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/6103/001-2/DC

UK Licence Number: PL 17907/0542-543

Bristol Laboratories Ltd.
LAY SUMMARY

Solifenacin succinate 5 mg film-coated tablets
Solifenacin succinate 10 mg film-coated tablets
(Solifenacin succinate, film-coated tablet, 5 mg and 10 mg)

This is a summary of the Public Assessment Report (PAR) for Solifenacin succinate 5 mg film-coated tablets (PL 17907/0542; UK/H/6103/001/DC) and Solifenacin succinate 10 mg film-coated tablets (PL 17907/0543; UK/H/6103/002/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 Solifenacin succinate 5 mg and 10 mg film-coated tablets.

The products will be collectively referred to as Solifenacin succinate tablets throughout the remainder of this public assessment report (PAR).

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

What are Solifenacin succinate tablets and what are they used for?
Solifenacin succinate tablets are a ‘generic medicine’. This means that Solifenacin succinate tablets are similar to a ‘reference medicine’ already authorised in the European Union (EU) called Vesicare 5 mg and 10 mg filmomhulde tabletten (Astellas Pharma Europe B.V, The Netherlands).

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 the patient wetting themselves because they could not get to the bathroom in time.

How does Solifenacin succinate tablets work?
The active substance in this medicine is solifenacin succinate which belongs to the 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 is Solifenacin succinate tablets used?
The pharmaceutical form of this medicine is a film-coated tablet, and the route of administration is oral (by mouth).

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

The patient should swallow the tablet whole with some liquid. Do not crush the tablets.

The recommended dose is 5 mg per day, unless the patient’s doctor has told them 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 tablets are used, refer to the package leaflet and Summary of Product Characteristics available on the Medicines and Healthcare products Regulatory
This medicine can only be obtained with a prescription.

**What benefits of Solifenacin succinate tablets have been shown in studies?**
Because Solifenacin succinate tablets is a generic medicine, studies in patients have been limited to tests to determine that it is bioequivalent to the reference medicine Vesicare 5 mg and 10 mg filmomhulde tabletten (Astellas Pharma Europe B.V, The Netherlands). Two medicines are bioequivalent when they produce the same levels of the active substance in the body.

**What are the possible side effects of Solifenacin succinate tablets?**
Because Solifenacin succinate tablets is a generic medicine and is bioequivalent to the reference medicine Vesicare 5 mg and 10 mg filmomhulde tabletten (Astellas Pharma Europe B.V, The Netherlands), its benefits and possible side effects are taken as being the same as the reference medicine.

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

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

**Why was Solifenacin succinate tablets approved?**
It was concluded that, in accordance with EU requirements, Solifenacin succinate tablets have been shown to have comparable quality and to be bioequivalent to Vesicare 5 mg and 10 mg filmomhulde tabletten (Astellas Pharma Europe B.V, The Netherlands). Therefore, the MHRA decided that, as for Vesicare 5 mg and 10 mg filmomhulde tabletten (Astellas Pharma Europe B.V, The Netherlands); 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 tablets?**
A risk management plan (RMP) has been developed to ensure that Solifenacin succinate tablets are used as safely as possible. Based on this plan, safety information has been included in the Summaries of Product Characteristics (SmPCs) and the package leaflet for Solifenacin succinate 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 tablets**
Germany and the UK agreed to grant Marketing Authorisations for Solifenacin succinate tablets on 16 September 2016. Marketing Authorisations were granted in the UK on 22 September 2016.

The full PAR for Solifenacin succinate tablets follows this summary.

For more information about treatment with Solifenacin succinate tablets, read the package leaflet, or contact your doctor or pharmacist.

This summary was last updated in November 2016.
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I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the Medicines and Healthcare products Regulatory Agency (MHRA) granted Bristol Laboratories Ltd, marketing authorisations for the medicinal product Solifenacin succinate tablets (PL 17907/0542-0543; UK/H/6103/001-2/DC) The product is a prescription-only medicine (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 as Concerned Member State (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 filmomhulde tabletten (licence numbers: RVG 29151 and RVG 29152) which were first authorised in The Netherlands to Astellas Pharma Europe B.V on 16 December 2003. The equivalent UK reference products are Vesicare 5mg and 10mg film-coated tablets (PL 00166/0197-198). The reference product used for the bioequivalence study has been taken from the French market (Vesicare 10 mg, comprime pellicule; Astellas Pharma S.A.S, France). It has been confirmed that the reference products are equivalent. This is acceptable.

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 was conducted in accordance with the rules for Good Clinical Practice (GCP), including International Conference on Harmonisation (ICH) Guidelines, Directive 2001/20/EC of the European Parliament and the most recent version of the declaration of Helsinki.

With the exception of the bioequivalence study, no new non-clinical or clinical data were submitted, which is acceptable given that the applications were based on being a generic medicinal product of an originator product that has been in clinical use for over 10 years.

The RMS has been assured that acceptable standards of Good Manufacturing Practice (GMP) 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 of 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 16 September 2016. After a subsequent national phase, licences were granted in the UK on 22 September
2016.
II QUALITY ASPECTS

II.1 Introduction
Each film-coated tablet contains 5 mg solifenacin succinate, corresponding to 3.8 mg solifenacin or 10 mg solifenacin succinate, corresponding to 7.5 mg solifenacin as the active ingredient. Other ingredients consist of the pharmaceutical excipients:

**Tablet core:**
Lactose monohydrate, maize starch, pregelatinised starch and magnesium stearate

**Film-coating:**
Hypromellose, titanium dioxide (E171), macrogol 8000, talc and iron oxide yellow (E172). The 5 mg tablet strength also contains iron oxide red (E172).

All strengths of the finished product are packaged in transparent PVC/PE/PVDC/aluminium blisters or aluminium/aluminium blister packs and are available in pack sizes of 3, 5, 10, 20, 30, 50, 60, 90, 100 or 200 tablets film-coated tablets. Not all pack sizes may be marketed.

Satisfactory specifications and Certificates of Analysis have been provided for all packaging components.

II.2 Drug Substance

1. **Solifenacin succinate**

   **INN:** Solifenacin succinate  
   **Chemical name:** (3R)-1-azabicyclo[2.2.2]oct-3-yl-(1S)-1-phenyl-3,4-dihydro-1H-isoquinoline-2-carboxylate monosuccinate.

   **Structure:**

   ![Solifenacin Succinate Structure](image)

   **Molecular formula:** C_{23}H_{26}N_{2}O_{2} . C_{4}H_{6}O_{4}  
   **Molecular weight:** 480.55 g/mol  
   **Description:** White to pale-yellowish white crystal or crystalline powder.  
   **Solubility:** Freely soluble in water and methanol

   Solifenacin succinate was not the subject of a European Pharmacopoeia monograph at the time of assessment.

   Synthesis of the active substance from the designated starting materials has been adequately described and appropriate in-process controls and intermediate specifications are applied. Satisfactory specification tests are in place for all starting materials and reagents, and these are supported by relevant Certificates of Analysis.

   Appropriate proof-of-structure data have been supplied for the active substance. All potential known impurities have been identified and characterised.
An appropriate specification is provided for the active substance. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications.

Batch analyses data are provided that comply with the proposed specification.

Satisfactory Certificates of Analysis have been provided for all working standards used.

Suitable specifications have been provided for all packaging used. The primary packaging has been shown to comply with current guidelines concerning contact with food.

Appropriate stability data have been generated supporting a suitable retest period when stored in the proposed packaging.

II.3. Medicinal Product
Pharmaceutical Development

The objective of the development programme was to formulate safe, efficacious film-coated tablets containing 5 mg solifenacin succinate, corresponding to 3.8 mg solifenacin or 10 mg solifenacin succinate, corresponding to 7.5 mg solifenacin per tablet, that are generic versions of the reference product Vesicare 5 mg and 10 mg filmomhulde tabletten (Astellas Pharma Europe B.V, The Netherlands). A satisfactory account of the pharmaceutical development has been provided.

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

All excipients comply with their respective European Pharmacopoeia monographs with the exception of the film coatings which are controlled to suitable in-house specifications. 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.

No genetically modified organisms (GMO) have been used in the preparation of this product.

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 specifications proposed are acceptable. Test methods have been described that have been adequately validated. Batch data have been provided that comply with the release specifications. 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 product in the packaging proposed for marketing. The data from these studies support a shelf-life of 36 months with no 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
Not applicable for this product type. Refer to section ‘III.1; Introduction’ detailed above.

III.5  Ecotoxicity/environmental risk assessment (ERA)
Since Solifenacin succinate 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 tablets can be considered bioequivalent to Vesicare 10 mg, comprime pellicule (Astellas Pharma S.A.S, France).

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

STUDY
A randomized, open label, two sequence, two treatment, two period, single dose, truncated, crossover, bioequivalence study of the applicant’s test product Solifenacin succinate 10 mg film-coated tablets (Bristol Laboratories Ltd) versus the reference product Vesicare 10 mg, comprime pellicule (Astellas Pharma S.A.S, France) in healthy, adult, subjects under fasting conditions.

Following an overnight fast of at least 10 hours, subjects were administered a single dose (1 x 10 mg tablet) of the test or the reference product with 240 mL of water.
Blood samples were collected for plasma levels before dosing and up to and including 72 hours after each administration. The washout period between the treatment phases was 20 days. The pharmacokinetic results are presented below:

**Table: Summary of Pharmacokinetic data for solifenacin (geometric means, % ratio and 90% confidence interval):**

<table>
<thead>
<tr>
<th>Parameters</th>
<th>*Geometric mean</th>
<th>% Ratio</th>
<th>90% Confidence Interval for Log-transformed data</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC₀-₇₂</td>
<td>Test (A)</td>
<td>Reference (B)</td>
<td>A/B</td>
</tr>
<tr>
<td></td>
<td>856.79</td>
<td>795.50</td>
<td>107.7043</td>
</tr>
<tr>
<td>C_max</td>
<td>21.97</td>
<td>20.29</td>
<td>108.2532</td>
</tr>
</tbody>
</table>

*Geometric mean was taken as the antilog (exponential) of the Least square mean of the log-transformed data.

**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 (Bristol Laboratories Ltd) is bioequivalent to the reference product Vesicare 10 mg, comprime pellicule (Astellas Pharma S.A.S, France).

**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 marketing authorisation holder (MAH) has submitted a risk management plan (RMP), 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 Solifenacin succinate tablets.

A summary of safety concerns and planned risk minimisation activities, as approved in the RMP, are listed below:
Summary table of safety concerns:

<table>
<thead>
<tr>
<th>Summary of safety concerns</th>
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<tbody>
<tr>
<td>Important identified risks</td>
<td>• Hypersensitivity reactions, including anaphylactic reaction, angioedema, erythema multiforme, exfoliative dermatitis</td>
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<td></td>
<td>• Urinary retention</td>
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<td></td>
<td>• Glaucoma</td>
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<td></td>
<td>• QTc prolongation, torsades de pointes</td>
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<td></td>
<td>• Ileus</td>
</tr>
<tr>
<td>Important potential risks</td>
<td>• None</td>
</tr>
<tr>
<td>Missing information</td>
<td>• None</td>
</tr>
</tbody>
</table>

Routine pharmacovigilance and routine risk minimisation are proposed for all safety concerns

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

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 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 (SmPC) and Patient Information Leaflets (PIL) 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/6103/001-2/DC
Solifenacin succinate 5 mg and 10 mg film-coated tablets