LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Pramipexol STADA
(pramipexole dihydrochloride monohydrate)

SE/H/1846/01-07/DC

This module reflects the scientific discussion for the approval of Pramipexol STADA. The procedure was finalised on 2019-05-17. For information on changes after this date please refer to the module 'Update'.

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I. INTRODUCTION

The application for Pramipexol STADA, 0.26 mg, 0.52 mg, 1.05 mg, 1.57 mg, 2.10 mg, 2.62 mg and 3.15 mg, prolonged-release tablet, is a generic application made according to Article 10(1) of Directive 2001/83/EC. The applicant, Kappler Pharma Consult GmbH, applies through the Decentralised Procedure with Sweden acting as reference member state (RMS) and AT, BE, DE, DK, FI, IS, IT (0.26 mg, 0.52 mg, 1.05 mg, 2.10 mg and 3.15 mg only) and LU as concerned member states (CMS).

The reference medicinal product chosen for the purposes of establishing the expiry of the data protection period is SIFROL, 0.26 mg, 0.52 mg, 1.05 mg, 1.57 mg, 2.10 mg, 2.62 mg and 3.15 mg, prolonged-release tablet authorised in The Community since 1997, with Boehringer Ingelheim International GmbH as marketing authorisation holder.

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

For approved indications, see the Summary of Product Characteristics.

For recommendations to the marketing authorisation not falling under Article 21a/22 of Directive 2001/83/EC and conditions to the marketing authorisation pursuant to Article 21a or 22 of Directive 2001/83/EC to the marketing authorisation, please see section VI.

II. QUALITY ASPECTS

II.1 Drug Substance

The structure of the drug substance has been adequately proven and its physico-chemical properties are sufficiently described.

The manufacture of the drug substance has been adequately described and satisfactory specifications have been provided for starting materials, reagents and solvents.

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

Stability studies confirm the retest period.

II.2 Medicinal Product

The medicinal product is formulated using excipients listed in section 6.1 in the Summary of Product Characteristics.

The manufacturing process has been sufficiently described and critical steps identified.

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 have been performed and data presented support the shelf life and special precautions for storage claimed in the Summary of Product Characteristics, sections 6.3 and 6.4.

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

The applied product is a prolonged-release single unit formulation. To support the application the applicant has submitted four bioequivalence studies comparing pramipexole prolonged release tablets with Sifrol prolonged release tablets; 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. No single-dose studies have been conducted with the 1.05, 1.57, 2.1, 2.62 and 3.15 mg strengths. However, a bracketing approach is considered acceptable. There are studies on the two lowest strengths of 0.26 mg and 0.52 mg and also on the highest strength of 3.15 mg. Regarding the study in the fed state, it is adequate to study the 0.52 mg strength since this is the highest strength possible to give to healthy volunteers in the fed state due to tolerability issues with higher doses. A multiple dose study with the highest 3.15mg strength is also adequate. Similar in vitro dissolution profiles have been demonstrated for all strengths compared to the 0.52 mg strength. In addition, similar in vitro dissolution profiles have been demonstrated between the test and the reference product for all strengths. Thus, the study package is considered as sufficient.

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 0.52 mg strength and 3.15 mg strength.

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.

IV.3 Risk Management Plan

The MAH has submitted an updated risk management plan, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Pramipexol STADA. v1.1:

Safety specification

Summary of safety concerns	
Important identified risks	• Binge eating, compulsive shopping, pathological gambling, hypersexuality and impulse control behaviour • Inappropriate antidiuretic hormone secretion • Cardiac failure • Hallicinations and confusion
Important potential risks	• Suicide-related behaviour • Augmentation, post treatment worsening after withdrawal and rebound in RLS patients • Delirium/mania • Retinal degeneration • Skin melanoma • Fibrotic events • Dopamine dysregulation syndrome
Important missing information	• None

Pharmacovigilance Plan

Routine pharmacovigilance is suggested and no additional pharmacovigilance activities are proposed by the applicant, which is endorsed.

Risk minimisation measures

Routine risk minimisation is suggested and no additional risk minimisation activities are proposed by the applicant, which is endorsed.

Summary of the RMP

The submitted Risk Management Plan, version 1.1 signed 2019-Feb-05 is considered acceptable. It is in line with the RMP (v. 8) of the reference product SIFROL.

V. 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.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The quality of the generic product, Pramipexol STADA, is found adequate. There are no objections to approval of Pramipexol STADA from a non-clinical and clinical point of view. Bioequivalence between the test and reference product has been adequately demonstrated. The product information is acceptable.
The application is therefore recommended for approval.

List of recommendations not falling under Article 21a/22 of Directive 2001/83/EC in case of a positive benefit risk assessment

N/A

List of conditions pursuant to Article 21a or 22 of Directive 2001/83/EC

N/A

VII. APPROVAL

The Decentralised procedure for Pramipexol STADA, 0.26 mg, 0.52 mg, 1.05 mg, 1.57 mg, 2.10 mg, 2.62 mg and 3.15 mg, prolonged-release tablet, was positively finalised on 2019-05-17.

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Public Assessment Report – Update

Procedure number*	Scope	Product Information affected	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse

*Only procedure qualifier, chronological number and grouping qualifier (when applicable)

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