IPAR

Public Assessment Report for a
Medicinal Product for Human Use

Scientific Discussion

Cabergoline 1 mg Tablets
Cabergoline
PA22865/011/001

The Public Assessment Report reflects the scientific conclusion reached by the Health Products Regulatory Authority (HPRA) at the end of the evaluation process and provides a summary of the grounds for approval of a marketing authorisation for a specific medicinal product for human use. It is made available by the HPRA for information to the public, after deletion of commercially sensitive information. The legal basis for its creation and availability is contained in Article 21 of Directive 2001/83/EC, as amended. It is a concise document which highlights the main parts of the documentation submitted by the applicant and the scientific evaluation carried out by the HPRA leading to the approval of the medicinal product for marketing in Ireland.

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I. INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the HPRA has granted a marketing authorisation for Cabergoline 1mg & 2mg Tablet, from Renata Pharmaceuticals (Ireland) Limited on 13th October 2023 indicated for:

Treatment of Parkinson's disease
If treatment with a dopamine agonist is being considered, cabergoline is indicated as second line therapy in patients who are intolerant or fail treatment with a non-ergot compound, as monotherapy, or as adjunctive treatment to levodopa plus dopa-decarboxylase inhibitor, in the management of the signs and symptoms of Parkinson's disease.

This decentralised application concerns a generic version of Cabergoline, under Cabergoline 1 mg and 2 mg Tablets trade name, submitted under Article 10.1 of European Directive 2001/83/EC.

The reference product is Cabaser 1 mg Tablets, PA 822/114/001 in IE, by Pfizer Healthcare Ireland, registered since 29th Oct 1999.

With Ireland as the Reference Member State in this Decentralized Procedure, Renata Pharmaceuticals (Ireland) Limited is applying for the Marketing Authorisations for Cabergoline 1 mg and 2 mg Tablets in CMS DE.

Cabergoline 1 mg and 2 mg Tablets are of the same indication, strength and route of administration as that of the reference medicinal product Cabaser 1 mg Tablets.

Product subject to prescription which may not be renewed in IE.

The Summary of Product Characteristics (SmPC) for this medicinal product is available on the HPRA's website at www.hpra.ie

Name of the product	Cabergoline 1mg Tablet
Name(s) of the active substance(s) (INN)	Cabergoline
Pharmacotherapeutic classification (ATC code)	N04BC06 cabergoline
Pharmaceutical form and strength(s)	1mg Tablet
Marketing Authorisation Number(s) in Ireland (PA)	PA22865/011/001
Marketing Authorisation Holder	Renata Pharmaceuticals (Ireland) Limited
MRP/DCP No.	IE/H/1233/001/DC
Reference Member State	IE
Concerned Member State	DE

II. QUALITY ASPECTS

II.1. Introduction

This application is for Cabergoline 1 mg & 2 mg Tablets.

II.2 Drug substance

The active substance is cabergoline, an established active substance described in the European Pharmacopoeia, and is manufactured in accordance with the principles of Good Manufacturing Practice (GMP).

The active substance specification is considered adequate to control the quality and meets current pharmacopoeial requirements. Batch analytical data demonstrating compliance with this specification has been provided.

II.3 Medicinal product

P.1 Composition

The tablets contain either 1 mg or 2 mg of the active substance cabergoline.

The excipients in the medicinal product are listed in section 6.1 of the SmPC.
A visual description of the product is included in section 3 of the SmPC.

P.2 Pharmaceutical Development

The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines.

P.3 Manufacture of the Product

The product is manufactured in accordance with the principles of good manufacturing practice (GMP) at suitably qualified manufacturing sites.

The manufacturing process has been validated according to relevant European/ICH guidelines and the process is considered to be sufficiently validated.

P.4 Control of Other Substances (Excipients)

All ingredients comply with Ph. Eur. or are adequately controlled by the manufacturers' specifications.

P.5 Control of Finished Product

The Finished Product Specification is based on the pharmacopoeial monograph for the dosage form, and the tests and control limits are considered appropriate for this type of product.

The analytical methods used are described in sufficient detail and are supported by validation data.

Batch analytical data for a number of batches from the proposed production site have been provided and demonstrate the ability of the manufacturer to produce batches of finished product of consistent quality.

P.6 Packaging material

The approved packaging for this product is described in section 6.5 of the SmPC.

Evidence has been provided that the packaging complies with Ph. Eur./EU legislation for use with foodstuffs requirements.

P.7 Stability of the Finished Product

Stability data on the finished product in the proposed packaging have been provided in accordance with EU guidelines and support the shelf-life and storage conditions listed in sections 6.3 and 6.4 of the SmPC.

II.4 Discussion on Chemical, Pharmaceutical and Biological Aspects

The important quality characteristics of the product are well-defined and controlled. Satisfactory chemical and pharmaceutical documentation has been provided, assuring consistent quality of Cabergoline 1 mg and 2 mg Tablets.

III. NON-CLINICAL ASPECTS

III.1 Introduction

This active substance cabergoline is a generic formulation of Cabasar on the European market. No new preclinical data have been submitted. As such, no pre-clinical assessment has been made on the application. This is acceptable for this type of application.

III.2 Ecotoxicity/environmental risk assessment

Since cabergoline is a generic product, it will not lead to an increased exposure to the environment. A justification for the absence of ERA studies was provided and is acceptable.

III.3 Discussion on the non-clinical aspects

Pharmacodynamic, pharmacokinetic and toxicological properties of cabergoline are well known. As cabergoline is a widely used, well-known active substance, the applicant has not provided additional nonclinical studies and further studies are not required.

IV. CLINICAL ASPECTS

IV.1 Introduction

This is a generic application submitted under article 10(1) of Directive 2001/83/EC. Cabergoline is a well-known active substance with established efficacy and tolerability.

The content of the SmPC approved during the decentralised procedure is in accordance with that accepted for the reference product Cabaser 1 mg Tablets, PA 822/114/001 marketed by Pfizer Healthcare Ireland.

For this generic application, the applicant has submitted one bioequivalence study in which the pharmacokinetic profile of the test product Cabergoline 1 mg tablet is compared with the pharmacokinetic profile of the reference product Cabaser 1 mg Tablets.

A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out. Cabergoline 1 mg tablet, Renata Ltd., was compared to the reference product Cabaser 1 mg Tablets, marketed by Pfizer Healthcare Ireland. Based on the pharmacokinetic parameters of cabergoline, the reference tablet Cabaser 1 mg Tablets marketed by Pfizer Healthcare Ireland and test tablet Cabergoline 1 mg tablet, Renata Ltd. are bioequivalent with extent to the rate and extent of absorption and fulfil the bioequivalence requirements outlined in the relevant CHMP Note for Guidance.

To support the application, a biowaiver is requested for the higher strength 2 mg tablet. A biowaiver to support the higher dose was an acceptable approach as per CHMP Guidance on the Investigation of Bioequivalence CPMP/EWP/QWP/1401/98 Rev. 1/ Corr **, Section 4.1.6, for products with linear pharmacokinetics and where the drug substance is highly soluble. The results of the bioequivalence study performed with the 1 mg tablets therefore apply to the 2 mg tablet strength.

The HPRA has been assured that GCP standards were followed in an appropriate manner in the studies conducted.

IV.2 Pharmacokinetics

The pharmacokinetic and metabolic profiles of cabergoline have been studied in healthy volunteers of both sexes, in female hyperprolactinemic patients and in parkinsonian patients. After oral administration of the labelled compound, radioactivity was rapidly absorbed from the gastrointestinal tract as the peak of radioactivity in plasma was between 0.5 and 4 hours. Ten days after administration about 18/20% and 55/72% of the radioactive dose (3H cabergoline/14C-cabergoline) was recovered in urine and faeces, respectively. Unchanged drug in urine accounted for 2-3% of the dose.

In urine, the main metabolite identified was 6-allyl-8b-carboxy-ergoline, which accounted for 4-6% of the dose. Three additional metabolites were identified in urine, which accounted overall for less than 3% of the dose. The metabolites have been found to be much less potent than cabergoline as D2 dopamine receptor agonists "in vitro".

The low urinary excretion of unchanged cabergoline has been confirmed also in studies with non-radioactive product. The elimination half-life of cabergoline, estimated from urinary excretion rates, is long (63-68 hours in healthy volunteers, 79- 115 hours in hyperprolactinemic patients).

The pharmacokinetics of cabergoline seem to be dose-independent both in healthy volunteers (doses of 0.5-1.5 mg) and parkinsonian patients (steady state of daily doses up to 7 mg/day).

On the basis of the elimination half-life, steady state conditions should be achieved after 4 weeks, as confirmed by the mean peak plasma levels of cabergoline obtained after a single dose (37±8 pg/ml) and after a 4 week multiple-regimen (101±43 pg/ml).

"In vitro" experiments showed that the drug at concentrations of 0.1-10 ng/ml is 41-42% bound to plasma proteins.

Food does not appear to affect absorption and disposition of cabergoline.

While renal insufficiency has been shown not to modify cabergoline kinetics, hepatic insufficiency of severe degree (> 10 Child-Pugh score, maximum score 12) has been shown to be associated with an increase of AUC.

IV.3 Pharmacodynamics

Cabergoline is a dopaminergic ergoline derivative endowed with potent and long-lasting dopamine D2 receptor agonist properties.

Cabergoline has showed to be effective in decreasing daily fluctuations in motor performance in Parkinsonian patients receiving levodopa/carbidopa therapy. Improvement of motor deficit has been demonstrated, while substantially decreasing the levodopa/carbidopa dose.

In healthy volunteers the administration of cabergoline at single oral doses of 0.3-2.5 mg was associated with a significant decrease in serum PRL levels. The effect is prompt (within 3 hours of administration) and persistent (up to 7-28 days). The PRL lowering effect is dose-related both in terms of degree of effect and duration of action.

The pharmacodynamic actions of cabergoline not linked to the therapeutic effect relate only to blood pressure decrease. The maximal hypotensive effect of cabergoline as a single dose usually occurs during the first 6 hours after drug intake and is dose-dependent both in terms of maximal decrease and frequency.

No new pharmacodynamic studies have been provided and none are required.

IV.4 Clinical Efficacy

The efficacy of cabergoline in the proposed indications is established in clinical use. No new clinical efficacy studies are provided, and none are required.

IV.5 Clinical Safety

The overall safety profile of cabergoline is established and generally known. No new safety studies are provided, and none are required.

The safety information in the SmPC and Package Leaflet are in line with those of the RMS and CMS reference products.

Risk Management Plan

The MAH has submitted a risk management plan (v 0.1, date of final sign-off 05/05/2022), 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 Cabergoline tablets.

Safety specification

The RMP (v0.1; date of final sign-off 05/05/2022) submitted with this application proposed the following list of safety concerns:

Summary of safety concerns	
Important identified risks	None
Important potential risks	None
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 0.1 signed 05/05/2022 is considered acceptable.

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the RMS;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time, but via different procedures.

Periodic Safety Update Report (PSUR)

With regard to PSUR submission, the MAH should take the following into account:

- PSURs shall be submitted in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal. Marketing authorisation holders shall continuously check the European medicines web-portal for the DLP and frequency of submission of the next PSUR.
- For medicinal products authorized under the legal basis of Article 10(1) or Article 10a of Directive 2001/83/EC, no routine PSURs need to be submitted, unless otherwise specified in the EURD list.
- In case the active substance will be removed in the future from the EURD list because the MAs have been withdrawn in all but one MS, the MAH shall contact that MS and propose DLP and frequency for further PSUR submissions together with a justification.

IV.6 Discussion on the clinical aspects

As this is a generic application under Article 10(1) of Directive 2001/83/EC, additional non-clinical and clinical studies to demonstrate efficacy and safety are not required.

The applicant has submitted the results of a suitable bioequivalence study, which has demonstrated the similarity of the test product Cabergoline 1 mg tablets of Renata Ltd against the reference product Cabaser 1mg Tablets of Pfizer Healthcare Ireland, in accordance with the relevant guidance. A justification for waiver of a study with the 2 mg strength has been provided. No additional tests are required for this application.

The applicant has also submitted a clinical overview and summary of the evidence demonstrating the efficacy and safety of this product in clinical practice.

V. OVERALL CONCLUSIONS

Cabergoline 1 mg and 2 mg Tablets, Renata Ltd. are a generic form of Cabaser 1 mg Tablets, Pfizer Healthcare Ireland. Cabaser 1 mg Tablet is a well-known medicinal product with a proven chemical-pharmaceutical quality and an established favourable efficacy and safety profile.

Bioequivalence has been shown to be in compliance with the CHMP guidance documents. The SmPC is consistent with that of the reference product.

The MAH has provided written confirmation that systems and services are in place to ensure compliance with their pharmacovigilance obligations.

The HPRA, on the basis of the data submitted considered that Cabergoline 1 mg and 2 mg Tablets, Renata Ltd. demonstrated bioequivalence with the reference product as well as a satisfactory risk/benefit profile and therefore granted a marketing authorisation.

VI. REVISION DATE

07.09.2028