COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Silodosine Sandoz 4 mg and 8 mg, hard capsules

(silodosin)

NL/H/4413/001-002/DC

Date: 13 August 2019

This module reflects the scientific discussion for the approval of Silodosine Sandoz 4 mg and 8 mg, hard capsules. The procedure was finalised at 3 April 2019. 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
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
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 granted a marketing authorisation for Silodosine Sandoz 4 mg and 8 mg, hard capsules, from Sandoz 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 indications and posology is given in the SmPC.

This decentralised procedure concerns a generic application claiming essential similarity with the innovator product Silodyx 4 and 8 mg hard capsules which has been registered in the EEA by Recordati Ireland Ltd. since 29 January 2010 through a centralised procedure (EU/1/09/607).

The concerned member states (CMS) involved in this procedure were Spain, France, Italy, Portugal and Slovenia.

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

II. QUALITY ASPECTS

II.1 Introduction

Sildosine Sandoz is a white hard capsule inked with an “S” in the lid and a “4” (4 mg strength) or “8” (8 mg strength) in the body. The capsules contain a white or almost white fine powder and contain respectively 4 mg or 8 mg silodosin.

The capsules are packed in PVC/PVDC (250-135)-Aluminium blister or PVC/PVDC (250-90)-Aluminium blisters.

The excipients are:
Capsule content - mannitol (E421), pregelatinised starch, sodium laurylsulfate (E487) and magnesium stearate (E470b)
Capsule shell - titatium dioxide (E171) and gelatin (E441)
Printing ink - shellac (E904), black iron oxide (E172) potassium hydroxide (E525)

The two strengths are dose proportional.

II.2 Drug Substance

The active substance is sildosin, an established active substance, not described in the European Pharmacopoeia (Ph.Eur.), British or United States Pharmacopoeia. The active substance is a white or almost white, crystalline powder, sparingly soluble in water with pH 1.2 – 4.0, slightly soluble in water with pH 5.0 – 6.0, practically insoluble in water with pH 7.0 – 13.0. Silodosin has one chiral centre, the active substance corresponds to the R-enantiomer, the S-enantiomer as isomer impurity is controlled in the drug substance. Silodosin exists in three crystal forms, including form α, form β and form γ. The polymorphic form of Silodosin manufactured by the proposed processes is in accordance with form β.

The Active Substance Master File (ASMF) procedure is used for the active substance. The main objective of the ASMF procedure, commonly known as the European Drug Master File (EDMF) procedure, is to allow valuable confidential intellectual property or 'know-how' of the manufacturer of the active substance (ASM) to be protected, while at the same time allowing the applicant or marketing authorisation holder (MAH) to take full responsibility for the medicinal product, the quality and quality control of the active substance. Competent Authorities/EMA thus have access to the complete information that is necessary to evaluate the suitability of the use of the active substance in the medicinal product.

Manufacturing process

The manufacturing process involves a five-step chemical synthesis followed by purification, drying and milling. The proposed starting materials are acceptable. The active substance has been adequately characterised and acceptable specifications have been adopted for the starting materials, solvents and reagents.

Quality control of drug substance

The active substance specification includes test for appearance, identification, water content, loss on drying, sulphated ash, assay, isomer, related substances, residual solvents and particle size and is considered adequate to control the quality. The specification is established in-house and based on the specifications of the ASMF-holder. Batch analytical data demonstrating compliance with this specification have been provided for three batches.

Stability of drug substance

Stability data on the active substance have been provided for three batches stored at 25°C/60% RH (24 months) and 40°C/75% RH (6 months). All parameters tested remain relatively stable as they were showing little or no change over time at all storing conditions. Based on the data submitted, a retest period could be granted of 48 months when stored in the original package in order to protect from light, is acceptable.

II.3 Medicinal Product

Pharmaceutical development

The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines. The choice of excipients is justified and their functions explained. During the procedure it was decided to change from polymorphic form. To check if the behaviour of the old and new polymorphic form is similar additional characterisation and formulation studies were carried out. The data of the studies shown that new form has a similar behaviour in the finished product to formulations carried out along the development with the old polymorphic form. The final formulation was selected for the medicinal product.

One bioequivalence study has been performed with the 8 mg capsule strength. Dissolution profiles in the three media (HCl 0.1N, buffer pH 4.5 and buffer pH 6.8) have been compared for the following pairs of batches: batches of 8 mg capsules used in the *in vivo* bioequivalence study, test batches of 8 mg and 4 mg capsules to support the waiver for the 4 mg capsules and test batches of 8 mg capsules manufactured with silodosin from the proposed manufacturer. The dissolution profiles of test medicinal products of the 4 mg and 8 mg strengths are considered similar without further calculation because the amount of silodosin dissolved at 15 minutes is higher than 85% in all cases. Overall, the pharmaceutical development of the product has been adequately performed.

Manufacturing process

The manufacturing process is a standard process and has been validated according to relevant European guidelines. It consist of conventional blending and encapsulation. Process validation data on the product have been presented for six pilot batches of blends manufactured with silodosin from the proposed providers and the corresponding to twelve batches of capsules (three for each strength manufactured with the drug substance from the proposed supplier and an additional three per strength from another drug substance supplier as additional information in accordance with the relevant European guidelines. Process validation for full-scale batches will be performed post authorisation.

Control of excipients

The excipients comply with the European Pharmacopoeia requirements. These specifications are acceptable.

Quality control of drug product

The finished product specifications are adequate to control the relevant parameters for the dosage form. The specification includes tests for appearance, uniformity of mass, water content, dissolution, identification, uniformity of dosage units by content uniformity, assay, related substances and microbiological examination. The release and shelf life limits are similar with exception of assay and total related substances. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product. Satisfactory validation data for the analytical methods have been provided. Batch analytical data twelve batches of the finished product, three batches each of silodosin capsules of 4

mg and 8 mg, and packaged in the two types of blister proposed from the proposed production site have been provided, demonstrating compliance with the specification.

Stability of drug product

Stability data on the product have been provided for twelve batches (as mentioned above) stored at 25°C/60%RH (up to 18 months), 30°C/ 75%RH (12 months) and 40°C/75%RH (6 months). The conditions used in the stability studies are according to the ICH stability guideline. The batches were stored in the two types of PVC/PVDC-Al blisters. Photostability studies were performed in accordance with ICH recommendations and showed that the product is not stable when exposed to light. On basis of the data submitted a shelf life was granted of 24 months with the storage conditions 'Store in the original package in order to protect from light. Do not store above 30°C' can be supported.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies

There are no substances of ruminant animal origin present in the product nor have any been used in the manufacturing of this product, so a theoretical risk of transmitting TSE can be excluded.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Silodosine Sandoz has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product. No post-approval commitments were made.

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Silodosine Sandoz 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.2 Discussion on the non-clinical aspects

This product is a generic formulation of Silodyx which is available on the European market. Reference is made to the preclinical data obtained with the innovator product. A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which is based on up-to-date and adequate scientific literature. The overview justifies why there is no need to generate additional non-clinical pharmacology, pharmacokinetics and toxicology data. Therefore, the member states agreed that no further non-clinical studies are required.

IV. CLINICAL ASPECTS

IV.1 Introduction

Silodosin is a well-known active substance with established efficacy and tolerability. A clinical overview has been provided, which is based on scientific literature. The overview justifies why there is no need to generate additional clinical data. Therefore, the member states agreed that no further clinical studies are required.

For this generic application, the MAH has submitted a bioequivalence study, which is discussed below.

IV.2 Pharmacokinetics

The MAH conducted a bioequivalence study in which the pharmacokinetic profile of the test product Silodosine Sandoz 8 mg, hard capsules (Sandoz B.V., NL) is compared with the pharmacokinetic profile of the reference product Silodyx 8 mg hard capsules (Recordati Ireland Ltd. (Co. Cork), Ireland).

The choice of the reference product in the bioequivalence study has been justified by comparison of dissolution results and compositions with the EU reference product. The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.

Biowaiver

For the additional lower strength of 8 mg a biowaiver is granted, based on the following:

- All products were manufactured by the same process
- The composition of the different strengths is qualitatively the same
- The composition of the strengths is dose proportional
- Comparable dissolution of the 4 mg and 8 mg strengths, at three pH's, has been shown.

With the above findings the general biowaiver criteria as stated in the *Guideline on the investigation of Bioequivalence* are fulfilled.

Bioequivalence study

Design

A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fed conditions in 32 healthy male subjects, aged 20-54 years. Each subject received a single dose (8 mg) of one of the 2 silodosin formulations. The tablet was orally administered with 240 ml water 30 minutes after start of intake of a high fat, high caloric breakfast. The breakfast consisted off whole milk, 2 large eggs, hash brown potatoes, 2 slices of toast, butter and 2 strips of bacon. There were 2 dosing periods, separated by a washout period of 14 days.

Blood samples were collected at pre-dose and at 0.25, 0.5, 0.75, 1, 1.33, 1.67, 2, 2.33, 2.67, 3, 3.5, 4, 5, 6, 9, 12, 16, 24, 36, 48 and 72 hours after administration of the products.

The design of the study is acceptable. According to the SmPC, the tablets should be taken with food. As such, the fed condition applied in the study is considered adequate.

Analytical/statistical methods
The analytical method has been adequately validated and is considered acceptable for analysis of the plasma samples. The methods used in this study for the pharmacokinetic calculations and statistical evaluation are considered acceptable.

Results
One subject withdrew from the study due to adverse event, one subject withdrew consent and one subject was withdrawn due to a protocol violation. Therefore, 29 subjects completed the study and were eligible for pharmacokinetic analysis.

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

Treatment N=29	**AUC_{0-t}** (ng.h/ml)	**$AUC_{0-\infty}$** (ng.h/ml)	**C_{max}** (ng/ml)	**t_{max}** (h)	**$t_{1/2}$** (h)
Test	329 ± 134	337 ± 134	50 ± 19	3.0 (0.75 – 5.0)	10 ± 3
Reference	302 ± 104	311 ± 105	45 ± 18	3.0 (1.0 – 6.0)	11 ± 6
***Ratio (90% CI)**	1.07 (0.97 – 1.17)	--	1.11 (1.01 – 1.22)	--	--
CV (%)	20.5	--	20.7	--	--

$AUC_{0-\infty}$ area under the plasma concentration-time curve from time zero to infinity
AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours
C_{max} maximum plasma concentration
t_{max} time for maximum concentration
$t_{1/2}$ half-life
CV coefficient of variation

**ln-transformed values*

Conclusion on bioequivalence study
The 90% confidence intervals calculated for AUC_{0-t} and C_{max} are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the submitted bioequivalence study Silodosine Sandoz is considered bioequivalent with Silodyx.

The MEB has been assured that the bioequivalence study has been conducted in accordance with acceptable standards of Good Clinical Practice (GCP, see Directive 2005/28/EC) and Good Laboratory Practice (GLP, see Directives 2004/9/EC and 2004/10/EC).

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 Silodosine Sandoz.

Table 2. Summary table of safety concerns as approved in RMP

Important identified risks	- Intraoperative Floppy Iris Syndrome (IFIS) - Orthostatic hypotension/hypotension - Syncope/loss of consciousness - Hypersensitivity (including allergic type reactions, such as facial edema, pharyngeal edema 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 - Gynecomastia, breast enlargement, breast tenderness - Use in patients with pre-existing cardiovascular disease - Concomitant use with other α-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 5-α-reductase inhibitors - Patients aged ≥ 75 years

For this product additional risk minimisation measures are in place. For the important identified risk 'intraoperative floppy iris syndrome' a direct healthcare professional communication, a flow chart and an education program for physicians (preoperative assessment and recommendations before surgery) should be provided to healthcare providers treating patients scheduled for cataract surgery.

IV.4 Discussion on the clinical aspects

For this authorisation, reference is made to the clinical studies and experience with the innovator product Silodyx. No new clinical studies were conducted. The MAH demonstrated through a bioequivalence study that the pharmacokinetic profile of the product is similar to the pharmacokinetic profile of this reference product. Risk management is adequately addressed. This generic medicinal product can be used instead of the reference product.

V. USER CONSULTATION

A user consultation with target patient groups on the package leaflet (PL) has been performed on the basis of a bridging report making reference to Silodyx. The bridging report submitted by the MAH has been found acceptable. The overall layout, design and writing style used in the Sandoz Silodosin leaflet is similar to several leaflets of Sandoz products which have been user tested. The layout has been successfully tested in more than 50 approved leaflet readability tests.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Silodosine Sandoz 4 mg and 8 mg, hard capsules have a proven chemical-pharmaceutical quality and are generic forms of Silodyx 4 and 8 mg hard capsules. Silodyx is a well-known medicinal product with an established favourable efficacy and safety profile.

Bioequivalence has been shown to be in compliance with the requirements of European guidance documents.

The Board followed the advice of the assessors.

There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The member states, on the basis of the data submitted, considered that essential similarity has been demonstrated for Silodosine Sandoz with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 3 April 2019.

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