COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Iloprost Eureco-Pharma 0.1 mg/ml, concentrate for solution for infusion (iloprost)

NL License RVG: 126966

Date: 28 November 2022

This module reflects the scientific discussion for the approval of Iloprost Eureco-Pharma 0.1 mg/ml, concentrate for solution for infusion. The marketing authorisation was granted on 15 February 2022. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

List of abbreviations

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
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EEA	European Economic Area
ERA	Environmental Risk Assessment
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
Ph.Eur.	European Pharmacopoeia
PL	Package Leaflet
RH	Relative Humidity
RMP	Risk Management Plan
SmPC	Summary of Product Characteristics
TSE	Transmissible Spongiform Encephalopathy

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Medicines Evaluation Board (MEB) of the Netherlands has granted a marketing authorisation for Iloprost Eureco-Pharma 0.1 mg/ml, concentrate for solution for infusion, from Eureco-Pharma B.V.

The product is indicated for:

- Treatment of the advanced stage of thromboangiitis obliterans (Buerger's disease) with severe limb ischaemia, in cases where revascularisation is not indicated.
- Treatment of severe, chronic limb ischaemia (peripheral arterial occlusive disease (PAOD) stage III & IV according to Fontaine) in cases where reconstructive vascular surgery or percutaneous transluminal angioplasty is no longer possible.

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

This national procedure concerns a generic application claiming essential similarity with the innovator product Ilomedine 0.1 mg/ml, concentrate for solution for infusion marketed by Bayer B.V., which has been authorised in the Netherlands since 15 May 1992 (RVG 15696).

The marketing authorisation has been granted pursuant to Article 10(1) of Directive 2001/83/EC.

II. QUALITY ASPECTS

II.1 Introduction

Iloprost is a colourless, clear solution, free of visible particles. One mL solution contains 0.134 mg iloprost tromethamine, equivalent to 0.1 mg iloprost.

The solution is packed in glass type I, colourless, 2 mL ampoules containing 0.5 mL of concentrate for solution for infusion.

The excipients are: tromethamine, ethanol 96% (v/v), sodium chloride, hydrochloric acid 1N and water for injection.

II.2 Drug Substance

The active substance is iloprost, an established active substance which is not described in the European or other pharmacopoeia (Ph.Eur.). A draft monograph is available in Ph. Eur. 20.1. Iloprost is a mixture of two epimers and it appears as a clear, colourless to pale yellowish viscous oil. It is slightly soluble in water, freely soluble in acetonitrile and in

methylene chloride, soluble in ethanol and in buffer pH 7, sparingly soluble in buffer pH 9, and very slightly soluble in buffer pH 3, and buffer pH 5.

The Active Substance Master File (ASMF) procedure is used for the active substance. The main objective of the ASMF procedure, commonly known as the European Drug Master File (EDMF) procedure, is to allow valuable confidential intellectual property or 'know-how' of the manufacturer of the active substance (ASM) to be protected, while at the same time allowing the applicant or marketing authorisation holder (MAH) to take full responsibility for the medicinal product, the quality and quality control of the active substance. Competent Authorities/EMA thus have access to the complete information that is necessary to evaluate the suitability of the use of the active substance in the medicinal product.

Manufacturing process

The manufacturing process of iloprost is composed of two distinct parts of five steps and four steps. The manufacturing process has been described in sufficient detail in the restricted part of the ASMF. The proposed three starting materials are acceptable. The active substance has been adequately characterized.

Quality control of drug substance

The active substance specification is in line with the iloprost Ph.Eur. monograph draft and it is acceptable. The following tests are performed: appearance, identification, specific optical rotation, water, related substances, Z-isomers, E-isomers, ethyl acetate, assay, residual solvents, benzene, bacterial endotoxins and microbial contamination. Batch analytical data demonstrating compliance with the drug substance specification have been provided for three full scale batches.

Stability of drug substance

The stability data of three batches of iloprost have been provided under accelerated (6 months) and long term (36 months) conditions. Out of specifications are observed for related substances and assay at 6 months under accelerated conditions. Under long term conditions, an increase is observed of impurities, with consequent decrease in assay. Nevertheless, all results comply with the specification. The results of the forced degradation studies have been provided. On the basis of the submitted data, the proposed retest period of 36 months and the storage condition "store in a freezer protected from light" are acceptable.

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 proposed generic drug product and the reference product have the same qualitative and quantitative composition and same chemical-pharmaceutical parameters. The essential similarity between the two products is sufficiently shown. In general, the pharmaceutical development of the product has been adequately performed, the choice of excipients has been justified and their

functions explained. The choices of the manufacturing process and packaging are sufficiently justified.

Manufacturing process

The manufacturing process has been validated according to relevant European guidelines. Process validation data on the product have been presented for six batches in accordance with the relevant European guidelines. The manufacturing process involves the aseptic filtration of a bulk solution of drug product, which is then aseptically filled in ampoules and sterilized by heat. The process has been described in sufficient detail. In general, the manufacturing process has been adequately validated; sufficient information about the aseptic filtration and hold times are provided. The manufacturing process is considered a standard process.

Control of excipients

The excipients comply with the Ph. Eur. requirements. The tests used to control the excipients are performed according to pharmacopoeial procedures. These specifications are 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 appearance, identification pH, osmolality, assay, related substances, particulate contamination, extractable volume, head-space oxygen, sterility and bacterial endotoxins. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product. The release and shelf life limits are identical.

The analytical methods have been adequately described and validated. Batch analytical data have been provided on six batches from the proposed production site, demonstrating compliance with the release specification. A risk evaluation for nitrosamines in the drug product, as well as the summary of the elemental impurities risk assessment report have been provided.

Stability of drug product

Stability data on the product have been provided for six batches stored at 25°C/60% RH (60 months), 30°C/65% RH (60 months) and 40°C/75% RH (6 months). The batches were stored in clear glass ampoules (type 1). The conditions used in the stability studies are according to the ICH guideline. No trends are observed and all results comply with the specification. Information with regards to the forced degradation studies performed have been provided. Additionally, an in-use stability study has been performed on two batches; however, analytical results for sterility related substances were missing. On the basis of the provided stability data, the shelf life of 60 months and storage condition of the concentrate for solution are accepted. The in-use shelf life of 24 hours upon dilution is also acceptable.

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

Statements from the manufacturers of the drug substance and the drug product have been provided and compliance with the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via medicinal products has been satisfactorily demonstrated.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the MEB considers that Iloprost Eureco-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 Ecotoxicity/environmental risk assessment (ERA)

Since Iloprost Eureco-Pharma 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.

III.2 Discussion on the non-clinical aspects

This product is a generic formulation of Ilomedine, which is available on the European market. Reference is made to the preclinical data obtained with the innovator product. A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which is 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 MEB finds that no further non-clinical studies are required.

IV. CLINICAL ASPECTS

IV.1 Introduction

Iloprost 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 MEB finds that no further clinical studies are required.

IV.2 Pharmacokinetics

Iloprost Eureco-Pharma 0.1 mg/ml, concentrate for solution for infusion is a parenteral formulation and therefore fulfils the exemption mentioned in the Note for Guidance on bioequivalence "5.1.6 parenteral solutions", which states that a bioequivalence study is not required if the product is administered as an aqueous intravenous solution containing the same active substance in the same concentration as the currently authorized reference medicinal product (NfG CPMP/EWP/QWP 1401/98). The quantitative composition of Iloprost Eureco-Pharma is entirely the same as the originator. Therefore, it may be considered as therapeutic equivalent, with the same efficacy/safety profile as known for the active substance of the reference medicinal product. The current product can be used instead of its reference product.

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 Iloprost Eureco-Pharma.

Table 1. Summary table of safety concerns as approved in RMP

Important identified risks	Bleeding events Hypotension
Important potential risks	Renal impairment Hepatic disorder Acute respiratory distress syndrome
Missing information	None

The MEB finds 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 Ilomedine. No new clinical studies were conducted. The MAH was granted

a biowaiver for demonstrating that the pharmacokinetic profile of the product is similar to the pharmacokinetic profile of the reference product. Risk management is adequately addressed. This generic medicinal product can be used instead of the reference product.

V. USER CONSULTATION

The package leaflet (PL) 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 Lithuanian. The test consisted of a pilot test with two participants, followed by two rounds with ten participants each. The questions covered the following areas sufficiently: traceability, comprehensibility and applicability. The results show that the PL 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.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Iloprost Eureco-Pharma 0.1 mg/ml, concentrate for solution for infusion has a proven chemical-pharmaceutical quality and is a generic form of Ilomedine 0.1 mg/ml, concentrate for solution for infusion. Ilomedine is a well-known medicinal product with an established favourable efficacy and safety profile.

Since both the reference and current product are intended for parenteral use, no bioequivalence study is deemed necessary. A biowaiver has been granted.

The Board followed the advice of the assessors.

The MEB, on the basis of the data submitted, considered that essential similarity has been demonstrated for Iloprost Eureco-Pharma with the reference product, and have therefore granted a marketing authorisation. The national procedure was finalised in the Netherlands with a positive outcome on 15 February 2022.

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
N/A	N/A	N/A	N/A	N/A	N/A