COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Solifenacinesuccinaat ELC 5 mg and 10 mg film-coated tablets

(solifenacin succinate)

NL/H/4441/001-002/DC

Date: 19 November 2019

This module reflects the scientific discussion for the approval of Solifenacinesuccinaat ELC 5 mg and 10 mg film-coated tablets. The procedure was finalised on 14 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
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 ELC 5 mg and 10 mg film-coated tablets from ELC GROUP s.r.o.

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 and 10 mg film-coated tablets (NL Licence RVG 29151-29152), 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.

The concerned member state (CMS) involved in this procedure was Germany.

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

II. QUALITY ASPECTS

II.1 Introduction

Solifenacinesuccinaat ELC 5 mg is a yellow, film-coated, round, biconvex tablet debossed with “SOL” on one side and “5” on the other side. Each tablet contains 5 mg solifenacin succinate, corresponding to 3.8 mg solifenacin.

Solifenacinesuccinaat ELC 10 mg is a pink, film-coated, round, biconvex tablet debossed with “SOL” on one side and “10” on the other side. Each tablet contains 10 mg solifenacin succinate, corresponding to 7.5 mg solifenacin.

The film-coated tablets are packed in PVC/Aluminium blisters.

The excipients are:
Tablet core – lactose monohydrate, corn starch, hydroxypropyl methyl cellulose (E464) and magnesium stearate (E572).
Tablet coating – hypromellose, talc, propylene glycol (E1520 or W490), titanium dioxide (E171), and only in the 5 mg strength; iron oxide yellow (E172). Only the 10 mg tablet contains iron oxide red (E172) as excipient.

The core tablets are fully dose proportional.

II.2 Drug Substance

The active substance solifenacin succinate is an established active substance, however not described in any Pharmacopoeia. The active substance is very soluble or freely soluble in water, soluble in ethanol (96%) and practically insoluble in heptane. Solifenacin succinate exhibits polymorphism. The manufacturer of the drug substance confirms the manufacturing of polymorph Form I. The polymorphic form is controlled in the drug substance specifications.

The CEP procedure is used for the active substance. Under the official Certification Procedures of the EDQM of the Council of Europe, manufacturers or suppliers of substances for pharmaceutical use can apply for a certificate of suitability concerning the control of the chemical purity and microbiological quality of their substance according to the corresponding specific monograph, or the evaluation of reduction of Transmissible Spongiform Encephalopathy (TSE) risk, according to the general monograph, or both. This procedure is meant to ensure that the quality of substances is guaranteed and that these substances comply with the Ph.Eur.

Manufacturing process

A CEP has been submitted; therefore no details on the manufacturing process have been included.

Quality control of drug substance

The active substance specification is in line with the Ph. Eur. with additional requirements for microbiological quality, particle size and X-ray diffraction. The specification is acceptable in view of the CEP and various European guidelines and considered adequate to control the quality. Batch analytical data demonstrating compliance with this specification have been provided for four batches.

Stability of drug substance

Stability data on the active substance have been provided for three batches stored at 25°C/60% RH (12 months), 30°/65% RH (12 months) and 40°C/75% RH (6 months). Based on the results provided the proposed re-test period of 12 months with storage “Store in dry place, Preserve in tight, light-resistant containers below 30°C” is acceptable.

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 manufacturing process optimisation studies. A bioequivalence study was performed with the 10 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. The biobatch is of sufficient size in relation to the intended commercial batch size. A biowaiver was requested for the 5 mg strength based on comparative dissolution data at three pH conditions.

Manufacturing process

The manufacturing process consists of sifting, mixing, lubrication, blending, compressing, coating, drying and packaging. The process has been adequately validated according to relevant European guidelines. Process validation data on the product have been presented for three full-scale batches of each strength. The product is manufactured using conventional manufacturing techniques and has been validated according to relevant European guidelines.

Control of excipients

All excipients used comply with the requirements of their respective European Pharmacopoeia (Ph.Eur.) or in-house requirements. The 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, identification, uniformity of mass, water content, uniformity of dosage units by content uniformity, dissolution, assay, related substances, microbiological examination, and residual solvents. The release and shelf life specifications are identical, except for assay, water content and some related substances. The analytical methods have been adequately described and validated. Batch analytical data from the proposed production site have been provided on three full-scale batches of each strength, demonstrating compliance with the release specification.

Stability of drug product

Stability data on the product have been provided three full-scale batches of each strength stored at 25°C/60% RH (18 months) and 30°/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 PVC/Alu blisters. Photostability studies show that the product is sensitive to light. On basis of the data submitted, a shelf life was granted of 20 when stored below 30°C and stored in the original package in order to protect from light.

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

None of the materials used is of animal or human origin except for lactose. The milk is sourced from healthy animals in the same conditions as milk collected for human consumption and complies with EU food hygiene regulations.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Solifenacinesuccinaat ELC 5 mg and 10 mg film-coated tablets have a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product.

No post-approval commitments were made during the procedure.

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Solifenacinesuccinaat ELC 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 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 the 10 mg tablet, which is discussed below.

IV.2 Pharmacokinetics

The MAH conducted a bioequivalence study in which the pharmacokinetic profile of the test product Solifenacinesuccinaat ELC 10 mg tablets (ELC GROUP s.r.o., Czech Republic) is compared with the pharmacokinetic profile of the reference product Vesicare 10 mg film-coated tablets (Astellas Pharma Ltd, UK).

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.

<u>Biowaiver</u>
A BCS-based biowaiver was requested for the 5 mg film-coated tablets. The biowaiver is acceptable as all of the following requirements are met:

- the drug substance has been proven to exhibit high solubility (and does not belong to the group of 'narrow therapeutic index' drugs) and complete absorption (BCS class I; measured extent of absorption has been demonstrated to be ≥85%) and
- either very rapid (> 85 % within 15 min) or similarly rapid (85 % within 30 min) in vitro dissolution characteristics of the test and reference product has been demonstrated using the specific guidance requirements and
- excipients that might affect bioavailability are qualitatively and quantitatively the same (in this case the products do not contain any excipients that will affect the rate or extent of absorption of the drug substance).

Bioequivalence study

Design

A single-dose, randomised, two-period, two-treatment, two-sequence, two-way crossover bioequivalence study was carried out under fasted conditions in 30 healthy male subjects, aged 20-41 years. Each subject received a single dose (10 mg) of one of the 2 solifenacin succinate formulations. The tablet was orally administered with 240 ml water after an overnight fast. There were 2 dosing periods, separated by a washout period of 28 days.

Blood samples were collected at pre-dose and at 1.00, 2.00, 2.50, 3.00, 3.33, 3.67, 4.00, 4.33, 4.67, 5.00, 5.33, 5.67, 6.00, 6.50, 7.00, 7.50, 8.00, 8.50, 9.00, 10.00, 12.00, 24.00, 36.00, 48.00 and 72.00 hours after administration of the products.

The design of the study is acceptable.

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

One subject did not report for the second period. 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 solifenacin under fasted conditions.

Treatment N=29	**AUC_{0-72}** ng.h/ml	**C_{max}** ng/ml	**t_{max}** h
Test	764 ± 270	18.27 ± 5.79	5.7 (2.5 – 8.5)
Reference	777 ± 307	18.66 ± 7.10	5.7 (3.3 – 8.0)
***Ratio (90% CI)**	0.99 (0.94– 1.05)	0.99 (0.93 – 1.05)	--

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

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 ELC 10 mg, film-coated tablets is considered bioequivalent with Vesicare 10 mg film-coated tablets.

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).

The justification for BCS (Biopharmaceutics Classification System) - based biowaiver can be accepted.

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 ELC.

- Summary table of safety concerns as approved in RMP

Important identified risks	- QT prolongation/Torsade de Pointes - Urinary retention - Hypersensitivity reactions, including anaphylactic reaction and angioedema - Glaucoma - Ileus
Important potential risks	None
Missing information	- Use of solifenacin in infants and children either exposed to solifenacin directly or exposed via breastfeeding - Use in 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

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 4 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

Solifenacinesuccinaat ELC 5 mg and 10 mg, film-coated tablets have a proven chemical-pharmaceutical quality and are generic forms of Vesicare 5 mg and 10 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 ELC 5 mg and 10 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 14 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