fatigue (mental or physical tiredness), stomach pain, fainting or nervousness.

If you take too many tablets, or if someone else has taken your medicine, tell a doctor or pharmacist straight away. Show them your pack of tablets.

**If you forget to take Ropinirole Film-coated Tablets**

Remember to take your medicine. If you have trouble remembering when to take your medicine, ask your pharmacist for some hints.

If you do forget to take a dose, leave out that dose completely. Take your next dose at the normal time. Do not take a double dose to make up for a forgotten tablet.

Uncommon Side Effects (they occur in between 1 and 10 per 1000 patients who receive treatment)

Mental side effects other than hallucinations, such as delirium, delusion, and paranoia,  
 Compulsive gambling,  
 Increased sexual drive,  
 Extreme sleepiness or sudden sleep onset episodes (suddenly falling asleep without any apparent warning)

Very rare (they occur in less than 1 per 10,000 patients who receive treatment)

Altered liver function (abnormal blood tests),  
 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

When ropinirole is taken with other medicines for Parkinson's Disease the following additional side effects have been reported:

Very Common Side Effects (they occur in more than 1 per 10 patients who receive treatment)

Unwanted jerky movements

Common Side Effects (they occur in between 1 and 10 per 100 patients who receive treatment)

Confusion

**5. HOW TO STORE ROPINIROLE FILM-COATED TABLETS**

Keep out of the reach and sight of children.

Do not store above 25°C.

Store in the original package in order to protect from light..  
 HDPE containers only: Keep the container tightly closed in order to protect from moisture.

Do not take Ropinirole Film-coated Tablets after the expiry date which is stated on the carton and blister foil or bottle label. (*\* only the marketed pack types will be stated on the printed leaflets*)

The expiry date refers to the last day of that month.

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

If you have missed taking your tablets for more than a few days, consult your doctor for advice on restarting.

**If you stop taking Ropinirole Film-coated Tablets**

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

If you wish to stop the treatment, this has to be done gradually. You must not stop taking Ropinirole Film-coated Tablets without your doctor's advice. If your symptoms worsen after you stop treatment with Ropinirole Film-coated Tablets, you should contact your doctor.

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

**4. POSSIBLE SIDE EFFECTS**

Like all medicines, Ropinirole Film-coated Tablets can cause side effects, although not everybody gets them.

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

The more common side effects of Ropinirole Film-coated Tablets sometimes occur when patients first start their therapy and/or when the dose is increased. The side effects are generally mild and may become less after you have taken the medicine for a short time.

**Parkinson's Disease**

The side effects reported in people taking ropinirole for Parkinson's Disease are listed below:

Very Common Side Effects (they occur in more than 1 per 10 patients who receive treatment)

Nausea (feeling sick), drowsiness

Common Side Effects (they occur in between 1 and 10 per 100 patients who receive treatment)

Hallucinations, dizziness (including vertigo), vomiting, stomach ache, heartburn, swelling of the legs, fainting, feeling dizzy or faint especially when you stand up suddenly (this is caused by a drop in blood pressure)

**6. FURTHER INFORMATION**

**What Ropinirole Film-coated Tablets contain**

The active substance is ropinirole (as ropinirole hydrochloride).

The other ingredients are:

*Tablet Core*

- Lactose Monohydrate
- Microcrystalline cellulose
- Pregelatinised starch
- Magnesium stearate

*Film Coating*

Opadry II 85F20521 (Polyvinyl alcohol, Titanium dioxide, Macrogol 3350, Talc, Indigo carmine aluminium lake (E132))

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

The 5 mg film-coated tablets are blue, round, biconvex and 10.5 mm in diameter.

They are marked R5 on one side.

*Pack sizes:*

\*(only the actual marketed pack sizes will be stated on the leaflet)

The tablets are available in blister packs or plastic containers of 2, 5, 7, 10, 12, 14, 20, 21, 28, 30, 50, 56, 60, 84, 100, 126 and 210 tablets.

**Marketing Authorisation Holder and Manufacturer**

Marketing Authorisation Holder:

CADUCEUS PHARMA LIMITED  
6<sup>th</sup> Floor  
94 Wigmore Street  
London  
W1U 3RF  
UK

Distributed by:

Actavis UK Ltd,  
Barnstaple EX32 8NS,  
UK

Manufacturer:

Actavis Ltd  
B16 Bulebel Industrial Estate  
Zejtun ZTN08  
Malta

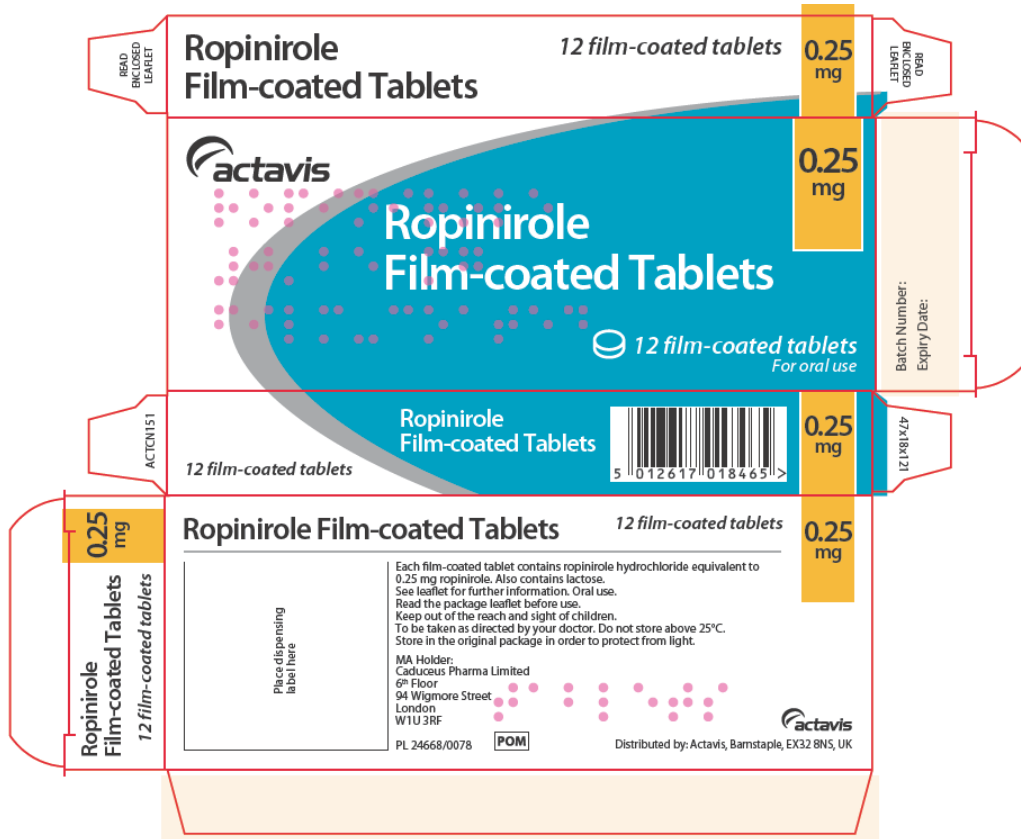
This leaflet was last approved in {MM/YYYY}.



## LABELLING

### Ropinirole 0.25 mg Film-Coated Tablets

Carton for blisters, with braille



### Braille translation

r o p i n i r o l e  
 Nums 0 Point 2 5 m g  
 f i l m c o a t e d  
 hyphen  
 t a b l e t s

r o p i n i r o l e  
 Nums 0 Point 2 5 m g  
 f i l m c o a t e d  
 hyphen  
 t a b l e t s

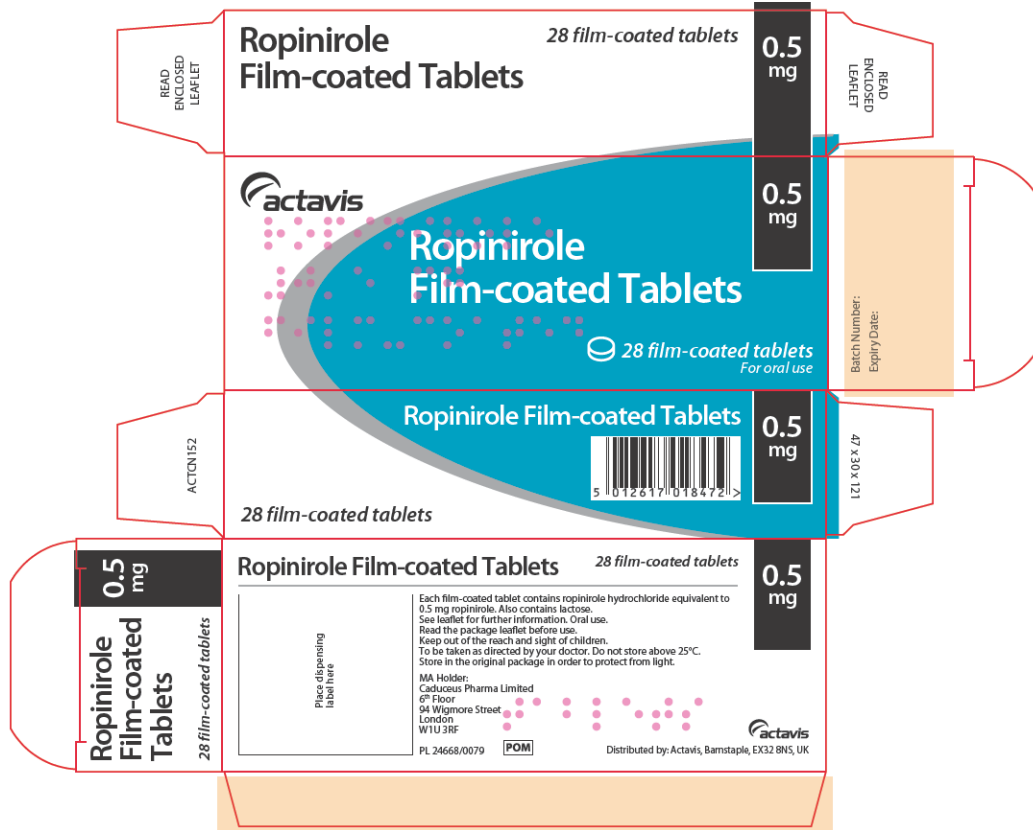
t a b l e t s

Blisters foil

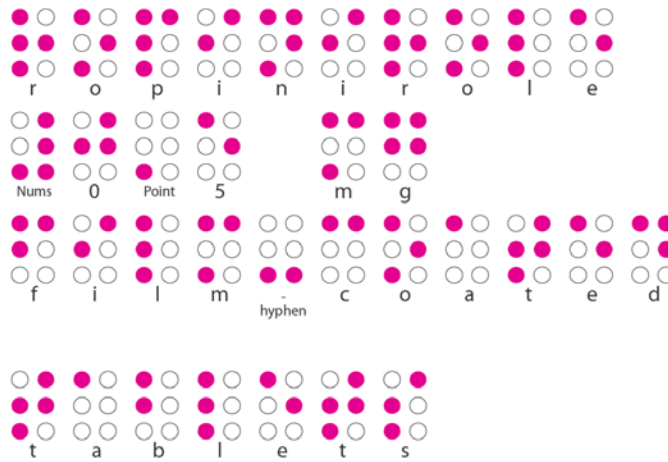


### Ropinirole 0.5 mg Film-Coated Tablets

Carton for blisters, with braille



#### Braille translation

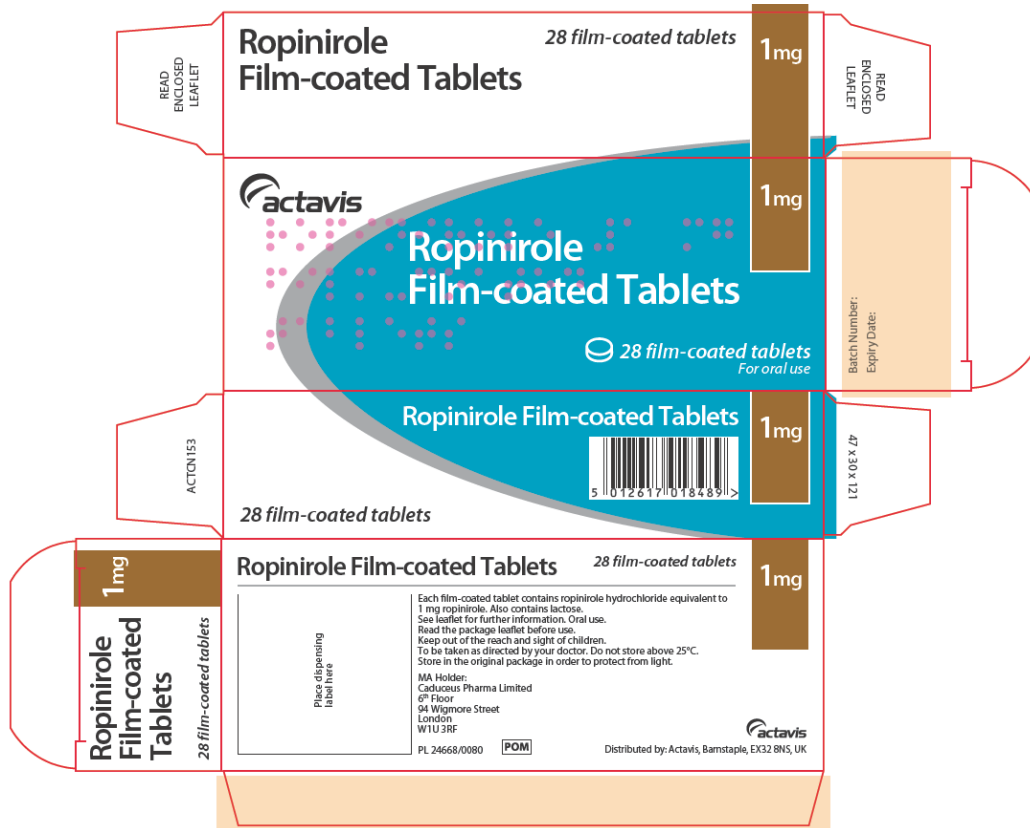


Blisters foil

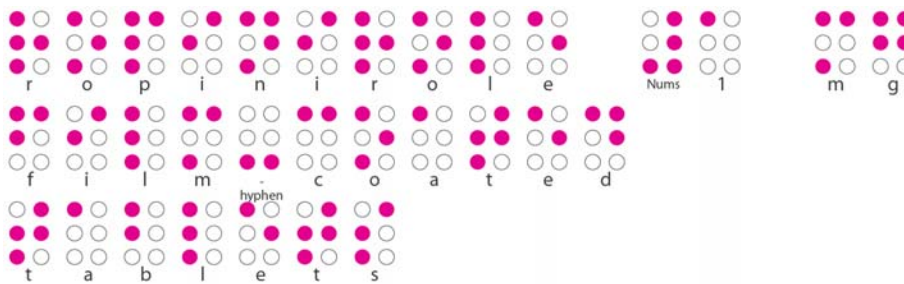


### Ropinirole 1 mg Film-Coated Tablets

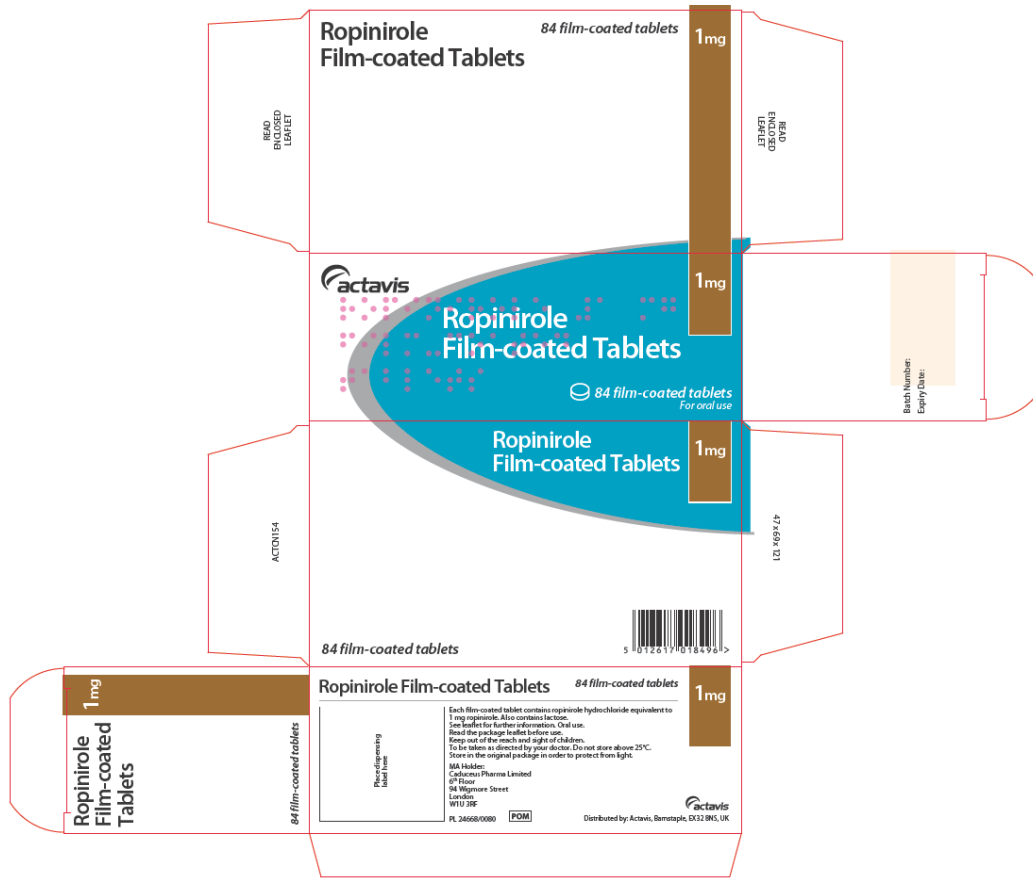
Carton for blisters, with braille



### Braille translation



Pack size 84

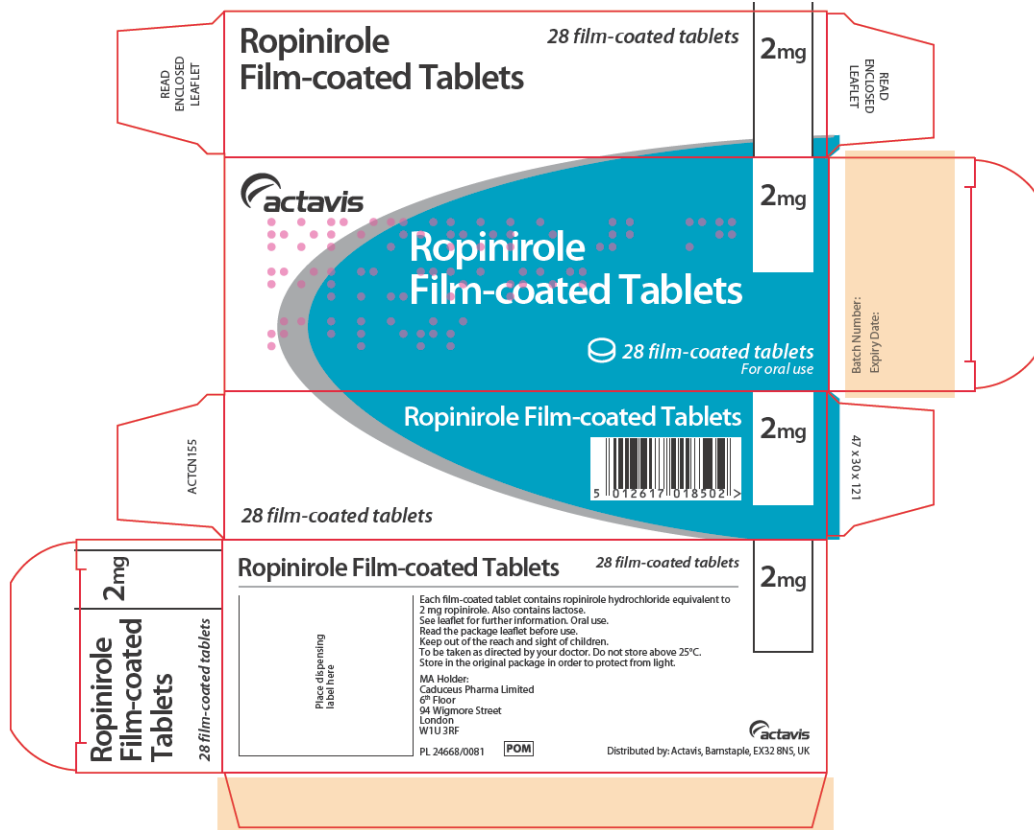


Blisters foil

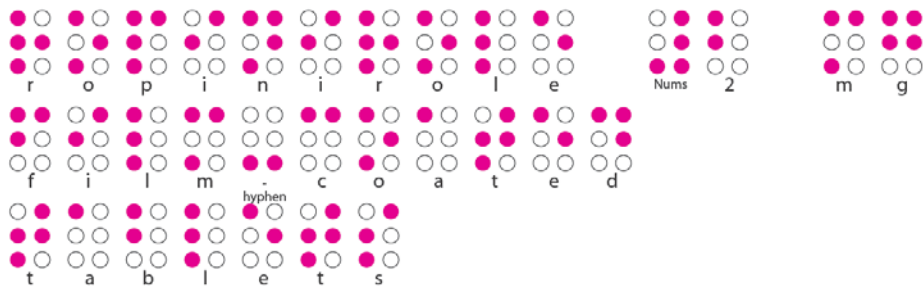


### Ropinirole 2 mg Film-Coated Tablets

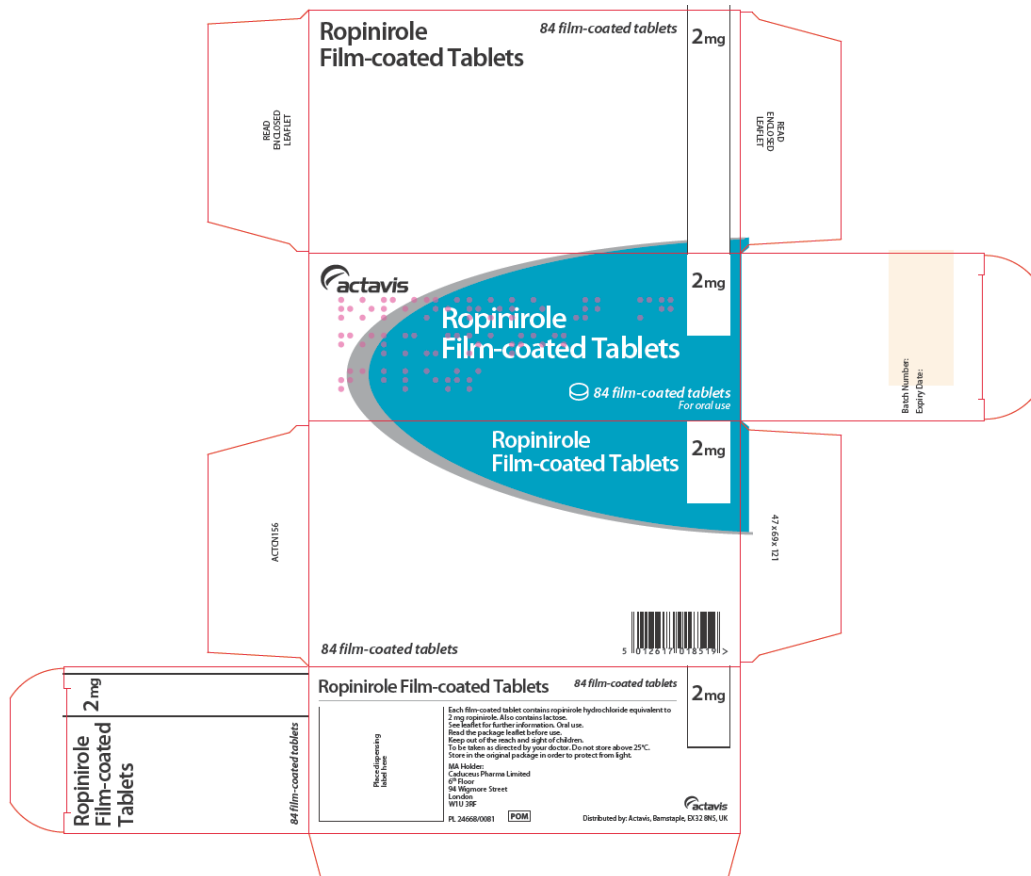
Carton for blisters, with braille



#### Braille translation



Pack size 84



Blisters foil





**Ropinirole 3 mg Film-Coated Tablets – text only****PARTICULARS TO APPEAR ON THE OUTER PACKAGING AND THE IMMEDIATE PACKAGING**

Carton for blister pack / Carton for HDPE container / Label on HDPE container

**1. NAME OF THE MEDICINAL PRODUCT**

Ropinirole 3 mg Film-coated Tablets

**2. STATEMENT OF ACTIVE SUBSTANCE(S)**

Each film-coated tablet contains ropinirole hydrochloride equivalent to 3 mg ropinirole.

**3. LIST OF EXCIPIENTS**

Also contains lactose.  
See leaflet for further information.

**4. PHARMACEUTICAL FORM AND CONTENTS**

2 film-coated tablets  
5 film-coated tablets  
7 film-coated tablets  
10 film-coated tablets  
12 film-coated tablets  
14 film-coated tablets  
20 film-coated tablets  
21 film-coated tablets  
28 film-coated tablets  
30 film-coated tablets  
50 film-coated tablets  
56 film-coated tablets  
60 film-coated tablets  
84 film-coated tablets  
100 film-coated tablets  
126 film-coated tablets  
210 film-coated tablets

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

Oral use.  
Read the package leaflet before use.

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

Keep out of the reach and sight of children.

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

To be taken as directed by your doctor.

**8. EXPIRY DATE**

Expiry Date:

**9. SPECIAL STORAGE CONDITIONS**

Do not store above 25°C.

Store in the original package in order to protect from light.

*HDPE containers only:* Keep the container tightly closed in order to protect from moisture.

**10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE****11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

Caduceus Pharma Limited  
6<sup>th</sup> Floor  
94 Wigmore Street  
London  
W1U 3RF

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

PL 24668/0082

**13. BATCH NUMBER**

Batch Number:

**14. GENERAL CLASSIFICATION FOR SUPPLY**

**POM**

**15. INSTRUCTIONS ON USE****16. INFORMATION IN BRAILLE**

*Cartons only:*

ropinirole 3 mg film-coated tablets

<b>MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS</b>
<b>Blister</b>

<b>1. NAME OF THE MEDICINAL PRODUCT</b>
---

Ropinirole 3 mg Film-coated Tablets

<b>2. NAME OF THE MARKETING AUTHORISATION HOLDER</b>
--

Caduceus Pharma LTD

<b>3. EXPIRY DATE</b>
-----------------------

EXP:

<b>4. BATCH NUMBER</b>
------------------------

LOT:

<b>5. OTHER</b>
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**Ropinirole 4 mg Film-Coated Tablets – text only****PARTICULARS TO APPEAR ON THE OUTER PACKAGING AND THE IMMEDIATE PACKAGING**

Carton for blister pack / Carton for HDPE container / Label on HDPE container

**1. NAME OF THE MEDICINAL PRODUCT**

Ropinirole 4 mg Film-coated Tablets

**2. STATEMENT OF ACTIVE SUBSTANCE(S)**

Each film-coated tablet contains ropinirole hydrochloride equivalent to 4 mg ropinirole.

**3. LIST OF EXCIPIENTS**

Also contains lactose.  
See leaflet for further information.

**4. PHARMACEUTICAL FORM AND CONTENTS**

2 film-coated tablets  
5 film-coated tablets  
7 film-coated tablets  
10 film-coated tablets  
12 film-coated tablets  
14 film-coated tablets  
20 film-coated tablets  
21 film-coated tablets  
28 film-coated tablets  
30 film-coated tablets  
50 film-coated tablets  
56 film-coated tablets  
60 film-coated tablets  
84 film-coated tablets  
100 film-coated tablets  
126 film-coated tablets  
210 film-coated tablets

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

Oral use.  
Read the package leaflet before use.

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

Keep out of the reach and sight of children.

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

To be taken as directed by your doctor.

**8. EXPIRY DATE**

Expiry Date:

**9. SPECIAL STORAGE CONDITIONS**

Do not store above 25°C.

Store in the original package in order to protect from light.

*HDPE containers only:* Keep the container tightly closed in order to protect from moisture.

**10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE****11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

Caduceus Pharma Limited  
6<sup>th</sup> Floor  
94 Wigmore Street  
London  
W1U 3RF

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

PL 24668/0083

**13. BATCH NUMBER**

Batch Number:

**14. GENERAL CLASSIFICATION FOR SUPPLY**

**POM**

**15. INSTRUCTIONS ON USE****16. INFORMATION IN BRAILLE**

*Cartons only:*

ropinirole 4 mg film-coated tablets

**MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS**

Blister

**1. NAME OF THE MEDICINAL PRODUCT**

Ropinirole 4 mg Film-coated Tablets

**2. NAME OF THE MARKETING AUTHORISATION HOLDER**

Caduceus Pharma LTD

**3. EXPIRY DATE**

EXP:

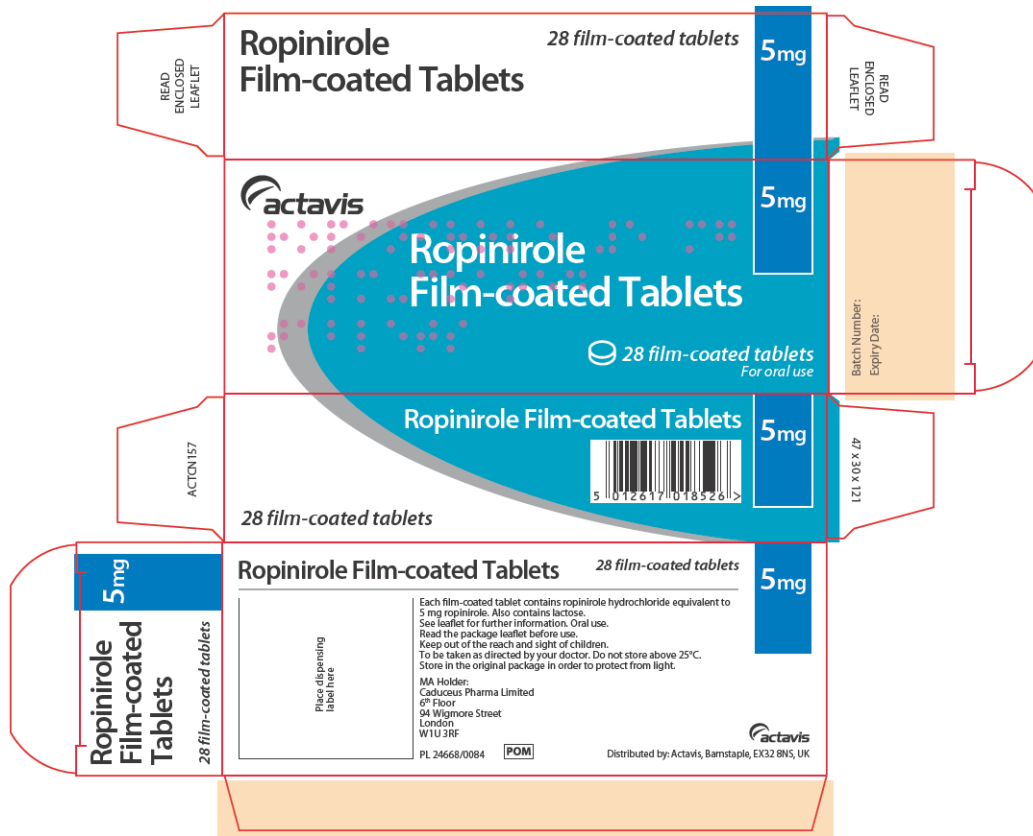
**4. BATCH NUMBER**

LOT:

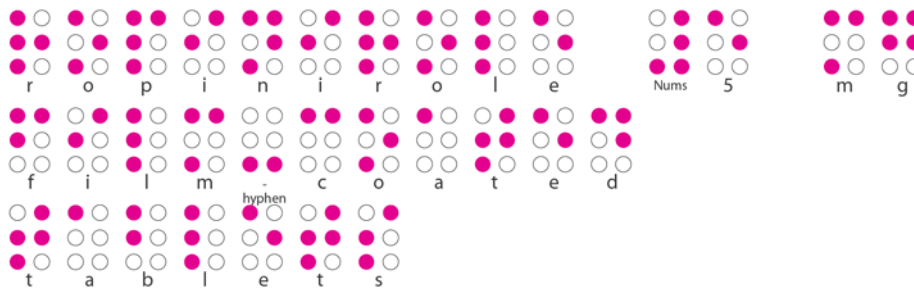
**5. OTHER**

### Ropinirole 5 mg Film-Coated Tablets

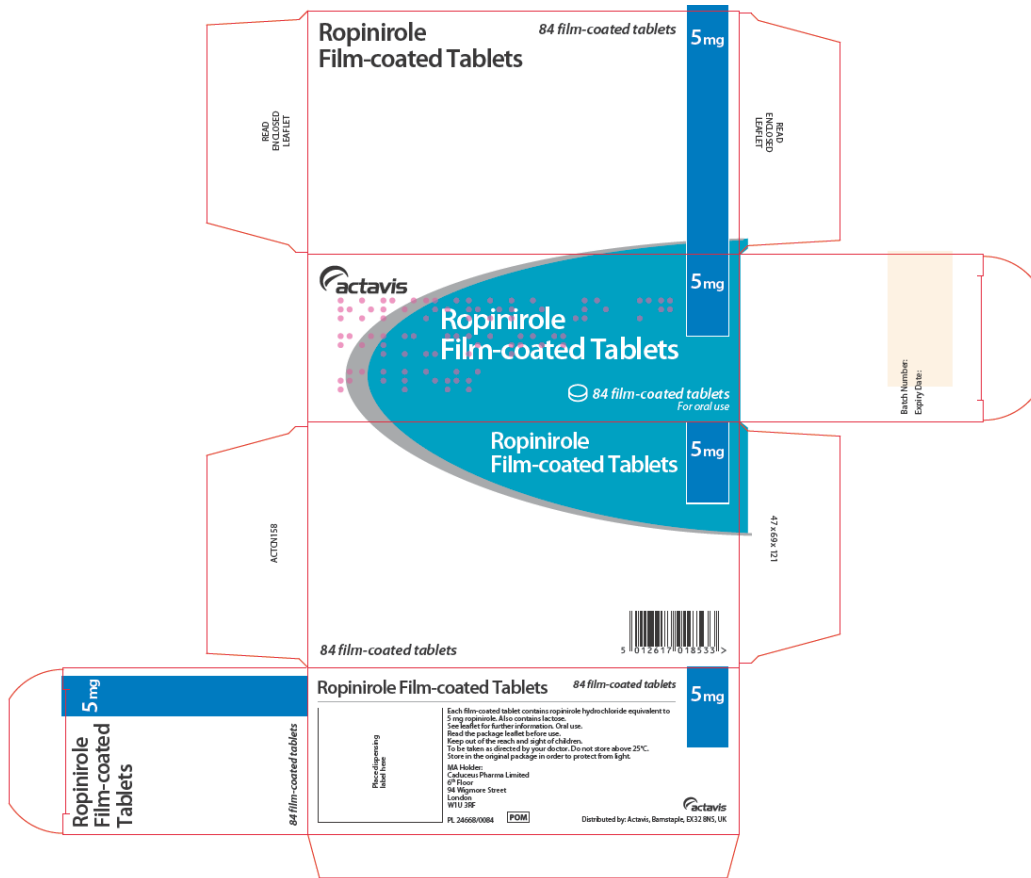
Carton for blisters, with braille



### Braille translation



Pack size 84



Blisters foil

