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PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

Veletri 0.5 mg and 1.5 mg, powder for solution for infusion
Veletri 0.5 mg and 1.5 mg, powder and solvent for solution for infusion
Actelion Registration Ltd., United Kingdom

epoprostenol sodium

This assessment report is published by the MEB pursuant Article 21 (3) and (4) of Directive 2001/83/EC. The report comments on the registration dossier that was submitted to the MEB and its fellow –organisations in all concerned EU member states.
It reflects the scientific conclusion reached by the MEB and all concerned member states at the end of the evaluation process and provides a summary of the grounds for approval of a marketing authorisation.
This report is intended for all those involved with the safe and proper use of the medicinal product, i.e. healthcare professionals, patients and their family and carers. Some knowledge of medicines and diseases is expected of the latter category as the language in this report may be difficult for laymen to understand.

This assessment report shall be updated by a following addendum whenever new information becomes available.

General information on the Public Assessment Reports can be found on the website of the MEB.

To the best of the MEB's knowledge, this report does not contain any information that should not have been made available to the public. The MAH has checked this report for the absence of any confidential information.

EU-procedure number: NL/H/2600/001-004/DC
Registration number in the Netherlands: RVG 111570-111573

22 July 2013

Pharmacotherapeutic group:	antithrombotic agents, platelet aggregation inhibitors excl. heparin
ATC code:	B01AC09
Route of administration:	intravenous
Therapeutic indication:	pulmonary arterial hypertension; renal dialysis
Prescription status:	prescription only
Date of authorisation in NL:	24 April 2013
Concerned Member States:	Decentralised procedure with CZ, FR, IT, PL, PT, UK
Application type/legal basis:	Directive 2001/83/EC, Article 10(3)

For product information for healthcare professionals and users, including information on pack sizes and presentations, see Summary of Product Characteristics (SmPC), package leaflet and labelling.

I INTRODUCTION

Based on the review of the quality, safety and efficacy data, the member states have granted a marketing authorisation for Veletri 0.5 mg and 1.5 mg, powder for solution for infusion, and Veletri 0.5 mg and 1.5 mg, powder and solvent for solution for infusion from Actelion Registration Ltd. The date of authorisation was on 24 April 2013 in the Netherlands.

The product is indicated for:

- Pulmonary Arterial Hypertension

Veletri 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

Veletri 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 (see section 5.1).

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

Epoprostenol sodium, the monosodium salt of epoprostenol, is a naturally occurring prostaglandin produced by the intima of blood vessels. Epoprostenol is the most potent inhibitor of platelet aggregation known. It is also a potent vasodilator.
Many of the actions of epoprostenol are exerted via the stimulation of adenylate cyclase, which leads to increased intracellular levels of cyclic adenosine 3'5' monophosphate (cAMP). A sequential stimulation of adenylate cyclase, followed by activation of phosphodiesterase, has been described in human platelets. Elevated cAMP levels regulate intracellular calcium concentrations by stimulating calcium removal, and thus platelet aggregation is ultimately inhibited by the reduction of cytoplasmic calcium, upon which platelet shape change, aggregation and the release reaction depends.

This decentralised procedure concerns a hybrid application claiming essential similarity with the innovator product Flolan 0.5 mg and 1.5 mg, powder for solution for infusion (NL License RVG 23523-23524) and Flolan 0.5 mg and 1.5 mg, powder and solvent for solution for infusion (NL License RVG 14469, 23525), which have been registered in the Netherlands by GlaxoSmithKline B.V. since 1992 (0.5 mg powder and solvent) and 1999 (other strengths).

The ready for use Flolan solutions for infusion have limited stability *i.e.*, 12 hours at 25ºC or 48 hours at 2-8ºC. Ambulatory patients must carry the solution with them in a special cooling device. Veletri has a slightly different composition and is shown to be more stable at room temperature.
The MAH developed two formulations: Epoprostenol for injection 1 (EFI1) and 2 (EFI2). EFI1 was approved to improve exercise capacity in patients with WHO Group 1 pulmonary arterial hypertension (PAH) in the US on 27 June 2008, on the basis of pharmaceutical data only. The product was granted a waiver for *in vivo* bioequivalence studies. Actelion developed the EFI formulation further to improve the in-use stability, resulting in EFI2. EFI2 was approved in the US on 28 June 2012 and launched on 15 November 2012 as an improved formulation. EFI2 under the name Caripul® was approved in Canada on 30 November 2012 and launch is planned for April 2013.

Compared to other epoprostenol diluted solutions, which are buffered with glycine, Veletri contains l-arginine, at lower buffering capacity. This leads to a broader range of pH values of the diluted solution. The pH decreases with dilution from 12.0 at a concentration of 90,000 ng/mL, 11.7 at a concentration of 45,000 ng/mL to 11.0 at a concentration of 3,000 ng/mL.

The marketing authorisation is granted based on article 10(3) of Directive 2001/83/EC, as bioequivalence cannot be demonstrated through bioavailability studies.

This type of application refers to information that is contained in the pharmacological-toxicological and clinical part of the dossier of the authorisation of the reference product. A reference product is a medicinal product authorised and marketed on the basis of a full dossier, i.e. including chemical, biological, pharmaceutical, pharmacological-toxicological and clinical data. This information is not fully available in the public domain. Authorisations for generic products are therefore linked to the 'original' authorised medicinal product, which is legally allowed once the data protection time of the dossier of the reference product has expired. Since the drug product is to be administered as an aqueous intravenous solution containing the same active substance in the same concentration as the reference product no bioequivalence study is required.

The rationale for therapeutic equivalence of the EFI formulations and Flolan is supported by the results of two pharmacokinetic/pharmacodynamic (PK/PD) studies. Study AC-066-101 was a head-to-head comparison of EFI1 and Flolan in 20 healthy male subjects. Study AC-066-102 comprised two head-to-head comparisons, one of which compared EFI1 to EFI2 and the second which compared EFI2 to Flolan, each in a further 20 healthy male subjects. These studies showed that the exposure to epoprostenol was comparable following administration of EFI1, EFI2 or Flolan. In addition, the average time profiles of the hemodynamic markers in these studies were essentially superimposable for EFI1 and Flolan in Study AC-066-101 and for EFI1, EFI2 and Flolan in Study AC-066-102. Assessment of the study results is discussed in section II.3 'Clinical aspects'.

Scientific advice was given to the MAH in July 2009 by the regulatory authorities of the UK and France, and by the Dutch MEB in August 2009.

No paediatric development programme has been submitted, as this is not required for a hybrid application.

II SCIENTIFIC OVERVIEW AND DISCUSSION

II.1 Quality aspects

Compliance with Good Manufacturing Practice
The MEB has been assured that acceptable standards of GMP (see Directive 2003/94/EC) are in place for this product type at all sites responsible for the manufacturing of the active substance as well as for the manufacturing and assembly of this product prior to granting its national authorisation.

Active substance
The active substance is epoprostenol sodium, an established active substance not described in the European Pharmacopoeia (Ph.Eur.*) or another pharmacopoeia. The active substance is a white or almost white, crystalline powder, which is very soluble in water and ethanol and soluble in acetonitrile. Isomerism is controlled by the route of synthesis. Epoprostenol sodium is hygroscopic from approximately 50% relative humidity and it is unstable in acidic and neutral milieu.

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
Epoprostenol sodium is manufactured by a three step synthesis. No class I solvents or heavy metal catalysts are used. The starting material has been sufficiently characterized. The used solvents and reagents have been adequately controlled.

Quality control of drug substance

The drug substance specification has been established in-house by the MAH with requirements for: appearance, identification, specific optical rotation, NaOH content, water content, assay, purity, residual solvents, bacterial endotoxins and microbial limits. The specification is acceptable.
Batch analytical data demonstrating compliance with the drug substance specification have been provided for 3 small-scale production batches and 3 full-scale production batches.

Stability of drug substance
Stability data on the active substance have been provided for 3 small-scale production batches stored at -18°C for 24 months and +5°C for 6 months. At +5°C a change in color of the solid material occurred. No changes or trends were observed in the data from the batches stored at -18°C. Furthermore it has been demonstrated by stress testing that the drug substance should be protected from moisture, light and high temperature.
The proposed retest period was granted: 12 months when stored below -18°C in a HDPE container placed in a PE-Al sachet in order to protect from light and moisture.

** Ph.Eur. is an official handbook (pharmacopoeia) in which methods of analysis with specifications for substances are laid down by the authorities of the EU.*

Medicinal Product

Composition
Veletri 0.5 mg and 1.5 mg is a white to off-white powder. The product contains 0.531 mg or 1.593 mg epoprostenol sodium per vial with an additional overage of 5%. The solvent for parenteral use is a clear, colourless solution.
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.

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 solvent is packed in plastic containers, made from low density polyethylene. The bottle is closed with a latex-free Type I rubber disk, fixed by a cap.

The excipients are:
Powder for solution for infusion - sucrose, arginine, sodium hydroxide (for pH adjustment).
Solvent for parenteral use – water for injection.

Pharmaceutical development
The development of the product has been described, the choice of excipients is justified and their functions explained. The aim of the development was to produce a drug product equivalent to the reference product, with better stability and an improved in-use stability. Therefore the MAH identified the qualitative/quantitative formula of the reference product, selected the primary packaging, identified the headspace gas of the reference product, studied the feasibility of the pharmaceutical process on industrial scale. The resulting packaging and manufacturing process, including sterilisation method, are justified.
The MAH has compared the properties of EFI1 and EFI2. The results are showing that the appearance of the lyophilisate is of EFI2 remains stable, while the lyophilisate of EFI1 turns translucent over time. Furthermore, the formulation EFI2 reconstituted solution is significantly more stable. The formulation development is considered acceptable. The compatibility of this high pH formulation with blood was studied in an *in-vitro* study of epoprostenol in human whole blood; no concerns were identified.
Each vial contains a ~5% overfill to compensate the volume increase during the reconstitution of the solution with the diluents. It will then assure the withdrawal of the full label dose after reconstitution.
Since the drug product is to be administered as an aqueous intravenous solution containing the same active substance in the same concentration as the reference product, no bioequivalence study is required.
The pharmaceutical development of the product has been adequately performed.

Manufacturing process
The manufacturing process consists of: preparation of the bulk solution, bioburden reduction, sterile filtration, filling of the vials and lyophilization/oversealing. The manufacturing process has been adequately validated according to relevant European guidelines. Process validation data on the product has been presented for 8 full-scale batches (4 batches of 0.5 mg and 4 batches of 1.5 mg).

Control of excipients
The excipients comply with the Ph.Eur. These specifications are acceptable.

Quality control of drug product
The product specification for the epoprostenol vials includes tests for appearance, identification, uniformity of dosage units, reconstitution time, water content, pH of vial content in water, appearance of the reconstituted solution, assay, related substances, sterility and endotoxins. The release and end-of-shelf-life specification for related substances are not identical.
The product specification for the solvent containers includes amongst others tests for appearance, pH, extractable volume, sub-visible particles, sterility and endotoxins. The specification is in conformation with the Ph.Eur. requirements. Release and shelf-life limits are identical.
The analytical methods have been adequately described and validated. Batch analytical data from the proposed production site of the epoprostenol vial have been provided on 3 pilot-scale batches per strength. Batch analytical data from the proposed production site of the solvent container have been provided on 3 full-scale batches. All data demonstrated compliance with the release specification.

Microbiological attributes
The medicinal product is for infusion use, therefore the microbiological characteristics are considered a critical parameter. In order to assure the microbiological quality, endotoxins and sterility tests are performed on the finished product. These tests are carried out routinely according the requirements of Ph.Eur. for sterile products. The container closure system integrity was demonstrated by performing a microbial challenge on containers filled with media and a physical integrity test (blue dye test).

Stability of drug product
Stability data on the product has been provided for three pilot-scale batches per strength and 3 batches of the solvent . The 0.5 mg and 1.5 mg epoprostenol batches were stored at 25°C/60% RH (24 months) and 30°C/65% RH (24 months) and 40°C/75% RH (6 months). The full-scale solvent batches were stored at 25°C/60% RH (36 months) and 40°C/75% RH (6 months). The conditions used in the stability studies are according to the ICH stability guideline. The batches were stored in the type I clear glass vials closed with a butyl rubber stopper and aluminium-PP flip-off cap.
At accelerated conditions a decrease in assay and increase in related substances was observed in the epoprostenol vials of both 0.5 mg and 1.5 mg. At intermediate conditions a very slight increase in related substances was observed. This was also observed at long term conditions. Photostability of the product was shown in line with the ICH conditions. The proposed shelf-life of three years without special storage conditions is justified when stored in type I clear glass vials with a butyl rubber stopper and a flip-off cap.
Chemical and physical in-use stability has been demonstrated for 8 days at 5°C. The in-use shelf-life of 8 days of the diluted solution stored at 2° to 8°C in the drug delivery reservoir is justified.

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. Sucrose is produced using raw materials of vegetable origin.

II.2 Non-clinical aspects

The active substance of Veletri is the monosodium salt of epoprostenol, which is a well-known medicinal substance.
The pharmacodynamic, pharmacokinetic and toxicological properties of epoprostenol are well known. As epoprostenol is a widely used, well-known active substance, the MAH has not provided additional studies and further studies are not required. Overview based on literature review is thus appropriate.

However, the EFI2 formulation of Veletri differs from the EFI1 formulation of the reference product FLOLAN with regards to the bulking agent, which is sucrose in EFI2 and mannitol in EFI1 (and Flolan), and by a pH setting of 13.2, which is closer to the relevant pKa of the buffer system used (L-arginine).
The non-clinical overview focuses on the pre-clinical pharmacology, pharmacokinetics and toxicology of epoprostenol in the EFI2 formulation. The non-clinical overview is adequate.

The potential of EFI2 to cause haemolysis was tested in vitro under conditions approximating the ratio of diluted product to blood when infused into a peripheral vein, a "worst-case scenario" compared to central venous dilution [Actelion Study Reference Number: T-10.529, January 2011, GLP]. This study showed no concerns since it was demonstrated that epoprostenol in the EFI2 formulation did not cause haemolysis *in vitro.*

The extractable and leachable profile of the administration system components (stopper, cassette and tubings) was evaluated. The following leachables were identified:
Isobutylene; Dodecanoic acid; Bisphenol A; Acetophenone; Acetone; Myristic acid; Diethylhexyl phthalate (DEHP); 2-Phenyl-2-propanol; Isopropanol; Pentadecanoic acid; Squalene; 2-Ethylhexanoic acid; Tert-butanol; Palmitic acid; Phthalic acid; Cyclohexanone; Heptadecanoic acid; 2-Ethyl-1-hexanol; Octanoic acid; Nonanoic acid; 2-Ethylhexyl-p-hydroxybenzoate; 3,5-Di-tert-butyl-4-hydroxybenzaldehyde; Decanoic acid; Stearic acid.
Based on the provided information in the report, the levels of these leachables in the infusion fluid are toxicologically justified.

Environmental risk assessment
The product is intended as a substitute for other identical products on the market. The approval of this product will not result in an increase in the total quantity of epoprostenol released into the environment. It does not contain any component, which results in an additional hazard to the environment during storage, distribution, use and disposal. Nevertheless, the MAH has provided an ERA. The calculated EMA Phase I $PEC_{surfacewater}$ for epoprostenol of 0.000075 µg/L is below the EMA action limit of 0.01 µg/L. For this reason, Phase II assessment is not required.

II.3 Clinical aspects

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 reference to the dossier of the innovator product Flolan.

Pharmacokinetics
Epoprostenol is rapidly metabolized, with a terminal half-life (t½) of approximately 6 minutes. The two main metabolites in man are 6-keto-Prostacyclin F1α, which is formed by spontaneous degradation and 6,15-diketo-13,14-dihydro-Prostacyclin F1α, which is formed by enzymatic degradation. A week after administration of tritium-labeled epoprostenol, the percentage of the radioactive dose recovered in the urine and feces were 82% and 4%, respectively, for the two metabolites. In reference animal models, the pharmacological activity of these two metabolites is less than that of epoprostenol.

The rationale for therapeutic equivalence of the EFI formulations and Flolan is further supported by the results of two PK/PD studies. Study AC 066 101 was a head-to-head comparison of EFI1 and Flolan in 20 healthy male subjects. Study AC 066 102 comprised two head-to-head comparisons, one of which compared EFI1 to EFI2 and the second which compared EFI2 to Flolan, each in a further 20 healthy male subjects.

In both submitted studies the two preparations of epoprostenol (EFI-1 and EFI-2) were compared with Flolan after infusion of both products in ascending doses 2, 4, 6 and 8 ng/ml/kg over a period of 8 hours (each dose infusion over a period of 2 hours). Both studies showed that the extent of exposure during those 8 hours are comparable. The 90% confidence intervals ratio's of the partial AUC's were all within the acceptance criteria for bioequivalence.

Clinical efficacy

The efficacy of continuous i.v. administration of epoprostenol described in this application is primarily based on relevant published data from studies conducted using Flolan in patients with Pulmonary Arterial Hypertension (PAH). The three controlled studies with Flolan comprised two studies in patients with idiopathic PAH (IPAH) and one in patients with PAH associated with scleroderma spectrum of disease (APAH-SSD). These studies compared i.v. epoprostenol plus conventional therapy with conventional therapy alone. Efficacy endpoints in these studies included exercise capacity (assessed using the 6-minute walk test [6MWT]), change in New York Heart Association (NYHA) functional class, and change in cardiac hemodynamic parameters. Survival was evaluated in patients with IPAH and in patients with scleroderma.

The effect of i.v. epoprostenol on long-term survival in patients with PAH was assessed in two large uncontrolled cohort studies, in a retrospective study in patients with PAH due to different etiologies, and in a registry of PAH patients treated with epoprostenol. Long-term efficacy in patients with PAH was assessed in two single-center observational studies.

In addition, current clinical experience with EFI1 and EFI2, which is based on two pharmacokinetic (PK)/pharmacodynamic (PD) studies conducted in healthy subjects [AC-066-101 and AC-066-102], a small completed study and its extension with EFI1 in PAH patients [AC-066-401/402] and a clinical study and its ongoing extension with EFI2 in PAH patients [AC-066-301/302- EPITOME-2) are included. Experience with EFI1 from post-marketing surveillance in the US, including an Actelion-sponsored patient registry is also described. According to Actelion, their sponsored studies were conducted in full compliance with Good Clinical Practice.

Efficacy data though not required in a generic application, could be supportive. No formal statistical analysis was conducted on the explored haemodynamic parameters measured in the PK/PD studies: Study AC-066-101/102. Submitted analysis show comparable results on different systemic and pulmonary haemodynamic data obtained when Flolan, EFI1 or EFI2 are administered. Data are reassuring, but no robust clinical conclusions can be made.

Study AC-066A401 (EPITOME-1) was conducted using the EFI1 formulation, and not the currently proposed formulation EFI2, limiting its use for the current application. It is also difficult to interpret the data, due to the high variability of the baseline characteristics and importantly, no formal statistical analysis was submitted. The conclusions of the MAH that efficacy data (6MWT, NYHA FC, SCVO2) are comparable between Flolan and EFI1 can not be supported based on such data.

The data of study EPITOME-2 [AC-066A301] (prospective, multicenter, single-arm, open label, Phase 3b study conducted in Europe and Canada) were submitted. Data from study Epitome-2 are the most relevant to the current application as it is specific to the EFI2 formulation. However, it is a single arm study limiting the interpretation of the data.

A total of 42 patients were enrolled into the study. Of these, 41 patients received study treatment and completed the study according to the protocol (3 months).

One patient prematurely discontinued the study due to withdrawal of informed consent prior to receiving study drug. There were no premature discontinuations of study treatment. All 41 treated patients entered into the ongoing open-label extension study (AC-066A302) to continue the evaluation of safety and tolerability of EFI2.

Doses. At the start of study treatment, the mean dose of EFI2 was 29.9 ± 15.1 ng/kg/min – the same as that of Flolan® – ranging from 7 to 76 ng/kg/min. Three patients had a dose adjustment, with one patient (201-004) starting treatment on a decreased dose (−2 ng/kg/min) and two patients (201-002 and 203-002) starting treatment on an increased dose (+1 ng/kg/min) of EFI2 vs Flolan®.

During the treatment period, the dose of EFI2 remained stable for 34 patients (82.9%). Seven patients (17.1%) received a dose adjustment at least once during the course of treatment. Of these, 4 patients received a dose increase and 3 patients a dose decrease. Dose adjustments for any reason occurred no

earlier than 3 weeks after switching from Flolan® to EFI2. This gives some support to the comparability of the doses used of EFI2 to Flolan.

Dose increases. During the treatment period, four patients required at least one increase in dose due to signs of persistence, relapse or worsening of PAH. Dose increases occurred no earlier than on treatment day 23. Over the treatment period, one of the 4 patients (205-001) deteriorated from FC II at baseline to FC III at EOT.

Patient 201-002 was switched from a Flolan® dose of 9 ng/kg/min to an EFI2 dose of 10 ng/kg/min which was subsequently up-titrated in 3 steps to 13 ng/kg/min in response to “relapse or worsening of PAH symptoms”. Patient 205-001 received a dose increase in 2 steps from 16 to 20 ng/kg/min due to “relapse or worsening of PAH symptoms”. In patient 206-002 the dose was up-titrated in 2 steps from 32 to 34 ng/kg/min in response to “shortness of breath on exertion and leg fatigue when walking”.

Patient 206-003 had a dose increase from 45 to 50 ng/kg/min due to “increased shortness of breath on exertion”.

During the 24-h safety follow-up period, one additional patient (202-011) received a dose increase from 45 to 47 ng/kg/min due to “relapse or worsening of PAH symptoms” while enrolled in the extension study.

Dose decreases. Two patients received dose decreases between treatment Days 25–85. The dose of patient 201-004 was decreased from 23 to 22 ng/kg/min in response to an increased cardiac output which was judged as indicative of too high a dose of drug by the investigator. For patient 206-004 the dose was decreased in 2 steps from 54 to 48 ng/kg/min due to increased skin sensitivity, jaw pain, flushing and feet pain. Subsequently, the dose was increased to 52 ng/kg/min at EOT. NYHA FC remained unchanged for both of the patients.

Efficacy endpoints were change from baseline to EOT in hemodynamics [pulmonary vascular resistance (PVR), mean pulmonary arterial pressure, right atrial pressure, pulmonary capillary wedge pressure, and cardiac index], 6-minute walk distance (6MWD), Borg dyspnea score, NYHA FC, and NT-proBNP.

In study AC-066A301, exploratory evaluation of efficacy on the basis of cardiac hemodynamics, exercise capacity, functional class and other disease parameters showed that these key efficacy variables were maintained unchanged 3 months after switch from Flolan® to EFI2.

Hemodynamic variables remained generally stable over the treatment period with similar mean and median values at baseline and EOT (Table E1). , resulting in no distinct changes from baseline. Change from baseline in PVR (n = 36) remained within ±10% (geometric mean of the percent ratio EOT/baseline: 97.98, 95% CL [91.28, 105.17]) (Table E1).

Table E1: Hemodynamics: Change from baseline to EOT, All-treated set (without imputation for missing values)

Hemodynamic parameter	Baseline	EOT	Change from baseline to EOT (mean, median) and Percent ratio EOT/baseline (geometric mean)
PVR, dyn/sec/cm^5 (n = 36)[a]	**Mean:** 595.70±237.14; 95% CL [515.47 , 675.94] **Median**: 563.64; 95% CL [501.49 , 681.97] [Q1, Q3] [446.9 , 729.8] [Min, Max] [155.6 , 1150.0]	**Mean:** 587.66±248.44; 95% CL [503.60 , 671.72] **Median:** 533.33; 95% CL [480.00 , 681.97] [Q1, Q3] [421.3 , 728.2] [Min, Max] [142.5 , 1261.5]	**Mean:** −8.04±116.83; 95% CL [−47.57 , 31.49] **Median**: 13.6; 95% CL [−54.03 , 37.78] [Q1, Q3] [−83.6 , 73.5] [Min, Max] [−225.0 , 232.7] **Geometric mean:** 97.98 95% CL [91.28 , 105.17]
TPR, dyn/sec/cm^5 (n = 41)	**Mean:** 752.44±260.91; 95% CL [670.08, 834.79] **Median**:727.27; 95% CL [623.53, 837.21] [Q1, Q3] [589.5, 864.5] [Min, Max] [300.0, 1440.0]	**Mean:** 757.51±296.82; 95% CL [663.82, 851.19] **Median**: 731.71; 95% CL [632.84, 839.34] [Q1, Q3] [560.0, 953.8] [Min, Max] [208.2, 1661.5]	**Mean:** 5.07±128.89; 95% CL [−35.61, 45.75] **Median**: 15.92; 95% CL [−28.09, 52.76] [Q1, Q3] [−68.3, 87.4] [Min, Max] [−288.2, 273.9] **Geometric mean:** 98.70 95% CL [93.22 , 104.49]

Hemodynamic parameter	Baseline	EOT	Change from baseline to EOT (mean, median) and Percent ratio EOT/baseline (geometric mean)
mPAP, mmHg (n = 41)	**Mean:** 51.9±11.5; 95% CL [48.3, 55.5]	**Mean:** 51.7±12.8; 95% CL [47.7, 55.7]	**Mean:** −0.2±7.0; 95% CL [−2.4, 2.0]
	Median: 53.0; 95% CL [48.0, 55.0] [Q1, Q3] [46, 60] [Min, Max] [22, 78]	**Median**: 53.0; 95% CL [50.0, 56.0] [Q1, Q3] [46, 60] [Min, Max] [19, 75]	**Median**: 0.0; 95% CL [−2.0, 2.0] [Q1, Q3] [−4, 4] [Min, Max] [−20, 17] **Geometric mean:** 98.6 95% CL [94.2 , 103.3]
RAP, mmHg (n = 41)	**Mean:** 7.9±4.6; 95% CL [6.4, 9.3]	**Mean:** 7.1±4.6; 95% CL [5.7, 8.6]	**Mean:** −0.8±3.6; 95% CL [−1.9, 0.4]
	Median: 7.0; 95% CL [6.0, 10.0] [Q1, Q3] [5, 10] [Min, Max] [0, 19]	**Median**: 6.0; 95% CL [5.0, 7.0] [Q1, Q3] [4, 10] [Min, Max] [0, 18]	**Median**: 0.0; 95% CL [−1.0, 1.0] [Q1, Q3] [−3, 1] [Min, Max] [−9, 6] **Geometric mean**[b]: 86.0 95% CL [70.3 , 105.1]
PCWP, mmHg (n = 36)[a]	**Mean:** 10.3±3.8; 95% CL [9.0, 11.5]	**Mean:** 10.1±4.3; 95% CL [8.6, 11.5]	**Mean:** −0.2±3.4; 95% CL [−1.3, 1.0]
	Median: 10.0; 95% CL [9.0, 12.0] [Q1, Q3] [9, 13] [Min, Max] [2, 21]	**Median**: 9.0; 95% CL [8.0, 12.0] [Q1, Q3] [7, 13] [Min, Max] [4, 22]	**Median**: −1.0; 95% CL [−1.0, 1.0] [Q1, Q3] [−2, 2] [Min, Max] [−9, 7] **Geometric mean:** 100.3 95% CL [84.9 , 118.6]
Cardiac Index, L/min/m² (n = 41)	**Mean:** 3.34±0.71; 95% CL [3.12, 3.57]	**Mean:** 3.38±0.81; 95% CL [3.13, 3.64]	**Mean:** 0.04±0.5; 95% CL [−0.12, 0.20]
	Median: 3.30; 95% CL [3.16, 3.46] [Q1, Q3] [3.0, 3.6] [Min, Max] [1.5, 5.3]	**Median**: 3.41; 95% CL [3.14, 3.70] [Q1, Q3] [2.8, 3.9] [Min, Max] [1.3, 5.6]	**Median**: 0.03; 95% CL [−0.14, 0.23] [Q1, Q3] [−0.3, 0.3] [Min, Max] [−1.0, 1.4] **Geometric mean:** 100.38 95% CL [95.92 , 105.03]

[a] Data missing for 5 patients. [b] n = 39; 2 patients were excluded because they had values of 0 mmHg at either baseline or EOT

6MWT. The mean (± standard deviation) and median 6MWDs observed at EOT (492.8 ± 81.6 m, 95% CL [466.7, 518.9] and 486.5 m, 95% CL [455.0, 543.0], respectively) were similar to those observed at baseline (498.1 ± 86.0 m, 95% CL [470.6, 525.6] and 500.5 m, 95% CL [468.0, 550.0], respectively), resulting in no change from baseline over the treatment period (geometric mean of percent ratio EOT/baseline: 99.1%, 95% CL [97.0, 101.3]; mean change: −5.3 ± 29.1 m, 95% CL [−14.6, 4.0]; median change: −7.5 m, 95% CL [−15.0, −1]).

As shown, the main efficacy results of EOT are comparable to baseline values which is reassuring, though no official statistical assumptions were made.

Exploratory evaluation of quality of life showed that EFI2 was associated with an increase in treatment satisfaction at the end of treatment, relating to the convenience of using EFI2.

Results of EPITOME-2 have to be considered in the context that such study is only supportive, as the application is mainly based on the quality data, due to the generic (hybrid) application. As such, the data are reassuring regarding the comparability of EFI2 to Flolan. Importantly in this study, a subgroup of patients (n=22) were administered EFI2 under the conditions very similar to normal clinical practice: concentration of > 45,000 ng/mL. The used concentrations correspond to a pH of the administered ready-to-use solution of 11.5–12.0 (for a concentration between 60,000 and 90,000 ng/mL), depending on the final concentration used.

The MAH also submitted registry data (PROSPECT) pertaining to formulation EFI1, and as such is of limited supportive value. The PROSPECT registry enrolled its last patient on 31 January 2012 (n = 354) and follows patients up for a 12-month period or until premature discontinuation (estimated last patient last visit 31 January 2013). An interim analysis of data from the first 100 enrolled patients (cut-off 20 November 2011) was performed and submitted with the initial application. In this analysis, data for only 44/239 of the database does not indicate a high drop out rate, as this reflects also patients who reached a study endpoint (deaths = 16) and patients who did not yet reach that study visit.
An updated interim analysis (cut off April 2012) includes data for 300 patients with different follow-up periods. Reasons for discontinuation are comparable to the first analysis.

Clinical safety
Post-marketing data pertaining to the formulation EFI1 is submitted. Data is generally reassuring. Specific to these formulations (EFI1 and EFI2) is the high pH. The MAH explained that no cases of extravasation have been reported to them. Extravasation is a serious condition that warrants special attention by healthcare professionals and patients involved in administering any intravenous medications, especially those that are highly alkaline or have high osmolarity. The revised proposed VELETRI SmPC addresses this risk by adopting the same sentence as the recently harmonised Flolan® SmPC: “Because of the high pH of the final infusion solutions, care should be taken to avoid extravasation during their administration and consequent risk of tissue damage.”

In addition, patients are requested in the package leaflet to check the injection area with respect to visible symptoms of extravasation (like tenderness, burning, stinging, swelling, redness, or even blistering and shedding of the skin at the injection site). If any symptoms occur, patients are asked to contact the hospital immediately for advice. In the case of extravasation, general supportive care would apply that is considered generic to all such instances and epoprostenol formulations. The MAH’s reasoning that in the clinical setting the overall risk of extravasation is not expected to be different between EFI2 and Flolan is accepted. Both the SmPC and the patient leaflet explain the associated risks of extravasation of such strongly alkaline solutions.

Another concern in the initial application was the risk associated with the injection of Veletri in peripheral veins. The MAH submitted available clinical data to address this issue. This was done for short durations and low concentrations, which is relevant to the clinical setting, as infusion through a peripheral vein is expected to occur only temporarily. This limited data does not point to any special safety concerns, different from the comparator Flolan. This is reassuring. Further warning is currently added in section 4.4 to explicitly warn against this risk "The pH of the “ready-to-use solution” increases with concentration, i.e., ranges from 11.0–12.0 for concentrations within the range of 3,000-90,000 ng/mL. Therefore, peripheral i.v. use should be restricted only to short duration and using only low concentrations."

Safety data of Study Epitome-2. The median duration of exposure to study drug regardless of interruptions (*i.e*. up to 7 h in 1 patient) was 87 days, with all 41 treated patients receiving study treatment for at least 10 weeks. Study treatment was received for at least 12 weeks and 14 weeks by 90.2% and 4.9% of patients, respectively.
During the treatment period, 78% of patients experienced at least one adverse event (AE). The most frequently reported AEs were headache (29.3%), nasopharyngitis (17.1%), jaw pain (14.6%), and flushing

(12.2%). The events most frequently reported as related were those known to be associated with i.v. epoprostenol treatment and included headache (26.8%), jaw pain (14.6%) and flushing (12.2%). There were no deaths and no AEs leading to discontinuation of study treatment reported during the study. Serious AE (SAE) recorded in the study are listed in Table S1.

Table S1: SAEs reported during study treatment and the safety follow-up period.

Patient Age / sex	SAEs	Outcome / Investigator assessment of treatment relationship	Treatment
SAEs during study treatment			
201-001 47 years / female	Diverticulitis	Unresolved[+] / Unrelated to EFI2	EFI2
202-003 40 years / male	Device-related infection (pseudomonas)	Resolved without sequelae / Unrelated to EFI2	EFI2
202-008 55 years / male	Device connection issue	Resolved without sequelae / Unrelated to EFI2	EFI2
202-009 54 years / female	Device connection issue	Resolved without sequelae / Unrelated to EFI2	EFI2
206-003 35 years / female	Right ventricular failure	Unresolved / Unrelated to EFI2	EFI2
208-002 31 years / female	Device damage	Resolved without sequelae / Unrelated to EFI2	EFI2
SAEs during 30-day follow-up*			
202-010 30 years / male	Device dislocation	Resolved without sequelae / Unrelated to EFI2	EFI2[&]

Overall, the AE profile of EFI2 appeared consistent with the known safety profile of i.v. epoprostenol as described in the recently harmonised SmPC of Flolan®. One case of total obstruction of central venous line in the Epitome-2 extension study was also reported. The company has analysed the precipitate found in a Groshung catheter. About 15% was originating from the product (excipients), the remaining components are leachables and lubricants originating from the bag, tubing and linings. The main components are polyethylene oxides (used in the production of plastics). The cause of the precipitation is not yet identified, but most probably it is due to a problem with the routine use of the system. The MAH is conducting further tests to identify the cause of precipitation. The results will be submitted.

Two serious cases of sepsis were reported in the ongoing Epitome-2 extension study. In both cases, it is difficult to assess the suspected higher risk of sepsis that could be related to the formulation, considering that with Flolan itself such a risk is common (harmonised SmPC). The first case (201-002) is further complicated with medical history of diabetes, a central line infection while on Flolan (3 months prior to study drug initiation) and a current abscess of left lower limb. The investigator considered the event as related to the use of EFI2. The second case (207-003) occurred in a patient with 4 previous line infections while on Flolan. The patient had also a history of contact dermatitis at catheter site and rash (secondary to Flolan), and allergy to adhesive tape. The event was considered by the investigator not related to EFI2. The change from Flolan to Veletri cannot be excluded as the cause of the repeated infections. However,

the contribution of some confounding factors to the infections reported can not be excluded either. At this stage it is difficult to robustly assess the causality. Further close follow-up of these cases is accordingly very important; and the MAH committed to do that during the 6 monthly PSUR submissions.

The MAH presented additionally the results of an ad-hoc Pharmacovigilance Report. The report covered three periods of 1.5 months each: before, during and after the switch from EFI1 to EFI2 on the US market. Based on the analysis of catheter infection reports received during the three interval periods, the overall reporting rates of catheter site or blood stream infections were consistent across the three interval periods. The report, which summarises post-marketing experience with EFI2 in more than 700 patients of up to 12 weeks' exposure per period concluded that there was no evidence of increase in the reporting rate of catheter site infection or blood stream infections, and no unusual pattern of infection was identified after the switch.
The MAH proposed active monitoring of all cases of catheter site or blood stream infection using a targeted questionnaire. Furthermore, the MAH confirmed that Veletri infections associated with the delivery system will be routinely discussed in the PSUR.

Conclusion on clinical aspects
The application contains an adequate review of published clinical data. Therapeutic equivalence of the EFI formulations and Flolan is supported by the results of two pharmacokinetic/pharmacodynamic (PK/PD) studies. Study AC-066-101 and AC-066-102 showed that exposure to epoprostenol was comparable following administration of EFI1, EFI2 or Flolan. In addition, the average time profiles of the hemodynamic markers in these studies were essentially superimposable for EFI1 and Flolan in Study AC-066-101 and for EFI1, EFI2 and Flolan in Study AC-066-102. Essential similarity with the reference product has been shown. Safety issues are adequately covered by the MAH.

Risk management plan
The proposed product label, which is in line with the harmonised Flolan SmPC, adequately characterises the product-specific risks and their management. Although there are differences between Veletri and the reference medicinal product Flolan, i.e. composition (different excipients), these are adequately described in section 6 of the proposed product label.
Based on the currently available data, the RMS considers that routine risk minimisation activities (including instructions for use, warnings and precautions, contraindications, and other areas of the SmPC, package leaflet, and labelling) are considered sufficient to mitigate the risks related to Veletri in clinical practice.

The RMS considers that at present, no risk management plan is needed. The MAH committed to submit a PSUR six months after registration. In the PSURs, the MAH committed to actively monitor and discuss any reported cases suggestive of central venous catheter-related or bloodstream infection through the use of a targeted questionnaire. In case any data necessitating the introduction of an RMP become available, the MAH should act upon this and not await a planned PSUR submission.

Product information

SmPC
The content of the SmPC approved during the decentralised procedure is in accordance with that accepted for the reference product Flolan.

Readability test
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 user consultation was performed on the leaflet for EFI1. In addition, the MAH has provided a bridging report, in order to extrapolate the results of the aforementioned user test with the package leaflet of EFI1 to the package leaflet of EFI2. The user test consisted of a pilot test, followed by two rounds with 10 participants each. The questions covered the following areas sufficiently: traceability, comprehensibility and applicability. Overall, each and every question meets criterion of 81% correct answers. The readability test has been sufficiently performed.

Bridging of the results is accepted, since both package leaflets are very similar and have the same lay-out.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Veletri 0.5 mg and 1.5 mg, powder for solution for infusion, and Veletri 0.5 mg and 1.5 mg, powder and solvent 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 solution) 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.

Therapeutic equivalence of the Veletri epoprostenol for injection formulations and Flolan is supported by the results of two pharmacokinetic/pharmacodynamic (PK/PD) studies. These studies showed that exposure to epoprostenol was comparable following administration of EFI1, EFI2 or Flolan. In addition, the average time profiles of the hemodynamic markers in these studies were essentially superimposable for Veletri and Flolan.

The MAH has provided written confirmation that systems and services are in place to ensure compliance with their pharmacovigilance obligations.

The SmPC is consistent with that of the reference product. The SmPC, package leaflet and labelling are in the agreed templates.

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 Veletri 0.5 mg and 1.5 mg with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finished on 21 March 2013. Veletri 0.5 mg and 1.5 mg, powder for solution for infusion, and Veletri 0.5 mg and 1.5 mg, powder and solvent for solution for infusion were authorised in the Netherlands on 24 April 2013.

The PSUR-cycle for epoprostenol is 5 years. However, the MAH committed to submit a PSUR six months after registration.

The date for the first renewal will be: 24 April 2018.

The following post-approval commitments have been made during the procedure:

<u>Quality - medicinal product</u>
- The MAH committed to perform the compatibility testing with the diluents WFI and 0.9% NaCl at the end of shelf-life (36 months).

<u>Clinical aspects</u>
- Related to the case of total obstruction of central venous line in the Epitome-2 extension study, the MAH committed to submit the results of the three studies tests, which will be performed to identify the cause of precipitation, when they are available.
- The MAH committed to submit the data of Epitome 2 extension when it becomes available

<u>Pharmacovigilance</u>
- The first PSUR will be submitted 6 months after registration. The MAH committed to actively monitor and discuss in the PSURs any reported cases suggestive of central venous catheter-related or bloodstream infection using a targeted questionnaire.

List of abbreviations

AE	Adverse Event
ASMF	Active Substance Master File
ATC	Anatomical Therapeutic Chemical classification
AUC	Area Under the Curve
BP	British Pharmacopoeia
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
C_{max}	Maximum plasma concentration
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CV	Coefficient of Variation
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EFI	Epoprostenol For Injection
EU	European Union
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
ICH	International Conference of Harmonisation
IPAH	Idiopathic Pulmonary Arterial Hypertension
MAH	Marketing Authorisation Holder
MEB	Medicines Evaluation Board in the Netherlands
OTC	Over The Counter (to be supplied without prescription)
PAH	Pulmonary Arterial Hypertension
PAR	Public Assessment Report
Ph.Eur.	European Pharmacopoeia
PIL	Package Leaflet
PSUR	Periodic Safety Update Report
SAE	Serious Adverse Event
SD	Standard Deviation
SmPC	Summary of Product Characteristics
$t_{½}$	Half-life
t_{max}	Time for maximum concentration
TSE	Transmissible Spongiform Encephalopathy
USP	Pharmacopoeia in the United States

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Scope	Procedure number	Type of modification	Date of start of the procedure	Date of end of the procedure	Approval/ non approval	Assessment report attached