LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Bisoprolol STADA Arzneimittel AG
(bisoprolol fumarate)

SE/H/2520/01-06/DC

This module reflects the scientific discussion for the approval of Bisoprolol STADA Arzneimittel AG. The procedure was finalised on 2025-02-26. For information on changes after this date please refer to the module 'Update'.

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I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, a marketing authorisation has been granted for Bisoprolol STADA Arzneimittel AG, 1,25 mg, 2,5 mg, 3,75 mg, 5 mg, 7,5 mg, 10 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 Bisoprolol STADA Arzneimittel AG, 1.25 mg, 2.5 mg, 3.75, 5 mg, 7.5 mg, 10 mg, film-coated tablet, is a Generic Art. 10(1) application submitted according to Directive 2001/83/EC. The applicant applies through the Decentralised Procedure with Sweden acting as reference member state (RMS) and the following concerned member states (CMS): DE and IT.

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

The reference product used in the bioequivalence study is Cardicor, 3.75 mg, 10 mg, film-coated tablet, purchased from UK, with Merck Serono Limited, United Kingdom, as marketing authorisation holder.

Potential similarity with orphan medicinal products
N/A

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

Pharmacology/Pharmacokinetics/Toxicology
Pharmacodynamic, pharmacokinetic and toxicological properties of bisoprolol fumarate are well known. As bisoprolol fumarate is a widely used, well-known active substance, no further studies are required, nor does the applicant provide any. Overview based on literature review is, thus, appropriate.

Environmental Risk Assessment (ERA)
Since Bisoprolol STADA Arzneimittel AG 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 Bisoprolol STADA Arzneimittel AG from a non-clinical point of view.

IV. CLINICAL ASPECTS

Pharmacokinetics
To support the marketing authorisation application the applicant has conducted two bioequivalence studies comparing Bisoprolol STADA Arzneimittel AG with the reference product Cardicor (Merck).

Pharmacokinetic properties of the active substance

Absorption
Bisoprolol is absorbed and has a biological availability of about 90% after oral administration.

Distribution
The distribution volume is 3.5 l/kg. The plasma protein binding of bisoprolol is about 30%.

Biotransformation and Elimination
Bisoprolol is excreted from the body by two routes. 50% is metabolised by the liver to inactive metabolites which are then excreted by the kidneys. The remaining 50% is excreted by the kidneys in an unmetabolised form. Total clearance is approximately 15 l/h. The half-life in plasma of 10-12 hours gives a 24 hour effect after dosing once daily.

Linearity
The kinetics of bisoprolol are linear and independent of age.

Study ARL/15/087 (10 mg)
Methods
This was a single-dose, two-way crossover study conducted in 23healthy volunteers, comparing Bisoprolol STADA Arzneimittel AG, 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 Bisoprolol STADA Arzneimittel AG, 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, 2.50 mg, 5 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, 2.50 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. As per EMA bioequivalence guideline (CPMP/EWP/QWP/1401/98 Rev. 1/ Corr **), "Where bioequivalence assessment at more than two strengths is needed, e.g. because of deviation from proportional composition, a bracketing approach may be used. In this situation it can be acceptable to conduct two bioequivalence studies, if the strengths selected represent the extremes, e.g. the highest and the lowest strength or the two strengths differing most in composition, so that any differences in composition in the remaining strengths is covered by the two conducted studies."
The 3.75 mg, 2.5 mg and 1.25 mg strengths are dose proportional and show equally the most difference in composition from 10 mg. 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.
The results of the study with the 3.75 mg strength can be extrapolated to 2.5mg and 1.25mg strengths, given their dose proportional composition. Thus, from a pharmacokinetic point of view, it is sufficient to establish bioequivalence with the 3.75 mg and 10 mg strengths.

Based on the submitted bioequivalence studies, Bisoprolol STADA Arzneimittel AG 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 Bisoprolol STADA Arzneimittel AG.

Part II Safety specification
The MAH has submitted the version 0.3 RMP dated 2025-02-12 and proposed the following summary safety concerns:

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

Having considered the data in the safety specification it is agreed that the safety concerns listed by the MAH are appropriate. It is in line with the HaRP Assessment Report for bisoprolol.

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

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

Part VI Summary of the RMP
The Summary of the RMP is endorsed.

Conclusion RMP assessment
The submitted Risk Management Plan, version 0.3 signed 2025-02-12 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

The package leaflet for 5 and 10 mg 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 PL 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.

A user consultation with target patient groups on the package information leaflet (PL) for 1.25 mg, 2.5 mg, 3.75 mg and 7.5 mg has been performed on the basis of a bridging report making reference to the leaflet for 5 mg and 10 mg. However, since the two leaflets has been merged into one, adding the strengths 1.25 mg, 2.5 mg, 3.75 mg and 7.5 mg to the leaflet for 5 and 10 mg only the user test for 5 and 10 mg has been assessed.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The quality of the generic product, Bisoprolol STADA Arzneimittel AG, is found adequate. There are no objections to approval of Bisoprolol STADA Arzneimittel AG, 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 benefit/risk is considered positive, and 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 STADA Arzneimittel AG, 1,25 mg, 2,5 mg, 3,75 mg, 5 mg, 7,5 mg, 10 mg, Film-coated tablet was positively finalised on 2025-02-26.

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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)

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