COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Spironolacton Prolepha 12.5 mg, 25 mg, 50 mg and 100 mg, film-coated tablets (spironolactone)

NL License RVGs: 126228, 126230, 126231 and 126232

Date: 20 February 2023

This module reflects the scientific discussion for the approval of Spironolacton Prolepha. The marketing authorisation was granted on 30 August 2021. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

List of abbreviations

ASMF	Active Substance Master File
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CMS	Concerned Member State
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EEA	European Economic Area
ERA	Environmental Risk Assessment
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
Ph.Eur.	European Pharmacopoeia
PL	Package Leaflet
RH	Relative Humidity
RMP	Risk Management Plan
SmPC	Summary of Product Characteristics
TSE	Transmissible Spongiform Encephalopathy

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Medicines Evaluation Board (MEB) of the Netherlands has granted a marketing authorisation for Spironolacton Prolepha 12.5 mg, 25 mg, 50 mg and 100 mg, film-coated tablets, from Prolepha Research B.V.

These products can be used for the following indications in adults and children:

- Congestive heart failure with oedema
- Severe heart failure (NYHA III-IV)
- Liver cirrhosis with ascites and oedema
- Nephrotic syndrome
- Diagnosis and treatment of primary aldosteronism

A comprehensive description of the indications and posology is given in the SmPC.

This national procedure concerns a generic application for the 25 mg, 50 mg and 100 mg strengths, in which essential similarity is claimed with the European reference product Aldactone film-coated tablets (PA0822/110/001) of the same strengths. Aldactone has been registered in Ireland by Pfizer Healthcare Ireland since March 1975 (the original product). Additionally, the new strength of 12.5 mg is applied for through a hybrid application. For the 12.5 mg tablets, a reference product with different strength is used, namely Aldactone 100 mg film-coated tablets.

The marketing authorisations have been granted pursuant to article 10(1) of Directive 2001/83/EC for the 25 mg, 50 mg, and 100 mg strengths and article 10(3) of Directive 2001/83/EC for the 12.5 mg strength.

II. QUALITY ASPECTS

II.1 Introduction

Spironolacton Prolepha are white to off-white, round biconvex film-coated tablets, of which the 12.5 mg, 25 mg, 50 mg and 100 mg strengths have an imprint on one side of “S1”, “S2”, “S3” and “S4”, respectively.

The tablets contain 12.5 mg, 25 mg, 50 mg and 100 mg of spironolactone respectively, and they are packed in PVC/aluminium blisters.

The excipients are:
Tablet core - lactose monohydrate, calcium sulphate dihydrate, crospovidone (E1202), povidone, maize starch and magnesium stearate (E470b).
Tablet coating - hypromellose, titanium dioxide and polyethylene glycol.

II.2 Drug Substance

The active substance is spironolactone, an established active substance described in the European Pharmacopoeia (Ph.Eur.). The active substance is a crystalline powder and is practically insoluble in water. Spironolactone shows polymorphism, it was demonstrated that polymorphic form II is consistently produced by the active substance manufacturer. The active substance is a chiral compound.

The CEP procedure is used for the active substance. Under the official Certification Procedures of the EDQM of the Council of Europe, manufacturers or suppliers of substances for pharmaceutical use can apply for a certificate of suitability concerning the control of the chemical purity and microbiological quality of their substance according to the corresponding specific monograph, or the evaluation of reduction of Transmissible Spongiform Encephalopathy (TSE) risk, according to the general monograph, or both. This procedure is meant to ensure that the quality of substances is guaranteed and that these substances comply with the Ph.Eur.

Manufacturing process

A CEP has been submitted; therefore no details on the manufacturing process have been included.

Quality control of drug substance

The active substance specification is in line with the Ph.Eur. monograph and CEP with additional tests for residual solvents. The absence of a test for the microbiological quality has been adequately justified. Furthermore, the particle size is considered a critical parameter and is controlled in the drug substance specification of the drug product manufacture. The specification is considered acceptable. Batch analytical data demonstrating compliance with the drug substance specification have been provided on three production scale batches.

Stability of drug substance

The active substance is stable for 24 months when stored under stated conditions. Assessment thereof was part of granting the CEP and has been granted by the EDQM.

II.3 Medicinal Product

Pharmaceutical development

The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines. The choice of excipients is justified and their functions explained. The choices of the packaging and manufacturing process are justified in relation to the reference product. The main development studies described in the dossier were the characterization of the reference products, formulation optimization studies and dissolution method development. A bioequivalence study was performed for the 100 mg strength. For the additional strengths, a biowaiver has been granted. The drug product batch used in the bioequivalence study was manufactured according to the finalised composition and manufacturing process and is representative. The different tablet strengths are manufactured by the same manufacturing process, their

qualitative composition is the same and the composition of the strengths is quantitatively proportional in line with the general biowaiver criteria for a waiver for additional strengths of the Guideline on the investigation of bioequivalence. Comparative dissolution studies complementary to the bioequivalence study and in support of the biowaiver for the 12.5 mg, 25 mg and 50 mg strengths have been provided. The *in vitro* dissolution data in support of the biowaiver for additional strengths is acceptable from a chemical-pharmaceutical point of view. The pharmaceutical development of the product has been adequately performed.

Manufacturing process

The main steps of the manufacturing process are dry mixing, wet granulation, drying, milling, blending and lubrication, compression and film-coating. The manufacturing process has been adequately validated according to relevant European guidelines. Process validation data on the product has been presented for three full scale batches of common blend that was used to manufacture three pilot scale batches of film-coated tablets for each strength. The product is manufactured using standard manufacturing techniques.

Control of excipients

The core excipients comply with Ph.Eur. requirements. The individual components of the film-coating material are of Ph.Eur. quality. The functionality related characteristic tests have been included to the corresponding excipient specification. These specifications are acceptable.

Quality control of drug product

The finished product specifications are adequate to control the relevant parameters for the dosage form. The specification includes tests for appearance, identification, water content, assay, uniformity of dosage units, dissolution, related substances and microbiological quality. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product. The release and shelf-life requirements are identical. The specification is acceptable. No potential nitrosamine risk has been identified and currently identified sources have been adequately addressed. No confirmatory testing is needed.

Satisfactory validation data for the analytical methods have been provided. Batch analytical data from the proposed production site have been provided for three pilot scale batches for each strength, demonstrating compliance with the release specification.

Stability of drug product

Stability data on the product have been provided on three production scaled batches for each strength stored at 30°/65% RH (12 months) and 40°C/75% RH (6 months).The conditions used in the stability studies are according to the ICH stability guideline. The batches were stored in PVC-Aluminium blisters. All parameters were within the specification limits and showed no clear trends or changes at both storage conditions. The photostability of the drug product has been performed. The photostability data for the 12.5 mg and 100 mg tablets showed that the product is photostable. On basis of the data submitted, a shelf life was granted of 24 months under the storage condition “Store in the original package in order to protect from moisture”.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies

Certificates of suitability issued by the EDQM have been provided for lactose monohydrate and compliance with the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via medicinal products has been satisfactorily demonstrated.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the MEB considers that Spironolacton Prolepha has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product. No post-approval commitments were made.

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Spironolacton Prolepha is intended for generic and hybrid substitution, this will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

III.2 Discussion on the non-clinical aspects

This product contains generic formulations of Aldactone 25 mg, 50 mg and 100 mg film-coated tablets and the 12.5 mg Spironolacton Prolepha product is a hybrid of Aldactone 100 mg film-coated tablets. Aldactone is available on the European market. Reference is made to the preclinical data obtained with the innovator products. A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which is based on up-to-date and adequate scientific literature. The overview justifies why there is no need to generate additional non-clinical pharmacology, pharmacokinetics and toxicology data. Therefore, the MEB agreed that no further non-clinical studies were required.

IV. CLINICAL ASPECTS

IV.1 Introduction

Spironolactone is a well-known active substance with established efficacy and tolerability. A clinical overview has been provided, which is based on scientific literature. The overview justifies why there is no need to generate additional clinical data. Therefore, the MEB agrees that no further clinical studies are required besides the bioequivalence study discussed below, comparing the 100 mg tablets under fed conditions.

IV.2 Pharmacokinetics

The MAH conducted a bioequivalence study in which the pharmacokinetic profile of the test product Spironolacton Prolepha 100 mg tablets (Prolepha Research B.V., The Netherlands) is compared with the pharmacokinetic profile of the reference product Aldactone 100 mg film-coated tablets (Pfizer Ltd., United Kingdom).

Biowaiver

A bio-waiver is requested for the 12.5 mg, 25 mg and 50 mg strengths. The following general requirements must be met where a waiver for additional strength is claimed, according to the EMA Bioequivalence guideline (Guideline on the Investigation of Bioequivalence CPMP/EWP/QWP/1401/98 Rev. 1/Corr*, section 4.1.6):

a. the pharmaceutical products are manufactured by the same manufacturing process,
b. the qualitative composition of the different strengths is the same,
c. the composition of the strengths are quantitatively proportional, i.e. the ratio between the amount of each excipient to the amount of active substance(s) is the same for all strengths (for immediate release products coating components, capsule shell, colour agents and flavours are not required to follow this rule),
d. appropriate *in vitro* dissolution data should confirm the adequacy of waiving additional *in vivo* bioequivalence testing.

The different strengths of Spironolacton Prolepha are manufactured by the same manufacturing process in the same manufacturing site, all the strengths have the same qualitative composition and the composition of the strengths is quantitatively proportional. The dissolution profile of the 12.5 mg, 25 mg and 50 mg Spironolactone tablets compared to the 100 mg strength from the bio-batch confirmed similarity in dissolution between the products. The calculated f_2 similarity factor values were within criteria (>50%). An f_2 value between 50 and 100% suggests that the two dissolution profiles are similar.

Therefore, it can be concluded that all requirements were fulfilled and the biowaiver for the 12.5 mg, 25 mg and 50 mg strengths can be granted.

Bioequivalence study – single dose, 100 mg, fed

Design

An open label, balanced, randomised, two-treatment, two-period, two-sequence, single oral dose, crossover, bioequivalence study was carried out under fed conditions in 130 healthy male subjects, aged 21-44 years. Each subject received a single dose (100 mg) of one of the two spironolactone formulations. After an overnight fast of at least ten hours, the subjects were served a high fat high calorie vegetarian breakfast after which the tablet was orally administered with 240 mL water. There were two dosing periods, separated by a washout period of seven days.

Blood samples were collected pre-dose and at 0.25, 0.5, 0.75, 1, 1.25, 1.5, 1.75, 2, 2.25, 2.5, 2.75. 3, 3.5, 4, 4.5, 5, 6, 7, 8, 10, 12, 16 and 24 hours after administration of the products.

The design of the study is acceptable. As stated in the SmPC, the film-coated tablets need to be taken after a meal, therefore the fed condition in the bioequivalence study is considered appropriate.

Analytical/statistical methods
The analytical method has been adequately validated and is considered acceptable for analysis of the plasma samples. The methods used in this study for the pharmacokinetic calculations and statistical evaluation are considered acceptable.

Results
Out of a total of 130 subjects, 116 of them were eligible for pharmacokinetic analysis. Fourteen subjects were withdrawn: four subjects due to medical reasons, four subjects due to non-compliance and six subjects withdrew on their own accord.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of Spironolactone (100 mg) under fed conditions.

Treatment N=116	**AUC_{0-t}** (ng.h/ml)	**$AUC_{0-\infty}$** (ng.h/ml)	**C_{max}** (ng/ml)	**t_{max}** (h)
Test	381 ± 149	396 ± 150	149 ± 68	2.25 (0.75– 6.0)
Reference	369 ± 135	380 ± 139	149 ± 64	2.0 (0.75 – 6.0)
***Ratio (90% CI)**	1.04 (1.00 – 1.08)	1.04 (1.00 – 1.08)	1.01 (0.95 – 1.08)	--

AUC_{0-t}	area under the plasma concentration-time curve from time zero to t hours
$AUC_{0-\infty}$	area under the plasma concentration-time curve from time zero to infinity
C_{max}	maximum plasma concentration
t_{max}	time for maximum concentration
CI	confidence interval

**ln-transformed values*

Conclusion on bioequivalence study
The 90% confidence intervals calculated for AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the submitted bioequivalence study Spironolacton Prolepha 100 mg film-coated tablets is considered bioequivalent with Aldactone 100 mg film-coated tablets. The results of the bioequivalence study with the 100 mg formulation can be extrapolated to the other strengths (12.5 mg, 25 mg and 50 mg) because of the biowaiver.

The MEB has been assured that the bioequivalence study has been conducted in accordance with acceptable standards of Good Clinical Practice (GCP, see Directive 2005/28/EC) and Good Laboratory Practice (GLP, see Directives 2004/9/EC and 2004/10/EC).

IV.3 Risk Management Plan

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 Spironolacton Prolepha.

Table 2. Summary of safety concerns as approved in RMP

Important identified risks	• Hyperkalaemia • Benign breast neoplasm • Renal insufficiency • Hormonal disturbances (gynaecomastia, voice alteration, Addison's disease and impotence) • Serious skin reactions (Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), drug rash with eosinophilia and systemic symptoms (DRESS)) • Interaction with other anti-hypertensive agents including other potassium-sparing diuretics, ACE inhibitors and potassium supplements • Agranulocytosis
Important potential risks	• Use in paediatric population
Missing information	• Use in pregnancy and lactation

The MEB agreed that routine pharmacovigilance activities and routine risk minimisation measures are sufficient for the risks and areas of missing information.

IV.4 Discussion on the clinical aspects

For this authorisation, reference is made to the clinical studies and experience with the innovator product Aldactone. No new clinical studies were conducted. The MAH demonstrated through a bioequivalence study and a biowaiver that the pharmacokinetic profile of the product is similar to the pharmacokinetic profile of this reference product. Risk management is adequately addressed. This generic medicinal product can be used instead of the reference product.

V. USER CONSULTATION

A user consultation with target patient groups on the package information leaflet (PIL) has been performed on the basis of a bridging report making reference to Spironolactone 12.5 mg, 25 mg, 50 mg and 100 mg film-coated tablets, PL 12762/0544-0547. The bridging report submitted by the MAH has been found acceptable.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Spironolacton Prolepha 12.5 mg, 25 mg, 50 mg and 100 mg, film-coated tablets have a proven chemical-pharmaceutical quality and are generic forms of Aldactone 12.5 mg, 25 mg, 50 mg and 100 mg, film-coated tablets. Aldactone is a well-known medicinal product with an established favourable efficacy and safety profile.

Bioequivalence has been shown to be in compliance with the requirements of European guidance documents.

The Board followed the advice of the assessors.

The MEB, on the basis of the data submitted, considered that essential similarity has been demonstrated for Spironolacton Prolepha 25 mg, 50 mg and 100 mg film-coated tablets with the reference products, and have therefore granted a marketing authorisation. Spironolacton Prolepha was authorised in the Netherlands on 30 August 2021.

For the 12.5 mg strength, the MEB, on the basis of the data submitted, considered that efficacy and safety has been shown, and has therefore granted a marketing authorisation. Spironolacton Prolepha 12.5 mg, film-coated tablets was authorised in the Netherlands on 30 August 2021.

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Procedure number	Scope	Product Information affected	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse
C.I.3.a	Change(s) in the Summary of Product Characteristics, Labelling or Package Leaflet of human medicinal products intended to implement the outcome of a procedure concerning PSUR or PASS, or the outcome of the assessment done by the competent authority under Articles 45 or 46 of Regulation 1901/ 2006 SmPC - Implementation of wording agreed by the competent authority	Yes	22-3-2022	Approved	N/A
B.II.b.2.c.1	Change to importer, batch release arrangements and quality control testing of the finished product - Replacement or addition of a manufacturer responsible for importation and/or batch release - Not including batch control/testing	Yes	1-4-2022	Approved	N/A