

## **PRAMIPEXOLE 88, 180, 350 & 700 MICROGRAM TABLETS**

**PL 29831/0472-5**

**UKPAR**

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**PRAMIPEXOLE 88, 180, 350 & 700 MICROGRAM TABLETS**  
**PL 29831/0472-5**

**LAY SUMMARY**

The Medicines and Healthcare products Regulatory Agency granted Wockhardt UK Limited Marketing Authorisations (licences) for the medicinal products Pramipexole 88 microgram (mcg), 180 mcg, 350 mcg and 700 mcg Tablets (PL 29831/0472-5) on 13 December 2011. These are prescription-only medicines (POM) and are used to treat:

- The symptoms of primary Parkinson's disease. They can be used alone or in combination with levodopa (another medicine for Parkinson's disease).
- The symptoms of moderate to severe primary Restless Legs Syndrome.

*Please note the indications are in-line with the brand leader, but these products may not be marketed to treat all the indications listed.*

Pramipexole Tablets belong to a group of medicines known as dopamine agonists, which stimulate dopamine receptors in the brain. Stimulation of the dopamine receptors triggers nerve impulses in the brain that help control body movements.

No new or unexpected safety concerns arose from these applications and it was, therefore, judged that the benefits of taking Pramipexole 88 mcg, 180 mcg, 350 mcg and 700 mcg Tablets outweigh the risks; hence Marketing Authorisations have been granted.

**Note:** A variation application to remove the therapeutic indication for use in Restless Legs syndrome was approved on 27 March 2012 (see Annex).

**PRAMIPEXOLE 88, 180, 350 & 700 MICROGRAM TABLETS**  
**PL 29831/0472-5**

**SCIENTIFIC DISCUSSION**

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## **INTRODUCTION**

The UK granted Marketing Authorisations for the medicinal products Pramipexole 88 mcg, 180 mcg, 350 mcg and 700 mcg Tablets (PL 29831/0472-5) to Wockhardt UK Ltd on 13 December 2011. These products are prescription-only medicines.

These applications were submitted as abridged applications according to Article 10(1) of Directive 2001/83/EC as amended. The products are claimed to be generic versions of the reference products authorised in the European community via the centralised procedure, Mirapexin® 88 micrograms (mcg) 180 mcg, 350 mcg and 700 mcg Tablets (Boehringer Ingelheim Pharma GmbH, & Co. KG, Germany; EU/1/97/051/001-006 and 0011-12) since 23 February 1998. The reference products have been authorised in the EU for more than 10 years, thus the period of exclusivity has expired.

The active ingredient, pramipexole, is a dopamine agonist that binds with high selectivity and specificity to the D2 subfamily of dopamine receptors of which it has a preferential affinity to D3 receptors, and has full intrinsic activity.

Pramipexole alleviates parkinsonian motor deficits by stimulation of dopamine receptors in the striatum. Animal studies have shown that pramipexole inhibits dopamine synthesis, release, and turnover.

With the exception of the bioequivalence study, no new non-clinical or clinical efficacy studies were performed, which is acceptable given that the applications were based on being generic versions of originator products that have been licensed for over 10 years.

A single-dose, bioequivalence study was submitted to support these applications, comparing the test product Pramipexole 180 mcg Tablets (Wockhardt UK Limited) versus the reference product Mirapexin® 180 mcg Tablets (Boehringer Ingelheim Pharma GmbH, & Co. KG, Germany) under fasting conditions. The bioequivalence study was carried out in accordance with Good Clinical Practice (GCP).

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 MHRA considers that the pharmacovigilance system as described by the Marketing Authorisation Holder (MAH) fulfils the requirements and provides adequate evidence that the MAH has the services of a Qualified person (QP) responsible for pharmacovigilance and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country. The MAH has provided a satisfactory Risk Management Plan.

The MAH has adequately justified non-submission of an Environmental Risk Assessment (ERA). It is not considered that these medical products represent any risk to the environment. These generic products will be used as substitute for the brand products. There is no reason to conclude that availability of these products will change the overall use pattern of the existing market.

No new or unexpected safety concerns arose during review of information provided by the Marketing Authorisation Holder and it was, therefore, judged that the benefits of taking Pramipexole 88 mcg, 180 mcg, 350 mcg and 700 mcg Tablets (PL 29831/0472-5) outweigh the risks; hence Marketing Authorisations were granted.

# PHARMACEUTICAL ASSESSMENT

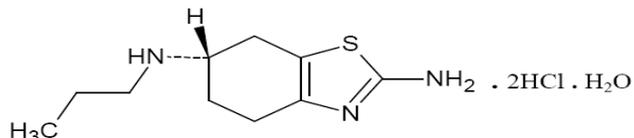
## DRUG SUBSTANCE

### **Pramipexole dihydrochloride monohydrate**

INN/ BAN: Pramipexole dihydrochloride monohydrate

**Chemical name:** (6*S*)-6-*N*-Propyl-4,5,6,7- tetrahydro-1,3-benzothiazole-2,6-diamine dihydrochloride monohydrate

### **Structure**



**Chemical Formula**  $\text{C}_{10}\text{H}_{17}\text{N}_3\text{S} \cdot 2\text{HCl} \cdot \text{H}_2\text{O}$   
**Molecular Weight** 302.3

### **General Properties**

Description: White to off-white crystalline powder.

Solubility: Freely soluble in water, soluble in methanol, sparingly soluble to slightly soluble in ethanol (96%) and practically insoluble in methylene chloride.

The active substance, pramipexole dihydrochloride monohydrate, is the subject of a European pharmacopoeial (Ph Eur) monograph.

### **Manufacture**

Synthesis of the drug substance from the designated starting materials has been adequately described and appropriate in-process controls and intermediate specifications are applied. Satisfactory specifications are in place for all starting materials and reagents and these are supported by relevant certificates of analysis.

Appropriate data have been supplied to characterise the active substance. All potential known impurities have been identified and characterised.

An appropriate specification is 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 specification.

Satisfactory certificates of analysis have been provided for all working standards.

Suitable specifications have been provided for all packaging used. The primary packaging has been shown to comply with current guidelines concerning contact with foodstuffs.

Appropriate stability data have been generated to support a suitable re-test period when stored in the proposed packaging.

## **DRUG PRODUCT**

### **Description and Composition**

The product is presented as white to off-white uncoated tablets with different shapes and markings (see SmPCs/patient information leaflet for full description of tablets). Each tablet contains pramipexole dihydrochloride monohydrate equivalent to 88 micrograms (mcg), 180 mcg, 350 mcg and 700 mcg pramipexole.

### **Other ingredients**

Other ingredients consist of pharmaceutical excipients, mannitol, maize starch, citric acid monohydrate, povidone (K-30), colloidal anhydrous silica and magnesium stearate. All ingredients within the tablet comply with their relevant Ph. Eur monographs. Appropriate justification for the inclusion of each excipient has been provided. Satisfactory Certificates of Analysis have been provided for all the excipients.

None of the excipients used contain material derived from animal or human origin. Furthermore, no genetically modified organisms are used in the manufacture of any of the excipients.

### **Pharmaceutical Development**

The objective of the pharmaceutical development process was to develop bioequivalent and stable formulations comparable to the innovator's products Mirapexin® 88 mcg, 180 mcg, 350 mcg and 700 mcg tablets. The applicant has provided suitable product development sections.

Comparative dissolution and impurity profiles were provided for test and reference products and were found to be similar.

### **Manufacture**

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

In-process controls are appropriate considering the nature of the product and the method of manufacture. Process validation studies have been conducted on suitable sized batches and are accepted. The validation data demonstrated consistency of the manufacturing process. A commitment has been made by the Manufacturing Authorisation Holder (MAH) that full process validation will be conducted on commercial scale batches in accordance with the process validation protocol.

### **Finished Product Specification**

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 adequately validated, as appropriate. Satisfactory batch analysis data are provided and accepted. The data demonstrate that the batches are compliant with the proposed specifications. Certificates of Analysis have been provided for any reference standards used.

### **Container Closure System**

The finished products are licensed for marketing in blister strips composed of aluminium. Each blister strip contains 10 tablets. The blister strips are placed with the Patient Information Leaflet (PIL) into cardboard outer cartons and are packaged in pack sizes of

30 and 100 tablets (Pramipexole 88 mcg Tablets are only available in a pack size of 30 tablets). The Marketing Authorisation Holder (MAH) has stated that not all pack sizes may be marketed however, the MAH has committed to submitting the proposed packaging/labelling for any pack size before it is 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 and results were within the proposed specification limits. Based on the results, a shelf-life of 18 months, with no special storage conditions required for these medicinal products.

### **Bioequivalence Study**

The applications are supported by a bioequivalence study comparing the pharmacokinetic profile of the test product, Pramipexole 180 mcg Tablets, to that of the clinical reference product Mirapexin® 180 mcg Tablets (Boehringer Ingelheim International GmbH). Certificates of Analysis have been provided for both the test and reference products.

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

### **Expert Report**

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

### **Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL), Labels**

The SmPC, PIL and labelling are pharmaceutically acceptable. Colour mock-ups of the labelling and PIL have been provided. The labelling is satisfactory and fulfils the statutory requirements for Braille.

A user consultation with target patient groups on the package information leaflet (PIL) has been performed on the basis of a bridging report making reference to the parent PIL Bendroflumethazide 2.5 mg and 5 mg Tablets (PL 29831/0022-23). The bridging report submitted by the applicant has been found acceptable. It can therefore be concluded that the package leaflet for Pramipexole 88 mcg, 180 mcg, 350 mcg and 700 mcg Tablets has been shown to be legible, clear, easy-to-use and understand in line with the requirements set out in Council Directive 2004/27/EC, Article 59 (3).

### **MAA Form**

The MAA forms are pharmaceutically satisfactory.

### **Conclusion**

There are no objections to the approval of Pramipexole 88 mcg, 180 mcg, 350 mcg and 700 mcg Tablets from a pharmaceutical point of view.

## **NON-CLINICAL ASSESSMENT**

These abridged applications, submitted under Article 10(1) of Directive 2001/83/EC, as amended, are for Pramipexole 88 mcg, 180 mcg, 350 mcg and 700 mcg Tablets, products claiming to be generic versions of the reference products Mirapexin® 88 mcg, 180 mcg, 350 mcg and 700 mcg Tablets authorised to Boehringer Ingelheim International GmbH, since 23 February 1998.

The pharmacodynamic, pharmacokinetic and toxicological properties of pramipexole are well-known. Therefore, no further studies are required and the applicant has provided none.

The non-clinical overall overview was written by a suitably qualified person and is satisfactory. The *curriculum vitae* of the expert has been provided.

No formal Environmental Risk Assessment has been provided. The applicant has justified the absence adequately. As a generic product, the use of this product is not expected to increase the overall use of pramipexole and so no additional increase in environmental risk has been identified.

The SmPCs are satisfactory from a non-clinical viewpoint and are consistent with those for the reference products.

There are no objections to the approval of Pramipexole 88 mcg, 180 mcg, 350 mcg and 700 mcg Tablets from a non-clinical point of view.

## **CLINICAL ASSESSMENT**

### **BACKGROUND**

Pramipexole is a synthetic amino-benzothiazole derivative, which has been shown to act as a non-ergot dopamine agonist (DA) with high affinity and selectivity for the DA D2 receptor subfamily, and particularly the D3 receptor subtype.

### **INDICATIONS**

Pramipexole is indicated in adults for treatment of the signs and symptoms of idiopathic Parkinson's disease, alone (without levodopa) or in combination with levodopa, i.e. over the course of the disease, through to late stages when the effect of levodopa wears off or becomes inconsistent and fluctuations of the therapeutic effect occur (end of dose or "on off" fluctuations).

Pramipexole is indicated in adults for symptomatic treatment of moderate to severe idiopathic Restless Legs Syndrome in doses up to 0.54 mg of base (0.75 mg of salt).

### **DOSE AND POSOLOGY**

Parkinson's disease

The daily dose is administered in equally divided doses 3 times a day.

The dose regime is in-line with the reference products.

### **CLINICAL PHARMACOLOGY**

#### **Pharmacokinetics**

Pramipexole is rapidly and completely absorbed following oral administration. The absolute bioavailability is greater than 90% and the maximum plasma concentrations occur between 1 and 3 hours. Concomitant administration with food did not reduce the extent of pramipexole absorption, but the rate of absorption was reduced. Pramipexole shows linear kinetics and a small inter-patient variation of plasma levels. In humans, the protein binding of pramipexole is very low (< 20%) and the volume of distribution is large (400 l). High brain tissue concentrations were observed in the rat (approx. 8-fold compared to plasma).

Pramipexole is metabolised in man only to a small extent.

Renal excretion of unchanged pramipexole is the major route of elimination. Approximately 90% of <sup>14</sup>C-labelled dose is excreted through the kidneys while less than 2% is found in the faeces. The total clearance of pramipexole is approximately 500 ml/min and the renal clearance is approximately 400 ml/min. The elimination half-life ( $t_{1/2}$ ) varies from 8 hours in the young to 12 hours in the elderly.

#### **Bioequivalence Study**

The applications are supported by a bioequivalence study comparing the pharmacokinetic profile of the test product Pramipexole 180 micrograms (mcg) Tablets, to that of the clinical reference product Mirapexin 180 mcg (Boehringer Ingelheim Pharma GmbH, & Co. KG, Germany). The study was of an appropriate design and was conducted to principles of Good Clinical Practice (GCP). Certificates of Analysis have been provided for both the test and reference products.

This was a randomised, single dose, open-label, two-treatment, two-period, two sequence, crossover comparative bioavailability study on the test formulation of Pramipexole 180 mcg tablet (containing 180 mcg of pramipexole base as 250 mcg Pramipexole dihydrochloride monohydrate) compared with Mirapexin 180 mcg tablet (containing 180 mcg of pramipexole base as 250 mcg Pramipexole dihydrochloride monohydrate) of Boehringer Ingelheim International GmbH, Germany in 26 healthy, adult, human subjects under fasting conditions. Following an overnight fast of 10 hours, a single dose of the investigational products was administered orally with 240 mL of drinking water.

A washout period of 7 days was maintained between the two dosing days in each subject to ensure zero plasma levels at the beginning of the next period of dosing.

Blood samples were taken pre-dose and at specified time points up to 36 hours after administration of test or reference products. A validated LC-MS/MS analytical method was used for quantification of pramipexole from the human plasma samples. Primary variables analysed were:  $C_{max}$ ,  $AUC_{(0-t)}$  and  $AUC_{(0-\infty)}$ .

*Pre-defined bioequivalence acceptance criteria*

Bioequivalence of the test product versus the reference products was concluded if the 90% Confidence Intervals (CI) fell within the acceptance range, 80-125% for log-transformed  $C_{max}$  and AUC ratios.

**Results:**

Bioequivalence results for log-transformed test/reference ratios with 90% Confidence Intervals:

Summary of PK & Statistical Results of Pramipexole

Parameters (Units)	Geometric Least Squares Mean N =25			90 % Confidence Interval
	Test (A)	Reference (B)	% Ratio (A/B)	
$C_{max}$ (pg/mL)	522.3448	530.6079	98.44 %	93.53 % - 103.61 %
$AUC_{0-t}$ (pg.hr/mL)	5431.6555	5588.6081	97.19 %	94.65 % - 99.80 %
$AUC_{0-\infty}$ (pg.hr/mL)	5643.9975	5805.6138	97.22 %	94.63 % - 99.87 %

Note: The bioequivalence acceptance limits 80.00 % - 125.00 % were used for  $C_{max}$ ,  $AUC_{0-t}$  and  $AUC_{0-\infty}$ .

**Conclusion on bioequivalence study:**

The results of the bioequivalence study show that  $C_{max}$  and AUC of the test product fall within the acceptance criteria range of 80-125% in line with the “Note for Guidance on the Investigation of Bioavailability and Bioequivalence (CPMP/EWP/QWP/1401/98)”. Therefore the test product Pramipexole 180 micrograms tablets is bioequivalent with the reference product Mirapexin 180 microgram tablets (Boehringer Ingelheim Pharma GmbH, & Co. KG, Germany).

Satisfactory justification is provided for a bio-waiver for Pramipexole 88 mcg, 350 mcg and 700 mcg Tablets. As Pramipexole 88 mcg, 350 mcg and 700 mcg Tablets meet the criteria specified in the “Note for Guidance on the Investigation of Bioavailability and

Bioequivalence (CPMP/EWP/QWP/1401/98)”, the results and conclusions of the bioequivalence study on the 180 mcg strength can be extrapolated to the 88 mcg, 350 mcg and 700 mcg strength tablets.

### **EFFICACY**

No new data have been submitted and none are required. The reference products are established and the applications depend upon the demonstration of bioequivalence. Efficacy is reviewed in the clinical overview. The efficacy of pramipexole 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 pramipexole is well-known.

### **PRODUCT INFORMATION:**

#### **Summary of Product Characteristics**

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

#### **Patient Information Leaflet**

The PIL is in line with the approved SmPCs and is satisfactory.

#### **Labelling**

The labelling is satisfactory.

### **CLINICAL OVERVIEW**

A satisfactory clinical overview was provided and prepared by an appropriately qualified expert. The CV of the clinical expert was supplied.

### **CONCLUSIONS**

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.

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

### **QUALITY**

The important quality characteristics of Pramipexole 88 mcg, 180 mcg, 350 mcg and 700 mcg 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.

### **NON-CLINICAL**

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

### **EFFICACY**

The applicant has submitted one bioequivalence study in support of these applications. Bioequivalence has been demonstrated between the applicant's Pramipexole 180 mcg Tablets with the reference product Mirapexin® 180 microgram tablets (Boehringer Ingelheim Pharma GmbH, & Co. KG, Germany) under fasting conditions. Satisfactory justification is provided for a bio-waiver for Pramipexole 88 mcg, 350 mcg and 700 mcg Tablets. As Pramipexole 88 mcg, 350 mcg and 700 mcg Tablets meet the criteria specified in the "Note for Guidance on the Investigation of Bioavailability and Bioequivalence (CPMP/EWP/QWP/1401/98)", the results and conclusions of the bioequivalence study on the 180 mcg strength can be extrapolated to the 88 mcg, 350 mcg and 700 mcg strength tablets.

No new or unexpected safety concerns arise from these applications.

The SmPC, PIL and labelling are satisfactory and consistent with those for the innovator products.

### **RISK BENEFIT ASSESSMENT**

The quality of the product is acceptable and no new non-clinical or clinical safety concerns have been identified. The bioequivalence study supports the claim that the applicant's products and the innovator products are interchangeable. Extensive clinical experience with pramipexole is considered to have demonstrated the therapeutic value of the compound. The risk benefit is, therefore, considered to be positive.

**PRAMIPEXOLE 88, 180, 350 & 700 MICROGRAM TABLETS**  
**PL 29831/0472-5**

**STEPS TAKEN FOR ASSESMENT**

1	The MHRA received the marketing authorisation application on 22 February 2011.
2	Following standard checks and communication with the applicant the MHRA considered the application valid on 1 March 2011.
3	Following assessment of the applications the MHRA requested further information relating to the quality dossiers on 15 September 2011.
4	The applicant responded to the MHRA's requests, providing further information on the quality dossier on 8 November 2011
5	The application was determined on 13 December 2011.

**PRAMIPEXOLE 88, 180, 350 & 700 MICROGRAM TABLETS**  
**PL 29831/0472-5**

**STEPS TAKEN AFTER AUTHORISATION – SUMMARY**

The following table lists non-safety updates to the Marketing Authorisation for this product that have been approved by the MHRA since the product was first licensed. The update has been added as an annex to this PAR. This is not a complete list of the post-authorisation changes that have been made to this Marketing Authorisation.

<b>Date submitted</b>	<b>Application type</b>	<b>Scope</b>	<b>Outcome</b>
04/01/2012	Medical Type 1B	To update the therapeutic indications by removing the use of the drug for symptomatic treatment of moderate to severe idiopathic Restless Legs Syndrome, and any reference or warnings associated to this usage; sections 4.1 (Therapeutic indications), 4.2 (Posology and method of administration) of the SmPC and consequentially the leaflet is amended.	Granted 27/03/2012

# PRAMIPEXOLE 88, 180, 350 & 700 MICROGRAM TABLETS PL 29831/0472-5

## SUMMARY OF PRODUCT CHARACTERISTICS

The UK Summary of Product Characteristics (SmPC) for Pramipexole 88 mcg, 180 mcg, 350mcg and 700 mcg Tablets (PL 29831/0472-5) is as follows:  
Differences are highlighted in yellow.

*Please note that the indications are in line with the brand leader, but these products may not be marketed with all the indications listed below.*

### 1 NAME OF THE MEDICINAL PRODUCT

Pramipexole 88 micrograms Tablets  
Pramipexole 180 micrograms Tablets  
Pramipexole 350 micrograms Tablets  
Pramipexole 700 micrograms Tablets

### 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

**For PL 29831/0472**

Each tablet contains 125 micrograms pramipexole dihydrochloride monohydrate equivalent to 88 micrograms pramipexole.

**PL 29831/0473**

Each tablet contains 250 micrograms pramipexole dihydrochloride monohydrate equivalent to 180 micrograms pramipexole.

**PL 29831/0474**

Each tablet contains 500 micrograms pramipexole dihydrochloride monohydrate equivalent to 350 micrograms pramipexole.

**PL 29831/0475**

Each tablet contains 1,000 micrograms pramipexole dihydrochloride monohydrate equivalent to 700 micrograms pramipexole.

*Please note:*

Pramipexole doses as published in the literature refer to the salt form.

Therefore, doses will be expressed in terms of both pramipexole base and pramipexole salt (in brackets).

For a full list of excipients, see section 6.1.

### 3 PHARMACEUTICAL FORM

Tablet

**For PL 29831/0472**

White to off white, round uncoated tablet, debossed "W  
II6" on one side and plain on the other.

**For PL 29831/0473**

White to off white, oval shaped uncoated tablet, debossed "W" on one side and "II7" on the other side of score line and plain on either side of the score line on the reverse side.

Tablets can be divided into equal halves.

**For PL 29831/0474**

White to off white, oval shaped uncoated tablet, debossed "W" on one side and "II8" on the other side of score line and plain on either side of the score line on the reverse side.

Tablets can be divided into equal halves.

**PL 29831/0475**

White to off white, round shaped uncoated tablet, debossed “W” on one side and “II9” on the other side of score line and plain on either side of the score line on the reverse side.

Tablets can be divided into equal halves.

**4 CLINICAL PARTICULARS****4.1 Therapeutic indications**

Pramipexole is indicated in adults for treatment of the signs and symptoms of idiopathic Parkinson's disease, alone (without levodopa) or in combination with levodopa, i.e. over the course of the disease, through to late stages when the effect of levodopa wears off or becomes inconsistent and fluctuations of the therapeutic effect occur (end of dose or “on off” fluctuations).

Pramipexole is indicated in adults for symptomatic treatment of moderate to severe idiopathic Restless Legs Syndrome in doses up to 540 micrograms of base (750 micrograms of salt) (see section 4.2).

**4.2 Posology and method of administration****Posology**Parkinson's disease

The daily dose is administered in equally divided doses 3 times a day.

Initial treatment

Doses should be increased gradually from a starting dose of 264 micrograms of base (375 micrograms of salt) per day and then increased every 5-7 days. Providing patients do not experience intolerable undesirable effects, the dose should be titrated to achieve a maximal therapeutic effect.

Ascending dose schedule of Pramipexole				
Week	Dose (micrograms of base)	Total Daily Dose (micrograms of base)	Dose (micrograms of salt)	Total Daily Dose (micrograms of salt)
1	3 x 88	264	3 x 125	375
2	3 x 180	540	3 x 250	750
3	3 x 350	1,100	3 x 500	1,500

If a further dose increase is necessary the daily dose should be increased by 540 micrograms of base (750 micrograms of salt) at weekly intervals up to a maximum dose of 3,300 micrograms of base (4,500 micrograms of salt) per day. However, it should be noted that the incidence of somnolence is increased at doses higher than 1,500 micrograms (of salt) per day (see section 4.8).

Maintenance treatment

The individual dose of pramipexole should be in the range of 264 micrograms of base (375 micrograms of salt) to a maximum of 3,300 micrograms of base (4,500 micrograms of salt) per day. During dose escalation in pivotal studies, efficacy was observed starting at a daily dose of 1,100 micrograms of base (1,500 micrograms of salt). Further dose adjustments should be done based on the clinical response and the occurrence of adverse reactions. In clinical trials approximately 5% of patients were treated at doses below 1,100 micrograms of base (1,500 micrograms of salt). In advanced Parkinson's disease, pramipexole doses higher than 1,100 micrograms of base (1,500 micrograms of salt) per day can be useful in patients where a reduction of the levodopa therapy is intended. It is recommended that the dose of levodopa is reduced during both the dose escalation and the maintenance treatment with Pramipexole, depending on reactions in individual patients (see section 4.5).

Treatment discontinuation

Abrupt discontinuation of dopaminergic therapy can lead to the development of a neuroleptic malignant syndrome. Pramipexole should be tapered off at a rate of 540 micrograms of base (750 micrograms of salt) per day until the daily dose has been reduced to 540 micrograms of base (750 micrograms of salt).

Thereafter the dose should be reduced by 264 micrograms of base (375 micrograms of salt) per day (see section 4.4).

#### Dosing in patients with renal impairment

The elimination of pramipexole is dependent on renal function. The following dose schedule is suggested for initiation of therapy:

Patients with a creatinine clearance above 50 ml/min require no reduction in daily dose or dosing frequency.

In patients with a creatinine clearance between 20 and 50 ml/min, the initial daily dose of Pramipexole should be administered in two divided doses, starting at 88 micrograms of base (125 micrograms of salt) twice a day (176 micrograms of base/250 micrograms of salt daily). A maximum daily dose of 1,570 micrograms pramipexole base (2,250 micrograms of salt) should not be exceeded.

In patients with a creatinine clearance less than 20 ml/min, the daily dose of Pramipexole should be administered in a single dose, starting at 88 micrograms of base (125 micrograms of salt) daily. A maximum daily dose of 1,100 micrograms pramipexole base (1,500 micrograms of salt) should not be exceeded.

If renal function declines during maintenance therapy the Pramipexole daily dose should be reduced by the same percentage as the decline in creatinine clearance, i.e. if creatinine clearance declines by 30%, then the Pramipexole daily dose should be reduced by 30%. The daily dose can be administered in two divided doses if creatinine clearance is between 20 and 50 ml/min and as a single daily dose if creatinine clearance is less than 20 ml/min.

#### Dosing in patients with hepatic impairment

Dose adjustment in patients with hepatic failure is probably not necessary, as approx. 90% of absorbed active substance is excreted through the kidneys. However, the potential influence of hepatic insufficiency on Pramipexole pharmacokinetics has not been investigated.

#### Paediatric population

The safety and efficacy of Pramipexole in children below 18 years has not been established. There is no relevant use of Pramipexole in the paediatric population in Parkinson's Disease.

#### Restless Legs Syndrome

The recommended starting dose of Pramipexole is 88 micrograms of base (125 micrograms of salt) taken once daily 2-3 hours before bedtime. For patients requiring additional symptomatic relief, the dose may be increased every 4-7 days to a maximum of 540 micrograms of base (750 micrograms of salt) per day (as shown in the table below).

Dose Schedule of Pramipexole		
Titration Step	Once Daily Evening Dose (micrograms of base)	Once Daily Evening Dose (micrograms of salt)
1	88	125
2*	180	250
3*	350	500
4*	540	750
* if needed		

Patient's response should be evaluated after 3 months treatment and the need for treatment continuation should be reconsidered. If treatment is interrupted for more than a few days it should be re-initiated by dose titration carried out as above.

#### Treatment discontinuation

Since the daily dose for the treatment of Restless Legs Syndrome will not exceed 540 micrograms of base (750 micrograms of salt) Pramipexole can be discontinued without tapering off. In a 26 week placebo

controlled trial, rebound of RLS symptoms (worsening of symptom severity as compared to baseline) was observed in 10% of patients (14 out of 135) after abrupt discontinuation of treatment. This effect was found to be similar across all doses.

#### Dosing in patients with renal impairment

The elimination of pramipexole is dependent on renal function. Patients with a creatinine clearance above 20 ml/min require no reduction in daily dose.

The use of Pramipexole has not been studied in haemodialysis patients, or in patients with severe renal impairment.

#### Dosing in patients with hepatic impairment

Dose adjustment in patients with hepatic failure is not required, as approx. 90% of absorbed active substance is excreted through the kidneys.

#### Paediatric population

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

#### Tourette Disorder

#### Paediatric population

Pramipexole is not recommended for use in children and adolescents below 18 years since the efficacy and safety has not been established in this population. Pramipexole should not be used in children or adolescents with Tourette Disorder because of a negative benefit-risk balance for this disorder (see section 5.1).

#### **Method of administration**

The tablets should be taken orally, swallowed with water, and can be taken either with or without food.

#### **4.3 Contraindications**

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

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

When prescribing Pramipexole in a patient with Parkinson's disease with renal impairment a reduced dose is suggested in line with section 4.2.

#### Hallucinations

Hallucinations are known as a side effect of treatment with dopamine agonists and levodopa. Patients should be informed that (mostly visual) hallucinations can occur.

#### Dyskinesia

In advanced Parkinson's disease, in combination treatment with levodopa, dyskinesia can occur during the initial titration of Pramipexole. If they occur, the dose of levodopa should be decreased.

#### Sudden onset of sleep and somnolence

Pramipexole 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 Pramipexole. Patients who have experienced somnolence and/or an episode of sudden sleep onset must refrain from driving or operating machines. Furthermore a reduction of the dose or termination of therapy may be considered. Because of possible additive effects, caution should be advised when patients are taking other sedating medicinal products or alcohol in combination with pramipexole (see sections 4.5, 4.7 and section 4.8).

#### Impulse control disorders and compulsive behaviours

Pathological gambling, increased libido and hypersexuality have been reported in patients treated with dopamine agonists for Parkinson's disease, including Pramipexole. Furthermore, patients and caregivers should be aware of the fact that other behavioural symptoms of impulse control disorders and compulsions such as binge eating and compulsive shopping can occur. Dose reduction/tapered discontinuation should be considered.

#### Patients with psychotic disorders

Patients with psychotic disorders should only be treated with dopamine agonists if the potential benefits outweigh the risks. Co-administration of antipsychotic medicinal products with pramipexole should be avoided (see section 4.5).

#### Ophthalmologic monitoring

Ophthalmologic monitoring is recommended at regular intervals or if vision abnormalities occur.

#### Severe cardiovascular disease

In case of severe cardiovascular disease, care should be taken. It is recommended to monitor blood pressure, especially at the beginning of treatment, due to the general risk of postural hypotension associated with dopaminergic therapy.

#### Neuroleptic malignant syndrome

Symptoms suggestive of neuroleptic malignant syndrome have been reported with abrupt withdrawal of dopaminergic therapy (see section 4.2).

#### Augmentation

Reports in the literature indicate that treatment of Restless Legs Syndrome with dopaminergic medicinal products can result in augmentation. Augmentation refers to the earlier onset of symptoms in the evening (or even the afternoon), increase in symptoms, and spread of symptoms to involve other extremities. Augmentation was specifically investigated in a controlled clinical trial over 26 weeks. Augmentation was observed in 11.8% of patients in the pramipexole group (N = 152) and 9.4% of patients in the placebo group (N = 149). Kaplan-Meier analysis of time to augmentation showed no significant difference between pramipexole and placebo groups.

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

#### Plasma protein binding

Pramipexole is bound to plasma proteins to a very low (< 20%) extent, and little biotransformation is seen in man. Therefore, interactions with other medicinal products affecting plasma protein binding or elimination by biotransformation are unlikely. As anticholinergics are mainly eliminated by biotransformation, the potential for an interaction is limited, although an interaction with anticholinergics has not been investigated. There is no pharmacokinetic interaction with selegiline and levodopa.

#### Inhibitors/competitors of active renal elimination pathway

Cimetidine reduced the renal clearance of pramipexole by approximately 34%, presumably by inhibition of the cationic secretory transport system of the renal tubules. Therefore, medicinal products that are inhibitors of this active renal elimination pathway or are eliminated by this pathway, such as cimetidine, amantadine, mexiletine, zidovudine, cisplatin, quinine, and procainamide, may interact with pramipexole resulting in reduced clearance of pramipexole. Reduction of the pramipexole dose should be considered when these medicinal products are administered concomitantly with Pramipexole.

#### Combination with levodopa

When Pramipexole is given in combination with levodopa, it is recommended that the dose of levodopa is reduced and the dose of other anti-parkinsonian medicinal products is kept constant while increasing the dose of Pramipexole.

Because of possible additive effects, caution should be advised when patients are taking other sedating medicinal products or alcohol in combination with pramipexole (see section 4.4, 4.7 and 4.8).

#### Antipsychotic medicinal products

Co-administration of antipsychotic medicinal products with pramipexole should be avoided (see section 4.4), e.g. if antagonistic effects can be expected.

### **4.6 Pregnancy and lactation**

#### **Pregnancy**

The effect on pregnancy and lactation has not been investigated in humans. Pramipexole was not teratogenic in rats and rabbits, but was embryotoxic in the rat at maternotoxic doses (see section 5.3).

Pramipexole should not be used during pregnancy unless clearly necessary, i.e. if the potential benefit justifies the potential risk to the foetus.

#### **Breast-feeding**

As pramipexole treatment inhibits secretion of prolactin in humans, inhibition of lactation is expected. The excretion of pramipexole into breast milk has not been studied in women. In rats, the concentration of active substance-related radioactivity was higher in breast milk than in plasma.

In the absence of human data, Pramipexole should not be used during breast-feeding. However, if its use is unavoidable, breast-feeding should be discontinued.

#### **Fertility**

No studies on the effect on human fertility have been conducted. In animal studies, pramipexole affected oestrous cycles and reduced female fertility as expected for a dopamine agonist. However, these studies did not indicate direct or indirect harmful effects with respect to male fertility.

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

Pramipexole can have a major influence on the ability to drive and use machines.

Hallucinations or somnolence can occur.

Patients being treated with Pramipexole 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 sections 4.4, 4.5 and 4.8).

#### **4.8 Undesirable effects**

##### Expected adverse reactions

The following adverse reactions are expected under the use of Pramipexole: abnormal dreams, amnesia, behavioural symptoms of impulse control disorders and compulsions such as binge eating, compulsive shopping, hypersexuality and pathological gambling; cardiac failure, confusion, constipation, delusion, dizziness, dyskinesia, dyspnoea, fatigue, hallucinations, headache, hiccups, hyperkinesia, hyperphagia, hypotension, insomnia, libido disorders, nausea, paranoia, peripheral oedema, pneumonia, pruritus, rash and other hypersensitivity; restlessness, somnolence, sudden onset of sleep, syncope, visual impairment including diplopia, vision blurred and visual acuity reduced, vomiting, weight decrease including decreased appetite, weight increase.

Based on the analysis of pooled placebo-controlled trials, comprising a total of 1,923 patients on pramipexole and 1,354 patients on placebo, adverse drug reactions were frequently reported for both groups. 63% of patients on pramipexole and 52% of patients on placebo reported at least one adverse drug reaction.

Tables 1 and 2 display the frequency of adverse drug reactions from placebo-controlled clinical trials in Parkinson's disease and Restless Legs Syndrome. The adverse drug reactions reported in these tables are those events that occurred in 0.1% or more of patients treated with pramipexole and were reported significantly more often in patients taking pramipexole than placebo, or where the event was considered clinically relevant. The majority of adverse drug reactions were mild to moderate, they usually start early in therapy and most tended to disappear even as therapy was continued.

Within the system organ classes, adverse reactions are listed under headings of frequency (number of patients expected to experience the reaction), using the following categories: very common ( $\geq 1/10$ ); common ( $\geq 1/100$  to  $< 1/10$ ); uncommon ( $\geq 1/1,000$  to  $< 1/100$ ); rare ( $\geq 1/10,000$  to  $< 1/1,000$ ); very rare ( $< 1/10,000$ ); not known (cannot be estimated from the available data).

##### Parkinson's disease, most common adverse reactions

The most commonly ( $\geq 5\%$ ) reported adverse drug reactions in patients with Parkinson's disease more frequent with pramipexole treatment than with placebo were nausea, dyskinesia, hypotension, dizziness, somnolence, insomnia, constipation, hallucination, headache and fatigue. The incidence of somnolence is increased at doses higher than 1,500 micrograms pramipexole salt per day (see section 4.2). A more

frequent adverse drug reaction in combination with levodopa was dyskinesia. Hypotension may occur at the beginning of treatment, especially if pramipexole is titrated too fast.

Table 1: Parkinson's disease

System Organ Class	Adverse Drug Reaction
Infections and infestations	
Uncommon	pneumonia
Psychiatric disorders	
Common	abnormal dreams, behavioural symptoms of impulse control disorders and compulsions, confusion, hallucinations, insomnia
Uncommon	binge eating <sup>1</sup> , compulsive shopping, delusion, hyperphagia <sup>1</sup> , hypersexuality, libido disorder, paranoia, pathological gambling, restlessness
Nervous system disorders	
Very common	dizziness, dyskinesia, somnolence
Common	headache
Uncommon	amnesia, hyperkinesia, sudden onset of sleep, syncope
Eye disorders	
Common	visual impairment including diplopia, vision blurred and visual acuity reduced
Cardiac disorders	
Uncommon	cardiac failure <sup>1</sup>
Vascular disorders	
Common	hypotension
Respiratory, thoracic, and mediastinal disorders	
Uncommon	dyspnoea, hiccups
Gastrointestinal disorders	
Very common	nausea
Common	constipation, vomiting
Skin and subcutaneous tissue disorders	
Uncommon	hypersensitivity, pruritus, rash
General disorders and administration site conditions	
Common	fatigue, peripheral oedema
Investigations	
Common	weight decrease including decreased appetite
Uncommon	weight increase

<sup>1</sup> This side effect has been observed in post-marketing experience. With 95% certainty, the frequency category is not greater than uncommon, but might be lower. A precise frequency estimation is not possible as the side effect did not occur in a clinical trial database of 2,762 patients with Parkinson's Disease treated with pramipexole.

Restless Legs Syndrome, most common adverse reactions

The most commonly ( $\geq 5\%$ ) reported adverse drug reactions in patients with Restless Legs Syndrome treated with pramipexole were nausea, headache, dizziness and fatigue. Nausea and fatigue were more often reported in female patients treated with Pramipexole (20.8% and 10.5%, respectively) compared to males (6.7% and 7.3%, respectively).

Table 2: Restless Legs Syndrome

System Organ Class	Adverse Drug Reaction
Infections and infestations	
Uncommon	pneumonia <sup>1</sup>
Psychiatric disorders	
Common	abnormal dreams, insomnia
Uncommon	behavioural symptoms of impulse control disorders and compulsions such as binge eating, compulsive shopping, hypersexuality, and pathological gambling <sup>1</sup> ; confusion, delusion <sup>1</sup> , hallucinations, hyperphagia <sup>1</sup> , libido disorder, paranoia <sup>1</sup> , restlessness
Nervous system disorders	
Common	dizziness, headache, somnolence
Uncommon	amnesia <sup>1</sup> , dyskinesia, hyperkinesias <sup>1</sup> , sudden onset of sleep, syncope
Eye disorders	
Uncommon	visual disturbance including diplopia, vision blurred and visual acuity reduced
Cardiac disorders	
Uncommon	cardiac failure <sup>1</sup>
Vascular disorders	
Uncommon	hypotension
Respiratory, thoracic, and mediastinal disorders	
Uncommon	dyspnoea, hiccups
Gastrointestinal disorders	
Very common	nausea
Common	constipation, vomiting
Skin and subcutaneous tissue disorders	
Uncommon	hypersensitivity, pruritus, rash
General disorders and administration site conditions	
Common	fatigue
Uncommon	peripheral oedema
Investigations	
Uncommon	weight decrease including decreased appetite, weight increase

<sup>1</sup> This side effect has been observed in post-marketing experience. With 95% certainty, the frequency category is not greater than uncommon, but might be lower. A precise frequency estimation is not possible as the side effect did not occur in a clinical trial database of 1,395 patients with Restless Legs Syndrome treated with pramipexole.

#### Somnolence

Pramipexole is commonly associated with somnolence and has been associated uncommonly with excessive daytime somnolence and sudden sleep onset episodes (see also section 4.4).

#### Libido disorders

Pramipexole may uncommonly be associated with libido disorders (increased or decreased).

#### Impulse control disorders and compulsive behaviours

Patients treated with dopamine agonists for Parkinson's disease, including Pramipexole, 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 (see also section 4.4).

In a cross-sectional, retrospective screening and case-control study including 3,090 Parkinson's disease patients, 13.6% of all patients receiving dopaminergic or non-dopaminergic treatment had symptoms of an impulse control disorder during the past six months. Manifestations observed include pathological gambling, compulsive shopping, binge eating, and compulsive sexual behaviour (hypersexuality). Possible independent risk factors for impulse control disorders included dopaminergic treatments and higher doses of dopaminergic treatment, younger age ( $\leq 65$  years), not being married and self-reported family history of gambling behaviours.

#### Cardiac failure

In clinical studies and post-marketing experience cardiac failure has been reported in patients with pramipexole. In a pharmacoepidemiological study pramipexole use was associated with an increased risk of cardiac failure compared with non-use of pramipexole (observed risk ratio 1.86; 95% CI, 1.21-2.85).

#### **4.9 Overdose**

There is no clinical experience with massive overdose. The expected adverse reactions would be those related to the pharmacodynamic profile of a dopamine agonist, including nausea, vomiting, hyperkinesia, hallucinations, agitation and hypotension. There is no established antidote for overdose of a dopamine agonist. If signs of central nervous system stimulation are present, a neuroleptic agent may be indicated. Management of the overdose may require general supportive measures, along with gastric lavage, intravenous fluids, administration of activated charcoal and electrocardiogram monitoring.

### **5 PHARMACOLOGICAL PROPERTIES**

#### **5.1 Pharmacodynamic properties**

Pharmacotherapeutic group: anti-Parkinson drugs, dopamine agonists, ATC code: N04BC05.

Pramipexole is a dopamine agonist that binds with high selectivity and specificity to the D2 subfamily of dopamine receptors of which it has a preferential affinity to D3 receptors, and has full intrinsic activity.

Pramipexole alleviates parkinsonian motor deficits by stimulation of dopamine receptors in the striatum. Animal studies have shown that pramipexole inhibits dopamine synthesis, release, and turnover.

The mechanism of action of pramipexole as treatment for Restless Legs Syndrome is unknown. Neuropharmacological evidence suggests primary dopaminergic system involvement.

In human volunteers, a dose-dependent decrease in prolactin was observed. In a clinical trial with healthy volunteers, where Pramipexole prolonged-release tablets were titrated faster (every 3 days) than recommended up to 3,150 micrograms pramipexole base (4,500 micrograms of salt) per day, an increase in blood pressure and heart rate was observed. Such effect was not observed in patient studies.

#### Clinical trials in Parkinson's disease

In patients pramipexole alleviates signs and symptoms of idiopathic Parkinson's disease. Placebo-controlled clinical trials included approximately 1,800 patients of Hoehn and Yahr stages I – V treated with pramipexole. Out of these, approximately 1,000 were in more advanced stages, received concomitant levodopa therapy, and suffered from motor complications.

In early and advanced Parkinson's disease, efficacy of pramipexole in controlled clinical trials was maintained for approximately six months. In open continuation trials lasting for more than three years there were no signs of decreasing efficacy.

In a controlled double blind clinical trial of 2 year duration, initial treatment with pramipexole significantly delayed the onset of motor complications, and reduced their occurrence compared to initial treatment with levodopa. This delay in motor complications with pramipexole should be balanced against a greater improvement in motor function with levodopa (as measured by the mean change in UPDRS-score). The overall incidence of hallucinations and somnolence was generally higher in the escalation phase with the pramipexole group. However, there was no significant difference during the maintenance phase. These points should be considered when initiating pramipexole treatment in patients with Parkinson's disease.

The European Medicines Agency has waived the obligation to submit the results of studies with Pramipexole in all subsets of the paediatric population in Parkinson's Disease (see section 4.2 for information on paediatric use).

#### Clinical trials in Restless Legs Syndrome

The efficacy of pramipexole was evaluated in four placebo-controlled clinical trials in approximately 1,000 patients with moderate to very severe idiopathic Restless Legs Syndrome.

The mean change from baseline in the Restless Legs Syndrome Rating Scale (IRLS) and the Clinical Global Impression-Improvement (CGI-I) were the primary efficacy outcome measures. For both primary endpoints statistically significant differences have been observed for the pramipexole dose groups 250 micrograms, 500 micrograms and 750 micrograms pramipexole salt in comparison to placebo. After 12 weeks of treatment the baseline IRLS score improved from 23.5 to 14.1 points for placebo and from 23.4 to 9.4 points for pramipexole (doses combined). The adjusted mean difference was -4.3 points (CI 95% -6.4; -2.1 points, p-value <0.0001). CGI-I responder rates (improved, very much improved) were 51.2% and 72.0% for placebo and pramipexole, respectively (difference 20% CI 95%: 8.1%; 31.8%, p<0.0005). Efficacy was observed with 88 micrograms of base (125 micrograms of salt) per day after the first week of treatment.

In a placebo-controlled polysomnography study over 3 weeks Pramipexole significantly reduced the number of periodic limb movements during time in bed.

Longer term efficacy was evaluated in a placebo-controlled clinical trial. After 26 weeks of treatment, there was an adjusted mean reduction in IRLS total score of 13.7 and 11.1 points in the pramipexole and placebo group, respectively, with a statistically significant (p = 0.008) mean treatment difference of -2.6. CGI-I responder rates (much improved, very much improved) were 50.3% (80/159) and 68.5% (111/162) for placebo and pramipexole, respectively (p = 0.001), corresponding to a number needed to treat (NNT) of 6 patients (95%CI: 3.5, 13.4).

The European Medicines Agency has deferred the obligation to submit the results of studies with Pramipexole in one or more subsets of the paediatric population in Restless Legs Syndrome (see section 4.2 for information on paediatric use).

#### Clinical trial in Tourette Disorder

The efficacy of pramipexole (62.5-500 micrograms/day) with paediatric patients aged 6-17 years with Tourette Disorder was evaluated in a 6-week, double-blind, randomised, placebo-controlled flexible dose study. A total of 63 patients were randomised (43 on pramipexole, 20 on placebo). The primary endpoint was change from baseline on the Total Tic Score (TTS) of the Yale Global Tic Severity Scale (YGTSS). No difference was observed for pramipexole as compared to placebo for either the primary endpoint or for any of the secondary efficacy endpoints including YGTSS total score, Patient Global Impression of Improvement (PGI-I), Clinical Global Impression of Improvement (CGI-I), or Clinical Global Impressions of Severity of Illness (CGI-S). Adverse events occurring in at least 5% of patients in the pramipexole group and more common in the pramipexole-treated patients than in patients on placebo were: headache (27.9%, placebo 25.0%), somnolence (7.0%, placebo 5.0%), nausea (18.6%, placebo 10.0%), vomiting (11.6%, placebo 0.0%), upper abdominal pain (7.0%, placebo 5.0%), orthostatic hypotension (9.3%, placebo 5.0%), myalgia (9.3%, placebo 5.0%), sleep disorder (7.0%, placebo 0.0%), dyspnoea (7.0%, placebo 0.0%) and upper respiratory tract infection (7.0%, placebo 5.0%). Other significant adverse events leading to discontinuation of study medication for patients receiving pramipexole were confusional state, speech disorder and aggravated condition (see section 4.2).

## **5.2 Pharmacokinetic properties**

Pramipexole is rapidly and completely absorbed following oral administration. The absolute bioavailability is greater than 90% and the maximum plasma concentrations occur between 1 and 3 hours. Concomitant administration with food did not reduce the extent of pramipexole absorption, but the rate of absorption was reduced. Pramipexole shows linear kinetics and a small inter-patient variation of plasma levels. In humans, the protein binding of pramipexole is very low (< 20%) and the volume of distribution is large (400 l). High brain tissue concentrations were observed in the rat (approx. 8-fold compared to plasma).

Pramipexole is metabolised in man only to a small extent.

Renal excretion of unchanged pramipexole is the major route of elimination. Approximately 90% of <sup>14</sup>C-labelled dose is excreted through the kidneys while less than 2% is found in the faeces. The total clearance of pramipexole is approximately 500 ml/min and the renal clearance is approximately 400 ml/min. The elimination half-life (t<sub>1/2</sub>) varies from 8 hours in the young to 12 hours in the elderly.

### **5.3 Preclinical safety data**

Repeated dose toxicity studies showed that pramipexole exerted functional effects, mainly involving the CNS and female reproductive system, and probably resulting from an exaggerated pharmacodynamic effect of pramipexole.

Decreases in diastolic and systolic pressure and heart rate were noted in the minipig, and a tendency to a hypotensive effect was discerned in the monkey.

The potential effects of pramipexole on reproductive function have been investigated in rats and rabbits. Pramipexole was not teratogenic in rats and rabbits but was embryotoxic in the rat at maternally toxic doses. Due to the selection of animal species and the limited parameters investigated, the adverse effects of pramipexole on pregnancy and male fertility have not been fully elucidated.

A delay in sexual development (i.e., preputial separation and vaginal opening) was observed in rats. The relevance for humans is unknown.

Pramipexole was not genotoxic. In a carcinogenicity study, male rats developed Leydig cell hyperplasia and adenomas, explained by the prolactin-inhibiting effect of pramipexole. This finding is not clinically relevant to man. The same study also showed that, at doses of 2 mg/kg (of salt) and higher, pramipexole was associated with retinal degeneration in albino rats. The latter finding was not observed in pigmented rats, nor in a 2-year albino mouse carcinogenicity study or in any other species investigated.

## **6 PHARMACEUTICAL PARTICULARS**

### **6.1 List of excipients**

Mannitol  
Maize Starch  
Citric Acid Monohydrate  
Povidone (K-30)  
Colloidal Anhydrous Silica  
Magnesium Stearate

### **6.2 Incompatibilities**

Not applicable.

### **6.3 Shelf life**

18 months

### **6.4 Special precautions for storage**

This medicinal product does not require any special storage conditions.

### **6.5 Nature and contents of container**

ALU/ALU blister packs.

#### **PL 29831/0472**

Each blister strip contains 10 tablets.  
Cartons containing 3 blister strips (30 tablets).

#### **PL 29831/0473-5**

Each blister strip contains 10 tablets.

Cartons containing 3 or 10 blister strips (30 or 100 tablets).

Not all pack sizes may be marketed.

**6.6 Special precautions for disposal**

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

**7 MARKETING AUTHORISATION HOLDER**

Wockhardt UK Ltd  
Ash Road North  
Wrexham  
LL13 9UF  
UK

**8 MARKETING AUTHORISATION NUMBER(S)**

PL 29831/0472

PL 29831/0473

PL 29831/0474

PL 29831/0475

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

13/12/2011

**10 DATE OF REVISION OF THE TEXT**

13/12/2011

# PRAMIPEXOLE 88, 180, 350 & 700 MICROGRAM TABLETS

## PL 29831/0472-5

### PATIENT INFORMATION LEAFLET

PLEASE NOTE THAT THE INDICATIONS LISTED ARE IN LINE WITH BRAND LEADER AND MAY NOT BE MARKETED TO TREAT ALL THE INDICATIONS LISTED IN SMPC AND PIL

**PATIENT INFORMATION LEAFLET**  
**Pramipexole 88 micrograms Tablets**  
**Pramipexole 180 micrograms Tablets**  
**Pramipexole 350 micrograms Tablets**  
**Pramipexole 700 micrograms Tablets**



**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 Pramipexole Tablets are and what they are used for
2. Before you take Pramipexole Tablets
3. How to take Pramipexole Tablets
4. Possible side effects
5. How to store Pramipexole Tablets
6. Further information

**1. WHAT PRAMIPEXOLE TABLETS ARE AND WHAT THEY ARE USED FOR**

Pramipexole Tablets belong to a group of medicines known as dopamine agonists, which stimulate dopamine receptors in the brain. Stimulation of the dopamine receptors triggers nerve impulses in the brain that help to control body movements.

**Pramipexole Tablets are used to:**

- treat the symptoms of primary Parkinson's disease. They can be used alone or in combination with levodopa (another medicine for Parkinson's disease).
- treat the symptoms of moderate to severe primary Restless Legs Syndrome.

**2. BEFORE YOU TAKE PRAMIPEXOLE TABLETS**

**Do not take Pramipexole Tablets**

- if you are allergic (hypersensitive) to pramipexole or to any of the other ingredients of the tablets (see Section 6, Further information).

**Take special care with Pramipexole Tablets**

Tell your doctor if you have (had) or develop any medical conditions or symptoms, especially any of the following:

- kidney disease
- hallucinations (seeing, hearing or feeling things that are not there). Most hallucinations are visual dyskinesia (e.g. abnormal uncontrolled movements of the limbs). If you have advanced Parkinson's disease and are also taking levodopa, you might develop dyskinesia with increased doses of Pramipexole Tablets
- sleepiness and episodes of suddenly falling asleep
- behavioural changes (e.g. pathological gambling, compulsive shopping), increased libido (e.g. increased sexual desire), binge eating
- psychosis (e.g. comparable with symptoms of schizophrenia)
- vision impairment. You should have regular eye examinations during treatment with Pramipexole Tablets
- severe heart or blood vessels disease. You will need to have your blood pressure checked regularly, especially at the beginning of treatment. This is to avoid postural hypotension (a fall in blood pressure on standing up)
- augmentation. You may experience that symptoms start earlier than usual, be more intense and involve other limbs.

**Children and adolescents**

Pramipexole Tablets are not recommended for use in children or adolescents under 18 years.

**Taking other medicines**

Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines. This includes medicines, herbal remedies, health foods or supplements that you have obtained without a prescription.

You should avoid taking Pramipexole Tablets together with antipsychotic medicines.

**Take care if you are taking the following medicines:**

- cimetidine (to treat excess stomach acid and stomach ulcers)
- amantadine (which can be used to treat Parkinson's disease)
- mexiletine (to treat irregular heartbeats, a condition known as ventricular arrhythmia)
- zidovudine (which can be used to treat the acquired immune deficiency syndrome (AIDS), a disease of the human immune system)
- cisplatin (to treat various types of cancers)
- quinine (which can be used for the prevention of painful night-time leg cramps and for the treatment of a type of malaria known as falciparum malaria (malignant malaria))
- procainamide (to treat irregular heart beat).

If you are taking levodopa, the dose of levodopa is recommended to be reduced when you start treatment with Pramipexole Tablets.

**Take care if you are using any medicines that calm you down (have a sedative effect) or if you are drinking alcohol.** In these cases Pramipexole Tablets may affect your ability to drive and operate machinery.

**Taking Pramipexole Tablets with food and drink**

You should be cautious while drinking alcohol during treatment with Pramipexole Tablets. Pramipexole Tablets can be taken with or without food.

**Pregnancy and breast-feeding**

Tell your doctor if you are pregnant, think you might be pregnant or if you intend to become pregnant. Your doctor will then discuss with you if you should continue to take Pramipexole Tablets.

The effect of Pramipexole Tablets on the unborn child is not known. Therefore, do not take Pramipexole Tablets if you are pregnant unless your doctor tells you to do so.

Pramipexole Tablets should not be used during breast-feeding. Pramipexole Tablets can reduce the production of breast milk. Also, they can pass into the breast milk and can reach your baby. If use of Pramipexole Tablets is unavoidable, breast-feeding should be stopped.

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

**Driving and using machines**

Pramipexole Tablets can cause hallucinations (seeing, hearing or feeling things that are not there), if affected, do not drive or use machines.

Pramipexole Tablets have been associated with sleepiness and episodes of suddenly falling asleep, particularly in patients with Parkinson's disease. If you experience these side effects, you must not drive or operate machinery. You should tell your doctor if this occurs.

**3. HOW TO TAKE PRAMIPEXOLE TABLETS**

Always take Pramipexole Tablets exactly as your doctor has told you. The doctor will advise you on the right dosing.

You can take Pramipexole Tablets with or without food. Swallow the tablets with water.

**Parkinson's disease**

The daily dose is to be taken divided into three equal doses.

During the first week, the usual dose is one Pramipexole 88 micrograms Tablet three times a day (equivalent to 264 micrograms daily).

	1st week
Number of tablets	One Pramipexole 88 micrograms Tablet three times a day
Total daily dose (micrograms)	264

This will be increased every 5-7 days as directed by your doctor until your symptoms are controlled (maintenance dose).

	2nd week	3rd week
Number of tablets	One Pramipexole 180 micrograms Tablet three times a day OR Two Pramipexole 88 micrograms Tablets three times a day	One Pramipexole 350 micrograms Tablet three times a day OR Two Pramipexole 180 micrograms Tablets three times a day
Total daily dose (micrograms)	540	1,100

The usual maintenance dose is 1,100 micrograms per day. However, your dose may have to be increased even further. If necessary, your doctor may increase your tablet dose up to a maximum of 3,300 micrograms of pramipexole a day. A lower maintenance dose of three Pramipexole 88 micrograms Tablets a day is also possible.

	Lowest maintenance dose	Highest maintenance dose
Number of tablets	One Pramipexole 88 micrograms Tablet three times a day	One Pramipexole 350 micrograms Tablet and one Pramipexole 700 micrograms Tablet three times a day
Total daily dose (micrograms)	264	3,150

**Patients with kidney disease**

If you have moderate or severe kidney disease, your doctor will prescribe a lower dose. In this case, you will have to take the tablets only once or twice a day. If you have moderate kidney disease, the usual starting dose is one Pramipexole 88 micrograms Tablet twice a day. In severe kidney disease, the usual starting dose is just one Pramipexole 88 micrograms Tablet a day.

**Restless Legs Syndrome**

The dose is usually taken once a day, in the evening, 2-3 hours before bedtime.

During the first week, the usual dose is one Pramipexole 88 micrograms Tablet once a day (equivalent to 88 micrograms daily).

	1st week
Number of tablets	One Pramipexole 88 micrograms Tablet
Total daily dose (micrograms)	88

This will be increased every 4-7 days as directed by your doctor until your symptoms are controlled (maintenance dose).

	2nd week	3rd week	4th week
Number of tablets	One Pramipexole 180 micrograms Tablet OR Two Pramipexole 88 micrograms Tablets	One Pramipexole 350 micrograms Tablet OR Three Pramipexole 180 micrograms Tablets	One Pramipexole 350 micrograms Tablet and One Pramipexole 180 micrograms Tablet OR Four Pramipexole 88 micrograms Tablets
Total daily dose (micrograms)	180	350	540

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The daily dose should not exceed six Pramipexole 88 micrograms Tablets or a dose of 540 micrograms (750 micrograms pramipexole salt).

If you stop taking your tablets for more than a few days and want to restart the treatment, you must start again at the lowest dose. You can then build up the dose again, as you did the first time. Ask your doctor for advice.

Your doctor will review your treatment after three months to decide whether or not to continue the treatment.

**Patients with kidney disease**

If you have severe kidney disease, Pramipexole Tablets may not be a suitable treatment for you.

**If you take more Pramipexole Tablets than you should**

- contact your doctor or nearest hospital casualty department immediately for advice
- you may experience vomiting, restlessness, or any of the side effects as described in chapter 4 "Possible side effects".

**If you forget to take Pramipexole Tablets**

Do not worry. Simply leave out that dose completely and then take your next dose at the right time. Do not try to make up for the missed dose.

**If you stop taking Pramipexole Tablets**

Do not stop taking Pramipexole Tablets without first talking to your doctor. If you have to stop taking this medicine, your doctor will reduce the dose gradually. This reduces the risk of worsening symptoms.

If you suffer from Parkinson's disease you should not stop treatment with Pramipexole Tablets abruptly. A sudden stop could cause you to develop a medical condition called neuroleptic malignant syndrome which may represent a major health risk. The symptoms include:

- akinesia (loss of muscle movement),
- rigid muscles,
- fever,
- unstable blood pressure,
- tachycardia (increased heart rate),
- confusion,
- depressed level of consciousness (e.g. coma).

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

#### 4. POSSIBLE SIDE EFFECTS

Like all medicines, Pramipexole Tablets can cause side effects, although not everybody gets them.

Evaluation of these side effects is based on the following frequencies:

Very common	affects more than 1 user in 10
Common	affects 1 to 10 users in 100
Uncommon	affects 1 to 10 users in 1,000
Rare	affects 1 to 10 users in 10,000
Very rare	affects less than 1 user in 10,000
Not known	frequency cannot be estimated from the available data

If you suffer from Parkinson's disease, you may experience the following side effects:

**Very common:**

- dyskinesia (e.g. abnormal, uncontrolled movements of the limbs)
- sleepiness
- dizziness
- nausea (sickness).

**Common:**

- urge to behave in an unusual way
- hallucinations (seeing, hearing or feeling things that are not there)
- confusion
- tiredness (fatigue)
- sleeplessness (insomnia)
- excess of fluid, usually in the legs (peripheral oedema)
- headache
- hypotension (low blood pressure)
- abnormal dreams
- constipation
- visual disturbance
- vomiting (being sick)
- weight loss including decreased appetite.

**Uncommon:**

- paranoia (e.g. excessive fear for one's own well-being)
- delusion
- excessive daytime sleepiness and suddenly falling asleep
- amnesia (memory disturbance)
- hyperkinesia (increased movements and inability to keep still)
- weight increase
- increased sexual desire (e.g. increased libido)
- allergic reactions (e.g. rash, itching, hypersensitivity)
- fainting
- pathological gambling, especially when taking high doses of Pramipexole Tablets
- hypersexuality
- increased eating (binge eating, hyperphagia)
- restlessness
- compulsive shopping
- dyspnoea (difficulties to breathe)
- heart failure
- hiccups
- pneumonia (infection of the lungs).

If you suffer from Restless Legs Syndrome, you may experience the following side effects:

**Very common:**

- nausea (sickness).

**Common:**

- changes in sleep pattern, such as sleeplessness (insomnia) and sleepiness
- tiredness (fatigue)
- headache
- abnormal dreams
- constipation
- dizziness
- vomiting (being sick).

**Uncommon:**

- pathological gambling, especially when taking high doses of Pramipexole Tablets
- hypersexuality
- compulsive shopping

- urge to behave in an unusual way
- increased eating (binge eating, hyperphagia)
- dyskinesia (e.g. abnormal, uncontrolled movements of the limbs)
- hyperkinesia (increased movements and inability to keep still)
- paranoia (e.g. excessive fear for one's own well-being)
- delusion
- amnesia (memory disturbance)
- hallucinations (seeing, hearing or feeling things that are not there)
- confusion
- excessive daytime sleepiness and suddenly falling asleep
- weight increase
- increased sexual desire (e.g. increased libido)
- hypotension (low blood pressure)
- heart failure
- excess of fluid, usually in the legs (peripheral oedema)
- allergic reactions (e.g. rash, itching, hypersensitivity)
- fainting
- restlessness
- visual impairment
- weight loss including decreased appetite
- dyspnoea (difficulties to breathe)
- hiccups
- pneumonia (infection of the lungs).

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

#### 5. HOW TO STORE PRAMIPEXOLE TABLETS

Keep out of the reach and sight of children.

Do not take Pramipexole Tablets after the expiry date which is stated on the pack. The expiry date refers to the last day of that month.

This medicinal product does not require any special storage conditions.

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

#### 6. FURTHER INFORMATION

**What Pramipexole Tablets contain**

The active substance is pramipexole.

Each tablet contains 88 micrograms, 180 micrograms, 350 micrograms or 700 micrograms pramipexole as 125 micrograms, 250 micrograms, 500 micrograms or 1,000 micrograms pramipexole dihydrochloride monohydrate, respectively.

The other ingredients are mannitol, maize starch, citric acid monohydrate, colloidal anhydrous silica, povidone K 30 and magnesium stearate.

**What Pramipexole Tablets look like and contents of the pack**

Pramipexole 88 micrograms Tablets are white to off white, round uncoated tablets, debossed "g" on one side and plain on the other.

Pramipexole 180 micrograms Tablets are white to off white, oval shaped uncoated tablets, debossed "W" on one side and "180" on the other side of score line and plain on either side of the score line on the reverse side.

Pramipexole 350 micrograms Tablets are white to off white, oval shaped uncoated tablets, debossed "W" on one side and "350" on the other side of score line and plain on either side of the score line on the reverse side.

Pramipexole 700 micrograms Tablets are white to off white, round shaped uncoated tablets, debossed "W" on one side and "700" on the other side of score line and plain on either side of the score line on the reverse side.

The 180 micrograms, 350 micrograms and 700 micrograms tablets can be divided into equal halves.

Pramipexole Tablets are available in Alu/Alu blister packs of ten tablets per strip. Pramipexole 88 micrograms Tablets are available in cartons containing three blister strips (30 tablets) and Pramipexole 180 micrograms, 350 micrograms and 700 micrograms Tablets are available in cartons containing three or ten blister strips (30 or 100 tablets). Not all pack sizes may be marketed.

**Other formats:**

To listen to or request a copy of this leaflet in Braille, large print or audio please call, free of charge:

0800 198 5000 (UK Only)

Please be ready to give the following information:

Product Name	Reference Number
Pramipexole 88 micrograms Tablets	PL 29831/0472
Pramipexole 180 micrograms Tablets	PL 29831/0473
Pramipexole 350 micrograms Tablets	PL 29831/0474
Pramipexole 700 micrograms Tablets	PL 29831/0475

This is a service provided by the Royal National Institute of Blind People.

**Marketing Authorisation Holder and Manufacturer**

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

**Manufacturer**

CP Pharmaceuticals Limited, Ash Road North, Wrexham, LL13 9UF, UK.

Leaflet prepared: July 2011.

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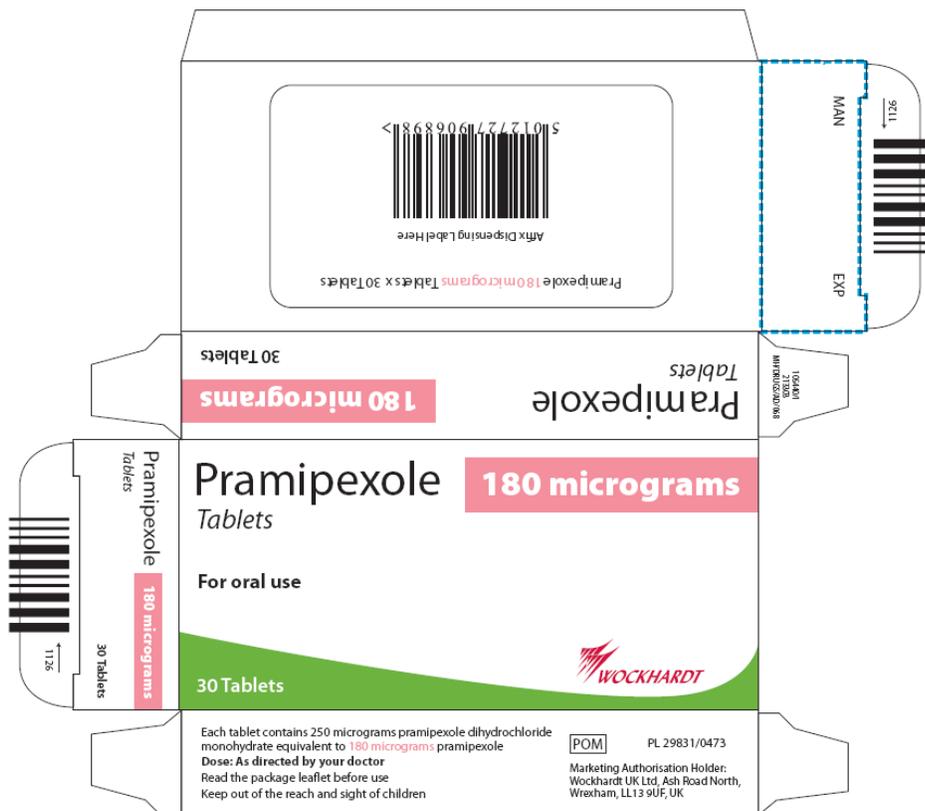
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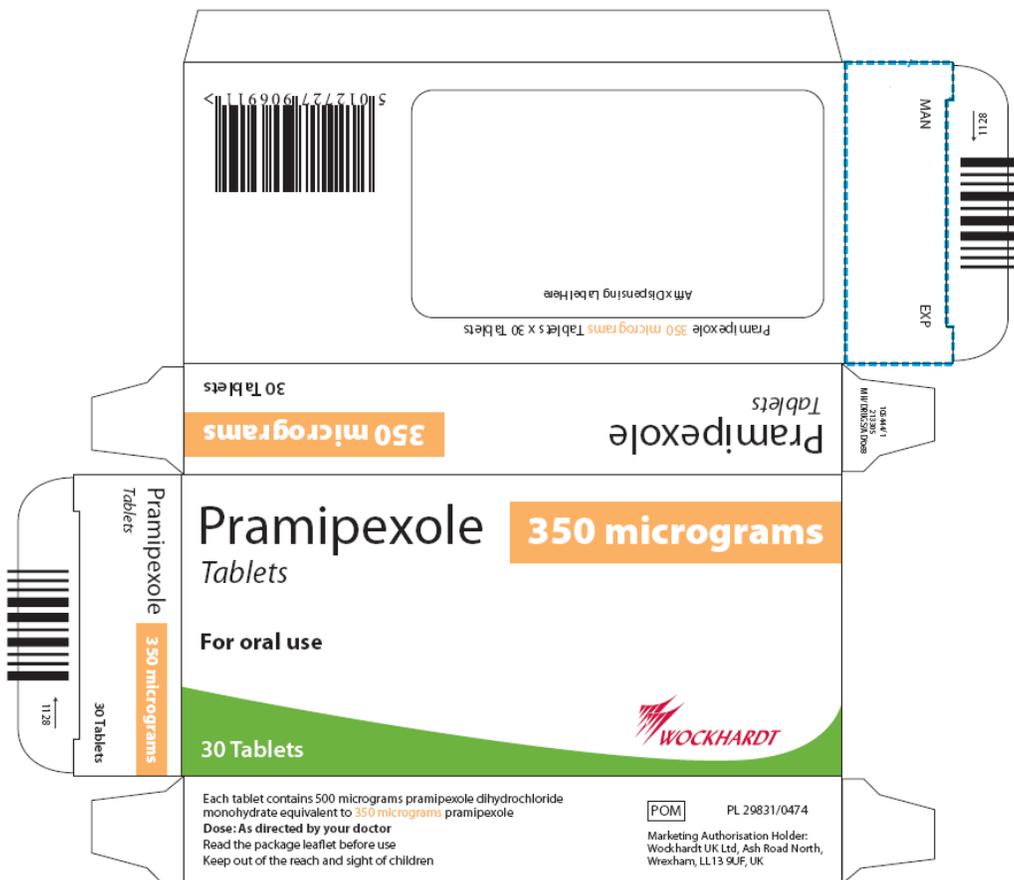
**CARTON**



**BLISTER FOIL**



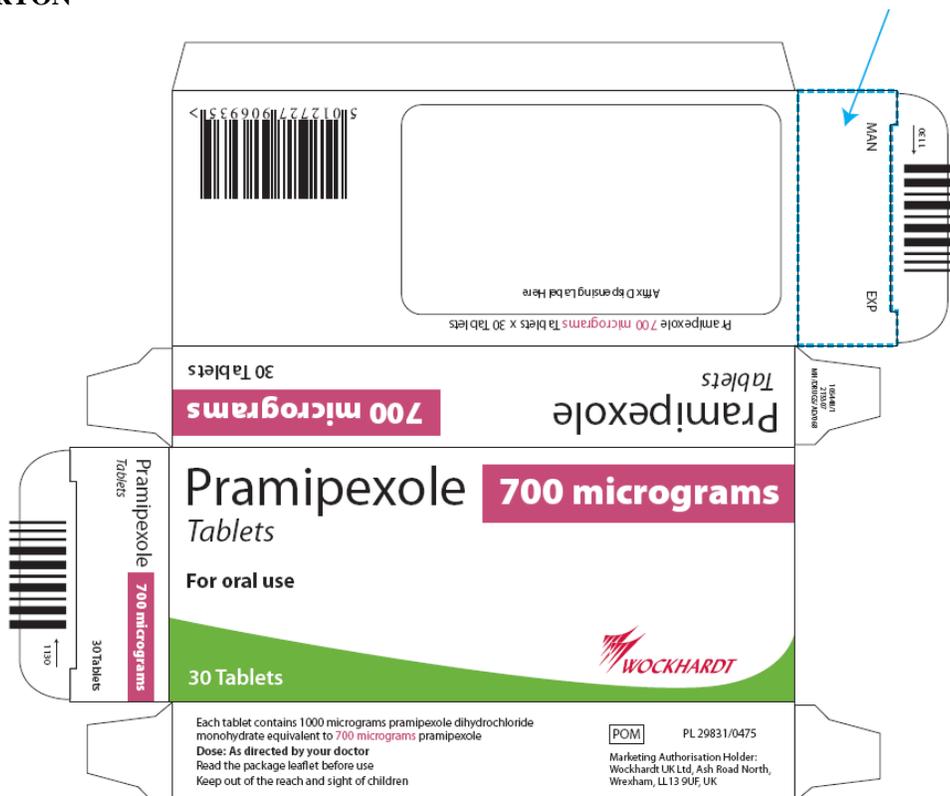
**CARTON**



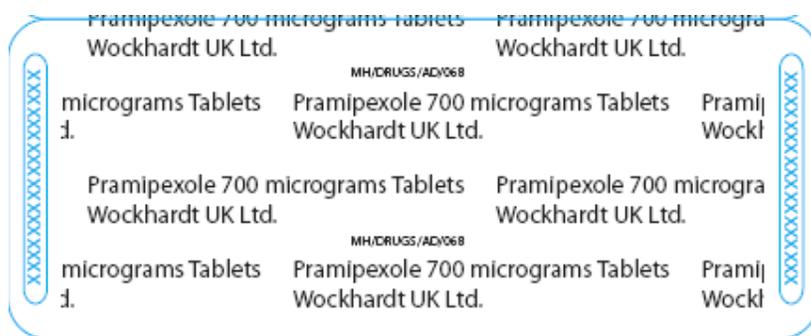
**BLISTER FOIL**



## CARTON



## BLISTER FOIL



## Annex

**Reference:** PL 29831/0472-5; application 0002

**Product:** Pramipexole 88 microgram (mcg), 180 mcg, 350 mcg and 700 mcg Tablets

**MAH:** Wockhardt UK Ltd

**Active Ingredient:** Pramipexole

**Reason:**

To update the therapeutic indications by removing the use of the drug for symptomatic treatment of moderate to severe idiopathic Restless Legs Syndrome (RLS), and any reference or warnings associated to this usage; sections 4.1 (Therapeutic indications), 4.2 (Posology and method of administration) of the SmPC and consequentially the leaflet is amended.

**Supporting evidence:**

The applicant has submitted the following updated documents:

Sections 4.1, 4.2, 4.4, 4.8 and 5.1 of the SmPC.

An updated mock-up of the PIL has been provided.

**Evaluation**

SmPC: The updated SmPC fragments and PIL are satisfactory.

The indication for RLS is to be removed as it is under patent but the safety information must remain. Therefore, fragments 4.1 and 4.2 are updated, whilst fragments 4.4, 4.8 and 5.1 are unchanged and retain information regarding RLS.

**Conclusion**

The variation was approved on 27 March 2012 and the following updated SmPC fragments and PIL have been incorporated into these Marketing Authorisations.

## Summary of Product Characteristics – updated

The fragments updated in view of the stated variation are reproduced below:

### 4.1. Therapeutic indications

Pramipexole is indicated in adults for treatment of the signs and symptoms of idiopathic Parkinson's disease, alone (without levodopa) or in combination with levodopa, i.e. over the course of the disease, through to late stages when the effect of levodopa wears off or becomes inconsistent and fluctuations of the therapeutic effect occur (end of dose or “on off” fluctuations).

### 4.2. Posology and Method of Administration

Posology

#### *Parkinson's disease*

The daily dose is administered in equally divided doses 3 times a day.

#### *Initial treatment*

Doses should be increased gradually from a starting dose of 264 micrograms of base (375 micrograms of salt) per day and then increased every 5-7 days. Providing patients do not experience intolerable undesirable effects, the dose should be titrated to achieve a maximal therapeutic effect.

Ascending dose schedule of Pramipexole				
Week	Dose (micrograms of base)	Total Daily Dose (micrograms of base)	Dose (micrograms of salt)	Total Daily Dose (micrograms of salt)
1	3 x 88	264	3 x 125	375
2	3 x 180	540	3 x 250	750
3	3 x 350	1,100	3 x 500	1,500

If a further dose increase is necessary the daily dose should be increased by 540 micrograms of base (750 micrograms of salt) at weekly intervals up to a maximum dose of 3,300 micrograms of base (4,500 micrograms of salt) per day. However, it should be noted that the incidence of somnolence is increased at doses higher than 1,500 micrograms (of salt) per day (see section 4.8).

#### *Maintenance treatment*

The individual dose of pramipexole should be in the range of 264 micrograms of base (375 micrograms of salt) to a maximum of 3,300 micrograms of base (4,500 micrograms of salt) per day. During dose escalation in pivotal studies, efficacy was observed starting at a daily dose of 1,100 micrograms of base (1,500 micrograms of salt). Further dose adjustments should be done based on the clinical response and the occurrence of adverse reactions. In clinical trials approximately 5% of patients were treated at doses below 1,100 micrograms of base (1,500 micrograms of salt). In advanced Parkinson's disease, pramipexole doses higher than 1,100 micrograms of base (1,500 micrograms of salt) per day can be useful in patients where a reduction of the levodopa therapy is intended. It is recommended that the dose of levodopa is reduced during both the dose escalation and the maintenance treatment with Pramipexole, depending on reactions in individual patients (see section 4.5).

#### *Treatment discontinuation*

Abrupt discontinuation of dopaminergic therapy can lead to the development of a neuroleptic malignant syndrome. Pramipexole should be tapered off at a rate of 540 micrograms of base (750 micrograms of salt) per day until the daily dose has been reduced to 540 micrograms of base (750 micrograms of salt). Thereafter the dose should be reduced by 264 micrograms of base (375 micrograms of salt) per day (see section 4.4).

#### *Dosing in patients with renal impairment*

The elimination of pramipexole is dependent on renal function. The following dose schedule is suggested for initiation of therapy:

Patients with a creatinine clearance above 50 ml/min require no reduction in daily dose or dosing frequency.

In patients with a creatinine clearance between 20 and 50 ml/min, the initial daily dose of Pramipexole should be administered in two divided doses, starting at 88 micrograms of base (125 micrograms of salt) twice a day (176 micrograms of base/250 micrograms of salt daily). A maximum daily dose of 1,570 micrograms pramipexole base (2,250 micrograms of salt) should not be exceeded.

In patients with a creatinine clearance less than 20 ml/min, the daily dose of Pramipexole should be administered in a single dose, starting at 88 micrograms of base (125 micrograms of salt) daily. A maximum daily dose of 1,100 micrograms pramipexole base (1,500 micrograms of salt) should not be exceeded.

If renal function declines during maintenance therapy the Pramipexole daily dose should be reduced by the same percentage as the decline in creatinine clearance, i.e. if creatinine clearance declines by 30%, then the Pramipexole daily dose should be reduced by 30%. The daily dose can be administered in two divided doses if creatinine clearance is between 20 and 50 ml/min and as a single daily dose if creatinine clearance is less than 20 ml/min.

#### *Dosing in patients with hepatic impairment*

Dose adjustment in patients with hepatic failure is probably not necessary, as approx. 90% of absorbed active substance is excreted through the kidneys. However, the potential influence of hepatic insufficiency on Pramipexole pharmacokinetics has not been investigated.

#### *Paediatric population*

The safety and efficacy of Pramipexole in children below 18 years has not been established. There is no relevant use of Pramipexole in the paediatric population in Parkinson's Disease.

#### Tourette Disorder

#### *Paediatric population*

Pramipexole is not recommended for use in children and adolescents below 18 years since the efficacy and safety has not been established in this population. Pramipexole should not be used in children or adolescents with Tourette Disorder because of a negative benefit-risk balance for this disorder (see section 5.1).

#### *Method of administration*

The tablets should be taken orally, swallowed with water, and can be taken either with or without food.

## **10 DATE OF REVISION OF THE TEXT**

27/03/2012

# Patient Information Leaflet - updated

## PATIENT INFORMATION LEAFLET Pramipexole 88 micrograms Tablets Pramipexole 180 micrograms Tablets Pramipexole 350 micrograms Tablets Pramipexole 700 micrograms Tablets

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 Pramipexole Tablets are and what they are used for
2. Before you take Pramipexole Tablets
3. How to take Pramipexole Tablets
4. Possible side effects
5. How to store Pramipexole Tablets
6. Further information

### 1. WHAT PRAMIPEXOLE TABLETS ARE AND WHAT THEY ARE USED FOR

Pramipexole Tablets belong to a group of medicines known as dopamine agonists, which stimulate dopamine receptors in the brain. Stimulation of the dopamine receptors triggers nerve impulses in the brain that help to control body movements.

#### Pramipexole Tablets are used to:

- treat the symptoms of primary Parkinson's disease. They can be used alone or in combination with levodopa (another medicine for Parkinson's disease).

Pramipexole which is contained in Pramipexole Tablets may also be 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 PRAMIPEXOLE TABLETS

#### Do not take Pramipexole Tablets

- if you are allergic (hypersensitive) to pramipexole or to any of the other ingredients of the tablets (see Section 6, "Further information").

#### Take special care with Pramipexole Tablets

Tell your doctor if you have (had) or develop any medical conditions or symptoms, especially any of the following:

- kidney disease
- hallucinations (seeing, hearing or feeling things that are not there). Most hallucinations are visual
- dyskinesia (e.g. abnormal, uncontrolled movements of the limbs). If you have

Pramipexole Tablets can be taken with or without food.

#### Pregnancy and breast-feeding

Tell your doctor if you are pregnant, think you might be pregnant or if you intend to become pregnant. Your doctor will then discuss with you if you should continue to take Pramipexole Tablets.

The effect of Pramipexole Tablets on the unborn child is not known. Therefore, do not take Pramipexole Tablets if you are pregnant unless your doctor tells you to do so.

Pramipexole Tablets should not be used during breast-feeding. Pramipexole Tablets can reduce the production of breast milk. Also, they can pass into the breast milk and can reach your baby. If use of Pramipexole Tablets is unavoidable, breast-feeding should be stopped.

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

#### Driving and using machines

Pramipexole Tablets can cause hallucinations (seeing, hearing or feeling things that are not there). If affected, do not drive or use machines.

Pramipexole Tablets have been associated with sleepiness and episodes of suddenly falling asleep, particularly in patients with Parkinson's disease. If you experience these side effects, you must not drive or operate machinery. You should tell your doctor if this occurs.

### 3. HOW TO TAKE PRAMIPEXOLE TABLETS

Always take Pramipexole Tablets exactly as your doctor has told you. The doctor will advise you on the right dosing.

You can take Pramipexole Tablets with or without food. Swallow the tablets with water.

#### Parkinson's disease

The daily dose is to be taken divided into three equal doses.

During the first week, the usual dose is one Pramipexole 88 micrograms Tablet three times a day (equivalent to 264 micrograms daily):

advanced Parkinson's disease and are also taking levodopa, you might develop dyskinesia with increased doses of Pramipexole Tablets

- sleepiness and episodes of suddenly falling asleep
- behavioural changes (e.g. pathological gambling, compulsive shopping), increased libido (e.g. increased sexual desire), binge eating
- psychosis (e.g. comparable with symptoms of schizophrenia)
- vision impairment. You should have regular eye examinations during treatment with Pramipexole Tablets
- severe heart or blood vessels disease. You will need to have your blood pressure checked regularly, especially at the beginning of treatment. This is to avoid postural hypotension (a fall in blood pressure on standing up)
- augmentation. You may experience that symptoms start earlier than usual, be more intense and involve other limbs.

#### Children and adolescents

Pramipexole Tablets are not recommended for use in children or adolescents under 18 years.

#### Taking other medicines

Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines. This includes medicines, herbal remedies, health foods or supplements that you have obtained without a prescription.

You should avoid taking Pramipexole Tablets together with antipsychotic medicines.

Take care if you are taking the following medicines:

- cimetidine (to treat excess stomach acid and stomach ulcers)
- amantadine (which can be used to treat Parkinson's disease)
- mexiletine (to treat irregular heartbeats, a condition known as ventricular arrhythmia)
- zidovudine (which can be used to treat the acquired immune deficiency syndrome (AIDS), a disease of the human immune system)
- cisplatin (to treat various types of cancers)
- quinine (which can be used for the prevention of painful night-time leg cramps and for the treatment of a type of malaria known as falciparum malaria (malignant malaria))
- procainamide (to treat irregular heart beat).

If you are taking levodopa, the dose of levodopa is recommended to be reduced when you start treatment with Pramipexole Tablets.

Take care if you are using any medicines that calm you down (have a sedative effect) or if you are drinking alcohol. In these cases Pramipexole Tablets may affect your ability to drive and operate machinery.

#### Taking Pramipexole Tablets with food and drink

You should be cautious while drinking alcohol during treatment with Pramipexole Tablets.

1st week	
Number of tablets	One Pramipexole 88 micrograms Tablet three times a day
Total daily dose (micrograms)	264

This will be increased every 5-7 days as directed by your doctor until your symptoms are controlled (maintenance dose).

	2nd week	3rd week
Number of tablets	One Pramipexole 180 micrograms Tablet three times a day OR Two Pramipexole 88 micrograms Tablets three times a day	One Pramipexole 350 micrograms Tablet three times a day OR Two Pramipexole 180 micrograms Tablets three times a day
Total daily dose (micrograms)	540	1,100

The usual maintenance dose is 1,100 micrograms per day. However, your dose may have to be increased even further. If necessary, your doctor may increase your tablet dose up to a maximum of 3,300 micrograms of pramipexole a day. A lower maintenance dose of three Pramipexole 88 micrograms Tablets a day is also possible.

	Lowest maintenance dose	Highest maintenance dose
Number of tablets	One Pramipexole 88 micrograms Tablet three times a day	One Pramipexole 350 micrograms Tablet and one Pramipexole 700 micrograms Tablet three times a day
Total daily dose (micrograms)	264	3,150

#### Patients with kidney disease

If you have moderate or severe kidney disease, your doctor will prescribe a lower dose. In this case, you will have to take the tablets only once or twice a day. If you have moderate kidney disease, the usual starting dose is one Pramipexole 88 micrograms Tablet twice a day. In severe kidney disease, the usual starting dose is just one Pramipexole 88 micrograms Tablet a day.

#### If you take more Pramipexole Tablets than you should

- If you accidentally take too many tablets,
- contact your doctor or nearest hospital casualty department immediately for advice
  - you may experience vomiting, restlessness, or any of the side effects as described in chapter 4 "Possible side effects".

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**If you forget to take Pramipexole Tablets**

Do not worry. Simply leave out that dose completely and then take your next dose at the right time.

Do not try to make up for the missed dose.

**If you stop taking Pramipexole Tablets**

Do not stop taking Pramipexole Tablets without first talking to your doctor. If you have to stop taking this medicine, your doctor will reduce the dose gradually. This reduces the risk of worsening symptoms.

If you suffer from Parkinson's disease you should not stop treatment with Pramipexole Tablets abruptly. A sudden stop could cause you to develop a medical condition called neuroleptic malignant syndrome which may represent a major health risk. The symptoms include:

- akinesia (loss of muscle movement),
- rigid muscles,
- fever,
- unstable blood pressure,
- tachycardia (increased heart rate),
- confusion,
- depressed level of consciousness (e.g. coma).

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

- falling asleep
- weight increase
- increased sexual desire (e.g. increased libido)
- hypotension (low blood pressure)
- heart failure
- excess of fluid, usually in the legs (peripheral oedema)
- allergic reactions (e.g. rash, itching, hypersensitivity)
- fainting
- restlessness
- visual impairment
- weight loss including decreased appetite
- dyspnoea (difficulties to breathe)
- hiccups
- pneumonia (infection of the lungs).

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.

**4. POSSIBLE SIDE EFFECTS**

Like all medicines, Pramipexole Tablets can cause side effects, although not everybody gets them.

Evaluation of these side effects is based on the following frequencies:

Very common	affects more than 1 user in 10
Common	affects 1 to 10 users in 100
Uncommon	affects 1 to 10 users in 1,000
Rare	affects 1 to 10 users in 10,000
Very rare	affects less than 1 user in 10,000
Not known	frequency cannot be estimated from the available data

*If you suffer from Parkinson's disease, you may experience the following side effects:*

**Very common:**

- dyskinesia (e.g. abnormal, uncontrolled movements of the limbs)
- sleepiness
- dizziness
- nausea (sickness).

**Common:**

- urge to behave in an unusual way
- hallucinations (seeing, hearing or feeling things that are not there)
- confusion
- tiredness (fatigue)
- sleeplessness (insomnia)
- excess of fluid, usually in the legs (peripheral oedema)
- headache
- hypotension (low blood pressure)
- abnormal dreams
- constipation
- visual disturbance
- vomiting (being sick)
- weight loss including decreased appetite.

**5. HOW TO STORE PRAMIPEXOLE TABLETS**

Keep out of the reach and sight of children.

Do not take Pramipexole Tablets after the expiry date which is stated on the pack. The expiry date refers to the last day of that month.

This medicinal product does not require any special storage conditions.

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

**6. FURTHER INFORMATION****What Pramipexole Tablets contain**

The active substance is pramipexole.

Each tablet contains 88 micrograms, 180 micrograms, 350 micrograms or 700 micrograms pramipexole as 125 micrograms, 250 micrograms, 500 micrograms or 1,000 micrograms pramipexole dihydrochloride monohydrate, respectively.

The other ingredients are mannitol, maize starch, citric acid monohydrate, colloidal anhydrous silica, povidone K 30 and magnesium stearate.

**What Pramipexole Tablets look like and contents of the pack**

Pramipexole 88 micrograms Tablets are white to off white, round uncoated tablets, debossed "W" on one side and plain on the other.

Pramipexole 180 micrograms Tablets are white to off white, oval shaped uncoated tablets, debossed "W" on one side and "117" on the other side of score line and plain on either side of the score line on the reverse side.

**Uncommon:**

- paranoia (e.g. excessive fear for one's own well-being)
- delusion
- excessive daytime sleepiness and suddenly falling asleep
- amnesia (memory disturbance)
- hyperkinesia (increased movements and inability to keep still)
- weight increase
- increased sexual desire (e.g. increased libido)
- allergic reactions (e.g. rash, itching, hypersensitivity)
- fainting
- pathological gambling, especially when taking high doses of Pramipexole Tablets
- hypersexuality
- increased eating (binge eating, hyperphagia)
- restlessness
- compulsive shopping
- dyspnoea (difficulties to breathe)
- heart failure
- hiccups
- pneumonia (infection of the lungs).

*If you suffer from Restless Legs Syndrome, you may experience the following side effects:*

**Very common:**

- nausea (sickness).

**Common:**

- changes in sleep pattern, such as sleeplessness (insomnia) and sleepiness
- tiredness (fatigue)
- headache
- abnormal dreams
- constipation
- dizziness
- vomiting (being sick).

**Uncommon:**

- pathological gambling, especially when taking high doses of Pramipexole Tablets
- hypersexuality
- compulsive shopping
- urge to behave in an unusual way
- increased eating (binge eating, hyperphagia)
- dyskinesia (e.g. abnormal, uncontrolled movements of the limbs)
- hyperkinesia (increased movements and inability to keep still)
- paranoia (e.g. excessive fear for one's own well-being)
- delusion
- amnesia (memory disturbance)
- hallucinations (seeing, hearing or feeling things that are not there)
- confusion
- excessive daytime sleepiness and suddenly

Pramipexole 350 micrograms Tablets are white to off white, oval shaped uncoated tablets, debossed "W" on one side and "118" on the other side of score line and plain on either side of the score line on the reverse side.

Pramipexole 700 micrograms Tablets are white to off white, round shaped uncoated tablets, debossed "W" on one side and "119" on the other side of score line and plain on either side of the score line on the reverse side.

The 180 micrograms, 350 micrograms and 700 micrograms tablets can be divided into equal halves.

Pramipexole Tablets are available in Alu/Alu blister packs of ten tablets per strip.

Pramipexole 88 micrograms Tablets are available in cartons containing three blister strips (30 tablets) and Pramipexole 180 micrograms, 350 micrograms and 700 micrograms Tablets are available in cartons containing three or ten blister strips (30 or 100 tablets). Not all pack sizes may be marketed.

**Other formats:**

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

Please be ready to give the following information:

Product Name	Reference Number
Pramipexole 88 micrograms Tablets	PL 29831/0472
Pramipexole 180 micrograms Tablets	PL 29831/0473
Pramipexole 350 micrograms Tablets	PL 29831/0474
Pramipexole 700 micrograms Tablets	PL 29831/0475

This is a service provided by the Royal National Institute of Blind People.

**Marketing Authorisation Holder and Manufacturer**

**Marketing Authorisation Holder**  
Wockhardt UK Limited, Ash Road North, Wrexham, LL13 9UF, UK

**Manufacturer**  
CP Pharmaceuticals Limited, Ash Road North, Wrexham, LL13 9UF, UK

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