LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

Public Assessment Report

Scientific discussion

Bisoprolol Medical Valley (bisoprolol fumarate)

SE/H/1780/01-06/DC

This module reflects the scientific discussion for the approval of Bisoprolol Medical Valley. The procedure was finalised on 2018-12-05. For information on changes after this date please refer to the module 'Update'.

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I. INTRODUCTION

The application for Bisoprolol Medical Valley, 1.25 mg, 2.5 mg, 3.75 mg, 5 mg, 7.5 mg and 10 mg, tablet, is a generic application made according to Article 10(1) of Directive 2001/83/EC. The applicant, Medical Valley Invest AB, applies through the Decentralised Procedure with Sweden acting as reference member state (RMS) and Denmark and Iceland as concerned member states (CMS).

The reference medicinal product chosen for the purposes of establishing the expiry of the data protection period is Cardicor, 10 mg, tablet authorised in United Kingdom since 2004, with Merck as marketing authorisation holder.

The reference product used in the bioequivalence study is Cardicor 3.75 mg and 10 mg, tablet from United Kingdom with Merck as marketing authorisation holder.

European Reference Product (ERP)
A European Reference Product is used in CMS IS: Cardicor, 1.25 mg, 2.5 mg, 3.75 mg, 5 mg, 7.5 mg and 10 mg, tablet authorised in Sweden since 1999, with Merck as marketing authorisation holder.
The justification to use this product is based on RMS's own files. The ERP information received from Sweden was circulated during validation period.

For approved indications, see the Summary of Product Characteristics.

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

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

III.1 Discussion on the non-clinical aspects

Since this product has been shown to be essentially similar and refer to a product approved based on a full application with regard to preclinical data, no further such data have been submitted or are considered necessary.

IV. CLINICAL ASPECTS

IV.1 Pharmacokinetics

To support the marketing authorisation application the applicant has conducted two bioequivalence studies comparing Bisoprolol Medical Valley (the 3.75 mg tablet and the 10 mg tablet, respectively) with the reference product Cardicor (Merck).

Pharmacokinetic properties of the active substance
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. The pharmacokinetics of bisoprolol is linear within the dose range 5 - 20 mg. The terminal half-life is 10-12 hours.

Study -10 mg

Methods
This was a single-dose, two-way crossover study conducted in 23 healthy volunteers, comparing Bisoprolol Medical Valley, 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}.

Results
The results from the pharmacokinetic and statistical analysis are presented in
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 3.75 mg

Methods
This was a single-dose, two-way crossover study conducted in 24 healthy volunteers, comparing Bisoprolol Medical Valley, 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}.

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

Table 1. 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, 2.5 mg, 5 mg and 7.5 mg.

Discussion and overall conclusion

The bioequivalence studies and its 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, 2.5 mg, 5 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 and since the pharmacokinetics of bisoprolol is linear between 5 mg and 20 mg.

Based on the submitted bioequivalence studies, Bisoprolol Medical Valley is considered bioequivalent with Cardicor.

IV.2 Discussion on the clinical aspects

Since this product has been shown to be essentially similar and refer to a product approved based on a full application with regard to clinical efficacy/safety data, no further such data have been submitted or are considered necessary.

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 Bisoprolol Medical Valley.

Safety specification

Summary of safety concerns	
Important identified risks	• Bradycardia • Aggravation (/worsening) of chronic heart failure • Bronchospasm (patients with bronchial asthma or chronic obstructive pulmonary disease) • Hypotension • Decreased diabetic control and masking of hypoglycemic effects • Syncope
Important potential risks	• Renal failure • Toxic skin reactions • Fibrosis conditions (Peyronie's disease, retroperitoneal fibrosis, pulmonary fibrosis) • Interstitial lung disease/Interstitial pneumonitits • Fatal hepatotoxicity
Missing information	• Children and adolescents under 18 years of age

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 1.1 signed 24 September 2018 is considered acceptable.

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

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 the user test of the medicinal product Bisoprolol Orifarm (UK/H/1817/01-04/DC) regarding content and to the medicinal product Candesartan Cilexetil 8 mg, 16 mg and 32 mg tablets leaflet (NL/H/2046/47/48/2279/2391) regarding layout. The bridging report submitted by the applicant has been found acceptable.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The quality of the generic product, Bisoprolol Medical Valley, is found adequate. There are no objections to approval of Bisoprolol Medical Valley, 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/22 of Directive 2001/83/EC in case of a positive benefit risk assessment

N/A

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

N/A

VII. APPROVAL

The Decentralised procedure for Bisoprolol Medical Valley, 1.25 mg, 2.5 mg, 3.75 mg, 5 mg, 7.5 mg, 10 mg, Tablet was positively finalised on 2018-12-05.

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Public Assessment Report – Update

Procedure number*	Scope	Product Information affected	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse

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

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