Bundesamt für Sicherheit im Gesundheitswesen

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Public Assessment Report

Scientific discussion

Vesisol 10 mg - Filmtabletten, Vesisol 5 mg - Filmtabletten

SOLIFENACIN SUCCINATE

AT/H/0594/001-002/DC

(Former MRP/DCP number: PT/H/1051/001-002/DC)

Date: 25.09.2014

This module reflects the scientific discussion for the approval of Vesisol 10 mg - Filmtabletten, Vesisol 5 mg - Filmtabletten. The procedure was finalised on 26.11.2013. For information on changes after this date please refer to the module 'Update'.

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Vesisol 5 mg and 10 mg - Filmtabletten, from G.L. Pharma GmbH.

The product is indicated 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.

The active substance in Vesisol 5 mg and 10 mg - Filmtabletten is solifenacin succinate. Solifenacin is a competitive, specific cholinergic-receptor antagonist. The urinary bladder is innervated by parasympathetic cholinergic nerves. Acetylcholine contracts the detrusor smooth muscle through muscarinic receptors of which the M_3 subtype is predominantly involved. *In vitro* and *in vivo* pharmacological studies indicate that solifenacin is a competitive inhibitor of the muscarinic M_3 subtype receptor. In addition, solifenacin showed to be a specific antagonist for muscarinic receptors by displaying low or no affinity for various other receptors and ion channels tested.

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

The originator product is Vesicare®, 5 mg and 10 mg strengths. Solifenacin obtained first approval for marketing authorisation by 2003 in the European Union following the favourable opinion adopted by the *CBG-MEB* from the Netherlands. Afterwards, the product was approved in several European countries through a MRP procedure, which finalised in June 2004.

II. QUALITY ASPECTS

II.1 Introduction

Vesisol 5 mg and 10 mg - Filmtabletten are film-coated tablets which are presented in OPA/AL/PVC / Al blisters containing 10, 14, 20, 28, 30, 50, 56, 60, 90, 98 or 100 tablets. Not all pack sizes may be marketed.

Vesisol 5 mg - Filmtabletten are yellow round biconvex film-coated tablets, diameter 6 mm. Each film-coated tablet contains 5 mg of solifenacin succinate (corresponding to 3.8 mg of solifenacin), as the active ingredient.

Vesisol 10 mg - Filmtabletten are pink round biconvex film-coated tablets, diameter 7 mm. Each film-coated tablet contains 10 mg of solifenacin succinate (corresponding to 7.5 mg of solifenacin), as the active ingredient.

II.2 Drug Substance

The active substance in Vesisol 5 mg and 10 mg - Filmtabletten is solifenacin succinate. The specification of the active substance meets the current scientific requirements. The adequate quality of the active substance has been shown by submitting the appropriate control data. The

stability of the active substance has been tested under ICH conditions. The results of the stability studies support the established retest-period.

II.3 Medicinal Product

Vesisol 5 mg - Filmtabletten contains the following excipients:

- Tablet core: 55.25 mg lactose monohydrate, maize starch, talc, magnesium stearate (E470b)
- Tablet coating:
    - Opadry yellow OY 32823: Hypromellose 6cP (E464), Titanium dioxide (E171), Macrogol 400 , Ferric oxide Yellow (E172), Ferric oxide Red (E172)

Vesisol 10 mg - Filmtabletten contains the following excipients:

- Tablet core: 110.5 mg lactose monohydrate, maize starch, talc, magnesium stearate (E470b)
- Tablet coating:
    - Opadry white 03B28796: Hypromellose 6cP (E464), Titanium dioxide (E171), Macrogol 400
    - Opadry brown 02F23883: Hypromellose 5cP (E464), Titanium dioxide (E171), Macrogol 6000 , Ferric oxide Yellow (E172), Ferric oxide Red (E172)

The development of the product has been sufficiently made and deemed appropriate. The usage of all the excipients has been described.

The release specification includes the check of all parameters relevant to this pharmaceutical form. Appropriate data concerning the control of the finished product support the compliance with the release specifications.

The packaging of the medicinal product complies with the current legal requirements.

Stability studies under ICH conditions have been performed and data presented support the shelf life claimed in the SmPC, with a shelf life of 24 months for Vesisol 5 mg - Filmtabletten and 36 months for Vesisol 10 mg - Filmtabletten. This medicinal product does not require any special storage conditions.

The pharmaceutical quality of Vesisol 5 mg and 10 mg - Filmtabletten has been adequately shown.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of active substance and medicinal product has been presented in a satisfactory manner. The results of tests carried out indicate satisfactory consistency and uniformity of important product quality characteristics.

III. NON-CLINICAL ASPECTS

Pharmacodynamic, pharmacokinetic and toxicological properties of solifenacin succinate are well known. As solifenacin succinate is a widely used, well-known active substance, the applicant has not provided additional studies and further studies are not required. Overview based on literature review is, thus, appropriate.

The non-clinical overview on the pre-clinical pharmacology, pharmacokinetics and toxicology is adequate.

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Vesisol 5 mg and 10 mg - Filmtabletten 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. To limit the release of Vesisol 5 mg and 10 mg - Filmtabletten to the environment a disposal advice has been added to the SmPC.

IV. CLINICAL ASPECTS

IV.1 Introduction

The pharmacokinetic properties of solifenacin succinate are well established. Based on the available published literature a summary of kinetics has been provided. In addition, one bioequivalence study has been provided.

As solifenacin succinate is a widely used, well-known active substance, no further studies are required for this application and the applicant provides none. Overview based on literature review is thus appropriate.

IV.2 Pharmacokinetics

Biowaiver

A biowaiver has been requested for the 5 mg film-coated tablets on the basis of the requirements stated in the *Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/Corr*),* which were all fulfilled:

- all strengths are manufactured by the same manufacturer & manufacturing process
- the qualitative composition of the different strengths is the same
- the composition of strengths is quantitatively proportional
- pharmacokinetics of solifenacin are linear in the dose range 5-10 mg
- appropriate in vitro dissolution data are available showing similar dissolution profiles.

The biowaiver is adequately addressed and justified.

Bioequivalence studies

The Applicant has submitted as a report a bioequivalence study to demonstrate the bioequivalence of Solifenacin Succinate 10 mg film-coated tablets (test formulation) with Vesicare® 10 mg film-coated tablets (reference formulation).

This was an open label, randomized, two-treatment, two-period, two-sequence, single dose crossover bioequivalence study on 32 (28+4 reserves) healthy adult human male subjects under fasting conditions.

The results from measured data based on 31 subjects are summarized in the following summary table:

Summary Statistics of Pharmacokinetic Parameters of solifenacin under fasting conditions (non-transformed values; arithmetic mean ± SD, t_{max} median, range)

Treatment	**AUC_{0-72} pg.h/ml**	**C_{max} pg/ml**	**t_{max} h**
Test	447848.384 ± 130713.727	12335.311 ± 3427.034	3.333 [2.00 – 8.00]
Reference	457118.056 ± 121596.004	12934.208 ± 3520.976	4.333 [2.00 – 10.00]
***Ratio T/R (90% CI)**	102.962 (98.622-107.493)	105.188 (100.159-110.471)	-
Residual CV%:	9.999	11.384	-

AUC_{0-72} Area under the plasma concentration curve from administration to last observed concentration at time 72h.

$AUC_{0-\infty}$ Area under the plasma concentration curve extrapolated to infinite (does not need to be reported when AUC_{0-72h} is reported.

C_{max} Maximum plasma concentration

t_{max} Time until Cmax is reached

**ln-transformed values*

The 90% confidence intervals for AUC_{0-t} and C_{max} are within 80-125%. Therefore, bioequivalence between test and reference formulations was appropriately demonstrated.

Conclusion on bioequivalence studies:

Based on the submitted bioequivalence study Vesisol 10 mg - Filmtabletten is considered bioequivalent with Vesicare® 10 mg film-coated tablets (Astellas Pharma Europe B.V.).

The results of the study with the 10 mg formulation can be extrapolated to the 5 mg strength, according to conditions in *Guideline on the Investigation of Bioequivalence CPMP/EWP/QWP/1401/98 Rev. 1*, section 4.1.6.

IV.3 Pharmacodynamics

Pharmacotherapeutic group: Urinary antispasmodics, ATC code: G04B D08.

The pharmacodynamics profile of solifenacin succinate is well established. No additional pharmacodynamics study has been submitted by the applicant and none is required.

IV.4 Clinical efficacy/safety

The indications claimed are in accordance with those of the reference product Vesicare® 5 mg and 10 mg film-coated tablets, Astellas Pharma Europe B.V.

The efficacy of solifenacin succinate is established and documented in controlled clinical studies. No new efficacy or safety data have been submitted and none are required for this generic application.

IV.5 Risk Management Plan and Summary of the Pharmacovigilance System Master File

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 Vesisol 5 mg and 10 mg - Filmtabletten.

- Summary table of safety concerns as approved in RMP version 1

Important identified risks	Severe renal impairment Moderate and severe hepatic impairment Concomitant use of a potent CYP3A4 inhibitor
Important potential risks	None
Missing information	Use of solifenacin in pregnant and breast-feeding women Use of solifenacin in paediatric population

- Summary of pharmacovigilance activities

Routine pharmacovigilance activities are considered sufficient to identify and to characterize the risks of the product. No additional pharmacovigilance activities are warranted for the time being.

- Summary of risk minimisation measures

Routine risk minimization measures are considered sufficient to minimize the risks of the product in the proposed indications. No additional risk minimization measure are deemed to be necessary for the time being

- If applicable: Table of Ongoing and Planned Additional Pharmacovigilance Studies / Activities in the Pharmacovigilance Plan as approved in RMP

Not applicable

Summary of the Pharmacovigilance System Master File

The applicant submitted the summary of the pharmacovigilance system in the scope of this procedure.

The summary includes the following elements:

- Proof that the applicant has at his disposal a qualified person responsible for

pharmacovigilance

- The Member States in which the qualified person resides and carries out his/her tasks
- The contact details of the qualified person
- A statement signed by the applicant to the effect that the applicant has the necessary means to fulfil the tasks and responsibilities listed in Title IX of Directive 2001/83/EC

IV.6 Discussion on the clinical aspects

The dossier contains an adequate review of published clinical data and bioequivalence has been shown.

V. USER CONSULTATION

The package leaflet 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 language used for the purpose of user testing the PIL was Czech.

The results show that the package leaflet 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.

The test consisted of a pilot test with four participants, followed by two rounds with 10 participants each. The questions covered the following areas sufficiently: traceability, comprehensibility and applicability.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The pharmaceutical quality of Vesisol 5 mg and 10 mg - Filmtabletten has been adequately shown, and no new non-clinical or clinical concerns have been identified.

Bioequivalence of Vesisol 10 mg - Filmtabletten with the reference product Vesicare® 10 mg film-coated tablets, Astellas Pharma Europe B.V. has been shown.

A biowaiver has been requested for the 5 mg film-coated tablets on the basis of the requirements stated in the *Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/Corr*),* which were all fulfilled. The results of the study with the 10 mg formulation can be extrapolated to the 5 mg strength.

The benefit/risk relation is considered positive.

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Update

Vesisol 10 mg - Filmtabletten, Vesisol 5 mg - Filmtabletten

SOLIFENACIN SUCCINATE

AT/H/0594/001-002/DC

(Former MRP/DCP number: PT/H/1051/001-002/DC)

This module reflects the procedural steps and scientific information after the finalisation of the initial procedure.

Procedure number	Scope	Product Information affected	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse
AT/H/0594/001-002/DC	RMS Transfer from PT to AT	No	25.09.2014	-	-
AT/H/0594/001-002/II/003	Active substance: Update of ASMF	No	26.02.2017	Approval	-
AT/H/0594/001-002/R/001	Renewal	Yes	08.11.2018	Approval	-