CMDh/223/2005
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Public Assessment Report

Scientific discussion

Bi-Prenessa 5 mg/5 mg
Bi-Prenessa 5 mg/10 mg
Bi-Prenessa 10 mg/5 mg
Bi-Prenessa 10 mg/10 mg
film-coated tablets

bisoprolol fumarate/perindopril arginine

SK/H/0333/001-004/DC

Date: November 2025

This module reflects the scientific discussion for the approval of Bi-Prenessa. The procedure was finalised at 26.06.2025. For information on changes after this date please refer to the module 'Update'.

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have agreed to grant a marketing authorisation for Bi-Prenessa 5 mg/5 mg film-coated tablet, 5 mg/10 mg film-coated tablet, 10 mg/5 mg film-coated tablet and 10 mg/10 mg film-coated tablet, from KRKA d.d., Novo Mesto, Slovenia.

The product is indicated for:

- Bi-Prenessa 5mg/5mg and 10mg/5mg indicated as substitution therapy for treatment of hypertension and/or stable coronary artery disease (in patients with a history of myocardial infarction and/or revascularisation) and/or stable chronic heart failure with reduced systolic left ventricular function in adult patients adequately controlled with bisoprolol and perindopril given concurrently at the same dose level.

and

- Bi-Prenessa 5mg/10mg and 10mg/10mg indicated as substitution therapy for treatment of hypertension and/or stable coronary artery disease (in patients with a history of myocardial infarction and/or revascularisation) in adult patients adequately controlled with bisoprolol and perindopril given concurrently at the same dose level.

A comprehensive description of the indications and posology is given in the SmPC.

The marketing authorisation has been granted pursuant to Article 10(1) of Directive 2001/83/EC. The application for Bi-Prenessa film-coated tablets is a generic application claiming essential similarity to the original product Bipressil® film-coated tablets (by Les Laboratories Servier).

II. QUALITY ASPECTS

II.1 Introduction

Bi-Prenessa film-coated tablets were developed as a generic to reference products Bipressil 10 mg/ 5 mg and Bipressil 10 mg/ 10 mg. Biowaiver for the additional strengths (5 mg/ 5 mg, and 5 mg/ 10 mg) is accepted, based on a very rapid release of both active substances from all concerned strengths.

The chosen excipients are well known and established for use in manufacturing process of solid dosage forms.

Bi-Prenessa film-coated tablets are manufactured in four different strengths: 5 mg/ 5 mg, 5 mg/ 10 mg, 10 mg/ 5 mg and 10 mg/ 10 mg. They are distinguished by colour and unique marks on the sides of the score line on the tablets and, in addition, the strength 5 mg/ 5 mg is of smaller size compared to the other strengths.

The product is packed in Aluminium (OPA/Al/PE+DES) / (Al/PE) blisters.

II.2 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.3 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 fumarate and perindopril arginine are well known. As bisoprolol fumarate and perindopril arginine are widely used, well-known active substances, the applicant has not provided additional studies, and further studies are not required. Overview based on literature review is, thus, appropriate.

There are no raised non-clinical issues regarding impurities. All excipients are well established.

The non-clinical overview on the pre-clinical pharmacology, pharmacokinetics and toxicology is adequate. The non-clinical section of the SmPC is acceptable and in accordance with the reference product information.

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Bi-Prenessa is intended for generic substitution, this will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

IV. CLINICAL ASPECTS

IV.1 Introduction

Bi-Prenessa contains two active ingredients, bisoprolol fumarate and perindopril arginine in one film-coated tablet.

Bisoprolol fumarate belongs to a group of medicines called beta-blockers. Beta-blockers slow down the heart rate and make the heart more efficient at pumping blood around the body.

Perindopril arginine is an angiotensin converting enzyme (ACE) inhibitor. It works by widening the blood vessels, which makes it easier for the heart to pump blood through the vessels.

Pharmacotherapeutic group: agents acting on the renin-angiotensin system, ACE inhibitors, other combinations, ATC code: C09BX02.

IV.2 Pharmacokinetics

Bioequivalence studies

To support the application, the applicant has submitted as report 2 bioequivalence studies (BE).

BE Study No. 22-745

A Single-Dose, Bioequivalence Study of Two Formulations of Bisoprolol/Perindopril 10 mg/10 mg Film-Coated Tablets under Fasting Conditions. Based on the submitted bioequivalence study (No. 22-745) Bi-Prenessa 10 mg/10 mg film-coated tablets is considered bioequivalent with Bipressil® 10 mg/10 mg film-coated tablets.

BE Study No. 22-746

A Single-Dose, Bioequivalence Study of Two Formulations of Bisoprolol/Perindopril 10 mg/5 mg Film-Coated Tablets under Fasting Conditions. Based on the submitted bioequivalence study (No. 22-746) Bi-Prenessa 10 mg/5 mg film-coated tablets is considered bioequivalent with Bipressil® 10 mg/5 mg film-coated tablets.

Biowaiver

The Applicant has requested a biowaiver for proposed strengths Bi-Prenessa 5 mg/5 mg and Bi-Prenessa 5 mg/10 mg based on a conducted bioequivalence studies No. 22-745 for Bi-Prenessa 10 mg/ 10 mg and No. 22-746 for Bi-Prenessa 10 mg/ 5 mg.

Strength 5 mg/10 mg may be waived to the strength 10 mg/10 mg. Strength 5 mg/5 mg is linear proportional to the highest strength 10 mg/10 mg.

The results of study No. 22-745 with 10 mg/10 mg formulation can be extrapolated to strengths 5 mg/5 mg and 5 mg/10 mg, according to conditions in Guideline on the Investigation of Bioequivalence CPMP/EWP/QWP/1401/98 Rev. 1/Corr*, section 4.1.6.

IV.3 Pharmacodynamics

No new data have been submitted. No data are required for an abridged application provided bioequivalence has been satisfactorily demonstrated.

IV.4 Clinical efficacy

The clinical overview on the clinical pharmacology, efficacy and safety is adequate.

IV.5 Clinical safety

The clinical overview on the clinical pharmacology, efficacy and safety is adequate.

IV.6 Risk Management Plan

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 Bi-Prenessa.

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.

V. USER CONSULTATION

A user consultation with target patient groups on the package information leaflet (PIL) has been performed on the basis of a bridging report.

As 'parent' leaflets for key safety messages, the leaflet of reference product Cosimprel 5 mg/5 mg, 5 mg/10 mg, 10mg/5 mg, 10 mg/10 mg film-coated tablets was used. The user test of the parent leaflet has been assessed and accepted in procedure HU/H/0390/001-004.

As 'parent' leaflets for design and layout, the leaflet of reference product Olmesartan/Amlodipine/HCTZ Krka 40 mg/5 mg/12,5 mg, 40 mg/5 mg/25 mg, 40 mg/10 mg/12,5 mg, 40 mg/10 mg/25 mg film-coated tablets was used. The user test of the parent leaflet has been assessed and accepted in procedure DK/H/3057-3058/001- 005/DC.

The bridging report submitted by the applicant has been found acceptable.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The dossier is acceptable from the quality perspective. There are no objections from a non-clinical point of view. From the clinical perspective, submitted clinical data are adequate to support the indication. The benefit/risk assessment for Bi-Prenessa 5 mg/5 mg film-coated tablet, 5 mg/10 mg film-coated tablet, 10 mg/5 mg film-coated tablet and 10 mg/10 mg film-coated tablet, from KRKA d.d., Novo Mesto, Slovenia is therefore considered positive.

The SmPC, PL and labelling were satisfactory.

Agreement between Member States was reached during the procedure. The concerned member states involved in this procedure were BG, HR, CZ, CY, DE, HU, LT, LV, PL, SI. There was no discussion in the CMDh. The decentralised procedure was finalised with a positive outcome on 26.06.2025. No conditions pursuant to Article 21a or 22 of Directive 2001/83/EC have been made during the procedure.