COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Solifenacinesuccinaat Vivanta 5 mg and 10 mg film-coated tablets

(solifenacin succinate)

NL/H/4288/001-002/DC

Date: 3 September 2019

This module reflects the scientific discussion for the approval of Solifenacinesuccinaat Vivanta 5 mg and 10 mg film-coated tablets. The procedure was finalised at 27 February 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

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 Vivanta 5 mg and 10 mg film-coated tablets from Vivanta Generics s.r.o.

The product is indicated for symptomatic treatment of urge incontinence and/or increased urinary frequency and urgency in patients with overactive bladder (OAB) 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 and 29152) which has been registered in The Netherlands by Astellas Pharma since 16 December 2003 (original product) by the procedure NL/H/0487/001-002/DC.

The concerned member states (CMS) involved in this procedure were Germany, Spain and Ireland.

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

II. QUALITY ASPECTS

II.1 Introduction

Solifenacinesuccinaat Vivanta is a film-coated tablet.

Each 5 mg tablet is a light yellow, round shaped, biconvex film-coated tablet debossed with 'S5' on one side and plain on other side, equivalent to 3.8 mg solifenacin.
Each 10 mg tablet is a light pink, round shaped, biconvex film-coated tablet debossed with 'S10' on one side and plain on other side, equivalent to 7.5 mg solifenacin.

The film-coated tablets are packed in a PVC/PVdC-Al blister.

The excipients are:
Tablet core -lactose monohydrate, hypromellose (E464), magnesium stearate (E572)
5 mg tablet coating - Opadry yellow 03K520019 (HPMC 2910/hypromellose (E464), titanium dioxide (E171), triacetin (E1518), talc (E553b), iron oxide yellow (E172))
10 mg tablet coating - Opadry pink 03K540030 (HPMC 2910/hypromellose (E464), titanium dioxide (E171), triacetin (E1518), talc (E553b), iron oxide red (E172))

The two tablet strengths are dose proportional.

II.2 Drug Substance

The active substance is solifenacin succinate, an established active substance described in the European Pharmacopoeia (Ph.Eur.). The drug substance is a white or light yellow crystalline powder soluble in water and ethanol. Solifenacin succinate drug substance exhibits polymorphism. The manufacturing process consistently produces the crystalline form. Solifenacin succinate consists of two asymmetric carbon atoms; hence two pairs of isomers are possible. The required isomer is adequately controlled. Other isomers have been controlled in the final drug substance specification.

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 considered adequate to control the quality and meets the requirements of the monograph in the Ph.Eur. It includes additional requirements for specific optical rotation, succinic acid content, heavy metals, assay, residual solvents, polymorphic identification, and particle size. Batch analytical data demonstrating compliance with this specification have been provided for three batches.

Stability of drug substance

The active substance is stable for 60 months when stored under the stated conditions. Assessment thereof was part of granting the CEP and has been granted by the EDQM.

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 excipients is justified and their functions explained. Development studies were performed to select the optimal excipients, the optimal concentration of binder and lubricant, and the optimal manufacturing process.

The pharmaceutical development of the product has been adequately performed, and the choices of the packaging and manufacturing process have been justified.

A bioequivalence study was performed between the 10 mg strength of the current product and the reference product Vesicare 10 mg. The test product was manufactured according to the intended commercial process. The batch of the test product and the reference product were analysed and the assay and impurity profile determined. It was demonstrated that the difference in assay of the test product bio-batch and the reference product bio-batch is less than 5% and that the level of impurities of test product is comparable with the reference product. Comparative dissolution profiles were determined in water, 0.1N HCl, pH 4.5 acetate buffer and pH 6.8 phosphate buffer for the batches used in the bioequivalence study. In water, 0.1N HCl, and pH 4.5 the dissolution profiles were similar, whereas, at pH 6.8 similarity could not be demonstrated, however, this is no issue as bioequivalence was shown in vivo.

The similarity of the dissolution profiles, in support of the biowaiver of strength, between the 10 mg strength and the 5 mg strength has been demonstrated and the biowaiver can be accepted.

Manufacturing process

The manufacturing process of involves sifting, pre-lubrication, lubrication, compression, coating, inspection and packaging. The process is summarised in a process flow diagram, and a stepwise description has been provided. The manufacturing process has been adequately validated according to relevant European guidelines. Process validation data on the product has been presented for three full scale batches of the common blend, and on three full scale batches of each strength. The product is manufactured using conventional manufacturing techniques.

Control of excipients

The excipients, except for the coating mixtures, comply with Ph.Eur. requirements. The individual components of the coating mixtures comply with 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 description, identification (drug substance and colourants), average mass, uniformity of dosage units, dissolution, assay, related substances, and microbiological quality. The release and shelf-life specification are identical, except for the limit for total impurities. The limit for total impurities is widened at shelf-life. 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 three full 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 three full scale batches of each strength, stored at 25°C/60% RH (18 months), and 40°C/75% RH (6 months). The conditions used in the stability studies are according to the ICH stability guideline. Photostability studies were performed in accordance with ICH recommendations and showed that the product is stable when exposed to light. All batches stay within specification under long term and accelerated conditions. On basis of the data submitted a shelf life was granted of two year (24 months) with no special storage condition defined.

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

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 Vivanta 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 Vivanta 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 one bioequivalence study, which is discussed below.

IV.2 Pharmacokinetics

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

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

Biowaiver

The results obtained for the 10 mg tablet can be extrapolated to the 5 mg tablet. The criteria for the waiver for additional strength have been fulfilled:

- the pharmaceutical products are manufactured by the same manufacturing process
- the qualitative composition of the different strengths is the same
- the composition of the strengths are quantitatively proportional
- pharmacokinetics of solifenacin are linear in the therapeutic dose-range.
- both test strengths have shown similar dissolution profiles at three pH conditions (1.2, 4.5 and 6.8).

  The similarity factor of the dissolution comparison using the same dose (1x 10 mg tablet vs 2x 5 mg tablets) at pH 1.2 was calculated using bootstrapping method.
  Dissolution comparison data of the single test 5 mg and 10 mg tablets with their respective reference products at pH 1.2 were provided. The similarity factor was calculated using the bootstrapping method due to high RSDs.
  It is accepted that in this case, based on the totatility of data, similar dissolution profiles may be concluded between the 10 mg and the 5 mg test products at pH 1.2, taking also the following into account:
  - Drug substance is highly soluble across the pH range from 1.2 to 6.8

- Comparisons of same strength of test versus reference have shown similar profiles at pH 1.2 (1x 10 mg test versus 1x 10 mg reference and 1x 5 mg test, versus 1x 5 mg reference: both 5% lower confidence limit for f2 >50)
- Variability (as indicated by RSD values) at pH 1.2 in the dissolution results was not higher for test product compared to reference product and was in general higher for this pH than for the other pH conditions

Overall, comparability between the 10 mg strength and the additional 5 mg strength is considered sufficiently proven.

Bioequivalence study

Design

An open label, randomized, two-treatment, single period, parallel single oral dose bioequivalence study was carried out under fasted conditions in 80 healthy male subjects, aged 19-42 years. Each subject received a single dose (10 mg) of one of the two solifenacin succinate formulations. The tablet was orally administered with 240 ml water after an overnight fast. There was one dosing period.

Blood samples were collected at 0.5, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 18, 24, 36, 48 and 72 hours after administration of the products.

The design of the study is acceptable. A fasting study is according to the bioequivalence guideline. The sampling times until 72 hours post-dose are sufficient to provide a reliable estimate of the extent of exposure for an immediate-release product. In general, a cross-over study design is preferred to limit variability, however, a parallel design is also acceptable.

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

All subjects were eligible for pharmacokinetic analysis.

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

Treatment N=80	**AUC_{0-t} (ng.h/ml)**	**C_{max} (ng/ml)**	**t_{max} (h)**
Test (N=40)	937 ± 242	21.39 ± 5.01	7.0 (3.0 – 10.0)
Reference (N=40)	933 ± 212	21.31 ± 4.20	6.0 (3.0 – 18.0)

***Ratio (90% CI)**	1.00 (0.91 – 1.10)	1.00 (0.92 – 1.08)	--
AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours **C_{max}** maximum plasma concentration **t_{max}** time for maximum concentration			

**In-transformed values*

Conclusion on bioequivalence study

The 90% confidence intervals calculated for AUC_{0-t} and C_{max} are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the submitted bioequivalence study Solifenacinesuccinaat Vivanta is considered bioequivalent with Vesicare.

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 Vivanta.

Table 2. 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	--
Missing information	• Use of solifenacin in children under the age of six months, either exposed to solifenacin directly or exposed via breast-feeding • 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, 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 Vivanta 5 mg and 10 mg film-coated tablets has a proven chemical-pharmaceutical quality and is a generic form 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 Vivanta with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 27 February 2019.

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