

IPAR



**Public Assessment Report for a
Medicinal Product for Human Use**

Scientific Discussion

Cabergoline 500 micrograms Tablets
Cabergoline
PA22865/014/001

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 500 microgram Tablets, from Renata Pharmaceuticals (Ireland) Limited on 11th October 2024 for:

Inhibition/suppression of lactation

Cabergoline is indicated for the prevention of postpartum lactation immediately after delivery and for the suppression of ongoing lactation for medical reasons, such as:

- After delivery, when breastfeeding is contraindicated for mother- or child-related medical reasons.
- After stillbirth or abortion.
- Hyperprolactinemia postpartum after a pregnancy following treatment with a dopamine-agonist.

Hyperprolactinaemic disorders

Cabergoline is indicated for the treatment of hyperprolactinaemic disorders in female patients, including amenorrhoea, oligomenorrhoea, anovulation and galactorrhoea.

Cabergoline is indicated in patients with prolactin-secreting pituitary adenomas (micro- and macroprolactinomas), idiopathic hyperprolactinaemia or empty sella syndrome associated with hyperprolactinaemia, which represents the basic underlying pathologies contributing to the above manifestations.

This decentralised application concerns a generic version of cabergoline, under Cabergoline 500 microgram tablets trade name, and is being submitted as a generic application under Article 10(1) of Directive 2001/83/EC as amended. With Ireland as the Reference Member State in this Decentralized Procedure, Renata Pharmaceuticals (Ireland) Ltd. is applying for Marketing Authorisation for Cabergoline 500 microgram tablets in Denmark, France, Italy, Netherlands, Norway, Portugal, Spain and Sweden. The originator product is: Dostinex (0.5mg tablets) by Pfizer Healthcare Ireland (PA0822/126/001)

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

Name of the product:	Cabergoline 500 micrograms Tablets
Name(s) of the active substance(s)(INN)	Cabergoline
Pharmacotherapeutic classification (ATC code)	Prolactin inhibitors, ATC code: G02CB03
Pharmaceutical form and strength(s)	Tablet 500 microgram
Marketing Authorisation Number(s) in Ireland (PA)	PA22865/014/001
Marketing Authorisation Holder:	Renata Pharmaceuticals (Ireland) Limited
MRP/DCP No.	(IE/H/1256/001/DC)
Reference Member State:	IE
Concerned Member State:	DK, ES, FR, IT, NL, NO, PT, SE.

II. QUALITY ASPECTS

II.1. Introduction

This application is for Cabergoline 500 microgram Tablets.

II.2 Drug substance

The active substance is Cabergoline, an established active substance described in the European/British 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

Each tablet contains 500 micrograms 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 manufacturer's 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(s) 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 500 microgram tablet.

III. NON-CLINICAL ASPECTS

III.1 Introduction

This active substance is a generic formulation of Dostinex 500 microgram tablets on the European market. No new preclinical data have been submitted.

III.2 Pharmacology

N/A

III.3 Pharmacokinetics

N/A

III.4 Toxicology

N/A

III.5 Ecotoxicity/environmental risk assessment

Since Cabergoline 500 microgram Tablets is a generic product, it will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

III.6 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 studies. This is acceptable for this type of application. Overview based on literature review is, thus, appropriate.

IV. CLINICAL ASPECTS

IV.1 Introduction

Cabergoline is a well-known active substance with established efficacy and tolerability.

For this generic application, the applicant has submitted one bioequivalence study in which the pharmacokinetic profile of the test product Cabergoline 500 microgram tablet is compared with the pharmacokinetic profile of the reference product Dostinex (0.5mg tablets) by Pfizer Pharma PFE GmbH Germany.

This was a single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out. Cabergoline 500 microgram tablets (2 tablets x 0.5 mg, i.e., 1 mg dose) vs Dostinex 0.5mg tablets (2 tablets x 0.5 mg, i.e., 1 mg dose) in normal, healthy, human, adult subject under fed conditions.

Based on the pharmacokinetic parameters of active substance, the test tablet Cabergoline 500 microgram tablets marketed by Renata Pharmaceuticals (Ireland) Limited and the reference tablet Dostinex 0.5mg tablets (Pfizer Pharma PFE GmbH Germany) are bioequivalent with extent to the rate and extent of absorption and fulfil the bioequivalence requirements outlined in the relevant CHMP Note for Guidance.

The content of the SmPC approved during the decentralised procedure is overall in accordance with that accepted for the reference product Dostinex (0.5mg tablets) by Pfizer Healthcare Ireland (PA0822/126/001)

IV.2 Pharmacokinetics

After oral administration cabergoline is rapidly absorbed from the gastrointestinal tract as the peak plasma concentration is received within 0.5 to 4 hours. *In vitro* experiments showed that cabergoline at concentrations of 0.1 – 10 ng/ml is 41-42% bound to plasma proteins.

The elimination half-life of cabergoline, is long; (63-68 hours in healthy volunteers and 79-115 hours in hyperprolactinaemic patients). 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) for 0.5 mg cabergoline dose. Ten days after administration about 18% and 72% of the dose is recovered in urine

and faeces, respectively. Unchanged cabergoline in urine accounts for 2-3% of the dose. The pharmacokinetic profile is linear up to 7 mg per day.

IV.3 Pharmacodynamics

Pharmacotherapeutic group: Prolactin inhibitors, ATC code: G02CB03

Cabergoline is a dopaminergic ergoline derivative endowed with a potent and long-lasting PRL-lowering activity. It acts by direct stimulation of the D2-dopamine receptors on pituitary lactotrophs, thus inhibiting PRL secretion. In rats the compound decreases PRL secretion at oral doses of 3-25 mcg/kg, and in vitro at a concentration of 45 pg/ml. In addition, cabergoline exerts a central dopaminergic effect via D2 receptor stimulation at oral doses higher than those effective in lowering serum PRL levels.

IV.4 Clinical Efficacy

The efficacy of the active substance is well established. Since this product has been shown to be essentially similar to the reference product which was approved based on a full application with regard to clinical efficacy no further such data have been submitted or are considered necessary.

IV.5 Clinical Safety

The safety of the active substance is well established. The safety review of the BE study did not raise any new or significant safety concerns.

Risk Management Plan

The MAH has submitted a 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 Cabergoline tablets.

Safety specification

Summary of safety concerns	
Important identified risks	<ul style="list-style-type: none"> • None
Important potential risks	<ul style="list-style-type: none"> • None
Missing information	<ul style="list-style-type: none"> • 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 0.3 signed 19/12/2022 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:

25 October 2024

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- 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)

Active substance is currently listed in the published EURD list

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

This is a generic abridged application which avoids the need for repetitive tests on humans. For these applications the bioequivalence study is pivotal, based on the submitted bioequivalence study the test product Cabergoline 500 microgram tablets marketed by Renata Pharmaceuticals (Ireland) Limited and the reference product Dostinex 0.5mg tablets (Pfizer Pharma PFE GmbH Germany) are considered bioequivalent.

V. OVERALL CONCLUSIONS

Cabergoline 500 microgram tablets are a generic form of Dostinex 0.5mg tablets. Dostinex 0.5mg 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 500 microgram tablets demonstrated bioequivalence with the reference product as well as a satisfactory risk/benefit profile and therefore granted a marketing authorisation.

VI. REVISION DATE

16.08.2029