LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

# Public Assessment Report
# Scientific discussion

# Bisoprolol Farmacia
# (bisoprolol fumarate, bisoprolol)

**This module reflects the scientific discussion for the approval of Bisoprolol Farmacia. The procedure was finalised at 2026-04-10. For information on changes after this date please refer to the module 'Steps taken after the finalisation of the initial procedure - Summary'.**

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# I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have agreed to grant a marketing authorisation for Bisoprolol Farmacia, 1,25 mg, 2,5 mg, 5 mg, Film-coated tablet.

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

# II. EXECUTIVE SUMMARY

## II.1 About the product

Pharmacotherapeutic group:
Beta blocking agents, selective; ATC Code: C07AB07

Mechanism of action
Bisoprolol is a highly beta1-selective-adrenoceptor blocking agent, lacking intrinsic stimulating and relevant membrane stabilising activity. It only shows low affinity to the beta2-receptor of the smooth muscles of bronchi and vessels as well as to the beta2-receptors concerned with metabolic regulation. Therefore, bisoprolol is generally not to be expected to influence the airway resistance and beta2-mediated metabolic effects. Its beta1-selectivity extends beyond the therapeutic dose range.

Claimed indications
- stable chronic heart failure with reduced systolic left ventricular function in addition to ACE inhibitors, and diuretics, and optionally cardiac glycosides
- hypertension and angina pectoris

## II.2 General comments on the submitted dossier

The application for Bisoprolol Farmacia, 1,25 mg, 2,5 mg, 5 mg, Tablet, is a Generic Art. 10(1) application submitted according to Directive 2001/83/EC. The applicant applies for a marketing authorisation in Sweden through a National Procedure.

The reference medicinal product chosen for the purposes of establishing the expiry of the data protection period is Emconcor, 2,5mg, film-coated tablet authorised in Sweden since 1999, with Merck as marketing authorisation holder.

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

## II.3 General comments on compliance with GMP, GLP, GCP and agreed ethical principles

The MPA has been assured that acceptable standards of GMP are in place for these product types at all sites responsible for the manufacture and assembly of this product.

For manufacturing sites within the European Community, the MPA has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

For manufacturing sites outside the European Community, the MPA has accepted copies of current GMP Certificates of satisfactory inspection summary reports, 'close-out letters' or 'exchange of information' issued by the inspection services of the competent authorities (or those countries with which the EEA has a Mutual Recognition Agreement for their own territories) as certification that acceptable standards of GMP are in place at those non-Community sites.

GMP active substance
Regarding the statement on GMP for the active substance statement/declaration is provided from the manufacturer(s) responsible for manufacture of the finished product and batch release situated in the EU.

GCP aspects
A statement on the application of appropriate GCP standards in the submitted studies has been provided. No issues regarding GCP have been identified. The clinical and the bioanalytical facilities were inspected by the SE and DK authority in 2014, without any critical findings. No inspection of the submitted bioequivalence studies is needed.

# III. SCIENTIFIC OVERVIEW AND DISCUSSION

## III.1 Quality aspects

**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.

**Drug 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.2 Non-clinical aspects

**Pharmacology/Pharmacokinetics/Toxicology**
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, nor does the applicant provide any. Overview based on literature review is, thus, appropriate.

**Environmental Risk Assessment (ERA)**
The Applicant has provided an ERA report for their bisoprolol product. The ERA report is not in line with the current CHMP ERA guideline (EMEA/CHMP/SWP/4447/00 Rev. 1- Corr.*, 22 August 2024) and is therefore not considered acceptable. No conclusion on the environmental risks of the present bisoprolol product can be drawn at this moment.
In specific, the submitted data indicate that a phase II ERA was triggered and it was conducted based on the data available on the internet (fass.se website) as well as QSAR data on ecotoxicity. Both are not considered acceptable according to the current guideline.
It is acknowledged that the Applicant has contacted original MAH and EMA for access to any previously obtained ERA studies with bisoprolol, which is accepted as a strategy. However, no answer from MAH or EMA has been obtained yet.
Therefore, at the moment it is unclear if there is any suitable reference product ERA for bisoprolol.

The Applicant has committed to provide an updated ERA. The ERA may refer to a previously approved ERA in case a reference product with an ERA has been identified and previous public assessment report provided. Alternatively, an ERA may consist of studies performed by other MAH provided that the Letter of Access to these studies has been obtained, and studies submitted together with the ERA. Finally, the ERA may consist of studies newly performed by the Applicant. In that case, the Applicant is encouraged to contact other companies, either directly or e.g. via Medicines for Europe, to share the costs for the required ERA studies for bisoprolol. The Applicant has submitted a signed commitment letter for providing an ERA for bisoprolol within a defined timeframe, preferably 5 years.

## III.3 Clinical aspects

**Pharmacokinetics**
The marketing authorisation application covers the 1.25 mg, 2.5 mg and 5 mg tablet strengths, while the pharmaceutical development covers the development of Bisoprolol fumarate, 1.25 mg, 2.5 mg, 3.75 mg, 5 mg, 7.5 mg and 10 mg, tablets.

To support the marketing authorisation application the applicant has conducted two bioequivalence studies (3.75 mg and 10 mg tablet strengths, respectively) comparing Bisoprolol Farmacia (Bisoprolol fumarate) 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 Bisoprolol fumarate, 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 a LC-MS/MS method. Analysis of variance (ANOVA) was performed on the ln-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 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 fumarate, 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 a LC-MS/MS method. Analysis of variance (ANOVA) was performed on the ln-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 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 (99.84-106.46)** | **-** |

**$AUC_{0-t}$** 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 applied strengths of 1.25 mg, 2.5 mg and 5 mg.

Discussion and overall conclusion
The bioequivalence studies and the 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) and ICH M13A Guideline on bioequivalence for immediate-release solid oral dosage forms (EMA/CHMP/ICH/953493/2022). The bioanalytical methods were adequately validated.

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

Absence of studies with the applied strengths of 1.25 mg, 2.5 mg and 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) 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 between doses of 1.25 mg and 3.75 mg is considered unlikely.

**Pharmacodynamics/Clinical efficacy/Clinical safety**
No new studies on pharmacodynamics, clinical efficacy or clinical safety have been submitted. As bioequivalence with the originator product has been demonstrated, additional data is not necessary.

**Pharmacovigilance system**
Proposed MAH : Farmacia Nordic AB

The Applicant has submitted a revised signed Summary of the Applicant's/Proposed Future MAH's Pharmacovigilance System. Provided that the Pharmacovigilance System Master File fully complies with the new legal requirements as set out in the Commission Implementing Regulation and as detailed in the GVP module, the MPA considers the Summary acceptable.

**Risk Management Plan**
The applicant 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 Farmacia.

Part I Product(s) Overview
The Product(s) Overview is endorsed.

Part II Safety specification

Table SVIII.1: Summary of safety concerns, as per the CMDh website

| Safety Specification | Additional PhV activities | Additional Risk minimisation measures | Essential Targeted Questionnaries |
|---|---|---|---|
| **Important identified risk** | | | |
| *None* | - | - | - |
| **Important potential risk** | | | |
| *None* | - | - | - |
| **Missing information** | | | |
| *None* | - | - | - |

The summary of safety concerns is aligned with the HaRP assessment report for bisoprolol and is thus endorsed.

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 0.1 signed 20 Feb 2026**, 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.

**Periodic Safety Update Report (PSUR)**

Active substance is currently listed in the published EURD list

With regard to PSUR submission, the MAH should take the following into account:

- PSURs shall be submitted in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal. Marketing authorisation holders shall continuously check the European medicines web-portal for the DLP and frequency of submission of the next PSUR.

- For medicinal products authorized under the legal basis of Article 10(1) or Article 10a of Directive 2001/83/EC, no routine PSURs need to be submitted, unless otherwise specified in the EURD list.

- In case the active substance will be removed in the future from the EURD list because the MAs have been withdrawn in all but one MS, the MAH shall contact that MS and propose DLP and frequency for further PSUR submissions together with a justification.>

**Renewal date**
The renewal date will be 5 years after approval date.

# IV. BENEFIT RISK ASSESSMENT

The quality of the generic product, Bisoprolol Farmacia, is found adequate.

There are no objections to approval of Bisoprolol Farmacia 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.

# V. RECOMMENDATIONS AND CONDITIONS FOR MARKETING AUTHORISATION AND PRODUCT INFORMATION

## V.1 List of recommendations not falling under Article 21a/22 of Directive 2001/83/EC

**Post approval commitments**

| Description | Due date |
|---|---|
| Environmental Risk Assessment (ERA) | Within 5 years |

## V.2 List of conditions pursuant to Article 21a or specific obligations pursuant to Article 22 of Directive 2001/83/EC

N/A

## V.3 Summary of Product Characteristics (SmPC)

The approved SmPC is available on the Swedish MPA website.

## V.4 Package Leaflet (PL)

### V.4.1 Package Leaflet

The approved PL is available on the Swedish MPA website.

### V.4.2 Assessment of User Testing

A user consultation with target patient groups on the package information leaflet (PL) has been performed on the basis of a bridging report making reference to Bisoprolol Bausch Health film-coated tablets (authorised via decentralised procedure SE/H/2152/01-03/DC), Emconcor 5 mg film-coated tablet (authorised via national procedure in SE) and Emconcor CHF filmcoated tablets (authorised via MR procedure SE/H/00184/001-006).

The provided bridging report is considered acceptable.

# VI. STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

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