Public Assessment Report

UK PAR

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

UK Licence Nos: PL 39352/0434-35

Kosei Pharma UK Limited
LAY SUMMARY
Solifenacin succinate 5 and 10 mg film-coated tablets
(Solifenacin succinate)

This is a summary of the Public Assessment Report (PAR) for Solifenacin succinate 5 and 10 mg film-coated tablets (PL 39352/0434-35). It explains how Solifenacin succinate 5 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 may be collectively referred to as Solifenacin tablets in this lay summary.

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

What are Solifenacin tablets and what are they used for?
Solifenacin tablets are ‘generic medicines’. This means that Solifenacin tablets are similar to ‘reference medicines’ already authorised in the UK called Vesicar 5 mg and 10 mg film-coated tablets (PL 00166/0197; Astellas Pharma Limited, UK).

Solifenacin tablets are 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 do Solifenacin tablets work?
The active substance in Solifenacin tablets is solifenacin (as 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 are Solifenacin tablets used?
The pharmaceutical form of these medicines is a film-coated tablet, and the route of administration is oral (by mouth).

The patient should always take this medicine exactly as the doctor or pharmacist has advised and check with his/her doctor or pharmacist if not sure.

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

The recommended dose is 5 mg per day, unless the patient’s doctor has advised the patient to take 10 mg per day. The 10 mg tablet can be divided into equal doses.

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 tablets are used, refer to the package leaflet available on the Medicines and Healthcare products Regulatory Agency (MHRA) website.

These medicines can only be obtained with a prescription.
What benefits of Solifenacin tablets have been shown in studies?
As Solifenacin tablets are generic medicines, studies have been limited to tests to determine that Solifenacin tablets are bioequivalent to the reference medicines Vesicare 5 mg and 10 mg film-coated tablets. 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 tablets?
Because Solifenacin tablets are generic medicines and are bioequivalent to the reference medicines Vesicare 5 mg and 10 mg film-coated tablets, the benefits and possible side effects are taken as being the same as for the respective medicines.

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

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

Why were Solifenacin tablets approved?
It was concluded that, in accordance with EU requirements, Solifenacin tablets have been shown to have comparable quality and to be bioequivalent to Vesicare 5 mg and 10 mg film-coated tablets. Therefore, the MHRA decided that, as for Vesicare 5 mg and 10 mg film-coated tablets, the benefits are greater than the risks and recommended that it can be approved for use.

What measures are being taken to ensure the safe and effective use of Solifenacin tablets?
A Risk Management Plan (RMP) has been developed to ensure that Solifenacin 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 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 tablets
Marketing Authorisations were granted in the UK to Kosei Pharma UK Limited on 11 February 2019.

The full PAR for Solifenacin tablets follows this summary.

This summary was last updated in March 2019.
SCIENTIFIC DISCUSSION

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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 Kosei Pharma UK Limited Marketing Authorisations for the medicinal products Solifenacin succinate 5 mg and 10 mg film-coated tablets (PL 39352/0434-35) on 11 February 2019. The products 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 products will be referred to as ‘Solifenacin tablets’ in this scientific discussion.

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 (PL 00166/0197-98; Astellas Pharma Limited, UK), which were first authorised in the UK on 16 August 2004 via an in-coming Mutual Recognition procedure (NL/H/0487/001-002) with the Netherlands as Reference Member State (RMS) and the UK as one of the Concerned Member States (CMS).

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.

A bioequivalence study was submitted to support these applications, comparing the applicant’s test product Solifenacin Súccinate 10 mg film coated tablets with the reference product Vesicare (solifenacin succinate) 10 mg film coated tablets (Astellas Pharma S.A.S, France), under fasting conditions. The applicant has stated that the bioequivalence study was conducted in accordance with current Good Clinical Practice guidelines.

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

A summary of the pharmacovigilance system and a detailed Risk Management Plan (RMP) have been provided with this application, and these are satisfactory.

The MHRA 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 and assembly of these products.

No new or unexpected safety concerns arose during the review of information provided by the Marketing Authorisation Holder and it was, therefore, judged that the benefits of taking Solifenacin tablets outweigh the risks and Marketing Authorisations were granted.
II QUALITY ASPECTS

II.1 Introduction
The submitted documentation concerning the proposed product is of sufficient quality and meets the current EU regulatory requirements.

The quality overall summary has been written by an appropriately qualified person and is a suitable summary of the pharmaceutical aspects of the dossier.

The 5 mg strength tablet is a light yellow, round biconvex film-coated tablet.

The 10 mg strength tablet is a light pink, biconvex film coated tablet with score line on one side and plain on the other.

Each film-coated tablet contains 5 mg or 10 mg of solifenacin succinate (corresponding to 3.8 mg or 7.5 mg of solifenacin) as the active substance. The tablets also contain pharmaceutical excipients lactose monohydrate, maize starch, starch (maize) partially pre-gelatinised, magnesium stearate, purified water making up the tablet core. The coating is composed of hypromellose 5cp, titanium dioxide (E171), macrogol 8000, talc, yellow iron oxide (E172), red iron oxide (E172; 10 mg formulation only) and purified water.

With the exception of iron yellow oxide (E172) and red ferric oxide (E172), which are controlled to their respective in-house specifications, all excipients comply with their respective European Pharmacopoeia monographs. 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 the milk used in the production of lactose monohydrate is sourced from healthy animals under the same conditions as that intended for human consumption. In addition, the supplier has confirmed that no ruminant material, other than calf rennet, is used during the production of lactose monohydrate. Confirmation has also been given that the magnesium stearate used in the tablets is of vegetable origin.

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

Solifenacin tablets are packaged in polyvinylchloride/polyethylene/polyvinylidene (PVC/PE/PVdC) aluminium/aluminium blisters in pack sizes of 3, 5, 10, 20, 30, 50, 60, 90, 100 or 200 film-coated 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 current European regulations concerning materials in contact with foodstuff.

II.2 Drug Substance
Solifenacin succinate
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

Structure:
Molecular formula: \( \text{C}_{23}\text{H}_{26}\text{N}_{2}\text{O}_{2} \cdot \text{C}_{4}\text{H}_{6}\text{O}_{4} \)
Molecular weight: 480.6 g/mol
Description: White or light yellow powder.
Solubility: Very soluble or freely soluble in water, soluble in ethanol (96 per cent), practically insoluble in heptane.

Solifenacin succinate is the subject of a European Pharmacopoeia monograph.

All aspects of the manufacture and control of the active substance, solifenacin succinate, are covered by European Directorate for the Quality of Medicines and Healthcare (EDQM) Certificates of Suitability.

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 corresponding to 3.8 mg or 7.5 mg solifenacin per tablet, which were generic versions of the reference products Vesicare 5 mg and 10 mg film-coated tablets (Astellas Pharma Limited, UK). Suitable pharmaceutical development data have been provided for these applications.

Comparative in-vitro dissolution profiles have been provided for the proposed and reference products. The dissolution profiles were satisfactory.

Manufacture of the products
Satisfactory batch formulae have been provided for the manufacture of each strength of the product, along with an appropriate account of the manufacturing processes. The manufacturing processes have been validated with full-scale production batches and have shown satisfactory results.

Control of Finished Products
The proposed finished product specifications are acceptable. The test methods have been described that have been adequately validated. Batch data that comply with the release specifications have been provided. Certificates of Analysis have been provided for all working standards used.

Stability of the Products
Finished product stability studies were performed in accordance with current guidelines on batches of finished product in the packaging proposed for marketing. Based on the results, a shelf-life of 3 years with no special storage instructions has been accepted.

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 point of view.
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 of solifenacin succinate.

III.2 Pharmacology
No new data have been submitted and none are required for applications of this type. Refer to Section III.1, Introduction, above.

III.3 Pharmacokinetics
No new data have been submitted and none are required for applications of this type. Refer to Section III.1, Introduction, above.

III.4 Toxicology
No new data have been submitted and none are required for applications of this type. Refer to Section III.1, Introduction, above.

III.5 Ecotoxicity/Environmental Risk Assessment (ERA)
The Marketing Authorisation Holder has provided adequate justification for not submitting an Environment Risk Assessment (ERA). As the applications are for generic versions of already authorised products, it is not expected that environmental exposure to solifenacin succinate will increase following approval of the Marketing Authorisations for the proposed products. 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, safety and efficacy of solifenacin succinate are well-known.

The applicant’s clinical overview has been written by an appropriately qualified person and is considered acceptable.

With the exception of data from the bioequivalence study detailed below, no new clinical data is provided or required for these applications.

IV.2 Pharmacokinetics
In support of the application, the applicant submitted the following bioequivalence study.

An open-label, randomised, two-sequence, two-treatment, two-period, single-dose, truncated, crossover, bioequivalence study comparing the test product Solifenacin Succinate 10 mg film coated tablets versus the reference product Vesicare (solifenacin succinate) 10 mg film coated tablets (Astellas Pharma S.A.S, France) in healthy adult subjects under fasting conditions.
Solifenacin succinate 5 mg and 10 mg film-coated tablets

Subjects were administered a single oral dose of either the test product or reference product with 240 ml of water after a 10-hour overnight fast. Blood sampling was performed pre-dose and up to 72 hours post dose in each treatment period. A washout period of 7 days was kept between each consecutive dosing period. The pharmacokinetic results are presented below:

**Table of Geometric Means, %Ratio and 90% Confidence Interval for Solifenacin (22)**

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Test (A)</th>
<th>Reference (B)</th>
<th>A/B</th>
<th>Lower Limit</th>
<th>Upper Limit</th>
</tr>
</thead>
<tbody>
<tr>
<td>C\text{max}</td>
<td>21.97</td>
<td>20.29</td>
<td>108.2532</td>
<td>102.1395</td>
<td>114.7328</td>
</tr>
<tr>
<td>AUC\text{0-72}</td>
<td>856.79</td>
<td>795.50</td>
<td>107.7043</td>
<td>101.6658</td>
<td>114.1013</td>
</tr>
</tbody>
</table>

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

C\text{max}  maximum plasma concentration

AUC\text{0-72}  area under the plasma concentration-time curve from time zero to 72 hours

**Bioequivalence Discussion and Conclusion**

The *Guideline on the Investigation of Bioequivalence* (CPMP/EWP/QWP/1401/98 Rev. 1/Corr*) defines the confidence limits for ratio of geometric means for acceptance of bioequivalence as 80.00% to 125.00% for C\text{max} and AUC\text{0-72} values. Thus, the results support the claim that applicant’s 10 mg strength product is bioequivalent to the reference product Vesicare (solifenacin succinate) 10 mg film coated tablets (Astellas Pharma S.A.S, France), under fasting conditions.

The justification for biowaiver for the 5 mg strength product can be accepted as the applicant’s 5 mg and 10 mg strength tablets meet the biowaiver criteria specified in the *Guideline on the Investigation of Bioequivalence* (CPMP/EWP/QWP/1401/98 Rev 1/Corr**).

**IV.3 Pharmacodynamics**

The clinical pharmacodynamic profile of a solifenacin succinate is well-known. No new pharmacodynamic data were submitted and none are required for applications of this type.

**IV.4 Clinical efficacy**

With the exception of the bioequivalence study, no new data were submitted, and none are required for applications of this type.

**IV.5 Clinical safety**

The safety profile of solifenacin succinate is well known. With the exception of the safety data from the bioequivalence study, no new data were submitted and none were required for applications of this type. No new or unexpected safety concerns arose from the bioequivalence study.

**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, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Solifenacin tablets.
A summary of safety concerns is listed in the table below:

<table>
<thead>
<tr>
<th>Important identified risks</th>
<th>Important potential risks</th>
<th>Missing Information</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inability to empty the bladder (Urinary retention)</td>
<td>Use of solifenacin in infants and children whether exposed to solifenacin directly or exposed via breast-feeding</td>
<td>Use in pregnancy</td>
</tr>
<tr>
<td>Allergic reactions (Hypersensitivity)</td>
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<td>Cardiac rhythm disorders (Cardiac rhythm disorders)</td>
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<tr>
<td>Eye diseases which result in damage to the optic nerve and vision loss (Glaucoma)</td>
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<td>Bowel obstruction (Ileus)</td>
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Routine pharmacovigilance and routine risk minimisation activities are acceptable to monitor the safety concerns described in the Risk Management Plan.

**IV.7 Discussion on the clinical aspects**
It is recommended that Marketing Authorisations are granted for Solifenacin tablets, from a clinical point of view.

**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 package leaflet 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 product 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 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 Solifenacin succinate 5 and 10 mg film-coated tablets is presented below:
Table of content of the PAR update

Steps taken after the initial procedure with an influence on the Public Assessment Report (Type II variations, PSURs, commitment)

<table>
<thead>
<tr>
<th>Date submitted</th>
<th>Application type</th>
<th>Scope</th>
<th>Outcome</th>
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