COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Bisoprololfumaraat/Hydrochloorthiazide Mylan 5 mg/12.5 mg and 10 mg/25 mg, film-coated tablets

(bisoprolol fumarate and hydrochlorothiazide)

NL/H/5616/001-002/DC

Date: 1 June 2022

This module reflects the scientific discussion for the approval of Bisoprololfumaraat/Hydrochloorthiazide Mylan 5 mg/12.5 mg and 10 mg/25 mg, film-coated tablets. The procedure was finalised at 19 April 2012 with Malta as RMS (MT/H/0138/001-002/DC). The current RMS is the Netherlands (NL/H/5616/001-002/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 Bisoprololfumaraat/Hydrochloorthiazide Mylan 5 mg/12.5 mg and 10 mg/25 mg, film-coated tablets, from Mylan B.V.

The product is indicated for essential hypertension. The fixed-dose combination of bisoprolol fumarate/hydrochlorothiazide 5 mg/12.5 mg or bisoprolol fumarate/hydrochlorothiazide 10 mg/25 mg is indicated in patients whose blood pressure cannot be adequately controlled using bisoprolol or hydrochlorothiazide 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 Concor 5 plus 5mg/12.5 mg and 10 mg/25 mg, film-coated tablets which has been registered in Germany by MERCK Serono GmbH since 1993.

The reference member state (RMS) of the initial procedure was Malta and the concerned member states (CMS) were Austria, Belgium, Finland, Germany, Hungary, Luxembourg and The Netherlands. The role of RMS was transferred to the Netherlands on 13 May 2022.

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

II. QUALITY ASPECTS

II.1 Introduction

Bisoprololfumaraat/Hydrochloorthiazide Mylan 5 mg/12.5 mg is a red-gray, film-coated, round, biconvex tablet, inscribed with 'BH4' over 'M' on one side and a score line on the other side.

The film-coated tablets are packed in blister packs comprising of OPA/AL/PVC film on one side and hard tempered aluminium foil coated with heat seal lacquer on the other side or white coloured high-density polyethylene (HDPE) bottle with white opaque polypropylene (PP) screw cap.

The excipients are:
Tablet core - cellulose microcrystalline (E460), lactose anhydrous, pregelatinised starch (maize), colloidal anhydrous silica (E551), magnesium stearate, sodium laurilsulfate and croscarmellose sodium (E468 and iron oxide red (E172).

Film-coating - titanium dioxide (E171), polydextrose FCC (E1200), hypromellose (E464), macrogol, iron oxide black (E172) and iron oxide red (E172).

II.2 Drug Substance

The active substances, Bisoprolol fumarate (Ph. Eur. monograph 04/2008:1710) and hydrochlorothiazide (Ph.Eur. monograph 04/2009:0394) are both described in the Ph. Eur. The CEP procedure is used for both active substances. The drug substance specifications are in line with the Ph. Eur. and with the additional tests and requirements given in the CEP.

II.3 Medicinal Product

The development of the product has been described, the choice of excipients is justified and their functions explained; excipients common to pharmaceutical manufacture have been selected. Validation of the analytical methods employed has been presented. Batch analysis has been performed on three batches of each strength (including the bio batch). The stability studies on the products in the containers proposed for marketing (blister packs and HDPE bottle packs) have been undertaken on three batches of each strength (including the bio batches). The proposed shelf life of 24 months (with no special storage conditions) for the commercial packs and 12 months (with no special storage conditions) for the simulated bulk pack can be accepted. An in-use shelf-life of 30 days has been established for the product in the HDPE containers.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Bisoprololfumaraat/Hydrochloorthiazide Mylan 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 Bisoprololfumaraat/Hydrochloorthiazide Mylan 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 Concor 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

Bisoprolol fumarate and 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.

For this generic application, the MAH has submitted three bioequivalence studies, which are discussed below.

IV.2 Pharmacokinetics

To support the application, the MAH has submitted 3 bioequivalence studies as follows:

1. Study 109-10 was conducted in fasting state comparing the 10 mg/25 mg tablets (Test) and Concor Plus Bisoprolol/Hydrochlorothiazide) 10 mg/25 mg tablets (Reference) of Merck, Germany.
2. Study 110-10 was conducted in fasting state comparing the MAH's Bisoprolol Fumarate/Hydrochlorothiazide 10 mg/6.25 mg tablets with Lodoz 10 mg/6.25 mg tablets of Merck, Germany.
3. Study 111-10 was conducted in fasting state comparing the MAH's Bisoprolol Fumarate/Hydrochlorothiazide 2.5 mg/6.25 mg tablets with Lodoz 2.5 mg/6.25 mg tablets of Merck, Germany.

Studies 110-10 and 111-10, have been conducted using a different reference product to this procedure, and therefore are not applicable even as supportive data for this application.

Study 109-10, showed bioequivalence in line with CPMP/EWP/QWP/1401/98 Rev. 1/ Corr ** between the 10/25 mg tablets (Test) and Concor Plus Bisoprolol/Hydrochlorothiazide) 10/25 mg tablets (Reference) of Merck, Germany.

Bioequivalence Study number 109/10

The study was an open label, balanced, randomised, two treatment, two sequence, two period, cross-over, single-dose comparative oral bioavailability study of Bisoprolol/Hydrochlorothiazide 10/25 mg tablets (Test) and Concor Plus

(Bisoprolol/Hydrochlorothiazide) 10/25 mg tablets (Reference) of Merck, Germany in healthy, adult, human subjects under fasting conditions. The company/CRO responsible for conduct of study, was the subject of a GCP inspection in February 2009 where it is understood that the GCP inspection did not find any critical or major issues.

The investigators have provided a statement to confirm that the study was conducted "in accordance with all requirements regarding the obligations of investigators and all other pertinent requirements of the ICH 'Guideline for Good Clinical Practice' and 'Good Laboratory Practice"

The schedule of blood collection was adequate for AUC_t > 80% of AUC_{inf}. The sampling frequency around T_{max} was adequate for accurate C_{max} estimation. The washout period of 8 days was adequate to avoid carry-over. The C_{max}, AUC_{0-t} , $AUC_{0-\infty}$ and T_{max} variables and statistical methodology is accepted.

Bioequivalence results for bisoprolol:

Parameters	Lntransformed Data			
	Geometric Mean		(A/B) Ratio (%)	90% Confidence Interval
	Test (A)	Reference(B)		
C_{max}	38.9643	36.4542	106.89	102.51-111.45
$AUC_{0\to t}$	593.9488	581.7698	102.09	97.65-106.74
$AUC_{0\to\infty}$	616.5318	603.3953	102.18	97.54-107.04

Bioequivalence results for hydrochlorothiazide:

Parameters	Lntransformed Data			
	Geometric Mean		(A/B) Ratio (%)	90% Confidence Interval
	Test (A)	Reference (B)		
C_{max}	154.0034	152.0379	101.29	94.87-108.15
$AUC_{0\to t}$	1074.4684	1107.6855	97.00	88.54-106.27
$AUC_{0\to\infty}$	1114.4379	1143.4780	97.46	89.68-105.92

The 90% confidence intervals for test/reference ratio lie within the acceptance criteria of 80 – 125%. This is acceptable.

<u>Conclusion for Bioequivalence Study number 109/10</u>

The 90% confidence intervals for test/reference ratio lie within the acceptance criteria of 80-125%. This is acceptable. The MAH has submitted results that are consistent with

bioequivalence between the test and reference products at the Bisoprolol fumarate/Hydrochlorothiazide 10 mg/25 mg presentation.

Biowaiver

With respect to the biowaiver request for the Bisoprolol fumarate and Hydrochlorothiazide 5mg/12.5mg tablets, according to the RMS the MAH has submitted an adequate justification as to why a biowaiver is acceptable and as well as reasoned grounds for accepting a deviation for condition c i as requested by CPMP/EWP/QWP/1401/98 Rev. 1, January 2010. This view was not shared by a CMS and raised a PSPRH on the lines that the conditions of CPMP/EWP/QWP/1401/98 Rev. 1, January 2010 with respect to Biowaiver request for the 5/12.5 mg strengths have not been met. Procedure was thus referred to CMDh. Another bioequivalence study proving bioequivalence for the 5 mg/12.5 mg tablets to reference product Concur 5 Plus was submitted by the MAH.

Bioequivalence Study 278-11

This was an open label, randomised, two treatment, two sequence, two period, crossover, single dose, fasting, comparative oral bioavailability study to establish comparative bioequivalence of Bisoprolol/Hydrochlorothiazide 5 mg/12.5mg tablets (test) and Concor 5 Plus (Bisoprolol/Hydrochlorothiazide 5 mg/12.5mg) (Reference) of Merck Pharma, Germany in healthy, Indian, adult, human subjects (aged between 18-55 years).

The MAH states that the study meets the requirements and principles of the Declaration of Helsinki and current ICH-GCP, GLP, National and European guideline norms. All the clinical procedures were conducted in accordance with the requirements of the study protocol, and ICH-GCP. The study protocol and the relevant submitted SOP's have been assessed and deemed to be acceptable

The bioequivalence study design and sampling periods were acceptable, with an adequate wash-out period which is greater than five times the $t_{1/2}$. The sampling frequency enabled an adequate estimation of C_{max}. Statistical data and a graphical representation to cover the plasma concentration time curve long enough to provide an estimate of the extent of absorption, i.e. AUC_{0-t} last is ≥80% $AUC_{0-\infty}$ has been provided.

The 90% confidence intervals calculated for the primary parameters C_{max}, and AUC_{0-t} for Bisoprolol and Hydrochlorothiazide fall within the 80 – 125% acceptance range after single dose administration under fasting conditions. Bioequivalence has been show.

Bioequivalence results for bisoprolol:

Parameter (Unit)	(Ln-transformed) Geometric Least Square Mean			90% Confidence Interval T vs R	Intra Subject CV (%)	Power (%)
	Test Product (T)	Reference Product (R)	Ratio (T/R)%			
C_{max} (ng/mL)	19.1097	19.4722	98.14	93.96-102.50	8.8	100
AUC_{0-t} (hr.ng/mL)	289.9344	290.0676	99.95	95.62-104.48	9.0	100

Bioequivalence results for hydrochlorothiazide:

Parameter (Unit)	(Ln-transformed) Geometric Least Square Mean			90% Confidence Interval T vs R	Intra Subject CV (%)	Power (%)
	Test Product (T)	Reference Product (R)	Ratio (T/R)%			
C_{max} (ng/mL)	74.4630	73.4044	101.44	94.01-109.47	15.4	100
AUC_{0-t} (hr.ng/mL)	519.8172	497.3246	104.52	96.29-113.46	16.7	100

Conclusion for Bioequivalence Study 278-11
Based on the submitted bioequivalence study, Bisoprololfumaraat/Hydrochloorthiazide Mylan is considered bioequivalent with Concur 5 Plus 5/12.5mg

IV.3 Discussion on the clinical aspects

For this authorisation, reference is made to the clinical studies and experience with the innovator product Concor. 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 package leaflet has 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 language used for the purpose of user testing the PIL was English. The results show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use. The test consisted of: a pilot test with 2 participants, followed by two rounds with 10 participants each. The questions covered the following areas sufficiently: traceability, comprehensibility and applicability.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Bisoprololfumaraat/Hydrochloorthiazide Mylan 5 mg/12.5 mg and 10 mg/25 mg, film-coated tablets have a proven chemical-pharmaceutical quality and are generic forms of Concor 5 plus 5 mg/12.5 mg and 10 mg/25 mg, film-coated tablets. Concor 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 Bisoprololfumaraat/Hydrochloorthiazide Mylan with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 19 April 2012.

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