CBG MEB

Public Assessment Report

Scientific discussion

Iloprost Solufarma 20 microgram/1 ml and 50 microgram/0.5 ml concentrate for solution for infusion

(iloprost)

NL/H/3585/001-002/DC

Date: 10 November 2017

This module reflects the scientific discussion for the approval of Iloprost Solufarma 20 microgram/1 ml and 50 microgram/0.5 ml concentrate for solution for infusion. The procedure was finalised on 3 May 2017. 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
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 Member States have granted a marketing authorisation for Iloprost Solufarma 20 microgram/1 ml and 50 microgram/0.5 ml concentrate for solution for infusion from Solufarma Produtos Farmaceuticos, Unipessoal, Lda.

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 decentralised procedure concerns a generic application claiming essential similarity with the innovator products:
- *Iloprost Solufarma 50 microgram/0.5 ml concentrate for solution for infusion* - Ilomedine, 0.1 mg/ml concentrate for solution for infusion which has been registered in the Netherlands (NL License RVG 15696) through a national procedure by Bayer B.V. since 15 May 1992.
- *Iloprost Solufarma 20 microgram/1 ml concentrate for solution for infusion* - Ilomedin, 20 microgram/ml concentrate for solution for infusion which has been registered in Denmark (marketing authorisation number 19398) by Bayer Pharma AG since 6 February 1992. In the Netherlands this product strength is not available on the market.

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

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

II. QUALITY ASPECTS

II.1 Introduction

Iloprost Solufarma is a colourless, clear solution free of visible particles with a pH of 7.5-8.5 and osmolality approximately of 400-440 mOm/kg (20 µg/ml strength) or 420-460 mOm/kg (50 µg/0.5 ml strength).

The 20 µg /ml strength is packed in glass type I, colourless, 1.5 ml ampoules containing 1 ml of concentrate for solution for infusion. One ampoule of 1 ml contains 20 µg of iloprost, as 26.8 µg of iloprost trometamol.
The 50 µg /0.5 ml strength is packed in glass type I, colourless, 1.5 ml ampoules containing 0.5 ml of concentrate for solution for infusion. One ampoule of 0.5 ml contains 50 µg of iloprost, as 67 µg of iloprost trometamol.

For both strengths after dilution for use in an infusion pump, the content of iloprost trometamol per ml is 0.268 µg (corresponding to 0.2 µg of iloprost). After dilution for use in an injector, the content of iloprost trometamol per ml is 2.68 µg (corresponding to 2.0 micrograms of iloprost).

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

II.2 Drug Substance

The active substance is iloprost, an established active substance that is not described in the European Pharmacopoeia (Ph.Eur.), United States Pharmacopoeia (USP) and British Pharmacopoeia (BP). A draft monograph has been published in Pharmeuropa 20.1 (2008). Iloprost is a colourless to pale

yellowish viscous oil, slightly soluble in water, freely soluble in acetonitrile and in methylene chloride, soluble in ethanol and in pH 7 buffer, sparingly soluble in pH 9 buffer, and very slightly soluble in pH 3 and pH 5 buffer. The active substance possesses six asymmetrical carbon atoms. No polymorphism is determined since the substance is oily.

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 is sufficiently described. It is composed of four steps. The starting materials are accepted.

Quality control of drug substance
The active substance specification is considered adequate to control the quality. It is in line with the monograph in the Pharmeuropa. Batch analytical data demonstrating compliance with this specification have been provided for two batches.

Stability of drug substance
Stability data on the active substance have been submitted for three batches, stored for 24 months at -20°C and six months at 5°C. In view of the results, a retest of '24 months, store and transport frozen (≤-20°C), store in the original packaging to protect from light' is accepted.

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 formulation development is based on similarity with the reference product. Both products contain the same amount of the same active substance and contain the same excipients. An overfill of 15% is applied to allow extraction of the labelled volume. The choices of the packaging and manufacturing process are also justified. As the products concern solutions to be diluted to solutions for intravenous infusion, a biowaiver for clinical studies is acceptable. Therapeutical equivalence can be assumed based on the submitted *in vitro* data regarding pH, osmolality and assay. It is also demonstrated that the active substance has the same isomeric composition as the reference product. Pharmaceutical development has been adequately performed.

Manufacturing process
The manufacturing process of the drug product is considered a standard manufacturing process and consists of a terminal steam sterilisation by autoclave of a filtered aqueous solution filled in ampoules. The manufacturing process has been validated according to relevant European/ICH guidelines. Process validation data on the product have been presented for sufficient small scale batches in accordance with the relevant European guidelines.

Control of excipients
For all excipients, including nitrogen, reference is made to the Ph.Eur. These specifications are acceptable.

Microbiological attributes
The drug product is filtered through a membrane filter before filling and terminally sterilisation. The specification complies with the requirements of the Ph.Eur., for the parenteral preparations-injectables.

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, extractable volume, pH, identification, assay, related substances, particulate contamination, sterility, and bacterial endotoxins. The release and

shelf-life requirements/limits are identical. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product.
Satisfactory validation data for the analytical methods have been provided. Batch analytical data from three batches of both strengths from the proposed production site have been provided, demonstrating compliance with the specification.

Stability of drug product
The results of stability studies on three batches of each strength have been provided. The batches have been stored for 18 months at 25°C/60% RH and six months at 40°C/75% RH. No results were out of specification. On the basis of the data submitted, a shelf-life of two years without specific storage conditions was granted. The drug product is not photosensitive. From microbiological point of view, once opened and diluted, the product should be used immediately.

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 Iloprost Solufarma 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 Solufarma 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 Ilomedin 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 member states agreed 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 member states agreed that no further clinical studies are required.

IV.2 Pharmacokinetics

Iloprost Solufarma 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 authorised reference medicinal product (NfG CPMP/EWP/QWP 1401/98). The quantitative composition of Iloprost Solufarma 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 Solufarma.

Summary table of safety concerns as approved in RMP:

Important identified risks	• Bleeding • Hypotension • Use during pregnancy and breast-feeding
Important potential risks	• Off label use • Renal insufficiency • Hepatic disorders • Acute respiratory distress syndrome
Missing information	--

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 Ilomedin. No new clinical studies were conducted. The MAH demonstrated that the pharmacokinetic profile of the product is similar to the pharmacokinetic profile of this 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 has (PL) 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 test consisted of: a pilot test with three participants, followed by two rounds with 10 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 PL of medicinal products for human use.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Iloprost Solufarma 20 microgram/1 ml and 50 microgram/0.5 ml concentrate for solution for infusion has a proven chemical-pharmaceutical quality and is a generic form of Ilomedin 20 microgram/1 ml and 50 microgram/0.5 ml concentrate for solution for infusion. Ilomedin 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.

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 that essential similarity has been demonstrated for Iloprost Solufarma with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 3 May 2017.

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

*Only procedure qualifier, chronological number and grouping qualifier (when applicable)