CMDh/223/2005
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Public Assessment Report

Scientific discussion

Cabergoline Aurobindo 0.5mg Tablets (Cabergoline)

MT/H/0612/001/DC

Date: 25th September 2023

This module reflects the scientific discussion for the approval of Cabergoline Aurobindo 0.5mg Tablets. The procedure was finalised at 20th September 2023 For information on changes after this date please refer to the module 'Update'.

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Cabergoline Aurobindo 0.5mg Tablets, from Aurobindo Pharma (Malta) Limited ; Vault 14 Level 2; Valletta Waterfront, Valletta FRN 1913, Malta.
The product 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 dopamin-agonist

Treatment of hyperprolactinaemic disorders:
Cabergoline Aurobindo 0.5 mg tablets is indicated for the treatment of dysfunctions related to hyperprolactinaemia, such as amenorrhoea, oligomenorrhoea, anovulation and galactorrhoea. Cabergoline Aurobindo 0.5 mg tablets is indicated in patients with prolactin-secreting pituitary adenoma (micro- and macroprolactinoma), idiopathic hyperprolactinaemia or empty sella syndrome associated with hyperprolactinaemia.

A comprehensive description of the indications and posology is given in the SmPC.

The marketing authorisation has been granted pursuant to Article 10(1) of Directive 2001/83/EC.

There are no conditions pursuant to Article 21a or 22 of Directive 2001/83/EC.

II. QUALITY ASPECTS

II.1 Introduction

Pharmaceutical form, formulation, container system, etc.

Cabergoline Aurobindo 0.5mg Tablets are available in white opaque round HDPE container closed with white opaque polypropylene child resistant closure. Each HDPE container contains a desiccant sachet/canister with silica gel, which should not be swallowed. The tablets are white to off-white, capsule shaped, approximately 8mm x 4mm, flat faced, bevel edged, uncoated tablets debossed with 'C 0.5' on one side and break line on other side.
The tablet can be divided into equal doses.

II.2 2.2Drug Substance

INN; chemical features like chemical class, chirality, manufacturing, specifications, stability

The active substance is an established active substance described in the European Pharmacopoeia (monograph 1773). The CEP procedure is used for the drug substance.
The available data from the initial, validation and annual batches, support the assigned shelf life of 60 months. The specification for the drug substance for the finished product manufacturer is adequately drawn up. The applicant has submitted PXRD spectra to support the statement that Form 1 is the polymorphic form manufactured by CEP holder Apotex Pharmachem India Pvt. Ltd.

II.3 Medicinal Product

Pharmaceutical development, manufacture of the product, product specification, stability of the product

The quantitative and qualitative composition has been described adequately overall. Excipients used in the formulation are common excipients used in pharmaceutical preparations. The specific grades of the excipients (where applicable) are included in the DP composition and the relevant sections of the dossier, including their specifications. The applicant has submitted a description of the studies which led to the final composition of the drug product in this application and has discussed the relevant physico-chemico characteristics of the API such as solubility, polymorphism and particle size.

The manufacturing process and process controls are on the whole adequately drawn up. The product specifications cover appropriate parameters for this dosage form; the control tests and specifications for drug product have been generally adequately drawn up.

The conditions used in the stability studies are according to the ICH stability guidelines. The control tests and specifications for drug product are generally adequately drawn up. Data has been submitted for 24 months of long-term studies at 25°C±2°C/60% ± 5% RH) and 6 months of accelerated studies at 40°C ± 2°C / 75% RH ± 5% RH for both the HDPE x2 and x8 sized containers.
The applicant's proposed shelf-life of 2 years and storage conditions (Store in the original package in order to protect from light) is acceptable. Special precaution with respect to protection from light is required for Cabergoline 0.5mg Tablets, so the relevant precaution as per Guidance on the declaration of storage conditions to protect the DP from light has been included in the PI.

II.4 Discussion on chemical, pharmaceutical and biological aspects

III. NON-CLINICAL ASPECTS

III.1 Introduction

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 and further studies are not required. Overview based on literature review is, thus, appropriate. The non-clinical overview on the pre-clinical pharmacology, pharmacokinetics and toxicology is adequate. The non-clinical data in the proposed SmPC is aligned to the latest approved SmPC of the reference medicinal product 'Dostinex 500 microgram tablets, authorised in Malta, MA505/01401'. No new significant concerns were identified through the provided non-clinical overview with respect to the preclinical safety profile of the proposed product. The non-clinical data in the proposed SmPC is therefore acceptable.

III.2 Ecotoxicity/environmental risk assessment (ERA)

The applicant has submitted a justification, in accordance with the Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use (EMEA/CHMP/SWP/4447/00 corr 2), that the authorisation and introduction of the proposed medicinal product on the market will not increase the exposure of cabergoline to the environment. Therefore, no ERA studies have been submitted.

Since the proposed cabergoline 0.5 mg tablets product is intended for generic substitution, this will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

III.3 Discussion on the non-clinical aspects

For generics: brief explanation that abridged applications avoid the need for repetitive tests on animals and humans. Reference to the reference medicinal product

IV. CLINICAL ASPECTS

IV.1 Introduction

IV.2 Pharmacokinetics

Bioequivalence studies

To support the application, the applicant has submitted an open label, balanced, randomised. two-treatment, two-sequence, two-period, crossover, single-dose, oral bioequivalence study in healthy, male, adult human subjects under fasting conditions.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} median, range)

Parameter (Units)	[4]Mean ± SD (Based on un-transformed data)	
	Test Product (T)	Reference Product (R)
C_{max} (pg/mL)	41.2022 ± 14.61942	39.9223 ± 12.47224
$AUC_{0\rightarrow t72}$(hr. pg/mL)	1574.7424± 517.48116	1571.1423 ± 543.40269
[3]T_{max} (hr)	4.50 (0.50-48.00)	4.50 (0.50-48.00)

[3] Median (Min, Max)

[4] Arithmetic Means (±SD) may be substituted by Geometric Mean (±CV %)

Bioequivalence evaluation of Cabergoline

Pharmacokinetic parameter	Geometric Mean Ratio Test/Ref	Confidence Intervals	CV%
AUC_{0-72}	100.48	96.60-104.52	12.7
C_{max}	102.21	95.23-109.70	23.5

Conclusion on bioequivalence studies:

Based on the submitted bioequivalence study (protocol number 290-19 Cabergoline 0.5 mg (2 x 0.5mg tablets) (Test: Aurobindo Pharma Limited, India) is considered bioequivalent with Dostinex tablets 0.5 mg (2 x 0.5mg tablets) (Reference MAH: Pfizer Holding, France).

IV.3 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 Aurobindo 0.5mg Tablets*

Safety specification

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.

V. USER CONSULTATION

A user consultation with target patient groups on the package information leaflet (PIL) has been performed on the basis of a bridging

- for format, design and layout with procedure SE/H/1201/01-02/DC (Metoprolol Aurobindo 50 mg & 100 mg film-coated tablets) which confirms that a full user consultation test of the Parent PL was performed and judged as acceptable. Real-size mock ups of both Parent and Daughter PLs in line with Aurobindo's in-house design and layout were provided.
- For content, the applicant submitted the comparison between Parent PILs Dostinex® 500 microgram Tablets and Cabergoline 0.5 mg Tablets (UK/H/0955/001-004/DC and PAR which confirms that a full user consultation test of the Parent PL), daughter PIL <Invented name> 0.5 mg Tablets and the entire safety information in given PILs is almost similar and the entire PIL text is in patient friendly language and is readable to the patient.

The bridging report submitted by the applicant has been found acceptable.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

There are no objections to the approval of the proposed medicinal product from a non-clinical point of view.

The application contains an adequate review of published non-clinical and clinical data and the bioequivalence has been shown. Based on the submitted bioequivalence study (protocol number 290-19 Cabergoline 0.5 mg (2 x 0.5mg tablets) (Test: Aurobindo Pharma Limited, India) is considered bioequivalent with Dostinex tablets 0.5 mg (2 x 0.5mg tablets) (Reference MAH: Pfizer Holding, France). Approval is recommended from the clinical point of view.

From a quality aspect the application is approvable and the benefit risk is positive.

Summary Public Assessment Report

Generics

Cabergoline Aurobindo 0.5mg Tablets (Cabergoline)

MT/H/0612/001/DC

Date: 25th September 2023

Summary Public Assessment Report

Generics

General guidance: In principle information from the PL should be included and standard texts/sentences should be used where possible.

Cabergoline Aurobindo 0.5mg Tablets

Cabergoline, tablets, 0.5mg

This is a summary of the public assessment report (PAR) for Cabergoline Aurobindo 0.5mg Tablets . It explains how Cabergoline Aurobindo 0.5mg Tablets was assessed and its authorisation recommended as well as its conditions of use. It is not intended to provide practical advice on how to use Cabergoline Aurobindo 0.5mg Tablets .

For practical information about using Cabergoline Aurobindo 0.5mg Tablets , patients should read the package leaflet or contact their doctor or pharmacist.

What is Cabergoline Aurobindo 0.5mg Tablets and what is it used for?

Cabergoline Aurobindo 0.5mg Tablets is a 'generic medicine'. This means that Cabergoline Aurobindo 0.5mg Tablets is similar to a 'reference medicine' already authorised in the European Union (EU) called Dostinex 0.5mg tablets.

Cabergoline Aurobindo is used:
- to interrupt/inhibit lactation (milk production) for medical reasons.
- to treat hormonal disturbances as a result of high prolactin levels, such as missing or irregular periods, infertility or milk flow not associated with childbirth.
- to treat high levels of prolactin due to a tumour in the pituitary gland.

How does Cabergoline Aurobindo 0.5mg Tablets work?

Cabergoline Aurobindo contains cabergoline which belongs to a group of medicines known as prolactin inhibitors. Prolactin is a hormone that is formed in the pituitary gland of your brain. Cabergoline Aurobindo decreases the levels of the hormone prolactin.

How is Cabergoline Aurobindo 0.5mg Tablets used?

The pharmaceutical form of Cabergoline Aurobindo 0.5mg Tablets is tablets and the route of administration is oral.

Please read section 3 of the PL for detailed information on dosing recommendations, the route of administration, and the duration of treatment.

It is recommended you take Cabergoline Aurobindo with or after food to help reduce feelings of nausea or vomiting.

- **To prevent/inhibit production of breast milk:**

You should take 2 tablets (1 mg of Cabergoline Aurobindo) as a single dose within 24 hours after giving birth.

- **To stop lactation once you have started to breast-feed:**
  You should take a single dose of a ½ tablet (0.25 mg of Cabergoline Aurobindo). This dose must not be exceeded.
- **To reduce prolactin levels in other conditions:**
  Usually the treatment is started with 0.5 mg per week, but higher doses may then be necessary. Your doctor will evaluate your response to the medicine and will adjust the treatment accordingly; also he/she will tell you for how long you must take your tablets.

You should not take more than 3 mg of Cabergoline Aurobindo in one day.

The medicine can only be obtained with a prescription.

What benefits of Cabergoline Aurobindo 0.5mg Tablets have been shown in studies?
Because Cabergoline Aurobindo 0.5mg Tablets is a generic medicine, studies in patients have been limited to tests to determine that it is bioequivalent to the reference medicine, Dostinex 500 microgram tablets. Two medicines are bioequivalent when they produce the same levels of the active substance in the body.

What are the possible side effects of Cabergoline Aurobindo 0.5mg Tablets ?

Because Cabergoline Aurobindo 0.5mg Tablets is a generic medicine and is bioequivalent to the reference medicine, its benefits and possible side effects are taken as being the same as the reference medicine.
For the full list of restrictions, see the package leaflet.

Why is Cabergoline Aurobindo 0.5mg Tablets approved?

It was concluded that, in accordance with EU requirements, Cabergoline Aurobindo 0.5mg Tablets has been shown to have comparable quality and to be bioequivalent/be comparable to **Dostinex tablets 0.5 mg**. Therefore, the Malta Medicines Authourity decided that, as for reference medicine called **Dostinex tablets 0.5 mg** , the benefits are greater than its risk and recommended that it can be approved for use.

What measures are being taken to ensure the safe and effective use of Cabergoline Aurobindo 0.5mg Tablets ?

A risk management plan has been developed to ensure that Cabergoline Aurobindo 0.5mg Tablets is used as safely as possible. Based on this plan, safety information has been included in the summary of product characteristics and the package leaflet for Cabergoline Aurobindo 0.5mg Tablets , including the appropriate precautions to be followed by healthcare professionals and patients.

Known side effects are continuously monitored. Furthermore new safety signals reported by patients/healthcare professionals will be monitored/reviewed continuously as well.

Other information about Cabergoline Aurobindo 0.5mg Tablets

The marketing authorisation for Cabergoline Aurobindo 0.5mg Tablets was granted on 25th September 2023.

The full PAR for Cabergoline Aurobindo 0.5mg Tablets can be found on the website https://medicinesauthority.gov.mt. For more information about treatment with Cabergoline Aurobindo 0.5mg Tablets , read the package leaflet (*https://medicinesauthority.gov.mt/medicine-details?id=103731*) or contact your doctor or pharmacist.

This summary was last updated in 09-2023.