COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Silodosine Aurobindo 4 mg and 8 mg, hard capsules (silodosin)

NL/H/6091/001-002/DC

Date: 16 July 2024

This module reflects the scientific discussion for the approval of Silodosine Aurobindo 4 mg and 8 mg, hard capsules. The procedure was finalised at 19 June 2019 in Portugal (PT/H/1935/001-002/DC). After a transfer on 7 March 2024, the current RMS is the Netherlands. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

List of abbreviations

ASMF	Active Substance Master File
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CMS	Concerned Member State
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EEA	European Economic Area
EMA	European Medicines Agency
ERA	Environmental Risk Assessment
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
Ph.Eur.	European Pharmacopoeia
PL	Package Leaflet
RH	Relative Humidity
RMP	Risk Management Plan
RMS	Reference Member State
SmPC	Summary of Product Characteristics
TSE	Transmissible Spongiform Encephalopathy

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have agreed in granting a marketing authorisation for Silodosine Aurobindo 4 mg and 8 mg, hard capsules, from Aurobindo Pharma B.V.
The product is indicated for the treatment of the signs and symptoms of benign prostatic hyperplasia (BPH) in adult men.
A comprehensive description of the up-to-date indications and posology is given in the current SmPC.

The marketing authorization was granted on 11-07-2019 based on Directive 2001/83/EC article 10.1 (a) (iii) first paragraph and the Marketing Authorisation Holder is Aurobindo Pharma B.V.

The concerned member states (CMS) involved in this procedure were Belgium, France, Italy and Poland.

II. QUALITY ASPECTS

II.1 Introduction

Silodosine Aurobindo 4 mg, hard capsule:
Size '3' capsules with white opaque hard gelatin cap imprinted with "SIL" and white opaque hard gelatin body imprinted with "4 mg" in black ink containing white to off- white powder.

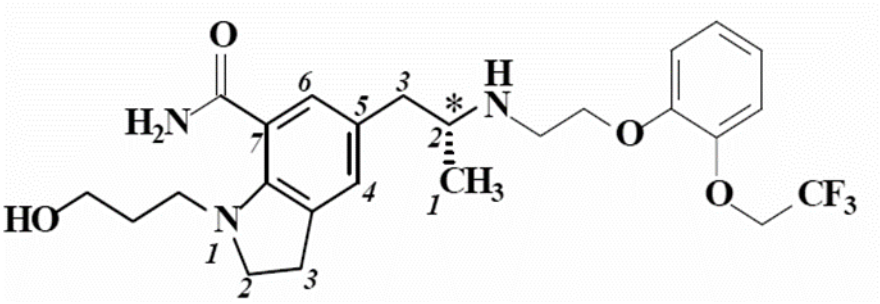
Silodosine Aurobindo 8 mg, hard capsule:
Size '1' capsules with white opaque hard gelatin cap imprinted with "SIL" and white opaque hard gelatin body imprinted with "8 mg" in black ink containing white to off - white powder.

Silodosine Aurobindo 4 mg and 8 mg, hard capsules are available in White Opaque PVC-Aluminium blister pack.

Pack sizes
4 mg- 5, 10, 20, 30, 50, 90, 100
8 mg- 5, 10, 20, 30, 50, 90, 100

II.2 Drug Substance

Nomenclature and structure
Silodosin



Silodosin hydrochloride chemical properties and biopharmaceutics:
Silodosin hydrochloride is chemically 1-(3-Hydroxipropyl)-2,3-Dihydro-5-[(2R)-2-[[2- [2-(2,2,2-Trifluoroethoxy)Phenoxy]Ethyl]Amino]Propyl]-1Hindole-7-Carboxamide.
The empirical formula of silodosin hydrochloride is C25H32F3N3O4 and its molecular weight is 495.53.

Quality control of drug substance
The chemical-pharmaceutical documentation and Quality Overall Summary in relation to silodosin hydrochloride are of sufficient quality in view of the present European regulatory requirements.

The control tests and specifications for drug substance product are adequately drawn up.

Stability of drug substance
Stability studies have been performed with the drug substance. No significant changes in any parameters were observed.

II.3 Medicinal Product

Pharmaceutical development
The development of the product has been described, the choice of excipients is justified and their functions explained.

Quality control of drug product
The product specifications cover appropriate parameters for this dosage form. Validations of the analytical methods have been presented. Batch analysis has been performed on 3 batches. The batch analysis results show that the finished products meet the specifications proposed.

Stability of drug product

The conditions used in the stability studies are according to the ICH stability guideline. The control tests and specifications for drug product are adequately drawn up.
The proposed shelf-life of 2 years without any special storage conditions for the drug product is considered acceptable.

III. NON-CLINICAL ASPECTS

Pharmacodynamic, pharmacokinetic and toxicological properties of silodosin hydrochloride are well known. As silodosin is a widely used, well-known active substance, the applicant has not provided additional studies and further studies are not required. An overview based on literature review is, thus, appropriate.

III.1 Ecotoxicity/environmental risk assessment (ERA)

An ERA was not submitted with this marketing authorization, because this medicinal product does not result in an increase of the total quantity of its active substances into the environment.

III.2 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 Introduction

This assessment report represents an evaluation of the key elements of the information provided by the company in the dossier. For more details, the reader should refer to the company's clinical overview and summary and to the clinical file.
The clinical overview is dated February 2018 and has been written by Nilanjan Saha (MBBS by the Calcutta University, India; MD [Pharmacology] and DM [Clinical Pharmacology] by the Postgraduate Institute of Medical Education and Research, Chandigarh, India). Report refers 61 publications up to year 2017.

The product contains the active ingredient silodosin, which belongs to the Pharmacotherapeutic Group: Urologicals, alpha-adrenoreceptor antagonists.
The therapeutic efficacy of silodosin for the treatment of the signs and symptoms of BPH has been confirmed in a number of double-blind, placebo-controlled, active comparator.

Treatment with silodosin produced rapid improvement in urinary symptoms that was sustained.

Safety data collected in 1581 patients exposed to chronic treatment with silodosin 8 mg OD have shown that the drug is safe and well-tolerated. The most common adverse reactions (>1%) in patients treated with silodosin were abnormal ejaculation, dizziness, orthostatic hypotension, nasal congestion, headache and diarrhoea. Silodosin treatment is associated with a favourable cardiovascular tolerability profile. Intraoperative floppy iris syndrome has been reported in some patients undergoing cataract surgery who are receiving or have previously received α1-adrenoceptor antagonists, including patients who had been treated with silodosin. This rare, drug class-related safety issue of intraocular floppy iris syndrome can be satisfactorily managed by warning patients to inform their ophthalmologist that they are or were on treatment with an α1-adrenoceptor blocker.

The clinical overview on the efficacy and safety is adequate.

IV.2 Pharmacokinetics

Bioequivalence studies

The Applicant developed a formulation of silodosin in the pharmaceutical form of hard capsules, with strength of 4 mg & 8 mg, Silodosina Aurovitas, to possess essential similarity with the reference medicinal product Silodyx, 4 mg & 8 mg, hard capsules, (Recordati Ireland Ltd., Ireland). Thus, this generic application is supported bibliographically and by the results of an open-label, randomised, two-treatment, two- sequence, two-period, crossover, single-dose, oral bioequivalence study on 48 healthy, adult, human male subjects under fed conditions to compare the applicant's product silodosin capsule 8 mg (Aurobindo Pharma Limited, India) and Silodyx 8 mg capsules (Recordati Ireland Ltd., Ireland). The Applicant requests a waiver for silodosin 4 mg capsules, hard.

IV.3 Risk Management Plan

Aurobindo Pharma B.V. submitted a Risk Management Plan for silodosin (v 1.0) dated of 22 March 2018.

The table below summarizes the proposed identified safety concerns for the product.

Table 1. Summary table of safety concerns

Important identified risks	Intraoperative Floppy Iris Syndrome (IFIS) Orthostatic hypotension/hypotension Syncope/loss of consciousness Hypersensitivity (including allergic type reactions, such as facial oedema, pharyngeal oedema and swollen tongue) Abnormal Liver Function Tests (LFTs) Tachycardia Palpitations

	Abnormal ejaculation, erectile dysfunction
Important potential risks	Use in moderate/severe renal impairment Misdiagnosis of prostate cancer Photosensitivity reactions Genital discomfort/burning Gynaecomastia, breast enlargement, breast tenderness Use in patients with pre-existing cardiovascular disease Concomitant treatment with strong CYP 3A4 inhibitors Concomitant use with other alpha-blockers Concomitant treatment with phosphodiesterase type 5 inhibitors Concomitant use with antihypertensive medicines
Missing information	Use in severe hepatic impairment Use in patients with a serum creatinine > 2.0 mg/dL Concomitant use of a 5-alpha-reductase inhibitors Patients aged≥75 years

IV.4 Discussion on the clinical aspects

This type of application refers to information that is contained in the pharmacological-toxicological and clinical part of the dossier of the authorisation of the reference product. A reference product is a medicinal product authorised and marketed on the basis of a full dossier, i.e. including chemical, biological, pharmaceutical, pharmacological-toxicological and clinical data. This information is not fully available in the public domain. Authorisations for generic products are therefore linked to the 'original' authorized medicinal product, which is legally allowed once the data protection time of the dossier of the reference product has expired. For this kind of application, it has to be demonstrated that the pharmacokinetic profile of the product is similar to the pharmacokinetic profile of the reference product. This generic product can be used instead of its reference product.

V. USER CONSULTATION

In order to comply with Article 59(3) of Council Directive 2001/83/EC, as amended, the applicant presented the readability test for the leaflet of silodosin .

The test results indicate that the leaflet is well organised and structured, easy to understand and written comprehensively. The test shows that the leaflet is readable and that patients / users are able to act according to the information contained.

In conclusion and given these results, it is deemed that the leaflet analysed complies with the readability requirements included in the "Guideline on the readability of the labelling and

package leaflet of medicinal products for human use. September 2009", and therefore complies satisfactorily with the Readability Test.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The application for Silodosine Aurobindo contains adequate quality, non-clinical and clinical data and the bioequivalence has been shown. A benefit/risk ratio comparable to the reference product can therefore be concluded.

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

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