CBG MEB

Public Assessment Report

Scientific discussion

Solifenacinesuccinaat CF 5 mg and 10 mg, film-coated tablets

(solifenacin succinate)

NL/H/3695/001-002/DC

Date: 25 April 2018

This module reflects the scientific discussion for the approval of Solifenacinesuccinaat CF 5 mg and 10 mg, film-coated tablets. The procedure was finalised on 14 June 2017. 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 CF 5 mg and 10 mg, film-coated tablets from Centrafarm B.V.

The product is indicated in adults for 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 tablets (NL License RVG 29151-2) which has been registered in the Netherlands by Astellas Pharma Europe through procedure NL/H/0487/001-002/DC since 16 December 2003.

The concerned member states (CMS) involved in this procedure were Austria, Belgium, Germany, Denmark, Spain, Finland, France, Ireland, Luxembourg, Poland, Sweden and Slovakia.

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

II. QUALITY ASPECTS

II.1 Introduction

Solifenacinesuccinaat CF is a film-coated tablet.

Each 5 mg tablet is a light yellow, round, biconvex film-coated tablet containing 5 mg solifenacin succinate, equivalent to 3.8 mg solifenacin.
Each 10 mg tablet is light pink, round, biconvex film-coated tablet containing 10 mg solifenacin succinate, equivalent to 7.5 mg solifenacin.

The film-coated tablets are packed in PVC-Aluminium blisters, PVC/PVdC-Aluminium blisters or OPA/Al/PVC-Aluminium blisters.

The excipients are:
Tablet core - lactose monohydrate, maize starch, hypromellose and magnesium stearate
Film Coating – hypromellose, titanium dioxide (E171), macrogol 8000, talc and Iron Oxide Yellow (E172) (5 mg strength only) or Iron Oxide Red (E172) (10 mg strength only)

The two different tablet strengths are not dose proportional, only with respect to the active substance. The difference in amount of active substance is compensated by the amount of filler added. For all other excipients in the tablet core the quantitative composition of the excipients is identical in both tablets.

II.2 Drug Substance

The active substance is solifenacin succinate, an established active substance described in the European Pharmacopoeia (Ph.Eur.). It is a white or light yellow powder. Solifenacin succinate is very soluble or freely soluble in water, soluble in ethanol (96%), and practically insoluble in heptane. There are two manufacturers for the active substance. The active substance shows polymorphism and is manufactured by both manufacturers as form I.

The Active Substance Master File (ASMF) procedure is used for one of the manufacturers of 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.

The CEP procedure is used for the second manufacturer of 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

Manufacturer-I

The active substance is yielded in a three step synthesis pathway. No metal catalyst is used. The active substance has been adequately characterised and acceptable specifications have been adopted for the starting materials, solvents and reagents.

Manufacturer-II

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

Quality control of drug substance

Manufacturer-I

The active substance specification is considered adequate to control the quality and meets the requirements of the monograph in the Ph.Eur. The specification has additional requirements for residual solvents, polymorph status and particle size distribution. Batch analytical data demonstrating compliance with the active substance specification have been provided for three batches from manufacturer-I.

Manufacturer-II

The active substance specification is considered adequate to control the quality. The specification is in line with the CEP and has additional requirements for residual solvents. Batch analytical data demonstrating compliance with the active substance specification have been provided for three batches from manufacturer-II.

Stability of drug substance

Manufacturer-I

Stability data on the active substance have been provided for six full scaled batches stored at 25°C/60% RH (two batches for 80 months and one batch each for 60, 36, 12 and 9 months) and 40°C/75% RH (three batches for 6 months). The conditions used in the stability studies are according to the ICH stability guideline. No clear trends or changes were observed at both storage conditions. Based on the data submitted, a retest period could be granted of 60 months without any special storage conditions.

Manufacturer-II

Stability data on the active substance have been provided for three full scaled batches stored at 25°C/60% RH (48 months) and 40°C/75% RH (6 months). The conditions used in the stability studies are according to the ICH stability guideline. No clear trends or changes were observed at both storage conditions. Based on the data submitted, a retest period could be granted of 48 months without any special storage conditions.

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 the excipients is justified and their functions explained. The main development study was performance of comparative dissolution studies. Dissolution profiles of scale-up batches were similar to the dissolution profiles of the reference products at both strengths.

The active substance is a BCS Class I active substance. A BCS-based biowaiver has been justified and the equivalence of *in vivo* performance can be proven by *in-vitro* data versus the reference product. From a chemical-pharmaceutical point of view the BCS-based biowaiver has been justified.
The pharmaceutical development of the product has been adequately performed.

Manufacturing process
The manufacturing process involves final mixture preparation, tabletting and film-coating. The manufacturing process has been validated according to relevant European/ICH guidelines. Process validation data on the product have been presented for four pilot scale batches of both the 5 mg and 10 mg in accordance with the relevant European guidelines. The product is manufactured using conventional manufacturing techniques. Process validation for full-scale batches will be performed post authorisation.

Control of excipients
The excipients comply with the requirements of their respective Ph.Eur. monographs. 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, identity, assay, water, related substances, uniformity of dosage units, dissolution and microbiological quality. 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 from four pilot scale batches from the proposed production site have been provided, demonstrating compliance with the specification.

Stability of drug product
Stability data on the product has been provided for two pilot scaled batches per strength stored at 25°C/60% 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-Al blister, PVC/PVDC-Al blister or oPA/Al/PVC-Al blister (two batches per strength for each packaging material).
No up or downward trends have been observed. On the basis of the data submitted, a shelf life was granted of 24 months, without any special storage condition.
Photostability testing has been carried out on two pilot batches for each strength and covering both active substance manufacturing sources. No significant trends or changes were observed in any of the tested parameters. The drug product is considered photostable.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
The applied manufacturing process for lactose monohydrate will not pose a risk of transmitting TSE. Scientific data and/or certificates of suitability issued by the EDQM have been provided and compliance with the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via medicinal products has been satisfactorily demonstrated.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Solifenacinesuccinaat CF 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 Solifenacinesuccinaat CF 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 5 mg and 10 mg tablets 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 comprehensive justification based on the requirements described in the guideline on Investigation of Bioequivalence and scientific advice given by the MEB regarding the possibility of obtaining a biowaiver for this medicinal product.

IV.2 Pharmacokinetics

Biowaiver
A Biopharmaceutics Classification System (BCS) based biowaiver has been requested for all strengths. The BCS is a scientific framework to classify drugs on the basis of their aqueous solubility, permeability and dissolution. Drug substances can be classified in three classes according to the BCS:

- Class 1: High Solubility – High Permeability
- Class 2: Low Solubility – High Permeability
- Class 3: High Solubility – Low Permeability

The BCS based biowaiver is applicable to Class 1 highly soluble drugs with known human absorption formulated as oral, immediate release formulations with the same pharmaceutical form as an innovator product. To fulfil the requirements for such a biowaiver, the MAH provided comprehensive documentation on solubility, permeability and dissolution of the product. The MAH was also required to show that the composition of the generic and innovator product is similar. In addition, a supportive discussion was provided about the therapeutic index of the product.

Solubility
Based on in-house solubility studies performed by the MAH, the solubility of solifenacin succinate was determined to be about 200-300 mg/ml in media within the range of pH 1-6.8 at 37±1°C. As this value clearly exceeded 0.04 mg/ml (maximum therapeutic single dose of 10 mg in 250 ml buffer), the drug substance has been proven to exhibit high solubility.

Permeability
According to the EMA guideline, the demonstration of complete absorption in humans is preferred for BCS-based biowaiver applications (EMA 2010; cf. WHO 2015). Complete absorption is generally related to high permeability, i.e., an active substance is considered to be "highly permeable" when it is absorbed to an extent of 85% or more.

Complete drug absorption should be justified based on reliable investigations in human. Data from absolute bioavailability can be used to support this claim. In a randomised, two-period, crossover, single-dose study, Kuipers (2004)* assessed the absolute bioavailability of a single oral dose of solifenacin 10 mg, which is twice the recommended starting dose. Solifenacin was administered orally as a 10 mg dose and intravenously as a 5 mg dose. Oral and intravenous doses were divided by a washout period of ≥14 days. The study group consisted of 12 healthy young men, aged 20-45 years.

Nine of whom completed the study and the pharmacokinetic analysis thus comprised nine subjects. In summary, a single oral dose of solifenacin 10 mg had a high absolute bioavailability of 88.0% (95% confidence interval: 0.76-1.02). Only 7% of solifenacin was excreted intact in the urine, both after oral and intravenous administration. It should be noted that pharmacokinetics of solifenacin is dose linear in the dose range of 5 to 40 mg.
Based on these data complete absorption of solifenacin has been shown.

In vitro dissolution
The dissolution profiles obtained for the Solifenacinesuccinaat CF 5 mg and 10 mg test batches and the Vesicare 5 mg and 10 mg reference batches are similar in pH 1.2, pH 4.5 and pH 6.8 medium: >85% dissolved in 30 minutes and all f_2 values >50. Individual values of 12 tablets of both the test and reference product, as well as the statistical data (e.g. RSD values) have been included.

Qualitative and quantitative composition
Both immediate release drug products (generic and reference) contain the same amount of active ingredient solifenacin succinate and excipient lactose monohydrate. The other excipients are qualitatively the same. Both products do not contain any excipients that might affect bioavailability.

Conclusion
Based on the available data solifenacin succinate is considered to be BCS class 1 (high solubility and high permeability). The justification for BCS-based biowaiver is accepted.

**Kuipers ME, Krauwinkel JJ, Mulder H and Visser N: Solifenacin Demonstrates High Absolute Bioavailability in Healthy Men. Drugs R D 2004; 5(2):73-81*

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 CF.

Summary table of safety concerns as approved in RMP:

Important identified risks	• Urinary retention • Hypersensitivity • Cardiac rhythm disorders • Glaucoma • Ileus
Important potential risks	• Use of solifenacin in infants and children whether exposed to solifenacin directly or exposed via breastfeeding
Missing information	• 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. No bioequivalence study was performed to support the application. Instead a BCS-based biowaiver was requested and granted. Dissolution is rapid and similar, and a difference in bioavailability is not expected. Risk management is adequately addressed. This generic medicinal product can be used instead of the reference product.

V. USER CONSULTATION

The package leaflet has (PL) 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 three, followed by two rounds of 15 questions 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 PL of medicinal products for human use.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Solifenacinesuccinaat CF 5 mg and 10 mg, film-coated tables has a proven chemical-pharmaceutical quality and is a generic form of Vesicare 5 mg and 10 mg tablets. Vesicare is a well-known medicinal product with an established favourable efficacy and safety profile.

For this generic application, the MAH submitted an argumentation for not performing a bioequivalence study. The MAH applied for a BCS (class I)-based biowaiver, based on criteria according to the Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98). The BCS-based biowaiver is fully justified and accepted.

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 CF with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 14 June 2017.

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
NL/H/3695/IA/001/G	**B.II.b.2.a (2x)** 2 microbiological testing sites shall be included in the dossier **B.III.1.a.3** rejected	--	14-12-2017	Partially approved	In the cover letter and application form a B.III.1.a.3 variation has been submitted; however the copy of the relevant page(s) from the Guideline that has been added is for a B.III.1.a.1 variation.
NL/H/3695/IA/002	Submission of a new CEP from the already approved active substance manufacturer The currently approved dossier of the medicinal product includes an Active Substance Master File for the active substance Solifenacin succinate	--	13-2-1018	Approved	--