Medicines & Healthcare products
Regulatory Agency

Public Assessment Report

National Procedure

Solifenacin succinate 5 mg Film-coated Tablets
Solifenacin succinate 10 mg Film-coated Tablets

solifenacin succinate

PL 20117/0395-0396

Morningside Healthcare Ltd.

LAY SUMMARY
Solifenacin succinate 5 mg and 10 mg Film-coated Tablets
solifenacin succinate

This is a summary of the Public Assessment Report (PAR) for Solifenacin succinate 5 mg and 10 mg Film-coated Tablets. It explains how these products 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.

These products will be referred to as Solifenacin succinate tablets in this lay summary for ease of reading.

For practical information about using Solifenacin succinate tablets, patients should read the Patient Information Leaflet (PIL) or contact their doctor or pharmacist.

What are Solifenacin succinate tablets and what are they used for?
These products are generic medicines. This means that these medicines are the same as, and considered interchangeable with, a reference medicines already authorised, called Vesicare 5 mg and 10 mg film-coated tablets.

Solifenacin succinate tablets are used to reduce the activity of an overactive bladder.
Solifenacin succinate tablets are used to treat the symptoms of a condition called overactive bladder. These symptoms of an overactive bladder are strong, sudden urge to urinate without prior warning, having to urinate frequently or wetting yourself because you could not get to the bathroom in time.

How do Solifenacin succinate tablets work?
Solifenacin succinate tablet belongs to the group of anticholinergics. These medicines are used to reduce the activity of an overactive bladder. By relaxing the muscles in the bladder, solifenacin improves the ability to control urination. This enables the patient to wait longer before having to go to the bathroom and increases the amount of urine that the bladder can hold.

How are Solifenacin succinate tablets used?
The pharmaceutical form of these medicines is a film-coated tablet, and the route of administration is oral (by mouth).

The recommended dose is 5 mg solifenacin succinate once daily, unless the patient's doctor told the patient to take 10 mg per day.

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

These medicines can only be obtained with a prescription.

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

What benefits of Solifenacin succinate tablets have been shown in studies?

Because Solifenacin succinate tablets are generic medicines, studies in healthy volunteers have been limited to tests to determine that it is bioequivalent to the reference medicine. 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?
For the full list of all side effects reported with these medicines, see Section 4 of the PIL or the SmPCs available on the MHRA website.

If a patient gets any side effects, they should talk to their doctor, pharmacist or nurse. This includes any possible side effects not listed in the product information or the PIL that comes with the medicine. Patients can also report suspected side effects themselves, or a report can be made on their behalf by someone else who cares for them, directly via the Yellow Card scheme at https://yellowcard.mhra.gov.uk or search for 'MHRA Yellow Card' online. By reporting side effects, patients can help provide more information on the safety of this medicine.

Because Solifenacin succinate tablets are generic medicines and are bioequivalent to the reference medicines, its benefits and possible side effects are considered to be the same as the reference medicines.

Why were Solifenacin succinate tablets approved?
It was concluded that, Solifenacin succinate tablets has been shown to be bioequivalent to the reference medicine. Therefore, the MHRA decided that, as for the reference medicine, 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 succinate tablets?
As for all newly-authorised medicines, a Risk Management Plan (RMP) has been developed for Solifenacin succinate tablets. The RMP details the important risks of Solifenacin succinate tablets, how these risks can be minimised, any uncertainties about Solifenacin succinate tablets (missing information), and how more information will be obtained about the important risks and uncertainties.

The following safety concerns have been recognised for Solifenacin succinate tablets:

Summary of safety concerns*	
Important identified risks	• Hypersensitivity reactions, including anaphylactic reaction and angioedema • Urinary retention • Cardiac rhythm disorders • Glaucoma • Ileus
Important potential risks	• None
Missing information	• Use during pregnancy • Use of solifenacin in infants and children either exposed to solifenacin directly or exposed via breast-feeding

The information included in the SmPC and the PIL is compiled based on the available quality, non-clinical and clinical data, and includes appropriate precautions to be followed by healthcare professionals and patients. Side effects of Solifenacin succinate tablets are continuously monitored and reviewed including all reports of suspected side-effects from patients, their carers, and healthcare professionals.

An RMP and a summary of the pharmacovigilance system have been provided with these applications and are satisfactory.

Other information about Solifenacin succinate tablets
Marketing authorisations for Solifenacin succinate tablets were granted in the United Kingdom (UK) on 28 March 2022.

The full PAR for Solifenacin succinate tablets follows this summary.

This summary was last updated in May 2024.

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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) considered that the applications for Solifenacin succinate 5 mg and 10 mg Film-coated Tablets (PL 20117/0395-0396) could be approved.

The products are approved for the following indications:
Symptomatic treatment of urge incontinence and/or increased urinary frequency and urgency as may occur in patients with overactive bladder syndrome.

The name of the active substance is solifenacin succinate which belongs to the group of anticholinergics, a competitive, specific cholinergic receptor antagonist.

Mechanism of action

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.

These application(s) was/were approved under Regulation 51B of The Human Medicines Regulation 2012, as amended (previously Article 10(1) of Directive 2001/83/EC, as amended), as a generic medicines of a suitable originator medicinal products, Vesicare 5 mg and 10 mg film-coated tablets that has been licensed for a suitable time, in line with the legal requirements.

No new non-clinical studies were conducted, which is acceptable given that the applications are for a generic medicinal products of a suitable reference products.

With the exception of the bioequivalence study, no new clinical studies were conducted, which is acceptable given that the applications are for generic medicinal products of a suitable reference products. The bioequivalence study was conducted in-line with current Good Clinical Practice (GCP).

The MHRA has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place for these products at all sites responsible for the manufacture, assembly and batch release of these products.

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

Marketing authorisations for Solifenacin succinate tablets were granted in the United Kingdom (UK) on 28 March 2022.

II QUALITY ASPECTS

II.1 Introduction

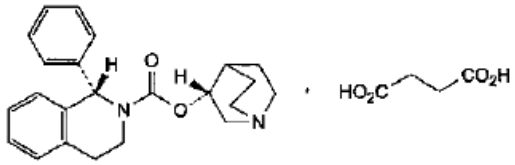
These products consist of tablets; each 5mg tablet contains 5 mg of solifenacin succinate, equivalent to 3.8 mg of solifenacin, and each 10 mg tablet contains 10 mg of solifenacin succinate, equivalent to 7.5 mg of solifenacin.
In addition to solifenacin succinate, these products also contain the excipients maize starch, lactose monohydrate, hypromellose, magnesium stearate, talc, titanium dioxide, macrogol, and iron oxide yellow.

The finished products are packaged in PVC/PVDC-Alu blister packs of 3, 5, 10, 20, 30, 50, 60, 90 and 100 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 regulations concerning materials in contact with food.

II.2 ACTIVE SUBSTANCE

rINN: solifenacin succinate
Chemical Name:
3*R*)-1-Azabicyclo[2.2.2]octan-3-yl (1*S*)-1-phenyl-3,4-dihydroisoquinoline-2(1*H*)-carboxylate hydrogen butanedioate
Molecular Formula: $C_{27}H_{32}N_2O_6$
Chemical Structure:



Molecular Weight: 480.6
Appearance: 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 are covered by a European Directorate for the Quality of Medicines and Healthcare (EDQM) Certificate of Suitability.

Suitable specifications have been provided for all packaging used. The primary packaging complies with the current regulations concerning materials in contact with food.

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

II.3 DRUG PRODUCTS

Pharmaceutical development
A satisfactory account of the pharmaceutical development was provided.

Comparative *in vitro* dissolution and impurity profiles were provided for the proposed and reference products.

All excipients comply with either their respective European/national monographs, or a suitable in-house specification. Satisfactory Certificates of Analysis were provided for all excipients.

With the exception of lactose monohydrate, no excipients of animal or human origin are used in the final products.

Confirmation has been given that the magnesium stearate used in the tablets is of vegetable origin.

These products do not contain or consist of genetically modified organisms (GMOs).

Manufacture of the products
A description and flow-chart of the manufacturing method has been provided.

Satisfactory batch formulation data have been provided for the manufacture of the products, along with an appropriate account of the manufacturing process. The manufacturing process has been validated and has shown satisfactory results.

Finished Product Specifications
The finished product specifications at release and shelf-life are satisfactory. The test methods have been described and adequately validated. Batch data have been provided that comply with the release specifications. Certificates of Analysis have been provided for any working standards used.

Stability
Finished product stability studies have been conducted in accordance with current guidelines, using batches of the finished product stored in the packaging proposed for marketing. Based on the results, a shelf-life of 3 years with no special the storage conditions required, is acceptable.

II.4 Discussion on chemical, pharmaceutical and biological aspects
The grant of marketing authorisations was recommended.

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.

III.2 Pharmacology
No new pharmacology data were provided, and none were required for these applications.

III.3 Pharmacokinetics
No new pharmacokinetic data were provided, and none were required for these applications.

III.4 Toxicology
No new toxicology data were provided, and none were required for these applications.

III.5 Ecotoxicity/Environmental Risk Assessment

A suitable justification was provided for non-submission of an Environmental Risk Assessment. As the applications are for generic versions of an already authorised products, an increase in environmental exposure is not anticipated following approval of the marketing authorisations for the proposed products.

III.6 Discussion on the non-clinical aspects

The grant of marketing authorisations was recommended.

IV CLINICAL ASPECTS

IV.1 Introduction

The clinical pharmacology, efficacy and safety of solifenacin succinate are well-known. With the exception of data from one bioequivalence study, no new clinical data are provided or are required for this type of application. An overview based on a literature review and a review of this study is, thus, satisfactory.

IV. 2 Pharmacokinetics

In support of the application, the applicant submitted the following BIOEQUIVALENCE STUDY 150301.

This study was a single oral dose open label, balanced, randomized two-treatment, two-period, two sequence, cross over study comparing the test product Solifenacin succinate 10 mg Film-coated tablets versus the reference product Vesicare 10 mg Film-Coated Tablets in subjects under fasted conditions.

Subjects were administered a single oral dose (10 mg) of test/reference product. Blood samples were taken pre-dose and up to 72 hours post dose, with a washout period of 35 days between the treatment periods.

A summary of the pharmacokinetic results is presented below:

Pharmacokinetic data for solifenacin and bioequivalence evaluation of solifenacin calculated 90 %-confidence intervals, geometric mean ratios (Test/Reference) and CVres (%).

PARAMETER	TEST (n=62)[b]		REFERENCE (n=62)[b]	
	MEAN	C.V. (%)	MEAN	C.V. (%)
C_{max} (pg/mL)	17612.40	(20.4)	18280.98	(23.9)
ln (C_{max})	9.7550	(2.2)	9.7850	(2.5)
T_{max} (hours)[a]	5.50	(3.00-8.00)	5.75	(3.50-8.00)
AUC_{0-72} (pg·h/mL)	607719.90	(22.9)	627639.33	(24.4)
ln (AUC_{0-72})	13.2903	(1.8)	13.3193	(1.9)
$AUC_{0-\infty}$ (pg·h/mL)	996857.73	(47.5)	979169.83	(40.2)
Residual area (%)	34.51	(34.9)	32.64	(33.8)
λ_Z (hours^{-1})	0.0157	(32.9)	0.0164	(28.8)
T_{half} (hours)	51.15	(56.4)	46.87	(37.6)

[a] Median and range are presented

[b] n=61 for $AUC_{0-\infty}$, residual area, λ_Z, and T_{half}

PARAMETER	INTRA-SUBJECT C.V. (%)	GEOMETRIC LSMEANS[a]		RATIO (%)	90% CONFIDENCE LIMITS (%)	
		TEST (n=62)	REFERENCE (n=62)		LOWER	UPPER
C_{max}	11.9	17224.00	17768.46	96.94	93.55	100.45
AUC_{0-72}	11.4	591062.01	609051.43	97.05	93.79	100.42

[a] units are pg/mL for C_{max} and pg·h/mL for AUC_{0-72}

In accordance with the regulatory requirements, the Test/Reference ratios and their 90% confidence intervals were within the specified limits to show bioequivalence between the test product and the reference product.

As the additional Solifenacin succinate 5 mg strength of the product meet the biowaiver criteria specified in the current bioequivalence guideline, the results and conclusions from the bioequivalence study on the product strength can be extrapolated to the other strengths.

IV.3 Pharmacodynamics

No new pharmacodynamic data were submitted for these applications and none were required.

IV.4 Clinical efficacy

No new efficacy data were submitted with these applications, and none were required.

IV.5 Clinical safety

With the exception of the safety data submitted with the bioequivalence study, no new safety data were submitted with these applications.

The safety data from the bioequivalence study showed that the test and reference products were equally well tolerated. No new or unexpected safety issues were raised from the bioequivalence study.

IV.6 Risk Management Plan (RMP)

The applicant has submitted an RMP, in accordance with the requirements of Regulation 182 of The Human Medicines Regulation 2012, as amended. The applicant proposes only routine pharmacovigilance and routine risk minimisation measures for all safety concerns. This is acceptable.

IV.7 Discussion on the clinical aspects

The grant of marketing authorisations was recommended for these applications.

V USER CONSULTATION

A full colour mock-up of the Patient Information Leaflet (PIL) was provided with the application in accordance with legal requirements, including user consultation.

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.

The Summary of Product Characteristics (SmPCs), Patient Information Leaflet (PIL) and labelling are satisfactory, in line with current guidelines and consistent with the reference products.

In accordance with legal requirements, the current approved UK versions of the SmPCs and PILs for these products are available on the MHRA website.

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Steps taken after the initial procedure with an influence on the Public Assessment Report (non-safety variations of clinical significance).

Please note that only non-safety variations of clinical significance are recorded below and in the annexes to this PAR. The assessment of safety variations where significant changes are made are recorded on the MHRA website or European Medicines Agency (EMA) website. Minor changes to the marketing authorisation are recorded in the current SmPC and/or PIL available on the MHRA website.

Application type	**Scope**	**Product information affected**	**Date of grant**	**Outcome**	**Assessment report attached Y/N**