COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Bisoprolol Syri Pharma 0.5 mg/ml, oral solution (bisoprolol fumarate)

NL/H/5906/001/DC

Date: 17 October 2025

This module reflects the scientific discussion for the approval of Bisoprolol Syri Pharma 0.5 mg/ml, oral solution. The procedure was finalised on 8 November 2024. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

List of abbreviations

ACE	Angiotensin-Converting Enzyme
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
CQA	Critical Quality Attributes
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EEA	European Economic Area
EMA	European Medicines Agency
ERA	Environmental Risk Assessment
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
Ph.Eur.	European Pharmacopoeia
PL	Package Leaflet
QTPP	Quality Target Product Profile
RH	Relative Humidity
RMP	Risk Management Plan
RMS	Reference Member State
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 Bisoprolol Syri Pharma 0.5 mg/ml, oral solution, from Syri Pharma Limited.

The product is indicated for:

- treatment of hypertension,
- treatment of chronic stable angina pectoris,
- treatment of stable chronic heart failure with reduced systolic left ventricular function in addition to Angiotensin-Converting Enzyme (ACE) inhibitors, and diuretics, and optionally cardiac glycosides.

A comprehensive description of the up-to-date indications and posology is given in the SmPC.

The marketing authorisation has been granted pursuant to Article 10(3) of Directive 2001/83/EC, which concerns a hybrid application.

In this decentralised procedure, therapeutic equivalence is proven between the new product and the innovator product Emcor Deco 2.5 mg film-coated tablets which has been registered in Sweden by Merck B.V. by the procedure SE/H/0184/002 (Swedish product name is Emconcor CHF). In the Netherlands, Emcor Deco has been registered since 1999 (NL RVG 24503).

Bisoprolol Syri Pharma 0.5 mg/ml, oral solution and Emcor Deco 2.5 mg film-coated tablets differ in quantitative composition in terms of strength (2.5 mg/5ml instead of 2.5 mg) and in pharmaceutical form. The legal base of the application is therefore considered appropriate.

The concerned member state (CMS) involved in this procedure was Ireland.

II. QUALITY ASPECTS

II.1 Introduction

Bisoprolol Syri Pharma is an oral solution. The solution is clear and colourless, with a target pH 6.0. One ml of solution contains bisoprolol fumarate equivalent to 0.42 mg of the active substance bisoprolol.

The excipients are: methyl parahydroxybenzoate (E218), propyl parahydroxybenzoate (E216, sodium dihydrogen phosphate monohydrate (E339), disodium phosphate (anhydrous disodium hydrogen phosphate) and purified water.

The oral solution is sustained in a 150 ml bottle of Ph. Eur. Type III amber glass, with a tamper evident, child-resistant white plastic (polyethylene/polypropylene) closure cap with expanded polyethylene (EPE) liner. The bottle comes with a 20 ml oral syringe with an adaptor as medical

device. The syringe has a 5 ml graduation, 1 ml intermediate graduation and 0.5 ml sub graduation.

II.2 Drug Substance

The active substance is bisoprolol fumarate, an established active substance described in the European Pharmacopoeia (Ph.Eur.). The active substance is a white or almost white, slightly hygroscopic powder very soluble in water and freely soluble in methanol. Bisoprolol exhibits polymorphism. However, this is of no influence since the drug substance is dissolved in the drug product.

The CEP procedure is used for the active substance. Under the official Certification Procedures of the EDQM of the Council of Europe, manufacturers or suppliers of substances for pharmaceutical use can apply for a certificate of suitability concerning the control of the chemical purity and microbiological quality of their substance according to the corresponding specific monograph, or the evaluation of reduction of Transmissible Spongiform Encephalopathy (TSE) risk, according to the general monograph, or both. This procedure is meant to ensure that the quality of substances is guaranteed and that these substances comply with the Ph.Eur.

Manufacturing process

A CEP has been submitted. Therefore no details on the manufacturing process have been included.

Quality control of drug substance

The active substance specification is considered adequate to control the quality and meets the requirements of the monograph in the Ph.Eur., with additional requirements for one specific impurity and one residual solvent according to the CEP and limits for microbial contamination. Batch analytical data demonstrating compliance with this specification have been provided for one batch by the drug product manufacturer and three batches by the drug substance manufacturer.

Stability of drug substance

The active substance is stable for 48 months when stored under the stated conditions. Assessment thereof was part of granting the CEP (and has been granted by the EDQM).

II.3 Medicinal Product

Pharmaceutical development

The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines. The choice of excipients is justified and their functions explained. The objective of the development was to formulate a generic oral solution that is bioequivalent to the reference product Sequacor 10 mg film coated tablets. A quality target product profile (QTPP) was defined and critical quality attributes (CQAs) were identified. The investigations during pharmaceutical development focused on critical parameters such as description, assay, pH, microbial testing and related substances, which could be impacted by a change to the drug product formulation or by a

change to the manufacturing process. Formulation development trials were carried out to assess the inclusion of each excipient and their minimal optimal levels. When a robust formulation had been developed, the next step involved scaling up the manufacturing process. Accuracy of the proposed dosing device has been demonstrated at worst case scenario. The pharmaceutical development of the drug product has been adequately performed.

Bioequivalence (BE) has been established between the test product and reference product Sequacor 10 mg film coated tablets. Comparative *in-vitro* dissolution profiles complementary to the BE study have been performed and showed similarity between test and reference product.

Manufacturing process

The main steps of the manufacturing process are dispensing of components, mixing and solubilisation, filtration, filling and capping, labelling and packing. The manufacturing process has been validated according to relevant European/ICH guidelines. Process validation data on the product have been presented for three pilot scaled batches in accordance with the relevant European guidelines. The product is manufactured using conventional manufacturing techniques. Process validation for full scaled batches will be performed post authorisation.

Control of excipients

The excipients, except for sodium dihydrogen phosphate monohydrate, comply with Ph.Eur. requirements. Sodium dihydrogen phosphate monohydrate is controlled by the British Pharmacopoeia. These specifications are acceptable.

Microbiological attributes

Sufficient information has been provided on the microbiological attributes. The drug product is a non-sterile oral solution. Anti-microbial and anti-fungal preservatives (methyl parahydroxybenzoate and propyl parahydroxybenzoate) have been included in the formulation in order to minimise microbial/fungal proliferation as multiple doses may be taken from the drug product container. The microbial limits are met according to Ph. Eur.
The acceptance limits for microbial quality are according to the requirements of Ph.Eur.5.1.4 for aqueous preparations for oral use. This is acceptable.

Quality control of drug product

The finished product specifications are adequate to control the relevant parameters for the dosage form. The specification includes tests for description, fill volume, pH, assay and identification of bisoprolol fumarate, methyl parahydroxybenzoate and propyl parahydroxybenzoate, related substances, density, uniformity and accuracy of delivered doses from multidose containers and microbial limits. The release and shelf life limits are similar except for assay of preservatives methyl parahydroxybenzoate and propyl parahydroxybenzoate. An adequate nitrosamines risk evaluation report has been provided. No risk for presence of nitrosamines in the drug product was identified.

Satisfactory validation data for the analytical methods have been provided.

Batch analytical data on three batches at minimum commercial batch size from the proposed production site have been provided, demonstrating compliance with the specification.

Stability of drug product

Stability data on the product have been provided from three production scale batches, stored at 2-8°C, 25°C/ 60% RH and 40°C/75% RH. For one batch, data is provided up to 6 months under accelerated conditions and 24 months under long term conditions. For the two other stability batches, stability data is provided up to 6 months under accelerated conditions and 12 months under long term conditions. The conditions used in the stability studies are in accordance with applicable European guidelines. Photostability studies were performed in accordance with ICH recommendations and showed that the product is stable when exposed to light. A small increase in impurities is observed at accelerated conditions. At long-term and refrigerated conditions, no clear trends or changes were seen in any of the tested parameters and all results were in compliance with the shelf-life specification.

On basis of the data submitted, a shelf life was granted of 24 months. The labelled storage conditions are "This medicinal product does not require any special storage conditions.".
In-use stability data have been provided demonstrating that the product remains stable for 60 days after first opening of the container, when stored at 25°/60% RH. This is acceptable.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies

There are no substances of ruminant animal origin present in the product nor have any been used in the manufacturing of this product, so a theoretical risk of transmitting TSE can be excluded.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Bisoprolol Syri Pharma 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 Pharmacology, pharmacokinetics and toxicology

Pharmacodynamic, pharmacokinetic and toxicological properties of bisoprolol fumarate are well known. As bisoprolol fumarate is a widely used, well-known active substance, the applicant has not provided additional studies and further studies are not required. Overview based on literature review is, thus, appropriate.

III.2 Ecotoxicity/environmental risk assessment (ERA)

Since Bisoprolol Syri Pharma is intended for hybrid substitution, this will not lead to an increased exposure to the environment. An environmental risk assessment was therefore not deemed necessary.

III.3 Discussion on the non-clinical aspects

This product is a hybrid formulation of Emcor Deco which is available on the European market. Reference was made to the preclinical data obtained with the innovator product. A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which was 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 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, beside one bioequivalence study, which is discussed below.

IV.2 Pharmacokinetics

The MAH conducted a bioequivalence study in which the pharmacokinetic profile of the test product Bisoprolol Syri Pharma 0.5 mg/ml, oral solution (Syri Pharma Limited, United Kingdom) was compared with the pharmacokinetic profile of the reference product Sequacor 10 mg film coated tablets (Dompe farmaceutici S.p.A., Italy) with procedure number SE/H/0184/006.

The choice of the reference product in the bioequivalence study has been justified by comparison of *in vitro* dissolution study results and composition. Dissolution profiles of the test product are determined in 0.1N HCl, pH4.5 acetate buffer and pH 6.8 phosphate buffer in line with the EMA Guideline on bioequivalence. Test and reference product demonstrate a very rapid dissolution of more than 85% in 15 minutes in all three media. Dissolution profiles of more than 85% in 15 minutes are considered very rapidly dissolving, making similarity acceptable without further mathematical calculation.
The formula and preparation of the bioequivalence batch were identical to the formula proposed for marketing.

Bioequivalence study

Design

A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fasted conditions in 18 healthy male (16) and female (2) subjects, aged 21-42 years. Each subject received a single dose (10 mg) of one of the two bisoprolol formulations. As for the test product, 20 ml oral solution was orally administered with 240 ml rinsing water from the syringe, after an overnight fast of at least ten hours. As for the reference product, the tablet was orally administered with 240 ml water after an overnight fast of at least ten hours. There were two dosing periods, separated by a washout period of seven days.

Blood samples were collected pre-dose and at 0.334, 0.667, 1, 1.334, 1.667, 2, 2.334, 2.667, 3, 3.334, 3.667, 4, 4.5, 5, 6, 8, 12, 16, 24, 36, 48 and 72 hours after administration of the products.

The design of the study is acceptable.

Analytical/statistical methods

The analytical method has been adequately validated and is considered acceptable for analysis of the plasma samples. The methods used in this study for the pharmacokinetic calculations and statistical evaluation are considered acceptable.

Results

18 Subjects enrolled in the study. One subject has withdrawn from period II due to personal reasons. In total 17 subjects were eligible for pharmacokinetic analysis.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of bisoprolol fumarate, 10 mg under fasted conditions.

Treatment N=17	**AUC_{0-t} (ng.h/mL)**	**C_{max} (ng/mL)**	**t_{max} (h)**
Test	781 ± 137	56.88 ± 8.67	1.67 (1.00 – 5.00)
Reference	786 ± 117	59.01± 9.52	1.67 (0.50 – 4.50)
***Ratio (90% CI)**	0.99 (0.95 – 1.04)	0.96 (0.93 – 1.00)	N.A.

AUC_{0-t}	Area under the plasma concentration-time curve from time zero to t = 72 hours
C_{max}	Maximum plasma concentration
t_{max}	Time after administration when maximum plasma concentration occurs
CI	Confidence interval

**In-transformed values*

Conclusion on bioequivalence study:
The 90% confidence intervals calculated for AUC_{0-t} and C_{max} are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the submitted bioequivalence study Bisoprolol Syri Pharma is considered bioequivalent with Emcor Deco.

The MEB has been assured that the bioequivalence study has been conducted in accordance with acceptable standards of Good Clinical Practice (GCP, see Directive 2005/28/EC) and Good Laboratory Practice (GLP, see Directives 2004/9/EC and 2004/10/EC).

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 Syri Pharma. At the time of approval, the most recent version of the RMP was version 0.2 dated 14 June 2024.

Table 2. Summary table of safety concerns as approved in RMP

Important identified risks	None
Important potential risks	None
Missing information	None

The member states agreed that routine pharmacovigilance activities and routine risk minimisation measures are sufficient for the risks and areas of missing information.

IV.4 Discussion on the clinical aspects

For this authorisation, reference is made to the clinical studies and experience with the innovator product Emcor Deco. 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 hybrid medicinal product can be used instead of the reference product. The clinical aspects of this product are approvable.

V. USER CONSULTATION

A user consultation with target patient groups on the package leaflet (PL) has been performed on the basis of a multiple bridging report making reference to Metoclopramide hydrochloride 5mg/5ml oral solution, DCP number MT/H/0358/001/DC for the design and lay-out, and making reference to both Propranolol Thame 5mg/5ml, 10mg/5ml, 40mg/5ml and 50mg/5ml oral solution, MRP number MT/H/0411/001-004/MR and Cardicor 2.5 mg film-coated tablets, procedure number SE/H/0184/002 for the content. The bridging report submitted by the MAH has been found acceptable; bridging is justified for both layout and content of the leaflet.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Bisoprolol Syri Pharma 0.5 mg/ml, oral solution has a proven chemical-pharmaceutical quality and is a hybrid form of Emcor Deco 2.5 mg film-coated tablets. Emcor Deco 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 therapeutic equivalence has been demonstrated for Bisoprolol Syri Pharma with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 8 November 2024.

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
NL/H/5906/001 /1A/001	Submission of a new or updated Ph. Eur. certificate of suitability or deletion of Ph. Eur. certificate of suitability: For an active substance, For a starting material/reagent/intermediate used in the manufacturing process of the active substance, For an excipient - European Pharmacopoeial Certificate of Suitability to the relevant Ph. Eur. Monograph - Updated certificate from an already approved manufacturer	No	11-03-2025-	Approved-	N.A.