CBG MEB

Public Assessment Report

Scientific discussion

Solifenacine Jubilant 5 mg and 10 mg film-coated tablets

(solifenacin succinate)

NL/H/3110/001-002/DC

Date: 13 October 2015

This module reflects the scientific discussion for the approval of Solifenacine Jubilant 5 mg and 10 mg film-coated tablets. The procedure was finalised on 13 January 2015. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Solifenacine Jubilant 5 mg and 10 mg film-coated tablets from Jubilant Pharmaceuticals N.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 (NL License RVG 29151-29152), which has been registered in the Netherlands since16 December 2003 by Astellas Pharma Europe B.V.
Subsequently -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 Cyprus, Denmark, Germany, Italy, 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

Solifenacine Jubilant 5 mg is a a light yellow coloured, round, biconvex, film-coated tablet of approximately 5.6 mm diameter, debossed with ‘D5’ on the one side and plain on the other side. Each tablet contains 5 mg solifenacin succinate, corresponding to 3.8 mg solifenacin.

Solifenacine Jubilant 10 mg is a light pink coloured, round, biconvex, film-coated tablet of approximately 7.7 mm diameter, debossed with ‘D6’ on the one side and plain on one the other side. Each tablet contains 10 mg solifenacin succinate, corresponding to 7.5 mg solifenacin.

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

The excipients are:
Tablet core - maize starch, lactose monohydrate, hypromellose 2910 (E464), magnesium stearate (E470b)
Film-coating - macrogol 8000, talc (E553b), hypromellose 2910 (E464), titanium dioxide (E171), iron oxide yellow (E172); *10 mg only* - iron oxide red (E172)

The different tablet strengths are dose proportional.

II.2 Drug Substance

The active substance is solifenacin succinate, an established active substance, however not described in the European, British or US Pharmacopoeia. The active substance is a white to pale-yellowish white crystal or crystalline powder, which is freely soluble in water and methanol. Solifenacin has two chiral centres and the drug substance is the 3R,1S isomer. Solifenacin exhibits polymorphism and the drug product contains form I.

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 a resolution step, two synthetic steps and purification steps. No metal catalysts are used. The proposed starting materials are acceptable. The active substance has been adequately characterised.

Quality control of drug substance
The drug substance specification is established in-house. The specification is acceptable in view of the route of synthesis and the various European guidelines.
Batch analytical data demonstrating compliance with the drug substance specification have been provided for three production-scale batches.

Stability of drug substance
Stability data on the active substance have been provided for three full-scale batches stored at 25°C/60% RH (24 months) and 40°C/75% RH (6 months). Slight increases in loss on drying were observed at both conditions. Results remained within specification limits. All other 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 30 months without special storage conditions was granted. However, no objections are raised against the proposed storage condition 'Store in airtight containers below 25°C. Under nitrogen environment. Protect from light and moisture'.

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. Bioequivalence studies were 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. Sufficient comparative dissolution data have been provided.
The core tablets of the 5 mg and 10 mg are fully dose proportional and the dissolution profiles are similar. Therefore a biowaiver of strength for the 5 mg tablets is acceptable from a chemical-pharmaceutical point of view.
The pharmaceutical development of the product has been adequately performed.

Manufacturing process
The manufacturing process consists of mixing, wet granulation, mixing, compression, coating and packaging. The manufacturing process has been adequately validated according to relevant European guidelines. Process validation data on the product has been presented for three batches of each strength of the smallest commercial scale. 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 Ph.Eur. or USP/NF monographs, except for the ready-to-use coating materials. In-house specifications have been provided for the coating materials. These specifications are acceptable.

Quality control of drug product
The product specification includes tests for appearance, identification, identification of the colorants, loss on drying, uniformity of dosage units, dissolution, related substances, assay and microbial quality. The release and shelf life specification are identical. The drug product specification is acceptable.
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 has been provided three batches of each strength of the smallest commercial batch size stored at 25°C/60% RH (24 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 clear PVC/Al blister.

Slight increases in one related substance were observed. 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, were performed and showed that the product is photostable.

Based on the stability data provided, the proposed shelf life of 24 months can be granted. Based on the stability data provided the proposed storage condition 'Do not store above 25°C' is not considered necessary, however acceptable.

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

Lactose is the only excipient of animal origin present in the product. Lactose monohydrate is prepared from milk and calf rennet. Milk is sourced from healthy animals in the same conditions as milk collected for human consumption (Complies EU food hygiene regulations). The production of calf rennet complies with the requirements defined in regulation 999/2001 and other applicable EU legislation.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Solifenacine Jubilant has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product.

The following post-approval commitments were made:

- The MAH committed to conduct validation on the first three consecutive commercial batches of both strengths.
- The MAH committed to the following regarding stability studies:
  - To continue the on going long-term stability studies.
  - To include three consecutive commercial scale batches of larger size than already included.

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Solifenacine Jubilant 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, which is discussed below.

IV.2 Pharmacokinetics

The MAH conducted a bioequivalence study in which the pharmacokinetic profile of the test product Solifenacine Jubilant 10 mg (Jubilant Pharmaceuticals N.V., Belgium) is compared with the pharmacokinetic profile of the reference product Vesicare 10 mg tablets (Astellas Pharma GmbH, Germany).

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
A bioequivalence study on the highest strength (10 mg strength) has been carried out. Pharmacokinetics are linear in the therapeutic dose range. A biowaiver is requested for the 5 mg strength as all the following criteria are fulfilled:

a) the pharmaceutical products are manufactured by the same manufacturing process
b) the qualitative composition of the different strengths is the same
c) the composition of the strengths are quantitatively proportional, i.e. the ratio between the amount of each excipient to the amount of active substance is the same for all strengths
d) appropriate in vitro dissolution data between the 5 and 10 mg biobatch at a pH of 1.2, 4.5 and 6.8 showing comparable dissolution have been submitted

The criteria for the waiver for the additional strength have been fulfilled, and therefore the biowaiver was granted.

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 19-42 years. Each subject received a single dose (10 mg) of one of the 2 solifenacin 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 28 days.

Blood samples were collected pre-dose and at 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 6.5, 7, 7.5, 8, 9, 10, 12, 16, 24, 36, 48, 60 and 72 hours after administration of the products.

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 dropped out. The remaining 27 subjects completed the study and were included in the analysis.

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

Treatment N=27	**AUC_{0-72}** ng.h/ml	**C_{max}** ng.h/ml	**t_{max}** h	**$t_{1/2}$** h
Test	785 ± 272	19.5 ± 5.7	4.5 (3.0 – 8.0)	50 ± 15
Reference	791 ± 225	19.9 ± 4.6	4.5 (2.5 – 9.0)	47 ± 19
***Ratio (90% CI)**	0.99 (0.94 – 1.03)	0.98 (0.92 – 1.04)	--	--
CV (%)	10.0	12.5	--	--

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
$t_{1/2}$ half-life
CV coefficient of variation

**ln-transformed values*

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 Solifenacine Jubilant 10 mg is considered bioequivalent with Vesicare 10 mg 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).

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 Solifenacine Jubilant.

- Summary of Safety Concerns and Planned Risk Minimisation Activities as approved in RMP

Safety concern	**Proposed pharmacovigilance activities (routine and additional)**	**Proposed risk minimisation activities (routine)**
Important identified risks		
Drug interaction with cytochrome P450 3A4 inhibitors	Routine PV	Appropriate text included in the proposed SmPC: - section 4.2 - section 4.3 - section 4.4 - section 4.5 - POM status
Important potential risks		
Anaphylactic reactions	Routine PV	Appropriate text included in the proposed SmPC: - section 4.4 - section 4.8 - POM status
QT prolongation and Torsade de Pointes	Routine PV	Appropriate text included in the proposed SmPC: - section 4.8 - section 4.9

		- POM status
Potential aggravation of existing medical conditions/ precipitation of other undesirable effects due to its anti-cholinergic properties. These include conditions of bladder obstruction/urinary retention, certain gastrointestinal (GI) disorders of obstruction, GI motility disorders, myasthenia gravis, narrow angle glaucoma	Routine PV	Appropriate text included in the proposed SmPC: - section 4.3 - section 4.4 - POM status
Angioedema	Routine PV	Appropriate text included in the proposed SmPC: - section 4.4 - section 4.8 - POM status
Use during lactation	Routine PV	Appropriate text included in the proposed SmPC: - section 4.6 - section 5.3 - POM status
Missing information		
Use in pregnancy	Routine PV	Appropriate text included in the proposed SmPC: - section 4.6 - POM status

The member states agreed that routine pharmacovigilance activities and routine risk minimisation measures are sufficient for the risks and areas of missing information.

The MAH committed to closely monitor the following adverse events:

- Cardiac disorders
  - Atrial fibrillation/Tachycardia
  - Atrioventricular block complete
  - Congestive heart failure
  - Coronary heart disease

- Eye disorders
  - Angle closure glaucoma/Glaucoma/Intraocular pressure increased

- Gastrointestinal disorders
  - Ileus paralytic/Intestinal obstruction

- Immune system disorders
  - Anaphylactic shock, other serious allergic reactions

- Nervous system disorders
  - Dementia
  - Parkinson's disease

- Respiratory, thoracic and mediastinal disorders
  - Interstitial lung disease

- Vascular disorders
  - Hypertension

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 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 2 participants, followed by two rounds with 10 participants each. The questions covered the following areas sufficiently: traceability, comprehensibility and applicability. No problems were identified regarding comprehensibility and usefulness of the information and thus no amendments were made during the process. 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.
Altogether the testing has been adequately performed. The final leaflet is considered acceptable from a readability point of view, with patients/users being able to act properly upon the information that it contains.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Solifenacine Jubilant 5 mg and 10 mg film-coated tablets have a proven chemical-pharmaceutical quality and are generic forms of Vesicare 5 and 10 mg. 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 Solifenacine Jubilant 5 mg and 10 mg with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 13 January 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