COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Epoprostenol SUN 0.5 mg and 1.5 mg, powder for solution for infusion

(epoprostenol sodium)

NL/H/3964/001-002/DC

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This module reflects the scientific discussion for the approval of Epoprostenol SUN 0.5 mg and 1.5 mg, powder for solution for infusion. The procedure was finalised at 2 August 2018. 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 Member States have granted a marketing authorisation for Epoprostenol SUN 0.5 mg and 1.5 mg, powder for solution for infusion, from SUN Pharmaceutical Industries Europe B.V.

The product is indicated for:

- Pulmonary arterial hypertension

Epoprostenol is indicated for the treatment of pulmonary arterial hypertension (PAH) (idiopathic or heritable PAH and PAH associated with connective tissue diseases) in patients with WHO Functional Class III–IV symptoms to improve exercise capacity.

- Renal dialysis

Epoprostenol is indicated for use in haemodialysis in emergency situations when use of heparin carries a high risk of causing or exacerbating bleeding or when heparin is otherwise contraindicated.

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

This decentralised procedure concerns a hybrid application claiming essential similarity with the innovator product Flolan 0,5 mg (RVG 14469) and 1,5 mg (RVG 23525), powder and solvent for solution for infusion which has been registered via a mutual recognition procedure in the Netherlands by GlaxoSmithKline B.V. since 1992 (0.5 mg) and 1999 (1.5 mg).

The concerned member states (CMS) involved in this procedure were Germany, Spain, France, Italy and the United Kingdom.

The marketing authorisation has been granted pursuant to Article 10(3) of Directive 2001/83/EC, a hybrid application as this product will be marketed as a powder for solution for infusion, whereas the dosage form of the innovator product is a powder and solvent for solution for infusion. The MAH stated that the dosage form differs, since the innovator product contains both a powder and a solvent, while this product contains only powder for solution for infusion.

II. QUALITY ASPECTS

II.1 Introduction

Epoprostenol SUN is a white to off-white powder for solution for infusion. The osmolality of the diluted solution is between 150 and 350 mOsm/kg. The pH of the diluted “ready-to-use solution” decreases with dilution, and ranges from 12.0 for a concentration of 90,000 ng/ml, 11.7 for a concentration of 45,000 ng/ml to 11.0 for a concentration of 3,000 ng/ml.

Therefore, peripheral intravenous use should be restricted to short duration only, using low concentrations.

Each Epoprostenol SUN 0.5 mg vial contains 0.531 mg epoprostenol sodium equivalent to 0.5 mg epoprostenol and one ml of reconstituted solution contains 0.1 mg epoprostenol (as epoprostenol sodium).
Each Epoprostenol SUN 1.5 mg vial contains 1.593 mg epoprostenol sodium equivalent to 1.5 mg epoprostenol and one ml of reconstituted solution contains 0.3 mg epoprostenol (as epoprostenol sodium).

The powder for solution for infusion is packed in a 10 ml colourless glass type I vial closed with a rubber stopper and an aluminium flip-off cap.

The excipients are glycine, sucrose and sodium hydroxide (for pH adjustment).

II.2 Drug Substance

The active substance is epoprostenol sodium, an established active substance. There is currently no pharmacopoeial monograph on epoprostenol. Epoprostenol sodium is a white to off-white powder and soluble in methanol and slightly soluble in isopropanol. Polymorphism on epoprostenol sodium is not reported in literature. The manufacturer of the active substance consistently produces the crystalline form.

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 the active substance is adequately described for both manufacturer. Full descriptions of the manufacturing steps and flow-charts are present for the chemical step and purification step for manufacturer one and for all six steps for manufacturer two. In addition, sufficient information has been provided on all materials, and reagents used during the synthesis. Overall, the manufacturing process is acceptable.

Quality control of drug substance
The active substance specification is considered adequate to control the quality and is identical to that of the ASMF holder. Batch analytical data demonstrating compliance with this specification have been provided for five batches.

Stability of drug substance

Stability data on the active substance have been provided for seven batches stored at - 20°C ± 5°C (four batches 24 months, two batches 6 months and one batch 3 months). Based on the available stability data the claimed re-test period of 2 years can be accepted, when stored under the stated conditions and between -25 to -15°C.

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 product was developed using a Quality by Design approach using elements such as a Quality Target Product Profile, Critical Quality Attributes, Critical Process Parameters, and repeated risk assessments. No multifactorial experiments were carried out and consequently, no design spaces are claimed. Conventional ranges are proposed for process parameters.

Development was guided by Veletri 0.5 mg and 1.5 mg, powder for solution for infusion, which is a generic of the official reference product Flolan. At the time of the development, Veletri was more convenient for patients as it is not necessary to apply the product using cool packs. In the meantime, the formulation of Flolan has been improved in order to avoid the necessity of cool packs. A pH of approximately 12 is crucial for in-use stability.

No bioequivalence study has been carried out as the drug product is administered as aqueous intravenous solution. One batch of each strength of the product at issue was shown to be comparable to one batch of the respective strength of Veletri and the reference product Flolan with regard to description, assay of epoprostenol, related substances, water content, reconstitution time, pH of reconstituted solution, osmolality, and particulate contamination.

The set up of the in-use stability studies of the product at issue was based on the SmPC of Veletri. Exchangeability with the improved formulation of Flolan has been shown as well.

Manufacturing process

The manufacturing process includes the preparation of the bulk solution, sterile filtration, filling, and lyophilisation. The manufacturing process is regarded as non standard due to low amount of drug substance (<2% of composition). The manufacturing process has been validated according to relevant European guidelines. Process validation data on the product have been presented for three full scale batches of each strength in accordance with the relevant European guidelines.

Control of excipients

All excipients comply with the Ph.Eur. 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 description, identification of epoprostenol, identification, reconstitution time, pH of reconstituted solution, osmolality, clarity and

completeness of constituted solution, particulate matter of constituted solution, particulate matter, uniformity of dosage units by mass variation, assay of epoprostenol, related substances, water content, glycine assay, residual solvents, sterility, and bacterial endotoxins. The release and shelf life specifications differ with regard to the acceptance criteria for related substances. 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 full scale batches of each strength 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 for three full scale batches of each strength stored at 25°C/60% RH (12 or 18 months) and 40°C/75% RH (6 months). The conditions used in the stability studies are according to the ICH stability guideline. Photostability studies were performed in accordance with ICH recommendations and showed that the product is not stable when exposed to light. No significant changes have been observed up to six months storage at accelerated and up to 18 months long term conditions. The provided stability data support the proposes shelf life of 24 months and the proposed storage condition of "Do not freeze. The product is sensitive to light. Keep vial in outer carton"

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 Epoprostenol SUN 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 Epoprostenol SUN is intended for hybrid 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 hybrid formulation of Flolan 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

Epoprostenol 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

The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.

Epoprostenol SUN 0.5 mg and 1.5 mg, powder 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 authorised reference medicinal product (NfG CPMP/EWP/QWP 1401/98). 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 Epoprostenol SUN.

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

Important identified risks	– Hypotension – Tachycardia and bradycardia

	– Bleeding events at varioud sites (e.g. pulmonary, GI, epistaxis, intracranial, post-procedureal, retroperitoneal) – Sepsis, septicaemia
Important potential risks	– Pulmonary oedema in patients with PVOD – Extravasation and tissue damage due to high pH of the final infusion solutions
Missing information	– Use during pregnancy – Use in paediatric patients – Use in elderly

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 Flolan. No new clinical studies were conducted. The application for Epoprostenol SUN is sufficiently supported by the submitted clinical overview. No additional clinical or pharmacokinetic studies were required as Epoprostenol SUN and the originator product Flolan are both administered as an aqueous intravenous solution containing the same active substance and both formulations have a comparable composition upon administration. Risk management is adequately addressed. This hybrid 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 test consisted of: a pilot test with 2 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 package leaflet of medicinal products for human use.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Epoprostenol SUN 0.5 mg and 1.5 mg, powder for solution for infusion have a proven chemical-pharmaceutical quality and are hybrid forms of Flolan 0,5 mg and 1,5 mg, powder

and solvent for solution for infusion. Flolan 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.

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 Epoprostenol SUN with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 2 August 2018.

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