LÄKEMEDELSVERKET
MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Pramipexol Teva Pharma
(pramipexole dihydrochloride monohydrate)

SE/H/1360/01-07/DC

This module reflects the scientific discussion for the approval of Pramipexol Teva Pharma. The procedure was finalised on 2014-12-01. For information on changes after this date please refer to the module 'Update'.

Postadress/Postal address: P.O. Box 26, SE-751 03 Uppsala, SWEDEN
Besöksadress/Visiting address: Dag Hammarskjölds väg 42, Uppsala
Telefon/Phone: +46 (0)18 17 46 00 Fax: +46 (0)18 54 85 66
Internet: www.mpa.se E-mail: registrator@mpa.se

I. INTRODUCTION

The application for Pramipexol Teva Pharma, 0.26 mg, 0.52 mg, 1.05 mg, 1.57 mg, 2.1 mg, 2.62 mg, 3.15 mg, prolonged-release tablets, is a generic application made according to Article 10(1) of Directive 2001/83/EC. The applicant, Teva Pharma B.V., applies through the Decentralised Procedure with Sweden acting as reference member state (RMS) and AT, BE, DE, DK, EE, FI, FR, HR, HU, IS, LT, LV, NL, RO, SK, UK as concerned member states (CMS).

The reference medicinal product chosen for the purposes of establishing the expiry of the data protection period is SIFROL, 1.1 mg tablets, authorised in DE since 1997, with Boehringer Ingelheim International GmbH as marketing authorisation holder.

The reference product used in the bioequivalence study is SIFROL, 0.26 mg, 0.52 mg and 3.15 mg, prolonged-release tablets from DE with Boehringer Ingelheim International GmbH as marketing authorisation holder.

For approved indications, see the Summary of Product Characteristics.

II. QUALITY ASPECTS

II.1 Introduction

Pramipexol Teva Pharma is presented in the form of tablets containing 0.375 mg, 0.75 mg, 1.5 mg, 2.25 mg, 3 mg, 3.75 mg, and 4.5 mg of Pramipexole Dihydrochloride Monohydrate which corresponds to 0.26 mg, 0.52 mg, 1.05 mg, 1.57 mg, 2.1 mg, 2.62 mg, and 3.15 mg of Pramipexole. The excipients are Hypromellose, Calcium hydrogen phosphate anhydrous, Magnesium stearate and Colloidal silicon dioxide anhydrous. The tablets are packed in aluminium/aluminium blister.

II.2 Drug Substance

Pramipexole dihydrochloride monohydrate has a monograph in the Ph Eur.

Pramipexole dihydrochloride monohydrate is a white, crystalline powder which is freely soluble in water. The structure of Pramipexole dihydrochloride monohydrate has been adequately proven and its physico-chemical properties sufficiently described. Relevant information on polymorphism, and chirality is presented. The route of synthesis has been adequately described and satisfactory specifications have been provided for starting materials, reagents and solvents.

The active substance specification includes relevant tests and the limits for impurities/degradation products have been justified. The analytical methods applied are suitably described and validated.

Stability studies under ICH conditions have been conducted and the data provided are sufficient to confirm the retest period.

II.3 Medicinal Product

Pramipexol Teva Pharma tablets are formulated using excipients described in the current Ph Eur. All raw materials used in the product are of non-animal origin.

The product development has taken into consideration the physico-chemical characteristics of the active substance.

The manufacturing process has been sufficiently described and critical steps identified. Results from the process validation studies confirm that the process is under control and ensure both batch to batch reproducibility and compliance with the product specification.

The tests and limits in the specification are considered appropriate to control the quality of the finished product in relation to its intended purpose.

Stability studies under ICH conditions have been performed and data presented support the shelf life claimed in the SPC, with no special storage precautions.

III. NON-CLINICAL ASPECTS

III.1 Discussion on the non-clinical aspects

Since this product has been shown to be essentially similar and refer to a product approved based on a full application with regard to preclinical data, no further such data have been submitted or are considered necessary.

IV. CLINICAL ASPECTS

IV.1 Pharmacokinetics

To support the application the applicant has submitted four bioequivalence studies comparing pramipexole prolonged release tablet with Sifrol prolonged release tablet; two single-dose fasting studies on the two lowest strengths of 0.26 and 0.52 mg, one single-dose fed study on the 0.52 mg strength and one multiple-dose study with the 0.52 mg and 3.15 mg strengths.

The three single-dose two-way cross-over studies (0.26 mg fasting, 0.52 mg fasting and 0.52 mg fed) were all conducted at Clinical Hospital of the Ministry of Health of Moldavian Republic. Blood samples were collected pre-dose and up to 72 hours post-dose. Plasma concentrations of pramipexole were determined with a validated LC-MS/MS method. For AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} the 90% confidence interval for the ratio of the test and reference products fell within the conventional acceptance range of 80.00-125.00%.

The multiple-dose study was performed with an up-titration phase and had a double randomised, multiple dose, four- period, two-sequence crossover design. The study was conducted at 3S-Pharmacological Consultation & Res in Romania. Blood samples were collected pre-dose at day 1, 4-7, 9-12, 25-28, 30-33 and pre-dose and up to 24 hours post-dose at day 8, 13, 29, and 34. Plasma concentrations of pramipexole were determined with a validated LC-MS/MS method. For $C_{max.ss}$, $C_{min.ss}$, $AUC_{0-\tau.ss}$ the 90% confidence interval for the ratio of the test and reference products fell within the conventional acceptance range of 80.00-125.00% for both the 0.52mg strength and 3.15mg strength.

The applied product is a prolonged-release single unit formulation and according to the Note for Guidance on modified release oral and transdermal dosage forms (CPMP/EWP/280/96 Corr), a single-dose fasting study should in general be conducted on each strength for a single-unit formulation. It is agreed that single-dose studies with the 1.57, 2.1, 2.62 and 3.15 mg strengths would probably be difficult to perform due to the risk of the known adverse events of pramipexole, such as nausea and lower blood pressure and syncope. However the 1.05mg strength would have been possible to study in healthy volunteers in fasting condition, but not in fed condition. Although it would have been desirable to conduct studies with as many strengths as possible, in this case a bracketing approach could be justified. In addition similar *in vitro* dissolution profiles has been demonstrated for all strengths compared to the 0.52 mg strength and similar *in vitro* dissolution profiles have been demonstrated between the test and the reference product for each strength. Thus the submitted study package is considered sufficient and no additional studies are considered necessary.

IV.2 Discussion on the clinical aspects

Since this product has been shown to be essentially similar and refer to a product approved based on a full application with regard to clinical efficacy/safety data, no further such data have been submitted or are considered necessary.

V. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

User consultation
The package leaflet has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The language used for the purpose of user testing the PIL was English.
The results show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

The risk/benefit ratio is considered positive and Pramipexol Teva Pharma, 0.26 mg, 0.52 mg, 1.05 mg, 1.57 mg, 2.1 mg, 2.62 mg, 3.15 mg, prolonged-release tablets is recommended for approval.

VI. APPROVAL

The Decentralised procedure for Pramipexol Teva Pharma, 0.26 mg, 0.52 mg, 1.05 mg, 1.57 mg, 2.1 mg, 2.62 mg, 3.15 mg, prolonged-release tablets was successfully finalised on 2014-12-01.

LÄKEMEDELSVERKET
MEDICAL PRODUCTS AGENCY

Public Assessment Report – Update

Scope	Procedure number	Product Information affected	Date of start of the procedure	Date of end of procedure	Approval/ non approval	Assessment report attached
						Y/N (version)

Postadress/Postal address: P.O. Box 26, SE-751 03 Uppsala, SWEDEN
Besöksadress/Visiting address: Dag Hammarskjölds väg 42, Uppsala
Telefon/Phone: +46 (0)18 17 46 00 Fax: +46 (0)18 54 85 66
Internet: www.mpa.se E-mail: registrator@mpa.se