Medicines & Healthcare products
Regulatory Agency

Public Assessment Report

National Procedure

Spironolactone 12.5 mg Film-coated Tablets
Spironolactone 25 mg Film-coated Tablets
Spironolactone 50 mg Film-coated Tablets
Spironolactone 100 mg Film-coated Tablets

spironolactone

PL 44041/0201-0204

Noumed Life Sciences Limited

LAY SUMMARY

Spironolactone 12.5 mg, 25 mg, 50 mg, and 100 mg Film-coated Tablets spironolactone

This is a summary of the Public Assessment Report (PAR) for Spironolactone 12.5 mg, 25 mg, 50 mg, and 100 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 Spironolactone Tablets in this lay summary for ease of reading.

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

What are Spironolactone 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 Aldactone 25 mg, 50 mg and 100 mg film-coated tablets, albeit with certain differences. In this case, Spironolactone 12.5 mg film-coated tablets, are a lower strength (of the active substance), than the reference product.

Spironolactone Tablets are used to help the patient lose the extra fluid from their body. Spironolactone Tablets are used in the treatment of the following illnesses:

- 'Nephrotic syndrome' - a kidney disorder that causes too much fluid in the patient's body
- 'Ascites' - too much fluid in the patient's abdomen and 'oedema' - accumulation of fluid beneath skin or in one or more cavities of the body that produces swelling, for example caused by cirrhosis of the liver
- 'Malignant ascites' fluid containing cancer cells that collect in the abdomen
- 'Primary aldosteronism' – extra fluid in the patient's body caused by too much of a hormone called 'aldosterone'.

How do Spironolactone Tablets work?
Spironolactone Tablets contain the active substance spironolactone. Spironolactone belongs to a group of medicines called 'diuretics' (also known as 'water' tablets).

Patients taking these medicines may have gone to their doctor because they had swollen ankles or were short of breath. This can happen when the heart's pumping action has become weak because of too much fluid in the body. This is called "congestive heart failure". Pushing extra fluid around the body means the patient's heart has to work harder.

Spironolactone works to help patients, with any of the diseases listed above, to get rid of the extra fluid from the body as urine and help the patient's heart to have to do less work.

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

The recommended dose is:
These medicines should be taken once a day with food.

Adults:
The adult dose varies from 25mg to 400mg spironolactone a day, depending on the condition being treated. The patient should ask their doctor/ pharmacist if they are not sure how much medicine to take.

Elderly:
The patient's doctor will start their patient on a low starting dose and gradually increase the dosage as needed to obtain the desired effect.

Use in children and adolescents:
The number of tablets that should be given to a child patient will depend on the child's weight. The patient's doctor will determine the number of tablets the patient should take.

For further information on how Spironolactone Tablets are used, refer to the PIL 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 Spironolactone Tablets have been shown in studies?
Because Spironolactone Tablets are a generic medicine, 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 Spironolactone 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 Spironolactone Tablets are a generic medicine 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 Spironolactone Tablets approved?
It was concluded that, Spironolactone Tablets has been shown to be comparable and 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 Spironolactone Tablets?

As for all newly authorised medicines, a Risk Management Plan (RMP) has been developed for Spironolactone Tablets. The RMP details the important risks of Spironolactone Tablets, how these risks can be minimised, any uncertainties about Spironolactone Tablets (missing information), and how more information will be obtained about the important risks and uncertainties.

The following safety concerns have been recognised for Spironolactone Tablets:

Summary of Safety Concerns	
Important identified risks	• Hyperkalaemia (hence contraindicated in acute kidney injury, Addison's disease, electrolyte imbalance, and with other potassium sparing diuretics, potassium supplements and drugs that cause hyperkalaemia).
Important potential risks	• Use in pregnancy. • Use in breast feeding.
Missing information	• None

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 Spironolactone 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 Spironolactone Tablets

Marketing authorisations for Spironolactone Tablets were granted in the United Kingdom (UK) on 09 January 2024.

The full PAR for Spironolactone Tablets follows this summary.

This summary was last updated in March 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 Spironolactone 12.5 mg, 25 mg, 50 mg, and 100 mg Film-coated Tablets (PL 44041/0201-0204) could be approved.

The products are approved for the following indications:

- Congestive cardiac failure
- Hepatic cirrhosis with ascites and oedema
- Malignant ascites
- Nephrotic syndrome
- Diagnosis and treatment of primary aldosteronism.
- Children should only be treated under guidance of a paediatric specialist. There is limited paediatric data available.

The name of the active substance is spironolactonethat belongs to the pharmacotherapeutic group potassium-sparing agents.

Mechanism of action

Spironolactone, as a competitive aldosterone antagonist, increases sodium excretion whilst reducing potassium loss at the distal renal tubule. It has a gradual and prolonged action.

These applications for Spironolactone 25 mg,50 mg and 100 mg film-coated Tablets 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, Aldactone 25 mg, 50 mg and 100 mg film-coated tablets that has been licensed for a suitable time, in line with the legal requirements.

The application for Spironolactone 12.5 mg film-coated Tablets was submitted under Article 10(3) of Directive 2001/83/EC, as amended, claiming to be a hybrid medicinal product of the suitable originator medicinal product, Aldactone 100 mg Film-coated Tablets. The hybrid application was necessary as the 12.5 mg strength of reference product does not exist.

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 product 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 Spironolactone Tablets were granted in the United Kingdom (UK) on 09 January 2024.

II QUALITY ASPECTS

II.1 Introduction

These products consist of 12.5 mg, 25 mg, 50 mg or 100 mg of spironolactone in each film-coated tablet.

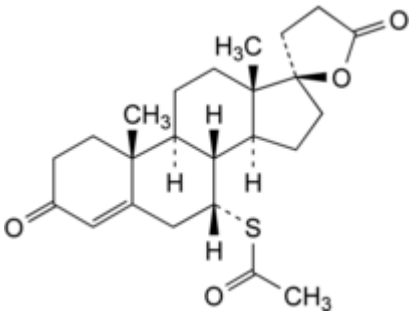
In addition to spironolactone, these products also contain the excipients calcium sulfate dihydrate, maize starch, povidone, magnesium stearate, hypromellose, titanium dioxide, polyethylene glycol, talc, and iron oxide yellow.

The finished products are packaged in clear, transparent PVC /aluminium blisters containing 28 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: spironolactone
Chemical Name: S-[(2′R)-3,5′-Dioxo-3′,4′-dihydro-5′H-spiro[androst-4-ene-17,2′-furan]-7α-yl] ethanethioate
Molecular Formula: $C_{24}H_{32}O_4S$
Chemical Structure:



Molecular Weight: 416.6 g/mol
Appearance: White or yellowish-white powder.
Solubility: Practically insoluble in water, soluble in ethanol (96 %).

Spironolactone 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.

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.

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 36 months without special storage conditions, 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 spironolactone 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 version of an already authorised product, an

increase in environmental exposure is not anticipated following approval of the marketing authorisation 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 spironolactone is well-known. With the exception of data from 0754-19 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 these studies is, thus, satisfactory.

IV. 2 Pharmacokinetics
In support of the application, the applicant submitted the following BIOEQUIVALENCE STUDY 0754-19.
This study was an open label, balanced, randomized, two-treatment, two-period, two-sequence, single oral dose, crossover, bioequivalence study comparing the test product Spironolactone 100 mg tablets versus the reference product Aldactone 100 mg tablets in subjects under fed conditions.

Subjects were administered single oral dose (100 mg) of either the test product or the reference product was administered to the subjects at 30 minutes after serving the breakfast. Blood samples were taken pre-dose and up to 16.000 hours post dose, with a washout period of 5 days between the treatment periods.

A summary of the pharmacokinetic results is presented below:

Parameters	Geometric Least Squares Means			90% Confidence Interval	Intra Subject CV (%)	Power (%)
	Test Product-T	Reference Product-R	Ratio (T/R) %			
lnC_{max}	122.964	131.981	93.2	85.70 - 101.28	32.1	99.7
$lnAUC_{0-t}$	322.859	321.383	100.5	95.44 - 105.75	19.4	100.0
$lnAUC_{0-\infty}$	332.814	332.306	100.2	95.15 - 105.42	19.4	100.0

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 12.5 mg, 25 mg and 50 mg tablets strengths 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 testing.

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 spironolactone 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**