LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Bisoprolol Bausch Health
(bisoprolol fumarate)

SE/H/2152/01-03/DC

This module reflects the scientific discussion for the approval of Bisoprolol Bausch Health. The procedure was finalised on 2022-03-02. For information on changes after this date please refer to the module 'Update'.

Postadress/Postal address: P.O. Box 26, SE-751 03 Uppsala, SWEDEN
Besöksadress/Visiting address: Dag Hammarskjölds väg 42, Uppsala
Telefon/Phone: +46 (0)18 17 46 00 Fax: +46 (0)18 54 85 66
Internet: www.lakemedelsverket.se E-mail: registrator@lakemedelsverket.se

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, a marketing authorisation has been granted for Bisoprolol Bausch Health, 1,25 mg, 3,75 mg, 7,5 mg, film-coated tablet.

The active substance is bisoprolol fumarate. A comprehensive description of the indication and posology is given in the SmPC.

For recommendations to the marketing authorisation not falling under Article 21a/22a/22 of Directive 2001/83/EC and conditions to the marketing authorisation pursuant to Article 21a/22a/ 22 of Directive 2001/83/EC to the marketing authorisation, please see section VI.

The application for Bisocard, 1.25, 3.75 and 7.5 mg, film-coated tablet, is a generic application made according to Article 10(1) of Directive 2001/83/EC. The applicant, Bausch Health Ireland Limited, applies through the Decentralised Procedure with Sweden acting as reference member state (RMS) and PL as concerned member state (CMS).

The reference medicinal product chosen for the purposes of establishing the expiry of the data protection period is Emconcor CHF, 1.25, 3.75 and 7.5 mg, film-coated tablet, authorised in SE since 1999, with Merck AB as marketing authorisation holder.

The reference product used in the bioequivalence studies is Cardicor, 3.75 and 10 mg, film-coated tablet, from UK with Merck Serono Ltd as marketing authorisation holder.

European Reference Product (ERP)
A European Reference Product is used in CMS PL: Emconcor CHF, 1.25, 3.75 and 7.5 mg, film-coated tablet, authorised in SE since 1999, with Merck AB as marketing authorisation holder.

The justification to use this product is based on the RMS's own files. The ERP information was circulated during validation period.

Potential similarity with orphan medicinal products
According to the application form and a check of the Community Register of orphan medicinal products there is no medicinal product designated as an orphan medicinal product for a condition relating to the indication proposed in this application.

II. QUALITY ASPECTS

II.1 Drug Substance

The structure of the drug substance has been adequately proven and its physico-chemical properties are sufficiently described.

The manufacture of the drug substance has been adequately described and satisfactory specifications have been provided for starting materials, reagents and solvents.

The drug substance specification includes relevant tests and the limits for impurities and degradation products have been justified. The analytical methods applied are suitably described and validated.

Stability studies confirm the retest period.

II.2 Medicinal Product

The medicinal product is formulated using excipients listed in section 6.1 in the Summary of Product Characteristics.

The manufacturing process has been sufficiently described and critical steps identified.

The tests and limits in the specification are considered appropriate to control the quality of the finished product in relation to its intended purpose.

Stability studies have been performed and data presented support the shelf life and special precautions for storage claimed in the Summary of Product Characteristics, sections 6.3 and 6.4.

III. NON-CLINICAL ASPECTS

Pharmacodynamic, pharmacokinetic and toxicological properties of bisoprolol are well known. As bisoprolol is a widely used, well-known active substance, no further studies are required and the applicant provides none. Overview based on literature review is, thus, appropriate.

Environmental Risk Assessment (ERA)
Since Bisocard is a generic product, it will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

There are no objections to approval of Bisocard from a non-clinical point of view.

IV. CLINICAL ASPECTS

Pharmacokinetics
The current marketing authorisation application covers the 1.25 mg, 3.75 mg and 7.5 mg tablet strengths. To support the marketing authorisation application the applicant has conducted two bioequivalence studies comparing Bisocard (3.75 mg and 10 mg tablet strengths, respectively) with the reference product Cardicor.

Pharmacokinetic properties of the active substance
Absorption: Bisoprolol has an oral bioavailability of 85-90 %. Following an oral dose of 5-20 mg maximal plasma concentrations occur at 2 to 4 hours. The pharmacokinetics of bisoprolol is not affected by food, and therefore there are no restrictions with respect to food in the SmPC of the originator.

Linearity: The pharmacokinetics of bisoprolol is linear within the dose range 5-20 mg.

Elimination: The terminal half-life is 10-12 hours.

Study ARL/15/087 (10 mg)
Methods
This was a single-dose, two-way crossover study conducted in 24 healthy volunteers, comparing Bisocard, 10 mg, tablet with Cardicor, 10 mg, tablet under fasting conditions. Blood samples for concentration analysis were collected pre-dose and up to 72 hours post-dose. Plasma concentrations of bisoprolol were determined with an LC-MS/MS method. Analysis of variance (ANOVA) was performed on the log-transformed data for AUC_{0-t} and C_{max}. The study was conducted between 08 February 2016 and 19 February 2016.

Results
The results from the pharmacokinetic and statistical analysis are presented in Table 1 below.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} median, range) for bisoprolol 10 mg, n=23.

Treatment	AUC_{0-t} ng*h/ml	C_{max} ng/ml	t_{max} h
Test	**706.6 ± 143.4**	**41.6 ± 6.66**	**2.67 (1.00 - 4.50)**
Reference	**658.8 ± 115.8**	**40.9 ± 5.99**	**2.67 (1.00 - 5.00)**
***Ratio (90% CI)**	**107.07 (102.54 - 111.79)**	**101.65 (98.52 - 104.87)**	**-**

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 plasma concentration

**calculated based on ln-transformed data*

For AUC_{0-t} and C_{max} the 90% confidence interval for the ratio of the test and reference products fell within the conventional acceptance range of 80.00-125.00%.

Study ARL/15/256 (3.75 mg)
Methods
This was a single-dose, two-way crossover study conducted in 24 healthy volunteers, comparing Bisocard, 3.75 mg, tablet with Cardicor, 3.75 mg, tablet under fasting conditions. Blood samples for concentration analysis were collected pre-dose and up to 72 hours post-dose. Plasma concentrations of bisoprolol were determined with an LC-MS/MS method. Analysis of variance (ANOVA) was performed on the log-transformed data for AUC_{0-t} and C_{max}. The study was conducted between 06 April 2016 and 17 April 2016.

Results
The results from the pharmacokinetic and statistical analysis are presented in Table 2 below.

Table 2. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} median, range) for bisoprolol 3.75 mg, n=24.

Treatment	AUC_{0-t} ng*h/ml	C_{max} ng/ml	t_{max} h
Test	**260.0 ± 46.5**	**16.7 ± 2.57**	**2.33 (2.00 - 5.00)**
Reference	**253.7 ± 51.3**	**16.2 ± 2.32**	**3.33 (1.50 - 4.50)**
***Ratio (90% CI)**	**102.94 (98.95 - 107.08)**	**103.09 (99.84 - 105.46)**	**-**

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 plasma concentration

**calculated based on ln-transformed data*

For AUC_{0-t} and C_{max} the 90% confidence interval for the ratio of the test and reference products fell within the conventional acceptance range of 80.00-125.00%.

A bracketing approach was taken with bioequivalence studies performed with the 3.75 mg and the 10 mg tablet strengths. A biowaiver was sought for the additional strengths of 1.25 mg and 7.5 mg.

Discussion and overall conclusion

The bioequivalence studies and their statistical evaluation were in accordance with accepted standards for bioequivalence testing, as stated in the Guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev 1/Corr **). The bioanalytical methods were adequately validated.

Absence of studies with the additional strengths of 1.25 mg and 7.5 mg is acceptable, as all conditions for biowaiver for additional strengths, as described in the Guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev 1/Corr **) are fulfilled. Pharmacokinetics of bisoprolol is linear between 5 and 20 mg. Linearity appears not to have been demonstrated for doses lower than 5 mg, but as bisoprolol is highly soluble and has a high bioavailability at doses from 5 mg and upwards, relevant non-linearity (less than proportional than dose) between doses of 1.25 mg and 3.75 mg is unlikely.

Based on the submitted bioequivalence studies, Bisocard is considered bioequivalent with Cardicor.

Pharmacodynamics/Clinical efficacy/Clinical safety

No new studies on pharmacodynamics, clinical efficacy or clinical safety have been submitted. Provided that bioequivalence with the originator product is demonstrated, additional data is not necessary.

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 Bisocard.

Safety specification

Summary of safety concerns	
Important identified risks	None
Important potential risks	None
Missing information	None

Pharmacovigilance Plan

Routine pharmacovigilance is suggested and no additional pharmacovigilance activities are proposed by the applicant, which is endorsed.

Risk minimisation measures

Routine risk minimisation is suggested and no additional risk minimisation activities are proposed by the applicant, which is endorsed.

Summary of the RMP

The submitted Risk Management Plan, version 1.0 signed 2021-04-07 is considered acceptable. The proposed safety specification, pharmacovigilance plan and risk minimisation measures are in line with the HaRP assessment report for Bisoprolol as published on the CMDh website in July 2019. A range of risks included in earlier agreed RMPs for bisoprolol products were considered appropriate to remove due to the absence of management plan for the risks, as can be seen in the HaRP report.

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the RMS;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time, but via different procedures.

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 Polish.
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.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The quality of the generic product, Bisocard, is found adequate. There are no objections to approval of Bisocard, from a non-clinical and clinical point of view. Bioequivalence between the test and reference product has been adequately demonstrated. The product information is acceptable. The application is therefore recommended for approval.

List of recommendations not falling under Article 21a/22a/22 of Directive 2001/83/EC in case of a positive benefit risk assessment

N/A

List of conditions pursuant to Article 21a/22a or 22 of Directive 2001/83/EC

N/A

VII. APPROVAL

The decentralised procedure for Bisoprolol Bausch Health, 1,25 mg, 3,75 mg, 7,5 mg, film-coated tablet was positively finalised on 2022-03-02.

LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

Public Assessment Report – Update

Procedure number*	Scope	Product Information affected (Yes/No)	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse

*Only procedure qualifier, chronological number and grouping qualifier (when applicable)

Postadress/Postal address: P.O. Box 26, SE-751 03 Uppsala, SWEDEN
Besöksadress/Visiting address: Dag Hammarskjölds väg 42, Uppsala
Telefon/Phone: +46 (0)18 17 46 00 Fax: +46 (0)18 54 85 66
Internet: www.lakemedelsverket.se E-mail: registrator@lakemedelsverket.se