

## **Public Assessment Report**

### **Scientific discussion**

**Spirolacton Accord 25 mg, 50 mg and  
100 mg film-coated tablets**

**(spironolactone)**

**NL/H/3508/001-003/MR**

**Date: 26 September 2016**

This module reflects the scientific discussion for the approval of Spirolacton Accord 25 mg, 50 mg and 100 mg film-coated tablets. The procedure was finalised on 2 December 2015. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

## List of abbreviations

AE	Adverse Event
ASMF	Active Substance Master File
BSE	Bovine Spongiform Encephalopathy
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
MRP	Mutual Recognition Procedure
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 Member States have granted a marketing authorisation for Spironolacton Accord 25 mg, 50 mg and 100 mg film-coated tablets from Accord Healthcare Ltd.

The product is indicated for:

- Oedema associated with congestive heart failure
- Severe heart failure, (NYHA III-IV)
- As an adjuvant in treatment of resistant hypertension
- Nephrotic syndrome
- Liver cirrhosis with ascites and oedema
- Diagnosis and treatment of primary hyperaldosteronism (Conn's syndrome)

A comprehensive description of the indications and posology is given in the SmPC. Children should only be treated under guidance of a paediatric specialist. There is limited paediatric data available (see sections 5.1 and 5.2 of the SmPC).

This mutual recognition procedure (MRP) concerns a generic application claiming essential similarity with the innovator product Aldactone 25 mg, 50 mg and 100 mg film-coated tablets, which has been registered by Pharmacia Limited UK in the United Kingdom since 7 February 2002. In the Netherlands Aldactone is currently not registered; therefore, reference to the UK innovator product is appropriate.

The concerned member states (CMS) involved in this procedure were Bulgaria, Cyprus (only 25 mg and 100 mg), Denmark, Estonia, Germany, Ireland, Latvia, Lithuania, Malta (only 25 mg and 100 mg), Poland, Slovakia, Spain, Sweden and the United Kingdom.

The marketing authorisation has been granted pursuant to Article 10(1) of Directive 2001/83/EC.

## II. QUALITY ASPECTS

### II.1 Introduction

Spironolacton Accord 25 mg is a white to pale white, round, biconvex tablet printed with "AD" on one side and no imprint on the other side.

Spironolacton Accord 50 mg is a white to pale white, round, biconvex tablet printed with "AE" on one side and no imprint on the other side.

Spironolacton Accord 100 mg is a white to pale white, round, biconvex tablet printed with "AF" on one side and no imprint on the other side.

The film-coated tablets are packed in PVC/aluminium blisters.

The excipients are:

Tablet core - lactose monohydrate, pregelatinised corn starch, anhydrous calcium hydrogen phosphate, povidone K25, peppermint oil, purified talc, colloidal anhydrous silica, magnesium stearate (E470b)

Film coating - hypromellose, macrogol, titanium dioxide (E171)

The tablets strengths are dose proportional.

### II.2 Drug Substance

The active substance is spironolactone, an established active substance described in the European Pharmacopoeia (Ph.Eur.). It is practically insoluble in water and soluble in ethanol. The active substance shows polymorphism and is present as the R-isomer.

The CEP procedure is used for both manufacturers of 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 European Pharmacopoeia.

Manufacturing process

CEPs have been submitted; therefore, no details on the manufacturing process have been included.

Quality control of drug substance

The drug substance specification is in line with the Ph.Eur. and the additional requirements stated in the CEPs, with additional product manufacturer requirements for particle size. The specification is acceptable in view of the various European guidelines. Batch analytical data demonstrating compliance with the drug substance specification have been provided for 3 full-scale batches of both suppliers.

Stability of drug substance

The active substance is stable for 3 years from one manufacturer, and for 2 years from the second supplier, when stored under the stated conditions. Assessment thereof was part of granting the CEP and has been granted by the EDQM.

**II.3 Medicinal Product**

Pharmaceutical development

The development of the product has been described, the choice of excipients is justified and their functions explained. Compatibility of the active substance with each excipient is proven. The finalized composition is adequately optimized. Information on the polymorphic form of the active substance used in the formulation is provided. *In-vitro* dissolution data have been provided of the biobatches at three pHs. Also the dissolution of the different strengths was compared in support of the biowaiver for the two lower strengths. The pharmaceutical development of the product has been adequately performed.

Manufacturing process

The manufacturing process consists of sifting materials, dry mixing, granulation, drying, lubrication, compression, film coating and packing. The product is manufactured using conventional manufacturing techniques. The process has been adequately validated according to relevant European guidelines. Process validation data on the product has been presented for 2 full-scale batches per tablet strength.

Control of excipients

The excipients comply with the relevant Ph.Eur. monographs. These specifications are acceptable.

Quality control of drug product

The product specification includes tests for appearance, identity, average mass, loss on drying, assay, dissolution, degradation, uniformity of dosage units and microbial purity. The shelf-life requirement for a single unknown impurity is widened with respect to the release requirement. The specifications are acceptable. The analytical methods have been adequately described and validated.

Batch analytical data from the proposed production site have been provided on 2 full-scale batches per tablet strength, demonstrating compliance with the release specification.

Stability of drug product

Stability data on the product has been provided for 2 full-scale batches per tablet strength, stored at 25°C/60% RH (36 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-Alu blisters.

The results show that the products are stable. The shelf-life of three years is justified. A photostability study was carried out as per ICH guidelines. The test result indicates that product is photostable in proposed packaging. Therefore, the storage condition is 'Store in the original package in order to protect from light'.

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

Lactose monohydrate is the only excipient of animal origin. A TSE/BSE declaration for lactose monohydrate has been provided 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 member states consider that Spironolacton Accord 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 Accord is 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.2 Discussion on the non-clinical aspects**

This product is a generic formulation of Aldactone, which is available on the European market. Reference is made to the preclinical data obtained with the innovator product. 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 member states agreed that no further non-clinical studies are 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 member states agreed that no further clinical studies are required.

For this generic application, the MAH has submitted a bioequivalence study, which is discussed below.

#### **IV.2 Pharmacokinetics**

The MAH conducted a bioequivalence study in which the pharmacokinetic profile of the test product Spironolacton Accord 100 mg (Accord Healthcare Ltd, UK) is compared with the pharmacokinetic profile of the reference product Aldactone 100 mg film-coated tablet (Pharmacia Ltd, UK).

The choice of the reference product in the bioequivalence study has been justified. The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.

#### Biowaiver

*In vivo* bioequivalence studies for the 25 mg and 50 mg tablet strength can be waived based in the following data (Guideline on the investigation of bioequivalence of CHMP- Doc. Ref.: CPMP/QWP/EWP/1401/98 Rev. 1):

- a) The different strengths are manufactured by the same manufacturing process at the same manufacturing site.
- b) All the three strengths (25 mg, 50 mg and 100 mg) have the same qualitative composition.
- c) The kinetics of spironolactone is linear over the therapeutic range.
- d) The composition of the strengths is quantitatively proportional, i.e. the ratio between the amount of each excipient to the amount of active substance is the same for all strengths.
- e) Appropriate *in-vitro* dissolution results suffice the requirements for biowaiver.

Bioequivalence study

*Design*

A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fed conditions in 60 healthy adult male subject. After an overnight fast of at least 10 hours, the subjects were served a non-high fat breakfast which they consumed completely within 30 minutes of its serving. The breakfast given to the subjects consisted of 100 ml Milk, 160 gram Poha, and 130 gram vegetable cutlets, with a total amount of protein: 13 gram (53 Kcal), carbohydrate: 100 gram (403 Kcal) and fat 23 gram (203 Kcal). The total amount of calories is 658 Kcal.

The subjects were administered a single oral dose (100 mg) of either the spironolactone test or the reference product at 30 minutes after serving the breakfast, with 240 ml of water. There were 2 dosing periods, separated by a washout period of 9 days.

Blood samples were collected pre-dose and at 0.25, 0.5, 0.75, 1, 1.25, 1.5, 1.75, 2, 2.33, 2.67, 3, 3.5, 4, 4.5, 5, 6, 8, 10, 12 and 16 hours after administration of the products.

The design of the study is acceptable. As the SmPC recommends to take the spironolactone tablets during the meals, a study design under fed condition is appropriate. The preferred condition according to the Bioequivalence guideline is a high fat and high calorie meal. However, since no specific meal recommendation is given in the SmPC and a non-high fat breakfast better mimics the clinical conditions, the choice of a non-high fat meal is sufficiently justified. The washout and sampling period were long enough for the estimation of spironolactone levels, the sampling scheme adequate to estimate the pharmacokinetic parameters.

*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*

One subject was found positive in alcohol test on the day of check-in of Period-II and withdrawn from the trial on grounds of protocol deviation. The remaining 59 subjects completed the clinical phase of the study successfully and were eligible for pharmacokinetic analysis.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean  $\pm$  SD,  $t_{max}$  (median, range)) of spironolactone under fed conditions

Treatment N=59	AUC <sub>0-t</sub> ng.h/ml	AUC <sub>0-∞</sub> ng.h/ml	C <sub>max</sub> ng/ml	t <sub>max</sub> h	t <sub>1/2</sub> h
<b>Test</b>	288 $\pm$ 103	300 $\pm$ 110	116 $\pm$ 55	2.0 (1.-6.0)	4.5 $\pm$ 1.8
<b>Reference</b>	288 $\pm$ 128	299 $\pm$ 134	119 $\pm$ 67	2.0 (1.0-6.0)	4.5 $\pm$ 1.6
<b>*Ratio (90% CI)</b>	1.03 (0.97-1.09)	1.03 (0.97-1.09)	1.01 (0.91-1.12)	--	--
<b>AUC<sub>0-∞</sub></b> area under the plasma concentration-time curve from time zero to infinity <b>AUC<sub>0-t</sub></b> area under the plasma concentration-time curve from time zero to t hours <b>C<sub>max</sub></b> maximum plasma concentration <b>t<sub>max</sub></b> time for maximum concentration <b>t<sub>1/2</sub></b> half-life <b>CV</b> coefficient of variation					

*\*In-transformed values*

Conclusion on bioequivalence study

The 90% confidence intervals calculated for AUC<sub>0-t</sub>, AUC<sub>0-∞</sub> and C<sub>max</sub> are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the submitted bioequivalence study Spironolacton Accord 100 mg is considered bioequivalent with Aldactone 100 mg film-coated tablets.

*Safety*

Four mild adverse events (AEs) were reported by two subjects during the study. Two AEs were reported following administration of the test product and two following the reference product. The causality was judged as possible for one AE (epigastric burning) and as unlikely for three AEs. There were no serious or significant AE reported during the course of the study.

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 Accord.

- Summary table of safety concerns as approved in RMP

Important identified risks	<ul style="list-style-type: none"> <li>- Hyperkalaemia</li> <li>- Renal insufficiency</li> <li>- Hormonal disturbances (gynaecomastia, voice alteration, and impotence)</li> <li>- Serious skin reactions</li> <li>- Agranulocytosis</li> </ul>
Important potential risks	None
Missing information	- Use in pregnancy

The member states 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 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**

The MAH did not perform a user test on the package leaflet (PL) but submitted a bridging statement. The already tested and approved package leaflet text of the reference product Aldactone is followed. Differences in wording in the proposed package leaflet as compared to the already tested and approved package leaflet of the reference product Aldactone mainly concern product specific information. These differences do not affect readability.

Moreover, the MAH’s design, layout and style of writing of the PL has been user tested in a previous procedure, for Mycophenolic acid 180 mg and 360 mg gastro-resistant tablets (ES/H/0183/001-002/DC). The member states agree that further user testing is not required.

## **VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION**

Spironolacton Accord 25 mg, 50 mg and 100 mg film-coated tablets have a proven chemical-pharmaceutical quality and are generic forms of Aldactone 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. In the Netherlands, the marketing authorisation for Spironolacton Accord was granted on 15 February 1999.

There was no discussion in the CMD(h) during the MRP. Agreement between member states was reached during a written procedure. The concerned member states, on the basis of the data submitted, mutually recognised the MEB's evaluation for marketing authorisation. Essential similarity has been demonstrated for Spironolacton Accord with the reference product. The mutual recognition procedure was finalised with a positive outcome on 2 December 2015.

**STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY**

Scope	Procedure number	Type of modification	Date of start of the procedure	Date of end of the procedure	Approval/ non approval	Assessment report attached