CBG MEB

Public Assessment Report

Scientific discussion

Solifenacinesuccinaat Mylan 5 mg and 10 mg, film-coated tablets.

(solifenacin succinate)

NL/H/3223/001-002/DC

Date: 13 June 2016

This module reflects the scientific discussion for the approval of Solifenacinesuccinaat Mylan 5 mg and 10 mg, film-coated tablets. The procedure was finalised on 16 September 2015. 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 Mylan 5 mg and 10 mg, film-coated tablets from Mylan 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 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 states (CMS) involved in this procedure were: Belgium, Cyprus, Czech Republic, Denmark, France, Germany, Greece, Iceland, Ireland, Italy, Luxembourg, Norway, Portugal, Slovak Republic, Spain, Sweden, 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 Mylan 5 mg is a yellow, film-coated, round, biconvex tablet debossed with “M” on one side and “SF” over “5” on the other side. Each tablet contains 5 mg solifenacin succinate, corresponding to 3.8 mg solifenacin.

Solifenacinesuccinaat Mylan 10 mg is a pink, film-coated, round, biconvex tablet debossed with “M” on one side and “SF” over “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 blister packs (PVC-Al) and high density polyethylene (HDPE) bottle packs with round wide mouth white HDPE bottle and a white opaque polypropylene (PP) cap with aluminium induction sealing liner wad.

The excipients are:
Tablet core – lactose monohydrate, maize starch, hypromellose, talc and magnesium stearate.
Tablet coating – hypromellose, titanium dioxide (E171), propylene glycol, iron oxide yellow (E172).
The 10 mg tablet also contains iron oxide red (E172) as excipient for colouring purposes.

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 freely soluble in water, methanol and chloroform. Solifenacin succinate exhibits polymorphism. The polymorphic form for this product matches the form used for the innovator product.

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 synthesis consists of five steps. No metal catalysts are used. The proposed starting materials are acceptable. The active substance has been adequately characterized and acceptable specifications have been adopted for the starting material, solvents and reagents.

Quality control of drug substance
The active substance specification is established in-house and considered adequate to control the quality. Batch analytical data demonstrating compliance with this specification have been provided for three production scale batches.

Stability of drug substance
Stability data on the active substance have been provided for three batches in accordance with applicable European guidelines for 48 months (stored at 25°C/60% RH) and 6 months (stored at 40°C/75% RH). All parameters tested remain relatively stable (with the exception of some analytical variance) at both storage conditions. Based on the stability data provided the proposed re-test period of 60 months without special storage conditions can be granted. However, no objections are raised against the proposed storage condition: ”Store in well closed container below 30°C, excursions permitted up to 40°C”.

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 mixing, wet granulation, mixing, compression, coating and packaging. The process has been adequately validated according to relevant European guidelines. Process validation data on the product have been presented for three batches of each strength of the smallest commercial size. The product is manufactured using conventional manufacturing techniques. Process validation for the larger commercial scale batches will be performed post authorisation.

Control of excipients
All excipients used comply with the requirements of their respective European Pharmacopoeia (Ph.Eur.), United States Pharmacopeia or National Formulary monographs, except for the ready to use coating materials. In-house specifications have been provided for the coating materials. 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, identification, identification of the colorants, water content, uniformity of dosage units, dissolution, related substances, assay and microbial quality. The release and shelf life specifications are identical, except for water content. The analytical methods have been adequately described and validated.
Batch analytical data from the proposed production site have been provided on three batches of each strength of the smallest commercial size, demonstrating compliance with the release specification.

Stability of drug product
Stability data on the product have been provided three batches of each strength of the smallest commercial size in accordance with applicable European guidelines. The data cover 6 months stored

at 25°C/60% RH and 12 months stored at 40°C/75% RH. The batches were stored in the proposed PVC/Al blisters and HDPE bottles with PP closure. Slight increases were observed in related substances. This was most pronounced in the 5 mg tablet packed in the HDPE bottle and stored at accelerated conditions. All other parameters tested remained relatively stable throughout the test periods at both test conditions and within specification limits. Photostability studies in line with ICH Q1B show that the product is not sensitive to light. On basis of the data submitted, a shelf life was granted of 36 months without special storage conditions.

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 to EU food hygiene regulations.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Solifenacinesuccinaat Mylan 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 Mylan 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 Mylan 10 mg tablets (Mylan B.V., NL) 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.

Biowaiver

A biowaiver was requested for the 5 mg film-coated tablets. The quantitative and qualitative composition of the 5 mg and 10 mg solifenacin tablets are the same. The composition of the strengths are quantitatively proportional (the ratio between the amount of each excipient to the amount of active substance is the same for all strengths). The 5 mg and 10 mg tablets show comparable dissolution: more than 85% dissolves within 15 minutes at pH 1.2, 4.5 and 6.8. Therefore, the criteria for the waiver for the additional strength have been fulfilled and the biowaiver is considered acceptable.

Bioequivalence study

Design

A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fasted conditions in 28 healthy male subjects, aged 26-44 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. Fasting was continued for 4 hours after dosing. There were 2 dosing periods, separated by a washout period of 21 days.

Blood samples were collected at pre-dose and at 1, 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.

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. The systemic clearance of solifenacin is about 9.5 L/h and the terminal half-life of solifenacin is 45-68 hours. The 90% confidence intervals for the ratio of test formulation over the reference formulation were calculated for ln-transformed C_{max} and $AUC_{0\text{-}72h}$.

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 was withdrawn from the study for protocol violation (positive alcohol breath test). Therefore, 27 subjects 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=27	**$AUC_{0\text{-}72}$** ng.h/ml	**C_{max}** ng/ml	**t_{max}** h	**$t_{1/2}$** h
Test	579 ± 169	13.9 ± 3.3	5.5 (3.0 -9.0)	70 ± 44
Reference	602 ± 193	14.5 ± 3.8	5.5 (3.5 – 8.5)	64 ± 24
***Ratio (90% CI)**	0.97 (0.93 – 1.00)	0.96 (0.93 – 0.99)	--	--
CV (%)	8.4	7.0	--	--

$AUC_{0\text{-}72}$ area under the plasma concentration-time curve from time zero to 72 hours
C_{max} maximum plasma concentration
t_{max} time for maximum concentration
$t_{1/2}$ half-life

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 Mylan 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 Mylan.

- Summary table of safety concerns as approved in RMP

Important identified risks	- Anaphylactic reactions - Urinary retention - QT prolongation/Torsade de Pointes - Glaucoma - Ileus
Important potential risks	- Use during lactation
Missing information	- Use in pregnancy - Use in children

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 MAH submitted a bridging report, including a focus test. The Parent package leaflet (PL) was for Tolterodine Mylan, which has been subject to user-testing. In the bridging report, differences in key safety messages between the Parent and Daughter PL have been identified. These differences were subject to a focus test, including five questions. The focus test was carried out in accordance with the requirements of the Guideline on the Readability of the package leaflet. In the focus test no problems were identified with regard to comprehensibility and usefulness of the information and thus no amendments were made during the process.
Altogether, the bridging report, including the focus test, is considered acceptable.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Solifenacinsuccinaat Mylan 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 Mylan 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 16 September 2015.

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