Public Assessment Report

Scientific discussion

Telmisartan/Hydrochlorothiazide Glenmark 40 mg/12.5 mg, 80 mg/12.5 mg and 80 mg/25 mg, tablets

(telmisartan and hydrochlorothiazide)

NL/H/3951/001-003/DC

Date: 1 November 2017

This module reflects the scientific discussion for the approval of Telmisartan/Hydrochlorothiazide Glenmark 40 mg/12.5 mg, 80 mg/12.5 mg and 80 mg/25 mg, tablets. The procedure was finalised on 24 February 2014 with Portugal as RMS (PT/H/1105/001-003/DC). The current RMS is the Netherlands (NL/H/3951/001-003/DC). 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 Member States have granted a marketing authorisation for Telmisartan/Hydrochlorothiazide Glenmark 40 mg/12.5 mg, 80 mg/12.5 mg and 80 mg/25 mg, tablets, from Glenmark Pharmaceuticals Europe Limited.

The product is indicated for the treatment of essential hypertension.
The product is a fixed dose combination, indicated in adults whose blood pressure is not adequately controlled on telmisartan alone.

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 Micardis Plus 40 mg/12.5 mg, 80 mg/12.5 mg and 80 mg/25 mg tablets, registered since 19 April 2002 by Boehringer Ingelheim through a centralised procedure (MA numbers EU/1/02/213/001-023).

The reference member state (RMS) of the initial procedure was Portugal and the concerned member states (CMS) were Germany, Spain, France, the Netherlands, Sweden and the United Kingdom. The role of RMS was transferred to the Netherlands on 28 December 2016.

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

II. QUALITY ASPECTS

II.1 Introduction

- Telmisartan/Hydrochlorothiazide Glenmark 40 mg/12.5 mg is a biconvex, uncoated, capsule-shaped tablet with two layers: a white to off-white hydrochlorothiazide layer, debossed with “423” and a mottled orange to reddish brown telmisartan layer, without debossing. The hydrochlorothiazide layer may contain reddish brown specks. Each tablet contains 40 mg telmisartan and 12.5 mg hydrochlorothiazide.
- Telmisartan/Hydrochlorothiazide Glenmark 80 mg/12.5 mg is a biconvex, uncoated, capsule-shaped tablet with two layers: a white to off-white hydrochlorothiazide layer, debossed with “424” and a mottled orange to reddish brown telmisartan layer, without debossing. The hydrochlorothiazide layer may contain reddish brown specks. Each tablet contains 80 mg telmisartan and 12.5 mg hydrochlorothiazide.
- Telmisartan/Hydrochlorothiazide Glenmark 80 mg/25 mg is a biconvex, uncoated, capsule-shaped tablet with two layers: a white to light yellow hydrochlorothiazide layer, debossed with “425” and a mottled orange to reddish brown telmisartan layer, without debossing. The hydrochlorothiazide layer may contain reddish brown specks. Each tablet contains 80 mg telmisartan and 25 mg hydrochlorothiazide.

The tablets are packed in Aluminium-Aluminium foil blisters.

The excipients are: crospovidone (Type A), hypromellose, lactose monohydrate, magnesium stearate, mannitol, meglumine, povidone K 25, colloidal anhydrous silica, sodium hydroxide, sodium stearyl fumarate, talc, red iron oxide (E172) and yellow iron oxide (E172)(only for the 80 mg/25 mg strength).

II.2 Drug Substances

The active substances are telmisartan and hydrochlorothiazide, that are both established active substances and described in the European Pharmacopoeia (Ph.Eur.).

The chemical-pharmaceutical documentation and Expert Report in relation to the drug substances are of sufficient quality in view of the present European regulatory requirements.

Stability studies have been performed with the drug substance. No significant changes in any parameters were observed.

II.3 Medicinal Product

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.

Satisfactory stability data are provided on batches of the proposed product packaged in the commercial marketing materials. The testing conditions and frequency are in line with the ICH requirements.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Telmisartan/Hydrochlorothiazide Glenmark 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 Telmisartan/Hydrochlorothiazide Glenmark 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 Micardis Plus 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

Telmisartan and hydrochlorothiazide are well-known active substances 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 two bioequivalence studies.

IV.2 Pharmacokinetics

The MAH conducted two bioequivalence studies in healthy subjects under fasting conditions:

- The pharmacokinetic profile of the test product Telmisartan/Hydrochlorothiazide Glenmark 40 mg/12.5 mg (Glenmark Pharmaceuticals Europe Limited, UK) is compared with the pharmacokinetic profile of the reference product Micardis Plus 40 mg/12,5 mg (Boehringer Ingelheim International GmbH, Germany).

- The pharmacokinetic profile of the test product Telmisartan/Hydrochlorothiazide Glenmark 80 mg/12.5 mg (Glenmark Pharmaceuticals Europe Limited, UK) is compared with the pharmacokinetic profile of the reference product Micardis Plus 80 mg/12,5 mg (Boehringer Ingelheim International GmbH, Germany).

The design of the study is acceptable.

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.

Conclusion
Based on the submitted bioequivalence studies Telmisartan/Hydrochlorothiazide Glenmark is considered bioequivalent with Micardis Plus.

The results of the study with the 80 mg/25 mg formulation can be extrapolated to the other strength 80 mg/12.5 mg, according to conditions in Guideline on the Investigation of Bioequivalence CPMP/EWP/QWP/1401/98 Rev. 1/Corr*, section 4.1.6.

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 Telmisartan/Hydrochlorothiazide Glenmark.

- Summary table of safety concerns as approved in RMP

Important identified risks	• Sepsis • Renal dysfunction as consequence of dual RAAS blockade • Foetotoxicity • Hypoglycaemia
Important potential risks	• Increase of hepatic related adverse reactions in the Japanese population • Rhabdomyolysis • Interstitial lung disease • Severe cutaneous reactions • Suicide/self-injury • Malignancies
Missing information	None

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 Micardis Plus. 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 readability of the package leaflet was successfully demonstrated.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Telmisartan/Hydrochlorothiazide Glenmark 40 mg/12.5 mg, 80 mg/12.5 mg and 80 mg/25 mg, tablets have a proven chemical-pharmaceutical quality and are generic forms of Micardis Plus 40 mg/12.5 mg, 80 mg/12.5 mg and 80 mg/25 mg tablets. Micardis Plus 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 Telmisartan/Hydrochlorothiazide Glenmark with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 24 February 2014.

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
Change(s) in the Summary of Product Characteristics, Labelling or Package Leaflet intended to implement the outcome of a Union referral procedure; The medicinal product is covered by the defined scope of the procedure Implementation of changes to the PI texts to be in line with the innovator product Micardis Plus (no new additional data are submitted by the MAH)	PT/H/1105/ 1-3/IB/001/G	IB	11-11-204	26-12-2014	Approved	N
Minor changes to an approved test procedure of the finished product for addition of note to analytical procedure for related substance	PT/H/1105/ 1-3/IA/002	IA	27-04-2015	27-05-2015	Approved	N
To submit updated Ph.Eur. Certificate of Suitability for telmisartan from already approved manufacturer Change in the name of finished product manufacture	PT/H/1105/ 1-3/IA/003/G	IA/G	08-12-2015	07-01-2016	Approved	N
Change to importer, batch release arrangements and quality control testing of the finished product	PT/H/1105/ 2/IB/004	IB	29-01-2016	08-02-2016	Approved	N
To change the invented name of the product in Spain	PT/H/1105/ 1-3/IB/006	IB	02-06-2016	14-06-2016	Approved	N