COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Silodosine Accord 4 mg and 8 mg hard capsules

(silodosin)

NL/H/4777/001-002/DC

Date: 14 September 2020

This module reflects the scientific discussion for the approval of Silodosine Accord. The procedure was finalised on 29 April 2020. 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 Accord 4 mg and 8 mg hard capsules from Accord Healthcare B.V.

The product is indicated for 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 Urorec hard capsules, which has been registered by Recordati Ireland Ltd through the Centralised Procedure since 29 January 2010 (EU/1/09/608/001-014).

The concerned member states (CMS) involved in this procedure were Bulgaria, France, Germany, Ireland, Italy, Poland, Portugal, Romania and Spain.

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

II. QUALITY ASPECTS

II.1 Introduction

Silodosine Accord 4 mg is a hard gelatin capsule of white body and blue cap (size 3) containing white powder.
Silodosine Accord 8 mg is a hard gelatin capsule of white body and cap (size 1) containing white powder.

The capsules are packed in PVC/PVDC/aluminium blisters.

The excipients are:

Capsule content - pregelatinised (maize) starch, mannitol (E421), maize starch, magnesium stearate, sodium laurilsulfate
Capsule shell - gelatin, titanium dioxide (E171), Brilliant Blue (E133) (For 4 mg), erythrosine (E127) (For 4 mg)

The capsule strengths are dose proportional.

II.2 Drug Substance

The active substance is silodosin, an established active substance described in the European Pharmacopoeia (Ph.Eur.). The active substance is freely soluble in acetic acid and ethanol and insoluble in water. Silodosin exhibits polymorphism. The polymorph produced is the crystalline α-form, which has been selected as the most stable. Silodosin is slightly hygroscopic and has one chiral centre, the active substance is the R isomer.

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 of silodosin comprises sufficient synthetic steps and one purification step. These starting materials are considered acceptable. Control of these materials is sufficient. No class 1 solvents are used in the manufacturing process. The control of organic, inorganic, elemental and potential genotoxic impurities which can arise from the manufacturing process is discussed in the ASMF. The active substance has been adequately characterized, and it has been demonstrated that the correct isomer is produced.

Quality control of drug substance

The MAH has adopted the drug substance specification of the ASMF-holder, which is acceptable based on the drug substance and drug product characteristics.
Descriptions of all analytical procedures have been provided. The analytical methods have been adequately validated. Batch analytical data from three drug substance batches have been provided in the ASMF. Analytical data from one batch tested by the drug product manufacturer is included as well. These results are consistently in compliance with the specification.

Stability of drug substance

No data have been provided by the MAH on the stability of the drug substance. Reference is made to the ASMF. The stability data provided in the ASMF support the claimed retest period and storage condition. The drug substance is stable for 60 months at 2-8°C.

II.3 Medicinal Product

Pharmaceutical development

The development of the product has been described, the choice of excipients is justified and their functions are explained. The same excipients as present in the reference product were selected, one additional excipient is introduced, maize starch. Justification of introduction

and quantity of this excipient, together with substantiation of its compatibility with the active substance is provided. A study to demonstrate stability of the polymorphic form of silodosin in presence of the excipients has been performed.
The development of the *in vitro* dissolution test method is discussed. The method is acceptable and the discriminatory power of this method is adequately demonstrated. Several dissolution profiles have been performed, the results showed in all cases a very fast dissolution, above 85% in 15 minutes. A bioequivalence study has been performed with the 8 mg product strength. Comparative dissolution profiles between test and reference product have been performed as requested in the Guideline on Bioequivalence. The batch of test product used in the bioequivalence study is acceptable from a pharmaceutical point of view.
A biowaiver of strength for the 4 mg strength is applied. Dissolution studies have been presented to sustain the claimed biowaiver, showing similar dissolution profiles, at the required pHs. The biowaiver of strengths is acceptable from a pharmaceutical point of view.

Manufacturing process
The manufacturing process consists of dispensing, dry mixing of excipients, wet granulation, drying, screening and milling of granules, lubrication, capsule filling and packing. Manufacturing process and controls are described in sufficient details. The process is considered to be a non-standard manufacturing process. The active substance accounts for about 2.3% of the capsule fill weight. The process validation approach is described in sufficient detail. Process validation has been performed on three batches of the 4 mg and 8 mg strengths, showing that the process is adequately validated.

Control of excipients
The excipients are tested in line with the Ph. Eur. requirements. Some additional in-house requirements have been included. For the empty hard gelatine capsules an in-house specification is provided which is considered acceptable. All specifications are acceptable.

Quality control of drug product
The drug product specification includes tests for description, identification, uniformity of weight, uniformity of dosage units, disintegration, dissolution, related substances, assay, residual solvents, identification of colouring matters and microbiological quality. The same specifications and acceptance limits are applied at release and at end of shelf life.
The analytical methods are adequately described and validated. Batch analytical data, demonstrating compliance with the specification, have been provided for three batches of 4 mg capsules and six batches of 8 mg capsules. All these batches are of the proposed commercial batch size.
A risk evaluation concerning the presence of nitrosamine impurities in the product is submitted and considered acceptable.

Stability of drug product
Stability data on the drug product have been provided for three batches of each capsule strength stored at accelerated conditions (40°C/75% RH) for six months and at long-term conditions (30 ± 2°C/65 ± 5% RH) for 24 months. Additional data from four other batches of 8 mg capsules is provided. The product was stored in the commercial packaging. A significant

trend of increase of an impurity is observed at accelerated conditions. At long-term conditions no significant changes or up- or downward trends in the tested parameters were observed and all results remained well within the specifications for the initial batches. For current batches a trend towards out of specification is noted, however, it is explained that the noted increase occurs in the initial phase and flattens in the later stage. No actual out of specification results are seen after 24 months of storage. Consequently, a shelf-life of 24 months can be assigned.
A photostability study has been performed, showing that the drug product is sensitive to light. Based on this, the storage condition states 'keep the blisters in the outer carton to protect from light'. The proposed storage condition (store below 30°C) is set in line with the Guideline on declaration of storage conditions.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
Except for the gelatine capsules, no materials derived from animal and/or human origin are used in the manufacture of the proposed drug product. BSE/TSE declarations have been provided for all components. For the gelatine capsules CEP certificates from all the vendors possibly involved are provided.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Silodosine Accord hard capsules 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 Accord 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 Urorec hard capsules, 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 Accord 8 mg (Accord Healthcare B.V., the Netherlands) is compared with the pharmacokinetic profile of the reference product Urorec 8 mg hard capsules (Recordati Ireland Ltd, Ireland).

The choice of the reference product in the bioequivalence study is justified as the reference product is authorised through a centralised procedure. The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.

Biowaiver

A biowaiver has been granted for the 4 mg strength, as the following conditions are met:

- The capsules are dose proportional.
- The capsules are manufactured by the same manufacturer and manufacturing process.
- Over the 4 - 8 mg dose range, silodosin shows linear pharmacokinetics.
- *In vitro* dissolution profiles of the 4 mg capsule and 8 mg capsule were demonstrated to be similar at pH 1.2, pH 4.5 and pH 6.8 (>85% dissolved < 15 min.)

Bioequivalence studies

Design

A single-dose, randomised, four-period, two-treatment, two-sequence, crossover full-replicate bioequivalence study was carried out under fed conditions in 24 healthy male subjects, aged 18-50 years. Each subject received a single dose (8 mg) of one of the 2 silodosin formulations. After an overnight fasting of at least 10 hours and 30 minutes after start of a high fat high calorie meal, the subjects were dosed with a single oral dose of Test Product (Silodosine Accord 8 mg capsule) or Reference Product (Urorec 8 mg capsule) with approximately 240 mL water as per the randomization schedule.

Subjects were assigned to one of the two treatment sequences Test/Reference/Test/ Reference (ABAB) and Reference/Test/Reference/Test (BABA) according to the plan of

randomization. Periods III and IV were repetitive of period I and II in regards to the sequence assignment. The washout period was 10 days between period I and period II, 13 days between period II and period III and 10 days between period III and period IV.
Blood samples were collected pre-dose and at 0.25, 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 12, 24, 36, 48 and 72 hours after administration of the products.

The design of the study is acceptable, the wash-out long enough, the sampling period (72 hours) long enough with regard to $t_{1/2}$ (11 hours), and sampling scheme adequate to estimate pharmacokinetic parameters. Sufficient samples are planned around the expected t_{max} (2.5 hours). Silodosin is advised to be taken with food. Subjects were provided a high caloric breakfast. The confidence interval limits for C_{max} depended on the observed intrasubject variability (TSV) for C_{max} of the Reference product.

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
A total of 24 subjects were dosed in each period, completed the study and were eligible for pharmacokinetic analysis.

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

Treatment N=24	**AUC_{0-t} (ng.h/ml)**	**$AUC_{0-\infty}$ (ng.h/ml)**	**C_{max} (ng/ml)**	**t_{max} (h)**	**$t_{1/2}$ (h)**
Test	314 +/- 248	318 +/- 251	45 +/- 24	3.0 (1.0-5.0)	--
Reference	313 +/- 267	318 +/- 270	47 +/- 31	3.0 (0.5-6.0)	--
***Ratio (90% CI)**	1.01 (0.96-1.07)	--	0.98 (0.90-1.07)	--	--
CV (%)	17.4	--	14.5	--	--

$AUC_{0-\infty}$ 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 intra-subject CV% of C_{max} of the Reference Product was 20.26%. Therefore, the geometric mean Test/Reference ratio of C_{max} had to be within the conventional acceptance range 0.80 – 1.25. The extrapolated AUC was not higher than 20% in any subject. No pre-dose levels are detected. The t_{max} was not observed in any subject in the first sample time.

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 Accord 8 mg is considered bioequivalent with Urorec 8 mg hard capsules.

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 Accord.

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

Important identified risks	• None
Important potential risks	• Misdiagnosis of prostatic cancer
Missing information	• None

The member states agreed that routine pharmacovigilance activities and routine risk minimisation measures are sufficient for the risks and areas of missing information.

IV.4 Discussion on the clinical aspects

For this authorisation, reference is made to the clinical studies and experience with the innovator product Urorec. 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

The package leaflet (PL) has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The test consisted of a pilot test with 2 participants, followed by two rounds with 10 participants each. The

questions covered the following areas sufficiently: traceability, comprehensibility and applicability. The results show that the PL meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Silodosine Accord 4 mg and 8 mg hard capsules have a proven chemical-pharmaceutical quality and are generic forms of Urorec 4 mg and 8 mg hard capsules. Urorec 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 Accord with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 29 April 2020.

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