Public Assessment Report

Scientific discussion

Hydrochlorothiazide Farmaprojects 12.5 mg and 25 mg tablets

(hydrochlorothiazide)

NL/H/3816/001-002/DC

Date: 2 November 2017

This module reflects the scientific discussion for the approval of Hydrochlorothiazide Farmaprojects 12.5 mg and 25 mg tablets. The procedure was finalised on 29 March 2017. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

List of abbreviations

CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CMS	Concerned Member State
EDQM	European Directorate for the Quality of Medicines
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 Hydrochlorothiazide Farmaprojects 12.5 mg and 25 mg tablets, from Farmaprojects, S.A.U.

Hydrochlorothiazide Farmaprojects tablets are indicated in adults for the treatment of essential arterial hypertension and for the treatment of cardiac, hepatic and renal oedema.

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 product Esidrex 25 mg tablets which has been registered in France by Novartis Pharma SAS since 20 June 1986. In the Netherlands, Esidrex 25 mg tablets has been withdrawn from the market since 31 December 2002.

The concerned member state (CMS) involved in this procedure was Luxembourg.

The marketing authorisation for the 25 mg strength has been granted pursuant to Article 10(1) of Directive 2001/83/EC (generic medicinal product). For the 12.5 mg strength the legal base is Article 10(3) of Directive 2001/83/EC (hybrid medicinal product), as there is no European reference product authorised for the strength of 12.5 mg that the MAH can refer to as a generic application.
The lower strength is indicated for the treatment against arterial hypertension. Hence the starting dose is one 12.5 mg hydrochlorothiazide tablet or one 25 mg hydrochlorothiazide tablet a day (12.5 – 25 mg hydrochlorothiazide/day).The long term dose is usually one 12.5 mg hydrochlorothiazide tablet a day (12.5 mg hydrochlorothiazide/day).

II. QUALITY ASPECTS

II.1 Introduction

Hydrochlorothiazide Farmaprojects 12.5 mg tablets are white, round, biconvex tablets. Each tablet contains 12.5 mg of hydrochlorothiazide.

Hydrochlorothiazide Farmaprojects 25 mg tablets are white, round, flat tablets and a score line on one side. Each tablet contains 25 mg of hydrochlorothiazide. The tablet can be divided into equal doses.

The tablets are packed in aluminium/red, transparent PVC foil blisters.

The excipients are lactose monohydrate, maize starch, talc, colloidal anhydrous silica and magnesium stearate.

The two tablet strengths are dose proportional.

II.2 Drug Substance

The active substance is hydrochlorothiazide, an established active substance described in the European Pharmacopoeia (Ph.Eur.). Hydrochlorothiazide is a white to almost white crystalline powder and is very slightly soluble in water. It has been adequately demonstrated that polymorphic form I is consistently manufactured.

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 considered adequate to control the quality. It meets the requirements of the monograph in the Ph.Eur. and justified limits for particle distribution. Batch analytical data demonstrating compliance with this specification have been provided for three production scaled batches.

Stability of drug substance
The active substance is stable for three years 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 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 formulation development studies are described, including manufacturing process development. Functionality of the score line of the 25 mg tablet has been demonstrated. The pharmaceutical development of the product has in general been adequately performed.

A bioequivalence study has been performed for the 25 mg tablets. The reference product is acceptable. Dissolution data at various pH values on the reference batch and the test batch used in the bioequivalence study have been included as well as dissolution data of both strengths to obtain a biowaiver of strength.

Manufacturing process
The manufacturing process comprises dry mixing, compression into tablets and packaging. The product is manufactured using conventional manufacturing techniques and is a standard process. The manufacturing process has been adequately validated according to relevant European guidelines. Process validation data on the product has been presented for three production scale batches of each strength.

Control of excipients
The excipients comply with the relevant Ph.Eur. monographs. 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, average weight, uniformity of dosage units, friability, hardness, disintegration, dissolution, identification, assay, related substances/degradation products and microbial limits. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product. Satisfactory validation data for the analytical methods have been provided. Batch analytical data from three production scaled batches of each strength from the proposed production site have been provided, demonstrating compliance with the specification.

Stability of drug product
Stability data on the product has been provided three production scale batches of each strength stored during 60 months at 25°C/60% RH and six months at 40°C/75% RH. The conditions used in the stability studies are according to the ICH stability guideline. No changes were observed. Photostability studies according to the ICH guideline have been submitted. The product is to be stored in the original packaging in order to protect from light.
On the basis of the data submitted a shelf life was granted of 24 months, when stored in the proposed packaging, without special temperature storage conditions.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
Scientific data and/or certificates of suitability issued by the EDQM have 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.
The only component of animal origin is lactose monohydrate. A BSE/TSE statement has been provided that the milk as source for this excipient is collected from healthy animals in the same conditions as milk collected for human consumption (EMEA/410/01 rev 2) and the lactose is prepared without the use of other ruminant materials than calf rennet. The calf rennet is declared to be in accordance with Public Statement EMEA/CPMP/571/02 of February 27 2002. The sourcing of the milk is constantly, officially supervised according to EC Hygiene Regulations (EC) No 852/2004 and (EC) No 853/2004.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Hydrochlorothiazide Farmaprojects 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 Hydrochlorothiazide Farmaprojects 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 Esidrex 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

Hydrochlorothiazide 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.

The MAH has submitted one 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 Hydrochlorothiazide Farmaprojects 25 mg (Farmaprojects, S.A.U., Spain) is compared with the pharmacokinetic profile of the reference product Esidrex 25 mg (Novartis Pharma SAS, France).

The choice of the reference product
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
For the 12.5 mg strength, the MAH requested a waiver for bioequivalence studies. According to the CPMP guideline "Note for guidance on the investigation of bioavailability and bioequivalence" (CPMP/EWP/QWP/1401/98 Rev. 1), a bioequivalence study investigating only one tablet strength may be acceptable if all of the following conditions are fulfilled:

- the pharmaceutical products are manufactured by the same manufacturing process.
- the qualitative composition of the different strengths is the same.
- the composition of the strengths are quantitatively proportional.
- appropriate *in vitro* dissolution data should confirm the adequacy of waiving additional *in vivo* bioequivalence testing.

Both tablets are dose proportional. Furthermore all biowaiver requirements were fulfilled, therefore a biowaiver for the 12.5 mg is acceptable.

Design
An open label, randomised , two-way bioequivalence study was carried out under fasted conditions in 24 healthy male (n=14) and female (n=10) subjects, aged 35.9 ± 12.2 years (mean age ± SD). Each subject received a single dose (25 mg) of one of the two hydrochlorothiazide formulations. The tablet was orally administered with 200 ml water after an overnight fast of 10 hours. There were two dosing periods, separated by a washout period of 18 days.

Blood samples were collected prior to dosing and at 0.5, 1.0, 1.5, 2.0, 2.5, 3.0, 3.5, 4.0, 4.5, 5.0, 6.0, 8.0, 12.0, 16.0, 24.0 and 36.0 hours after administration of the products.

The design of the study is acceptable. Hydrochlorothiazide should be taken during breakfast for safety reasons. As the bioavailability is not strongly affected by a breakfast a study under fasting conditions is justified.

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
All 24 subjects were eligible for pharmacokinetic analysis.

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

Treatment N=24	**AUC_{0-t}** ng.h/ml	**$AUC_{0-\infty}$** ng.h/ml	**C_{max}** ng/ml	**t_{max}** h
Test	1160.38 ± 292.65	1220.03 ± 305.18	185.72 ± 56.09	2.00 (1.00 – 3.00)
Reference	1143.49 ± 217.13	1207.89 ± 231.62	168.80 ± 39.20	2.00 (1.50 – 5.00)
***Ratio (90% CI)**	1.00 (0.96 – 1.04)	1.00 (0.96 – 1.03)	1.08 (1.01 – 1.15)	--

$AUC_{0-\infty}$ area under the plasma concentration-time curve from time zero to infinity
AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours
C_{max} maximum plasma concentration
t_{max} time for maximum concentration
$t_{1/2}$ half-life

**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 Hydrochlorothiazide Farmaprojects 25 mg tablets is considered bioequivalent with Esidrex 25 mg tablets.

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 Hydrochlorothiazide Farmaprojects.

Summary table of safety concerns as approved in RMP:

Important identified risks	• Electrolyte abnormalities • Foetotoxicity
Important potential risks	• Renal impairment • Liver function disorder
Missing information	• Drug exposure during lactation • Paediatric population

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 Esidrex. 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 and hybrid medicinal product can be used instead of the reference product.

V. USER CONSULTATION

The package leaflet has (PL) been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The test consisted of: a pilot test with two participants, followed by two rounds with 10 participants each. The questions covered the following areas sufficiently: traceability, comprehensibility and applicability. The results show that the PL meets the criteria for readability as set out in the Guideline on the readability of the label and PL of medicinal products for human use.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Hydrochlorothiazide Farmaprojects 12.5 mg and 25 mg tablets has a proven chemical-pharmaceutical quality. The 25 mg strength is a generic form of Esidrex 25 mg; the 12.5 mg strength is a hybrid form. Esidrex 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 Hydrochlorothiazide Farmaprojects with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 29 March 2017.

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