Public Assessment Report

Decentralised Procedure

Solifenacin succinate 5 mg film-coated tablets

Solifenacin succinate 10 mg film-coated tablets

(Solifenacin succinate)

Procedure No: UK/H/6830/001-002/DC
UK Licence Number: PL 11311/0594-95

Tillomed Laboratories Ltd
This is a summary of the Public Assessment Report (PAR) for Solifenacin succinate 5 mg film-coated tablets (PL 11311/0594; UK/H/6830/001/DC) and Solifenacin succinate 10 mg film-coated tablets (PL 11311/0595; UK/H/6830/002/DC). It explains how Solifenacin succinate 5 mg and 10 mg film-coated tablets were assessed and their authorisation recommended, as well as their conditions of use. It is not intended to provide practical advice on how to use these products.

The products will be collectively referred to as 'Solifenacin succinate film-coated tablets' throughout the remainder of this PAR.

For practical information about using Solifenacin succinate film-coated tablets, patients should read the package leaflet or contact their doctor or pharmacist.

**What are Solifenacin succinate film-coated tablets and what are they used for?**

Solifenacin succinate film-coated tablets are ‘generic medicines’. This means that Solifenacin succinate film-coated tablets are similar to ‘reference medicines’ already authorised in the European Union (EU) called Vesicare 5mg and 10 mg film-coated tablet (Astellas Pharma Ltd, UK).

This medicine is used to treat the symptoms of a condition called overactive bladder. These symptoms include: having a strong, sudden urge to urinate without prior warning, having to urinate frequently or wetting oneself because of not getting to the bathroom in time.

**How do Solifenacin succinate film-coated tablets work?**

The active substance of Solifenacin succinate film-coated tablets, solifenacin succinate, belongs a group of medicines called anticholinergics. These medicines are used to reduce the activity of an overactive bladder. This enables the patient to wait longer before having to go to the bathroom and increases the amount of urine that can be held by the bladder.

**How are Solifenacin succinate film-coated tablets used?**

The pharmaceutical form of this medicine is a film-coated tablet and the route of administration is oral (by mouth).

The patient should always take this medicine exactly as their doctor or pharmacist has told them to. The patient should check with their doctor or pharmacist if they are not sure.

The patient should swallow the whole tablet with some liquid. It can be taken with or without food, according to the patient’s preference. Do not crush the tablets.

The usual dose is 5 mg per day, unless the patient’s doctor has told the patient to take 10 mg per day.

Please read section 3 of the package leaflet for detailed dosing recommendations, the route of administration, and the duration of treatment.

For further information on how Solifenacin succinate film-coated tablets are used, refer to the package leaflet and Summaries of Product Characteristics available on the Medicines and Healthcare products Regulatory Agency (MHRA) website.

This medicine can only be obtained with a prescription.

**What benefits of Solifenacin succinate film-coated tablets have been shown in studies?**

Because Solifenacin succinate film-coated tablets are generic medicines, studies in healthy volunteers have been limited to tests to determine that they are bioequivalent to the reference medicines Vesicare 5 mg and 10 mg film-coated tablet.
5mg and 10 mg film-coated tablet (Astellas Pharma Ltd, UK). Two medicines are considered to be bioequivalent when they produce the same levels of the active substance in the body.

**What are the possible side effects of Solifenacin succinate film-coated tablets?**
Solifenacin succinate film-coated tablets are generic medicines and are bioequivalent to the reference medicines Vesicare 5mg and 10 mg film-coated tablet (Astellas Pharma Ltd, UK) so the benefits and possible side effects are taken as being the same as for the reference medicines.

For the full list of restrictions, see the package leaflet.

For the full list of all side effects reported with Solifenacin succinate film-coated tablets, see section 4 of the package leaflet available on the MHRA website.

**Why was Solifenacin succinate film-coated tablets approved?**
It was concluded that, in accordance with EU requirements, Solifenacin succinate film-coated tablets have been shown to have comparable quality and to be bioequivalent to Vesicare 5mg and 10 mg film-coated tablet (Astellas Pharma Ltd, UK). Therefore, the MHRA decided that, as for Vesicare 5mg and 10 mg film-coated tablet (Astellas Pharma Ltd, UK), the benefits are greater than the risks and recommended that they can be approved for use.

**What measures are being taken to ensure the safe and effective use of Solifenacin succinate film-coated tablets?**
A risk management plan (RMP) has been developed to ensure that Solifenacin succinate film-coated tablets are used as safely as possible. Based on this plan, safety information has been included in the SmPCs and the package leaflet for Solifenacin succinate film-coated tablets including the appropriate precautions to be followed by healthcare professionals and patients.

Known side effects are continuously monitored. Furthermore, new safety signals reported by patients/healthcare professionals will be monitored/reviewed continuously.

**Other information about Solifenacin succinate film-coated tablets**
Germany, Spain, Italy and the UK agreed to grant Marketing Authorisations for Solifenacin succinate film-coated tablets on 03 December 2018. Marketing Authorisations were granted in the UK on 24 December 2018.

The full PAR for Solifenacin succinate film-coated tablets follows this summary.

This summary was last updated in February 2019.
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I INTRODUCTION
Based on the review of the data on quality, safety and efficacy, the Member States considered that the applications for Solifenacin succinate film-coated tablets (PL 11311/0594-95; UK/H/6830/001-002/DC), are approvable. Solifenacin succinate film-coated tablets are Prescription-Only Medicines (POM) indicated for the symptomatic treatment of urge incontinence and/or increased urinary frequency and urgency as may occur in patients with overactive bladder syndrome.

The applications were submitted using the Decentralised Procedure (DCP), with the UK as Reference Member State (RMS), and Germany, Spain and Italy as Concerned Member States (CMS). The applications were submitted under Article 10(1) of Directive 2001/83/EC, as amended, as generic applications. The reference medicinal products for these applications are Vesicare 5 mg and 10 mg film-coated tablets which were first authorised to the marketing authorisation holder (MAH), Astellas Pharma Ltd (PL 00166/0197-98) in the UK on 16 August 2004.

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 M3 subtype is predominantly involved. In vitro and in vivo pharmacological studies indicate that solifenacin is a competitive inhibitor of the muscarinic M3 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.

One bioequivalence study (conducted under fasting conditions) was submitted to support these applications. The applicant has stated that the bioequivalence study were conducted in accordance with Good Clinical Practice (GCP) guidelines.

The RMS has been assured that acceptable standards of Good Manufacturing Practice are in place for this product type at all sites responsible for the manufacture, assembly and batch release of these products.

For manufacturing sites within the Community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

For manufacturing sites outside the community, the RMS has accepted copies of current GMP Certificates or satisfactory inspection summary reports, ‘close-out letters’ or ‘exchange of information’ issued by the inspection services of the competent authorities (or those countries with which the EEA has a Mutual Recognition Agreement for their own territories) as certification that acceptable standards of GMP are in place at those non-Community sites.

The RMS and CMS considered that the applications could be approved at the end of procedure on 03 December 2018. After a subsequent national phase, licences were granted in the UK on 24 December 2018.
II QUALITY ASPECTS

II.1 Introduction

Each film-coated tablet contains 5 mg or 10 mg of solifenacin succinate as the active ingredient. Other ingredients consist of the pharmaceutical excipients:

**Tablet core:**
Lactose monohydrate, hydroxypropyl methylcellulose and magnesium stearate.

**Coating material:**
- 5 mg tablet strength (Opadry Yellow 03K520019):
  HPMC 2910/Hypromellose (6mPas), titanium dioxide, triacetin, talc and iron oxide yellow.
- 10 mg tablet strength (Opadry Pink 03K540030):
  HPMC 2910/Hypromellose (6mPas), titanium dioxide, triacetin, talc and red iron oxide

Both strengths of the finished product are packaged in PVC/Aluminium blisters in pack sizes of 10, 20, 30, 50 and 90 tablets.

Not all pack sizes may be marketed.

Satisfactory specifications and Certificates of Analysis have been provided for all packaging components. All primary packaging complies with the current European regulations concerning materials in contact with food.

II.2 Drug Substance

**INN:** Solifenacin succinate

**Chemical name:**
- (3R)-1-Azabicyclo[2.2.2]octan-3-yl(1S)-1-phenyl-3,4-dihydroisoquinoline-2(1H)-carboxylate hydrogen butanedioate
- Or
  - (1S)-3,4-Dihydro-1-phenyl-2(1H)-isoquinoline carboxylic acid (3R)-1-azabicyclo[2.2.2]oct-3-yl ester succinate.
- Or
  - (1S, 3’R)-3’quinuclidinyl-1-phenyl-1, 2, 3, 4-tetrahydro-2-Isoquinoline carboxylate succinate.
- Or
  - Butanedioic acid, compound with (1S) - (3R) -1-azabicyclo[2.2.2] oct-3-yl 3, 4-dihydro-1-phenyl-2(1H)-carboxylate (1:1).
- Or
  - (3R)-1-azabicyclo [2. 2. 2] oct-3-yl (1S)-1-phenyl-3, 4-dihydroisoquinoline-2 (1H)- carboxylate monosuccinate.
- Or
  - (+)-(1S, 3’R)-quinuclidin-3’-yl-1 phenyl-1, 2, 3, 4-Tetrahydroquinoline-2-carboxylate monosuccinate.

**Structure:**

![Solifenacin Succinate Structure](image)

**Molecular formula:** C_{27}H_{32}N_{2}O_{6}

**Molecular weight:** 480.6 g/mol

**Appearance:** White or light yellow powder.

**Solubility:** Very soluble and freely soluble in water, soluble in ethanol (96 percent), practically insoluble in heptane.

Solifenacin succinate is the subject of a European Pharmacopeia monograph.
II.3. Medicinal Product

Pharmaceutical Development

The objective of the development programme was to formulate safe, efficacious, film-coated tablets containing 5 mg or 10 mg solifenacin succinate per tablet, that are generic versions of the reference products, Vesicare 5mg and 10 mg film-coated tablet (Astellas Pharma Ltd, UK). A satisfactory account of the pharmaceutical development has been provided.

Comparative in vitro dissolution profiles have been provided for the proposed and originator products.

All excipients comply with their respective European Pharmacopoeia (Ph.Eur) monograph with the exception of the film coatings Opadry Yellow 03K520019 and Opadry Pink 03K540030, which are controlled to a suitable in-house specification. Satisfactory Certificates of Analysis have been provided for all excipients. Suitable batch analysis data have been provided for each excipient.

With the exception of lactose monohydrate none of the excipients used contain material of animal or human origin. The supplier of lactose monohydrate has confirmed that it is sourced from healthy animals under the same conditions as milk for human consumption.

This product does not contain or consist of genetically modified organisms (GMO).

Manufacture of the product

Satisfactory batch formulae have been provided for the manufacture of the product, along with an appropriate account of the manufacturing process. The manufacturing process has been validated at commercial scale batch size and has shown satisfactory results.

Finished Product Specification

The finished product release and shelf life specifications proposed are acceptable. Test methods have been described that have been adequately validated. Batch data have been provided which comply with the release specification. Certificates of Analysis have been provided for all working standards used.

Stability of the Product

Finished product stability studies were performed in accordance with current guidelines on batches of the finished products in the packaging proposed for marketing. The data from these studies support a shelf-life of 30 months. This medicinal product does not require any special storage conditions.

Suitable post approval stability commitments have been provided to continue stability testing on batches of finished product.

II.4 Discussion on chemical, pharmaceutical and biological aspects

There are no objections to the approval of these applications from a pharmaceutical viewpoint.

III NON-CLINICAL ASPECTS

III.1 Introduction

As the pharmacodynamic, pharmacokinetic and toxicological properties of solifenacin succinate are well-known, no new non-clinical studies are required and none have been provided. An overview based on the literature review is, thus, appropriate.

The applicant’s non-clinical expert report has been written by an appropriately qualified person and is satisfactory, providing an appropriate review of the relevant non-clinical pharmacology, pharmacokinetics and toxicology.
III.2 Pharmacology
Not applicable for this product type. Refer to section ‘III.1; Introduction’ detailed above.

III.3 Pharmacokinetics
Not applicable for this product type. Refer to section ‘III.1; Introduction’ detailed above.

III.4 Toxicology
There are no toxicological concerns regarding the impurity profile in the drug substance and drug product specifications. The proposed limits are within the ICH Impurities in New Drug Products Q3B(R2) limits.

III.5 Ecotoxicity/environmental risk assessment (ERA)
Since Solifenacin succinate film-coated tablets are 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.6 Discussion on the non-clinical aspects
There are no objections to the approval of these applications from a non-clinical viewpoint.

IV CLINICAL ASPECTS
IV.1 Introduction
The clinical pharmacology of solifenacin succinate is well-known. With the exception of data from the bioequivalence study detailed below, no new pharmacodynamics or pharmacokinetic data are provided or are required for these applications.

No new efficacy or safety studies have been performed and none are required for this type of application. A comprehensive review of the published literature has been provided by the applicant, citing the well-established clinical pharmacology, efficacy and safety of solifenacin succinate.

Based on the data provided, Solifenacin succinate film-coated tablets can be considered bioequivalent to Vesicare 5mg and 10 mg film-coated tablet (Astellas Pharma Ltd, UK).

IV.2 Pharmacokinetics
In support of these applications, the applicant submitted the following bioequivalence study:

STUDY
A randomised, open-label, two treatment, single period, parallel, single dose, crossover bioequivalence study of the applicant's test product, Solifenacin succinate 10 mg film-coated tablets (Tillomed Laboratories Ltd, UK) versus the reference product Vesicare 10 mg film-coated tablet (Astellas Pharma Ltd, UK), in healthy, adult, subjects under fasting conditions.

Subjects were administered a single oral dose (1 x 10 mg tablet) of the test or reference product with approximately 240mL of water after a supervised overnight fast of at least 10 hours.

Blood samples were collected for plasma levels before dosing and up to and including 72 hours after each administration. There was no washout period between study drug administration due to the parallel study design. The pharmacokinetic results are presented below:
Table: Summary of pharmacokinetic data for solifenacin (means, SD (untransformed data)):

<table>
<thead>
<tr>
<th>Parameter (Unit)</th>
<th>Mean ± SD (Un-transformed data)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Reference Product (R)</td>
</tr>
<tr>
<td>C_{max} (ng/mL)</td>
<td>21.3126±4.19854</td>
</tr>
<tr>
<td>AUC_{0-72} (hr. ng/mL)</td>
<td>933.0048±211.40972</td>
</tr>
<tr>
<td>T_{max} (hr)*</td>
<td>6.00 (3.00-18.00)</td>
</tr>
</tbody>
</table>

*For T_{max} Median has been represented instead of Mean and Range instead of SD.

Table: Bioequivalence conclusion data for solifenacin (geometric least square mean, ratios, 90% confidence intervals):

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Geometric Mean</th>
<th>90% Confidence Interval</th>
<th>Inter Subject CV (%)</th>
<th>Power (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test-T</td>
<td>Reference -R</td>
<td>(T/R) Ratio %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>C_{max}</td>
<td>20.9032</td>
<td>20.8564</td>
<td>99.78</td>
<td>21.7</td>
</tr>
<tr>
<td>AUC_{0-72}</td>
<td>908.0891</td>
<td>906.5883</td>
<td>99.83</td>
<td>25.7</td>
</tr>
</tbody>
</table>

Study conclusion
The 90% confidence intervals of the test/reference ratio for AUC and C_{max} values for solifenacin lie within the acceptable limits of 80.00% to 125.00%, in line with the guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev 1/Corr*). Thus, the data support the claim that the applicant’s test product, Solifenacin succinate 10 mg film-coated tablets (Tillomed Laboratories Ltd, UK) is bioequivalent to the reference product Vesicare 10 mg film-coated tablet (Astellas Pharma Ltd, UK)

As the 5 mg and 10 mg strength test products meet the biowaiver criteria specified in the current bioequivalence guidance, the results and conclusions of the bioequivalence study with the 10 mg tablet strength can be extrapolated to the 5 mg strength tablets.

IV.3 Pharmacodynamics
No new pharmacodynamic data were submitted and none were required for applications of this type.

IV.4 Clinical efficacy
No new efficacy data were submitted, and none were required for applications of this type.

IV.5 Clinical safety
No new safety data were submitted and none are required.

IV.6 Risk Management Plan (RMP) and Pharmacovigilance System
The MAH has submitted a risk management plan, in accordance with the requirements of Directive 2001/83/EC as amended.

There are no differences from the reference product in terms of proposed uses, maximum pack size / strength or pharmaceutical form / formulation that would have any implications for safety.

In line with the reference product, the applicant proposes only routine pharmacovigilance and routine risk minimisation measures for all safety concerns (labelling in the SmPC and the PIL). This is agreed.

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:
- At the request of the RMS;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time, but via different procedures.

IV.7 Discussion on the clinical aspects
The grant of marketing authorisations is recommended for these applications from a clinical viewpoint.

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 English.

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.

VI Overall conclusion, benefit/risk assessment and recommendation
The quality of the products is acceptable, and no new non-clinical or clinical safety concerns have been identified. Extensive clinical experience with solifenacin succinate is considered to have demonstrated the therapeutic value of the compound. The products are bioequivalent to the marketed reference products and their risks and benefits are considered similar. The benefit-risk is, therefore, considered to be positive.
Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and Labels

In accordance with Directive 2010/84/EU the Summaries of Product Characteristics (SmPCs) and Patient Information Leaflets (PILs) for products granted Marketing Authorisations at a national level are available on the MHRA website.

The approved labelling for this medicine is presented below:
PAR Solifenacin succinate 5 mg and 10 mg film-coated tablets

UK/H/6830/001-002/DC

Marketing Authorisation Holder:
Tillotson Laboratories Ltd
229 Butterfield, Great Marlings
Luton, LU2 9DL, UK
PL 11311/0591
Code No. TS/DEUCS/5/2014

Braille:
solifenacin succinate
#5 mg
film-coated tablets
PAR Solifenacin succinate 5 mg and 10 mg film-coated tablets

UK/H/6830/001-002/DC
Braille:
solifenacin
succinate
#10 mg
film-coated
tablets
Annex 1

Table of content of the PAR update for MRP and DCP
Steps taken after the initial procedure with an influence on the Public Assessment Report (Type II variations, PSURs, commitments)

<table>
<thead>
<tr>
<th>Scope</th>
<th>Procedure number</th>
<th>Product information affected</th>
<th>Date of start of the procedure</th>
<th>Date of end of procedure</th>
<th>Approval/ non approval</th>
<th>Assessment report attached Y/N (version)</th>
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