Public Assessment Report

Decentralised Procedure

Iloprost 100 micrograms/ml concentrate for solution for infusion

(Iloprost)

Procedure No: UK/H/6800/001/DC
UK Licence Number: PL 41344/0046

Colonis Pharma Ltd
LAY SUMMARY

Iloprost 100 micrograms/ml concentrate for solution for infusion

(Iloprost)

This is a summary of the Public Assessment Report (PAR) for Iloprost 100 micrograms/ml concentrate for solution for infusion (PL 41344/0046; UK/H/6800/001/DC). It explains how Iloprost 100 micrograms/ml concentrate for solution for infusion was assessed and its authorisation recommended, as well as its conditions of use. It is not intended to provide practical advice on how to use this product.

The product will be referred to as 'Iloprost 100 micrograms/ml' throughout the remainder of this PAR.

For practical information about using Iloprost 100 micrograms/ml, patients should read the package leaflet or contact their doctor or pharmacist.

What is Iloprost 100 micrograms/ml and what is it used for?
Iloprost 100 micrograms/ml is a 'generic medicine'. This means that Iloprost 100 micrograms/ml is similar to a 'reference medicine' already authorised in the European Union (EU) called ILOMEDINE 0.1 mg/ml, solution injectable pour perfusion (NL 1556234009 557; Bayer Healthcare SAS, France).

Iloprost 100 micrograms/ml is used in adults in the treatment of:
- Severe chronic ischaemia of lower limbs (decreased blood supply) in patients at risk of amputation, in whom surgical revascularisation or angioplasty (repair of blood vessel) has failed or is not indicated, following the meeting of physicians, surgeons and radiologists.
- Severe Raynaud’s phenomena (reduced blood flow to fingers and toes) in patients with progressive trophic disorders.

How does Iloprost 100 micrograms/ml work?
Iloprost 100 micrograms/ml contains the active ingredient iloprost which imitates a natural substance in the body called prostacyclin. Iloprost 100 micrograms/ml and prostacyclin prevent unwanted blockages or narrowing of blood vessels and allow improved blood flow in the arteries.

Iloprost 100 micrograms/ml promotes the healing of wounds caused by insufficient blood flow (ischemia) by providing better oxygenation, and relieving pain in severe, chronic disorders of the blood circulation.

How is Iloprost 100 micrograms/ml used?
The pharmaceutical form of this medicine is a concentrate for solution for infusion and the route of administration is intravenous (into a vein).

Iloprost 100 micrograms/ml should be used by physicians or healthcare professionals only under strict monitoring in hospitals or out-patient clinics with adequate facilities.

Iloprost 100 micrograms/ml is a solution contained in a glass ampoule. The content of the ampoule is diluted with 0.9% physiological sodium chloride solution or a 5% glucose solution. The infusion solution should be prepared just before the infusion daily, to ensure sterility. The content of the ampoule and the diluent must be mixed thoroughly. Iloprost 100 micrograms/ml must be used only after dilution.

The solution is infused intravenously with a venous catheter directly into one of the veins in the patient’s arm or into a central intravenous catheter inserted into a vein near the neck.

Iloprost 100 micrograms/ml is administered as infusion over 6 hours daily. The dose is adjusted according to individual tolerability within the range of 0.5 to 2.0 ng iloprost/kg body weight/min. The patient’s blood pressure and heart rate will be measured at the start of the infusion and after every dose increase.
**How much Iloprost 100 micrograms/ml is given**

During the first 2-3 days, the individually tolerated dose is established.

For this purpose, the patient’s doctor will start the treatment at a low dose. Treatment should be started at an infusion rate of 0.5 ng/kg/ min for 30 minutes. The dose should then be increased at intervals of 30 minutes in steps of 0.5 ng/kg/min up to 2.0 ng/kg/min. The exact infusion speed should be calculated on the basis of body weight to reach an infusion within the range of 0.5 to 2.0 ng/kg/min.

If adverse effects occur, such as headache and nausea or an undesirable drop in blood pressure, the patient should tell their doctor immediately. The infusion rate should be reduced until the tolerable dose is found. If the adverse effects are severe, the infusion should be interrupted. For the remaining duration, the treatment should be continued with the dose found to be tolerated in the first 2 to 3 days.

The doctor will determine whether Iloprost 100 micrograms/ml will be infused intravenously by an infusion pump or with syringe driver. If Iloprost 100 micrograms/ml is administered with an infusion pump, it will be diluted before infusion to a final concentration of 0.2 micrograms/ml. If Iloprost 100 micrograms/ml is administered with a syringe driver, it will be diluted before infusion to a final concentration of 2 micrograms /ml.

If the patient has renal failure requiring dialysis or liver cirrhosis, iloprost elimination is reduced and a dose reduction (e.g. half the recommended dose) is necessary. The patient should tell their doctor if they have problems with their liver or kidneys.

Please read section 3 of the package leaflet for detailed dosing recommendations, the route of administration, and the duration of treatment.

**How long Iloprost 100 micrograms/ml is given:**

The duration of treatment is up to 4 weeks.

The safety and efficacy of Iloprost 100 micrograms/ml have not been studied for treatment longer than 4 weeks or after repetitive treatment cycles.

Continuous infusion over several days is not recommended, because it can lead to reduced effect on platelets and increased platelet aggregation (platelet hyperaggregability) at the end of treatment. No clinical complications associated with these phenomena have been reported.

For further information on how Iloprost 100 micrograms/ml is used, refer to the package leaflet and the Summary of Product Characteristics available on the Medicines and Healthcare products Regulatory Agency (MHRA) website.

This medicine can only be obtained with a prescription.

**What benefits of Iloprost 100 micrograms/ml have been shown in studies?**

No additional clinical studies were needed as Iloprost 100 micrograms/ml is a generic medicine that is given as an aqueous solution by infusion and contains the same active as the reference medicine ILOMEDINE 0.1 mg/ml, solution injectable pour perfusion (Bayer Healthcare SAS, France).

**What are the possible side effects of Iloprost 100 micrograms/ml?**

Because Iloprost 100 micrograms/ml is a generic medicine, its benefits and possible side effects are taken as being the same as the reference medicine.

For the full list of restrictions, see the package leaflet.

For the full list of all side effects reported with Iloprost 100 micrograms/ml, see section 4 of the package leaflet available on the MHRA website.

**Why was Iloprost 100 micrograms/ml approved?**
It was concluded that, in accordance with EU requirements, Iloprost 100 micrograms/ml has been shown to be comparable to ILOMEDINE 0.1 mg/ml, solution injectable pour perfusion (Bayer Healthcare SAS, France). Therefore, the MHRA decided that, as for ILOMEDINE 0.1 mg/ml, solution injectable pour perfusion (Bayer Healthcare SAS, France), the benefits are greater than the risks and recommended that it can be approved for use.

**What measures are being taken to ensure the safe and effective use of Iloprost 100 micrograms/ml?**
A risk management plan (RMP) has been developed to ensure that Iloprost 100 micrograms/ml is used as safely as possible. Based on this plan, safety information has been included in the SmPC and the package leaflet for Iloprost 100 micrograms/ml including the appropriate precautions to be followed by healthcare professionals and patients.

Known side effects are continuously monitored. Furthermore, new safety signals reported by patients/healthcare professionals will be monitored/reviewed continuously.

**Other information about Iloprost 100 micrograms/ml**
A Marketing Authorisation was granted in the UK on 15 February 2019.

The full PAR for Iloprost 100 micrograms/ml follows this summary.

This summary was last updated in February 2019.
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INTRODUCTION
The Medicines and Healthcare products Regulatory Agency (MHRA) granted Colonis Pharma Ltd a Marketing Authorisation for the medicinal product Iloprost 100 micrograms/ml (PL 41344/0046; UK/H/6800/001/DC) on 15 January 2019. The product is a prescription only medicine (POM) indicated in adults for:

- Treatment of severe chronic ischaemia of lower limbs in patients at risk of amputation, in whom surgical revascularisation or angioplasty has failed or is not indicated, following an interdisciplinary meeting of physicians, surgeons and radiologists.
- Treatment of severe Raynaud’s phenomena in patients with progressive trophic disorders.

The application was submitted using the Decentralised procedure (DCP) with the UK as Reference Member State (RMS) and Malta as Concerned Member State (CMS); subsequently during the procedure, Malta was withdrawn as a CMS on 17 July 2018.

The application were submitted under Article 10(1) of Directive 2001/83/EC, as amended, as a generic application. The European reference medicinal product for this application is ILOMEDINE 0.1 mg/ml, solution injectable pour perfusion which was first authorised to the marketing authorisation holder (MAH), Bayer Healthcare SAS, in France on 16 June 1992 (NL 1556234009 557).

Iloprost is a synthetic prostacyclin analogue. The following pharmacological effects have been observed:

- Inhibition of platelet aggregation, platelet adhesion and release reaction
- Dilation of arterioles and venules
- Increase of capillary density and reduction of vascular hyperpermeability caused by mediators such as serotonin or histamine in the microcirculation
- Stimulation of endogenous fibrinolytic potential

Anti-inflammatory effects such as inhibition of leukocyte adhesion after an endothelial lesion and of leukocyte accumulation in injured tissue, and reduced release of tumour necrosis factor (TNF).

No new non-clinical studies were conducted, which is acceptable given that the application was based on being a generic medicinal product of an originator product that has been licensed for over 10 years.

No new clinical data have been submitted and none are required for applications of this type. Since this application concerns a generic version of iloprost, with essential similarity to the reference product, ILOMEDINE 0.1 mg/ml, solution injectable pour perfusion (Bayer Healthcare SAS, France) intended for parenteral use, a bioequivalence study is not required (Appendix II of CPMP/EWP/QWP/1401/98 Rev 1).

The RMS has been assured that acceptable standards of Good Manufacturing Practice are in place for this product type at all sites responsible for the manufacture, assembly and batch release of these products.

For manufacturing sites within the Community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

For manufacturing sites outside the community, the RMS has accepted copies of current GMP Certificates or satisfactory inspection summary reports, ‘close-out letters’ or ‘exchange of information’ issued by the inspection services of the competent authorities (or those countries with which the EEA has a Mutual Recognition Agreement for their own territories) as certification that acceptable standards of GMP are in place at those non-Community sites.
The RMS considered that the application could be approved at the end of procedure on 24 December 2018. After a subsequent national phase, a licence was granted in the UK on 15 January 2019.
II QUALITY ASPECTS

II.1 Introduction
Each 1 ml concentrate for solution for infusion contains 100 micrograms iloprost (equivalent to 134 iloprost trometamol) as the active ingredient. Other ingredients consist of the pharmaceutical excipients trometamol, ethanol 96 % (v/v), sodium chloride, hydrochloric acid and water for injection.

The finished product is packaged in glass ampoules from glass type I (Type I hydrolytic class glass) and is available in pack sizes of:
- Box of 1 or 5 ampoules, each with 0.5 ml concentrate for solution for infusion
- Box of 1 or 5 ampoules, each with 1 ml concentrate for solution for infusion

Not all pack sizes may be marketed.

Satisfactory specifications and Certificates of Analysis have been provided for all packaging components. All primary packaging complies with the current European regulations concerning materials in contact with food.

II.2 Drug Substance
INN: iloprost
Chemical name: \((5E)-5-[((3aS,4R,5R,6aS)-5-Hydroxy-4-[(1E,3S,4RS)-3-hydroxy-4-methyloct-1-en-6-yn-1-yl]hexahydropentalen-2(1H)-ylidene]pentanoic acid

Structure:

Molecular formula: \(C_{22}H_{32}O_{4}\)
Molecular weight: 360.49
Appearance: Clear, colourless to pale yellowish viscous oil.
Solubility: 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.

Iloprost is the subject of an Active Substance Master File (ASMF).

Synthesis of the active substance from the designated starting materials has been adequately described and appropriate in-process controls and intermediate specifications are applied. Satisfactory specification tests are in place for all starting materials and reagents, and these are supported by relevant Certificates of Analysis.

Appropriate proof-of-structure data have been supplied for the active substance. All potential known impurities have been identified and characterised.

An appropriate specification is provided for the active substance. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications.

Batch analyses data are provided that comply with the proposed specification.

Satisfactory Certificates of Analysis have been provided for all working standards used.
Suitable specifications have been provided for all packaging used. The primary packaging has been shown to comply with current guidelines concerning contact with food.

Appropriate stability data have been generated supporting a suitable retest period when stored in the proposed packaging.

II.3. Medicinal Product
Pharmaceutical Development
The objective of the development programme was to formulate a safe, efficacious, concentrate for solution for infusion containing 100 micrograms iloprost per 1ml of concentrate for solution for infusion, that is a generic version of the reference product, ILOMEDINE 0.1 mg/ml, solution injectable pour perfusion (Bayer Healthcare SAS, France).

A satisfactory account of the pharmaceutical development has been provided.

All excipients comply with their respective European Pharmacopoeia (Ph.Eur) monograph. Satisfactory Certificates of Analysis have been provided for all excipients. Suitable batch analysis data have been provided for each excipient.

None of the excipients used contain material of animal or human origin.

This product does not contain or consist of genetically modified organisms (GMO).

Manufacture of the product
Satisfactory batch formulae have been provided for the manufacture of the product, along with an appropriate account of the manufacturing process. The manufacturing process has been validated at commercial scale and has shown satisfactory results.

Finished Product Specification
The finished product release and shelf life specifications proposed are acceptable. Test methods have been described that have been adequately validated. Batch data have been provided which comply with the release specification. Certificates of Analysis have been provided for all working standards used.

Stability of the Product
Finished product stability studies were performed in accordance with current guidelines on batches of the finished products in the packaging proposed for marketing. The data from these studies support a shelf-life of 30 months for the unopened ampoule. This medicinal product does not require any special storage conditions.

After opening and dilution:
Chemical and physical in-use stability has been demonstrated for 24 hours at 25ºC.

From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2-8ºC, unless the dilution has taken place in controlled and validated aseptic conditions.

Suitable post approval stability commitments have been provided to continue stability testing on batches of finished product.

II.4 Discussion on chemical, pharmaceutical and biological aspects
There are no objections to the approval of this application from a pharmaceutical viewpoint.
III  NON-CLINICAL ASPECTS

III.1  Introduction
As the pharmacodynamic, pharmacokinetic and toxicological properties of iloprost are well-known, no new non-clinical studies are required and none have been provided. An overview based on the literature review is, thus, appropriate.

The applicant’s non-clinical expert report has been written by an appropriately qualified person and is satisfactory, providing an appropriate review of the relevant non-clinical pharmacology, pharmacokinetics and toxicology.

III.2  Pharmacology
Not applicable for this product type. Refer to section ‘III.1; Introduction’ detailed above.

III.3  Pharmacokinetics
Not applicable for this product type. Refer to section ‘III.1; Introduction’ detailed above.

III.4  Toxicology
The proposed limits for specified and unspecified impurities within the drug substance, and the proposed release and shelf-life limits within the drug product, are in line with their respective limits as specified in ICH Q3A (R2) and ICH Q3B (R2). In addition, the proposed limits for residual solvents within the drug substance are in line with the limits as specified in ICH Q3C (R6).

III.5  Ecotoxicity/environmental risk assessment (ERA)
Since Iloprost 100 micrograms/ml 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.6  Discussion on the non-clinical aspects
There are no objections to the approval of this application from a non-clinical viewpoint.

IV  CLINICAL ASPECTS

IV.1  Introduction
This is a generic product and the application is made in accordance with article 10.1 of the directive 2001/83/EC as amended. The originator has been authorised in France since 1992. Thus the legal basis of this application based on an European reference product is justified.

According to the regulatory requirements of CHMP Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/Corr**) a bioequivalence study is not required for parenteral aqueous solutions and the applicant has not submitted any.

No new efficacy or safety studies have been performed and none are required for this type of application. A comprehensive review of the published literature has been provided by the applicant, citing the well-established clinical pharmacology, efficacy and safety of iloprost.

Based on the data provided, Iloprost 100 micrograms/ml can be considered a generic of ILOMEDINE 0.1 mg/ml, solution injectable pour perfusion (Bayer Healthcare SAS, France).

IV.2  Pharmacokinetics
In accordance with the Note for Guidance on the Investigation of Bioavailability and Bioequivalence (CPMP/QWP/1401/98 Rev 1, Jan 2010) a bioequivalence study is not required for a product administered as an aqueous intravenous solution containing the same active substance in the same concentration as the currently authorised product and therefore none is submitted. Iloprost 100 micrograms/ml concentrate for solution for infusion is a solution containing the same excipients to the reference product ILOMEDINE 0.1 mg/ml, solution injectable pour perfusion (Bayer Healthcare SAS, France).
IV.3 Pharmacodynamics
No new pharmacodynamic data were submitted and none were required for applications of this type.

IV.4 Clinical efficacy
No new efficacy data were submitted, and none were required for applications of this type.

IV.5 Clinical safety
No new safety data were submitted and none are required.

IV.6 Risk Management Plan (RMP) and Pharmacovigilance System
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, characterize, prevent or minimize risks relating to the product. The submitted RMP reflects the SmPC of the reference product.

In line with the reference product, the applicant proposes only routine pharmacovigilance and routine risk minimisation measures for all safety concerns (labelling in the SmPC and the PIL). This is agreed.

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:
- At the request of the RMS;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time, but via different procedures.

IV.7 Discussion on the clinical aspects
The grant of marketing authorisations is recommended for these applications from a clinical viewpoint.

V User consultation
The package leaflet 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 PIL was English.

The results show that the package leaflet 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
The quality of the products is acceptable, and no new non-clinical or clinical safety concerns have been identified. Iloprost 100 micrograms/ml contains the same qualitative composition as the reference product ILOMEDINE 0.1 mg/ml, solution injectable pour perfusion (Bayer Healthcare SAS, France).

Given a product administered as an aqueous intravenous solution containing the same active substance in the same concentration as the reference product, a bioequivalence study is not required. Extensive clinical experience with iloprost is considered to have demonstrated the therapeutic value of the compound. The benefit-risk is, therefore, considered to be positive.
Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and Labels

In accordance with Directive 2010/84/EU the Summaries of Product Characteristics (SmPCs) and Patient Information Leaflets (PILs) for products granted Marketing Authorisations at a national level are available on the MHRA website.

The approved labelling for this medicine is presented below:
Iloprost 100 micrograms/ml concentrate for solution for infusion

Each 1 ml of concentrate for solution for infusion contains 100 micrograms of iloprost (equivalent to 134 micrograms iloprost tromethamol). Contains tromethamol, ethanol, sodium chloride, hydrochloric acid (pH adjustment) and water for injection.

Keep out of the sight and reach of children.

For intravenous use

Dilute before use
Annex 1

**Table of content of the PAR update for MRP and DCP**
Steps taken after the initial procedure with an influence on the Public Assessment Report (Type II variations, PSURs, commitments)

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