CBG MEB

Public Assessment Report

Scientific discussion

Eplerenon Accord 25 mg and 50 mg film-coated tablets

(eplerenone)

NL/H/3257/001-002/DC

Date: 29 August 2016

This module reflects the scientific discussion for the approval of Eplerenon Accord 25 mg and 50 mg film-coated tablets. The procedure was finalised on 29 July 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

ASMF	Active Substance Master File
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CMS	Concerned Member State
EDMF	European Drug Master File
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 Member States have granted a marketing authorisation for Eplerenon Accord 25 mg and 50 mg film-coated tablets, from Accord Healthcare Ltd.

The product is indicated:
- in addition to standard therapy including beta-blockers, to reduce the risk of cardiovascular mortality and morbidity in stable patients with left ventricular dysfunction (LVEF ≤ 40 %) and clinical evidence of heart failure after recent myocardial infarction
- in addition to standard optimal therapy, to reduce the risk of cardiovascular mortality and morbidity in adult patients with New York Heart Association (NYHA) class II (chronic) heart failure and left ventricular systolic dysfunction (LVEF ≤30%)

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

This decentralised procedure concerns a generic application claiming essential similarity with the innovator products Inspra 25 mg and 50 mg film-coated tablets (NL License RVG 29963-4) which have been registered by Pfizer Ltd. since 16 March 2004 via the national procedure in The Netherlands. Subsequently Inspra was registered in several other member states by a Mutual Recognition Procedure (reference number NL/H/0506/001-002/DC).

The concerned member states (CMS) involved in this decentralised procedure were Austria, Bulgaria, Cyprus, Denmark, Estonia, Ireland, France, Italy, Latvia, Sweden and the UK. After finalisation, Eplerenon Accord 25 mg and 50 mg was registered in Germany, Spain, Norway and Poland through a repeat-use procedure NL/H/3257/001-002/E/001.

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

II. QUALITY ASPECTS

II.1 Introduction

Eplerenon Accord is a film-coated tablet.

For the 25 mg tablet: Yellow diamond shaped biconvex film-coated tablets, debossed with “E1” on one side and plain on other side.

For the 50 mg tablet: Yellow diamond shaped biconvex film-coated tablets, debossed with “E2” on one side and plain on other side.

Each tablet contains 25 mg or 50 mg of eplerenone.

The film-coated tablets are packed in Alu-White Opaque PVC blisters.

The excipients are:

Tablet core:
- Lactose monohydrate
- Cellulose microcrystalline
- Hypromellose
- Croscarmellose sodium
- Talc
- Magnesium stearate

Tablet coating
Opadry13B520013 yellow:
- Hypromellose
- Titanium dioxide (E171)
- Macrogol 400
- Polysorbate 80
- Iron oxide yellow (E172)
- Iron oxide red (E172)

Both strengths are dose proportional.

II.2 Drug Substance

The active substance is eplerenone, an established active substance described in the European Pharmacopoeia (Ph.Eur.). The active substance is slightly soluble in water but soluble in buffer solutions pH 1-6.8. The molecule contains eight chiral centres and shows polymorphism. The form produced is Form-L which has been shown to be stable during manufacturing and storage.

The Active Substance Master File (ASMF) procedure is used for the active substance. The main objective of the ASMF procedure, commonly known as the European Drug Master File (EDMF) procedure, is to allow valuable confidential intellectual property or 'know-how' of the manufacturer of the active substance (ASM) to be protected, while at the same time allowing the applicant or marketing authorisation holder (MAH) to take full responsibility for the medicinal product, the quality and quality control of the active substance. Competent Authorities/EMA thus have access to the complete information that is necessary to evaluate the suitability of the use of the active substance in the medicinal product.

Manufacturing process
The manufacturing process consist of 6 steps. Three manufacturing sites are used for the synthesis of the intermediate and eplerenone. Acceptable specifications have been adopted for the reagents and solvents, as well as for the starting material. The active substance has been adequately characterised.

Quality control of drug substance
The drug substance specification has been established in-house by the MAH, based on the specification of the ASMF-holder. The specification is acceptable in view of the route of synthesis and the currently valid Ph.Eur. monograph. As the monograph came into force during the application procedure (April 2015), the commitment of the MAH to comply with the Ph.Eur. specifications after finalisation is acceptable.
Batch analytical data demonstrating compliance with the drug substance specification have been provided for six full scaled batches (ASMF-holder) and two full scaled batches (MAH).

Stability of drug substance
Stability data on the active substance have been provided for four small scale production batches and one large scale production batch stored at 25°C/60% RH (up to 48 months) and 40°C/75% RH (up to 6 months).Based on the data submitted, a retest period could be granted of 48 months.

II.3 Medicinal Product

Pharmaceutical development
The product is an established pharmaceutical form and its development is adequately performed and described in accordance with the relevant European guidelines. The excipients and packaging are usual for this type of dosage form.

One *in vivo* bioequivalence study was submitted to demonstrate bioequivalence between Eplerenon Accord 50 mg film-coated tablets and reference product, Inspra 50 mg film-coated tablets. The bioequivalence study test batch was manufactured according to the finalised manufacturing process and composition. Sufficient comparative dissolution data between the test and reference product have been provided, demonstrating similarity.

A biowaiver was requested for the 25 mg strength. This is acceptable considering that both strengths (25 mg and 50 mg) are fully dose proportional and are manufactured using the same manufacturing process. In addition dissolution profiles of both strength across the physiological pH range are similar (rapid dissolution >85% at 15 min). The general biowaiver criteria are thereby met and the requested biowaiver for the 25 mg strength can be granted.

Manufacturing process
The manufacturing process is a wet-granulation process consisting of the following steps: raw material sifting, granulation, blending and lubrication, compression, film-coating and packaging. The manufacturing process has been validated according to relevant European/ICH guidelines. Process validation data on the product have been presented for two batches of each strength in accordance with the relevant European guidelines. Process validation for the third batches will be performed post authorisation.

Control of excipients
The excipients comply with Ph.Eur. requirements or in-house specifications (colourant). These specifications are acceptable, and the functionality-related characteristics are included in the specification if relevant.

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 description, average weight, identification, loss on drying, dissolution, uniformity of dosage units, related substances, assay and microbial examination. The release and shelf-life requirements are identical except for loss on drying. These are acceptable. The analytical methods have been adequately described and validated. Batch analytical data from the proposed production site have been provided on two small production scale batches, demonstrating compliance with the release specification.

Stability of drug product
Stability data on the product has been provided on two small production scaled batches stored at 25°C/60% 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 white opaque PVC – Aluminium blisters. No changes are observed. The proposed shelf-life of 24 months is acceptable based on the data of 12 months. The product is not sensitive to light. The storage restriction reads: This medicinal product does not require any special storage conditions, which is acceptable.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
The only excipient of animal origin is lactose monohydrate. The manufacturer of lactose monohydrate has confirmed that it does not have potential risk for TSE/BSE and it is derived from milk, sourced from healthy animals in the same conditions as milk collected for human consumption and is prepared in accordance with the relevant requirements laid down in Note for Guidance EMEA/410/01, rev3.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Eplerenon 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 Eplerenon 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 Inspra 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

Eplerenone 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

Bioequivalence study
The MAH conducted a bioequivalence study in which the pharmacokinetic profile of the test product Eplerenon Accord 50 mg (Accord Healthcare Ltd, UK) is compared with the pharmacokinetic profile of the reference product Inspra 50 mg film-coated tablets (Pfizer Ltd, UK).

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

Biowaiver
A biowaiver was requested for the 25 mg strength based on the Note for Guidance on the Investigation of Bioavailability and Bioequivalence CPMP/EWP/QWP/1401/98. The biowaiver can be granted as the following criteria are all met:

- 25 mg and 50 mg film-coated tablets are manufactured at the same manufacturing site using a similar manufacturing process.
- Eplerenone demonstrates linear pharmacokinetics over the therapeutic dose range.
- The qualitative composition of 25 mg film-coated tablets are the same as that of 50 mg film-coated tablets.
- The formulations of both the strengths are dose proportional, i.e. the ratio between the amounts of each excipient to the amount of active substance are the same for both strengths.
- *In-vitro* dissolution profile is similar (rapid dissolution >85% at 15 min) under identical conditions for the additional strengths and the strength of the batch used in the bioequivalence study, tested at three relevant pH values.

Design
A randomised, two period, single dose, two-way cross-over bioequivalence study was carried out under fasted conditions in 36 healthy subjects, aged 18-45 years. Each subject received a single dose (50 mg) of one of the 2 eplerenone formulations. The tablet was orally administered with 240 ml water at ambient temperature with the subjects in sitting posture after an overnight fast of 10 hours. There were 2 dosing periods, separated by a washout period of 5 days.

Blood samples were collected at pre-dose and at 0.25, 0.5, 0.75, 1, 1.25, 1.5, 1.75, 2, 2.33, 2.67, 3, 3.33, 3.67, 4, 4.5, 5, 6, 8, 10, 12, 16, and 24 hours post dose in each period.

The design of the study is acceptable. The number of measurements around the C_{max} and the duration of sample-collection are sufficient. The wash-out period is long enough not to detect carry-over effect. The study under fasting conditions is appropriate, as Eplerenone may be administered with or without food. Absorption is not affected by food.

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 withdrawn from the study on grounds of protocol violation, and four other subjects discontinued in period II on their own accord. 31 subjects were eligible for pharmacokinetic analysis.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of eplerenone 50 mg under fasted conditions.

Treatment N=31	AUC_{0-t} ng.h/ml	$AUC_{0-\infty}$ ng.h/ml	C_{max} ng/ml	t_{max} h	$t_{1/2}$ h
Test	9625.45 ± 4216.15	9961.56 ± 4609.07	1489.19 ± 419.27	1.00 (0.50 – 3.67)	3.98 ± 1.28
Reference	9279.64 ± 4532.72	9627.93 ± 5030.60	1409.10 ± 450.24	1.75 (0.75 – 4.50)	3.88 ± 1.40
***Ratio (90% CI)**	1.05 (1.01 – 1.09)	1.05 (1.01 – 1.10)	1.07 (1.02 - 1.11)	--	--
CV (%)	9.0	9.3	9.1	--	--

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
$t_{1/2}$ half-life
CV coefficient of variation

**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 Eplerenon Accord 50 mg is considered bioequivalent with Inspra 50 mg.

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 Eplerenon Accord.

Summary table of safety concerns as approved in RMP:

Important identified risks	• Myocardial infarction • Hyperkalaemia • Renal impairment • Pruritus, rash
Important potential risks	--
Missing information	--

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 Inspra. 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

A user consultation with target patient groups on the package leaflet (PL) has been performed on the basis of a bridging report making reference to Inspra. In addition, the proposed PL is similar with regard to lay-out, design and style of writing to the PL of the satisfactorily user tested PL of Mycophenolic acid 180 mg and 360 mg gastro-resistant tablets (ES/H/0183/001-002/DC). The bridging report submitted by the MAH has been found acceptable.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Eplerenon Accord 25 mg and 50 mg film-coated tablets have a proven chemical-pharmaceutical quality and are generic forms of Inspra 25 mg and 50 mg film-coated tablets. Inspra 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.

There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The member states, on the basis of the data submitted, considered that essential similarity has been demonstrated for Eplerenon Accord with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 29 July 2015.

There were no post-approval commitments made during the decentralised procedure. However, during the repeat-use procedure, finalised 4 January 2016, the following commitments were made:

- A commitment to update the RMP within 3 months after finalisation of the repeat-use procedure.
- A commitment to revise sections of the quality dossier to include a description of the control testing sites and to state the excipients grade of hypromellose through a variation.
- A commitment to submit revised product information to include the excipient grade.

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
Repeat use procedure to register the product in Germany, Spain, Norway and Poland.	NL/H/3257/ 001-002/E/ 001	E	21-10-2015	4-1-2016	Approved	No