COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Solifenacinesuccinaat SUN 5 mg, film-coated tablets

(solifenacin succinate)

NL/H/3734/003/DC

Date: 14 November 2019

This module reflects the scientific discussion for the approval of Solifenacinesuccinaat SUN 5 mg film-coated tablets. The procedure was finalised on 6 August 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
SGPT	Serum Glutamic-Pyruvic Transaminase
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 Solifenacinesuccinaat SUN 5 mg film-coated tablets from Sun Pharmaceutical Industries Europe B.V.

The product is indicated in adults for the symptomatic treatment of urge incontinence and/or increased urinary frequency and urgency as may occur in patients with overactive bladder syndrome.

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 Vesicare 5 mg film-coated tablets (NL License RVG 29151), which has been registered in the Netherlands since 16 December 2003 by Astellas Pharma Europe B.V. Vesicare was registered throughout the EU via mutual recognition procedure NL/H/0487/001-002/MR.

The application concerns a line extension to the existing marketing authorisation of Solifenacinesuccinaat SUN 10 mg film-coated tablets, registered through a decentralised procedure (NL/H/3734/002/DC) registered on 3 April 2019. The extension concerns the addition of the 5 mg strength.

The concerned member states (CMS) involved in this procedure were Germany, Spain, Poland and the United Kingdom.

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

II. QUALITY ASPECTS

II.1 Introduction

Solifenacinesuccinaat SUN 5 mg is an off-white to yellow coloured, round, biconvex film-coated tablet debossed with 'RK75' on one side and plain on the other side. Each tablet contains 5 mg solifenacin succinate corresponding to 3.8 mg solifenacin.

The film-coated tablets are packed in PVC/PVDC strips comprises of PVDC coated PVC clear film with a backing of hard tempered aluminium foil-coated with heat seal lacquer on inner side and/or HDPE bottles.

The excipients are:

Tablet core – lactose, maize starch, hypromellose (E464), maize starch and magnesium stearate (E470b),
Film-coating –hypromellose (E464), macrogol 6000 (E1521), titanium dioxide (E171), talc (E553b) and yellow ferric oxide (E172).

II.2 Drug Substance

The active substance solifenacin succinate is an established active substance, described in the European Pharmacopoeia (Ph. Eur.). The active substance is very or freely soluble in water, soluble in ethanol (96%) and very slightly soluble to practically insoluble in heptane. The substance shows polymorphism and Form-I is produced. The molecule contains two chiral centres and exhibits isomerism. It is produced as the succinate salt.

Two manufactures are in place, both using the ASFM procedures. The main objective of The Active Substance Master File (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 consists of an 8 step synthesis pathway. No class I solvents are used. 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 has been established in-house by the MAH and is identical to the specification of the ASMF-holder, and complies with the Ph.Eur. specification, apart from bulk/tap density and particle size distribution. The specification is acceptable in view of the route of synthesis and the various European guidelines. Batch analytical data demonstrating compliance with the currently proposed active substance specification has been provided.

Stability of drug substance
Stability data on the active substance has been provided for three commercial scale batches stored at 25°C/60% RH (60 months) and at 40°C/75% RH (6 months). The stability data showed no clear trends or changes. Based on the stability data provided the claimed re-test period of 60 months without special storage conditions can be granted.

II.3 Medicinal Product

Pharmaceutical development

The development of the product has been described, the choice of excipients is justified and their functions explained. The main development studies were formulation trials and comparative dissolution studies with the innovator product.
A bioequivalence study was performed with the 5 mg drug product. The batch used in the bioequivalence study has the same composition and is manufactured in the same way as the future commercial batches. Overall, the pharmaceutical development of the product has been adequately performed.

Manufacturing process

The manufacturing process is a dry granulation process and involves sifting, blending, compaction, lubrication, compression followed by film coating. The process has been adequately validated according to relevant European guidelines. Process validation data on the product has been presented for three batches. The product is manufactured using conventional manufacturing techniques.

Control of excipients

All excipients used comply with the requirements of their respective Ph. Eur. monographs. The specifications of the excipients 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, identity, water content, uniformity of dosage units, assay, X-ray diffraction, related substances, dissolution and microbiological quality. The drug product specification is acceptable. The analytical methods have been adequately described and validated. Batch analytical data from the proposed production site have been provided on three commercial scaled batches, demonstrating compliance with the release specification.

Stability of drug product

Stability data on the product have been provided for four batches stored at 25°C/60% RH (24 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 proposed blisters and bottles. When stored under both long term and accelerated conditions a slight increase is observed in one of the specified impurities only. No clear trends or changes were seen in the other tested parameters. Photostability studies show that the product is not sensitive to light The claimed shelf-life of 2 years with storage condition 'This medicinal product does not require any special storage conditions' is justified.

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

Lactose is the only substance of animal origin. The applied manufacturing process for lactose anhydrous will not pose a risk of transmitting TSE.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Solifenacinesuccinaat SUN 5 mg film-coated tablets have a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product.

There were no post-approval commitments made during the procedure.

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Solifenacinesuccinaat SUN tablets are 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 Vesicare, 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

Solifenacin succinate 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 with, which is discussed below.

IV.2 Pharmacokinetics

The MAH conducted a bioequivalence study in which the pharmacokinetic profile of the test product Solifenacinesuccinaat SUN 5 mg, film-coated tablets (Sun Pharmaceutical Industries Europe B.V., NL) is compared with the pharmacokinetic profile of the reference product Vesicare 5 mg tablets (Astellas Pharma Europe B.V., NL).

The choice of the reference product in the bioequivalence study is accepted. The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.

Bioequivalence study

Design

A single-dose, open-label, balanced, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fasted conditions in 26 healthy male subjects, aged 19-44 years. Each subject received a single dose (5 mg) of one of the 2 solifenacin formulations. The tablet was orally administered with 240 ml water after an overnight fast of at least 10 hours. There were 2 dosing periods, separated by a washout period of 35 days.

Blood samples were collected pre-dose and at 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 6.5, 7, 7.5, 8, 8.5, 9, 10, 12, 16, 24, 36, 48 and 72 hours after administration of the products.

A single dose, crossover study to assess bioequivalence is considered adequate. Fasting conditions have been applied, which is appropriate. Food intake does not affect the C_{max} and AUC of solifenacin.

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

5 subjects dropped out or withdrew from the study. The remaining 21 subjects completed the study and were eligible for the pharmacokinetic and statistical analysis.

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

Treatment N=21	AUC_{0-72} ng.h/ml	C_{max} ng/ml	t_{max} h
Test	320 ± 82	7.96 ± 1.73	5.5 (2.5 – 8.0)
Reference	334 ± 100	8.14 ± 1.74	5.0 (3.0 – 8.0)
***Ratio (90% CI)**	0.96 (0.91 – 1.02)	0.98 (0.93 – 1.03)	--

AUC_{0-72}	area under the plasma concentration-time curve from time zero to 72 hours
C_{max}	maximum plasma concentration
t_{max}	time for maximum concentration

**ln-transformed values*

Conclusion on bioequivalence study

The 90% confidence intervals calculated for AUC_{0-72} and C_{max} are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the submitted bioequivalence study Solifenacinesuccinaat SUN 5 mg film-coated tablets is considered bioequivalent with the Vesicare 5 mg film-coated tablet.

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 Solifenacinesuccinaat SUN.

- Summary table of safety concerns as approved in RMP

Important identified risks	- Urinary retention - Ileus - Glaucoma - Hypersensitivity reactions including anaphylactic reaction and angioedema - Cardiac rhythm disorders
Important potential risks	- Use during lactation - Toxicity in infants and children
Missing information	- Use during pregnancy

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 Vesicare. 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

For the package leaflet (PL), a user test was performed as part of the initial DCP NL/H/3734/002/DC. The readability testing was performed in accordance with current legislation. It included an appropriate testing panel of 11 male and 9 female subjects of various age and education. The questions covered various sections of the PL and addressed key messages. The data shows the participants were able to correctly answer the questions in 19 out of 20 subjects. The participants were given ample time to answer each question. The interviewer performed the testing in an appropriate fashion. No issues have been identified. Therefore, the PL is considered acceptable.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Solifenacinesuccinaat SUN 5 mg film-coated tablets have a proven chemical-pharmaceutical quality and is a generic form of Vesicare 5 mg film-coated tablets. Vesicare 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 Solifenacinesuccinaat SUN 5 mg film-coated tablets with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 6 August 2019.

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Scope	Procedure number	Type of modification	Date of start of the procedure	Date of end of the procedure	Approval/ non approval	Assessment report attached