TITLE: Module 1.8.2 European Union Risk Management Plan for Flolan (epoprostenol sodium)

PART I: PRODUCT(S) OVERVIEW

Active substance(s) (INN or common name):	Epoprostenol sodium
Pharmaco-therapeutic group (ATC Code):	Antithrombotic Agents; Platelet aggregation inhibitors excl. heparin (B01AC09)
Name of Marketing Authorisation Holder or Applicant:	GlaxoSmithKline (MAH holder varies each National Market; see Annex 3)
Number of medicinal products to which this RMP refers:	One
Product(s) concerned (brand name(s)):	Flolan 0.5 mg and 1.5 mg Powder and Solvent for Solution for Infusion

Data lock point for this EU RMP:	1 Sep 2014
Version Number:	2
Date of final sign off:	11 May 2015

Administrative Information on the RMP

Part	Module/annex	Date last updated for submission (sign off date)	*Version number of RMP when last submitted/ or Not Applicable
PART II Safety Specification	SI Epidemiology of the indication and target population(s)	14 Nov 2014	1
	SII Non-clinical part of the safety specification	11 May 2015	2
	SIII Clinical trial exposure	11 May 2015	2
	SIV Populations not studied in clinical trials	11 May 2015	2
	SV Post-authorisation experience	11 May 2015	2
	SVI Additional EU requirements for the safety specification	11 May 2015	2
	SVII Identified and potential risks	11 May 2015	2
	SVIII Summary of the safety concerns	14 Nov 2014	1
PART III Pharmacovigilance Plan		11 May 2015	2
PART IV Plan for post-authorisation efficacy studies		14 Nov 2014	1
PART V Risk Minimisation Measures		11 May 2015	2
PART VI Summary of RMP		11 May 2015	2
PART VII Annexes	ANNEX 2 Current or proposed SmPC/PIL	11 May 2015	2
	ANNEX 3 Worldwide marketing status by country	14 Nov 2014	1
	ANNEX 4 Synopsis of clinical trial programme	11 May 2015	2
	ANNEX 5 Synopsis of pharmacoepidemiological study programme		Not applicable

Part	Module/annex	Date last updated for submission (sign off date)	*Version number of RMP when last submitted/ or Not Applicable
	ANNEX 6 Protocols for proposed and on-going studies in Part III		Not applicable
	ANNEX 7 Specific adverse event follow-up forms		Not applicable
	ANNEX 8 Protocols for studies in Part IV		Not applicable
	ANNEX 9 Synopsis of newly available study reports in Parts III-IV	11 May 2015	2
	ANNEX 10 Details of proposed additional risk minimisation activities		Not applicable
	ANNEX 11 Mock up examples	11 May 2015	2
	ANNEX 12 Other supporting data	14 Nov 2014	1

** A new RMP version number should be assigned each time any Parts/modules are updated*

QPPV Name	Dr Steve Hobbiger, BSc, FRCP(Ed), FFPM Vice President and EU QPPV, Global Clinical Safety and Pharmacovigilance, GlaxoSmithKline Research & Development, Stockley Park West, 1-3 Iron Bridge Rd, Uxbridge, Middlesex, UB11 1BT, UK
QPPV Signature	PPD
Contact person for this EU RMP	PPD
E-mail address or telephone number of contact person	PPD

Overview of versions:

Version number	1
Agreed within	Not applicable
Version number	2
Agreed within	Not applicable

Current RMP versions under evaluation:

RMP Version number	**Submitted on**	**Submitted within**
Not applicable	Not applicable	Not applicable

Invented name(s) in the European Economic Area (EEA)	Flolan 0.5 mg Powder and Solvent for Solution for Infusion; Flolan 1.5 mg Powder and Solvent for Solution for Infusion
Authorisation procedure	Mutual Recognition Procedure (MRP)
Brief description of the product	Flolan is epoprostenol, the monosodium salt of epoprostenol, 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 depend.
Indication(s) in the EEA	Current Indications: Pulmonary arterial hypertension: Flolan 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: Flolan 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.
	Proposed indication: No changes proposed
Posology and route of administration in the EEA	Current posology and method of administration: Pulmonary Arterial Hypertension Epoprostenol is only indicated for continuous infusion by intravenous route. Treatment should only be initiated and monitored by a physician experienced in the treatment of pulmonary arterial hypertension.

	Short-term (acute) dose ranging: This procedure should be conducted in a hospital with adequate resuscitation equipment. A short-term dose-ranging procedure administered via either a peripheral or central venous line is required to determine the long-term infusion rate. The infusion rate is initiated at 2 nanograms/kg/min and increased by increments of 2 nanograms/kg/min every 15 min or longer until maximum haemodynamic benefit or dose-limiting pharmacological effects are elicited. If the initial infusion rate of 2 nanograms/kg/min is not tolerated, a lower dose which is tolerated by the patient should be identified. *Long-term continuous infusion:* Long-term continuous infusion of Flolan should be administered through a central venous catheter. Temporary peripheral i.v. infusions may be used until central access is established. Long-term infusions should be initiated at 4 nanograms/kg/min less than the maximum tolerated infusion rate determined during short-term dose-ranging. If the maximum tolerated infusion rate is 5 nanograms/kg/min or less, then the long-term infusion should be started at 1 nanograms/kg/min. *Dosage adjustments:* Changes in the long-term infusion rate should be based on persistence, recurrence or worsening of the patient's symptoms of pulmonary arterial hypertension or the occurrence of adverse reaction due to excessive doses of Flolan. In general, the need for increases in dose from the initial long-term dose should be expected over time. Increases in dose should be considered if symptoms of pulmonary arterial hypertension persist, or recur after improving. The infusion rate should be increased by 1 to 2 nanograms/kg/min increments at intervals sufficient to allow assessment of clinical response; these intervals should be of at least 15 min. Following establishment of a new infusion rate, the patient should be observed, and erect and supine blood pressure and heart rate monitored for several hours to ensure that the new dose is tolerated. During long-term infusion, the occurrence of dose-related pharmacological events similar to those observed during the dose-ranging period may necessitate a decrease in infusion rate, but the adverse reactions may occasionally resolve

	without dosage adjustment. Dosage decreases should be made gradually in 2 nanograms/kg/min decrements every 15 min or longer until the dose-limiting effects resolve. Abrupt withdrawal of Flolan or sudden large reductions in infusion rates should be avoided due to the risk of potential fatal rebound effect. Except in life-threatening situations (e.g. unconsciousness, collapse, etc) infusion rates of Flolan should be adjusted only under the direction of a physician. Renal Dialysis Flolan is suitable for continuous infusion only, either intravascularly or into the blood supplying the dialyser. The following schedule of infusion has been found effective in adults: Prior to dialysis: 4 nanograms/kg/min intravenously for 15 mins During dialysis: 4 nanograms/kg/min into the arterial inlet of the dialyser The infusion should be stopped at the end of dialysis. The recommended dose for renal dialysis should be exceeded only with careful monitoring of patient blood pressure. *Elderly* There is no specific information on the use of Flolan in patients over 65 years for renal dialysis or pulmonary arterial hypertension. In general, dose selection for an elderly patient should be made carefully, reflecting the greater frequency of decreased hepatic, renal (in the case of pulmonary arterial hypertension) or cardiac function and of concomitant disease or other medicine therapy. *Paediatric population* The safety and efficacy of epoprostenol in children younger than 18 years have not yet been established. Method of administration *Preparation of Flolan intravenous injectable solution:* Reconstituted solutions, prepared in real time, must not be administered over more than 12 hours when they are used at room temperature (between 15°C and 25°C). They should be kept under 25°C and protected from light. It is possible to refrigerate Flolan reconstituted solutions, before they are used at room temperature, ranging between 2°C and 8°C and without exceeding 40 hour storage. In this case, the solutions should not be used over more than 8

	hours when administered at room temperature. The reconstituted solution should be examined prior to administration. Its use is forbidden in the presence of a discoloration or particles. Epoprostenol must not be administered as a bolus injection. Proposed posology and method of administration (Only subsections with revised text are included here): <u>Method of administration</u> *Precautions to be taken before handling or administering the medicinal product* Pulmonary Arterial Hypertension Freshly prepared solutions for infusion (either as a concentrated solution or a further diluted solution) can be administered immediately or stored for up to 8 days at 2°C to 8°C prior to administration. Following this preparation or storage, the solution for infusion should be used within 72 hours at up to 25°C, or 48 hours at up to 30ºC, or 24 hours at up to 35 ºC, or 12 hours at up to 40 ºC. Renal Dialysis Freshly prepared solutions for infusion (either as a concentrated solution or a further diluted solution) can be administered for up to 12 hours at up to 25°C. The reconstituted solution should be examined prior to administration. Its use is forbidden in the presence of a discoloration or particles. Epoprostenol must not be administered as a bolus injection.
Pharmaceutical form(s) and strengths Current (if applicable) Proposed (if applicable)	Current pharmaceutical form and strength: Powder for concentrate for solution for infusion: White or off-white freeze dried powder Solvent for parenteral use: Clear, colourless solution (pH 10.3 – 10.8) Epoprostenol 0.5mg Powder for Solution for Infusion: Each vial contains epoprostenol sodium equivalent to 0.5 mg epoprostenol. Epoprostenol 1.5mg Powder for Solution for Infusion: Each vial contains epoprostenol sodium equivalent to 1.5 mg epoprostenol.

	Proposed pharmaceutical form and strength (Only subsections with revised text are included here): Powder and solvent for solution for infusion. Powder for solution for infusion: - White or off-white freeze dried powder Solvent for parenteral use: - Clear, colourless solution (pH 11.7 – 12.3) Epoprostenol 0.5mg powder for solution for infusion: Each vial contains epoprostenol sodium equivalent to 0.5 mg epoprostenol. Epoprostenol 1.5mg powder for solution for infusion: Each vial contains epoprostenol sodium equivalent to 1.5 mg epoprostenol.
Country and date of first authorisation worldwide	United Kingdom, 18 March 1981
Country and date of first launch worldwide	United Kingdom, 18 March 1981
Country and date of first authorisation in the EEA	United Kingdom, 18 March 1981
Is the product subject to additional monitoring in the EU?	No

Abbreviations

6MW	6-Minute Walk
ADR	Adverse Drug Reaction
AE	Adverse Event
AKI	Acute Kidney Injury
aPAH	Pulmonary Arterial Hypertension Associated with Connective Tissue Disease
ARDS	Acute Respiratory Distress Syndrome
BMPR2	Bone Morphogenetic Receptor-2
BNP	Brain Natriuretic Peptide
cAMP	Cyclic Adenosine Monophosphate
cGMP	Cyclic Guanosine Monophosphate
CI	Confidence Interval
CNS	Central Nervous System
CTD	Connective Tissue Disease
CTEPH	Chronic Thromboembolic Pulmonary Hypertension
EEA	European Economic Area
ERS	European Respiratory Society
ESC	European Society of Cardiology
EU	European Union
GSK	GlaxoSmithKline
HCP	Health Care Provider
HIT	Heparin Induced Thrombocytopenia
HIV	Human Immunodeficiency Virus
hPAH	Heritable Pulmonary Arterial Hypertension
ICU	Intensive Care Unit
IMS	Intercontinental Medical Statistics
iPAH	Idiopathic Pulmonary Arterial Hypertension
IV	Intravenous
KDIGO	Kidney Disease: Improving Global Outcomes
KG	Kilogram
MAH	Marketing Authorisation Holder
MedDRA	Medical Dictionary for Regulatory Activities
MIN	Minute
ML	Milliliter
MMWR	Morbidity and Mortality Weekly Report
MRP	Mutual Recognition Procedure
Ng	Nanogram
NIH	National Institutes of Health
NSAID	Non-Steroidal Anti-Inflammatory Drug
NYHA	New York Heart Association
PAH	Pulmonary Arterial Hypertension
PCH	Pulmonary Capillary Hemangiomatosis
PH	Pulmonary Hypertension
PL	Package Leaflet
PPH	Primary Pulmonary Hypertension
PV	Pharmacovigilance
PVOD	Pulmonary Veno-Occlusive Disease
QPPV	Qualified Person for Pharmacovigilance
RA	Right Atrium
RMP	Risk Management Plan

RRT	Renal Replacement Therapy
RV	Right Ventricle
SC	Subcutaneous
SD	Standard Deviation
SmPC	Summary of Product Characteristics
SMQ	Standardised MedDRA Query
SOC	System Organ Class
SPH	Secondary Pulmonary Arterial Hypertension
t-PA	Tissue Plasminogen Activator
TTP	Thrombotic Thrombocytopenic Purpura
UK	United Kingdom
US	United States
USPI	United States Prescribing Information
WHO	World Health Organization

Trademark Information

Trademarks of the GlaxoSmithKline group of companies
FLOLAN

Trademarks not owned by the GlaxoSmithKline group of companies
VELETRI
VENTAVIS
REMODULIN

TABLE OF CONTENTS

PAGE

LIST OF ANNEXES

PART II MODULE SI.A – PAH: EPIDEMIOLOGY OF THE INDICATION AND TARGET POPULATION

Indication: Pulmonary arterial hypertension (idiopathic or heritable PAH and PAH associated with connective tissue diseases) in patients with WHO functional class III-IV symptoms to improve exercise capacity

Brand Names of Concerned Products (with this indication): Flolan

SI.A.1 Epidemiology of the disease

Pulmonary hypertension is a vasculopathy of the pulmonary arteries, defined via right heart catheterization of a mean pulmonary artery pressure of 25 mm Hg or more. Patients with pulmonary arterial hypertension (PAH) develop progressive narrowing of the pulmonary arteries from an imbalance of vasoactive mediators. This leads to an increased right ventricular afterload, right heart failure, and premature death (Kiely et al. 2013). PAH symptoms are non-specific and can include dyspnoea (exertional dyspnoea and tachypnoea), unproductive cough, fatigue, dizziness, syncope/near syncope, hepatomegaly, oedema/peripheral oedema, and in some cases, chest pain. These symptoms, even in later stages of disease, can be confused with other cardiac and pulmonary disorders (Rich et al. 1987; Rich 2012). Progression of PAH results in right ventricular failure which is manifested by progressive hypoxemia, tachycardia, hypotension, and oedema/peripheral oedema. Mean age at diagnosis is >50 years, and the disease is more common among women than men. Most patients present with moderate-to-severe disease and the prognosis is poor (Berger et al. 2012).

Incidence and prevalence

Worldwide, it is estimated that 130,000 to 260,000 persons have PAH (Berger et al. 2012). The prevalence of PAH is estimated at 15-52 per million (Humbert et al. 2006; Peacock et al. 2007; Condliffe et al. 2008; Hurdman et al. 2012; Ling et al. 2012). A recent systematic review estimated the prevalence of PAH in patients with connective tissue disease (CTD) being 12 cases per million population (95% CI 5-22) (Yang et al. 2013).

By contrast, PAH is high in certain patient groups, such as those with systemic sclerosis (9%), portal hypertension (2-6%), congenital heart disease (5-10%), and HIV (0.5%) (Avouac et al. 2010; Hadengue et al. 1991; Colle et al. 2003; Gatzoulis et al. 2009; Sitbon 2008).

The estimated incidence (per million per year) of idiopathic, heritable, and anorexigen-associated PAH in the United Kingdom and Ireland is 0.7, 0.9, and 1.1 in 2001–2003, 2004–2006, and 2007–2009, respectively. The estimated prevalence in 2009 was 6.6 cases per million population (Ling et al. 2012).

Demographics of the target population – age, sex, race/ethnic origin.

In the US, females account for 56.3% and 69.1% of diagnosed PAH cases aged <65 and 65+, respectively (Kirson et al 2011). A recent study from the UK Pulmonary

Hypertension (PH) registry showed that patients diagnosed between 2007 and 2009 were older, more obese and had lower percent diffusing capacity of carbon monoxide and more co-morbidities but better survival compared to previous cohorts (Ling et al. 2012). Similar findings were observed in the ASPIRE registry (Hurdman et al. 2012).

Risk factors for the disease

Half of all PAH cases referred to pulmonary vascular centres have no identifiable risk factor, corresponding to idiopathic (sporadic) (iPAH) and familial PAH. The other PAH subcategories include a number of associated conditions, such as connective tissue diseases, congenital heart diseases, portal hypertension and HIV infection (Humbert et al. 2007), as well as PAH associated with exposure to certain medications (e.g. anorexigens) or toxins. Pulmonary hypertension is more common in severe respiratory and cardiac disease, occurring in 18-50% of patients assessed for transplantation or lung volume reduction surgery, and in 7-83% of those with diastolic heart failure (Thabut et al. 2005; Lam et al. 2009; Damy et al. 2010; Arcasoy et al. 2003). Risk of PAH varies, with the highest overall risk seen among patients with certain forms of congenital heart disease, such as a large ventricular septal defect or patent ductus arteriosus. Congenital heart disease PAH patients often have higher pulmonary arterial pressures and better cardiac output at diagnosis than patients with idiopathic PAH and, subsequently, longer survival times (Chin and Rubin 2008).

PAH is increasingly recognized in patients with sickle cell disease, with a prevalence reported as high as 30% in echocardiography-based studies (Castro et al. 2003; Gladwin et al. 2004). In the developing world, highly prevalent diseases, such as schistosomiasis in parts of South America and Africa or sickle cell disease in populations of African origin, are associated with a marked risk of pulmonary hypertension. In addition, hypoxia is a major worldwide risk factor for pulmonary hypertension (Humbert et al. 2007). Other anemias, including homozygous beta-thalassemia and hereditary spherocytosis have also been associated with the development of pulmonary hypertension (Aessopos et al. 2001; Hayag-Barin et al. 1998).

PAH is inherited in less than 10% of cases (McLaughlin et al. 2009). Between 11% and 40% of patients with iPAH and 70% of patients with a family history of PAH carry a mutation in the gene encoding bone morphogenetic receptor-2 (BMPR2); however, penetrance is low as carriers have a 20% lifetime risk of developing pulmonary hypertension (Thomson et al. 2000; Fessel et al. 2011). Mutations have also been identified in 10% to 25% of patients with sporadic PAH and 9% of patients with PAH associated with fenfluramine use (Chin and Rubin 2008).

Main treatment options

PAH therapies include oral, inhaled, and continuous infusion formulations (Badesch et al. 2007). The goal is to control symptoms of the disease and hopefully slow its progression (Berger et al. 2012; Hanson, 2013). Given differing mechanisms of action, the use of combination therapy for PAH is common (McLaughlin et al. 2009).

Calcium channel blockers: High doses of calcium channel blocker (e.g diltiazem or nifedipine) has been suggested to exhibit long term clinical response with near

normalization of prognosis in iPAH patients with a positive response to vasoreactivity testing at right heart catheterisation (Rich et al. 1992; Sitbon et al. 2005). However, less than 5% of patients exhibit vasoreactivity on right heart catheterisation.

Prostanoid pathway: Prostanoids are potent vasodilators. Epoprostenol (IV) was the first PAH specific drug shown to be efficacious in a small randomised clinical trial, demonstrating improvements in exercise capacity, haemodynamics, and survival (Barst et al. 1996). Development of other prostanoids has led to treatments with improved stability and/or half life and new routes of administration including epoprostenol (IV), iloprost (IV,inhaled), treprostinil (IV, SC, inhaled, oral-US only). An oral synthetic prostanoid receptor agonist, selexipag, is in phase III clinical trials.

Endothelin receptor antagonists: Endothelin is a potent vasoconstrictor of vascular smooth muscle. Ambrisentan, bosentan and macitentan are licensed oral endothelin receptor antagonists.

Phophodiesterase-5 inhibitors: Two oral phophodiesterase-5 inhibitors (sildenafil and tadalafil), inhibit the breakdown of nitric-oxide activated cGMP, leading to vasodilatation. These drugs have important interactions with nitrates, so concomitant use is contraindicated.

Guanylate cyclase (sGC)/Nitric Oxide/GMP pathway: Riociguat is a stimulator of soluble guanylate cyclase, and represents a class of drug that restores the Nitric Oxide-sGC-cGMP pathway, by independently stimulating the production of cGMP, with subsequent vasodilatation.

Anticoagulation is required for patients with chronic thromboembolic pulmonary hypertension (CTEPH) and is recommended in iPAH, its role in PAH associated with other conditions is less clear (Frank et al. 1997; Johnson et al. 2006). Diuretics are used to treat heart failure. Lung transplantation is indicated in severe PAH or inoperable CTEPH if medical management fails, and has an overall five-year survival of around 50% (Christie et al. 2012). For other types of pulmonary hypertension, such as that due to left heart failure, treatment is best directed at the underlying condition, and currently PAH specific treatments are not recommended.

Mortality and morbidity (natural history)

The National Institutes of Health (NIH) Registry from 1981 to 1985 estimated the median survival of patients with iPAH as 2.8 years with 1, 3 and 5-year survival rates of 68%, 48% and 34%, respectively (D'Alonzo et al. 1991). However, given the advancement of medical therapy, survival in PAH has increased (McLaughlin et al. 2002; Badesch et al. 2009). A recent study from the ASPIRE registry has shown increased survival rates. The 3-yr survival rate was 68% for PAH, 73% for PAH associated with left heart disease, 44% for pulmonary hypertension associated with lung disease, 71% for CTEPH and 59% for miscellaneous pulmonary hypertension (Hurdman et al. 2012).

Predictors of a poor prognosis include: advanced functional class, poor exercise capacity as measured by 6-minute walk (6MW) test or cardiopulmonary exercise test, high right atrial (RA) pressure, significant right ventricular (RV) dysfunction, evidence of RV

failure, low cardiac index, elevated brain natriuretic peptide (BNP), and underlying diagnosis of scleroderma spectrum of diseases (McLaughlin et al. 2009).

All large published evaluations implicate haemodynamics as an important predictor of survival (McLaughlin et al. 2009). Lower cardiac output and stroke volume, greater right ventricular end-diastolic volume, and lower right ventricular ejection fraction at baseline are strong determinants of survival in PAH irrespective of the level of pulmonary vascular resistance (Kawut et al. 2005; van Wolferen et al. 2007; van de Veerdonk et al. 2011). To date, no single haemodynamic parameter uniformly predicts survival in PAH. Though a number of individual parameters have been investigated in PAH, few have demonstrated a predictive association with mortality in all, or even the majority of, studies (Saggar and Sitbon 2012).

SI.A.2 Concomitant medication(s) in the target population

Disease-specific concomitant medications used in the target population are discussed in the Main Treatment Options section above.

SI.A.3 Important co-morbidities found in the target population

As there are numerous aetiologies from which PAH can arise, the co-morbidities of the target population are referenced in the Risk Factors section above.

PART II MODULE SI.B – HAEMODIALYSIS: EPIDEMIOLOGY OF THE INDICATION AND TARGET POPULATION

Indication: Haemodialysis in emergency situations when use of heparin carries a high risk of causing or exacerbating bleeding or when heparin is otherwise contraindicated

Brand Names of Concerned Products (with this indication): Flolan

SI.B.1 Epidemiology of the disease

Acute kidney injury (AKI) is a global term used to describe changes in renal function that can range from minor increases in biochemical markers of kidney function to complete absence of renal function resulting in derangements in electrolyte and fluid balance requiring emergent institution of renal replacement therapy (RRT), including haemodialysis. Studies evaluating the epidemiology of AKI are complicated by the many and varied definitions of AKI, though more recently, there has been coalescence around a central core of fairly widely accepted criteria.

Incidence and prevalence

AKI may occur in one in five adults and one in three children hospitalized with acute illness as estimated in a systematic review of 312 cohort studies, which included 49 million patients mostly from high-income countries (Susantitaphong et al. 2013). The community-based incidence of AKI requiring RRT was estimated at 24.4 per 100,000 persons-years. A population-based study in northern Scotland estimated an AKI annual incidence of 2147 per million population, with sepsis as the most common precipitating factor (47%) (Ali et al. 2007). Over the time between 1996 and 2003, this incidence has increased from 19.5 to 29.5 per 100,000 person-years (Hsu et al. 2007). Regional variation has been described in the US, with incidence rates ranging from 457 to 523 cases per million person-years (Hsu et al. 2013).

When evaluating a cohort of critically ill patients, studies have reported AKI in 22-36% (Thakar et al. 2009; Ostermann and Chang 2007), with hospital mortality rates of 21-57% depending on severity of AKI as compared to 8% for those patients without AKI (Ostermann and Chang 2007). The population-based incidence of critically ill patients who required RRT was estimated at 11–19 cases per 100,000, which represents 4–8% of all critically ill patients (Bagshaw et al. 2005; Uchino et al. 2005; Clec'h et al. 2011; Vaara et al. 2012). Another study has placed the incidence of RRT-requiring AKI from 22 per million population per year to 203 per million population per year (Metcalfe et al. 2002). Nearly five percent of intensive care unit admissions have been reported to include RRT-requiring AKI (Metnitz et al. 2002).

Demographics of the target population – age, sex, race/ethnic origin.

As AKI is generally associated with any number of patient and clinical characteristics, the demography for RRT-requiring AKI is necessarily variable and reflective of the underlying medical conditions. See Risk factors for the disease.

Risk factors for the disease

Risk factors for AKI include those patients at either end of the age spectrum, male gender, as well as those with underlying renal disease or conditions that predispose to chronic renal disease such as hypertension, diabetes mellitus, liver disease, heart failure, and heart disease. In addition, conditions for which admission to an intensive care unit is often required, particularly sepsis, but also trauma and major surgeries especially cardiac and vascular surgeries, as well as procedures and medications often required to care for patients in the intensive care unit, such as exposure to contrast media for radiological imaging studies and nephrotoxic medications have also been implicated as risk factors for AKI (Uchino et al. 2005; Ali et al. 2007; Bagshaw et al. 2007). AKI is thought to be relatively uncommon after major non-cardiac surgery, though patient and operative factors can affect frequency of occurrence (Kheterpal et al. 2007), whereas the estimated incidence after cardiac surgery is much higher (11-30%) with RRT-requiring AKI occurring in 1-2% of these patients (Ho et al. 2012; Bastin et al. 2013; Swaminathan et al. 2010; Kuitunen et al. 2006; Chertow et al. 1998).

Main treatment options

In order to prevent thrombosis in the extracorporeal circuit during haemodialysis, some form of anticoagulation is often required. Heparin is employed frequently for this purpose, though occasionally situations arise when an alternative to heparin is necessary such as a pre-existing risk of haemorrhage or a history of heparin-induced thrombocytopenia. The absolute risk of HIT in surgical and medical patients with low molecular weight heparin and unfractionated heparin has been estimated to be 0.2% and 2.6%, respectively (Martel et al. 2005).

A survey of modalities of RRT in adult intensive care units in the UK reported that 96% of responding hospital reported using unfractionated heparin, and 88% reported using epoprostenol. No additional information was provided as to the how often epoprostenol was used as compared to heparin, or what factors were included in the decision to use one agent versus another (Gatward et al. 2008).

In a survey conducted of nearly 350 physicians, 75% of whom were based in Europe, regarding clinical practice for continuous RRT including which anticoagulants were in use, it was found that heparin was used very frequently by approximately 50% of respondents and very rarely by approximately 30%, whereas prostacyclin was used very rarely according to 75% and very frequently by 4% (Ronco et al. 2001).

Mortality and morbidity (natural history)

Occurrence of AKI has been shown to be associated with increased risk of mortality and morbidity across a variety of clinical inciting events. The estimated unadjusted mortality

associated with an episode of AKI has been reported as 23.9% in adults and 13.8% in children (Susantitaphong et al. 2013).

As might be reasonably expected, mortality associated with AKI is highest among patients who require RRT, with estimated in-hospital mortality approaching 60% (Bagshaw et al. 2005; Uchino et al. 2005; Palevsky et al. 2008). Encouragingly, more recent data may suggest that mortality is lower (RENAL Replacement Therapy Investigators 2009; Vaara et al. 2012; Waikar 2006). The rate of continued need for RRT at hospital discharge was 13–29% in cohorts of critically ill patients with RRT-requiring AKI (Bagshaw et al. 2005; Uchino et al. 2005; Bell et al. 2007; Korkeila et al. 2000; Silvester et al. 2001), and not surprisingly, pre-existing chronic kidney disease is a risk factor for AKI as well as progression to end-stage renal disease (Cho and Hsu 2010; Lafrance et al. 2010).

Studies evaluating of quality of life for patients with AKI which occurred in the setting of a critical illness, primarily associated with RRT, have largely found decreases in reported quality of life when compared to the general population (Vaara et al. 2012; Ahlstrom et al. 2005; Delannoy et al. 2009; Hofhuis et al. 2013; Johansen et al. 2010; Joyce et al. 2012).

SI.B.2 Concomitant medication(s) in the target population

There are numerous aetiologies from which RRT-requiring AKI can arise, many of which are associated with differing medication requirements. Alternative medications used for anticoagulation in patients receiving RRT are referenced in the Main Treatment Options section above.

SI.B.3 Important co-morbidities found in the target population

As there are numerous aetiologies from which RRT-requiring AKI can arise, the co-morbidities of the target population are referenced in the Risk Factors section above.

PART II: MODULE SII - NON-CLINICAL PART OF THE SAFETY SPECIFICATION

Flolan has been available in Europe since 1981. For this submission, GSK is proposing to increase the pH of the diluent for Flolan from 10.5 to 12. There are no changes to the existing freeze-dried powder containing the active substance, epoprostenol sodium.

Table 1 Key safety findings from non-clinical studies

Key Safety findings (from non- clinical studies)	Relevance to human usage
Toxicity including: Single and repeat-dose toxicity: Mice given intravenous epoprostenol up to 10 mg/kg epoprostenol IV produced decreased activity, bradypnea, ataxia and flushed skin (Report numbers BPAT 78/32, BPAT 78/34, BPAT 78/43). In rats, doses up to 100 mg/kg in rats produced collapse and death; the LD50 value was estimated at 66.3 mg/kg (Report number BPAT 80/22). A dose ranging study in which pairs of rats were dosed at 1, 10, 30 and 60 mg/kg/day SC for 7 days showed transient clinical signs of depressed activity, bradypnea and hypothermia (as seen in the acute studies), variations in the ECG trace and some evidence of hypotension. These effects were transient. Histology revealed subendocardial necrosis of the left ventricles of all but one treated animals (Report number BPAT 77/12). In rats which were given epoprostenol at 1, 10 or 100 ug/kg/day SC for 14 days, similar ECG changes were seen at the highest dose, along with tachycardia and reduced systolic blood pressure (Report number BPAT 78/10). These changes were transient and no myocardial lesions were found. Continuous intravenous infusion of 56, 180 or 560 ng/kg/min epoprostenol to rats for 14 days indicated that the animals showed adaptation in their clinical response to the drug. Animals exhibited hyperaemia in paws and ears, reduced rectal temperature, reduced body weight, decreased platelet count and food consumption at the high dose. However, no gross lesions or histopathological changes were attributable to treatment. Beagle dogs were administered a continuous infusion of 12.5, 40 or 125 ng/kg/min epoprostenol IV for 30 days (Report number 7205/80/7263/005). They showed varying degrees of gastrointestinal distress at the high dose, including emesis and soft stools, decreased activity, food consumption, body weight, skin temperature and platelet counts. No cardiac pathology was reported. The reversibility of the thrombocytopenia was evaluated in beagle dogs following IV dose of epoprostenol at 12.5ng/kg/min for 30 days; by day 20 post-dose, platelet	Non-clinical data revealed no special hazard for humans based on studies of safety pharmacology, repeated dose toxicity, genotoxicity, and toxicity to reproduction and development. No long-term animal studies have been conducted to determine the carcinogenic potential of epoprostenol.

numbers had stabilized at normal levels (Report number 7205/80/7263/006). In a longer study, epoprostenol sodium was administered to male and female dogs by continuous IV infusion at 12.5, 40 or 125 ng/kg/min for 26 weeks with additional animals at 125 ng/kg/min as recovery animals (Report number WD1998/00052/00). Dose related clinical signs of soft stool or diarrhoea were observed at 40 and 125 ng/kg/min with a low incidence of bloody stool. These signs diminished during the recovery period. Decreased in platelet counts were seen throughout the dosing period in animals given 125 ng/kg/min with evidence of normalization during the recovery period. In 2 males given 125 ng/kg/min, black viscous material on the gastric mucosa and black jejuna contents or red dots on the rectal mucosa were observed with very slight haemorrhage in the lamina propria of the rectal mucosa in 1 of these males observed microscopically. In a preliminary study, a single *E. patas* monkey was administered daily SC injections of 1, 10, 30, 60 and 60 mg/kg over 5 consecutive days (Report number BPAT 77/16). This resulted in tachycardia, reduced blood pressure and rectal temperature and a reduced bleeding time. Apart from the increased heart rate, no other changes in the ECG were detected, and at post mortem, fluid was found in the pericardial sac. Furthermore, histological analysis showed necrotic lesions in the papillary muscles of the left ventricle. A further subacute study was performed in these monkeys, in which animals received 0.01, 0.1 or 1.0 g/kg/min IV epoprostenol for 1 hour, 3 times a week over a period of 14 days, a total of seven infusions (Report number BPAT 78/16). Transient clinical signs were detected as described above, but again, tachycardia was the only ECG change. Histology showed that one of the four high dose animals showed a single focal area of necrosis in one papillary muscle. Reproductive: Rats were given 0, 10, 30 or 100 g/kg/day SC epoprostenol for 74 days (males) or 63 days (females) (Report number 7205/81/7263/006). Depression and ataxia were seen for up to two hours in all animals and all dose levels. Weight gain decreased in mid and high dose male animals. However, no effects were seen on fertility of either sex or their F1 offspring, oestrus cycles, gestation, developmental milestones of offspring or behavioural tests in offspring.	

Developmental toxicity: In an embryofetal toxicity study, pregnant female rats were given 0, 1, 10 or 100 g/kg/day SC epoprostenol on Days 6 to 16 of gestation (Report number BPAT 78/27). No alterations in body weights, gestation, numbers of corpora lutea, numbers of implantation sites, numbers of live and dead fetuses, sex ratios, body weights or morphologic characteristics of fetuses were found. In an embryofetal toxicity study in rabbits, pregnant females were given 0, 1, 10 or 100 g/kg/day SC epoprostenol on Days 6 to 18 of gestation, producing transient signs of lethargy and prostration, which occurred earlier in the dose schedule as the dose was increased (Report number BPAT 78/31). However, this study was flawed due to problems with the artificial insemination procedure which produced an abnormally low pregnancy rate and fetal abnormalities. A repeat of this study with only the highest epoprostenol dose produced no adverse effects on embryonic survival or on fetal development and growth, and no changes in blood pressure, heart rate or ECG findings (Report number BPAT 79/21). In a peri- and post-natal study, rats were given 0, 10, 30 or 100 g/kg/day SC epoprostenol from Day 15 of gestation to 21 days post-partum (Report number 7205/80/7263/004). Transient clinical signs at all dose levels were depression and ataxia, with a dose-related increase in severity. Reproductive changes were an increase in gestation length, though it was thought not to be clinically significant. Local toxicity: Epoprostenol, applied in 0.1 mL quantities of a 1 mg/mL solution 3 times a day for 1, 2, 3, 4 or 6 days to abraded skin of CFLP mice did not influence the proliferative response of the epidermis. Epoprostenol was administered to three male dogs in pH 12 Flolan diluent (glycine, sodium chloride, water for injection and sodium hydroxide solution) at 0.18 mg/kg/day by continuous intravenous infusion (4 mL/hr, 125 ng/kg/min). A further 3 male dogswere included as controls and were given 0.9% saline pH 7.4. Animals were treated for either 3 or 4 days. There were no macroscopic or microscopic signs of local intolerance to treatment in the vessels and tissues adjacent to the infusion site in any animal and no evidence of haemolysis	

in the haematology and clinical biochemistry examinations. Genotoxicity: Epoprostenol was tested for mutagenic effects in the Salmonella/microsome (Ames) test using the most sensitive strains available (TA98, TA100, TA1535, TA1537 and TA1538) (Report number 7200/80/7263/001). Epoprostenol was added to the bacteria at concentrations of 250, 500, 1000 and 2000 g/plate. The tests showed no evidence of bacterial mutagenicity at any concentration, with or without S9 microsomal metabolic activation. An alkaline elution assay was carried out on epoprostenol to assess its ability to induce DNA damage in Chinese hamster lung fibroblast cells (Report number 7263/80/7263/023). Concentrations of 0.03, 0.3, 1.0 and 3.0 mM were applied to cells, but no detectable DNA damage was seen at any concentration, with or without S9 metabolic activation. Epoprostenol was tested in the micronucleus test for chromosome damage (Report number 0013/81/7263/002). Male rats were given total doses of 10, 20 or 40 mg/kg epoprostenol IP in two equal doses 24 hours apart. Five rats of each dose level were killed after 30 and 48 hours post first dose. Bone marrow was examined for the presence of micronucleated cells, but treatment with epoprostenol was not found to increase this over control levels. Carcinogenicity: Although conventional life time carcinogenicity studies were not conducted, the potential carcinogenic effects of epoprostenol were investigated in male F344/DuCrj rats in a study focusing on hepatic changes. Two weeks after being given a single, initiating IP dose of 200 mg/kg N-nitrosodiethylamine, animals received SC doses of epoprostenol at 0, 1, 10 or 100 g/kg/day for 6 weeks. Partial hepatectomy was carried out at 3 weeks and the animals were killed at 8 weeks. Epoprostenol did not significantly increase the appearance of glutathione S-transferase positive liver cell foci, indicating that epoprostenol lacks modifying potential for liver carcinogenesis in this medium term assay (Kawabe et al., 2001).	

General safety pharmacology: Cardiovascular: Studies of the effects of epoprostenol on cardiac arrhythmias after coronary occlusion have produced conflicting results (Vane et al., 1982). In vivo, epoprostenol produced an increase in arrhythmias in the rat and cat after acute coronary artery occlusion. Epoprostenol in the rat increased arrhythmias and ventricular fibrillation following coronary artery occlusion, but decreased infarct size in the survivors. In a study in conscious dogs however, epoprostenol was found to reduce ventricular fibrillation following coronary artery occlusion. This reduction in ventricular fibrillation was independent of any effect of epoprostenol on antecedent ectopic rhythms. Respiratory: Studies of the bronchodilator effects of epoprostenol on lung function in various animals have generally shown it either to have no effect or to reduce lung resistance and increase compliance. Many studies have shown that epoprostenol reverses the bronchoconstrictor effects of PGF2, 5-HT, carbachol and histamine, although there has been one report of epoprostenol elevating the bronchoconstrictor response to PGF2, acetylcholine and histamine in the guinea pig (Vargaftig and Lefort, 1981). Since it is able to dilate the constricted pulmonary vascular bed, prevent intrapulmonary platelet aggregation induced by ADP (Hyman and Kadowitz, 1979) and dilate constricted airways, epoprostenol may play a role in modulating the physiological or pathophysiological responses of the pulmonary circulation. Epoprostenol infused intravenously, reversed oleic acid-induced respiratory distress in the dog by protecting against the impairment of gas exchange following increased pulmonary vascular permeability and oedema (Miyazawa et al., 1982). In a study on experimental pulmonary embolism induced by an autologous blood clot in the dog, epoprostenol infusion reversed many of the cardiopulmonary abnormalities, including hypoxia, increased physiological dead space and shunting, while maintaining cardiac output (Utsunomiya et al., 1980). Reproductive system: Uterine tissue produces epoprostenol (Ylikorkala and Makila, 1985) and this production has been shown to be elevated during pregnancy in the rat, rabbit, dog and human uterus.	Non-clinical data revealed no special hazard for humans based on conventional studies of safety pharmacology.

Epoprostenol contracts rat uterine strips in vitro but is much less active than PGE2 or PGF2a. Epoprostenol had a biphasic response (short lasting contraction, followed by long lasting relaxation and disappearance of spontaneous tone) on human myometrium and relaxed human fallopian tubes and partially reversed PGF2-induced contractions. Single large intravenous bolus doses of epoprostenol increase serum prolactin and luteinising hormone concentrations in oestradiol-treated ovariectomised rats. However, daily administration subcutaneously for 7 days depressed serum luteinising hormone concentrations in intact male and female rats and decreased testosterone concentrations in males. Serum follicle stimulating hormone and prolactin concentrations of male and female rats were not altered (Kimball et al., 1979).	

Mechanisms for drug interactions: Intravenously administered epoprostenol is rapidly distributed from blood to tissue and metabolised. In rats, two minutes after a single injection, only 10% of the drug remained in the circulation (Pace-Asciak et al., 1979). In rabbits, the elimination half-life of epoprostenol was 2.9 minutes, the whole body distribution was 1015 mL/kg and the whole body clearance was 4.27 mL/kg/sec (Skrinska et al., 1983). Similarly, in dogs, stopping infusion of epoprostenol resulted in a decline of plasma levels with a half-life of 0.7 to 1.6 minutes. A second, slower elimination was calculated at 10 to 19 minutes, but this was attributed to release of the administered epoprostenol from tissues (Salmon et al., 1979). Steady state plasma levels of epoprostenol plus 6-keto-PGF1 during constant infusion of 1 g/kg/min to dogs ranged between 29 and 64 ng/mL. The tissue distribution of epoprostenol and its metabolites was determined in rats following intravenous injection of radiolabelled epoprostenol (Taylor and Sun, 1980). Highest levels were found in the liver, kidney and small intestine. Tissue levels declined rapidly, with no evidence for accumulation or long term retention of a drug-related compound. Similar results were obtained by injection via the subcutaneous route. The rapid metabolism of epoprostenol has been attributed to the action of the liver. In anaesthetised dogs, 74 to 87% of epoprostenol was removed by first pass liver metabolism, 43% was seen in the kidney and 43 to 61% was present in the hind quarters. In the rat, the liver is thought to be pivotal in metabolic clearance of epoprostenol (Taylor and Sun, 1980). Organ perfusion studies with rat lung (Hawkins et al., 1978), rabbit lung (Wong et al., 1978; Wong et al., 1979b), liver (Wong et al., 1980) and kidney (Wong et al., 1979a; Wong et al., 1979b) were consistent with the findings in dogs. Unlike other prostaglandins, little epoprostenol is removed from the circulation by the lungs (Moncada et al., 1978; Gryglewski, 1979). Metabolism of epoprostenol is extensive. It generally undergoes non-enzymatic hydrolysis to 6-keto-PGF1 prior to a subsequent transformation to a number of other products. The various metabolic products which have been identified are the results of various combinations of four biotransformation pathways: oxidation of the C-15 hydroxyl group by 15-hydroxyl prostaglandin dehydrogenase; reduction of the C-13, 14 trans double bond by delta 13 reductase; oxidation yielding dinor metabolites; and C-19 and C-20 hydroxylation via gamma or	Due to the chemical instability, high potency and short half-life of epoprostenol, no precise and accurate assay has been identified as appropriate for quantifying epoprostenol in biological fluids. Given the short in vivo half life and the metabolism of epoprostenol is generally non-enzymatic, pharmacokinetic interactions of clinical relevance are considered to be unlikely.

gamma-1 oxidation (Rosenkranz et al., 1981). Excretion of metabolites of epoprostenol is rapid following administration of radiolabelled epoprostenol to rats (Sun and Taylor, 1978; Sun et al., 1979) and dogs. Urinary excretion accounted for approximately 40% of the dose in rats and nearly 90% in dogs. In both species, urinary excretion was greater than 95% complete within 25 hours of dosing. Excretion of metabolites in faeces as a result of biliary excretion accounted for the remainder of the dose (Taylor and Sun, 1980). In cynomolgus monkeys, which had received ^{3}H-epoprostenol by IV infusion for three days, urinary excretion only accounted for 45% of the infused radioactivity.	

Other toxicity-related information or data The following is a summary of nonclinical investigations undertaken to understand the impact of an increase in the pH of the diluent for Flolan from 10.5 to 12 of in subjects receiving epoprostenol infusions.	
Negligible haemolysis: Haemolytic potential for pH 12 diluent or Flolan reconstituted with pH 12 diluent was assessed *in vitro* in human whole blood. No haemolysis or only negligible haemolysis was evident, therefore the test was deemed negative in human blood for formulations of Flolan up to 60000ng/mL in the pH 12 diluent (Report 2011N125526_00).	This *in vitro* finding supports that the increase in pH of Flolan solution prepared with pH 12 diluent does not suggest an increased risk of haemolysis.
No local infusion site reactions during short-term infusions: In dogs who had received 72-96 hour Flolan infusions with solution reconstituted with pH 12 diluent using an ambulatory surgically cannulated model, there were no clinical observations, clinical pathology or pathological findings that would indicate local intolerance at the port access site or at the tissue associated with the cannula tip. There was also no indication from the haematology results or clinical pathology plasma samples of haemolysis (Report 2011N119711_00).	This finding supports that the increase in pH of Flolan solution prepared with pH 12 diluent is not associated with local infusion site reactions and haemolysis in vivo.
Compatibility with central venous catheters: Compatibility testing (measurement of leachables and physical stability) with three common types of central venous catheters did not identify any concerns.	This finding supports that the increase in pH of the reconstituted medication does not appear to be associated with catheter degradation or incompatibility.
Compatibility with filters: Compatibility testing with a common type of administration filter did not identify issues with incompatibility.	This finding supports that the increase in pH of the reconstituted medication does not appear to be associated with incompatibility with filters commonly used for preparation

Compatibility with container system: Owing to the identification of glass corrosion products in pH 12 diluent stored in glass vials, compatibility testing with plastic vials was performed and did not identify any concerns with compatibility.	of infusion solutions. This finding supports use of plastic vials for storage of pH 12 diluent. Incompatibility of alkaline diluent for Flolan with glass vials has been mitigated via replacement of glass vials with plastic vials, thereby eliminating the presence of glass corrosion products.

SII Conclusions on non-clinical data

Table 2 Safety Concerns

Important identified risks (confirmed by clinical data)	None
Important potential risks (not refuted by clinical data or which are of unknown significance)	None
Missing information	None

PART II: MODULE SIII - CLINICAL TRIAL EXPOSURE

Flolan has been available in Europe since 1981, therefore this product was on the market greater than 10 years before the requirement for an RMP was established. For this submission, GSK is proposing to increase the pH of the diluent for Flolan from 10.5 to 12. There are no changes to the existing freeze-dried powder containing the active substance, epoprostenol sodium. This RMP is not due to an application for a significant change to an existing marketing authorisation.. Owing to the mature nature of the product and extensive clinical safety experience, the historical clinical trial programme for the active ingredient in Flolan will be described on an aggregate level (Table 3). Additional detail is provided for the single clinical study that was conducted to support use of Flolan reconstituted with pH 12 diluent in a small cohort of patients currently being treated with Flolan for PAH (Tables 4-7).

SIII.1 Brief overview of development

Flolan was initially approved in Europe in 1981 for use in renal dialysis when use of heparin carries a high risk of causing or exacerbating bleeding or is otherwise contraindicated. Flolan was later developed for the treatment of pulmonary arterial hypertension (PAH) (idiopathic or heritable PAH; iPAH and hPAH) in patients with WHO Functional Class III-IV symptoms to improve exercise capacity, with the first European approval in 2001. The PAH indication was subsequently expanded to include PAH associated with connective tissue diseases (aPAH). It should be noted that at the time of the pivotal trials in PAH, idiopathic and heritable PAH were grouped as Primary Pulmonary Hypertension (PPH) and aPAH was called Secondary Pulmonary Hypertension (SPH). The nomenclature has evolved over time, and all forms of pulmonary arterial hypertension, whether idiopathic, heritable, or associated with connective tissue diseases, are grouped under the heading of PAH (Simonneau et al., 2009). Most recently, GSK has reformulated the diluent for Flolan by increasing the target pH of the diluent from 10.5 to 12, with the aim of simplifying reconstitution by patients and providing greater stability of the product over time.

Renal Dialysis

Epoprostenol was evaluated in 14 studies designed to define its role in renal dialysis. Three crossover, heparin controlled studies evaluated epoprostenol over a range of doses during renal dialysis of patients with end stage renal disease. One study looked at sequentially decreasing infusion rates of epoprostenol to determine the minimal constant infusion rate that would allow effective dialysis and yet prevent clotting in the extracorporeal circuit. In contrast, another evaluated dialyses with increasing constant epoprostenol infusion rates to determine patient tolerance, improvement in dialysis efficiency and any observed dose-related decrease in clotting. The third study was designed primarily to compare the safety and efficacy of epoprostenol and heparin-facilitated dialyses using bicarbonate or acetate-buffered dialysates with a high sodium concentration.

Six major controlled studies, and 5 emergency studies, were designed to compare epoprostenol versus heparin, and to primarily measure intradialytic removal of BUN and

creatinine, intradialytic removal of fluid (ultrafiltration), and clotting within the extracorporeal circuit. In addition, bleeding associated with renal dialysis was assessed in patients at increased haemorrhagic risk and platelet counts were monitored in patients with documented heparin-associated thrombocytopenia.

Epoprostenol and heparin has been compared successfully with hollow fiber, coil and parallel plate geometries and cuprophane or cellulose membranes. However, dialysis has been limited in general to bicarbonate-buffered dialysates. Hollow fiber geometries with cuprophane or cellulose membranes and low sodium bicarbonate dialysates were used predominantly in the efficacy studies.

PAH: Idiopathic or heritable Pulmonary Arterial Hypertension (iPAH/hPAH)

Flolan, for the treatment of iPAH/hPAH, has been evaluated in 14 industry sponsored clinical studies, five of which were clinical pharmacology studies that will not be discussed further. Nine studies, conducted by GSK or GSK legacy companies, are discussed below: 3 Acute Dose-Ranging Studies, 2 Chronic Administration Studies (the pivotal controlled trials), and 4 open label, uncontrolled Continuation Treatment Studies.

Acute Dose Ranging Studies: The acute haemodynamic effects of epoprostenol administration were evaluated under right heart catherization in patients with PPH during acute dose-ranging procedures in two multicenter, sequential, non-randomised, uncontrolled studies (Studies 05/10 and 20). The acute effects of epoprostenol were also evaluated in Study 21 (a multicenter, non-randomised, controlled study) in patients with iPAH/hPAH, and included those with SPH. Further, acute dose-ranging procedures were incorporated into the 2 open, randomised, parallel, standard therapy controlled studies (Studies 35/36, and 46).

Chronic Administration Studies: The effects of chronic administration of epoprostenol were evaluated in Studies 35/36, and 46, which comprosed the pivotal controlled trials. Patients with documented PPH and classified as New York Heart association (NYHA) functional class I- IV were enrolled in Study 35/36. Each patient who met all inclusion/exclusion criteria was randomised to receive either 8 weeks of epoprostenol plus any other standard therapy deemed appropriate or standard therapy only. Only patients classified as NYHA class III or IV entered study 46, and patients were randomised one-to-one to epoprostenol therapy plus standard therapy or standard therapy alone for 12 weeks. In each study, chronic doses of epoprostenol were adjusted based on recurrence of PPH symptoms and the occurrence of adverse events. Exercise capacity (6 minute walk test) and quality of life were assessed at baseline and the conclusion of each study. Survival was monitored throughout the 8 and 12 week treatment periods.

Continuation Treatment Studies: At the conclusion of Studies 35/36 and 46, all patients could elect epoprostenol therapy in one of the uncontrolled continuation treatment studies: Study 37 for patients enrolled in Study 35/36 and Study 47 for patients enrolled in Study 46. In these studies, epoprostenol was administered indefinitely to each patient until death, transplantation or until the patient elected to discontinue therapy. Survival continued to be monitored in both uncontrolled studies. Studies 49 and 50 were initiated

to allow provide Flolan more widely on a compassionate-use basis. Only serious adverse events and survival were collected.

PAH: Pulmonary Hypertension Secondary to Scleroderma Spectrum of Diseases (aPAH)

The chronic effects of epoprostenol administration were evaluated in patients with PAH due to scleroderma spectrum of diseases study during one pivotal, multicenter, randomised, parallel group, controlled study, VA1A4001. Similar to the other PAH studies, aPAH patients were randomised to receive epoprostenol plus conventional therapy or conventional therapy alone for 12 weeks. The treatment period was 12 weeks and the primary endpoint was exercise capacity (6-minute walk test). At the conclusion of Study VA1A4001, all patients could elect to receive epoprostenol therapy in the uncontrolled continuation treatment Study VA1A4002.

PAH: Overview of development of the pH 12 diluent

Flolan treatment requires administration by continuous intravenous infusion via an indwelling central venous catheter given its instability in solution and rapid metabolism *in vivo*. At present, Flolan requires reconstitution and dilution every 2 days and the reconstituted solution may only be administered up to 24 hours when it is maintained between a temperature of 2°C and 8°C during infusion, thereby necessitating the use of a cold pouch. In addition, the cold pouch used to maintain the temperature of the reconstituted solution must be changed every 12 hours.

GSK has reformulated the diluent for Flolan by increasing the target pH of the diluent from 10.5 to 12, as epoprostenol is more stable in a higher pH solution. No change has been made to the vial that contains the lyophilised epoprostenol. The reformulated product may be reconstituted and diluted less frequently and is stable for longer periods of time at room temperature; it does not require the use of a cold pouch or frequent changes of the cassette. The change in the formulation will allow for reconstituted solutions to be stable for up to 8 days at refrigerated conditions (2ºC to 8ºC) followed by up to 72 hours at up to 25ºC, up to 48 hours at up to 30ºC, up to 24 hours at up to 35ºC and up to 12 hours at up to 40ºC.

Thus, the reformulated product is anticipated to provide an added level of convenience to patients through reduction in the frequency of reconstitution/dilution, and elimination of the need for a cold pouch, even in countries with high ambient temperatures. As the change was limited only to the diluent with the active part of the formulation remaining intact, no impact on the pharmacodynamic actions of Flolan is anticipated, and the clinical profile for Flolan prepared with pH 12 diluent is expected to be the same as that of Flolan prepared with the pH 10.5 diluent.

The study in subjects with PAH (Study FLR115332) was carried out to describe the effect of Flolan reconstituted with pH 12 diluent on quality of life in subjects switching from Flolan reconstituted with the pH 10.5 diluent, and to determine if there were any dose titration requirements during the switch to the Flolan reconstituted with the reformulated pH 12 diluent. The study sample size was based on feasibility and formal

hypothesis testing was not performed. Study subjects had to be taking Flolan for PAH, and been on a stable dose of Flolan for at least three months and a stable dose of any other PAH medications for at least one month prior to screening. No new safety signals were identified during the study. The observed safety profile for the Flolan prepared with pH 12 diluent was consistent with the currently available product and pH 10.5 diluent.

SIII.2 Clinical Trial exposure

Though summary documents are available for the historical GSK Renal Dialysis and PAH Clinical Development Programs, the individual study listings with exposure data in sufficient detail to recreate exact exposures are not consistently available. Thus the data populated in the exposure tables below represent best-available estimates only.

The PAH exposure data is displayed separately for the Acute Dose ranging studies, which generally contain patients with exposure duration of hours, and the Chronic Administration studies (Pivotal and Continuation) with exposures of months. The Pivotal and Continuation Studies are further separated, as the Pivotal Studies contain unique patients, and the Continuation Studies contain both new and previously chronically exposed patients.

Table 3 Clinical Trial Exposure: Duration of Exposure (by indication)

Indication 1: Renal dialysis		
Duration of exposure (minutes)	Persons	Person time[1]
Total person time	142	
Indication 2: PAH: Idiopathic or Heritable Pulmonary Arterial Hypertension (iPAH/hPAH) *and* Pulmonary Arterial Hypertension associated with Connective Tissue Diseases (aPAH)		
Acute Dose-Ranging Studies		
Duration of exposure (minutes)	Persons	Person time[1]
Total person time	303	
Pivotal, Chronic Administration Studies		
Duration of exposure (months)	Persons	Person time (months)
2 m	11	22
3 m	97	291
Total person time		313 months
Open label, Continuation Treatment Studies[2]		
Duration of exposure (months)	Persons	Person time (months)[3]
6 m	252	1512
12 m	165	1980
18m	120	2160
24m	77	1848

30m	45	1350
36m	18	648
42m	6	252
48m	6	288
56m	5	280
57m	5	285
58m	5	290
59m	5	295
60m	5	300
70m	3	210
71m	3	213
72m	3	216
73m	1	73
Total person time		12200 months
Indication 2: PAH (Flolan prepared with pH 12 diluent)		
Duration of exposure (days)	Persons	Person time (days)
<45	1	43
45-179	3	518
180-269	12	2753
>269	0	0
Total person time		3314 days
1. Records of duration of exposure in historical renal dialysis studies and acute dose ranging studies in PAH are generally not available, thus person time is not calculated. Person time is not expected to be significant, as most studies were noted to have lasted minutes or hours. Duration of treatment was not consistently available, but may have lasted through out an entire dialysis period. 2. Data for Months 6-73 obtained from 1997 MAA submission documents and therefore contains exposure for subjects with iPAH and hPAH.		

Table 4 Clinical Trial Exposure: By Dose (by indication)

Indication: PAH (Flolan prepared with pH 12 diluent)		
Dose (ng/kg/min)	Persons	Person time (days)
<20	1	181
20-39	7	1353
40-59	6	1432
>59	2	348

Table 5 Clinical Trial Exposure: By Age Group and Gender (by indication)

Indication: PAH (Flolan prepared with pH 12 diluent)		
Age (years)	Persons	Person time (days)
<18	0	0
18-64	14	2821
65-74	2	493
>74	0	0
Gender		
Male	4	810
Female	12	2504
Total	16	3314

Table 6 Clinical Trial Exposure: By Ethnic or Racial Origin (by indication)

Indication: PAH (Flolan prepared with pH 12 diluent)		
Ethnic/racial origin	Persons	Person time (days)
White	15	3081
Black	0	0
Asian	0	0
Other	0	0
Unknown	1	233
Total	16	3314

Table 7 Clinical Trial Exposure: Special Populations (by indication)

Indication: PAH (Flolan prepared with pH 12 diluent)		
	Persons	Person time
Pregnant women	0 (exclusion criterion for FLR115332)	
Lactating women	0 (exclusion criterion for FLR115332)	
Renal impairment	Unknown	
Hepatic impairment	Unknown (active hepatitis B or C was exclusion criterion for FLR115332)	
Cardiac impairment	Unknown (cardiac impairment may occur as a consequence of PAH)	
Sub populations with genetic polymorphism	Not applicable	
Immuno-compromised	Unknown	
PAH subtypes iPAH or familial PAH PAH associated with underlying condition Other	 12 3 1	

PART II: MODULE SIV - POPULATIONS NOT STUDIED IN CLINICAL TRIALS

SIV.1 Limitations of ADR detection common to clinical trial development programmes

Summary documents are available for the historical Renal Dialysis and PAH Clinical Development Programs, the individual study listings with exposure and demographic data in sufficient detail to recreate exact exposures, or populations typically under-represented in clinical trial development programs, are not consistently available. Therefore, the data populated in the tables below represent best-available estimates only.

Table 8 Limitations of ADR detection common to clinical trial development programmes

Ability to detect adverse reactions	Limitation of trial programme	Discussion of implications for target population
Which are infrequent	The PAH clinical development program (pivotal controlled trials) was comprised of 411 unique patients (acute dosing ranging studies and pivotal chronic administration studies). The Renal Dialysis clinical development was comprised of 142 unique patients.	ADRs with a frequency greater than 1 in 137 could be detected if the background incidence was zero.
Due to prolonged exposure	Chronic exposure in clinical trials for PAH was over 12500 person-months. Exposure times in the clinical trials for renal dialysis were limited generally to minutes to hours.	No adverse reactions have been identified in association with prolonged exposure in the PAH Continuation Studies. Survival does appear to be a benefit associated with prolonged exposure. A significant improvement in survival after 12 weeks continuous exposure was seen in Study 46 and in a post-hoc analysis of survival of studies of 35/36, 37, 46 and 47. A median survival of 40.4 months for Flolan treated patients compared to 8.8 months for conventional therapy treated patients was observed. (1997 MAA submission).

Ability to detect adverse reactions	Limitation of trial programme	Discussion of implications for target population
		Given the comparatively short durations of epoprostenol exposure during Renal Dialysis, prolonged exposure should not be pertinent.
Due to cumulative effects	Patients in the PAH open label continuation studies were followed for periods ranging from 6 months (252 patients) to greater than 5 years (5 patients). Exposure times in the clinical trials for renal dialysis were limited generally to minutes to hours.	No adverse reactions or specific organ toxicity have been identified in association with prolonged exposure in the PAH continuation studies. Given the comparatively short durations of exposure during Renal Dialysis, accumulation of epoprostenol is not anticipated to be of clinical significance. Based on one pharmacokinetic study in rabbits, epoprostenol is projected to have a very high clearance and a small volume of distribution in man; as a result, accumulation of epoprostenol should not occur to any significant extent (see Module SII).
Which have a long latency	Patients in the PAH Continuation Studies were evaluated at periods ranging from 6 months (252 patients) to greater than 5 years (5 patients).	No adverse reactions have been identified as being the result of a long latency period from the clinical trial program.

SIV.2 Effect of exclusion criteria in the clinical trial development plan

Table 9 Exclusion criteria which will remain as contraindications

Criteria	Implications for target population
Epoprostenol is contraindicated in patients with congestive heart failure arising from severe left ventricular dysfunction	This exclusion criterion was included in the aPAH pivotal study only, and was based on the results of a trial comparing patients with severe congestive heart failure (CHF) receiving chronic administration of Flolan plus conventional therapy to patients receiving conventional therapy alone. CHF patients receiving Flolan had a decreased median survival compared to those on conventional therapy alone (Califf et al., 1997).
Epoprostenol should not be used chronically in patients who develop pulmonary oedema during dose-ranging.	Though not a specified exclusion criterion in the PAH clinical studies, some patients have developed pulmonary oedema during dose-ranging, which may reflect an 'unmasking' of underlying pulmonary veno-occlusive disease (PVOD). The clinical presentations of PVOD and PAH are often indistinguishable and unrecognized antemortem (Simonneau et al., 2004), but the response to medical therapy in quite different (Montani et al., 2008).

Table 10 Exclusion criteria which are NOT proposed to remain as contraindications

Criteria	Reason for being an exclusion criterion	Justification for not being a contraindication
Pregnancy	There is a limited amount of data from the use of epoprostenol in pregnant women.	Post-marketing data in this population is detailed in Section SV.3 (Post-authorisation use in pregnant or Breast-feeding Women). Given the absence of alternative medicines, epoprostenol can be used in those women who choose to continue their pregnancy, despite the known risk of pulmonary arterial hypertension during pregnancy.
Lactation	It is unknown if epoprostenol or its metabolites are excreted in human milk.	Post-marketing data in this population is detailed in Section SV.3 (Post-authorisation use in pregnant or Breast-feeding Women). A risk to the breastfeeding child cannot be excluded. Breast-feeding should be discontinued during treatment with Flolan.

SIV.3 Limitations in respect to populations typically under-represented in clinical trial development programmes

Children

Data submitted in an Article 46 Paediatric Regulation No 1901/2006 in 2012 included 63 paediatric patients with PAH less than 16 years of age enrolled in acute open label, non-randomised, baseline controlled dose ranging studies. The data demonstrated safety and significantly improved haemodynamic parameters in patients <16 years of age with acute use. Only 5 paediatric patients study patients were exposed to chronic epoprostenol therapy. Clinical trial experience in paediatric patients for renal dialysis is limited.

Based on the post-authorization experience, the benefit-risk in the pediatric population to date appears to be similar to that of the adult population, as detailed in Section SV.3 (Post-authorisation use in Paediatrics).

Elderly

Clinical trial experience in the elderly is limited. The PAH studies included a minimum of 16 patients greater than 65 years of age. The early studies in Renal Dialysis excluded those greater than 65, summary data from later studies include older subjects but are insufficient to determine numbers of elderly subjects.

Based on the post-authorization experience, the benefit-risk in the elderly population to date appears to be similar to that of the adult population, as detailed in Section SV.3 (Post-authorisation use in elderly).

Pregnant or Breast Feeding Women

Pregnant and/or lactating women were excluded from the PAH and the Renal Dialysis clinical trials; available post-marketing data in this population is detailed in Section SV.3 (Post-authorisation use in pregnant or Breast-feeding Women).

Patients with Hepatic Impairment

Patients with hepatic impairment were not generally excluded from the PAH and the Renal Dialysis clinical trials; therefore an accurate number of clinical study patients with hepatic impairment is unknown.

Use of Flolan off-label to treat certain subtypes of pulmonary hypertension arising from hepatic impairment has been reported. For example, portopulmonary hypertension accounts for approximately 5-10% of patients with PAH, as estimated from registries in the United States and France (Fritz et al. 2013), as detailed in Section SV.3.

Patients with Renal Impairment

Flolan was evaluated in patients with end stage renal disease for the Renal Dialysis indication. The idiopathic and heritable PAH clinical studies did not specifically exclude patients with renal impairment; therefore an accurate number of clinical study patients with renal impairment in PAH is unknown. It should be noted that renal impairment can occur in associated with heart failure, a consequence of PAH, as well as connective tissue

disorders, a cause of PAH. Available post-marketing data in this population is detailed in Section SV.3.

Patients with Other Relevant Co-morbidity

PAH can arise in the setting of multiple underlying medical conditions (Section SI.A), however the clinical trial program includes subjects with iPAH, hPAH and PAH associated with connective tissue disease, primarily scleroderma spectrum of diseases. Patients with PAH due to other causes were not included in the clinical development programme.

Patients with a Disease Severity different from the Inclusion Criteria in the Clinical Trial Population

The clinical trial program included predominantly patients with the most severe symptoms (WHO functional classes III and IV). Patients with less severe manifestation of PAH were generally not included in the clinical development programme. Subsequent post marketing experience has not identified any significant safety concerns in populations that were not studied in the clinical trial programme.

Sub-populations carrying known and relevant polymorphisms

Genetic data are not available. Subsequent post marketing experience has not identified any significant safety concerns in populations that were not studied in the clinical trial programme.

Patients of Different Racial and/or Ethnic Origin

The majority of clinical trial subjects in the PAH development programme were White/Caucasian, whereas in the Renal Dialysis development programme, subjects were predominantly White/Caucasian or Black. Subsequent post marketing experience has not identified any significant safety concerns in populations that were not studied in the clinical trial programme.

SIV.4 Conclusions on the populations not-studied and other limitations of the clinical trial development programme

Missing information

The clinical trial program for both PAH and Renal dialysis is generally limited in scope; however the significant post marketing experience has not identified any significant safety concerns in populations that were not studied in the clinical trial programme.

Table 11 Safety concerns due to limitations of the clinical trial programme

Safety concern	Comment	Outstanding concern?
Use in paediatric patients	Available post-marketing data in this population is detailed in Section SV.3 (Post-authorisation use in Paediatrics).	Yes. There is limited information, therefore this is considered to be missing information.
Use in patients over 65 years	Available post-marketing data in this population is detailed in Section SV.3 (Post-authorisation use in elderly).	Yes. There is limited information, therefore this is considered to be missing information.
Use in pregnant and lactating women	Available post-marketing data in this population is detailed in Section SV.3 (Post-authorisation use in pregnant or Breast-feeding Women).	Yes. There is limited information, therefore this is considered to be missing information.

PART II: MODULE SV - POST-AUTHORISATION EXPERIENCE

SV.1 Action taken by regulatory authorities and/or marketing authorisation holders for safety reasons

Flolan has been available in Europe since 1981. For this submission, GSK is proposing to increase the pH of the diluent for Flolan from 10.5 to 12. There are no changes to the existing freeze-dried powder containing the active substance, epoprostenol sodium.

The SmPC serves as the reference document for cumulative important risks associated with epoprostenol, therefore only actions taken by regulatory authorities as a result of the proposal to reformulate the diluent are included below. GSK provided information regarding the presence of glass corrosion products in Table 9 below as some regulatory agencies did treat the presence of glass corrosion products as a potential safety issue (including issuance of a DHCPL and revision of product labelling).

Table 12 Detailed description of action taken by regulatory authorities and/or marketing authorisation holders for safety reasons since last update to this module

Safety issue	
Background to issue	Not applicable.
Evidence source	
Action taken	
Countries affected	
Date(s) of action	

Table 13 Cumulative list of actions taken by regulatory authorities and/or marketing authorisation holders for safety reasons

Safety concern 1: Presence of glass corrosion products in Sterile Diluent for Flolan and pH 12 Sterile Diluent for Flolan			
Country(ies)	Action taken	Comment	Date(s)
United States, Canada, Japan	Withdrawal of application for pH 12 diluent		August 2012
EU	Notification of withdrawal of previously expressed intent to submit application for pH 12 diluent		August 2012
United States, Canada, Netherlands	Discontinuation of extension phase of FLR115332	Due to suspension of manufacture of investigational pH 12 diluent for Flolan	August 2012
All markets	100% visual inspection	Using semi-automated	November 2012

Safety concern 1: Presence of glass corrosion products in Sterile Diluent for Flolan and pH 12 Sterile Diluent for Flolan			
	of vials of diluent for Flolan	Tyndallised light during release	
United States	Field alert report	Presence of potential glass-corrosion products in Flolan diluents	January 2013
United States, Canada, Japan	Distribution of Dear Health Care Provider Letter and revision of product labeling	Informing HCPs about presence of glass corrosion products (glass-related particles) in diluent for Flolan	Complete as of April 2013 (US, Canada); May 2013 (Japan) [Note: DHCPL and labeling variation was submitted in Europe, but was subsequently declined]
United States, Canada	Provided additional information in response to regulatory agency queries	Filter-effectiveness testing, impact of storage and terminal sterilization	Complete as of August 2013 (Canada), December 2013 (US),
EU	Type IA Variation	Update of the release specification to the include the Tyndallised beam test in the EU	December 2013

SV.2 Non-study post-authorisation exposure

Estimated cumulative exposure to Flolan solution for infusion prepared with the pH 10.5 diluent is 656,104 patient courses from January 1995 to December 2013, based on IMS (Intercontinental Medical Statistics) Health data.

SV.2.1 Method used to calculate exposure

Patient courses of treatment for Flolan solution prepared with the pH 10.5 diluent were estimated from the number and strength of standard units sold and an assumed average dose per treatment. IMS does not provide data on the number of patients using any particular drug. It does, however, provide details on the number and strength of standard units sold.

These assumptions apply to all marketed packs of epoprostenol and pH 10.5 diluent. The average dose per treatment was calculated as follows:

Duration of therapy	Average patient weight	Average dose	Average dose / treatment
12 weeks	70kg	10ng/kg/min	700ng/min

Average dose per 12 week treatment period
(12 x 7 x 24 x 60) x 700 ng = 85mg

SV.2.2 Exposure

Table 14 Exposure by age group and gender

Age Group	Persons		Exposure (e.g. packs or person years)	
	M	F	M	F
Flolan is not indicated for use in children, though off-label use of epoprostenol has been reported in children with PAH and other varients of pulmonary hypertension. See SV.3 and SV.4. Estimates of post-marketing exposure do not include information on age group or gender.				

Table 15 Exposure by indication

	Persons	Exposure (e.g. packs or person years)
Flolan is indicated for the treatment of PAH (idiopathic or heritable PAH and PAH associated with connective tissue diseases) or for use in haemodialysis in emergency situations when use of heparin carries a high risk of causing or exacerbating bleeding, though off-label use of epoprostenol has been reported. See SV.4. Estimates of post-marketing exposure do not include information on indication.		

Table 16 Exposure by route of administration

	Persons	Exposure (e.g. packs or person years)
Flolan is only intended for intravenous administration, though off-label use of inhalation of aerosolised epoprostenol has been reported. See SV.4. Estimates of post-marketing exposure do not include information on route of administration.		

Table 17 Exposure by dose

	Persons	Exposure (e.g. packs or person years)
Estimates of post-marketing exposure do not include information on dose.		

Table 18 Exposure by country

	Persons	Exposure (e.g. patient courses)
EU		69,949
France		40,979
Italy		5,436
Spain		6,921
Belgium		2,908
United Kingdom		6,175
Netherlands		4,484
Czech Republic		536
Ireland		270
Austria		35
Denmark		216
Norway		1,235
Poland		463
Germany		284
Non-EU		586,156

SV.3 Post-authorisation use in populations not studied in clinical trials

Table 19 Post-authorisation use in Paediatrics

Estimated use	Number*	Comment on any variation in benefit or risk from overall target population
Child (not further specified) Neonates (birth to 27 days) Infants and toddlers (1 month to 23 months) Children (2 years to 11 years) Adolescents (e.g. 12 years to 19 years)	3 42 70 123 132 European markets from which post marketing case reports in paediatric patients have been received are France, Germany, Ireland, Netherlands, Norway, Spain and the United Kingdom.	The safety and efficacy of epoprostenol in children younger than 18 years have not yet been established. Flolan is not indicated for use in children, though off-label use of epoprostenol has been reported in children with PAH and other varients of pulmonary hypertension. Estimates of post-marketing exposure do not include information on patient age groups, therefore a reliable estimate of Flolan exposure in this patient population is unavailable. An evaluation of the adverse event reports within the GSK Worldwide Clinical Safety Database suggests that the safety profile is not markedly different in children or adolescents when compared to that of the adult population. Data submitted in an Article 46 Paediatric Regulation No 1901/2006 in 2012 included 63 paediatric patients with pulmonary arterial hypertension less than 16 years of age enrolled in acute open label, non-randomised, baseline controlled dose ranging studies. The
*Data source: GSK Worldwide Clinical Safety Database as of 1 Sep 2014		

Estimated use	Number*	Comment on any variation in benefit or risk from overall target population
Method of calculation: Based on the number of spontaneous and post-marketing surveillance reports received cumulatively to 1 September 2014.		data demonstrated safety and significantly improved haemodynamic parameters in patients <16 years of age with acute use. Only 5 paediatric patients study patients were exposed to chronic epoprostenol therapy. According to the National Institutes of Health (NIH) Primary Pulmonary Hypertension Registry, the prognosis of PAH was substantially worse in children with a median survival of 10 months as compared to a combined median survival of 2.8 years in adults and children (D'Alonzo et al. 1991). Supporting evidence for therapeutic outcomes in paediatric patients being similar to adults with chronic epoprostenol use is shown in a review by Barst et al. (1999) describing their 13 year experience with vasodilator therapy in pediatric patients diagnosed with idiopathic pulmonary hypertension between 1982 and 1995. Over this time, 31 patients received epoprostenol (age 8yrs +/- 4) and 28 received conventional therapy (age 8yrs +/- 5). Survival rates on epoprostenol therapy were 100% at 1 year and 94% at 2, 3, and 4 years compared with 50% at 1 year, 43% at 2 years, and 38% at 3 and 4 years for the children treated with conventional therapy alone (*P*=0.002). After follow-up was extended until 2002, a sustained treatment effect with epoprostenol was demonstrated with a mean survival time of 84±6 months (Yung et al. 2004). The survival rates at 1, 3, 5, and 10 years were 94%, 88%, 81%, and 61%, respectively. Lammers et al. (2007) examined 39 children (median age: 5.4 years; range: 4 months to 7 years) in WHO functional class III or IV treated with intravenous epoprostenol between 1997 and 2005. Twenty-five patients had idiopathic PAH and 14 had PAH associated with congenital heart disease, connective tissue disease, chronic lung disease or HIV. The mean (SD) follow-up period was 27 (21) months. The survival rate at 1, 2, and 3 years was 94%, 90%, and 84%, respectively. The European Society of Cardiology Guidelines and Expert Consensus Document (Galie et al. 2009) notes that paediatric

Estimated use	Number*	Comment on any variation in benefit or risk from overall target population
		pulmonary hypertension is similar to the adult disease, and recommends that the PAH therapeutic algorithm proposed for adults (which include epoprostenol) should also be considered in children. The benefit - risk in the pediatric population to date appears to be similar to that of the adult population. No significant new safety information particular to this patient population has been identified from post marketing data (spontaneous case reports) or the literature.

Table 20 Post-authorisation use in the elderly

Estimated use	Number*	Comment on any variation in benefit or risk from overall target population
Elderly (not further specified) Age specified as: 65 – 74 years 75 – 84 years 85+ years	15 394 76 14	There is no specific information on the use of Flolan in patients over 65 years for renal dialysis or pulmonary arterial hypertension. In general, dose selection for an elderly patient should be made carefully, reflecting the greater frequency of decreased hepatic, renal (in the case of pulmonary arterial hypertension) or cardiac function and of concomitant disease or other medicine therapy. Estimates of post-marketing exposure do not include information on patient age groups, therefore a reliable estimate of Flolan exposure in this patient population is unavailable. The conclusions here are based on evaluation of the adverse event reports with the GSK Worldwide Clinical Safety Database. The benefit-risk in this population to date has been similar to that of the adult population. No significant new safety information particular to this patient population has been identified from post marketing data (spontaneous case reports.)
*Data source: GSK Worldwide Clinical Safety Database as of 1 Sep 2014 Method of calculation: Based on the number of spontaneous and post-marketing surveillance reports received cumulatively to 1 September 2014.		

Table 21 Post-authorisation use in pregnant or breast feeding women

Estimated use	Number*	Comment on any variation in benefit or risk from overall target population
Pregnant women Lactating women	75 0	There is a limited amount of data from the use of epoprostenol in pregnant women. Given the absence of alternative medicines, epoprostenol can be used in those women who choose to continue their pregnancy, despite the known risk of pulmonary arterial hypertension during pregnancy. It is unknown if epoprostenol or its metabolites are excreted in human milk. A risk to the breastfeeding child cannot be excluded. Breast-feeding should be discontinued during treatment with Flolan. There is a limited amount of data from the use of epoprostenol in lactating women. Estimates of post-marketing exposure do not include information on patient pregnancy or lactation status, therefore a reliable estimate of Flolan exposure in this patient population is unavailable. The conclusions here are based on evaluation of the adverse event reports with the GSK Worldwide Clinical Safety Database. Numbers of pregnant or breast feeding women exposed to epoprostenol cannot be easily determined. A total of 75 reports of exposure to epoprostenol during pregnancy have been received by GSK as of 01 September 2014. Forty-four reports documented a live infant with no apparent congenital anomaly, 2 indicated the infant had a congenital anomaly, 6 were elective terminations, there was 1 spontaneous abortion and 17 pregnancies were ongoing or lost to follow-up. Pulmonary hypertension during pregnancy is associated with considerable risks of maternal mortality and morbidity. The haemodynamic changes of pregnancy are not well tolerated in women with pulmonary hypertension and mortality has been described in up to 50% of women with pulmonary hypertension. The European Society of Cardiology Guidelines and Expert Consensus Document (Galie et al. 2009) note that PAH is usually considered a contra-indication to pregnancy. The patient who becomes pregnant should be informed of the high risk of pregnancy, and termination of
*Data source: GSK Worldwide Clinical Safety Database as of 1 Sep 2014 Method of calculation: Based on the number of spontaneous and post-marketing surveillance reports received cumulatively to 1 September 2014.		

Estimated use	Number*	Comment on any variation in benefit or risk from overall target population
		pregnancy discussed. Those patients who choose to continue pregnancy should be treated with disease-targeted therapies, planned elective delivery, and effective close collaboration between obstetricians and the PAH team. The use of prostacyclin antenatally and peripartum to improve haemodynamics during delivery is acknowledged by the Task Force on the Management of Cardiovascular Diseases during Pregnancy of the European Society of Cardiology. Unfortunately, no adequate studies have been performed to date in pregnant patients. However, Pieper et al. (2014) carried out a systematic review of the literature to analyse the outcome of pregnancy in women with pulmonary hypertension who had been treated with targeted pulmonary hypertension treatments. Thirty-one studies were included with 77 parturients who were treated with targeted pulmonary hypertension treatments. Prostacyclin derivates were the most commonly used targeted medication (n = 61). This review indicates a considerable decrease of mortality since a previous review in 1998 conducted by Weiss et al. (1998) (16% vs 38%), and a further non-significant decrease in mortality (16% vs 25%) since the latest review in 2009 conducted by Bedard et al (2009). The authors concluded that the initiation of targeted pulmonary hypertension therapy well before delivery seemed to contribute to favourable outcome in their review. Other factors, such as the timely institution of these treatments, and early planned delivery, may also contribute to better outcome. The benefit-risk in this population to date has been similar to that of the adult population. No significant new safety information particular to this patient population has been identified from post marketing data (spontaneous case reports.)

Table 22 Post-authorisation use in hepatic impairment

Estimated use	Number*	Comment on any variation in benefit or risk from overall target population
Viral and other hepatitides Portopulmonary hypertension Other	35 13 52	Use of Flolan off-label to treat certain subtypes of pulmonary hypertension arising from hepatic impairment has been reported. For example, portopulmonary hypertension accounts for approximately 5-10% of patients with PAH, as estimated from registries in the United States and France (Fritz et al. 2013). Estimates of post-marketing exposure do not include information on patients with hepatic impairment, therefore the number of patients receiving Flolan with underlying hepatic impairment cannot easily be determined. Through 1 Sep 2014, there have been a total of 126 adverse event reports identified in the GSK Worldwide Clinical Safety Database in which the patients had a concurrent condition(s) that coded to the 'Hepatobiliary' System Organ Class in MedDRA. Twenty-six of the reports contained terms that could be consistently with sequelae of right heart failure.
*Data source: GSK Worldwide Clinical Safety Database as of 1 Sep 2014 Method of calculation: Based on the number of spontaneous and post-marketing surveillance reports received cumulatively to 1 September 2014 with coded concurrent medical conditions in the 'Hepatobiliary' MedDRA SOC..		

Table 23 Post-authorisation use in renal impairment

Estimated use	Number*	Comment on any variation in benefit or risk from overall target population
Chronic kidney disease Chronic renal insufficiency, chronic renal failure, end stage renal failure Other	7 11 43	Flolan 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. However, the incidence of this use is not known and estimates of post-marketing exposure do not include information on patients with renal impairment. The number of patients receiving Flolan with underlying renal impairment cannot easily be determined. Through 1 Sep 2014, there have been a total of 61 adverse event reports identified in the GSK Worldwide Clinical Safety Database in which the patients had a concurrent condition(s) that coded to the 'Renal and urinary disorders' System Organ Class in MedDRA. Of the 61 reports, the indication for Flolan was reported as dialysis in 1 report and 42 for PAH or pulmonary hypertension. It should be noted that renal impairment can occur in associated with heart failure, a consequence of PAH, as well as connective tissue disorders, a cause of PAH.
*Data source: GSK Worldwide Clinical Safety Database as of 1 Sep 2014 Method of calculation: Based on the number of spontaneous and post-marketing surveillance reports received cumulatively to 1 September 2014 with coded concurrent medical conditions in the 'Renal and urinary disorders' MedDRA SOC..		

Table 24 Post-authorisation use in other use (specify)

Estimated use	Number	Comment on any variation in benefit or risk from overall target population
Not applicable		

SV.4 Post-authorisation off-label use

Table 25 EU Post-authorisation off-label use

Off label category	Country	Source of information	Comment
Use in paediatrics for PAH (non-authorised population)	Post-marketing event reports in pediatric patients reported from Europe have been received from France, Germany, Ireland, Netherlands, Norway, Spain and the United Kingdom.	GSK Worldwide Clinical Safety Database as of 1 Sep 2014 (see Table 25).	An evaluation of the adverse event reports within the GSK Worldwide Clinical Safety Database suggests that the safety profile is not markedly different in children or adolescents when compared to that of the adult population. According to the 2009 ESC/ERS guidelines for the diagnosis and treatment of pulmonary hypertension (Galie et al. 2009), PAH therapy for adults should also be considered for children. The benefit-risk in the pediatric population to date appears to be similar to that of the adult population.
Use in other subtypes of PAH and other types of pulmonary hypertension (non-authorised indication)	Only 1 of the 54 post-marketing adverse event reports for off-label use was reported from Europe (France).	GSK Worldwide Clinical Safety Database as of 1 Sep 2014.	There are 54 reports for off-label use in the GSK Worldwide Clinical Safety Database as of 1 Sep 2014. The majority of the reports described use of inhaled epoprostenol, use in pediatric patients, or use in PAH patients of WHO Functional Class I and II. In general, other subtype of PAH and other types of pulmonary hypertension were not specified.

Off label category	Country	Source of information	Comment
			According to the ESC/ERS guidelines (Galie et al. 2009), epoprostenol is recommended for patients with all subtypes of Group 1 PAH with WHO Functional Class III or IV (recommendation class I; evidence level A), is not recommended for some types (Group 2, Group 3) and is conditionally suggested with caution for carefully selected patients with other types (Group 1', Group 4).
Use as inhaled medication (non-authorised route of administration) for various indications (many non-authorised)	Only 4 of the 54 post-marketing adverse event reports described dosing of Flolan via inhalation were reported from Europe (Denmark, Spain, United Kingdom).	GSK Worldwide Clinical Safety Database as of 1 Sep 2014.	There are 54 reports that describe use of inhaled epoprostenol in the GSK Worldwide Clinical Safety Database as of 1 Sep 2014, though all but four were reported from the United States or Canada. The ages of the patients ranged from infancy to elderly. The indication for use of inhaled epoprostenol (when specified) included PAH, persistent pulmonary hypertension of the newborn and ARDS. A large proportion of reports had fatal outcomes, reflecting the critically-ill nature of patients who have been described to receive inhaled epoprostenol. The SmPC for Flolan

Off label category	Country	Source of information	Comment
			specifies that Flolan is indicated only for continuous intravenous infusion only (PAH) or continuous intravascular or into dialyser infusion (renal dialysis).

SV.5 Epidemiological study exposure

Table 26 Epidemiological study exposure

Study title and study type (e.g. cohort or case/control)	Objectives	Population studied (data source and country)	Duration (study period)	Number of persons (in each group or of cases and controls) and person time (if appropriate)	Comment
					No epidemiological studies have been conducted to elucidate safety or efficacy issues.

PART II: MODULE SVI - ADDITIONAL EU REQUIREMENTS FOR THE SAFETY SPECIFICATION

Flolan has been available in Europe since 1981. For this submission, GSK is proposing to increase the pH of the diluent for Flolan from 10.5 to 12. There are no changes to the existing freeze-dried powder containing the active substance, epoprostenol sodium. This RMP is not due to an application for a significant change to an existing marketing authorisation, rather this RMP is intended primarily to address safety concerns that are specifically affected by the planned transition from the pH 10.5 diluent to the reformulated pH 12 diluent, though some of the more significant safety concerns for epoprostenol are addressed in this module as well.

SVI.1 Potential for harm from overdose

Flolan

Epoprostenol is a potent vasodilator, therefore overdose during epoprostenol infusion can be associated with cardiovascular effects, particularly profound hypotension. As errors in Flolan dosing are associated with errors in preparation or administration, the potential for harm from overdose is discussed in the SmPC as a component of the potential consequences associated with medication errors.

Flolan solution prepared with pH 12 diluent

The proposed change includes only an increase in the diluent pH from 10.5 to 12, with no associated change to the existing freeze-dried powder containing the active substance, epoprostenol sodium, therefore there is no potential for harm from overdose that is specific to Flolan solution for infusion reconstituted with pH 12 diluent.

SVI.2 Potential for transmission of infectious agents

Flolan

Because of the short half-life of epoprostenol, Flolan is administered via continuous intravenous infusion. As a consequence, patients who are receiving Flolan must have permanent central venous access, a known risk factor for catheter-site related and bloodstream infections. The risk of infections is addressed in the SmPC.

Flolan solution prepared with pH 12 diluent

There is no potential for transmission of infectious agents that is specific to Flolan solution for infusion reconstituted with pH 12 diluent. Sterility testing is performed as a release test and at prescribed intervals during the stability testing of the product which demonstrates that the sterility of the product is consistently achieved at manufacture and maintained throughout its shelf-life.

SVI.3 Potential for misuse for illegal purposes

There is no potential for misuse for illegal purpose for Flolan prepared with either the pH 10.5 or pH 12 diluent.

SVI.4 Potential for medication errors

Flolan

Epoprostenol preparation and administration is associated with multiple factors that increase the risk of medication errors. Kingman et al. (2010), in a review of in-hospital medication errors specifically occurring in association with use of prostacyclins, noted that adverse reactions can occur with even modest dosing errors owing to the narrow therapeutic index for individual patients with tenuous haemodynamic status at baseline, complex and individualized dosing requirements that do not allow for standardized dosing protocols, and lack of experience for many caregivers owing to the small patient population who are receiving intravenous prostacyclins. In addition, reconstitution of Flolan is a multistep process that must be done aseptically through a series requiring dissolution, dilution and transfer. As a result, the risk of medication errors is inherent to the risk assessment for Flolan and is addressed in the SmPC including the need for intense and ongoing patient education during treatment with Flolan.

Flolan solution prepared with pH 12 diluent

Pulmonary arterial hypertension: Based on the medically critical nature of Flolan, it is not possible to withdraw the pH 10.5 diluent and subsequently launch the pH 12 diluent, therefore it is planned that there will be a period of time in each market during which both the pH 10.5 diluent and the reformulated pH 12 diluent formulations will be simultaneously available. Therefore, during this transition period, there is the possibility of incorrect use of both diluents for Flolan and the risk of medication errors may be expected to increase. Use of the reformulated pH 12 diluent according to the storage and administration instructions intended for the pH 10.5 diluent would not be expected to produce any adverse consequences, as the stability of the drug would be unchanged if used with cold pouch. However, the inverse situation is potentially more serious. Reconstitution of epoprostenol with the pH 10.5 diluent for Flolan followed by subsequent prolonged refrigeration or infusion over 24 hours without use of a cold pouch could result in reduced efficacy, including possible rebound of PAH symptoms due to diminished room temperature stability of the reconstituted product when mixed with the pH 10.5 diluent.

Renal dialysis: Reconstitution of epoprostenol with the pH 10.5 diluent for Flolan followed by subsequent prolonged refrigeration or infusion over 24 hours without use of a cold pouch could result in reduced antiplatelet effects when being used during RRT. The SmPC suggests that solutions for renal dialysis should be used immediately after reconstitution and dilution. To address the possibility that this may not always occur, mitigation measures that are being proposed to address risks of medication errors that associated with the transition to pH 12 diluent for Flolan for PAH will also be targeted to reach pharmacies of hospitals that are potentially using Flolan during renal dialysis.

Information to support duration of transition: Patients who are receiving Flolan for treatment of PAH are dependent on the medication. Therefore, the introduction of the pH 12 diluent must minimise the possibility of inadequate supply of diluent for Flolan and educate prescribers to facilitate successfully transition of their patients when switching to Flolan prepared with pH 12 diluent.

The transition period is defined as the period of time during which both the pH 10.5 diluent and the reformulated pH 12 diluent formulations will be simultaneously available in each market. The duration of the transition period is based on the anticipated amount of time needed for prescribers to see and/or transition their patients (as per the individual prescriber's practice). It will also give GSK time to supply sufficient pH 12 diluent to ensure that the various distributors of Flolan will be adequately stocked so as to avoid the possibility of a low inventory situation.

To understand the amount of time the prescriber community will need to transition their patients from Flolan prepared with the pH 10.5 diluent to Flolan prepared with the reformulated pH 12 diluent, GSK requested feedback from the local operating companies in markets within Europe in which Flolan is marketed, as well as external experts, particularly major prescribers, to assess usual practice as well as local operating company and physician expectations regarding a change in the diluent for Flolan. Specifically, GSK wished to understand the time, process, and materials needed to successfully transition patients.

Prescribers preferred to see patients in the office to oversee changes to their current PAH treatment. Prescribers stated that in general, most patients are usually seen every three months. According to GSK local operating companies in the European markets in which Flolan is approved, it was generally agreed that 6 months would allow sufficient time for patients to be transitioned via routinely scheduled appointments with their PAH specialists. Several of the markets serve only a handful of patients, and particularly for those markets, there was interest in timing each patient's transition to when they would be scheduled to exhaust a delivery of medication and supplies, to minimize the need to collect and return pH 10.5 diluent.

However, certain European GSK local operating companies expressed an interest in a shorter period of availability for the pH 10.5 diluent and the reformulated pH 12 diluent. Reasons included prescriber preference, and limited number of patients currently receiving Flolan within that market. GSK does not oppose individual markets proposing shorter transition times. Monitoring of the status of the transition in each market is part of this RMP, therefore countries that identify that all patients have been switched in advance of the end of the anticipated transition period may also complete their transition early, at which time shipments of the pH 10.5 diluent to that market would be discontinued.

GSK proposes a transition time period of 6 months from the time of launch of the pH 12 diluent following national approval in each market to allow patients to transition to using Flolan prepared with pH 12 diluent and markets to build sufficient pH 12 diluent stock.

SVI.4.1 Description of medication errors during the clinical trial programme

Table 27 Medication errors during the clinical trial programme

Flolan

A review of post-marketing reports of medication errors for Flolan is included in SVI.4.4.

Flolan solution prepared with pH 12 diluent

There is one clinical study (Study FLR115332) that was conducted to evaluate use of Flolan reconstituted with pH 12 diluent in a small cohort of patients currently being treated with Flolan for PAH, and there were no reported medication errors reported during that study.

Product name: Flolan				
Description of error	Number of occurrences	Analysis of cause	Steps taken to prevent	Comment
	None			

SVI.4.2 Preventive measures for the final product(s) being marketed

Prevention of error due to wrong medication

Flolan

The risk of medication errors is inherent to the risk assessment for Flolan and is addressed in the SmPC including the need for intense and ongoing patient education during treatment with Flolan.

Flolan solution prepared with pH 12 diluent

Mitigation measures proposed to minimise the risk of inappropriate use of pH 10.5 diluent during the time period during which both the pH 10.5 and pH 12 diluents will be available include revision of the SmPC and PL to include information on differences in product preparation, storage and administration. In addition, the vial material as well as the color of the vial cap, vial label and external packaging for the pH 12 diluent will be different from the pH 10.5 diluent (See Section SVI.4). Additional risk minimisation measures beyond revision of the SmPC and PL and product packaging are discussed in part V of this RMP.

Prevention of error due to wrong dose (strength, form, concentration)

Flolan

The risk of medication errors is inherent to the risk assessment for Flolan and is addressed in the SmPC including the need for intense and ongoing patient education during treatment with Flolan.

Flolan solution prepared with pH 12 diluent

There is no potential for error due to wrong dose that is specific to Flolan solution for infusion reconstituted with pH 12 diluent. There is no change to the vial of freeze-dried epoprostenol sodium as a result of the reformulation of the diluent, therefore no increased risk of use of the incorrect vial strength is anticipated to occur. In addition, the types of packs containing pH 12 diluent, in terms of number of vials of diluents and lyophile, will be the same as the packs containing pH 10.5 diluent.

Prevention of error due to wrong route of administration

Flolan

Flolan is intended for intravenous administration (PAH) or intravascular or dialyzer infusion (renal dialysis) and the SmPC specifies that only these routes of administration are approved.

Flolan solution prepared with pH 12 diluent

There is no potential for error due to wrong route of administration that is specific to Flolan solution for infusion reconstituted with pH 12 diluent.

SVI.4.3 Effect of device failure

Flolan

The risk of device complications is inherent to the risk assessment for Flolan and is addressed in the SmPC including the need for intense and ongoing patient education during treatment with Flolan.

Flolan solution prepared with pH 12 diluent

There is no potential for error due to device failure that is specific to Flolan solution for infusion reconstituted with pH 12 diluent. Pre-clinical catheter and medication cassette compatibility studies have not identified any risks associated with Flolan solution for infusion reconstituted with pH 12 diluent. See S2.

SVI.4.4 Reports of medication errors with the marketed product(s)

Flolan

Available data from spontaneous adverse event reports of medication errors with Flolan prepared with pH 10.5 diluent is discussed in Table 28.

Flolan solution prepared with pH 12 diluent

As the reformulated pH 12 diluent is not yet available, there are no instances in which misuse of the incorrect diluent has been reported, but the potential for medication errors associated with inappropriate confusion of the two diluents is discussed in Section SVI.4.

Table 28 Reports of medication errors with the marketed product(s)

Product name(s)				
Description of error	Number of occurrences	Analysis of cause	Steps taken to prevent	Comment
Dosing errors	17	Many reports are incompletely documented, but causes included incorrect preparation of the solution (using wrong diluent or incorrect amount of lyophile) or inadvertent administration of solution to incorrect patient.	Addressed in SmPC	As of 1 Sep 2014, there were 100 reports in the GSK Worldwide Clinical Safety Database that are potentially consistent with medication errors reported in association with epoprostenol. A subset of errors occur because of lack of adherence to product labeling, such as using a single medication cassette beyond the recommended duration, whereas others occur as a result of caregiver or patient error, such as incorrect reconstitution of lyophile with diluent, incorrect infusion rate, failure to turn on the infusion pump after replacement of the medication cassette or accidental dislodging of the central venous catheter. No significant new safety
Administration errors	11	Causes included infusing from one cassette beyond recommended duration or inadvertently administering boluses while priming line or clearing obstruction.	Addressed in SmPC	
Central venous line errors	11	Causes included accidental dislodging of line or damage to line during use.	Patient and caregiver training	
Pump error	20	Causes included incorrect programming of pump or forgetting to turn pump on following cassette change.	Patient and caregiver training	
Cutaneous or ocular exposure	6	Causes included spilling or splashing onto skin or into eyes while preparing or administering, generally associated with a self-limited rash or no reaction.	Patient and caregiver training	
Wrong route of administration	11	Most reports described intentional administration via inhalation route.	Addressed in SmPC	

Product name(s)				
				information particular to medication errors has been identified from post marketing data (spontaneous case reports).

SVI.5 Potential for off-label use

Flolan

GSK is aware that Flolan as currently marketed is used off-label (see SV.4 and SVII.3) particularly for patients with certain other subtypes of PAH (excluding idiopathic or heritable PAH and PAH associated with connective tissue diseases) and pulmonary hypertension (non-authorised indications). Use of Flolan in patients with pulmonary veno-occlusive disease is associated with a risk of acute pulmonary oedema, though pulmonary oedema has been reported in patients receiving epoprostenol on-label.

Flolan solution prepared with pH 12 diluent

There is no increased potential for off-label use that is specific to Flolan solution for infusion reconstituted with pH 12 diluent.

Although GSK does not support off-label use of Flolan, the mitigation measures that are being proposed in association with the introduction of the pH 12 diluent will also cover those HCPs and patients who are prescribing or receiving Flolan off-label in order to minimise the risk of harm to these patients.

SVI.6 Specific paediatric issues

SVI.6.1 Issues identified in paediatric investigation plans

There is no paediatric investigation plan for Flolan.

Table 29 Issues identified in paediatric investigation plans

Product Name and PIP		
Issue (safety or long term efficacy)	Background	Relevance to indications covered in this RMP and how, if appropriate, it will be addressed.
Not applicable		

SVI.6.2 Potential for paediatric off-label use

Flolan

GSK is aware that Flolan as currently marketed is used off-label in pediatric patients for PAH as well as other types of pulmonary hypertension (non-authorised population; see SV.3 and SV.4).

Flolan solution prepared with pH 12 diluent

There is no increased potential for off-label use in paediatrics that is specific to Flolan solution for infusion reconstituted with pH 12 diluent.

Although GSK does not support off-label use of Flolan, the mitigation measures that are being proposed in association with the introduction of the pH 12 diluent will also cover those HCPs and paediatric patients who are prescribing or receiving Flolan off-label in order to minimise the risk of harm to these patients.

SVI.7 Conclusions

Table 30 Safety concerns from this module

Safety concern	Comment
Safety concern specific for Flolan solution prepared with pH 12 diluent	
Medication errors	Parenteral prostacyclin preparation and administration, including that for Flolan, is associated with multiple factors that increase the risk of medication errors, including a narrow therapeutic index for individual patients, complex and individualized dosing requirements, and lack of experience for many caregivers. As a result, the risk of medication errors is inherent to the risk assessment for Flolan. However, the risk of medication errors can reasonably be expected to increase during the transition from the pH 10.5 to the pH 12 diluent. Based on the medically critical nature of Flolan, there will be a period of time in each market during which both the pH 10.5 diluent and the reformulated pH 12 diluent formulations will be simultaneously available, therefore the risk of medication errors may occur during this transition period. There is the possibility of incorrect use of both diluents for Flolan,. Reconstitution of epoprostenol with the pH 10.5 diluent for Flolan followed by subsequent prolonged refrigeration or infusion over 24 hours without use of a cold pouch could result in reduced efficacy owing to diminished room temperature stability of Flolan prepared with the pH 10.5 diluent as compared to Flolan prepared with the pH 12 diluent.
Safety concerns for Flolan	
Hypotension	Epoprostenol is a potent vasodilator, therefore overdose can be associated with cardiovascular effects, particularly profound hypotension.
Sepsis, septicaemia (mostly related to delivery system for Flolan)	Flolan is administered via continuous intravenous infusion. As a consequence, patients who are receiving Flolan must have permanent central venous access, a known risk factor for catheter-site related and bloodstream infections, including sepsis and septicaemia. Patients are also regularly required to prepare solution, a multistep process involve dissolution, dilution and solution transfer, allowing the possibility of inadvertent contamination of the sterile drug product.
Pulmonary oedema	Some patients with PAH have developed pulmonary oedema during dose-ranging, which may be associated with pulmonary veno-occlusive disease. Flolan must not be used chronically in patients who develop pulmonary edema during dose initiation. Pulmonary veno-occlusive disease is categorized as WHO Group I' PAH, whereas Flolan is indicated only for certain subtypes of WHO Group I (idiopathic or heritable PAH and PAH associated with connective tissue diseases).

PART II: MODULE SVII - IDENTIFIED AND POTENTIAL RISKS

SVII.1 Newly identified safety concerns (since this module was last submitted)

This section is not applicable as this is the first version of a risk management plan for Flolan (epoprostenol sodium).

Table 31 Newly identified safety concerns (since this module was last submitted)

Safety concern
Details
Source
New studies proposed in pharmacovigilance plan?
New risk minimisation actions proposed?

SVII.2 Recent study reports with implications for safety concerns

There are no recent study reports with implications for safety concerns.

SVII.3 Details of important identified and potential risks from clinical development and post-authorisation experience (including newly identified)

Table 32 Identified and Potential Risks

Identified/potential Risk	Medication errors
Frequency with 95 % CI	Flolan Epoprostenol preparation and administration is associated with multiple factors that increase the risk of medication errors. Kingman et al. (2010), in a review of in-hospital medication errors specifically occurring in association with use of prostacyclins, noted that adverse reactions can occur with even modest dosing errors owing to the narrow therapeutic index for individual patients with tenuous haemodynamic status at baseline, complex and individualized dosing requirements that do not allow for standardized dosing protocols, and lack of experience for many caregivers owing to the small patient population who are receiving intravenous prostacyclins. A review of adverse event reports associated with Flolan medication errors in the GSK Worldwide Clinical Safety Database suggested that a subset of errors occur because of lack of adherence to product labeling, such as using a single medication cassette beyond the recommended duration, whereas others occur as a result of caregiver or patient error, such as incorrect reconstitution of lyophile with diluent, incorrect infusion rate or

Identified/potential Risk	**Medication errors**
	failure to turn on the infusion pump after replacement of the medication cassette. <u>Flolan solution prepared with pH 12 diluent</u> During the transition period, the pH 10.5 diluent and pH 12 diluent for Flolan will simultaneously be available, therefore, there is the possibility of incorrect use of both diluents for Flolan and the potential for an overall increased risk of medication errors. An estimation of the frequency of occurrence of this specific subtype of medication error is not possible, as there is only one diluent currently available.
Seriousness/outcomes	<u>Flolan</u> Outcomes of the adverse event reports associated with Flolan medication errors (Flolan prepared with pH 10.5 diluent) in the GSK Worldwide Clinical Safety Database as of 1 Sep 2014 included 22% fatal outcomes, 17% unresolved or worse, 17% resolved or improved and 44% unknown or not applicable, though it should be noted that the outcome may have been due to other events in the report not related to the circumstances of the medication error. <u>Flolan solution prepared with pH 12 diluent</u> Use of the pH 12 diluent under storage and administration instructions intended for the pH 10.5 diluent would not be expected to produce any consequences, as the stability of the drug would be unchanged if used with cold pouch. However, the inverse situation is potentially more serious. Reconstitution of epoprostenol with the current sterile diluent for Flolan followed by subsequent prolonged refrigeration or infusion over 24 hours without use of a cold pouch could result in reduced efficacy including possible rebound of PAH symptoms due to decreased room temperature stability of the epoprostenol when mixed with the pH 10.5 diluent.
Severity and nature of risk	<u>Flolan and Flolan solution prepared with pH 12 diluent</u> Acute withdrawal of epoprostenol in patients with PAH can be associated with rebound pulmonary hypertension, including death. The situation that would occur owing to inappropriate use of Flolan prepared with the pH 10.5 diluent following storage or administration conditions intended for Flolan prepared with the pH 12 diluent would be a more gradual decrease in dose as degradation of the active product continued.

Identified/potential Risk	**Medication errors**
Background incidence/prevalence	<u>Flolan and Flolan solution prepared with pH 12 diluent</u> Not applicable, as there is only one diluent currently available.
Risk groups or risk factors	<u>Flolan</u> A review of the 100 adverse event reports associated with Flolan medication errors (Flolan prepared with pH 10.5 diluent) in the GSK Worldwide Clinical Safety Database as of 1 Sep 2014 suggested errors primarily occur because of lack of adherence to product labeling or as a result of caregiver or patient error. <u>Flolan solution prepared with pH 12 diluent</u> Risk factors during the transition period from pH 10.5 diluent to pH 12 diluent would occur with inadvertent dispensation or use of left-over pH 10.5 diluent following a patient having been transitioned to Flolan prepared with pH 12 diluent.
Potential mechanisms	<u>Flolan and Flolan solution prepared with pH 12 diluent</u> Owing to the short half life, acute withdrawal of epoprostenol in patients with PAH can be associated with rebound pulmonary hypertension.
Preventability	<u>Flolan</u> Yes, with appropriate education regarding preparation, storage and administration of Flolan. The SmPC contains information on the importance of avoiding abrupt interruptions in therapy and that the patient must be willing to commit to the significant challenges associated with successful Flolan administration. <u>Flolan solution prepared with pH 12 diluent</u> Yes, with appropriate education to facilitate identification of different diluent formulations and understanding of appropriate storage and administration conditions for different diluent formulations.
Impact on individual patient	<u>Flolan</u> Administration of Flolan for treatment of PAH is notably complex, and even modest dosing errors may be associated with adverse events owing to the tenuous haemodynamic status of PAH patients. <u>Flolan solution prepared with pH 12 diluent</u> As inappropriate use of pH 10.5 diluent under storage and administration conditions intended for pH 12 diluent could result in

Identified/potential Risk	**Medication errors**
	lower-than-expected doses of Flolan reaching the patient, it is possible that a rebound pulmonary hypertension could occur, which could be associated with serious events, including death.
Potential public health impact of safety concern	<u>Flolan and Flolan solution prepared with pH 12 diluent</u> It is not anticipated that the misuse of epoprostenol would be associated with general public health issues, as epoprostenol is generally used chronically only for the treatment of PAH, a rare disease, and is otherwise only used in hospitals.
Evidence source	Literature and spontaneous adverse event reports for epoprostenol in GSK Worldwide Clinical Safety Database
MedDRA terms	Accidental exposure to product, Accidental overdose, Circumstance or information capable of leading to medication error, Drug administration error, Drug dispensing error, Drug prescribing error, Inappropriate schedule of drug administration, Incorrect dose administered, Incorrect drug administration duration, Incorrect route of drug administration, Incorrect storage of drug, Medication error, Overdose, Poor quality drug administered, Prescribed overdose, Underdose, Wrong technique in drug usage process

Identified/potential Risk	**Local infusion site reactions during long-term infusion**
Frequency with 95 % CI	<u>Flolan</u> Because of the high pH of the final Flolan infusion solutions, care should be taken to avoid extravasation during administration and consequent risk of tissue damage. An estimation of the frequency of occurrence of local infusion site reactions is complicated by the fact that many of the signs can occur in association with local infections as well. In clinical trials with Flolan prepared with pH 10.5 diluent, injection site pain was seen in 7 of 108 subjects who were receiving Flolan, and injection site inflammation or reaction was seen in 11 of 108 subjects who were receiving Flolan. In addition, there are published reports of using Flolan solution off-label, either via IV infusion in unapproved populations or via unapproved routes (e.g. inhalation via nebulisation). Patients who are receiving long-term epoprostenol infusions, even if off-label, will likely require a central venous catheter to ensure continuous venous access. With regards to inhalation of nebulised epoprostenol, it should be noted that the hourly rate of delivery of nebulised epoprostenol is relatively small when considering the large surface area of the lungs. In addition, it should be noted that the SmPC for Flolan specifies that Flolan is only to be administered via continuous infusion by intravenous route (PAH) or continuous infusion, either intravascularly or into the blood

Identified/potential Risk	Local infusion site reactions during long-term infusion
	supplying the dialyzer (renal dialysis). Flolan solution prepared with pH 12 diluent As drugs with elevated pH have been associated with phlebitis, particularly when administered peripherally, the increase in pH of the diluent for Flolan and thus the reconstituted solution for infusion could potentially be associated with an increased risk of vein irritancy or infusion site reactions. For chronic infusion, the SmPC recommends placement of a long-term central venous catheter, therefore the risk of local infusion site reactions due to extravasation is anticipated to be low. It should be noted that the infusion rate of Flolan is extremely low when compared with blood flow even in a peripheral vein. In addition, the buffer capacity of the Flolan solution for infusion is not changed when reconstituted with the reformulated pH 12 diluent for Flolan, therefore it is anticipated that the solution will drop to physiologic pH upon mixing with the blood. In addition, neither the in vitro haemolysis study, the in vivo dog study or the small clinical trial in patients who received Flolan prepared with pH 12 diluent identified concerns with regards to local tolerance. A 2012 review of administration site reaction, infusion reactions, device issues, device complications and phlebitis reports in the United States Food and Drug Administration Adverse Events Reporting System for Flolan and Veletri, a higher pH epoprostenol formulation for intravenous infusion, did not suggest any increased risk of local or vascular reactions associated Veletri (final pH >11 for reconstituted solution) as compared to Flolan (final pH 10.5) (VELETRI SmPC). In addition, two studies evaluating use of Veletri, one in subjects with PAH switched from Flolan to Veletri, did not identify any tolerability concerns (Chin et al. 2014; Sitbon et al. 2014). Unlike the recommendations for Flolan infusion via a central venous catheter in chronic use in the treatment of PAH, there is less limitation of the route of intravascular infusion of Flolan for renal dialysis. The unchanged buffer capacity of the solution reconstituted with the pH 12 diluent as compared to the pH 10.5 diluent and the high rate of blood flow even in peripheral blood vessels as compared to the infusion rate of Flolan provide reassurance that even peripheral infusion is unlikely to be associated with reactions.
Seriousness/outcomes	Flolan There are 240 reports that are potentially consistent with infusion site reactions for epoprostenol (Flolan prepared with pH 10.5 diluent) in the GSK Worldwide Clinical Safety Database as of 1 Sep 2014. It should be noted that some of the reports in the GSK Worldwide Clinical Safety Database may have occurred during use of other parenteral epoprostenol formulations which may have

Identified/potential Risk	**Local infusion site reactions during long-term infusion**
	higher solution pHs. Outcomes of the adverse event reports potentially consistent with local infusion site reactions included 11% fatal outcomes, 28% unresolved or worse, 18% resolved or improved and 43% unknown or not applicable, though it should be noted that the outcome may have been due to other events in the report not related to the local infusion site reaction. The majority of the reports are very much more likely to be associated with infections of the central venous catheter site or reactions to dressing material used at catheter sites. Reports associated with accidental cutaneous or ocular exposure to reconstituted Flolan described either no reaction or minor reactions that resolved without intervention. There are 54 reports that describe use of inhaled epoprostenol (Flolan prepared with pH 10.5 diluent) in the GSK Worldwide Clinical Safety Database as of 1 Sep 2014 (See SV.4). Outcomes of the adverse event reports in patients treated with inhaled delivery of epoprostenol included 56% fatal outcomes, 7% unresolved or worse, 7% resolved or improved and 30% unknown or not applicable, though it should be noted that the outcome may have been due to other events in the report. The indication for use of inhaled epoprostenol (when specified) included PAH, persistent pulmonary hypertension of the newborn and ARDS. The large proportion of reports with fatal outcomes, reflecting the critically-ill nature of patients who have been described to receive inhaled epoprostenol. However, many of the fatalities were considered due to the underlying condition for which nebulised epoprostenol was being used, with only a small number of reports suggesting that epoprostenol-associated complications contributed to the outcome. <u>Flolan solution prepared with pH 12 diluent</u> There was one clinical study (Study FLR115332) that was conducted to evaluate use of Flolan reconstituted with pH 12 diluent in a small cohort of patients currently being treated with Flolan for PAH during which no new safety signals were identified.
Severity and nature of risk	<u>Flolan</u> The spectrum of infusion site reactions and phlebitis range from minor- self-limited irritations to more significant complications that in the most severe presentation could potentially eliminate the future use of that central line insertion site. With regards to off-label use of epoprostenol solution as an inhaled product, the risk is more difficult to quantify as there is limited available information on inhalation of highly pH solutions via nebulisation and approved solutions for inhalation have pHs that range between 3 and 8. This risk assessment is further complicated by the critically ill nature of the patients in whom this

Identified/potential Risk	**Local infusion site reactions during long-term infusion**
	treatment has been described in the published literature. Habler et al. (1996) found no significant histopathological consequences following 8 hours of nebulised epoprostenol (reconstituted in pH 10.5 diluent) compared to nebulised saline in lambs, whereas van Heerden et al. (2000) found mild acute tracheitis in pigs, though the comparison in this case was between nebulised pH 10.5 diluent and nebulised epoprostenol in pH 10.5 diluent. Dzierba et al. (2014) reviewed the available published data for use of nebulised epoprostenol primarily for acute respiratory distress syndrome, all of which was small uncontrolled case series and concluded that there was insufficient evidence to support routine use in patients with ARDS. Flolan solution prepared with pH 12 diluent There was one clinical study (Study FLR115332) that was conducted to evaluate use of Flolan reconstituted with pH 12 diluent in a small cohort of patients currently being treated with Flolan for PAH during which no new safety signals were identified.
Background incidence/prevalence	Flolan and Flolan solution prepared with pH 12 diluent Not applicable, as there is no risk of local infusion sites in patients who are not receiving the medication.
Risk groups or risk factors	Unknown
Potential mechanisms	Flolan and Flolan solution prepared with pH 12 diluent Increased alkalinity of chronically infused solution could result in local tissue reactions.
Preventability	Flolan and Flolan solution prepared with pH 12 diluent Yes, for patients who are receiving Flolan continuously for treatment of PAH, appropriate monitoring of infusion sites could mitigate the risk of local reactions. Yes, local reactions arising as a result of administration of Flolan via other dosing routes (primarily inhaled) could be prevented, as there are other vasodilator products approved for delivery via inhalation, including both prostanoids as well as other classes of agents.
Impact on individual patient	Flolan and Flolan solution prepared with pH 12 diluent The spectrum of infusion site reactions and phlebitis range from minor self-limited irritations to more significant complications that in the most severe presentation could potentially eliminate the future use of that central line insertion site. As PAH patients who are receiving Flolan require continuous central venous access,

Identified/potential Risk	**Local infusion site reactions during long-term infusion**
	loss of insertion sites could conceivably result in need for additional medical procedures to replace ventral access and in the most severe case, inability to continue to receive Flolan owing to lack of central venous access.
Potential public health impact of safety concern	<u>Flolan and Flolan solution prepared with pH 12 diluent</u> It is not anticipated that these local reactions would be associated with general public health issues.
Evidence source	Literature, GSK clinical trial data and spontaneous adverse event reports for epoprostenol in GSK Worldwide Clinical Safety Database
MedDRA terms	Application site discharge, Application site discolouration, Application site dryness, Application site erythema, Application site hypersensitivity, Application site induration, Application site irritation, Application site pain, Application site papules, Application site pruritus, Application site reaction, Application site swelling, Application site vesicles, Catheter site discharge, Catheter site discolouration, Catheter site erythema, Catheter site hypersensitivity, Catheter site inflammation, Catheter site oedema, Catheter site pain, Catheter site pruritus, Catheter site rash, Catheter site related reaction, Catheter site swelling, Catheter site vesicles, Infusion site dermatitis, Infusion site discolouration, Infusion site discomfort, Infusion site erythema, Infusion site extravasation, Infusion site induration, Infusion site irritation, Infusion site pain, Infusion site pruritus, Infusion site reaction, Infusion site swelling, Infusion site vesicles, Infusion site warmth, Injection site discolouration, Injection site dryness, Injection site erythema, Injection site inflammation, Injection site irritation, Injection site pain, Injection site pruritus, Injection site rash, Injection site reaction, Injection site swelling, Injection site vesicles, Injection site warmth, Phlebitis, Thrombophlebitis, Vasculitis

Identified/potential Risk	**Sepsis, septicaemia (mostly related to delivery system for Flolan)**
Frequency with 95 % CI	<u>Flolan</u> In patients receiving Flolan for treatment of PAH, epoprostenol is infused continuously through a permanent indwelling central venous catheter via a small, portable infusion pump. Because of the parenteral route of administration, the long-term need for an indwelling central venous catheter, as well as the fact that PAH patients are not infrequently receiving immunosuppressive medications, catheter-related infections, up to and including septicaemia and sepsis, occur frequently in patients receiving Flolan. Sepsis and septicaemia (mostly related to delivery system

Identified/potential Risk	Sepsis, septicaemia (mostly related to delivery system for Flolan)
	for Flolan) occur commonly (between 1% and 10% of subjects in clinical trials with Flolan prepared with pH 10.5 diluent for PAH) in patients receiving Flolan, as described in the SmPC for Flolan. Overall, the rate of catheter-related infections is considered to be relatively low in patients receiving epoprostenol infusions as compared to other patient populations who have indwelling central venous catheter (Oudiz et al. 2004). Rates of catheter-related infections have been reported between 0.26 per 1000 catheter-days (Oudiz et al. 2004) and 0.19 per patient-year (Sitbon et al. 2002) and blood stream infections of 0.42 per 1000 treatment-days (Kallen et al. 2008) and 0.43 per 1000 medicine-days (Centers for Disease Control and Prevention 2007). There is a relatively high incidence of infections due to Micrococcus in patients receiving epoprostenol, perhaps as a result of relative tolerance of Micrococcal species to alkaline conditions, as found in reconstituted epoprostenol solutions (Hirata et al. 2009, Yap and Mermel 2003, Valdivia-Arenas 2009, Oudiz et al. 2004). In addition, catheter-related infection rates, including those due to gram-negative bacilli, are occur more frequently in patients receiving a different intravenous prostanoid, treprostinil, which can be prepared in more pH neutral solvent as a result of its greater stability (Centers for Disease Control and Prevention 2007; Ivy et al. 2009; Kallen et al. 2008). A follow-up study has shown that infection rates are comparable to those for epoprostenol if the administered treprostinil solution is prepared with the alkaline diluents for epoprostenol (Rich et al. 2012). <u>Flolan solution prepared with pH 12 diluent</u> The frequency of this event is not expected to change as a result of introduction of pH 12 diluent. There was one clinical study (Study FLR115332) that was conducted to evaluate use of Flolan reconstituted with pH 12 diluent in a small cohort of patients currently being treated with Flolan for PAH. There were two reports of device-related infection during the run-in period (subjects were receiving Flolan prepared with pH 10.5 diluent) and three reports of device-realted infection during the extension phase (subjects were receiving Flolan prepared with pH 12 diluent).
Seriousness/outcomes	<u>Flolan</u> There are 707 reports that are potentially consistent with catheter-related infections (both localized infections such as exit site, tunnel or line infections or systemic infections such as bacteraemia or sepsis) in the GSK Worldwide Clinical Safety Database as of 1 Sep 2014. Outcomes of the adverse event reports potentially consistent with catheter-related infections included 25% fatal outcomes, 10% unresolved or worse, 40%

Identified/potential Risk	**Sepsis, septicaemia (mostly related to delivery system for Flolan)**
	resolved or improved and 25% unknown or not applicable, though it should be noted that the outcome may have been due to other events in the report not related to the catheter-related infection. Once initiated in patients with PAH, Flolan treatment should not be abruptly discontinued owing to the risk of rebound symptoms of pulmonary arterial hypertension. As a result, patients with catheter-related infections frequently require hospitalization for treatment, often including removal of the infection line, temporary placement of central venous access followed by replacement of a permanent line once the infection has been cleared. Flolan solution prepared with pH 12 diluent The outcomes of this event are not expected to change as a result of introduction of pH 12 diluent.
Severity and nature of risk	Flolan and Flolan solution prepared with pH 12 diluent The clinical consequences of catheter-related infections vary depending on the degree of systemic involvement. Local infections of the catheter skin exit site can sometimes be treated successfully with antibiotics, though recurrent exit site infections, tunnel infections, and catheter infections are more likely to require removal of the central venous catheter. As patients are dependent on the central line for delivery of epoprostenol, a temporary central line must be placed to allow continuation of epoprostenol, as well as parenteral antibiotics in many cases. Blood-stream infections can result in disseminated infection (such as endocarditis) or sepsis with concurrent poor systemic perfusion that can result in substantial morbidity or mortality.
Background incidence/prevalence	Flolan and Flolan solution prepared with pH 12 diluent The risk of sepsis and septicaemia is primarily due to the long-term presence of the central venous catheter, therefore there is little risk for patients with PAH who do not have a central venous catheter. It should be noted that the risk of catheter-related infections, including bloodstream infections, in patients receiving epoprostenol for PAH is less than that for other patient populations who commonly have central venous access.
Risk groups or risk factors	Flolan and Flolan solution prepared with pH 12 diluent The risk for patients receiving Flolan is primarily due to the presence of the central venous line, and less not due to the medication itself, though of course, contamination during preparation could result in development of an infection. The alkalinity of Flolan solution may be somewhat protective against certain types of infections. Studies have shown catheter-related infection rates, including those due to gram-negative bacilli, are occur more frequently in patients receiving a different intravenous prostanoid, treprostinil, which can be prepared in more pH neutral

Identified/potential Risk	**Sepsis, septicaemia (mostly related to delivery system for Flolan)**
	solvent as a result of its greater stability (Centers for Disease Control and Prevention 2007; Ivy et al. 2009, Kallen et al. 2008). A follow-up study has shown that infection rates are comparable to those for epoprostenol if the administered treprostinil solution is prepared with the alkaline diluents for epoprostenol (Rich et al. 2012).
Potential mechanisms	Flolan and Flolan solution prepared with pH 12 diluent Contamination of the central venous line or infusion solution with environmental or commensal microorganisms can result in line or blood-stream infections. Catheter-site or tunnel infections can occur as a result of inappropriate catheter care as well as invasion of damaged skin integrity.
Preventability	Flolan and Flolan solution prepared with pH 12 diluent Patients and the caregivers of patients receiving Flolan receive training on best practices for home-based medication preparation and administration. Published clinical guidelines for patients with PAH who are receiving chronic prostanoid infections have been developed (Doran et al. 2008) and individual PAH center have evaluated closed hub systems to further decrease the rate of infections (Akagi et al. 2007; Ivy et al. 2009). The SmPC specifies that therapy with Flolan requires significant commitment on the part of the patient.
Impact on individual patient	Flolan and Flolan solution prepared with pH 12 diluent The clinical consequences of a catheter-related infection are variable. Given the fragility of PAH patients, the haemodynamic derangements associated with sepsis may be poorly tolerated and result in death. In addition, some episodes of catheter-related infections could potentially eliminate the future use of that central line insertion site. As PAH patients who are receiving Flolan require continuous central venous access, loss of insertion sites could conceivably result in need for additional medical procedures to replace ventral access and in the most severe case, inability to continue to receive Flolan owing to lack of central venous access.
Potential public health impact of safety concern	Flolan and Flolan solution prepared with pH 12 diluent It is not anticipated that catheter-related infections would be associated with general public health issues, as these infections occur in patients with central venous catheters.

Identified/potential Risk	**Sepsis, septicaemia (mostly related to delivery system for Flolan)**
Evidence source	<u>Flolan and Flolan solution prepared with pH 12 diluent</u> Literature, GSK clinical trial data and spontaneous adverse event reports for epoprostenol in GSK Worldwide Clinical Safety Database
MedDRA terms	Bacteraemia, Bacterial infection, Bacterial sepsis, Blood culture positive, Catheter site cellulitis, Catheter site infection, Catheter site pustule, Corynebacterium sepsis, Device related infection, Device related sepsis, Enterobacter bacteraemia, Enterobacter infection, Fungal sepsis, Infusion site cellulitis, Infusion site infection, Injection site cellulitis, Injection site infection, Klebsiella infection, Micrococcal sepsis, Micrococcus infection, Pneumococcal infection, Pneumococcal sepsis, Pseudomonal sepsis, Sepsis, Sepsis syndrome, Septic shock, Serratia infection, Serratia sepsis, Staphylococcal bacteraemia, Staphylococcal infection, Staphylococcal sepsis, Streptococcal infection, Streptococcal sepsis

Identified/potential Risk	**Pulmonary oedema**
Frequency with 95 % CI	<u>Flolan</u> In controlled clinical trials for Flolan prepared with pH 10.5 diluent, a total of 3 patients with PAH (of 108 total study subjects receiving Flolan) developed pulmonary oedema, for an overall reporting rate of 2%, as compared to 1 subject with PAH who was receiving conventional therapy and developed pulmonary oedema (of 109 total study subjects receiving conventional therapy). During uncontrolled dose-ranging studies, there was one single event of pulmonary oedema, among 391 unique study subjects, for a reporting rate of 0.2%. <u>Flolan solution prepared with pH 12 diluent</u> There is one clinical study (Study FLR115332) that was conducted to evaluate use of Flolan reconstituted with pH 12 diluent in a small cohort of patients currently being treated with Flolan for PAH during which no new safety signals were identified. The frequency of pulmonary oedema is not expected to change as a result of introduction of pH 12 diluent.
Seriousness/outcomes	<u>Flolan</u> Of the clinical trial cases for Flolan prepared with pH 10.5 diluent, one case was reported as serious, but outcome data was otherwise not available. There are 75 reports of pulmonary oedema in patients receiving

Identified/potential Risk	**Pulmonary oedema**
	Flolan in the GSK Worldwide Clinical Safety Database as of 1 Sep 2014. Outcomes of the adverse event reports for pulmonary oedema included 51% fatal outcomes, 5% unresolved or worse, 24% resolved or improved and 20% unknown or not applicable, though it should be noted that the outcome was often considered to be due to underlying disease progression and may have in other cases been due to other events in the report not related to the pulmonary oedema. Review of the reports suggested that many of the cases were associated with events during dose-ranging, often in patients who were later found to have pulmonary veno-occlusive disease (PVOD), a known risk factor for development of pulmonary oedema during Flolan therapy that is addressed in the SmPC. <u>Flolan solution prepared with pH 12 diluent</u> The outcomes of this event are not expected to change as a result of introduction of pH 12 diluent.
Severity and nature of risk	<u>Flolan and Flolan solution prepared with pH 12 diluent</u> Acute pulmonary oedema may be immediately life-threatening requiring urgent intervention.
Background incidence/prevalence	<u>Flolan and Flolan solution prepared with pH 12 diluent</u> Because of their chronically elevated pulmonary arterial pressures, patients with PAH who are not receiving Flolan are likely at higher risk of developing pulmonary oedema than healthy people, as evidenced by the fact that pulmonary oedema was seen in 1 subject with PAH who was receiving conventional therapy (of 109 total conventional therapy subjects) in clinical trials for Flolan prepared with pH 10.5 diluent.
Risk groups or risk factors	<u>Flolan and Flolan solution prepared with pH 12 diluent</u> Pulmonary oedema may occur as a result of a variety of pathophysiologic mechanisms: (1) imbalance of Starling forces (e.g., increased pulmonary capillary pressure, decreased plasma oncotic pressure, increased negative interstitial pressure), (2) damage to the alveolar-capillary barrier, (3) lymphatic obstruction, and (4) idiopathic or unknown mechanism. Increased hydrostatic pressure leading to pulmonary oedema may result from many causes, including excessive intravascular volume administration, pulmonary venous outflow obstruction (e.g., mitral stenosis or left atrial myxoma), non-cardiogenic causes e.g., veno-occlusive disease, hyperkinetic states, e.g., thyrotoxicosis, or left ventricular failure secondary to systolic or diastolic dysfunction of the LV. Cardiogenic pulmonary oedema may lead to progressive deterioration of alveolar gas exchange and respiratory failure.

Identified/potential Risk	**Pulmonary oedema**
Potential mechanisms	Flolan and Flolan solution prepared with pH 12 diluent Pulmonary oedema refers to extravasation of fluid from the pulmonary vasculature into the interstitium and alveoli of the lung. PVOD is a condition in which small pulmonary veins become fibrotic leading to a fixed venous obstruction. When vasodilators such as epoprostenol are given, it is possible that dilation of the pulmonary arterioles may actually improve right ventricular output and lead to an increase in pulmonary artery pressure because outflow is obstructed, resulting in increased hydrostatic pressure and pulmonary oedema.
Preventability	Flolan and Flolan solution prepared with pH 12 diluent Initiation of Flolan should only be initiated and monitored by a physician experienced in the treatment of PAH, and should only occur in a hospital with adequate resuscitation equipment. In addition, dose ranging should begin with a low dose titrated upward slowly and cautiously. The SmPC for Flolan contains information in Sections 4.2, 4.3, 4.4 and 4.8 referencing the need for caution during dose initiation, and the risk associated with development of pulmonary oedema.
Impact on individual patient	Flolan and Flolan solution prepared with pH 12 diluent In patients who develop pulmonary oedema during dose-ranging, Flolan must not be used chronically. According to the ESC/ERS guidelines (Galie et al. 2009), epoprostenol is is conditionally suggested with caution for carefully selected patients with other types including Group 1' which includes PVOD and pulmonary capillary Hemangiomatosis (PCH). (Montani et al. 2009 and Ogawa et al. 2012) published small case series with a combined total of 20 patients with either PVOD or PCH who were successfully treated with epoprostenol as bridge to transplantation when possible or as long-term therapy in those patients for whom transplantation was not possible. In both reports, the authors stressed the need for cautious use, but that the medication was associated with some clinical and/or haemodynamic improvement and could represent a potential option in carefully treated patients.
Potential public health impact of safety concern	Flolan and Flolan solution prepared with pH 12 diluent It is not anticipated that pulmonary oedema seen in association with Flolan administration would be associated with any impact on public health.
Evidence source	Literature, GSK clinical trial data and spontaneous adverse event reports for epoprostenol in GSK Worldwide Clinical Safety Database

Identified/potential Risk	**Pulmonary oedema**
MedDRA terms	Acute pulmonary oedema, Pulmonary oedema, Pulmonary veno-occlusive disease

Identified/potential Risk	**Hypotension**
Frequency with 95 % CI	Flolan The frequency of hypotension in patients receiving Flolan is between 1% and 10% based on findings from subjects in clinical trials for Flolan prepared with pH 10.5 diluent for PAH, as described in the SmPC for Flolan. Hypotension is considered to be a dose-related response that can be managed via cautious and careful dose titration and avoidance of abrupt dose increases. Flolan solution prepared with pH 12 diluent The frequency of this event is not expected to change as a result of introduction of pH 12 diluent.
Seriousness/outcomes	Flolan There are 204 reports of hypotension in patients receiving Flolan prepared with pH 10.5 diluent in the GSK Worldwide Clinical Safety Database as of 1 Sep 2014. Outcomes of the adverse event reports for hypotension included 51% fatal outcomes, 6% unresolved or worse, 23% resolved or improved and 20% unknown or not applicable, though it should be noted that the outcome was often considered to be due to underlying disease progression or concurrent complications such as sepsis. Flolan solution prepared with pH 12 diluent The outcomes of this event are not expected to change as a result of introduction of pH 12 diluent.
Severity and nature of risk	Flolan and Flolan solution prepared with pH 12 diluent If excessive hypotension occurs during administration of Flolan, the dose should be reduced or the infusion discontinued. Hypotension may be profound in overdose and may result in loss of consciousness. Patients with PAH may be unable to compensate for significant systemic vasodilation because of impaired cardiac output, thereby leading to haemodynamic collapse.
Background incidence/prevalence	Flolan and Flolan solution prepared with pH 12 diluent Because of their decreased cardiac output, patients with PAH who are not receiving Flolan may be somewhat more likely to have low

Identified/potential Risk	**Hypotension**
	baseline blood pressures, as evidenced by the fact that hypotension was seen in 17 of 109 subjects with PAH who were receiving conventional therapy, as compared to 21 of 108 subjects who were receiving Flolan.
Risk groups or risk factors	<u>Flolan and Flolan solution prepared with pH 12 diluent</u> Because epoprostenol is a vasodilator, hypotension is somewhat dose related, and is therefore more likely to occur with higher doses, particularly overdoses. Other conditions that contributes to decreased intravascular volume (e.g. dehydration) or additional vasodilation (e.g. use of other vasodilators, sepsis) likely can contribute to epoprostenol-associated hypotension.
Potential mechanisms	<u>Flolan and Flolan solution prepared with pH 12 diluent</u> Flolan is a potent but short-lived pulmonary and systemic vasodilator. Hypotension owing to systemic vasodilation can be considered to be an expected consequence of epoprostenol administration, particularly in the case of rapid dose increases or overdose.
Preventability	<u>Flolan and Flolan solution prepared with pH 12 diluent</u> Initiation of Flolan should only be initiated and monitored by a physician experienced in the treatment of PAH, and should only occur in a hospital with adequate resuscitation equipment. In addition, dose ranging should begin with a low dose titrated upward slowly and cautiously. If excessive hypotension occurs during administration of Flolan, the dose should be reduced or the infusion discontinued. Blood pressure and heart rate should be monitored during administration of Flolan. The vasodilator effects of Flolan may augment or be augmented by concomitant use of other vasodilators. For renal dialysis, the recommended dose is 4 ng/kg/min which the SmPC specifies should not be exceeded unless patient blood pressure is closely monitored. In addition, the possibility of additive effects on blood pressure decreases associated with acetate buffer in the dialysis bath are described, so that dialysis materials can be chosen appropriately. The SmPC for Flolan contains information in Sections 4.2, 4.4, 4.5 and 4.8 referencing the need for careful monitoring of vital signs during dosing, and the additive risks associated with use of other vasodilators.
Impact on individual patient	<u>Flolan and Flolan solution prepared with pH 12 diluent</u> The clinical consequences of hypotension are variable. Given the fragility of PAH patients, the haemodynamic derangements

Identified/potential Risk	**Hypotension**
	associated with severe hypotension may be poorly tolerated. Mild hypotension may limit physical activity, but as the symptoms of undertreated PAH are similar, the net impact of epoprostenol on individual patients' clinical condition is generally considered to be neutral.
Potential public health impact of safety concern	<u>Flolan and Flolan solution prepared with pH 12 diluent</u> It is not anticipated that hypotension seen in association with Flolan administration would be associated with any impact on public health.
Evidence source	GSK clinical trial data and spontaneous adverse event reports for epoprostenol in GSK Worldwide Clinical Safety Database
MedDRA terms	Hypotension

Identified/potential Risk	**Bleeding events at various sites**
Frequency with 95 % CI	<u>Flolan</u> The frequency of bleeding in patients receiving Flolan is between 1% and 10%, as described in the SmPC for Flolan. In clinical trials for Flolan prepared with pH 10.5 diluent, epistaxis was seen in 5 of 109 subjects with PAH who were receiving conventional therapy, as compared to 7 of 108 subjects who were receiving Flolan. Haemoptysis was seen in 3 of 109 subjects with PAH who were receiving conventional therapy, as compared to 1 of 108 subjects who were receiving Flolan prepared with pH 10.5 diluent. Hemorrhage (including various sites) was seen in 8 of 109 subjects with PAH who were receiving conventional therapy, as compared to 17 of 108 subjects who were receiving Flolan prepared with pH 10.5 diluent. Ecchymoses or petechiae were seen in 2 of 109 subjects with PAH who were receiving conventional therapy, as compared to 2 of 108 subjects who were receiving Flolan prepared with pH 10.5 diluent. Hematuria was seen in 0 of 109 subjects with PAH who were receiving conventional therapy, as compared to 3 of 108 subjects who were receiving Flolan prepared with pH 10.5 diluent. <u>Flolan solution prepared with pH 12 diluent</u> The frequency of this event is not expected to change as a result of introduction of pH 12 diluent.
Seriousness/outcomes	<u>Flolan</u> There are 477 reports of bleeding events in patients receiving Flolan prepared with pH 10.5 diluent in the GSK Worldwide

Identified/potential Risk	**Bleeding events at various sites**
	Clinical Safety Database as of 1 Sep 2014. Outcomes of the adverse event reports for bleeding events included 36% fatal outcomes, 15% unresolved, worse or resolved with sequelae, 24% resolved or improved and 25% unknown, though it should be noted that the outcome may have been due to other events in the report not related to the bleeding event. Broken down by location of bleeding, there were 118 reports involving the pulmonary system, 73 involving the gastrointestinal system, 49 during or after procedures or accidents, 36 of epistaxis, 27 involving the central nervous system, 10 involving the genitourinary system, 5 involving the eye and 4 involving the renal system. The remaining reports were either included multiple bleeding sites or multiple different episodes of bleeding, other sites, did not specify sites and were not consistent with bleeding episodes. Proportions of reports associated with fatal outcomes were highest in reports describing CNS (55%) and pulmonary hemorrhages (47%). <u>Flolan solution prepared with pH 12 diluent</u> The outcomes of this event are not expected to change as a result of introduction of pH 12 diluent.
Severity and nature of risk	<u>Flolan and Flolan solution prepared with pH 12 diluent</u> Excessive bleeding can lead to anaemia and diminished oxygen delivery to tissues and in extreme cases, to hypovolemic shock. As PAH patients have impaired haemodynamic compensatory mechanisms, they may be less able to recover.
Background incidence/prevalence	<u>Flolan and Flolan solution prepared with pH 12 diluent</u> Epoprostenol is a potent inhibitor of platelet aggregation. In general, most bleeding manifestations were more common in clinical trial subjects with PAH who were receiving Flolan prepared with pH 10.5 diluent as compared to conventional therapy. In general, patients with PAH should not have an increased propensity for bleeding. However, haemoptysis occurred in 3 of 109 subjects receiving conventional therapy, as compared to 1 of 108 receiving perhaps as a manifestation of increased pulmonary pressures in these subjects.
Risk groups or risk factors	<u>Flolan and Flolan solution prepared with pH 12 diluent</u> Patients with PAH are commonly receiving anticoagulation and so may be have iatrogenically increased risk of bleeding, apart from the contribution of epoprostenol. Among the spontaneous reports for bleeding events in patients receiving Flolan (prepared with pH 10.5 diluent) in the GSK Worldwide Clinical Safety Database, 46% of reports described concurrent use of an anticoagulant in addition

Identified/potential Risk	**Bleeding events at various sites**
	to Flolan, 29% described concurrent use of another PAH medication with increased bleeding risk, 8% described concurrent use of NSAIDs and 6% described concurrent use of another medication with increased bleeding risk, such as selective serontonin reuptake inhibitors. In addition, certain types of pulmonary hypertension may arise from or result in hepatic damage, which can also predispose to bleeding diastheses.
Potential mechanisms	<u>Flolan and Flolan solution prepared with pH 12 diluent</u> Flolan is not a conventional anticoagulant but is a potent inhibitor of platelet aggregation. Flolan has been successfully used instead of heparin in renal dialysis. The effects of epoprostenol on platelet aggregation is dose-related when between 2 and 16 nanograms/kg/min is administered intravenously, and significant inhibition of aggregation induced by adenosine diphosphate is observed at doses of 4 nanograms/kg/min and above. Higher circulating doses of epoprostenol (20 nanograms/kg/min) disperse circulating platelet aggregates and increase by up to two fold the cutaneous bleeding time. Epoprostenol potentiates the anticoagulant activity of heparin by approximately 50%, possibly reducing the release of heparin neutralising factor.
Preventability	<u>Flolan and Flolan solution prepared with pH 12 diluent</u> Flolan is a potent inhibitor of platelet aggregation, therefore, an increased risk for haemorrhagic complications should be considered, particularly for patients with other risk factors for bleeding. When NSAIDS or other drugs affecting platelet aggregation are used concomitantly, there is the potential for Flolan to increase the risk of bleeding. The SmPC for Flolan contains information in Sections 4.4, 4.5 and 4.8 referencing the risk of bleeding events, particularly when used in combination with other medications with antiplatelet activity.
Impact on individual patient	<u>Flolan and Flolan solution prepared with pH 12 diluent</u> The clinical consequences of bleeding are variable, depending on the site, rate and total volume of blood loss. Given the fragility of PAH patients, the haemodynamic derangements associated with acute blood loss may be poorly tolerated.
Potential public health impact of safety concern	<u>Flolan and Flolan solution prepared with pH 12 diluent</u> It is not anticipated that bleeding seen in association with Flolan administration would be associated with any impact on public health.

Identified/potential Risk	**Bleeding events at various sites**
Evidence source	GSK clinical trial data and spontaneous adverse event reports for epoprostenol in GSK Worldwide Clinical Safety Database
MedDRA terms	GSK Standardized MedDRA Query Hemorrhage (broad)

Identified/potential Risk	**Tachycardia**
Frequency with 95 % CI	Flolan Tachycardia occurs commonly in patients receiving Flolan, as described in the SmPC for Flolan. In clinical trials for Flolan prepared with pH 10.5 diluent, tachycardia was seen in 36 of 109 subjects with PAH who were receiving conventional therapy, as compared to 42 of 108 subjects who were receiving Flolan. Flolan solution prepared with pH 12 diluent The frequency of this event is not expected to change as a result of introduction of pH 12 diluent.
Seriousness/outcomes	Flolan There are 49 reports of tachycardia in patients receiving Flolan (prepared with pH 10.5 diluent) in the GSK Worldwide Clinical Safety Database as of 1 Sep 2014. Outcomes of the adverse event reports for tachycardia included 23% fatal outcomes, 2% unresolved, 45% resolved or improved and 30% unknown, though it should be noted that the outcome may have been due to other events in the report not related to the tachycardia. On review, many of the fatal events in which tachycardia was reported, the tachycardia was much more likely related to disease progression, underlying infection or other haemodynamic derangement than to epoprostenol. Flolan solution prepared with pH 12 diluent The outcomes of this event are not expected to change as a result of introduction of pH 12 diluent.
Severity and nature of risk	Flolan and Flolan solution prepared with pH 12 diluent Owing to decreased cardiac output and decreased haemodynamic compensatory reserve, tachycardia may not be well-tolerated in PAH patients.
Background incidence/prevalence	Flolan and Flolan solution prepared with pH 12 diluent Because of their decreased cardiac output, patients with PAH who are not receiving Flolan may be somewhat more likely to have

Identified/potential Risk	**Tachycardia**
	tachycardia, as evidenced by the fact that tachycardia was seen in 36 of 109 subjects with PAH who were receiving conventional therapy, as compared to 42 of 108 subjects who were receiving Flolan prepared with pH 10.5 diluent.
Risk groups or risk factors	<u>Flolan and Flolan solution prepared with pH 12 diluent</u> As described in the SmPC, tachycardia has been reported as a response to low dose Flolan. In the adverse events in the GSK Worldwide Clinical Safety Database, there were a number of reports of tachycardia, generally associated with concurrent events of flushing, from clinical trials in healthy volunteers as well as patients with angina or TTP, who were receiving doses of between 2 and 12 ng/kg/min. The combination of flushing and tachycardia suggests a compensatory tachycardia in response to systemic vasodilation.
Potential mechanisms	<u>Flolan and Flolan solution prepared with pH 12 diluent</u> Flolan is a potent vasodilator. Following an effective increase in circulatory volume as a result of generalized vasodilation, tachycardia is the initial compensatory response.
Preventability	<u>Flolan and Flolan solution prepared with pH 12 diluent</u> Initiation of Flolan should only be initiated and monitored by a physician experienced in the treatment of PAH, and should only occur in a hospital with adequate resuscitation equipment. In addition, dose ranging should begin with a low dose titrated upward slowly and cautiously. Blood pressure and heart rate should be monitored during administration of Flolan. The SmPC for Flolan contains information in Sections 4.2, 4.4 and 4.8 describing the risk of tachycardia and the need for close monitoring of vital signs during initiation and dose adjustments.
Impact on individual patient	<u>Flolan and Flolan solution prepared with pH 12 diluent</u> The clinical consequences of tachycardia are variable. Given the fragility of PAH patients, the haemodynamic derangements associated with tachycardia may be poorly tolerated, though given the ability to titrate the dose individually allows the balancing of adverse reactions and disease symptoms, the net impact of epoprostenol on individual patients' clinical condition is generally considered to be neutral.
Potential public health impact of safety concern	<u>Flolan and Flolan solution prepared with pH 12 diluent</u> It is not anticipated that tachycardia seen in association with Flolan administration would be associated with any impact on

Identified/potential Risk	**Tachycardia**
	public health.
Evidence source	<u>Flolan and Flolan solution prepared with pH 12 diluent</u> GSK clinical trial data and spontaneous adverse event reports for epoprostenol in GSK Worldwide Clinical Safety Database
MedDRA terms	Sinus tachycardia, Tachycardia

Identified/potential Risk	**Bradycardia**
Frequency with 95 % CI	<u>Flolan</u> Bradycardia occurs commonly in patients receiving Flolan, as described in the SmPC for Flolan. In clinical trials, tachycardia was seen in 6 of 109 subjects with PAH who were receiving conventional therapy, as compared to 9 of 108 subjects who were receiving Flolan prepared with pH 10.5 diluent. <u>Flolan solution prepared with pH 12 diluent</u> The frequency of this event is not expected to change as a result of introduction of pH 12 diluent.
Seriousness/outcomes	<u>Flolan</u> There are 53 reports of bradycardia in patients receiving Flolan (prepared with pH 10.5 diluent) in the GSK Worldwide Clinical Safety Database as of 1 Sep 2014. Outcomes of the adverse event reports for tachycardia included 73% fatal outcomes, 19% unresolved, 4% resolved or improved and 4% unknown, though it should be noted that the outcome may have been due to other events in the report not related to the bradycardia. On review, many of the fatal events in which bradycardia was reported, the bradycardia was much more likely related to disease progression, underlying infection or other haemodynamic derangement than to epoprostenol. <u>Flolan solution prepared with pH 12 diluent</u> The outcomes of this event are not expected to change as a result of introduction of pH 12 diluent.
Severity and nature of risk	<u>Flolan and Flolan solution prepared with pH 12 diluent</u> Owing to decreased cardiac output and decreased haemodynamic compensatory reserve, bradycardia may not be well-tolerated in PAH patients.

Identified/potential Risk	**Bradycardia**
Background incidence/prevalence	<u>Flolan and Flolan solution prepared with pH 12 diluent</u> Because of their decreased cardiac output, patients with PAH who are not receiving Flolan may be somewhat more likely to have bradycardia than do people without PAH, as evidenced by the fact that bradycardia was seen in 6 of 109 subjects with PAH who were receiving conventional therapy, as compared to 9 of 108 subjects who were receiving Flolan prepared with pH 10.5 diluent.
Risk groups or risk factors	<u>Flolan and Flolan solution prepared with pH 12 diluent</u> As described in the SmPC, bradycardia, sometimes in association with orthostatic hypotension, has been reported as a response to somewhat higher doses of Flolan when administered to healthy volunteers, suggesting the possibility of a vagal response. In the adverse events in the GSK Worldwide Clinical Safety Database, the doses associated with bradycardia in healthy volunteers seemed to be higher than the doses administered to patients (when reported) who experienced events of bradycardia. However, many of the events in patients were bradycardia occurred in the setting of complex medical complications (e.g. seizure, aspiration, cardiogenic shock), therefore there is not sufficient evidence for a causal relationship with epoprostenol alone.
Potential mechanisms	<u>Flolan and Flolan solution prepared with pH 12 diluent</u> Flolan is a potent vasodilator. Given the combination of orthostatic hypotension and bradycardia seen with higher dose infusion in healthy volunteers, a vagal reaction cannot be excluded as a potential aetiology.
Preventability	<u>Flolan and Flolan solution prepared with pH 12 diluent</u> Initiation of Flolan should only be initiated and monitored by a physician experienced in the treatment of PAH, and should only occur in a hospital with adequate resuscitation equipment. In addition, dose ranging should begin with a low dose titrated upward slowly and cautiously. Blood pressure and heart rate should be monitored during administration of Flolan. The SmPC for Flolan contains information in Sections 4.2, 4.4 and 4.8 describing the risk of bradycardia and the need for close monitoring of vital signs during initiation and dose adjustments.
Impact on individual patient	<u>Flolan and Flolan solution prepared with pH 12 diluent</u> The clinical consequences of bradycardia are variable. Given the fragility of PAH patients, the haemodynamic derangements associated with bradycardia may be poorly tolerated, though given the ability to titrate the dose individually allows the balancing of

Identified/potential Risk	Bradycardia
	adverse reactions and disease symptoms, the net impact of epoprostenol on individual patients' clinical condition is generally considered to be neutral.
Potential public health impact of safety concern	Flolan and Flolan solution prepared with pH 12 diluent It is not anticipated that bradycardia seen in association with Flolan administration would be associated with any impact on public health.
Evidence source	GSK clinical trial data and spontaneous adverse event reports for epoprostenol in GSK Worldwide Clinical Safety Database
MedDRA terms	Bradycardia, Sinus bradycardia

SVII.4 Identified and potential interactions

SVII.4.1 Overview of potential for interactions

Flolan is a potent vasodilator and anti-platelet agent, therefore additive effects with use of other vasodilators and anti-platelet agents may be expected, as described in the SmPC.

SVII.4.2 Important identified and potential interactions

As the proposed change is limited only to the diluent for Flolan with the active part of the formulation, epoprostenol, remaining unchanged, no impact on the pharmacodynamic actions of Flolan is anticipated, and the clinical profile of Flolan prepared with pH 12 diluent is expected to be the same as that of Flolan prepared with pH 10.5 diluent. Interactions that are currently described within the SmPC generally arise from additive effects from the vasodilator and anti-platelet activities of epoprostenol.

Table 33 Important identified and potential interactions

Interacting substance(s)	Anticoagulants
Effect of interaction	When Flolan is administered to patients receiving concomitant anticoagulants standard anticoagulant monitoring is advisable.
Evidence source	Published literature (Galie et al., 2009; Fuster et al., 1984; Rich et al., 1992)
Possible mechanisms	As epoprostenol is a potent inhibitor of platelet aggregation, an increased risk for haemorrhagic complications should be considered, particularly for patients with other risk factors for bleeding.

Interacting substance(s)	Anticoagulants
Potential health risk	Excessive bleeding can lead to anaemia and diminished oxygen delivery to tissues and in extreme cases, to hypovolemic shock. As PAH patients have impaired haemodynamic compensatory mechanisms, they may be less able to recover.
Discussion	There is a limited amount of data to support oral anticoagulation in patients with PAH, primarily for the indications of idiopathic and heritable PAH. A high prevalence of vascular thrombotic lesions has been reported in patients with idiopathic PAH. Finally, patients receiving epoprostenol have risk factors for venous thromboembolism, including the presence of a central venous catheter, heart failure and limited mobility.

Interacting substance(s)	Vasodilators
Effect of interaction	The vasodilator effects of Flolan may augment or be augmented by concomitant use of other vasodilators.
Evidence source	Clinical overview (Module 2.5 of 2011 submission for Article 30)
Possible mechanisms	Concurrent use of epoprostenol and other vasodilators could accentuate the frequency or severity of hypotension, headache and tachycardia.
Potential health risk	Flolan is a potent pulmonary and systemic vasodilator. Hypotension may be profound in overdose and may result in loss of consciousness. If excessive hypotension occurs during administration of Flolan, the dose should be reduced or the infusion discontinued.
Discussion	Of the more commonly reported adverse events in patients receiving epoprostenol, the following adverse reactions tended to be more frequent in patients receiving concurrent vasodilators that those not receiving concurrent vasodilators: chest pain, palpitation, arrhythmia, tachycardia, jaw pain, myalgia, cough, arthralgia, hypotension, and heart failure. It is not possible to determine whether an epoprostenol-oral vasodilator interaction

Interacting substance(s)	Vasodilators
	was the cause of the increased incidence of an adverse event, whether the vasodilator was prescribed in part due to the adverse event, or whether there was no relation. Complicating the analysis was the use of multiple medications by patients, and the occurrence of adverse events known to be related to concomitant medications such as cough with captopril, edema with nifedipine, headache with nitrates, cardiac conduction disturbances with diltiazem and verapamil, tachycardia with hydralazine and worsening heart failure with verapamil.

Interacting substance(s)	Tissue plasminogen activator (t-PA)
Effect of interaction	As reported with other prostaglandin analogues, Flolan may reduce the thrombolytic efficacy of tissue plasminogen activator (t-PA) by increasing hepatic clearance of t-PA.
Evidence source	Published literature (Topol et al., 1989)
Possible mechanisms	The precise mechanism for this interaction is not known, but may occur as a result of an increase in hepatic blood flow potentially resulting in accelerated clearance of t-PA.
Potential health risk	t-PA is used for thrombolysis in the setting of acute ischaemic stroke, myocardial infarction, and pulmonary embolism, as well as for unblocking central venous catheters that are occluded by thrombus, resulting in the possibility that thrombolysis may take more difficult to achieve.
Discussion	In a study of 50 patients with acute myocardial infarction, 11 of 25 (40%) who received combined therapy with iloprost and t-PA were found to have patent infarct-related blood vessels, as compared to 15 of 25 (60%) who received t-PA alone. Less degradation of hemostatic proteins by t-PA and iloprost was noted, suggesting the possibility of lower levels of t-PA.

Interacting substance(s)	NSAIDS or other drugs affecting platelet aggregation
Effect of interaction	When NSAIDS or other drugs affecting platelet aggregation are used concomitantly, there is the potential for Flolan to increase the risk of bleeding.
Evidence source	Published literature (Rudd et al., 1990)
Possible mechanisms	The mechanism by which antiplatelet prostaglandins modulate the effect of plasmin on platelet function is not completely understood, though it may reflect increased clearance of mediators as a result of vasodilation.
Potential health risk	Excessive bleeding can lead to anaemia and diminished oxygen delivery to tissues and in extreme cases, to hypovolemic shock. As PAH patients have impaired haemodynamic compensatory mechanisms, they may be less able to recover.
Discussion	Measurement of *ex vivo* platelet aggregation following infusion of t-PA in rabbits yielded a biphasic response, in which platelet aggregation was initially enhanced and then reduced. Co-infusion of antiplatelet prostaglandins, including epoprostenol, abolished the initial hyperaggregable phase that was seen with t-PA infusion alone and extended the hypoaggregable phase, as this hypoaggregable phase occurred earlier and persisted following the completion of the infusion. Plasma plasmin activity increased with t-PA infusion alone, but this increased was blunted with co-infusion of prostaglandin. The dose of prostaglandin used alone did not appreciably alter platelet function. The effects of thrombolytic agents on platelet function are complex and can be modulated by antiplatelet prostaglandins.

Interacting substance(s)	Digoxin
Effect of interaction	Patients on digoxin may show elevations of digoxin concentrations after initiation of therapy with Flolan, which although transient, may be clinically significant in patients prone to digoxin toxicity.
Evidence source	Clinical trial (THRS/94/0016)

Interacting substance(s)	Digoxin
Possible mechanisms	May be due to decreased systemic clearance, increased bioavailability, or some combination, but cannot be determined from available data.
Potential health risk	Consequences of digoxin toxicity can include a variety of ECG changes and cardiac arrhythmias, some potentially serious, as well as gastrointestinal symptoms such as anorexia, nausea and vomiting, dizziness, central nervous system disturbances, fatigue, malaise and visual disturbances.
Discussion	The effect of epoprostenol on digoxin pharmacokinetics was a secondary objective of the pilot epoprostenol trial. Plasma digoxin concentrations were determined from 278 blood samples collected from 30 severe, refractory congestive heart failure patients receiving conventional therapy alone or conventional therapy plus epoprostenol. Blood samples were collected on study day 1 (baseline) and on days 3 and 87 (of the 12 week treatment phase). Multivariate analysis predicted a 15% decrease in apparent oral clearance of digoxin on study day 3 for epoprostenol patients, but essentially no difference can be observed comparing study day 1 (baseline) and study day 87 in the patients studied. Simulations based on this pilot study revealed that the interaction is probably not significant in most patients. Clinicians should, however, be aware of the potential for short-term elevations of digoxin concentrations (high trough concentrations) after acute epoprostenol therapy in patients, especially patients prone to digoxin toxicity.

SVII.5 Pharmacological class effects

Epoprostenol is a potent vasodilator as well as possessing significant anti-platelet activity.

SVII.5.1 Pharmacological class risks already included as important identified or potential risks

Table 34 Pharmacological class risks already included as important identified or potential risks

Risk	Frequency in clinical trials of medicinal product	Frequency seen with other products in same pharmacological class (source of data/journal reference)	Comment
Hypotension	Between 1 and 10%	Iloprost (inhaled) - between 1 and 10% Treprostinil (subcutaneous) – between 1 and 10%	Data for inhaled iloprost is taken from the VENTAVIS UK SmPC. Data for subcutaneous treprostinil is taken from the REMODULIN USPI.
Hemorrhage or bleeding events	Between 1 and 10%	Iloprost (inhaled) - >10% Treprostinil (subcutaneous) – site bruising and bleeding noted but not quantified	

SVII.5.2 Important pharmacological class effects not discussed above

None applicable.

Table 35 Other important pharmacological class effects

Potential Risk	
Seriousness/outcomes	Not applicable
Severity and nature of risk	
Frequency with other members of the same or similar pharmacological class with 95 % CI	
Risk groups or risk factors	
Potential mechanisms	
Comment	

PART II: MODULE SVIII - SUMMARY OF THE SAFETY CONCERNS

Table 36 Summary of Safety Concerns

Summary of safety concerns	
Important identified risks	Medication errors* Sepsis, septicaemia (mostly related to delivery system for Flolan) Pulmonary oedema Hypotension Bleeding events at various sites Tachycardia Bradycardia
Important potential risks	Local infusion site reactions during long-term infusion**
Missing information	Use in paediatric patients Use in patients over 65 years Use in pregnant and lactating women

*This safety concern may be more likely to occur during the transition from pH 10.5 diluent to pH 12 diluent.
**This safety concern may be more likely to occur with use of Flolan solution prepared with pH12 diluent.

PART III: PHARMACOVIGILANCE PLAN

III.1 Safety concerns and overview of planned pharmacovigilance actions

Table 37 Safety concerns and overview of planned pharmacovigilance actions

Safety concern: MEDICATION ERRORS (particularly those associated with pH 12 diluent or confusion between diluents during transition period)		
Areas requiring confirmation or further investigation	Proposed routine and additional PhV activities	Objectives
None	Routine PV (Configuration changes to the GSK safety database and revision of adverse event data collection forms, where available, will be made to allow diluent formulation to be captured in spontaneous adverse event reports during the transition period.)	To collect information on circumstances surrounding any adverse events consistent with medication errors, including specific formulation of diluent in use at the time

Safety concern: LOCAL INFUSION SITE REACTIONS DURING LONG-TERM INFUSION (associated with pH 12 diluent)		
Areas requiring confirmation or further investigation	Proposed routine and additional PhV activities	Objectives
None	Routine PV (Configuration changes to the GSK safety database and revision of adverse event data collection forms, where available, will be made to allow diluent formulation to be captured in spontaneous adverse event reports during the transition period.)	To collect information on circumstances surrounding any adverse events consistent with local or infusion site reactions, including vascular reactions, including specific formulation of diluent in use at the time of the event

Safety concern: SEPSIS AND SEPTICAEMIA (MOSTLY RELATED TO DELIVERY SYSTEM FOR FLOLAN)		
Areas requiring confirmation or further investigation	Proposed routine and additional PhV activities	Objectives
None	Routine PV	To collect information on circumstances surrounding adverse events consistent with catheter-related infections.

Safety concern: PULMONARY OEDEMA		
Areas requiring confirmation or further investigation	Proposed routine and additional PhV activities	Objectives
None	Routine PV	To collect information on circumstances surrounding adverse events consistent with pulmonary oedema.

Safety concern: HYPOTENSION		
Areas requiring confirmation or further investigation	Proposed routine and additional PhV activities	Objectives
None	Routine PV	To collect information on circumstances surrounding adverse events consistent with hypotension.

Safety concern: BLEEDING EVENTS AT VARIOUS SITES		
Areas requiring confirmation or further investigation	Proposed routine and additional PhV activities	Objectives
None	Routine PV	To collect information on circumstances surrounding adverse events consistent with bleeding events.

Safety concern: TACHYCARDIA		
Areas requiring confirmation or further investigation	Proposed routine and additional PhV activities	Objectives
None	Routine PV	To collect information on circumstances surrounding adverse events consistent with tachycardia.

Safety concern: BRADYCARDIA		
Areas requiring confirmation or further investigation	Proposed routine and additional PhV activities	Objectives
None	Routine PV	To collect information on circumstances surrounding adverse events consistent with bradycardia.

Safety concern: USE IN PEDIATRIC PATIENTS		
Areas requiring confirmation or further investigation	Proposed routine and additional PhV activities	Objectives
To monitor for adverse events associated with off-label use of epoprostenol in adolescents and children	Routine PV in accordance with GSK's regular and pro-active process for identifying and monitoring safety signals	To characterise the use and safety profile of epoprostenol in children and adolescents. Use of Flolan in paediatric patients is off-label, and as such is an area of interest to be discussed in periodic reports in the event that any safety concerns are identified. Routine PV is intended to collect available data from published literature as well as individual and aggregate spontaneous reports to identify potential areas of concern in specific patient populations, including children.

Safety concern: USE IN PATIENTS OVER 65 YEARS		
Areas requiring confirmation or further investigation	Proposed routine and additional PhV activities	Objectives
To monitor for adverse events associated with use of epoprostenol in patients over 65	Routine PV in accordance with GSK's regular and pro-active process for identifying and	To characterise the use and safety profile of epoprostenol in patients over 65 years. Use of

Safety concern: USE IN PATIENTS OVER 65 YEARS		
years	monitoring safety signals	Flolan in patients over 65 years of age is an area of interest to be discussed in periodic reports in the event that any safety concerns are identified. Routine PV is intended to collect available data from published literature as well as individual and aggregate spontaneous reports to identify potential areas of concern in specific patient populations, including patients over 65 years of age.

Safety concern: USE IN PREGNANT AND LACTATING WOMEN		
Areas requiring confirmation or further investigation	Proposed routine and additional PhV activities	Objectives
To monitor for adverse events associated with use of epoprostenol in pregnant or lactating women	Routine PV in accordance with GSK's regular and pro-active process for identifying and monitoring safety signals	To characterise the use and safety profile of epoprostenol in pregnant or lactating women. Use of Flolan in pregnant or lactating women is an area of interest to be discussed in periodic reports in the event that any safety concerns are identified. Routine PV is intended to collect available data from published literature as well as individual and aggregate spontaneous reports to identify potential areas of concern in specific patient populations, including pregnant or lactating women.

III.2 Additional pharmacovigilance activities to assess effectiveness of risk minimisation measures

Table 38 Additional PV activities to assess the effectiveness of risk minimisation measures

Risk minimisation measure:)		
Component measured	**Activity(ies)**	**Rationale**
None		

III.3 Studies and other activities completed since last update of Pharmacovigilance Plan

Not applicable.

Table 39 Studies and other activities completed since last update of Pharmacovigilance Plan

Study/activity title	
Safety concern(s)/risk minimisation measure investigated	
Brief summary of results	
Implications	

III.4 Details of outstanding additional pharmacovigilance activities

There are no outstanding additional proposed PV activities.

III.4.1 Imposed mandatory additional pharmacovigilance activity (key to benefit risk)

Table 40 Imposed Activities considered Key to the Benefit Risk of the Product

	Description of activity (or study title if known)	Milestone(s)	Due Date(s)
None			

III.4.2 Mandatory additional Phamacovigilance Activity (being a Specific Obligation)

Table 41 Specific Obligations

	Description of activity (or study title if known)	Milestone(s)	Due Date(s)
None			

Non-interventional studies included in categories 1 and 2 are subject to the supervision exercised under Articles 107 (m)-(q) of Directive 2001/83.

III.4.3 Required additional pharmacovigilance activities to address specific safety concerns or to measure effectiveness of risk minimisation measures

Table 42 Required Additional Pharmacovigilance Activities

	Description of activity (or study title if known)	Milestone(s)	Due Date(s)
None			

III.4.4 Stated additional pharmacovigilance activities

Table 43 Stated Additional Pharmacovigilance Activities

	Description of activity (or study title if known)	Expected date of report
None		

III.5 Summary of the Pharmacovigilance Plan

III.5.1 On-going and planned additional PhV studies/activities in the Pharmacovigilance Plan

Table 44 Table of on-going and planned additional PhV studies/activities in the Pharmacovigilance Plan

Study/activity Type, title and category (1-3)	Objectives	Safety concerns addressed	Status (planned, started)	Date for submission of interim or final reports (planned or actual)
None				

III.5.2 Completed studies/activities from the Pharmacovigilance Plan

Table 45 Completed studies/activities from the Pharmacovigilance Plan

Study/activity Type, title and category (1-3)	Objectives	Safety concerns addressed	Status (planned, started)	Date for submission of interim or final reports (planned or actual)
None				

PART IV: PLANS FOR POST-AUTHORISATION EFFICACY STUDIES

IV.1 Applicability of efficacy to all patients in the target population

GSK has reformulated the diluent for Flolan by increasing the target pH of the diluent from 10.5 to 12, as epoprostenol is more stable in a higher pH solution. No change has been made to the vial that contains the lyophilised epoprostenol. As the change was limited only to the diluent with the active part of the formulation remaining intact, no impact on the pharmacodynamic actions of Flolan is anticipated, and the clinical profile of Flolan prepared with pH 12 diluent is expected to be the same as that of Flolan prepared with pH 10.5 diluent, therefore no post-authorisation efficacy studies are planned.

IV.2 Tables of post-authorisation efficacy studies

Table 46 Efficacy Studies Which are Specific Obligations and/or Conditions of the MA

Description of study (including objectives and study number)	Milestone(s)	Due Date(s)
None		

Table 47 Other Efficacy/Effectiveness Studies

Description of study (including objectives and study number)	Milestone(s)	Due Date(s)
None		

IV.3 Summary of Post authorisation efficacy development plan

Table 48 Summary of Post authorisation efficacy development plan

Study (type and study number)	Objectives	Efficacy uncertainties addressed	Status (planned, started)	Date for submission of interim or final reports
Not applicable				

IV.4 Summary of completed Post authorisation efficacy studies

Study (type and study number)	Objectives	Efficacy uncertainties addressed	Status (Completed, Study report submitted)	Date of submission of final study report
Not applicable				

PART V: RISK MINIMISATION MEASURES

V.1 Risk minimisation measures by safety concern

Table 49 Risk minimisation measures by safety concern

Safety concern	Medication errors (associated with pH 12 diluent or confusion between diluents during transition period)
Objective(s) of the risk minimisation measures	In all markets, patients are managed by physicians and nurses based in PAH referral centres. At a minimum, these physicians are responsible for providing the initial prescription for Flolan. However, in most centres, all prescribing of Flolan is done by these PAH specialists. In addition, much of the training of patients in preparation and administration of Flolan is done by nurses within these specialty centres. In order to assure that patients have been appropriately educated in the differences in preparation, storage and administration of Flolan solution for infusion reconstituted with pH 12 diluent, these prescribers and nurses within these specialty centres will need to be educated. Dispensing of Flolan following the initial prescription varies, with either referral center-affiliated pharmacies or local pharmacies providing subsequent supplies of Flolan. It is important that pharmacists who dispense Flolan understand that the pH 10.5 and pH 12 diluents are not interchangeable, and that patients may not receive the pH 12 diluent formulation until they have been transitioned by their prescriber and received appropriate training. In addition, stock will need to be managed to maintain adequate supply of both diluents during the transition and to discontinue supply of pH 10.5 diluent to the market once all patients have been transitioned. GSK will make available educational documents, as it is anticipated that all markets will undertake an educational programme. However the specific programmes of education are to be developed within each country and will be applied differently across markets following local consultation. No single approach to prescriber, pharmacist and patient education is being proposed across Europe, owing to the wide variability in numbers of prescribers, pharmacies and patients, therefore the educational programme will not be discussed further in this EU-RMP. Because of the large variability in the number of prescribers, pharmacies and patients in each market, the supply of diluent and timing of discontinuation will be managed on a market by market basis and will not be discussed further in this EU RMP.
Routine risk minimisation measures	The external carton of combination packs that contain vials of both Flolan lyophile and the pH 12 diluent will contain a flash warning for at least six months following introduction of the pH 12 diluent formulation): “New formulation of solvent (pH 12)- see leaflet inside for use.” The prevailing colour of the external carton of the combination pack that contains pH 12 diluent will be different from the current colour. The flip-off cap on the vial for the pH 12 diluent will be purple, as compared to yellow for the pH 10.5 diluent. In addition, the vial for the pH 12 diluent will be plastic, as

Safety concern	**Medication errors (associated with pH 12 diluent or confusion between diluents during transition period)**
	compared to glass for the pH 10.5 diluent.The SmPC will contain information specific to the pH 12 diluent in Sections 1 (Name of the medicinal product), 2 (Qualitative and quantitative composition), 3 (Pharmaceutical form), 4.2 (Posology and method of administration), 6.3 (Shelf life), 6.5 (Nature and contents of container) and 6.6 (Special precautions for disposal and other handling). The PL will contain information specific to the pH 12 diluent in sections 5 (How to store Flolan).
	Comment None
	Other routine risk minimisation measures None
Additional risk minimisation measure(s) DHCPL (prescribers, nurses, pharmacists)	Objective and justification of why needed. Owing to the age and the familiarity that regular prescribers have with epoprostenol, HCPs may not necessarily review revised product labeling, therefore additional outreach is considered necessary to highlight the proposed changes to the diluent formulation and risks during transition period from the pH 10.5 diluent to the pH 12 diluent.
	Proposed actions/components and rationale A Dear Healthcare Provider letter (see Annex 11) will be mailed to PAH specialists, hospital pharmacies and pharmacists at the time of launch of the pH 12 diluent in that market. The distribution within each market will depend on the details of prescription, and post-prescription dispensing in that particular market. Flolan is also 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. It is considered likely that this use of Flolan is limited to hospital settings, therefore distribution of the DHCPL to hospital pharmacies is intended to target these hospitals that use Flolan for renal dialysis as well.

Safety concern	**Local infusion site reactions during long-term infusion (associated with pH 12 diluent)**
Objective(s) of the risk minimisation measures	To communicate information to prescribers regarding the risk of local infusion site reactions with epoprostenol, to ensure that patients are informed to consult with their healthcare provider immediately upon experiencing any symptoms.
Routine risk minimisation measures	As part of routine risk minimisation, risks associated with extravasation of an alkaline fluid are included in Section 4.4 of the SmPC and are detailed in Section 2 of the PL. In addition, Section 4.2 recommends that long-term infusion should be given via a central venous catheter. Section 4.2 also specifies that Flolan is only indicated for continuous intravenous infusion (PAH) or continous infusion, either intravascularly or in the blood supplying the

Safety concern	**Local infusion site reactions during long-term infusion (associated with pH 12 diluent)**
	dialyser (renal dialysis). Routine risk management in the form of labeling is considered sufficient and additional risk minimisation is not considered necessary. Should a change to the benefit-risk be identified, it is intended that the EU-RMP and labeling will be updated accordingly.
	Comment None
	Other routine risk minimisation measures None
Additional risk minimisation measure(s)	Objective and justification of why needed. Routine measures are considered sufficient.
	Proposed actions/components and rationale Not applicable.

Safety concern	**Sepsis, septicaemia (mostly related to delivery system for Flolan)**
Objective(s) of the risk minimisation measures	To communicate information to prescribers regarding the risk of catheter-related infections, including sepsis and septicaemia, with epoprostenol, to ensure that patients are informed to consult with their healthcare provider immediately upon experiencing any symptoms.
Routine risk minimisation measures	As part of routine risk minimisation, the need for patients who are receiving Flolan to adhere to aseptic technique during Flolan preparation and catheter care is addressed in Section 4.4 of the SmPC and is also included in Section 3 of the PL. Sepsis and septicaemia is included as a common event in Section 4.8 of the SmPC and is also included in Section 4 of the PL. Routine risk management in the form of labeling is considered sufficient and additional risk minimisation is not considered necessary. Should a change to the benefit-risk be identified, it is intended that the EU-RMP and labeling will be updated accordingly.
	Comment None
	Other routine risk minimisation measures None
Additional risk minimisation measure(s)	Objective and justification of why needed. Routine measures are considered sufficient.
	Proposed actions/components and rationale Not applicable.

Safety concern	**Pulmonary oedema**
Objective(s) of the risk minimisation measures	To communicate information to prescribers regarding the risk of pulmonary oedema with epoprostenol, to ensure that patients are informed to consult with their healthcare provider immediately upon experiencing any symptoms.
Routine risk minimisation measures	As part of routine risk minimisation, the importance of not using Flolan chronically in patients who develop pulmonary oedema during dose-ranging is addressed in Section 4.3 and 4.4 of the SmPC and is also included in Section 2 of the PL. Pulmonary oedema is included in Section 4.8 of the SmPC and is also included in Section 4 of the PL. Routine risk management in the form of labeling is considered sufficient and additional risk minimisation is not considered necessary. Should a change to the benefit-risk be identified, it is intended that the EU-RMP and labeling will be updated accordingly.
	Comment None
	Other routine risk minimisation measures None
Additional risk minimisation measure(s)	Objective and justification of why needed. Routine measures are considered sufficient.
	Proposed actions/components and rationale Not applicable.

Safety concern	**Hypotension**
Objective(s) of the risk minimisation measures	To communicate information to prescribers regarding the risk of hypotension with epoprostenol, to ensure that patients are informed to consult with their healthcare provider immediately upon experiencing any symptoms.
Routine risk minimisation measures	As part of routine risk minimisation, the risk of hypotension during dose-ranging and thereafter as well as in association with other vasodilating medicines and overdose is addressed in Sections 4.2, 4.4, 4.5 and 4.9 of the SmPC and is also included in Sections 2 and 3 of the PL. Pulmonary oedema is included as a common adverse reaction in Section 4.8 of the SmPC and is also included in Section 4 of the PL. Routine risk management in the form of labeling is considered sufficient and additional risk minimisation is not considered necessary. Should a change to the benefit-risk be identified, it is intended that the EU-RMP and labeling will be updated accordingly.
	Comment None
	Other routine risk minimisation measures None
Additional risk	Objective and justification of why needed.

Safety concern	**Hypotension**
minimisation measure(s)	Routine measures are considered sufficient.
	Proposed actions/components and rationale Not applicable.

Safety concern	**Bleeding events at various sites**
Objective(s) of the risk minimisation measures	To communicate information to prescribers regarding the risk of bleeding events with epoprostenol, to ensure that patients are informed to consult with their healthcare provider immediately upon experiencing any symptoms.
Routine risk minimisation measures	As part of routine risk minimisation, the risk of bleeding events in association with Flolan therapy, particularly when combined with other antiplatelet medicines, is addressed in Sections 4.4, 4.5 and 5.1 of the SmPC and is also included in Section 2 of the PL. Bleeding is included as a common adverse reaction in Section 4.8 of the SmPC and is also included in Section 4 of the PL. Routine risk management in the form of labeling is considered sufficient and additional risk minimisation is not considered necessary. Should a change to the benefit-risk be identified, it is intended that the EU-RMP and labeling will be updated accordingly.
	Comment None
	Other routine risk minimisation measures None
Additional risk minimisation measure(s)	Objective and justification of why needed. Routine measures are considered sufficient.
	Proposed actions/components and rationale Not applicable.

Safety concern	**Tachycardia**
Objective(s) of the risk minimisation measures	To communicate information to prescribers regarding the risk of tachycardia with epoprostenol, to ensure that patients are informed to consult with their healthcare provider immediately upon experiencing any symptoms.
Routine risk minimisation measures	As part of routine risk minimisation, the risk of tachycardia in association with Flolan therapy is addressed in Sections 4.2 and 4.4 of the SmPC and is also included in Sections 2 and 3 of the PL. Tachycardia is included as a common adverse reaction in Section 4.8 of the SmPC and is also included in Section 4 of the PL. Routine risk management in the form of labeling is considered sufficient and additional risk minimisation is not considered necessary. Should a change to the benefit-risk be identified, it is intended that the EU-RMP and labeling will be updated accordingly.

Safety concern	**Tachycardia**
	Comment None
	Other routine risk minimisation measures None
Additional risk minimisation measure(s)	Objective and justification of why needed. Routine measures are considered sufficient.
	Proposed actions/components and rationale Not applicable.

Safety concern	**Bradycardia**
Objective(s) of the risk minimisation measures	To communicate information to prescribers regarding the risk of bradycardia with epoprostenol, to ensure that patients are informed to consult with their healthcare provider immediately upon experiencing any symptoms.
Routine risk minimisation measures	As part of routine risk minimisation, the risk of bradycardia in association with Flolan therapy is addressed in Sections 4.2 and 4.4 of the SmPC and is also included in Sections 2 and 3 of the PL. Bradycardia is included as a common adverse reaction in Section 4.8 of the SmPC and is also included in Section 4 of the PL. Routine risk management in the form of labeling is considered sufficient and additional risk minimisation is not considered necessary. Should a change to the benefit-risk be identified, it is intended that the EU-RMP and labeling will be updated accordingly.
	Comment None
	Other routine risk minimisation measures None
Additional risk minimisation measure(s)	Objective and justification of why needed. Routine measures are considered sufficient.
	Proposed actions/components and rationale Not applicable.

Safety concern	**Use in paediatric patients**
Objective(s) of the risk minimisation measures	To inform physicians that epoprostenol is not licensed for adolescent or pediatric use..
Routine risk minimisation measures	SmPC Section 4.2 describes that epoprostenol is not recommended for use in children and adolescents as data on safety and efficacy have not been established.

Safety concern	**Use in paediatric patients**
	Routine risk management in the form of labeling is considered sufficient and additional risk minimisation is not considered necessary. Should a change to the benefit-risk be identified, it is intended that the EU-RMP and labeling will be updated accordingly.
	Comment None
	Other routine risk minimisation measures None
Additional risk minimisation measure(s)	Objective and justification of why needed. Routine measures are considered sufficient.
	Proposed actions/components and rationale Not applicable.

Safety concern	**Use in patients over 65 years**
Objective(s) of the risk minimisation measures	To communicate the potential risks of epoprostenol use in patients over 65 years of age. Physicians should be aware of underlying medical conditions such as decreased cardiac, renal and hepatic function which may increase the level of risk of use of epoprostenol in patients over 65 years of age.
Routine risk minimisation measures	SmPC Section 4.2 states that there is no specific data available on safety and efficacy of epoprostenol in patients over 65 years. It is recommended that dose selection for patients over 65 years should be made carefully, bearing in mind concurrent organ system dysfunction, other medical conditions and medicines. Routine risk management in the form of labeling is considered sufficient and additional risk minimisation is not considered necessary. Should a change to the benefit-risk be identified, it is intended that the EU-RMP and labeling will be updated accordingly.
	Comment None
	Other routine risk minimisation measures None
Additional risk minimisation measure(s)	Objective and justification of why needed. Routine measures are considered sufficient.
	Proposed actions/components and rationale Not applicable.

Safety concern	**Use in pregnant or lactating women**
Objective(s) of the risk	To communicate the risks of epoprostenol use in pregnant or lactating women.

Safety concern	**Use in pregnant or lactating women**
minimisation measures	
Routine risk minimisation measures	SmPC Section 4.6 recommends that there is a limited amount of data for the use of epoprostenol during pregnancy. Given the absence of alternative medicines, epoprostenol can be used in those women with PAH who choose to continue their pregnancy. It is not known if epoprostenol or its metabolites are excreted in human milk, therefore breast-feeding should be discontinued during treatment with Flolan. Instructions to contact a healthcare provider in the event of pregnancy or lactation are included in Section 2 of the PL. Routine risk management in the form of labeling is considered sufficient and additional risk minimisation is not considered necessary. Should a change to the benefit-risk be identified, it is intended that the EU-RMP and labeling will be updated accordingly.
	Comment None
	Other routine risk minimisation measures None
Additional risk minimisation measure(s)	Objective and justification of why needed. Routine measures are considered sufficient.
	Proposed actions/components and rationale Not applicable.

Table 50 Effectiveness of risk minimisation measures

Effectiveness of risk minimisation measures: Medication errors (associated with pH 12 diluent or confusion between diluents during transition period)	
How effectiveness of risk minimisation measures for the safety concern will be measured	Spontaneously reported adverse events will be reviewed on an ongoing basis during the transition period from the pH 10.5 diluent to the pH 12 diluent. In addition, each market will be regularly assessing the status of the transition. Because of the wide variability in numbers of prescribers, pharmacies and patients, the specific programmes of education are to be developed within each country and will be applied differently across markets following local consultation. As a result of these differences, the duration of the period during which both the pH 10.5 and pH 12 diluents will be available will vary, though it should not exceed 6 months. In consultation with national competent authorities, individual markets may choose to seek external feedback during the transition to assess whether there are outstanding areas of concern and whether key messages related to the use of pH 12 diluent have been understood.
Criteria for judging the success of the proposed risk minimisation measures	A qualitative assessment will be made of available data from the local operating companies at least twice during the transition period, as well as spontaneously reported adverse events on an ongoing basis, to determine whether additional interventions are necessary.
Planned dates for assessment	Spontaneously reported adverse events will be reviewed on an ongoing basis as part of routine pharmacovigilance and will be summarized in periodic reports as necessary. Should the need for additional interventions be identified during the transition, these will be communicated to regulatory authorities via established procedures. The EU-RMP and labeling will be updated as necessary.
Results of effectiveness measurement	Not applicable.
Impact of risk minimisation	Not applicable.
Comment	Not applicable.

Effectiveness of risk minimisation measures: Local infusion site reactions (associated with pH 12 diluent)	
How effectiveness of risk minimisation measures for the safety concern will be measured	Spontaneously reported adverse events will be reviewed on an ongoing basis during the transition period from the pH 10.5 diluent to the pH 12 diluent.
Criteria for judging the success of the proposed risk minimisation	Review of spontaneously reported adverse events relating to local reactions will be conducted to determine whether events during use of Flolan prepared

Effectiveness of risk minimisation measures: Local infusion site reactions (associated with pH 12 diluent)	
measures	with pH 12 diluent seem to be more frequent or severe than events during use of Flolan prepared with the pH 10.5 diluent.
Planned dates for assessment	Spontaneously reported adverse events will be reviewed on an ongoing basis as part of routine pharmacovigilance and will be summarized in periodic reports as necessary.
Results of effectiveness measurement	Not applicable.
Impact of risk minimisation	Not applicable.
Comment	Not applicable.

Effectiveness of risk minimisation measures: Sepsis, septicaemia	
How effectiveness of risk minimisation measures for the safety concern will be measured	This will be managed by routine PV to monitor any changes in terms of severity or frequency.
Criteria for judging the success of the proposed risk minimisation measures	Regular review of spontaneously reported adverse events relating to catheter-related infections will be conducted as part of routine pharmacovigilance.
Planned dates for assessment	Spontaneously reported adverse events will be reviewed on an ongoing basis as part of routine pharmacovigilance and will be summarized in periodic reports as necessary.
Results of effectiveness measurement	Not applicable.
Impact of risk minimisation	Not applicable.
Comment	Not applicable.

Effectiveness of risk minimisation measures: Pulmonary oedema	
How effectiveness of risk minimisation measures for the safety concern will be measured	This will be managed by routine PV to monitor any changes in terms of severity or frequency.

Effectiveness of risk minimisation measures: Pulmonary oedema	
Criteria for judging the success of the proposed risk minimisation measures	Regular review of spontaneously reported adverse events relating to pulmonary oedema will be conducted as part of routine pharmacovigilance.
Planned dates for assessment	Spontaneously reported adverse events will be reviewed on an ongoing basis as part of routine pharmacovigilance and will be summarized in periodic reports as necessary.
Results of effectiveness measurement	Not applicable.
Impact of risk minimisation	Not applicable.
Comment	Not applicable.

Effectiveness of risk minimisation measures: Hypotension	
How effectiveness of risk minimisation measures for the safety concern will be measured	This will be managed by routine PV to monitor any changes in terms of severity or frequency.
Criteria for judging the success of the proposed risk minimisation measures	Regular review of spontaneously reported adverse events relating to hypotension will be conducted as part of routine pharmacovigilance.
Planned dates for assessment	Spontaneously reported adverse events will be reviewed on an ongoing basis as part of routine pharmacovigilance and will be summarized in periodic reports as necessary.
Results of effectiveness measurement	Not applicable.
Impact of risk minimisation	Not applicable.
Comment	Not applicable.

Effectiveness of risk minimisation measures: Bleeding events	
How effectiveness of risk minimisation measures for the safety concern	This will be managed by routine PV to monitor any changes in terms of severity or frequency.

Effectiveness of risk minimisation measures: Bleeding events	
will be measured	
Criteria for judging the success of the proposed risk minimisation measures	Regular review of spontaneously reported adverse events relating to bleeding events will be conducted as part of routine pharmacovigilance.
Planned dates for assessment	Spontaneously reported adverse events will be reviewed on an ongoing basis as part of routine pharmacovigilance and will be summarized in periodic reports as necessary.
Results of effectiveness measurement	Not applicable.
Impact of risk minimisation	Not applicable.
Comment	Not applicable.

Effectiveness of risk minimisation measures: Tachycardia	
How effectiveness of risk minimisation measures for the safety concern will be measured	This will be managed by routine PV to monitor any changes in terms of severity or frequency.
Criteria for judging the success of the proposed risk minimisation measures	Regular review of spontaneously reported adverse events relating to tachycardia will be conducted as part of routine pharmacovigilance.
Planned dates for assessment	Spontaneously reported adverse events will be reviewed on an ongoing basis as part of routine pharmacovigilance and will be summarized in periodic reports as necessary.
Results of effectiveness measurement	Not applicable.
Impact of risk minimisation	Not applicable.
Comment	Not applicable.

Effectiveness of risk minimisation measures: Bradycardia	
How effectiveness of risk minimisation measures	This will be managed by routine PV to monitor any changes in terms of

Effectiveness of risk minimisation measures: Bradycardia	
for the safety concern will be measured	severity or frequency.
Criteria for judging the success of the proposed risk minimisation measures	Regular review of spontaneously reported adverse events relating to bradycardia will be conducted as part of routine pharmacovigilance.
Planned dates for assessment	Spontaneously reported adverse events will be reviewed on an ongoing basis as part of routine pharmacovigilance and will be summarized in periodic reports as necessary.
Results of effectiveness measurement	Not applicable.
Impact of risk minimisation	Not applicable.
Comment	Not applicable.

Effectiveness of risk minimisation measures: Use in paediatric patients	
How effectiveness of risk minimisation measures for the safety concern will be measured	This will be managed by routine PV to monitor use in paediatric patients.
Criteria for judging the success of the proposed risk minimisation measures	Ongoing evaluation of spontaneous reports in children and adolescents to assess the level of off-label use and the safety profile in this population.
Planned dates for assessment	Spontaneously reported adverse events will be reviewed on an ongoing basis as part of routine pharmacovigilance and will be summarized in periodic reports as necessary.
Results of effectiveness measurement	Not applicable.
Impact of risk minimisation	Not applicable.
Comment	Not applicable.

Effectiveness of risk minimisation measures: Use in patients over 65	
How effectiveness of risk minimisation measures for the safety concern will be measured	This will be managed by routine PV to monitor use in patients over 65 years of age.
Criteria for judging the success of the proposed risk minimisation measures	Ongoing evaluation of spontaneous reports in patients over 65 years of age to assess the level of use and the safety profile in this population.
Planned dates for assessment	Spontaneously reported adverse events will be reviewed on an ongoing basis as part of routine pharmacovigilance and will be summarized in periodic reports as necessary.
Results of effectiveness measurement	Not applicable.
Impact of risk minimisation	Not applicable.
Comment	Not applicable.

Effectiveness of risk minimisation measures: Use in pregnant or lactating women	
How effectiveness of risk minimisation measures for the safety concern will be measured	This will be managed by routine PV to monitor use in pregnant or lactating women.
Criteria for judging the success of the proposed risk minimisation measures	Ongoing evaluation of spontaneous reports in patients who are pregnant or lactating to assess the level of use and the safety profile in this population.
Planned dates for assessment	Spontaneously reported adverse events will be reviewed on an ongoing basis as part of routine pharmacovigilance and will be summarized in periodic reports as necessary.
Results of effectiveness measurement	Not applicable.
Impact of risk minimisation	Not applicable.
Comment	Not applicable.

V.2 Risk minimisation measure failure (if applicable)

No risk minimisation measures have been judged to have failed.

Table 51 Risk minimisation measure failure

Safety concern	Risk minimisation measure
Not applicable.	

V.2.1 Analysis of risk minimisation measure(s) failure

No risk minimisation measures have been judged to have failed.

Table 52 Analysis of risk minimisation measure(s) failure

Safety concern	
Risk minimisation measure(s)	
Component 1	
Component 2 etc.	
Discussion	

V.2.2 Revised proposal for risk minimisation

No risk minimisation measures have been judged to have failed.

Table 53 Revised proposal for risk minimisation

Safety concern	
Objective(s) of the risk minimisation activities	
Routine risk minimisation activities	Synopsis of (proposed) text in SmPC
	Comment (e.g. on any differences between SmPCs)
	Other routine risk minimisation activities
Additional risk minimisation measure(s) z	Objective and justification of why needed.
	Proposed actions/components and rationale
Comment on how revised proposals will address failings	
Effectiveness of risk minimisation measures	
How effectiveness of risk minimisation measures for the safety concern will be measured	
Criteria for judging the success of the proposed risk minimisation measures	

V.3 Summary of risk minimisation measures

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Medication errors (associated with pH 12 diluent or confusion between diluents during transition period)	Changes in packaging color (including vial label, flip-off cap and carton) and addition of flash warning to allow for easy differentiation between the pH 10.5 and pH 12 diluents and to alert patients of need to review new SmPC and PL. Update in SmPC Sections 1, 2, 3, 4.2, 6.3, 6.5 and 6.6 and PL Section 5 to include information relevant to pH 12 diluent including revised post-reconstitution storage and administration conditions for Flolan prepared with pH 12 diluent.	Dear Health Care Provider Letter for prescribers and pharmacists (see Annex 11).
Local reactions (associated with pH 12 diluent)	Recommendation in Section 4.2 for long-term infusions to be given via central venous catheter. Warning in Section 4.4 to avoid extravasation. Addressed in Section 2 of PL.	No additional risk minimisation measures proposed.
Sepsis, septicaemia	Importance of adherence to aseptic technique during preparation of Flolan and catheter care in Section 4.4. Listed in Section 4.8. Addressed in Sections 3 and 4 of PL.	No additional risk minimisation measures proposed.
Pulmonary oedema	Importance of not using Flolan chronically in patients who develop pulmonary oedema during dose-ranging is discussed in Sections 4.3 and 4.4. Listed in Section 4.8. Addressed in Sections 2 and 4 of PL.	No additional risk minimisation measures proposed.
Hypotension	Importance of monitoring blood pressure during dose-ranging and subsequent dose changes is discussed in Section 4.2. Risk and management of hypotension is discussed in Sections 4.4 and 4.9. Other medicines that can contribute to hypotension from Flolan are discussed in	No additional risk minimisation measures proposed.

Safety concern	**Routine risk minimisation measures**	**Additional risk minimisation measures**
	Sections 4.4 and 4.5. Listed in Section 4.8. Addressed in Sections 2, 3 and 4 of PL.	
Bleeding events	Risk of bleeding events is discussed in Section 4.4. Other medicines that can contribute to bleeding events from Flolan are discussed in Sections 4.5 and 5.1. Listed in Section 4.8. Addressed in Sections 2 and 4 of PL.	No additional risk minimisation measures proposed.
Tachycardia	Importance of monitoring heart rate during dose-ranging and subsequent dose changes is discussed in Section 4.2. Risk of tachycardia is discussed in Section 4.4. Listed in Section 4.8. Addressed in Sections 2, 3 and 4 of PL.	No additional risk minimisation measures proposed.
Bradycardia	Importance of monitoring heart rate during dose-ranging and subsequent dose changes is discussed in Section 4.2. Risk of bradycardia is discussed in Section 4.4. Listed in Section 4.8. Addressed in Sections 2, 3 and 4 of PL.	No additional risk minimisation measures proposed.
Use in paediatric patients	Lack of data discussed in Section 4.2.	No additional risk minimisation measures proposed.
Use in patients over 65 years	Lack of data discussed in Section 4.2.	No additional risk minimisation measures proposed.
Use in pregnant or lactating women	Recommendation for use in women with PAH who choose to continue their pregnancies given absence of alternative medicines discussed in Section 4.6. Addressed in Section 2 and PL.	No additional risk minimisation measures proposed.

PART VI: SUMMARY OF ACTIVITIES IN THE RISK MANAGEMENT PLAN BY PRODUCT

VI.1 Elements for summary tables in the EPAR

Summary of safety concerns	
Important identified risks	Medication errors* Sepsis, septicaemia (mostly related to delivery system for Flolan) Pulmonary oedema Hypotension Bleeding events at various sites Tachycardia Bradycardia
Important potential risks	Local infusion site reactions during long-term infusion**
Missing information	Use in paediatric patients Use in patients over 65 years Use in pregnant and lactating women

*This safety concern may be more likely to occur during the transition from pH 10.5 diluent to pH 12 diluent.
**This safety concern may be more likely to occur with use of Flolan solution prepared with pH12 diluent.

VI.1.2 Table of on-going and planned additional PhV studies/activities in the Pharmacovigilance Plan

Study/activity Type, title and category (1-3)	Objectives	Safety concerns addressed	Status (planned, started)	Date for submission of interim or final reports (planned or actual)
None				

VI.1.3 Summary of post authorisation efficacy development plan

Study (type and study number)	Objectives	Efficacy uncertainties addressed	Status	Date for submission of interim or final reports
Not applicable				

VI.1.4 Summary table of Risk Minimisation Measures

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Medication errors (associated with pH 12 diluent or confusion between diluents during transition period)	Changes in packaging color (including vial label, flip-off cap and carton) and addition of flash warning to allow for easy differentiation between the pH 10.5 and pH 12 diluents and to alert patients of need to review new SmPC and PL. Update in SmPC Sections 1, 2, 3, 4.2, 6.3, 6.5 and 6,6 and PL Section 5 to include information relevant to pH 12 diluent including revised post-reconstitution storage and administration conditions for Flolan prepared with pH 12 diluent.	Dear Health Care Provider Letter for prescribers and pharmacists (see Annex 11).
Local reactions (associated with pH 12 diluent)	Recommendation in Section 4.2 for long-term infusions to be given via central venous catheter. Warning in Section 4.4 to avoid extravasation. Addressed in Section 2 of PL.	No additional risk minimisation measures proposed.
Sepsis, septicaemia	Importance of adherence to aseptic technique during preparation of Flolan and catheter care in Section 4.4. Listed in Section 4.8. Addressed in Sections 3 and 4 of PL.	No additional risk minimisation measures proposed.
Pulmonary oedema	Importance of not using Flolan chronically in patients who develop pulmonary oedema during dose-ranging is discussed in Sections 4.3 and 4.4. Listed in Section 4.8. Addressed in Sections 2 and 4 of PL.	No additional risk minimisation measures proposed.
Hypotension	Importance of monitoring blood pressure during dose-ranging and subsequent dose changes is discussed in Section 4.2. Risk and management of hypotension is discussed in Sections 4.4 and 4.9. Other medicines that can contribute to hypotension from Flolan are discussed in	No additional risk minimisation measures proposed.

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	Sections 4.4 and 4.5. Listed in Section 4.8. Addressed in Sections 2, 3 and 4 of PL.	
Bleeding events	Risk of bleeding events is discussed in Section 4.4. Other medicines that can contribute to bleeding events from Flolan are discussed in Sections 4.5 and 5.1. Listed in Section 4.8. Addressed in Sections 2 and 4 of PL.	No additional risk minimisation measures proposed.
Tachycardia	Importance of monitoring heart rate during dose-ranging and subsequent dose changes is discussed in Section 4.2. Risk of tachycardia is discussed in Section 4.4. Listed in Section 4.8. Addressed in Sections 2, 3 and 4 of PL.	No additional risk minimisation measures proposed.
Bradycardia	Importance of monitoring heart rate during dose-ranging and subsequent dose changes is discussed in Section 4.2. Risk of bradycardia is discussed in Section 4.4. Listed in Section 4.8. Addressed in Sections 2, 3 and 4 of PL.	No additional risk minimisation measures proposed.
Use in paediatric patients	Lack of data discussed in Section 4.2.	No additional risk minimisation measures proposed.
Use in patients over 65 years	Lack of data discussed in Section 4.2.	No additional risk minimisation measures proposed.
Use in pregnant or lactating women	Recommendation for use in women with PAH who choose to continue their pregnancies given absence of alternative medicines discussed in Section 4.6. Addressed in Section 2 and PL.	No additional risk minimisation measures proposed.

VI.2 Elements for a Public Summary

VI.2.1 Overview of disease epidemiology

Flolan is used to treat a lung condition called pulmonary arterial hypertension (PAH). This is where the pressure is high in the blood vessels in the lungs. Flolan widens the blood vessels to lower the blood pressure in the lungs. Symptoms of PAH can include shortness of breath, cough, tiredness, fainting or lightheadedness and can easily be confused with other diseases of the heart and lungs. PAH is a rare disease, occurring in fewer than 260,000 people in the world. PAH can run in families, occur as a result of certain other diseases (for example, connective tissue diseases, congenital heart disease, sickle cell disease or HIV), or it can occur with no identifiable cause. When PAH is not treated, more than half of patients will die within a few years.

Flolan is used to prevent blood clotting during kidney dialysis in emergency situations when heparin cannot be used. The kidney normally functions to remove certain harmful substances from the body and can stop working for a variety of reasons, including a variety of illnesses and diseases. When kidneys stop working, a person may need to have a 'dialysis' machine do the job of the kidney, either temporarily or permanently. The machine may use a medicine such as heparin or infrequently epoprostenol to keep the blood from clotting during dialysis.

VI.2.2 Summary of treatment benefits

Flolan was first approved in 1981 and is effective in treating certain types of PAH and is also used during emergency kidney dialysis when heparin cannot be used. In clinical trials, patients with PAH who received Flolan were able to walk further over a 6 minute period than they were able to before they started Flolan. Flolan was also shown to improve survival in one group of PAH patients in clinical trials.

Flolan comes as two different vials. One type of vial contains the dried medicine and one type of vial contains a special liquid used to dissolve and dilute the medicine to make a solution of the medicine that can be administered into the blood. The liquid used to dissolve and mix Flolan is being changed to allow Flolan solution made with the changed liquid to be stored and given over a longer period of time at higher temperatures. The vial containing the medicine is not changing, so how well Flolan solution works to treat PAH will not change.

VI.2.3 Unknowns relating to treatment benefits

There is a limited amount of information describing use of Flolan in children, the elderly or women who are pregnant or breast-feeding. However, that data which is available has not suggested any unexpected risks when using Flolan in these groups.

VI.2.4 Summary of safety concerns

Important identified risks

Risk	What is known	Preventability
Mistakes in mixing, storing and giving Flolan (medication errors)	For a limited amount of time, there will be two different diluents for Flolan available. When mixed with these diluents, Flolan has different instructions for how long it can be stored and given to a person who is getting Flolan. If the wrong instructions are used, the person being given Flolan could have a worsening of the high blood pressure in their lungs, which can cause dizziness, weakness, worsening shortness of breath, and maybe even death.	Yes, by using the correct directions for how long Flolan mixed with that diluent type can be stored and given to a person who is getting Flolan.
Infection of the blood (sepsis or septicaemia)	People who are getting Flolan usually have a permanent tubes (central line) fitted into a vein. Because central lines go through the skin and into a vessel, they can get infected. An infection can be at the skin where the central line goes in or can spread into the blood. Infections of the blood occur in between 1 in 100 and 10 in 100 people who are using Flolan. Infections of the blood can be very serious, and can even sometimes cause death.	The risk of getting infections of the blood can be made less by being very careful to follow the instructions from your doctor for mixing, storing and giving Flolan and for taking care of the central line.
Build up of fluid in the lungs (pulmonary oedema)	While using Flolan, some people can get a build up of fluid in the lungs that can make it hard to breathe well. This usually happens soon after Flolan is started for the first time, but can happen later during use too. This build-up of fluid occurs in about 3 in 100 people with PAH who are using Flolan, versus about 1 in 100 people with PAH who are not using Flolan.	A doctor will closely watch when Flolan is started in case signs of fluid build-up start so that Flolan can be stopped and the fluid build-up can be treated.
Low blood pressure (hypotension)	Flolan causes the blood vessels in the body to open up. This can	A doctor will closely watch when Flolan is started in case blood

Risk	What is known	Preventability
	make blood pressure go down, which can cause people to be dizzy and feel faint, especially after standing. This can particularly occur if too much Flolan is given. Low blood pressure happens in between 1 in 100 and 10 in 100 people who are using Flolan.	pressure gets too low so that Flolan can be slowed down and the low blood pressure treated if needed. The risk of getting too much Flolan can be made less by being very careful to follow the instructions from your doctor for mixing, storing and giving Flolan.
Bleeding and bruising more easily than usual (bleeding events)	Flolan stops blood from clotting which can cause bleeding or bruising that occurs even without a cut or fall before the bleeding. Bleeding or bruising happens in between 1 in 100 and 10 in 100 people who are using Flolan.	People who are getting Flolan should be careful to avoid hurting or cutting themselves as much as possible.
Fast heart beat (tachycardia)	Flolan can cause the heart to beat faster and happens commonly in people who are using Flolan.	A doctor will closely watch when Flolan is started in case the heart beat gets too fast and will change the dose to try to decrease the heart beat if needed.
Slow heart beat (bradycardia)	Flolan can cause the heart to beat slower and happens commonly in people who are using Flolan.	A doctor will closely watch when Flolan is started in case the heart beat gets too slow and will change the dose to try to increase the heart beat if needed.

Important potential risks

Risk	What is known (Including reason why it is considered a potential risk)
Irritation or pain where using medicine (local infusion site reactions)	Medicines like Flolan that are high in pH can be painful or irritating to skin and blood vessels when given. The new diluent is higher in pH than the old diluent so there could be more of a risk of irritation or pain. People who are getting Flolan for a long time have special permanent lines to get their Flolan which keep the Flolan from coming into contact with their skin or small blood vessels which should prevent irritation or pain at the places where the medicine is given.

Missing information

Risk	What is known
Use in paediatric patients	As the safety and efficacy of Flolan has not been established in children, Flolan should not be given to children. An evaluation of the limited clinical trial data and adverse event reports in which Flolan was given to children suggests that the safety profile is not significantly different in children when compared to adults.
Use in patients over 65 years	There is no specific information on the use of Flolan in patients over 65 years for renal dialysis or PAH. An evaluation of the limited clinical trial data and adverse event reports suggests that the safety profile is not signficantly different in patients over 65 years when compared to all adults. Dosingfor an elderly patient should done carefully, as elderly patients are more likely to have underlying diseases, problems with heart, liver or kidneys, or to be on other medicines.
Use in pregnant and lactating women	There is a limited amount of data from the use of epoprostenol in pregnant women. Pulmonary hypertension during pregnancy is associated with considerable risks to the mother and baby and some other PAH medicines are associated with birth defects when given during pregnancy. Given the absence of other medicines, epoprostenol can be used in those women who choose to continue their pregnancy, despite the known risk of pulmonary arterial hypertension during pregnancy. It is unknown if epoprostenol or its metabolites are excreted in human milk, therefore breast-feeding should be discontinued during treatment with Flolan.

VI.2.5 Summary of additional risk minimisation measures by safety concern

All medicines have a Summary of Product Characteristics (SmPC) which provides physicians, pharmacists and other health care professionals with details on how to use the medicine, the risks and recommendations for minimising them. An abbreviated version of this in lay language is provided in the form of the package leaflet (PL). The measures in these documents are known as routine risk minimisation measures.

This medicine has special conditions and restrictions for its safe and effective use (additional risk minimisation measures). How these conditions are implemented in each country however will depend upon agreement between the manufacturer and the national authorities.

These additional risk minimisation measures are for mistakes while using the medicine (medication errors).

Risk minimisation measures: Mistakes in mixing, storing and giving Flolan (medication errors)
Objective and rationale: Using the old diluent to mix Flolan and then storing and giving the medicine with the directions for the new diluent could make PAH symptoms worse, including dizziness, weakness, shortness of breath, and maybe even death. Patients and healthcare providers will understand how to use the new diluent and how to tell the difference between the two diluent formulations to prevent wrong use of either diluent during the time when both diluents will be available. **Proposed action:** Direct HCP communication at the time of launch highlighting the differences in stored and given Flolan mixed with the two different diluents.

VI.2.6 Planned post authorisation development plan

List of studies in post authorisation development plan

Study/activity (including study number)	Objectives	Safety concerns /efficacy issue addressed	Status	Planned date for submission of (interim and) final results
None applicable				

Studies which are a condition of the marketing authorisation

There are no studies that are a condition of the marketing authorisation.

VI.2.7 Summary of changes to the Risk Management Plan over time

Table 54 Major Changes to the Risk Management Plan Over Time

Version	Date	Safety Concerns	Comment
Not applicable			

REFERENCES

0013/81/7263/002. The micronucleus test with prostacyclin .

2011N119711_00 (D29550). Flolan: Local tolerance study by intravenous infusion administration to male Beagle dogs for 4 days.

2011N125526_00 (V29864). Flolan: In vitro haemolytic potential in human peripheral blood.

7200/80/7263/001. Evaluation of U-53, 217A in the Salmonella/microsome test (Ames Assay).

7205/80/7263/004. U-53, 217A; a segment III peri-post natal study.

7205/80/7263/005. U-53, 217A; 30 day continuous intravenous infusion study in unanaesthetised Beagle dogs

7205/80/7263/006. U-53, 217A; formation and reversibility of haematological changes in Beagle dogs.

7205/81/7263/006. Epoprostenol sodium; A Segment I reproduction study in the rat.

7263/80/7263/023. Evaluation of U-53, 217A (PGI2; epoprostenol sodium) in the DNA damage/alkaline elution assay. Aessopos A et al. Cardiac involvement in thalassemia intermedia: a multicenter study. Blood 2001; 97:3411-3416.

Ahlstrom A et al. Survival and quality of life of patients requiring acute renal replacement therapy. Intensive Care Med 2005;31:1222–1228.

Akagi S et al. Prevention of catheter-related infections using a closed hub system in patients with pulmonary arterial hypertension. Circ J 2007;71:559 – 564.

Ali T et al. Incidence and outcomes in acute kidney injury: a comprehensive population-based study. J Am Soc Nephrol 2007;18:1292–1298.

Arcasoy SM et al. Echocardiographic assessment of pulmonary hypertension in patients with advanced lung disease. Am J Respir Crit Care Med 2003;167:735–740.

Avouac J et al. Prevalence of pulmonary hypertension in systemic sclerosis in European caucasians and metaanalysis of 5 studies. J Rheumatol 2010;37:2290-2298.

Badesch DB et al. Medical therapy for pulmonary arterial hypertension: Updated ACCP evidence-based clinical practice guidelines. Chest 2007;131(6):1917-1928.

Badesch DB et al. Longterm survival among patients with scleroderma-associated pulmonary arterial hypertension treated with intravenous epoprostenol. J Rheumatol 2009;36:2244-2249.

Bagshaw SM et al. Prognosis for long-term survival and renal recovery in critically ill patients with severe acute renal failure: a population-based study. Crit Care 2005;9:R700–R709.

Bagshaw SM et al. Septic acute kidney injury in critically ill patients: clinical characteristics and outcomes. Clin J Am Soc Nephrol 2007;2:431–439.

Barst RJ, for the Primary Pulmonary Hypertension Study Group. A comparison of continuous intravenous epoprostenol (prostacyclin) with conventional therapy for primary pulmonary hypertension. N Engl J Med 1996;334(5):296-301.

Barst RJ et al. Vasodilator therapy for primary pulmonary hypertension in children. Circulation 1999;99:1197-1208.

Bastin AJ et al. Acute kidney injury after cardiac surgery according to risk/injury/failure/loss/end-stage, acute kidney injury network, and kidney disease: improving global outcomes classifications. J Crit Care 2013;28:389–396.

Bedard E et al. Has there been any progress made on pregnancy outcomes among women with pulmonary arterial hypertension? Eur Heart J 2009;30:256–265.

Bell M et al. Continuous renal replacement therapy is associated with less chronic renal failure than intermittent haemodialysis after acute renal failure. Intensive Care Med 2007;33:773–780.

Berger A et al. Changes in healthcare utilization and costs associated with sildenafil therapy for pulmonary arterial hypertension: a retrospective cohort study. BMC Pulmonary Medicine 2012;12:75.

BPAT 77/12. Preliminary toxicological findings from the subacute administration of prostacyclin in the rat.

BPAT 77/16. Dose range study of prostacyclin in the monkey.

BPAT 78/10. A subacute toxicity study of 4UA76 (prostacyclin sodium) by subcutaneous injection in the rat.

BPAT 78/16. A subacute toxicity study of 4UA76 (prostacyclin sodium) by intravenous injection in anaesthetised monkeys.

BPAT 78/27. Foetal toxicity and teratogenicity study of subcutaneous prostacyclin in the rat.

BPAT 78/31. Foetal toxicity and teratogenicity study of subcutaneous prostacyclin in the rabbit.

BPAT 78/32. An acute toxicity study of prostacyclin sodium by single intravenous dose administration to mice.

BPAT 78/34. A further acute toxicity study of prostacyclin sodium by single intravenous dose administration to mice.

BPAT 78/43. A further acute toxicity study of prostacyclin sodium by single intravenous dose administration to mice.

BPAT 79/21. A supplementary fetal toxicity and teratogenicity study of subcutaneous prostacyclin in the rabbit.

BPAT 80/22. An acute single-dose intravenous toxicity study with prostacyclin sodium in rats.

Califf RM et al. A randomized controlled trial of epoprostenol therapy for severe congestive heart failure: the Flolan International Randomized Survival Trial (FIRST). Am Heart J 1997;134:44-54.

Castro O et al. Pulmonary hypertension in sickle cell disease: cardiac catheterization results and survival. Blood 2003;101:1257-1261.

Centers for Disease Control and Prevention (CDC). Bloodstream infections among patients treated with intravenous epoprostenol or intravenous treprostinil for pulmonary arterial hypertension--seven sites, United States, 2003-2006. MMWR Morb Mortal Wkly Rep 2007;56(8):170-172.

Chertow GM et al. Independent association between acute renal failure and mortality following cardiac surgery. Am J Med 1998;104:343–348.

Chin K and Rubin L. Pulmonary arterial hypertension. J Am Coll Cardiol 2008;51(16):1527-1538.

Chin KM et al. Two formulations of epoprostenol sodium in the treatment of pulmonary arterial hypertension: EPITOME-1 (epoprostenol for injection in pulmonary arterial hypertension), a phase IV, open-label, randomized study. Am Heart J 2014;167(2):218-225.

Cho K and Hsu CY. Quantifying severity of chronic kidney disease as a risk factor for acute kidney injury. J Am Soc Nephrol 2010;21:1602–1604.

Christie JD et al. The registry of the International Society for Heart and Lung Transplantation: 29th Adult Lung and Heart-Lung Transplant Report—2012. J Heart Lung Transplant 2012:31(10):1073-1086.

Clec'h C et al. Multiple-center evaluation of mortality associated with acute kidney injury in critically ill patients: a competing risks analysis. Crit Care 2011;15:R128.

Colle IO et al. Diagnosis of portopulmonary hypertension in candidates for liver transplantation: a prospective study. Hepatology 2003;37:401-409.

Condliffe R et al. Improved outcomes in medically and surgically treated chronic thromboembolic pulmonary hypertension. Am J Respir Crit Care Med 2008;177:1122–1127.

D'Alonzo GE et al. Survival in patients with primary pulmonary hypertension: results from a national prospective registry. Ann Intern Med 1991;115(5):343-349.

Damy T et al. Determinants and prognostic value of pulmonary arterial pressure in patients with chronic heart failure. Eur Heart J 2010;31:2280–2290.

Delannoy B et al. Six-month outcome in acute kidney injury requiring renal replacement therapy in the ICU: a multicentre prospective study. Intensive Care Med 2009;35:1907–1915.

Doran AK et al. Guidelines for the prevention of central venous catheter related blood stream infections with prostanoid therapy for pulmonary arterial hypertension. Int J Clin Pract 2008:62(S160):5–9.

Dzierba AL et al. A review of inhaled nitric oxide and aerosolized epoprostenol in acute lung injury or acute respiratory distress syndrome. Pharmacotherapy 2014;34(3):279-290.

Fessel JP et al. The genetics of pulmonary arterial hypertension in the post-BMPR2 era. Pulmonary Circulation 2011;1(3):305-319.

Frank H et al. The effect of anticoagulant therapy in primary and snorectic drug-induced pulmonary hypertension. Chest 1997; 112:714-721.

Fritz et al. Pulmonary vascular complications of liver disease. Am J Respir Crit Care Med 2013; 187(2):133-143.

Fuster V et al. Primary pulmonary hypertension: natural history and the importance of thrombosis. Circulation 1984: 70(4):580-587.

Galie N et al. Guidelines for the diagnosis and treatment of pulmonary hypertension: the task force for the diagnosis and treatment of pulmonary hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS), endorsed by the International Society of Heart and Lung Transplantation (ISHLT). Eur Heart J 2009;30:2493–2537.

Gatward JJ et al. Renal replacement therapy for acute renal failure: a survey of practice in adult intensive care units in the United Kingdom. Anaesthesia 2008;63:959-966.

Gatzoulis MA et al. Pulmonary arterial hypertension in paediatric and adult patients with congenital heart disease. Eur Respir Rev 2009;18:113:154–161.

Gladwin MT et al. Pulmonary hypertension as a risk factor for death in patients with sickle cell disease. N Engl J Med 2004;350:886-895.

GlaxoSmithKline Internal Document Number THRS/94/0016. A pilot study of the effects of FLOLAN (epoprostenol sodium) on the pharmacokinetics of digoxin in severe

CHF patients - a population pharmacokinetic analysis. Report Date 28-Feb-2005.

Gryglewski RJ. Prostacyclin as a circulatory hormone. Biochem Pharmacol 1979; 28: 3161-6.

Habler O et al. Eight hours' inhalation of prostacyclin (PGI_2) in healthy lambs: effects on tracheal, bronchial, and alveolar morphology. Intensive Care Med 1996;22:1232-1238.

Hadengue A et al. Pulmonary hypertension complicating portal hypertension: prevalence and relation to splanchic hemodynamics. Gastroenterology 1991;100:500-528.

Hanson R. Current and emerging therapies for pulmonary arterial hypertension. Hosp Pharm 2013;48(S4):S7–S14.

Hawkins HJ, Smith JB, Nicolaou KC, Eling TE. Studies of the mechanisms involved in the fate of prostacyclin (PGI2) and 6-keto-PGF1 in the pulmonary circulation. Prostaglandins 1978; 16: 871-84.

Hayag-Barin JE et al. Hereditary spherocytosis, thrombocytosis, and chronic pulmonary emboli: a case report and review of the literature. Amer J Hematol 1998;57:82–84.

Hirata Y et al. Comparative analysis of *Micrococcus luteus* isolates from blood cultures of patients with pulmonary hypertension receiving epoprostenol continuous infusion. J Infect Chemother. 2009;15(6):424-425.

Ho J et al. Serum creatinine measurement immediately after cardiac surgery and prediction of acute kidney injury. Am J Kidney Dis 2012;59:196–201.

Hofhuis JG et al. The effect of acute kidney injury on long-term health-related quality of life: a prospective follow-up study. Crit Care 2013;17:R17.

Hsu CY et al. Community-based incidence of acute renal failure. Kidney Int 2007;72: 208–212.

Hsu RK et al. Regional variation in the incidence of dialysis-requiring AKI in the United States. Clin J Am Soc Nephrol 2013;8:1476-1481.

Humbert M et al. Results of European post-marketing surveillance of bosentan in pulmonary hypertension. Eur Respir J 2007;30(2):338-344.

Humbert M et al. Pulmonary arterial hypertension in France: results from a national registry. Am J Respir Crit Care Med 2006;173:1023–1030.

Hurdman J et al. ASPIRE registry: Assessing the Spectrum of Pulmonary hypertension Identified at a REferral centre. Eur Respir J 2012; 39: 945–955.

Hyman AL, Kadowitz PJ. Pulmonary vasodilator activity of prostacyclin (PGI2) in the cat. Circ Res 1979; 45: 404-9.

Ivy DD et al. Closed-hub systems with protected connections and the reduction of risk of catheter-related bloodstream infection in pediatric patients receiving intravenous prostanoid therapy for pulmonary hypertension. Infect Control Hosp Epidemiol 2009;30:823-829.

Johansen KL et al. Predictors of health utility among 60-day survivors of acute kidney injury in the Veterans Affairs/National Institutes of Health acute renal failure trial network study. Clin J Am Soc Nephrol 2010;5:1366–1372.

Johnson SR et al. Anticoagulation in pulmonary arterial hypertension: a qualitative systematic review. Eur Respir J 2006;28:999–1004.

Joyce VR et al. Health-related quality of life as a predictor of mortality among survivors of AKI. Clin J Am Soc Nephrol 2012;7:1063–1070.

Kallen AJ et al. Bloodstream infections in patients given treatment with intravenous prostanoids. Infect Control Hosp Epidemiol 2008;29(4):342-349.

Kawabe M, Hagiwara A, Yoshino H, Miyashita K, Nakanishi T, Sano M et al. Epoprostenol sodium, a prostaglandin I2, lacks tumour promoting effects in a medium-term liver carcinogenesis bioassay in rats. Cancer Lett 2001; 162: 141-7.

Kawut SM et al. New predictors of outcome in idiopathic pulmonary arterial hypertension. Am J Cardiol 2005;95:199-203.

Kheterpal S et al. Predictors of postoperative acute renal failure after noncardiac surgery in patients with previously normal renal function. Anesthesiology 2007;107:892–902.

Kidney Disease: Improving Global Outcomes (KDIGO) Acute Kidney Injury Work Group. KDIGO Clinical Practice Guideline for Acute Kidney Injury. Kidney Int Suppl. 2012;2:1–138.

Kiely DG et al. Pulmonary hypertension: diagnosis and management. BMJ 2013;346.

Kimball FA, Porteus SE, Kirton KT, Frielink RD, Creasy DM, Dayan AD. Prostacyclin (PGI2) effects on anterior pituitary hormones in the rat in vivo. Prostaglandins 1979; 18: 377-85.

Kingman MS et al. Prostacyclin administration errors in pulmonary arterial hypertension patients admitted to hospitals in the United States: a national survey. J Heart Lung Transplant 2010;29(8):841-846.

Kirson NY et al. Prevalence of pulmonary arterial hypertension and chronic thromboembolic pulmonary hypertension in the United States. Curr Med Res Opin 2011;27(9):1763-1768.

Korkeila M et al. Costs of care, long-term prognosis and quality of life in patients requiring renal replacement therapy during intensive care. Intensive Care Med 2000;26:1824–1831.

Kuitunen A et al. Acute renal failure after cardiac surgery: evaluation of the RIFLE classification. Ann Thorac Surg 2006;81:542–546.

Lafrance JP et al. Incidence and outcomes of acute kidney injury in a referred chronic kidney disease cohort. Nephrol Dial Transplant 2010;25:2203–2209.

Lam C et al. Pulmonary artery systolic pressure is an independent predictor of exercise capacity in hypertrophic cardiomyopathy. J Cardiac Failure 2009;15(6S).

Lammers AE et al. Epoprostenol treatment in children with severe pulmonary hypertension. Heart 2007;93:739-743.

Ling Y et al. Changing demographics, epidemiology, and survival of incident pulmonary arterial hypertension: results from the pulmonary hypertension registry of the United Kingdom and Ireland. Am J Respir Crit Care Med 2012;186(8):790–796.

Martel N et al. Risk For heparin-induced thrombocytopenia with unfractionated and low-molecular-weight heparin thromboprophylaxis: a meta-analysis. Blood 2005;106:2710-2715.

McLaughlin VV et al. ACCF/AHA 2009 expert consensus document on pulmonary hypertension. J Am Coll Cardiol 2009;53(17):1573-1619.

McLaughlin VV et al. Survival in primary pulmonary hypertension: the impact of epoprostenol therapy. Circulation 2002;106:1477-1482.

Metcalfe W et al. Acute renal failure requiring renal replacement therapy: incidence and outcome. QJM 2002;95:579–583.

Metnitz PGH et al. Effect of acute renal failure requiring renal replacement therapy on outcome in critically ill patients. Crit Care Med 2002;30:2051–2058.

Miyazawa T, Hiramoto M, Hiramoto T, Nishida O. Reversal of oleic acid-induced respiratory distress by prostacyclin (PGI2). Resp Physiol 1982; 47: 351-64.

Moncada S, Korbut R, Bunting S, Vane JR. Prostacyclin is a circulating hormone. Nature 1978; 273: 767-8.

Montani D et al. Cautious epoprostenol therapy is a safe bridge to lung transplantation in pulmonary veno-occlusive disease Eur Respir J 2009;34:1348–1356

Montani D, Achouh L, Dorfmüller P, et al. Pulmonary venoocclusive disease: clinical, functional, radiologic, and hemodynamic characteristics and outcome of 24 cases confirmed by histology. Medicine (Baltimore) 2008;87:220 –33.

Ogawa A et al. Safety and efficacy of epoprostenol therapy in pulmonary veno-occlusive disease and pulmonary capillary hemangiomatosis. Circ J 2012;76:1729-1736.

Ostermann M and Chang RW. Acute kidney injury in the intensive care unit according to RIFLE. Crit Care Med 2007;35:1837–1843.

Oudiz RJ et al. *Micrococcus*-associated central venous catheter infection in patients with pulmonary arterial hypertension. Chest 2004;126:90-94.

Pace-Asciak CR, Rosenthal A, Domazet Z. Comparison between the in vivo rate of metabolism of prostaglandin I2 and its blood-pressure-lowering response after intravenous administration in the rat. Biochim Biophys Acta 1979; 574: 182-6.

Palevsky PM et al. Intensity of renal support in critically ill patients with acute kidney injury. N Engl J Med 2008;359:7–20.

Peacock AJ et al. An epidemiological study of pulmonary arterial hypertension. Eur Respir J 2007;30:104–109.

Pieper PG et al. Pregnancy and pulmonary hypertension. Best Pract Res Clin Obstet Gynaecol 2014;28(4):579-591.

Regitz-Zagrosek V et al. ESC Guidelines on the management of cardiovascular diseases during pregnancy: the Task Force on the Management of Cardiovascular Diseases during Pregnancy of the European Society of Cardiology (ESC). Eur Heart J 2011;32:3147–3197.

REMODULIN (treprostinil) USPI. United Therapeutics Corp. Research Triangle Park, NC US. 2013. Accessed 23 October 2014. http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/021272s020lbledt.pdf.

RENAL Replacement Therapy Study Investigators. Intensity of continuous renal-replacement therapy in critically ill patients. N Engl J Med 2009;361:1627–1638.

Rich JD et al. The effect of diluent pH on bloodstream infection rates in patients receiving IV treprostinil for pulmonary arterial hypertension. Chest 2012;141(1):36–42.

Rich SChapter 250: Pulmonary Hypertension. In: Longo DL, Fauci AS, Kasper DL, Hauser SL, Jameson J, Loscalzo J. eds. *Harrison's Principles of Internal Medicine, 18e*. New York, NY: McGraw-Hill; 2012. Accessed October 23, 2014. http://accesspharmacy.mhmedical.com/content.aspx?bookid=331&Sectionid=40727029.

Rich S et al. Primary pulmonary hypertension: a national prospective study. Ann Intern Med 1987;107(2):216-223.

Rich S et al. The effect of high doses of calcium-channel blockers on survival in primary pulmonary hypertension. N Engl J Med 1992;327:76-81.

Ronco C et al. Management of severe acute renal failure in critically ill patients: an international survey in 345 centres. Nephrol Dial Transplant 2001;16:230-237.

Rosenkranz B, Fischer C, Frolich JC. Prostacyclin metabolites in human plasma. Clin Pharmacol Ther 1981; 29: 420-4.

Rudd MA et al. Temporal effects of thrombolytic agents on platelet function in vivo and their modulation by prostaglandins. Circ Res 1990;67:1175-1181.

Saggar R and Sitbon O. Hemodynamics in pulmonary arterial hypertension: current and future perspectives. Am J Cardiol 2012;110[suppl]:9S–15S.

Salmon JA, Mullane KM, Dusting GJ, Moncada S, Vane JR. Elimination of prostacyclin (PGI2) and 6-oxo-PGF1 in anaesthetised dogs. J Pharm Pharmacol 1979; 31: 529-32.

Silvester W et al. Epidemiology, management, and outcome of severe acute renal failure of critical illness in Australia. Crit Care Med 2001;29:1910–1915.

Simonneau G, Galiè N, Rubin LJ, et al. Clinical classification of pulmonary hypertension. J Am Coll Cardiol 2004;43:5S–12S.

Simonneau G, Robbins IM, Beghetti M, et al. Updated clinical classification of pulmonary hypertension. J Am Coll Cardiol 2009;54:S43-S54.

Sitbon O et al. EPITOME-2: an open-label study assessing the transition to a new formulation of intravenous epoprostenol in patients with pulmonary arterial hypertension. Am Heart J 2014;167(2):210-217.

Sitbon O. HIV-related pulmonary arterial hypertension: clinical presentation and management. AIDS 2008, 22(suppl 3):S55–S62.

Sitbon O et al. Long-term intravenous epoprostenol infusion in primary pulmonary hypertension: prognostic factors and survival. J Am Coll Cardiol 2002;40:780-788.

Sitbon O et al. Long-Term Response to calcium channel blockers in idiopathic pulmonary arterial hypertension. Circulation. 2005;111:3105-3111.

Skrinska VA, Lucas FV, Chisolm GM. Pharmacokinetics of prostacyclin. Thromb Haemostas 1983; 50: 341.

Sun FF, Taylor BM. Metabolism of prostacyclin in the rat. Biochemistry 1978; 17: 4096-101.

Sun FF, Taylor BM, McGuire JC, Wong PYK, Malik KU, McGiff JC. Metabolic disposition of prostacyclin. In: Vane JR, Bergstrom S (Editors). Prostacyclin New York: Raven Press, 1979: 119-31.

Susantitaphong P et al. World incidence of AKI: a meta-analysis. Clin J Am Soc Nephrol 2013;8:1482–1493.

Swaminathan M et al. Impact of early renal recovery on survival after cardiac surgery-associated acute kidney injury. Ann Thorac Surg 2010;89:1098–1104.

Taylor BM, Sun FF. Tissue distribution and biliary excretion of prostacyclin metabolites in the rat. J Pharmacol Exp Ther 1980; 214: 24-30.

Thabut G et al. Influence of donor characteristics on outcome after lung transplantation: a multicenter study. J Heart Lung Transplant 2005;24:1347–1353.

Thakar CV et al. Incidence and outcomes of acute kidney injury in intensive care units: a Veterans Administration study. Crit Care Med 2009;37:2552–2558.

Thomson JR et al. Sporadic primary pulmonary hypertension is associated with germline mutations of the gene encoding BMPR-II, a receptor member of the TGF-α family. J Med Genet 2000;37:741–745.

Topol EJ et al. Combined tissue-type plasminogen activator and prostaccyclin therapy for acute myocardial infarction. JACC 1989;14(4):877-884.

Uchino S et al. Acute renal failure in critically ill patients: a multinational, multicenter study. JAMA 2005;294:813–818.

Utsunomiya T, Krausz MM, Valeri CR, Shepro D, Hechtman HB. Treatment of pulmonary embolism with prostacyclin. Surgery 1980; 88: 25-30.

Vaara S et al. Population-based incidence, mortality and quality of life in critically ill patients treated with renal replacement therapy- a nationwide retrospective cohort study in Finnish ICUs. Crit Care 2012;16:R13.

Valdivia-Arenas MA. Bloodstream infections due to *Micrococcus* spp and intravenous epoprostenol. Infect Control Hosp Epidemiol 2009;30:1237.

van de Veerdonk MC et al. Progressive right ventricular dysfunction in patients with pulmonary arterial hypertension responding to therapy. J Am Coll Cardiol 2011;58(24):2511-2519.

van Heerden PV et al. Pulmonary toxicity of inhaled aerosolized prostacyclin therapy- an observational study. Anaesth Intensive Care 2000;28:161-166.

van Wolferen SA et al. Prognostic value of right ventricular mass, volume, and function in idiopathic pulmonary arterial hypertension. Eur Heart J 2007;28:1250–1257.

Vane JR, Bunting S, Moncada S. Prostacyclin in physiology and pathophysiology. Int Rev Exp Pathol 1982; 23: 161-207.

Vargaftig BB, Lefort J. Enhancement by prostacyclin of the contractility of the guinea pig airways smooth muscle. Eur J Pharmacol 1981; 74: 141-8.

VELETRI 1.5 mg, Powder for Solution for Infusion (epoprostenol) UK SmPC. Actelion Pharmaceuticals. Allschwil, Switzerland. 2013. Accessed 23 October 2014. http://www.medicines.org.uk/emc/medicine/27734.

VENTAVIS 10 micrograms/ml nebulizer solution (iloprost) UK SmPC. Bayer AG. Leverkusen, Germany. 2013. Accessed 23 October 2014. http://www.medicines.org.uk/emc/medicine/13743.

Waikar SS et al. Declining mortality in patients with acute renal failure, 1988 to 2002. J Am Soc Nephrol 2006;17:1143–1150.

WD1998/00052/00 (SBL 77-58). Epoprostenol sodium: Six month continuous infusion toxicity study in the Beagle dog.

Weiss BM et al. Outcome of pulmonary vascular disease in pregnancy: a systematic overview from 1978 through 1996. J Am Coll Cardiol 1998;31:1650–1657.

Wong PYK, McGiff JC, Sun FF, Malik KU. Pulmonary metabolism of prostacyclin (PGI2) in the rabbit. Biochem Biphys Res Comm 1978; 83: 731-8.

Wong PYK, McGiff JC, Cagen L, Malik KU, Sun FF. Metabolism of prostacyclin in the rabbit kidney. J Biol Chem 1979a: 254: 12-4.

Wong PYK, Sun FF, Malik KU, Cagen L, McGiff JC. Metabolism of prostacyclin in the isolated kidney and lung of the rabbit. In: Vane JR, Bergstrom S, editors. Prostacyclin. New York: Raven Press, 1979b: 133-45.

Wong PYK, Malik KU, Desiderio DM, McGiff JC, Sun FF. Hepatic metabolism of prostacyclin (PGI2) in the rabbit. Formation of a potent novel inhibitor of platelet aggregation. Biochem Biophys Res Comm 1980; 93: 486-94.

Yang X et al. Prevalence of pulmonary arterial hypertension in patients with connective tissue diseases: a systematic review of the literature. Clin Rheumatol 2013;32:1519-1531.

Yap RL and Mermel LA. *Micrococcus* infection in patients receiving epoprostenol by continuous infusion. Eur J Clin Microbiol Infect Dis 2003;22:704-705.

Ylikorkala O, Makila U-M. Prostacyclin and thromboxane in gynecology and obstetrics. Am J Obs Gynecol 1985; 152; 318-29.

Yung D et al. Outcomes in children with idiopathic pulmonary arterial hypertension. Circulation 2004;110:660-665.

ANNEX 1. EUDRAVIGILANCE INTERFACE

ANNEX 2. SMPC & PACKAGE LEAFLET

Note to Requestor:

Please be aware that the SMPC and Package leaflet included in the EU-RMP is not current and does not reflect the current registered details in the EU.

For example: Section 6.3 makes reference to a shelf-life of 18 months, however this has been extended in the EU to 36 months and is reflected in the current UK labelling, which can be accessed via the electronics medicine compendium.

ANNEX III

SUMMARY OF PRODUCT CHARACTERISTICS, LABELLING AND PACKAGE LEAFLET

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Flolan 0.5 mg powder and solvent for solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Epoprostenol 0.5mg powder for solution for infusion:
Each vial contains epoprostenol sodium equivalent to 0.5 mg epoprostenol.

One ml of reconstituted concentrate solution contains epoprostenol (as epoprostenol sodium) 10,000 nanogram (0.5 mg epoprostenol in 50 ml of solvent).

Excipients with known effect:
The amount of sodium present in the reconstituted concentrate solution equals 73 mg approximately.
The amount of sodium present in the powder for solution for infusion equals 3 mg approximately per vial.
The amount of sodium present in the solvent for parenteral use equals 70 mg approximately per vial.
For a full list of excipents, see section 6.1

3. PHARMACEUTICAL FORM

Powder and solvent for solution for infusion.

Powder for solution for infusion:
- White or off-white freeze dried powder

Solvent for parenteral use:
- Clear, colourless solution (pH 11.7 – 12.3)

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Flolan is indicated for:

Pulmonary Arterial Hypertension
Flolan 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 (see section 5.1).

Renal Dialysis
Flolan 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).

4.2 Posology and method of administration

Posology

Pulmonary Arterial Hypertension

Epoprostenol is only indicated for continuous infusion by intravenous route.

Treatment should only be initiated and monitored by a physician experienced in the treatment of pulmonary arterial hypertension.

Short-term (acute) dose ranging:

This procedure should be conducted in a hospital with adequate resuscitation equipment.

A short-term dose-ranging procedure administered via either a peripheral or central venous line is required to determine the long-term infusion rate. The infusion rate is initiated at 2 nanograms/kg/min and increased by increments of 2 nanograms/kg/min every 15 min or longer until maximum haemodynamic benefit or dose-limiting pharmacological effects are elicited.
If the initial infusion rate of 2 nanograms/kg/min is not tolerated, a lower dose which is tolerated by the patient should be identified.

Long-term continuous infusion:

Long-term continuous infusion of Flolan should be administered through a central venous catheter. Temporary peripheral i.v. infusions may be used until central access is established. Long-term infusions should be initiated at 4 nanograms/kg/min less than the maximum tolerated infusion rate determined during short-term dose-ranging. If the maximum tolerated infusion rate is 5 nanograms/kg/min or less, then the long-term infusion should be started at 1 nanograms/kg/min.

Dosage adjustments:

Changes in the long-term infusion rate should be based on persistence, recurrence or worsening of the patient's symptoms of pulmonary arterial hypertension or the occurrence of adverse reaction due to excessive doses of Flolan.

In general, the need for increases in dose from the initial long-term dose should be expected over time. Increases in dose should be considered if symptoms of pulmonary arterial hypertension persist, or recur after improving. The infusion rate should be increased by 1 to 2 nanograms/kg/min increments at intervals sufficient to allow assessment of clinical response; these intervals should be of at least 15 min. Following establishment of a new infusion rate, the patient should be observed, and erect and supine blood pressure and heart rate monitored for several hours to ensure that the new dose is tolerated.

During long-term infusion, the occurrence of dose-related pharmacological events similar to those observed during the dose-ranging period may necessitate a decrease in infusion rate, but the adverse reactions may occasionally resolve without dosage adjustment. Dosage decreases should be made gradually in 2 nanograms/kg/min decrements every 15 min or longer until the dose-limiting effects resolve. Abrupt withdrawal of Flolan or sudden large reductions in infusion rates should be avoided due to the risk of potential fatal rebound effect (see section 4.4). Except in life-threatening situations (e.g. unconsciousness, collapse, etc) infusion rates of Flolan should be adjusted only under the direction of a physician.

Renal Dialysis

Flolan is suitable for continuous infusion only, either intravascularly or into the blood supplying the dialyser.

The following schedule of infusion has been found effective in adults:
Prior to dialysis: 4 nanograms/kg/min intravenously for 15 mins
During dialysis: 4 nanograms/kg/min into the arterial inlet of the dialyser

The infusion should be stopped at the end of dialysis.
The recommended dose for renal dialysis should be exceeded only with careful monitoring of patient blood pressure.

Elderly
There is no specific information on the use of Flolan in patients over 65 years for renal dialysis or pulmonary arterial hypertension. In general, dose selection for an elderly patient should be made carefully, reflecting the greater frequency of decreased hepatic, renal (in the case of pulmonary arterial hypertension) or cardiac function and of concomitant disease or other medicine therapy.

Paediatric population
The safety and efficacy of epoprostenol in children younger than 18 years have not yet been established.

Method of administration

Precautions to be taken before handling or administering the medicinal product

Pulmonary Arterial Hypertension
Freshly prepared solutions for infusion (either as a concentrated solution or a further diluted solution) can be administered immediately or stored for up to 8 days at 2°C to 8°C prior to administration. Following this preparation or storage, the solution for infusion should be used within 72 hours at up to 25°C, or 48 hours at up to 30ºC, or 24 hours at up to 35 ºC, or 12 hours at up to 40 ºC.

Renal Dialysis
Freshly prepared solutions for infusion (either as a concentrated solution or a further diluted solution) can be administered for up to 12 hours at up to 25°C.

The reconstituted solution should be examined prior to administration. Its use is forbidden in the presence of a discoloration or particles.

For instructions on reconstitution and dilution of the medicinal product before administration, see section 6.6.

Epoprostenol must not be administered as a bolus injection.

4.3 Contraindications

Flolan is contraindicated in patients:
- with known hypersensitivity to the active substance(s) or to any of the excipients listed in section 6.1.
- with congestive heart failure arising from severe left ventricular dysfunction.
- Flolan must not be used chronically in patients who develop pulmonary oedema during dose-ranging.

4.4 Special warnings and precautions for use

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.

Flolan is a potent pulmonary and systemic vasodilator. The cardiovascular effects during infusion disappear within 30 min of the end of administration.

Flolan is a potent inhibitor of platelet aggregation, therefore, an increased risk for haemorrhagic complications should be considered, particularly for patients with other risk factors for bleeding (see section 4.5).

If excessive hypotension occurs during administration of Flolan, the dose should be reduced or the infusion discontinued. Hypotension may be profound in overdose and may result in loss of consciousness (see section 4.9).

Blood pressure and heart rate should be monitored during administration of Flolan.

Flolan may either decrease or increase heart rate. The change is thought to depend on both the basal heart rate and the concentration of Flolan administered.

The effects of Flolan on heart rate may be masked by concomitant use of drugs which affect cardiovascular reflexes.

Extreme caution is advised in patients with coronary artery disease.

Elevated serum glucose levels have been reported (see section 4.8).

The solvent contains no preservative; consequently a vial should be used once only and then discarded.

This medicinal product contains sodium, which should be taken into consideration by patients on a controlled sodium diet.

Pulmonary Arterial Hypertension
Some patients with pulmonary arterial hypertension have developed pulmonary oedema during dose-ranging, which may be associated with pulmonary veno-occlusive disease. Flolan must not be used chronically in patients who develop pulmonary oedema during dose initiation (see section 4.3).

Abrupt withdrawal or interruption of infusion must be avoided, except in life-threatening situations. An abrupt interruption of therapy can induce a rebound of pulmonary arterial hypertension resulting in dizziness, asthenia, increased dyspnoea, and may lead to death (see section 4.2).

Flolan is infused continuously through a permanent indwelling central venous catheter via a small, portable infusion pump. Thus, therapy with Flolan requires commitment by the patient to sterile drug reconstitution, drug administration, care of the permanent central venous catheter, and access to intense and ongoing patient education.

Sterile technique must be adhered to in preparing the drug and in the care of the catheter. Even brief interruptions in the delivery of Flolan may result in rapid symptomatic deterioration. The decision to administer Flolan for pulmonary arterial hypertension should be based upon the patient's understanding that there is a high likelihood that therapy with Flolan will be needed for prolonged periods, possibly years, and the patient's ability to accept and care for a permanent i.v. catheter and infusion pump should be carefully considered.

Renal Dialysis
The hypotensive effect of Flolan may be enhanced by the use of acetate buffer in the dialysis bath during renal dialysis.

During renal dialysis with Flolan it should be ensured that the cardiac output increases more than minimally so that delivery of oxygen to peripheral tissue is not diminished.

Flolan is not a conventional anticoagulant. Flolan has been successfully used instead of heparin in renal dialysis but in a small proportion of dialyses clotting has developed in the dialysis circuit, requiring termination of dialysis. When Flolan is used alone, measurements such as activated whole blood clotting time may not be reliable.

4.5 Interaction with other medicinal products and other forms of interaction
When Flolan is administered to patients receiving concomitant anticoagulants standard anticoagulant monitoring is advisable.

The vasodilator effects of Flolan may augment or be augmented by concomitant use of other vasodilators.

As reported with other prostaglandin analogues, Flolan may reduce the thrombolytic efficacy of tissue plasminogen activator (t-PA) by increasing hepatic clearance of t-PA.

When NSAIDS or other drugs affecting platelet aggregation are used concomitantly, there is the potential for Flolan to increase the risk of bleeding.

Patients on digoxin may show elevations of digoxin concentrations after initiation of therapy with Flolan, which although transient, may be clinically significant in patients prone to digoxin toxicity.

4.6 Fertility, pregnancy,and lactation

Pregnancy
There is a limited amount of data from the use of epoprostenol in pregnant women.
Animal studies did not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section 5.3).
Given the absence of alternative medicines, epoprostenol can be used in those women who choose to continue their pregnancy, despite the known risk of pulmonary arterial hypertension during pregnancy.

Breast-feeding
It is unknown if epoprostenol or its metabolites are excreted in human milk. A risk to the breastfeeding child cannot be excluded. Breast-feeding should be discontinued during treatment with Flolan.

Fertility
There are no data on the effects of epoprostenol on fertility in humans. Reproductive studies in animals have shown no effects on fertility (see section 5.3).

4.7 Effects on ability to drive and use machines

Pulmonary arterial hypertension and its therapeutic management may affect the ability to drive and operate machinery.

There are no data regarding the effect of Flolan used in renal dialysis on the ability to drive or operate machinery.

4.8 Undesirable effects

Adverse events are listed below by system organ class and frequency. Frequencies are defined as follows: very common ≥1/10 (≥10%); common ≥1/100 and <1/10 (≥1% and <10%); uncommon ≥1/1000 and <1/100 (≥0.1% and <1%); rare ≥1/10,000 and <1/1000 (≥0.01% and <0.1%); very rare <1/10,000 (< 0.01%) and not known (cannot be estimated from the available data).

Infections and Infestations	
Common	Sepsis, septicaemia (mostly related to delivery system for Flolan)[1]
Blood and Lymphatic System Disorders	
Common	Decreased platelet count, bleeding at various sites (e.g. pulmonary, gastrointestinal, epistaxis, intracranial, post-procedural, retroperitoneal)
Unknown	Splenomegaly, Hypersplenism
Endocrine Disorders	
Very rare	Hyperthyroidism
Psychiatric Disorders	
Common	Anxiety, nervousness
Very rare	Agitation
Nervous System Disorders	
Very common	Headache

Cardiac Disorders	
Common	Tachycardia[2], bradycardia[3],
Vascular Disorders	
Very common	Facial flushing (seen even in the anaesthetised patient)
Common	Hypotension
Very rare	Pallor
Not known	Ascites
Respiratory, thoracic and mediastinal disorders	
Unknown	Pulmonary oedema
Gastrointestinal Disorders	
Very common	Nausea, vomiting, diarrhoea
Common	Abdominal colic, sometimes reported as abdominal discomfort
Uncommon	Dry mouth
Skin and Subcutaneous Tissue Disorders	
Common	Rash
Uncommon	Sweating
Musculoskeletal and Connective Tissue Disorders	
Very common	Jaw pain
Common	Arthralgia
General Disorders and Administration Site Conditions	
Very common	Pain (unspecified)
Common	Pain at the injection site*, chest pain
Rare	Local infection*
Very rare	Erythema over the infusion site*, occlusion of the long i.v. catheter*, lassitude, chest tightness
Investigations	
Unknown	Blood glucose increased
* Associated with the delivery system for Flolan	
[1] Catheter-related infections caused by organisms not always considered pathogenic (including micrococcus) have been reported.	
[2] Tachycardia has been reported as a response to Flolan at doses of 5 nanograms/kg/min and below.	
[3] Bradycardia, sometimes accompanied by orthostatic hypotension, has occurred in healthy volunteers at doses of Flolan greater than 5 nanograms/kg/min. Bradycardia associated with a considerable fall in systolic and diastolic blood pressure has followed i.v. administration of a dose of Flolan equivalent to 30 nanograms/kg/min in healthy conscious volunteers.	

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

The main feature of overdose is likely to be hypotension.
In general, events seen after overdose of Flolan represent exaggerated pharmacological effects of the drug (e.g. hypotension and complications of hypotension).
If overdose occurs reduce the dose or discontinue the infusion and initiate appropriate supportive measures as necessary; for example plasma volume expansion and/or adjustment to pump flow.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antithrombotic Agents; Platelet aggregation inhibitors excl. heparin,
ATC code: B01AC09

Mechanism of action
Epoprostenol Sodium, the monosodium salt of epoprostenol, 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.

Pharmacodynamic effects
An infusion of 4 nanograms/kg/min for 30 minutes has been shown to have no significant effect on heart rate or blood pressure, although facial flushing may occur at these levels.

Pulmonary Arterial Hypertension

Intravenous epoprostenol infusions of up to 15 minutes have been found to produce dose-related increases in cardiac index (CI) and stroke volume (SV), and dose-related decreases in pulmonary vascular resistance (PVR), total pulmonary resistance (TPR) and mean systemic arterial pressure (SAPm). The effects of epoprostenol on mean pulmonary artery pressure (PAPm) in patients with PPH were variable and minor.

Renal Dialysis

The effects of epoprostenol on platelet aggregation is dose-related when between 2 and 16 nanograms/kg/min is administered intravenously, and significant inhibition of aggregation induced by adenosine diphosphate is observed at doses of 4 nanograms/kg/min and above.

Effects on platelets have been found to disappear within 2 hours of discontinuing the infusion, and haemodynamic changes due to epoprostenol to return to baseline within 10 minutes of termination of 60 minutes infusion at 1 to 16 nanograms/kg/min.

Higher circulating doses of epoprostenol (20 nanograms/kg/min) disperse circulating platelet aggregates and increase by up to two fold the cutaneous bleeding time.

Epoprostenol potentiates the anticoagulant activity of heparin by approximately 50%, possibly reducing the release of heparin neutralising factor.

Clinical efficacy and safety

Pulmonary Arterial Hypertension

Chronic continuous infusions of epoprostenol in patients with idiopathic or heritable PAH were studied in 2 prospective, open, randomised trials of 8 and 12 weeks' duration (N=25 and N=81, respectively) comparing epoprostenol plus conventional therapy to conventional therapy alone. Conventional therapy varied among patients and included some or all of the following: anticoagulants in essentially all patients; oral vasodilators, diuretics, and digoxin in one half to two thirds of patients; and supplemental oxygen in about half the patients. Except for 2 New York Heart Association (NYHA) functional Class II patients, all patients

were either functional Class III or Class IV. As results were similar in the 2 studies, the pooled results are described. The combined baseline 6-minute walk test median values for the conventional therapy group and epoprostenol plus conventional therapy group was 266 meters and 301 meters, respectively.

Improvements from baseline in cardiac index (0.33 vs. -0.12 L/min/m^2), stroke volume (6.01 vs. -1.32 mL/beat), arterial oxygen saturation (1.62 vs. -0.85%), mean pulmonary artery pressure (-5.39 vs. 1.45 mm Hg), mean right atrial pressure (-2.26 vs. 0.59 mm Hg), total pulmonary resistance (-4.52 vs. 1.41 Wood U), pulmonary vascular resistance (-3.60 vs. 1.27 Wood U), and systemic vascular resistance (-4.31 vs. 0.18 Wood U) were statistically different between patients who received epoprostenol chronically and those who did not. Mean systemic arterial pressure was not significantly different between the two groups (-4.33 vs. -3.05 mm Hg). These haemodynamic improvements appeared to persist when epoprostenol was administered for at least 36 months in an open, nonrandomized study.

Statistically significant improvement was observed in exercise capacity (p=0.001), as measured by the 6MWT in patients receiving continuous intravenous epoprostenol plus conventional therapy (N=52) for 8 or 12 weeks compared to those receiving conventional therapy alone (N=54) (combined week 8 and 12 change from baseline – median: 49 vs. -4 meters; mean: 55 vs. -4 meters). Improvements were apparent as early as the first week of therapy. At the end of the treatment period in the 12 weeks study, survival was improved in NYHA functional Class III and Class IV patients. Eight of 40 (20%) patients receiving conventional therapy alone died, whereas none of the 41 patients receiving epoprostenol died (p=0.003).

Chronic continuous infusions of epoprostenol in patients with PAH/SSD were studied in a prospective, open, randomised trial of 12 weeks' duration comparing epoprostenol plus conventional therapy (N = 56) to conventional therapy alone (N = 55). Except for 5 NYHA functional Class II patients, all patients were either functional Class III or Class IV. Conventional therapy varied among patients and included some or all of the following: anticoagulants in essentially all patients, supplemental oxygen and diuretics in two thirds of the patients, oral vasodilators in 40% of the patients, and digoxin in a third of the patients. The primary efficacy endpoint for the study was improvement in the 6MWT. The median baseline value for the conventional therapy group and epoprostenol plus conventional therapy group was 240 meters and 270 meters, respectively. A statistically significant increase in CI, and statistically significant decreases in PAPm, RAPm, PVR, and SAPm after 12 weeks of treatment were observed in patients who received epoprostenol chronically compared to those who did not.

Over 12 weeks, a statistical difference (p<0.001) in the change from baseline for the 6MWT was observed in the group receiving epoprostenol and conventional therapy as compared to the group receiving conventional therapy alone (median: 63.5 vs. -36.0 meters; mean: 42.9 vs. -40.7 meters). Improvements were apparent in some patients at the end of the first week of therapy. Increases in exercise capacity were accompanied by statistically significant improvements in dyspnoea, as measured by the Borg Dyspnea Index. At week 12, NYHA functional class improved in 21 of 51 (41%) patients treated with epoprostenol compared to none of the 48 patients treated with conventional therapy alone. However, more patients in both treatment groups (28/51 [55%] with epoprostenol and 35/48 [73%] with conventional therapy alone) showed no change in functional class, and 2/51 (4%) with epoprostenol and 13/48 (27%) with conventional therapy alone worsened.

No statistical difference in survival over 12 weeks was observed in PAH/SSD patients treated with epoprostenol as compared to those receiving conventional therapy alone. At the end of the treatment period, 4 of 56 (7%) patients receiving epoprostenol died, whereas 5 of 55 (9%) patients receiving conventional therapy alone died.

Renal Dialysis Six heparin-controlled studies and five emergency studies explored the place of epoprostenol in the general management of renal dialysis, using different techniques. Primary measurements of efficacy included intradialytic removal of BUN and creatinine, intradialytic removal of fluid (ultrafiltration), and clotting within the extracorporeal circuit.

Major clotting (dialysis permanently suspended, or requiring changing of artificial kidney) occurred in approximately 9% (n=56) of all epoprostenol dialyses and in <1% (n=1) of heparin dialyses in major

controlled studies and emergency studies. Most epoprostenol dialyses (67%) that required replacement of artificial kidney were completed subsequently with epoprostenol without clotting. However, 9 of 27 epoprostenol dialyses were unsuccessful following multiple attempts.

Independent of technical difficulties which occurred rarely with either treatment, major dialysis-limiting clotting did not occur in 93% of all epoprostenol dialyses and 99% of all heparin dialyses.

Minor clotting (sufficient to require intervention, but not permanently suspending dialysis or requiring changing of the artificial kidney) was reported more frequently during epoprostenol than during heparin dialyses. None of the dialyses using heparin and 5% (n=32) of dialyses using epoprostenol had minor clotting.
Visible clotting (not necessitating intervention) was reported in another 31% of epoprostenol dialyses and 5% of heparin dialyses.

To establish that renal dialysis patients at increased risk of haemorrhage bleed less frequently with epoprostenol than heparin, 2 major prospectively controlled studies were conducted. Each patient was randomly assigned to a sequence of heparin or epoprostenol dialyses and received up to 6 dialyses per entry in one study and up to 3 dialyses per entry in another study.

Bleeding risk was defined as:

- Very high risk – presence of active bleeding at the time of dialysis initiation

- High risk – having had within 3 days prior to dialysis an active bleed that stopped at the pre-dialysis phase; or having incurred surgical or traumatic wounds within 3 days prior to dialysis

Twelve patients at very high risk of haemorrhage received 35 epoprostenol dialyses and 11 patients received 28 heparin dialyses in major controlled studies. Sixteen patients received 24 epoprostenol dialyses in emergency studies.

In major controlled studies, when all dialyses were combined for each treatment (heparin or epoprostenol), more heparin patients bled during the day prior to dialysis (N=13/17 vs. 8/23), dialysis day (N=25/28 vs. 16/35) and the day following dialysis (N=16/24 vs. 5/24) than epoprostenol patients during the same time periods.

Those patients who continued to bleed were evaluated for changes in bleeding severity. Severity of bleeding in those patients was improved more frequently with epoprostenol the day prior to dialysis and on dialysis day (predialysis: N=4/8; dialysis: N=6/16) than with heparin (predialysis: N=4/13; dialysis: N=4/25). However, the reverse was observed for postdialysis days with epoprostenol (N=1/5) compared to heparin (N=8/16). Bleeding severity worsened during only 1 dialysis day with epoprostenol (N=1/16) whereas severity worsened during 5 dialysis days (N=5/25) and 2 predialysis days (N=2/13) with heparin.

Patients who did not have clear evidence of bleeding just prior to their first study dialysis, but who bled within 3 days prior were classified as high risk of haemorrhage. Nineteen patients received 51 heparin dialyses and 19 received 44 epoprostenol dialyses in major controlled studies.

When all dialyses were combined, slightly more epoprostenol patients appeared to bleed during the predialysis (N=12/25 vs. 8/32), dialysis (23/44 vs. 14/51) and postdialysis (8/34 vs. 5/44) days compared to heparin patients during the same periods.

5.2 Pharmacokinetic properties

Due to the chemical instability, high potency and short half-life of epoprostenol, no precise and accurate assay has been identified as appropriate for quantifying epoprostenol in biological fluids.

Intravenously administered epoprostenol is rapidly distributed from blood to tissue.

At normal physiological pH and temperature, epoprostenol breaks down spontaneously to 6-oxo-prostaglandin F_1 alpha, although there is some enzymatic degradation to other products.

Following the administration of radiolabelled epoprostenol to humans, at least 16 metabolites were found, 10 of which were structurally identified.

Unlike many other prostaglandins, epoprostenol is not metabolised during passage through the pulmonary circulation.

The half-life for the spontaneous breakdown to 6-oxo-prostaglandin F_1 alpha in man is expected to be no more than 6 minutes, and may be as short as 2 to 3 minutes, as estimated from *in vitro* rates of degradation of epoprostenol in human whole blood.

Following the administration of radiolabelled epoprostenol to humans, the urinary and faecal recoveries of radioactivity were 82% and 4%, respectively.

5.3 Preclinical safety data

Non-clinical data revealed no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, and toxicity to reproduction and development. No long-term animal studies have been conducted to determine the carcinogenic potential of epoprostenol.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Powder for solution for infusion:
Mannitol
Glycine
Sodium Chloride
Sodium Hydroxide (for pH adjustment)

Solvent for parenteral use:
Glycine
Sodium Chloride
Sodium Hydroxide (for pH adjustment)
Water for Injection

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

Unopened vials

Powder for solution for infusion: 3 years

Solvent for parenteral use: 18 months

Stability during administration

Reconstituted/diluted solutions using solvent for pulmonary arterial hypertension
Freshly prepared solutions for infusion (either as a concentrated solution or a further diluted solution) can be administered immediately or stored for up to 8 days at 2°C to 8°C prior to administration. Following this preparation or storage, the solution for infusion should be used within:

- 72 hours at up to 25°C or
- 48 hours at up to 30ºC or
- 24 hours at up to 35 ºC or
- 12 hours at up to 40 ºC

Discard any unused solution after this time.

Reconstituted solutions using solvent for renal dialysis
Reconstitution and subsequent dilution should be carried out immediately prior to use (see section 6.6). Freshly prepared solutions for infusion (either as a concentrated solution or a further diluted solution) can be administered for up to 12 hours at up to 25°C.

Discard any unused solution after this time.

6.4 Special precautions for storage

Powder for solution for infusion:
Do not store vials above 25°C. Protect from light. Keep dry. Do not freeze. Store in the original package.

Solvent for parenteral use:
Do not store vials above 25°C. Do not freeze. Protect from light. Store in the original package.
The solvent contains no preservative; consequently a vial should be used once only and then discarded.

For storage conditions after reconstitution and dilution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

Powder for solution for infusion:
Clear (type 1) glass vials with synthetic butyl rubber stoppers and an aluminium collar with a snap-off top.

Solvent for parenteral use:
Clear plastic vials with synthetic butyl rubber stoppers and an external aluminium collar with a purple plastic flip-top cover.

Pack sizes:
Pulmonary Arterial Hypertension
There are three presentations available in 0.5 mg for use in the treatment of pulmonary arterial hypertension, as follows:
- One 0.5 mg powder vial and one solvent vial and a filter unit.
- One 0.5 mg powder vial and two solvent vials and a filter unit.
- One 0.5 mg powder vial.

Renal Dialysis
There is only one presentation available for use in the treatment of renal dialysis, as follows:

- One 0.5 mg powder vial and one solvent vial and a filter unit.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

The stability of solutions of Flolan is pH dependent. Only the solvent supplied should be used for reconstitution of freeze-dried Flolan and only the recommended infusion solutions, in the stated ratio, should be used for further dilution, otherwise the required pH may not be maintained.

Reconstitution and dilution of Flolan must be carried out using aseptic technique, ideally immediately prior to clinical use.

Reconstitution, dilution and calculation of infusion rate:

Particular care should be taken in the preparation of the infusion and in calculating the rate of infusion. The procedure given below should be closely followed.

Pulmonary Arterial Hypertension

There are three 0.5 mg packs available for use in the treatment of pulmonary arterial hypertension, as follows:

- One vial containing sterile, freeze-dried Flolan equivalent to 0.5 mg Flolan, supplied with one 50 mL vial of solvent and a filter unit.

- One vial containing sterile, freeze-dried Flolan equivalent to 0.5 mg Flolan, supplied with two 50 mL vials of solvent and a filter unit.

- One vial containing sterile, freeze-dried Flolan equivalent to 0.5 mg Flolan supplied alone.

There are also three 1.5 mg packs available for use in the treatment of pulmonary arterial hypertension.

Initially a pack containing solvent for parenteral use must be used. During chronic Flolan therapy the final concentration of solution may be increased by the addition of a further 0.5 mg or 1.5 mg vial of freeze-dried Flolan.

Only vials of the same amount as that included in the initial starter pack may be used to increase the final concentration of solution.

Reconstitution:

1. Use only the sterile solvent solution provided for reconstitution.

2. Withdraw approximately 10 mL of the sterile solvent solution into a sterile syringe, inject it into the vial containing the freeze-dried epoprostenol and shake gently until the powder has dissolved.

3. Draw up the resulting epoprostenol solution into the syringe, re-inject it into the remaining volume of the sterile solvent solution and mix thoroughly.

This solution is now referred to as the concentrated solution.

- Where a pack containing 0.5 mg epoprostenol is reconstituted with 50 mL sterile solvent the resultant concentration is 10,000 nanograms/mL epoprostenol.

Only this concentrated solution is suitable for further dilution prior to use.

Dilution:

Flolan may be used either as concentrated solution or in a diluted form for the treatment of pulmonary arterial hypertension. Only the solvent provided may be used for the further dilution of reconstituted Flolan. Sodium chloride 0.9% w/v solution must not be used when Flolan is to be used for the treatment of pulmonary arterial hypertension. Flolan must not be administered with other parenteral solutions or medications when used for pulmonary arterial hypertension.

To dilute the concentrated solution, draw it up into a larger syringe and then attach the sterile filter provided to the syringe.

Dispense the concentrated solution directly into the solvent using firm but not excessive pressure; the typical time taken for filtration of 50 mL of concentrated solution is 70 seconds. Mix well.

The filter unit must be used once only and then discarded.

Concentrations commonly used in the treatment pulmonary arterial hypertension are as follows:

- 5,000 nanograms/mL - One vial containing 0.5 mg Flolan reconstituted and diluted to a total volume of 100 mL in solvent.

- 10,000 nanograms/mL - Two vials containing 0.5 mg Flolan reconstituted and diluted to a total volume of 100 mL in solvent.

Calculation of infusion rate:

The infusion rate may be calculated from the formula given above for renal dialysis. Examples for some concentrations commonly used in pulmonary arterial hypertension are shown below.

Infusion rates for a concentration of 5,000 nanograms/mL

Example For Dosing Using a Concentration of 5,000 nanograms/mL										
Dosage (nanograms/ kg/ min)	Bodyweight (kg)									
		20	30	40	50	60	70	80	90	100
2		0.5	0.7	1.0	1.2	1.4	1.7	1.9	2.2	2.4
4		1.0	1.4	1.9	2.4	2.9	3.4	3.8	4.3	4.8
6		1.4	2.2	2.9	3.6	4.3	5.0	5.8	6.5	7.2
8		1.9	2.9	3.8	4.8	5.8	6.7	7.7	8.6	9.6
10		2.4	3.6	4.8	6.0	7.2	8.4	9.6	10.8	12.0
12		2.9	4.3	5.8	7.2	8.6	10.1	11.5	13.0	14.4
14		3.4	5.0	6.7	8.4	10.1	11.8	13.4	15.1	16.8
16		3.8	5.8	7.7	9.6	11.5	13.4	15.4	17.3	19.2
	Flow rates in **mL/h**									

Infusion rates for a concentration of 10,000 nanograms/mL

Example For Dosing Using a Concentration of 10,000 nanograms/mL									
Dosage (nanograms/ kg/ min)	Bodyweight (kg)								
	20	30	40	50	60	70	80	90	100
2	0.2	0.4	0.5	0.6	0.7	0.8	1.0	1.1	1.2
4	0.5	0.7	1.0	1.2	1.4	1.7	1.9	2.2	2.4
6	0.7	1.1	1.4	1.8	2.2	2.5	2.9	3.2	3.6
8	1.0	1.4	1.9	2.4	2.9	3.4	3.8	4.3	4.8
10	1.2	1.8	2.4	3.0	3.6	4.2	4.8	5.4	6.0
12	1.4	2.2	2.9	3.6	4.3	5.0	5.8	6.5	7.2
14	1.7	2.5	3.4	4.2	5.0	5.9	6.7	7.6	8.4
16	1.9	2.9	3.8	4.8	5.8	6.7	7.7	8.6	9.6
	Flow rates in **mL/h**								

Higher infusion rates, and therefore, more concentrated solutions may be necessary with long-term administration of Flolan.

Renal Dialysis

The pack suitable for use in renal dialysis contains 0.5 mg freeze-dried Flolan plus 50 mL solvent.

Reconstitution:

Ideally reconstitution should be carried out immediately prior to use.

The pack suitable for use in renal dialysis contains 0.5 mg freeze-dried epoprostenol and one 50 mL sterile solvent.

1. Use only the solvent provided for reconstitution.

2. Withdraw approximately 10 mL of the solvent into a sterile syringe, inject it into the vial containing 0.5 mg freeze-dried Flolan powder and shake gently until the powder has dissolved.

3. Draw up the resulting Flolan solution into the syringe, re-inject it into the remaining volume of the solvent and mix thoroughly.

This solution is now referred to as the concentrated solution and contains 10,000 nanograms/mL Flolan. Only this concentrated solution is suitable for further dilution prior to use.

When 0.5 mg Flolan powder for i.v. infusion is reconstituted with 50 mL of solvent, the final injection has a pH of approximately 12 and a sodium ion content of approximately 73 mg.

Dilution:

The concentrated solution is normally further diluted immediately prior to use. It may be diluted with sodium chloride 0.9% w/v (saline) solution, in a ratio of 2.3 volumes of saline to 1 volume of concentrated solution, e.g. 50 mL of concentrated solution further diluted with 117 mL of saline.

Other common i.v. fluids are unsatisfactory for the dilution of concentrated solution as the required pH is not attained. Flolan solutions are less stable at low pH.

To dilute the concentrated solution, draw it up into a larger syringe and then attach the sterile filter provided to the syringe.

Dispense the concentrated solution directly into the chosen infusion solution using firm but not excessive pressure; the typical time taken for filtration of 50 mL of concentrated solution is 70 seconds. Mix well. The filter unit must be used once only and then discarded.

For administration using a pump capable of delivering small volume constant infusions, suitable aliquots of concentrated solution may be diluted with sterile sodium chloride 0.9% w/v solution.

When reconstituted and diluted as directed above, Flolan infusion solutions will retain 90% of their initial potency for approximately 12 hours at 25°C.

Calculation of infusion rate:
The infusion rate may be calculated from the following formula:

$$\text{Infusion rate (mL/min)} = \frac{\text{dosage (nanogram/kg/min) x bodyweight (kg)}}{\text{concentration of solution (nanogram/mL)}}$$

Infusion rate (mL/h) = Infusion rate (mL/min) x 60

Infusion rate formulae – examples

When used in renal dialysis Flolan may be administered as the concentrated solution (a) or in diluted form (b).

a. Using concentrated solution, i.e. 10,000 nanograms/mL Flolan:

Example For Dosing Using a Concentration of 10,000 nanograms/mL								
Dosage (nanograms/ kg/min)	Bodyweight (kg)							
	30	40	50	60	70	80	90	100
1	0.18	0.24	0.30	0.36	0.42	0.48	0.54	0.60
2	0.36	0.48	0.60	0.72	0.84	0.96	1.08	1.20
3	0.54	0.72	0.90	1.08	1.26	1.44	1.62	1.80
4	0.72	0.96	1.20	1.44	1.68	1.92	2.16	2.40
5	0.90	1.20	1.50	1.80	2.10	2.40	2.70	3.00
	Flow rates in **mL/h**							

b. *Diluted*: A commonly used dilution is:

15 mL concentrated solution + 35 mL sodium chloride 0.9% w/v solution.
Resultant concentration = 3,000 nanograms/mL Flolan:

Example For Dosing Using a Concentration of 3,000 nanograms/mL								
Dosage (nanograms/ kg/min)	Bodyweight (kg)							
	30	40	50	60	70	80	90	100
1	0.60	0.80	1.00	1.20	1.40	1.60	1.80	2.00
2	1.20	1.60	2.00	2.40	2.80	3.20	3.60	4.00
3	1.80	2.40	3.00	3.60	4.20	4.80	5.40	6.00
4	2.40	3.20	4.00	4.80	5.60	6.40	7.20	8.00
5	3.00	4.00	5.00	6.00	7.00	8.00	9.00	10.00
	Flow rates in **mL/h**							

7. MARKETING AUTHORISATION HOLDER

<{See Annex I - To be completed nationally}>

{Name and address}
<{tel}>
<{fax}>
<{e-mail}>

8. MARKETING AUTHORISATION NUMBER(S)

<{To be completed nationally}>

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

<{To be completed nationally}>

10. DATE OF REVISION OF THE TEXT

<{To be completed nationally}>

1. NAME OF THE MEDICINAL PRODUCT

Flolan 1.5 mg powder and solvent for solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Epoprostenol 1.5mg powder for solution for infusion:
Each vial contains epoprostenol sodium equivalent to 1.5 mg epoprostenol.

One ml of reconstituted concentrate solution contains epoprostenol (as epoprostenol sodium) 30,000 nanogram (1.5 mg epoprostenol in 50 ml of solvent).

Excipients with known effect:
The amount of sodium present in the reconstituted concentrate solution equals 73mg approximately.
The amount of sodium present in the powder for solution for infusion equals 3 mg approximately per vial.
The amount of sodium present in the solvent for parenteral use equals 70 mg approximately per vial.

For a full list of excipents, see section 6.1

3. PHARMACEUTICAL FORM

Powder and solvent for solution for infusion.

Powder for solution for infusion:
- White or off-white freeze dried powder

Solvent for parenteral use:
- Clear, colourless solution (pH 11.7 – 12.3)

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Flolan 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 (see section 5.1).

4.2 Posology and method of administration

Posology

Epoprostenol is only indicated for continuous infusion by intravenous route.

Treatment should only be initiated and monitored by a physician experienced in the treatment of pulmonary arterial hypertension.

Short-term (acute) dose ranging:

This procedure should be conducted in a hospital with adequate resuscitation equipment.

A short-term dose-ranging procedure administered via either a peripheral or central venous line is required to determine the long-term infusion rate. The infusion rate is initiated at 2 nanograms/kg/min and increased

by increments of 2 nanograms/kg/min every 15 min or longer until maximum haemodynamic benefit or dose-limiting pharmacological effects are elicited.
If the initial infusion rate of 2 nanograms/kg/min is not tolerated, a lower dose which is tolerated by the patient should be identified.

Long-term continuous infusion:

Long-term continuous infusion of Flolan should be administered through a central venous catheter. Temporary peripheral i.v. infusions may be used until central access is established. Long-term infusions should be initiated at 4 nanograms/kg/min less than the maximum tolerated infusion rate determined during short-term dose-ranging. If the maximum tolerated infusion rate is 5 nanograms/kg/min or less, then the long-term infusion should be started at 1 nanograms/kg/min.

Dosage adjustments:

Changes in the long-term infusion rate should be based on persistence, recurrence or worsening of the patient's symptoms of pulmonary arterial hypertension or the occurrence of adverse reaction due to excessive doses of Flolan.

In general, the need for increases in dose from the initial long-term dose should be expected over time. Increases in dose should be considered if symptoms of pulmonary arterial hypertension persist, or recur after improving. The infusion rate should be increased by 1 to 2 nanograms/kg/min increments at intervals sufficient to allow assessment of clinical response; these intervals should be of at least 15 min. Following establishment of a new infusion rate, the patient should be observed, and erect and supine blood pressure and heart rate monitored for several hours to ensure that the new dose is tolerated.

During long-term infusion, the occurrence of dose-related pharmacological events similar to those observed during the dose-ranging period may necessitate a decrease in infusion rate, but the adverse reactions may occasionally resolve without dosage adjustment. Dosage decreases should be made gradually in 2 nanograms/kg/min decrements every 15 min or longer until the dose-limiting effects resolve. Abrupt withdrawal of Flolan or sudden large reductions in infusion rates should be avoided due to the risk of potential fatal rebound effect (see section 4.4). Except in life-threatening situations (e.g. unconsciousness, collapse, etc) infusion rates of Flolan should be adjusted only under the direction of a physician.

Elderly

There is no specific information on the use of Flolan in patients over 65 years for pulmonary arterial hypertension. In general, dose selection for an elderly patient should be made carefully, reflecting the greater frequency of decreased hepatic, renal or cardiac function and of concomitant disease or other medicine therapy.

Paediatric population
The safety and efficacy of epoprostenol in children younger than 18 years have not yet been established.

Method of administration

Precautions to be taken before handling or administering the medicinal product

Freshly prepared solutions for infusion (either as a concentrated solution or a further diluted solution) can be administered immediately or stored for up to 8 days at 2°C to 8°C prior to administration. Following this preparation or storage, the solution for infusion should be used within 72 hours at up to 25°C, or 48 hours at up to 30ºC, or 24 hours at up to 35 ºC, or 12 hours at up to 40 ºC.

The reconstituted solution should be examined prior to administration. Its use is forbidden in the presence of a discoloration or particles.

For instructions on reconstitution and dilution of the medicinal product before administration, see section 6.6.

Epoprostenol must not be administered as a bolus injection.

4.3 Contraindications

Flolan is contraindicated in patients:

- with known hypersensitivity to the active substance(s) or to any of the excipients listed in section 6.1.
- with congestive heart failure arising from severe left ventricular dysfunction.
- Flolan must not be used chronically in patients who develop pulmonary oedema during dose-ranging.

4.4 Special warnings and precautions for use

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.

Flolan is a potent pulmonary and systemic vasodilator. The cardiovascular effects during infusion disappear within 30 min of the end of administration.

Flolan is a potent inhibitor of platelet aggregation, therefore, an increased risk for haemorrhagic complications should be considered, particularly for patients with other risk factors for bleeding (see section 4.5).

If excessive hypotension occurs during administration of Flolan, the dose should be reduced or the infusion discontinued. Hypotension may be profound in overdose and may result in loss of consciousness (see section 4.9).

Blood pressure and heart rate should be monitored during administration of Flolan.

Flolan may either decrease or increase heart rate. The change is thought to depend on both the basal heart rate and the concentration of Flolan administered.

The effects of Flolan on heart rate may be masked by concomitant use of drugs which affect cardiovascular reflexes.

Extreme caution is advised in patients with coronary artery disease.

Elevated serum glucose levels have been reported (see section 4.8).

The solvent contains no preservative; consequently a vial should be used once only and then discarded.

This medicinal product contains sodium, which should be taken into consideration by patients on a controlled sodium diet.

Some patients with pulmonary arterial hypertension have developed pulmonary oedema during dose-ranging, which may be associated with pulmonary veno-occlusive disease. Flolan must not be used chronically in patients who develop pulmonary oedema during dose initiation (see section 4.3).

Abrupt withdrawal or interruption of infusion must be avoided, except in life-threatening situations. An abrupt interruption of therapy can induce a rebound of pulmonary arterial hypertension resulting in dizziness, asthenia, increased dyspnoea, and may lead to death (see section 4.2).

Flolan is infused continuously through a permanent indwelling central venous catheter via a small, portable infusion pump. Thus, therapy with Flolan requires commitment by the patient to sterile drug reconstitution,

drug administration, care of the permanent central venous catheter, and access to intense and ongoing patient education.

Sterile technique must be adhered to in preparing the drug and in the care of the catheter. Even brief interruptions in the delivery of Flolan may result in rapid symptomatic deterioration. The decision to administer Flolan for pulmonary arterial hypertension should be based upon the patient's understanding that there is a high likelihood that therapy with Flolan will be needed for prolonged periods, possibly years, and the patient's ability to accept and care for a permanent i.v. catheter and infusion pump should be carefully considered.

4.5 Interaction with other medicinal products and other forms of interaction

When Flolan is administered to patients receiving concomitant anticoagulants standard anticoagulant monitoring is advisable.

The vasodilator effects of Flolan may augment or be augmented by concomitant use of other vasodilators.

As reported with other prostaglandin analogues, Flolan may reduce the thrombolytic efficacy of tissue plasminogen activator (t-PA) by increasing hepatic clearance of t-PA.

When NSAIDS or other drugs affecting platelet aggregation are used concomitantly, there is the potential for Flolan to increase the risk of bleeding.

Patients on digoxin may show elevations of digoxin concentrations after initiation of therapy with Flolan, which although transient, may be clinically significant in patients prone to digoxin toxicity.

4.6 Fertility, pregnancy,and lactation

Pregnancy

There is a limited amount of data from the use of epoprostenol in pregnant women.
Animal studies did not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section 5.3).
Given the absence of alternative medicines, epoprostenol can be used in those women who choose to continue their pregnancy, despite the known risk of pulmonary arterial hypertension during pregnancy.

Breast-feeding

It is unknown if epoprostenol or its metabolites are excreted in human milk. A risk to the breastfeeding child cannot be excluded. Breast-feeding should be discontinued during treatment with Flolan.

Fertility

There are no data on the effects of epoprostenol on fertility in humans. Reproductive studies in animals have shown no effects on fertility (see section 5.3).

4.7 Effects on ability to drive and use machines

Pulmonary arterial hypertension and its therapeutic management may affect the ability to drive and operate machinery.

4.8 Undesirable effects

Adverse events are listed below by system organ class and frequency. Frequencies are defined as follows: very common ≥1/10 (≥10%); common ≥1/100 and <1/10 (≥1% and <10%); uncommon ≥1/1000 and <1/100 (≥0.1% and <1%); rare ≥1/10,000 and <1/1000 (≥0.01% and <0.1%); very rare <1/10,000 (< 0.01%) and not known (cannot be estimated from the available data).

Infections and Infestations	
Common	Sepsis, septicaemia (mostly related to delivery system for Flolan)[1]
Blood and Lymphatic System Disorders	
Common	Decreased platelet count, bleeding at various sites (e.g. pulmonary, gastrointestinal, epistaxis, intracranial, post-procedural, retroperitoneal)
Unknown	Splenomegaly, Hypersplenism
Endocrine Disorders	
Very rare	Hyperthyroidism
Psychiatric Disorders	
Common	Anxiety, nervousness
Very rare	Agitation
Nervous System Disorders	
Very common	Headache
Cardiac Disorders	
Common	Tachycardia[2], bradycardia[3],
Vascular Disorders	
Very common	Facial flushing (seen even in the anaesthetised patient)
Common	Hypotension
Very rare	Pallor
Not known	Ascites
Respiratory, thoracic and mediastinal disorders	
Unknown	Pulmonary oedema
Gastrointestinal Disorders	
Very common	Nausea, vomiting, diarrhoea
Common	Abdominal colic, sometimes reported as abdominal discomfort
Uncommon	Dry mouth
Skin and Subcutaneous Tissue Disorders	
Common	Rash
Uncommon	Sweating
Musculoskeletal and Connective Tissue Disorders	
Very common	Jaw pain
Common	Arthralgia
General Disorders and Administration Site Conditions	
Very common	Pain (unspecified)
Common	Pain at the injection site*, chest pain
Rare	Local infection*
Very rare	Erythema over the infusion site*, occlusion of the long i.v. catheter*, lassitude, chest tightness
Investigations	
Unknown	Blood glucose increased
* Associated with the delivery system for Flolan	
[1] Catheter-related infections caused by organisms not always considered pathogenic (including micrococcus) have been reported.	
[2] Tachycardia has been reported as a response to Flolan at doses of 5 nanograms/kg/min and below.	
[3] Bradycardia, sometimes accompanied by orthostatic hypotension, has occurred in healthy volunteers at doses of Flolan greater than 5 nanograms/kg/min. Bradycardia associated with a considerable fall in systolic and diastolic blood pressure has followed i.v. administration of a dose of Flolan equivalent to 30 nanograms/kg/min in healthy conscious volunteers.	

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

The main feature of overdose is likely to be hypotension.
In general, events seen after overdose of Flolan represent exaggerated pharmacological effects of the drug (e.g. hypotension and complications of hypotension).
If overdose occurs reduce the dose or discontinue the infusion and initiate appropriate supportive measures as necessary; for example plasma volume expansion and/or adjustment to pump flow.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antithrombotic Agents; Platelet aggregation inhibitors excl. heparin,
ATC code: B01AC09

Mechanism of action
Epoprostenol Sodium, the monosodium salt of epoprostenol, 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.

Pharmacodynamic effects
An infusion of 4 nanograms/kg/min for 30 minutes has been shown to have no significant effect on heart rate or blood pressure, although facial flushing may occur at these levels.

Intravenous epoprostenol infusions of up to 15 minutes have been found to produce dose-related increases in cardiac index (CI) and stroke volume (SV), and dose-related decreases in pulmonary vascular resistance (PVR), total pulmonary resistance (TPR) and mean systemic arterial pressure (SAPm). The effects of epoprostenol on mean pulmonary artery pressure (PAPm) in patients with PPH were variable and minor.

Clinical efficacy and safety
Chronic continuous infusions of epoprostenol in patients with idiopathic or heritable PAH were studied in 2 prospective, open, randomised trials of 8 and 12 weeks' duration (N=25 and N=81, respectively) comparing epoprostenol plus conventional therapy to conventional therapy alone. Conventional therapy varied among patients and included some or all of the following: anticoagulants in essentially all patients; oral vasodilators, diuretics, and digoxin in one half to two thirds of patients; and supplemental oxygen in about half the patients. Except for 2 New York Heart Association (NYHA) functional Class II patients, all patients were either functional Class III or Class IV. As results were similar in the 2 studies, the pooled results are described. The combined baseline 6-minute walk test median values for the conventional therapy group and epoprostenol plus conventional therapy group was 266 meters and 301 meters, respectively.

Improvements from baseline in cardiac index (0.33 vs. -0.12 L/min/m^2), stroke volume (6.01 vs. -1.32 mL/beat), arterial oxygen saturation (1.62 vs. -0.85%), mean pulmonary artery pressure (-5.39 vs. 1.45 mm Hg), mean right atrial pressure (-2.26 vs. 0.59 mm Hg), total pulmonary resistance (-4.52 vs. 1.41 Wood U),

pulmonary vascular resistance (-3.60 vs. 1.27 Wood U), and systemic vascular resistance (-4.31 vs. 0.18 Wood U) were statistically different between patients who received epoprostenol chronically and those who did not. Mean systemic arterial pressure was not significantly different between the two groups (-4.33 vs. -3.05 mm Hg). These haemodynamic improvements appeared to persist when epoprostenol was administered for at least 36 months in an open, nonrandomized study.

Statistically significant improvement was observed in exercise capacity (p=0.001), as measured by the 6MWT in patients receiving continuous intravenous epoprostenol plus conventional therapy (N=52) for 8 or 12 weeks compared to those receiving conventional therapy alone (N=54) (combined week 8 and 12 change from baseline – median: 49 vs. -4 meters; mean: 55 vs. -4 meters). Improvements were apparent as early as the first week of therapy. At the end of the treatment period in the 12 weeks study, survival was improved in NYHA functional Class III and Class IV patients. Eight of 40 (20%) patients receiving conventional therapy alone died, whereas none of the 41 patients receiving epoprostenol died (p=0.003).

Chronic continuous infusions of epoprostenol in patients with PAH/SSD were studied in a prospective, open, randomised trial of 12 weeks' duration comparing epoprostenol plus conventional therapy (N = 56) to conventional therapy alone (N = 55). Except for 5 NYHA functional Class II patients, all patients were either functional Class III or Class IV. Conventional therapy varied among patients and included some or all of the following: anticoagulants in essentially all patients, supplemental oxygen and diuretics in two thirds of the patients, oral vasodilators in 40% of the patients, and digoxin in a third of the patients. The primary efficacy endpoint for the study was improvement in the 6MWT. The median baseline value for the conventional therapy group and epoprostenol plus conventional therapy group was 240 meters and 270 meters, respectively. A statistically significant increase in CI, and statistically significant decreases in PAPm, RAPm, PVR, and SAPm after 12 weeks of treatment were observed in patients who received epoprostenol chronically compared to those who did not.

Over 12 weeks, a statistical difference ($p<0.001$) in the change from baseline for the 6MWT was observed in the group receiving epoprostenol and conventional therapy as compared to the group receiving conventional therapy alone (median: 63.5 vs. -36.0 meters; mean: 42.9 vs. -40.7 meters).
Improvements were apparent in some patients at the end of the first week of therapy. Increases in exercise capacity were accompanied by statistically significant improvements in dyspnoea, as measured by the Borg Dyspnea Index. At week 12, NYHA functional class improved in 21 of 51 (41%) patients treated with epoprostenol compared to none of the 48 patients treated with conventional therapy alone. However, more patients in both treatment groups (28/51 [55%] with epoprostenol and 35/48 [73%] with conventional therapy alone) showed no change in functional class, and 2/51 (4%) with epoprostenol and 13/48 (27%) with conventional therapy alone worsened.

No statistical difference in survival over 12 weeks was observed in PAH/SSD patients treated with epoprostenol as compared to those receiving conventional therapy alone. At the end of the treatment period, 4 of 56 (7%) patients receiving epoprostenol died, whereas 5 of 55 (9%) patients receiving conventional therapy alone died.

5.2 Pharmacokinetic properties

Due to the chemical instability, high potency and short half-life of epoprostenol, no precise and accurate assay has been identified as appropriate for quantifying epoprostenol in biological fluids.

Intravenously administered epoprostenol is rapidly distributed from blood to tissue.
At normal physiological pH and temperature, epoprostenol breaks down spontaneously to 6-oxo-prostaglandin F_1 alpha, although there is some enzymatic degradation to other products.

Following the administration of radiolabelled epoprostenol to humans, at least 16 metabolites were found, 10 of which were structurally identified.

Unlike many other prostaglandins, epoprostenol is not metabolised during passage through the pulmonary circulation.

The half-life for the spontaneous breakdown to 6-oxo-prostaglandin F_1 alpha in man is expected to be no more than 6 minutes, and may be as short as 2 to 3 minutes, as estimated from *in vitro* rates of degradation of epoprostenol in human whole blood.

Following the administration of radiolabelled epoprostenol to humans, the urinary and faecal recoveries of radioactivity were 82% and 4%, respectively.

5.3 Preclinical safety data

Non-clinical data revealed no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, and toxicity to reproduction and development. No long-term animal studies have been conducted to determine the carcinogenic potential of epoprostenol.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Powder for solution for infusion:
Mannitol
Glycine
Sodium Chloride
Sodium Hydroxide (for pH adjustment)

Solvent for parenteral use:
Glycine
Sodium Chloride
Sodium Hydroxide (for pH adjustment)
Water for Injection

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

Unopened vials

Powder for solution for infusion: 3 years

Solvent for parenteral use: 18 months

Stability during administration

Freshly prepared solutions for infusion (either as a concentrated solution or a further diluted solution) can be administered immediately or stored for up to 8 days at 2°C to 8°C prior to administration. Following this preparation or storage, the solution for infusion should be used within:

- 72 hours at up to 25°C or
- 48 hours at up to 30ºC or
- 24 hours at up to 35 ºC or
- 12 hours at up to 40 ºC

Discard any unused solution after this time.

6.4 Special precautions for storage

Powder for solution for infusion:
Do not store vials above 25°C. Protect from light. Keep dry. Do not freeze. Store in the original package.

Solvent for parenteral use:
Do not store vials above 25°C. Do not freeze. Protect from light. Store in the original package.
The solvent contains no preservative; consequently a vial should be used once only and then discarded.

For storage conditions after reconstitution and dilution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

Powder for solution for infusion:
Clear (type 1) glass vials with synthetic butyl rubber stoppers and an aluminium collar with a snap-off top.

Solvent for parenteral use:
Clear plastic vials with synthetic butyl rubber stoppers and an external aluminium collar with a purple plastic flip-top cover.

Pack sizes:
There are three presentations available in 1.5 mg for use in the treatment of pulmonary arterial hypertension, as follows:
- One 1.5 mg powder vial and one solvent vial and a filter unit.
- One 1.5 mg powder vial and two solvent vials and a filter unit.
- One 1.5 mg powder vial.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

The stability of solutions of Flolan is pH dependent. Only the solvent supplied should be used for reconstitution of freeze-dried Flolan and only the recommended infusion solutions, in the stated ratio, should be used for further dilution, otherwise the required pH may not be maintained.

Reconstitution and dilution of Flolan must be carried out using aseptic technique, ideally immediately prior to clinical use.

Reconstitution, dilution and calculation of infusion rate:

Particular care should be taken in the preparation of the infusion and in calculating the rate of infusion. The procedure given below should be closely followed.

There are three 1.5 mg packs available for use in the treatment of pulmonary arterial hypertension, as follows:

- One vial containing sterile, freeze-dried Flolan equivalent to 1.5 mg Flolan, supplied with one 50 mL vial of solvent and a filter unit.
- One vial containing sterile, freeze-dried Flolan equivalent to 1.5 mg Flolan, supplied with two 50 mL vials of solvent and a filter unit.
- One vial containing sterile, freeze-dried Flolan equivalent to 1.5 mg Flolan supplied alone.

There are also three 0.5 mg packs available for use in the treatment of pulmonary arterial hypertension.

Initially a pack containing solvent for parenteral use must be used. During chronic Flolan therapy the final concentration of solution may be increased by the addition of a further 0.5 mg or 1.5 mg vial of freeze-dried Flolan.

Only vials of the same amount as that included in the initial starter pack may be used to increase the final concentration of solution.

Reconstitution:

1. Use only the sterile solvent solution provided for reconstitution.
2. Withdraw approximately 10 mL of the sterile solvent solution into a sterile syringe, inject it into the vial containing the freeze-dried epoprostenol and shake gently until the powder has dissolved.
3. Draw up the resulting epoprostenol solution into the syringe, re-inject it into the remaining volume of the sterile solvent solution and mix thoroughly.

This solution is now referred to as the concentrated solution.

- Where a pack containing 1.5 mg epoprostenol is reconstituted with 50 mL sterile solvent the resultant concentration is 30,000 nanograms/mL.

Only this concentrated solution is suitable for further dilution prior to use.

Dilution:

Flolan may be used either as concentrated solution or in a diluted form for the treatment of pulmonary arterial hypertension. Only the solvent provided may be used for the further dilution of reconstituted Flolan. Sodium chloride 0.9% w/v solution must not be used when Flolan is to be used for the treatment of pulmonary arterial hypertension. Flolan must not be administered with other parenteral solutions or medications when used for pulmonary arterial hypertension.

To dilute the concentrated solution, draw it up into a larger syringe and then attach the sterile filter provided to the syringe.

Dispense the concentrated solution directly into the solvent using firm but not excessive pressure; the typical time taken for filtration of 50 mL of concentrated solution is 70 seconds. Mix well.

The filter unit must be used once only and then discarded.

Concentrations commonly used in the treatment pulmonary arterial hypertension are as follows:

- 15,000 nanograms/mL - 1.5 mg Flolan reconstituted and diluted to a total volume of 100mL in solvent.

- 30,000 nanograms/mL - Two vials containing 1.5 mg Flolan reconstituted and diluted to a total volume of 100 mL in solvent.

Calculation of infusion rate:

The infusion rate may be calculated from the following formula:

$$\text{Infusion rate (mL/min)} = \frac{\text{dosage (nanogram/kg/min) x bodyweight (kg)}}{\text{concentration of solution (nanogram/mL)}}$$

Infusion rate (mL/h) = Infusion rate (mL/min) x 60

Examples for some concentrations commonly used in pulmonary arterial hypertension are shown below.

Infusion rates for a concentration of 15,000 nanograms/mL

Example For Dosing Using a Concentration of 15,000 nanograms/mL								
Dosage (nanograms/ kg/ min)	Bodyweight (kg)							
	30	40	50	60	70	80	90	100
4	0.5	0.6	0.8	1.0	1.1	1.3	1.4	1.6
6	0.7	1.0	1.2	1.4	1.7	1.9	2.2	2.4
8	1.0	1.3	1.6	1.9	2.2	2.6	2.9	3.2
10	1.2	1.6	2.0	2.4	2.8	3.2	3.6	4.0
12	1.4	1.9	2.4	2.9	3.4	3.8	4.3	4.8
14	1.7	2.2	2.8	3.4	3.9	4.5	5.0	5.6
16	1.9	2.6	3.2	3.8	4.5	5.1	5.8	6.4
	Flow rates in **mL/h**							

Infusion rates for a concentration of 30,000 nanograms/mL

Example For Dosing Using a Concentration of 30,000 nanograms/mL								
Dosage (nanograms/ kg/ min)	Bodyweight (kg)							
	30	40	50	60	70	80	90	100
6	0.4	0.5	0.6	0.7	0.8	1.0	1.1	1.2
8	0.5	0.6	0.8	1.0	1.1	1.3	1.4	1.6
10	0.6	0.8	1.0	1.2	1.4	1.6	1.8	2.0
12	0.7	1.0	1.2	1.4	1.7	1.9	2.2	2.4
14	0.8	1.1	1.4	1.7	2.0	2.2	2.5	2.8
16	1.0	1.3	1.6	1.9	2.2	2.6	2.9	3.2
18	1.1	1.4	1.8	2.2	2.5	2.9	3.2	3.6
20	1.2	1.6	2.0	2.4	2.8	3.2	3.6	4.0
	Flow rates in **mL/h**							

Higher infusion rates, and therefore, more concentrated solutions may be necessary with long-term administration of Flolan.

7. MARKETING AUTHORISATION HOLDER

<{See Annex I - To be completed nationally}>

{Name and address}
<{tel}>
<{fax}>
<{e-mail}>

8. MARKETING AUTHORISATION NUMBER(S)

<{To be completed nationally}>

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

<{To be completed nationally}>

10. DATE OF REVISION OF THE TEXT

<{To be completed nationally}>

LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON box for powder vials and solvent vials:
Flolan 0.5 mg powder and solvent for solution for infusion

1. NAME OF THE MEDICINAL PRODUCT

Flolan 0.5 mg powder and solvent for solution for infusion

Epoprostenol

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each vial contains epoprostenol sodium equivalent to 0.5 mg epoprostenol.

3. LIST OF EXCIPIENTS

Powder for solution for infusion: Mannitol, glycine, sodium chloride, sodium hydroxide(for pH adjustment)

Solvent for parenteral use: glycine, sodium chloride, sodium hydroxide (for pH adjustment), water for injection

This medicine contains sodium: See package leaflet for further information

4. PHARMACEUTICAL FORM AND CONTENTS

Powder and solvent for solution for infusion
Powder for solution for infusion
Solvent for parenteral use

0.5 mg vial powder for solution for infusion, 1 vial of solvent and 1 filter unit
0.5 mg vial powder for solution for infusion, 2 vials of solvent and 1 filter unit

5. METHOD AND ROUTE(S) OF ADMINISTRATION

The powder needs to be reconstituted and diluted before infusion.
Read the package leaflet before use.
Intravenous use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Use as directed by your physician

8. EXPIRY DATE

EXP
Read the package leaflet for the shelf-life of the reconstituted/diluted product

9. SPECIAL STORAGE CONDITIONS

Powder for solution for infusion:
Store vials below 25°C. Protect from light. Keep dry. Do not freeze. Store in the original package.

Solvent for parenteral use:
Store the solvent below 25°C. Do not freeze. Protect from light. Store in the original package.
The solvent contains no preservative; consequently a vial should be used once only and then discarded.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

[See Annex I - To be completed nationally]

{Name and Address}
<{tel}>
<{fax}>
<{e-mail}>

12. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicine subject to medicinal prescription

15. INSTRUCTIONS ON USE

New formulation of solvent (pH 12) – read leaflet inside before use

16. INFORMATION IN BRAILLE

[To be completed nationally]

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON box for powder vials and solvent vials:
Flolan 1.5 mg powder and solvent for solution for infusion

1. NAME OF THE MEDICINAL PRODUCT

Flolan 1.5 mg powder and solvent for solution for infusion

Epoprostenol

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each vial contains epoprostenol sodium equivalent to 1.5 mg epoprostenol.

3. LIST OF EXCIPIENTS

Powder for solution for infusion: Mannitol, glycine, sodium chloride, sodium hydroxide(for pH adjustment)

Solvent for parenteral use: glycine, sodium chloride, sodium hydroxide (for pH adjustment), water for injection

This medicine contains sodium: See package leaflet for further information

4. PHARMACEUTICAL FORM AND CONTENTS

Powder and solvent for solution for infusion
Powder for solution for infusion
Solvent for parenteral use

1.5 mg vial powder for solution for infusion, 1 vial of solvent and 1 filter unit
1.5 mg vial powder for solution for infusion, 2 vials of solvent and 1 filter unit

5. METHOD AND ROUTE(S) OF ADMINISTRATION

The powder needs to be reconstituted and diluted before infusion.
Read the package leaflet before use.
Intravenous use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Use as directed by your physician

8. EXPIRY DATE

EXP
Read the package leaflet for the shelf-life of the reconstituted/diluted product

9. SPECIAL STORAGE CONDITIONS

Powder for solution for infusion:
Store vials below 25°C. Protect from light. Keep dry. Do not freeze. Store in the original package.

Solvent for parenteral use:
Store the solvent below 25°C. Do not freeze. Protect from light. Store in the original package.
The solvent contains no preservative; consequently a vial should be used once only and then discarded.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

[See Annex I - To be completed nationally]

{Name and Address}
<{tel}>
<{fax}>
<{e-mail}>

12. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicine subject to medicinal prescription

15. INSTRUCTIONS ON USE

New formulation of solvent (pH 12) – read leaflet inside before use

16. INFORMATION IN BRAILLE

[To be completed nationally]

MINIMUM PARTICULARS TO APPEAR ON IMMEDIATE PACKAGING

LABEL for solvent vial

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Solvent for parenteral use for Flolan
Intravenous use

2. METHOD OF ADMINISTRATION

Intravenous use
Read the package leaflet before use.

3. EXPIRY DATE

EXP
Read the package leaflet for the shelf-life of the reconstituted/diluted product

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

Each vial contains 50ml solvent for parenteral use.

6. OTHER

MINIMUM PARTICULARS TO APPEAR ON IMMEDIATE PACKAGING

LABEL for 0.5 mg powder vial

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Flolan 0.5 mg powder for solution for infusion
Intravenous use
Epoprostenol

2. METHOD OF ADMINISTRATION

Intravenous use
Read the package leaflet before use.

3. EXPIRY DATE

EXP
Read the package leaflet for the shelf-life of the reconstituted/diluted product

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

Each vial contains 0.5mg epoprostenol (as epoprostenol sodium)

6. OTHER

MINIMUM PARTICULARS TO APPEAR ON IMMEDIATE PACKAGING

LABEL for 1.5 mg powder vial

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Flolan 1.5 mg powder for solution for infusion
Intravenous use
Epoprostenol

2. METHOD OF ADMINISTRATION

Intravenous use
Read the package leaflet before use.

3. EXPIRY DATE

EXP
Read the package leaflet for the shelf-life of the reconstituted/diluted product

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

Each vial contains 1.5mg epoprostenol (as epoprostenol sodium)

6. OTHER

PACKAGE LEAFLET

Package leaflet: Information for the user

Flolan 0.5 mg powder and solvent for solution for infusion
Flolan 1.5 mg powder and solvent for solution for infusion

Epoprostenol

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet:

1. What Flolan is and what it is used for

What Flolan is

Flolan contains the active substance epoprostenol which belongs to a group of medicines called prostaglandin, which stops blood from clotting and widens the blood vessels.

What Flolan is used for

- Flolan is used to treat a lung condition called ‘pulmonary arterial hypertension’. This is where the pressure is high in the blood vessels in the lungs. Flolan widens the blood vessels to lower the blood pressure in the lungs.

- Flolan is used to prevent blood clotting during kidney dialysis in emergency situations when heparin cannot be used.

2. What you need to know before you use Flolan

Do not use Flolan

- **if you are allergic** to Flolan or any of the other ingredients of this medicine (listed in section 6).
- if you have **heart failure**.
- if you start to develop a build-up of fluid in your lungs causing breathlessness after starting this treatment.

If you think any of these apply to you, **don’t use Flolan** until you have checked with your doctor.

Warnings and precautions

Talk to your doctor before using Flolan:
- if you have any problems with **bleeding**.
- if you are on a controlled sodium diet.

Skin damage at the injection site

Flolan is injected into a vein. It is important that the medicine does not leak out of the vein into the surrounding tissue. If it does, the skin could be damaged. The symptoms of this are:
- tenderness
- burning
- stinging
- swelling
- redness.

This may be followed by blistering and shedding of the skin. While you are being treated with Flolan it is important that you check the injection area.

Contact the hospital immediately for advice if the area becomes sore, painful or swollen or you notice any blistering or shedding.

Effect of Flolan on blood pressure and heart rate

Flolan can cause your heart to beat faster or slower. Also your blood pressure can become too low. While you are being treated with Flolan your heart rate and blood pressure will be checked. The symptoms of low blood pressure include **dizziness** and **fainting**.

Tell your doctor if you get these symptoms. Your dose may need to be reduced or your infusion stopped.

Other medicines and Flolan

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines, including medicines obtained without a prescription.

Some medicines may affect how Flolan works, or make it more likely that you'll have side effects. Flolan can also affect how some other medicines work if taken at the same time. These include:
- medicines used to **treat high blood pressure**
- medicines used to **prevent blood clots**
- medicines used to **dissolve blood clots**
- medicines to treat **inflammation or pain** (also called 'NSAIDs')
- digoxin (used to treat **heart disease**).

Tell your doctor or pharmacist if you are taking any of these.

Pregnancy and breast-feeding

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before using this medicine as your symptoms could worsen during pregnancy.

It is not known whether the ingredients of Flolan can pass into breast-milk. **You should stop breast-feeding your child during treatment with Flolan**.

Driving and using machines

Your treatment may have an effect on the ability to drive or use machinery.

Don't drive or use machines unless you're feeling well.

Flolan contains Sodium
This medicinal product contains sodium. To be taken into consideration by patients on a controlled sodium diet.

3. How to use Flolan

Always use this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

Your doctor will decide how much Flolan is right for you. The amount you are given is based on your body weight, and your type of illness. Your dose may be increased or decreased depending on how well you respond to treatment.

Flolan is given by slow infusion (drip) into a vein.

Pulmonary arterial hypertension
Your first treatment will be given to you in a hospital. This is because your doctor needs to monitor you and find the best dose for you.

You will start with an infusion of Flolan. The dose will be increased, until your symptoms are relieved, and any side effects are manageable. Once the best dose has been found, a permanent tube (line) will be fitted into one of your veins. You can then be treated using an infusion pump.

Kidney dialysis
You will be given an infusion of Flolan for the duration of your dialysis.

Using Flolan at home (only for treatment of Pulmonary Arterial Hypertension)
If you are treating yourself at home, your doctor or nurse will show you how to prepare and use Flolan. They will also advise you how to stop treatment if necessary. Stopping Flolan must be done gradually. It is very important that you follow **all** their instructions carefully.

Flolan comes as a powder in a glass vial. Before use, the powder needs to be dissolved in the liquid provided. The liquid does not contain a preservative. If you have any of the liquid left over, it must be thrown away.

Looking after the injection line
If you have been fitted with a 'line' into a vein it is **very important** to keep this area clean, otherwise you could get an infection. Your doctor or nurse will show you how to clean your 'line' and the area around it. It is very important that you follow all of their instructions carefully.

If you use more Flolan than you should

Seek urgent medical attention if you think you have used or been given too much Flolan. Symptoms of overdose may include headache, nausea, vomiting, fast heart rate, warmth or tingling, or feeling like you might pass out (feeling faint/dizziness).

If you forget to use Flolan
Do not take a double dose to make up for a forgotten dose.

If you stop using Flolan
Stopping Flolan must be done gradually. If the treatment is stopped too quickly you may get serious side effects, including dizziness, feeling weak and breathing difficulties. If you have problems with the infusion pump or injection line that stops, or prevents treatment with Flolan, **contact your doctor, nurse or hospital** immediately.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist or nurse.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Tell your doctor or nurse immediately, as these may be signs of infection of the blood or low blood pressure or serious bleeding:
- You feel that your heart is beating faster, or you have chest pain or shortness of breath.
- You feel dizzy or feel faint, especially on standing.
- You have fevers or chills.
- You have more frequent, or longer periods of bleeding.

Talk to your doctor or pharmacist or nurse about any other side effects, including those not listed in this leaflet.

Very common side effects
These may affect **more than 1 in 10** people:
- headache
- jaw pain
- pain
- being sick (vomiting)
- feeling sick (nausea)
- diarrhoea
- redness of your face (flushing)

Common side effects
These may affect **up to 1 in 10** people:
- infection of the blood (*septicaemia*)
- heart beating faster
- slow heart beat
- low blood pressure
- bleeding at various sites and bruising more easily than normal, for example from the nose or gums
- stomach discomfort or pain
- chest pain
- joint pain
- feeling anxious, feeling nervous
- rash
- pain at the injection site

Common side effects that may show up in blood tests
- decrease in the number of blood platelets (cells that help the blood to clot)

Uncommon side effects
These may affect **up to 1 in 100** people:
- sweating
- dry mouth

Rare side effects
These may affect **up to 1 in 1,000** people:
- infection at the injection site

Very rare side effects
These may affect **up to 1 in 10,000** people:
- feeling of tightness around the chest
- feeling tired, weak
- feeling agitated
- pale skin
- redness at the injection site
- overactive thyroid gland
- blockage of the injection catheter

Other side effects
It is not known how many people are affected:
- enlarged or overactive spleen
- build up of fluid in the lungs (pulmonary oedema)
- increase in sugar (glucose) in the blood
- swelling due to build up of fluid around the stomach

Reporting of side effects
If you get any side effects, talk to your doctor or pharmacist or nurse. This includes any possible side effects not listed in this leaflet.
You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Flolan

Keep this medicine out of the sight and reach of children.
Do not use this medicine after the expiry date which is stated on the label.
Do not store above 25°C.
Store Flolan in a dry place.
Store in the original outer carton, to protect from light.
Do not freeze.

Pulmonary arterial hypertension
Once Flolan powder has been dissolved, and diluted, it should ideally be used immediately.
Freshly prepared Flolan solution or Flolan solution stored for a maximum of 8 days at refrigerated conditions (2 to 8^{o}C), can be stored in the medication cassette and used within a maximum time of:

- 72 hours at up to 25°C or
- 48 hours at up to 30ºC or
- 24 hours at up to 35 ºC or
- 12 hours at up to 40 ºC

Renal Dialysis
Once Flolan has been dissolved and diluted, any unused solution can be stored at 25^{o}C and used within 12 hours.

6. Contents of the pack and other information

What Flolan contains

The active substance is epoprostenol sodium. Flolan Injection comes in different strengths.

Each vial contains either:
- 0.5 mg epoprostenol sodium or
- 1.5 mg epoprostenol sodium.

The other ingredients are Mannitol, Glycine, Sodium Chloride, Sodium Hydroxide and Water.

What Flolan looks like and contents of the pack

Injection:

Flolan is a solution for injection made up of powder and solution. The powder is white or off-white and the solution is clear and colourless.

There are six packs of Flolan available for use in the treatment of pulmonary arterial hypertension, the contents of each pack include:
- One 0.5 mg powder vial and one solvent vial and a filter unit.
- One 0.5 mg powder vial and two solvent vials and a filter unit.
- One 1.5 mg powder vial and one solvent vial and a filter unit.
- One 1.5 mg powder vial and two solvent vials and a filter unit.
- One 0.5 mg powder vial.
- One 1.5 mg powder vial.

There is only one pack of Flolan available for use in renal dialysis, the contents of each pack include:
- One 0.5 mg powder vial and one solvent vial and a filter unit.

Not all pack sizes are available in all markets.

Marketing Authorisation Holder and Manufacturer

[See Annex I - To be completed nationally]

{Name and address}
<{tel}>
<{fax}>
<{e-mail}>

This medicinal product is authorised in the Member States of the EEA under the following names:

[See Annex I - To be completed nationally]

This leaflet was last revised in {MM/YYYY}.

[To be completed nationally]

<----------
The following information is intended for medical or healthcare professionals only:

7. INFORMATION FOR HEALTHCARE PROFESSIONALS

Pulmonary arterial hypertension

There are six packs available for use in the treatment of pulmonary arterial hypertension, as follows:

- One 0.5 mg powder vial and one solvent vial and a filter unit.
- One 0.5 mg powder vial and two solvent vials and a filter unit.
- One 1.5 mg powder vial and one solvent vial and a filter unit.
- One 1.5 mg powder vial and two solvent vials and a filter unit.
- One 0.5 mg powder vial.
- One 1.5 mg powder vial.

Not all pack sizes are available in all markets.

Initially, a pack containing solvent must be used. During chronic therapy with Flolan the final concentration of solution may be increased by the addition of a further 0.5 mg or 1.5 mg vial of freeze-dried Flolan. Only vials of the same amount as that included in the initial starter pack may be used to increase the final concentration of solution.

Reconstitution:

1. Use only the solvent provided for reconstitution.
2. Withdraw approximately 10mL of the solvent into a sterile syringe, inject the contents of the syringe into the vial containing Flolan powder and shake gently until the powder has dissolved.
3. Draw up the resulting Flolan solution into the syringe, re-inject it into the remaining volume of the solvent and mix thoroughly.

This solution is now referred to as the concentrated solution and contains either 10,000 (for the 0.5 mg strength) or 30,000 nanogram per mL Flolan (for the 1.5 mg strength). Only these concentrated solutions are suitable for further dilution prior to use. When 0.5 mg Flolan powder is reconstituted with 50 mL of the solvent, the final injection has a pH of approximately 12 and a sodium ion content of approximately 73 mg.

Dilution:

Flolan may be used either as concentrated solution or in a diluted form for the treatment of pulmonary arterial hypertension. Only the solvent provided may be used for the further dilution of reconstituted Flolan.

Sodium chloride 0.9% w/v solution must not be used when Flolan is to be used for the treatment of pulmonary arterial hypertension.

To dilute the concentrated solution, draw it up into a larger syringe and then attach the sterile filter provided to the syringe.

Dispense the concentrated solution directly into the solvent using firm but not excessive pressure; the typical time taken for filtration of 50 mL of concentrated solution is 70 seconds. Mix well.

The filter must be used once only and then discarded.

Concentrations commonly used in the treatment pulmonary arterial hypertension are as follows:

- 5,000 nanogram/mL – One vial containing 0.5 mg Flolan reconstituted and diluted to a total volume of 100 mL in solvent.
- 10,000 nanogram/mL – Two vials containing 0.5 mg Flolan reconstituted and diluted to a total volume of 100 mL in solvent.
- 15,000 nanogram/mL – One vial containing 1.5 mg Flolan reconstituted and diluted to a total volume of 100 mL in solvent.
- 30,000 nanogram/mL – Two vials containing 1.5 mg Flolan reconstituted and diluted to a total volume of 100 mL in solvent.

Calculation of infusion rate:

The infusion rate may be calculated from the following formula:

$$\text{Infusion rate (mL/min)} = \frac{\text{dosage (nanogram/kg/min) x bodyweight (kg)}}{\text{concentration of solution (nanogram/mL)}}$$

Infusion rate (mL/h) = Infusion rate (mL/min) x 60

Higher infusion rates, and therefore, more concentrated solutions may be necessary with long-term administration of Flolan.

Special precautions for storage

Don't store above 25°C.
Keep container in the outer carton to protect from light.
Keep dry.
Do not freeze.

Ideally reconstitution and dilution should be carried out immediately prior to use. For additional details of stability following reconstitution, see section 5 ('How to store Flolan').
The solvent contains no preservative; consequently a vial should be used once only and then discarded.

Renal Dialysis

There is only one pack available for use in renal dialysis:
- One 0.5 mg powder vial and one solvent vial and a filter unit

Reconstitution:

1. Use only the solvent provided for reconstitution
2. Withdraw approximately 10mL of the solvent into a sterile syringe, inject it into the vial containing 0.5 mg freeze-dried Flolan powder and shake gently until the powder has dissolved
3. Draw up the resulting Flolan solution into the syringe, re-inject it into the remaining volume of the solvent and mix thoroughly.

This solution is now referred to as the concentrated solution and contains 10,000 nanogram per mL Flolan. Only this concentrated solution is suitable for further dilution prior to use. When 0.5 mg Flolan powder is reconstituted with 50 mL of the solvent, the final injection has a pH of approximately 12 and a sodium ion content of approximately 73 mg.

Dilution:

The concentrated solution is normally further diluted immediately prior to use. It may be diluted with sodium chloride 0.9% w/v (saline) solution, in a ratio of 2.3 volumes of saline to 1 volume of concentrated solution, e.g. 50 mL of concentrated solution further diluted with 117 mL of saline. Other common intravenous fluids are unsatisfactory for the dilution of the concentrated solution as the required pH is not attained. Flolan solutions are less stable at low pH.

To dilute the concentrated solution, draw it up into a larger syringe and then attach the sterile filter provided to the syringe.

Dispense the concentrated solution directly into the chosen infusion solution using firm but not excessive pressure; the typical time taken for filtration of 50 mL of concentrated solution is 70 seconds. Mix well. The filter unit must be used once only and then discarded.

When reconstituted and diluted as directed above, Flolan infusion solutions will retain 90% of their initial potency for approximately 12 hours at 25°C.

Calculation of infusion rate:

The infusion rate may be calculated from the following formula:

$$\text{Infusion rate (mL/min)} = \frac{\text{dosage (nanogram/kg/min) x bodyweight (kg)}}{\text{concentration of solution (nanogram/mL)}}$$

Infusion rate (mL/h) = Infusion rate (mL/min) x 60

For administration using a pump capable of delivering small volume constant infusions, suitable aliquots of concentrated solution may be diluted with sterile sodium chloride 0.9% w/v solution.

ANNEX 3. WORLDWIDE MARKETING AUTHORISATION BY COUNTRY (INCLUDING EEA)

A3.1 Licensing status in the EEA

Country	Current licence status	Date of licence action [1]	Date first marketed in country	Brand name(s)	Comments
Austria	Approved	2-Jul-93 16-Jan-01	Not available	Flolan	MAH: Austria, GlaxoSmithKline Pharma GmbH EU national licenses were transferred to MRP.
Belgium	Approved	8-Sep-97 19-Jun-00 7-Jan-13	6-Jan 98 1-Oct-00	Flolan	MAH: Belgium, GlaxoSmithKline Pharmaceuticals s.a. EU national licenses were transferred to MRP.
Czech Republic	Approved	5-Dec-01	Not available	Flolan	MAH: UK, The Wellcome Foundation Limited EU national licenses were transferred to MRP.
Denmark	Approved	10-May-94 3-Jan-00	10-Apr-95 30-Oct-00	Flolan	MAH: Denmark, GlaxoSmithKline Pharma A/S EU national licenses were transferred to MRP.
Estonia	Pending cancellation	26-Apr-00	26-Apr-00	Flolan	MAH: Denmark, GlaxoSmithKline Pharma A/S EU national license was transferred to MRP.
France	Approved	6-Mar-98	13-Oct-98 13-Nov-98	Flolan	MAH: France, Laboratoire GlaxoSmithKline EU national licenses

Country	Current licence status	Date of licence action [1]	Date first marketed in country	Brand name(s)	Comments
					were transferred to MRP.
Ireland	Approved	17-Dec-92 20-Dec-00	1-Jan-93 17-Jan-93 1-Feb 93 20-Jan-01	Flolan	MAH: Ireland, GlaxoSmithKline (Ireland) Limited EU national licenses were transferred to MRP.
Italy	Approved	12-Dec-92 27-Mar-00	2-Mar-94 8-Jan-01	Flolan	MAH: Italy, GlaxoSmithKline SpA and UK, The Wellcome Foundation Limited EU national licenses were transferred to MRP.
Luxembourg	Approved	30-Apr-97 25-Oct-00 20-Mar-14	1-Jul-97	Flolan	MAH: Belgium, GlaxoSmithKline Pharmaceuticals s.a. EU national licenses were transferred to MRP.
Malta	Approved, supplied on tender	13-Sep-04 14-Aug-06	Not available	Flolan	MAH: UK, Glaxo Wellcome UK Ltd and UK, The Wellcome Foundation Limited EU national licenses were transferred to MRP.
Netherlands	Approved	24-Jun-92 25-May-99	20-May-97 1-Sep-99	Flolan	MAH: Netherlands, GlaxoSmithKline BV EU national licenses were transferred to MRP.
Norway	Approved	27-Aug-00 28-Aug-00	1-Dec-00	Flolan	MAH: Norway, GlaxoSmithKline AS EU national licenses were transferred to MRP.

Country	Current licence status	Date of licence action [1]	Date first marketed in country	Brand name(s)	Comments
Poland	Cancelled/ withdrawn	30-Apr-04	Not available	Flolan	EU national licenses were transferred to MRP.
Spain	Approved	1-May-88 10-May-99	10-Sep-88	Flolan	MAH: Spain, GlaxoSmithKline S.A. EU national licenses were transferred to MRP.
United Kingdom	Approved	18-Mar-81 7-Mar-01	8-Jul-83 18-Jul-83 2-Apr-01	Flolan	MAH: UK, Glaxo Wellcome UK Ltd EU national licenses were transferred to MRP.

1 Enter the date of the most recent change to the licence status: eg date of approval or date of suspension

A3.2 Licensing status in the rest of the world

Country	Current licence status	Date of licence action 1	Date first marketed in country	Brand name(s)	Comments
Argentina	Cancelled/ withdrawn	19-May-00	Not available	Flolan	
Australia	Approved	15-Feb-02	Not available	Flolan	
Canada	Approved	10-Mar-97 3-Jun-97	3-Jul-97	Flolan	
Chile	Cancelled/ withdrawn	26-Nov-03	Not available	Flolan	
Colombia	Approved	21-Feb-02	Not available	Flolan	
Israel	Approved	27-Oct-98	Not available	Flolan	
Japan	Approved	25-Jan-99 15-Mar-01	1-Apr-99 16-Jul-01	Flolan	
New Zealand	Cancelled/ withdrawn	27-Aug-92	27-Aug-92	Flolan	
Singapore	Approved	4-Jul-88	Not available	Flolan	
Switzerland	Approved	26-Apr-00	1-Apr-01	Flolan	
Syrian Arab	Approved	17-Dec-00	Not available	Flolan	

Country	Current licence status	Date of licence action 1	Date first marketed in country	Brand name(s)	Comments
Republic					
Taiwan	Approved	29-Jun-09	Not available	Flolan	
United States	Approved	20-Sep-95	Not available	Flolan	

ANNEX 4. SYNOPSIS OF ON-GOING AND COMPLETED CLINICAL TRIAL PROGRAMME

Study	Description (Phase, short description of study (1 – 2 sentences including comparator name(s)/ placebo))	Countries	Study design	Planned/ actual number of patients	Duration of follow up	Estimated/ Actual completion date
Main or pivotal studies						
FLR115332	A Single-arm, Open Label Study Evaluating the Impact on Life- style of a New Thermo Stable Formulation of FLOLAN™ in Subjects with Pulmonary Arterial Hypertension (PAH) Phase IV	Canada, Netherlands, United States	Multicentre, open label, single arm study in patients who are already receiving FLOLAN for the treatment of PAH	20/15-16	28 days with optional extension phase	16 May 2012 (main study) 08 Nov 2012 (optional extension phase)
35/36	Multicenter evaluation of long-term Flolan infusions in patients with primary pulmonary hypertension	United States	Multicentre, randomized, parallel controlled, open label	Epoprost-enol: 11 Standard Therapy: 14	8 weeks	28 Feb 1990
46	A Multicenter, Open-Label, Randomized, Parallel Comparison of the Safety and Efficacy of Chronic FLOLAN (epoprostenol sodium) Infusions Plus Conventional Therapy to Conventional Therapy Alone in Patients with Severe Primary Pulmonary Hypertension: A Twelve Week Study	United States, Canada	Controlled, chronic, open, randomised, parallel, multicenter	Epoprost-enol: 41 Standard therapy: 40	12 weeks	13 Aug 1992
VA1A4001	A Multicenter, Open-Label, Randomized, Parallel Comparison of the Safety and	United States, Canada	Controlled, chronic, open, randomised,	Epoprost-enol: 56 Standard	12 weeks	26 Feb 1998

Study	Description (Phase, short description of study (1 – 2 sentences including comparator name(s)/ placebo))	Countries	Study design	Planned/ actual number of patients	Duration of follow up	Estimated/ Actual completion date
	Efficacy of Chronic FLOLAN (epoprostenol sodium) Infusions Plus Conventional Therapy to Conventional Therapy Alone in Patients with Pulmonary Hypertension Secondary to the Scleroderma Spectrum of Diseases: A Twelve Week Study		parallel, multicenter	therapy: 55		
2.1	To compare safety (clinical laboratories, vital signs, electrocardiograms, and adverse events) and efficacy (removal of BUN, creatinine, and potassium) of Flolan with heparin-facilitated haemodialysis in patients with chronic renal failure	United States	Open-label, nonrandomised, heparin controlled, crossover	Epoprost-enol: 12 Heparin: 11	Not available	Not available
2.2	To compare safety (clinical laboratories, vital signs, electrocardiograms, and adverse events) and efficacy (removal of BUN, creatinine, and potassium) of Flolan with heparin-facilitated haemodialysis in patients with chronic renal failure	United States	Open-label, non-random-ised, heparin controlled, crossover	Epoprost-enol: 14 Heparin: 12	Not available	Not available
19	To compare safety (clinical laboratories, vital signs,	United States	Open-label, parallel group,	Epoproste nol: 21	Epoprost-enol: Up to 30	Clinical study report available:

Study	Description (Phase, short description of study (1 – 2 sentences including comparator name(s)/ placebo))	Countries	Study design	Planned/ actual number of patients	Duration of follow up	Estimated/ Actual completion date
	electrocardiograms, and adverse events) and efficacy (removal of BUN, creatinine, potassium; clearance of BUN and creatinine; ultrafiltration rate; bleeding) of Flolan with heparin-facilitated haemodialysis in patients with chronic renal failure and with a range of hemorrhagic risks		randomised	Heparin: 14	minutes predialysis; Until completion of dialysis	1983
27	To compare safety (clinical laboratories, vital signs, electrocardiograms, and adverse events) and efficacy (removal of BUN, creatinine, potassium, and fluid; blood loss assessments) during haemodialysis using Flolan versus heparin in patients with acute or chronic renal failure and high or very high risks of hemorrhage	United States	Open-label, parallel group, randomised, 3 dialysis periods, categorised into 2 groups of haemorr-hagic risk (high or very high)	Epoprost-enol: 19 Heparin: 22	Epoprost-enol: Up to 30 minutes predialysis; Until completion of dialysis	Clinical study report available: 1984
30	To compare within individuals the long-term safety (clinical laboratories, vital signs, ECGs, and adverse events) and efficacy (decrements in BUN, creatinine, potassium; fluid removal) of haemodialysis using epoprostenolversus heparin in chronic	United States	Randomised, crossover, heparin-controlled	Epoprost-enol: 10 Heparin: 9	Not available	Not available

Study	Description (Phase, short description of study (1 – 2 sentences including comparator name(s)/ placebo))	Countries	Study design	Planned/ actual number of patients	Duration of follow up	Estimated/ Actual completion date
	renal failure patients					
31	To compare between individuals the long-term safety (clinical laboratories, vital signs, ECGs, and adverse events) and efficacy (decrements in BUN, creatinine, potassium; fluid removal) of haemodialysis using Flolan versus heparin in chronic renal failure patients	United States	Randomised, parallel group, heparin controlled, 24 consecutive dialyses	Epoprost-enol: 15 Heparin: 16	Not Available	Available as abstract: 1989
Further safety/efficacy studies						
None planned						
Studies in special populations (e.g. paediatric, elderly)						
None planned						

ANNEX 5. SYNOPSIS OF ON-GOING AND COMPLETED PHARMACOEPIDEMIOLOGICAL STUDY PROGRAMME

Study	Research question	Study design	Population & study size	Duration of follow up	Milestones & dates	Status
Not applicable						

ANNEX 6. PROTOCOLS FOR PROPOSED AND ON-GOING STUDIES IN CATEGORIES 1-3 OF THE SECTION "SUMMARY TABLE OF ADDITIONAL PHARMACOVIGILANCE ACTIVITIES" IN RMP PART III

Overview of included protocols

Study title	Protocol status [1]	Version of protocol	Date of protocol version
Not applicable			

ANNEX 7. SPECIFIC ADVERSE EVENT FOLLOW-UP FORMS

Not applicable

ANNEX 8. PROTOCOLS FOR PROPOSED AND ON-GOING STUDIES IN RMP PART IV

Study title	Protocol status [1]	Version of protocol	Date of protocol version
Not applicable			

ANNEX 9. NEWLY AVAILABLE STUDY REPORTS FOR RMP PARTS III & IV

Not applicable

ANNEX 10. DETAILS OF PROPOSED ADDITIONAL RISK MINIMISATION MEASURES (IF APPLICABLE)

See Annex 11.

ANNEX 11. MOCK-UP OF PROPOSED ADDITIONAL RISK MINIMISATION MEASURES (IF APPLICABLE)

GLAXOSMITHKLINE SAFETY ADVISORY

Date: *28 October 2014*

TITLE: FLOLAN (epoprostenol) – Two different sterile diluents for FLOLAN will be temporarily available, each with different instructions for reconstitution, storage and administration of FLOLAN solution.

Dear Healthcare Professional,

Therapeutic Indication

FLOLAN (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 and 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. FLOLAN is administered via continuous intravenous infusion and is supplied as two vials, one containing freeze-dried active drug and the other containing specialized diluent for reconstituting the active drug to produce the final solution for intravenous infusion.

GlaxoSmithKline (GSK) would like to inform you that a reformulated Solvent for Solution for Infusion for FLOLAN is now available. Reconstituted FLOLAN solution is more stable when prepared with the reformulated Solvent for Solution for Infusion which eliminates the need for use of a cold pouch during administration.

GSK is alerting prescribers to the launch of the reformulated Solvent for Solution for Infusion and differences in storage and administration to ensure proper use of each of the diluents during the period when patients should be transitioned from FLOLAN prepared with Solvent for Solution for Infusion to FLOLAN prepared with the reformulated Solvent for Solution for Infusion.

Key Messages

- Storage and administration conditions when using FLOLAN to treat PAH

FLOLAN solution prepared with Solvent for Solution for Infusion:	FLOLAN solution prepared with reformulated Solvent for Solution for Infusion (pH 12):
Should be used within 12 hours at 25°C if freshly prepared, OR May be stored for up to 40 hours between 2°C and 8°C and then used within 8 hours at 25°C, OR May be stored for up to 24 hours between 2°C and 8°C and then used over 24 hours between 2°C and 8°C with use of a cold pouch changed to as necessary throughout the day.	Freshly prepared solutions for infusion can be administered immediately or stored for up to 8 days at 2°C to 8°C prior to administration. Following this preparation or storage, the solution for infusion should be used within: • 72 hours at up to 25°C or • 48 hours at up to 30ºC or • 24 hours at up to 35 ºC or • 12 hours at up to 40 ºC

- Accidental use of Solvent for Solution for Infusion in place of the reformulated Solvent for Solution for Infusion (pH 12) without concurrent use of a cold pouch for the FLOLAN solution could result in possible decrease in efficacy due to drug degradation. Decreased drug delivery could result in rebound of PAH symptoms resulting in dizziness and dyspnoea.

- There will be a period of time in which both the Solvent for Solution for Infusion and the reformulated Solvent for Solution for Infusion (pH 12) will be on the market simultaneously while existing Solvent for Solution for Infusion supplies are transitioned to the reformulated Solvent for Solution for Infusion (pH 12).

- It is important that you are aware of this diluent reformulation to ensure that the correct instructions for reconstitution, storage and administration of FLOLAN are given to your patients who are receiving FLOLAN for the treatment of PAH.

- The change in the diluent formulation does not affect the reconstitution or administration of FLOLAN solution for use in renal dialysis.

- The change in the diluent formulation does not affect the dosing of FLOLAN solution for treatment of PAH or use in renal dialysis.

Action Being Taken by GlaxoSmithKline

GSK has clearly distinguished the reformulated diluent with a statement on the external carton of FLOLAN highlighting the change to the diluent, “New formulation of solvent (pH 12)- see leaflet inside for use”, as well as changing the predominant label colour and flip-top lid colour to purple from yellow to ensure that the reformulated Solvent for Solution for Infusion (pH 12) looks different from Solvent for Solution for Infusion. The reformulated Solvent for Solution for Infusion can be further distinguished as it is contained in a plastic vial compared to the glass vial of Solvent for Solution for Infusion.

These changes are intended to minimize any potential for medication errors given the different instructions related to storage and administration of the two formulations.

(include pictures of the established and reformulated diluent vials and external packaging cartons here)

GSK has updated product labeling for FLOLAN to include information regarding use of both the reformulated Solvent for Solution for Infusion (pH 12) and Solvent for Solution for Infusion.

Action required by Health Care Providers

- You are advised to read the revised product labeling related to use of Solvent for Solution for Infusion (pH 12) for preparation of FLOLAN solution. The new version is attached to this communication. Please share this information with relevant health care personnel under your supervision.

- You are advised to ensure patients being treated for PAH with FLOLAN are aware of the reformulated Solvent for Solution for Infusion (pH 12) as well as appropriate instructions for reconstitution, storage and administration of FLOLAN prepared with the reformulated Solvent for Solution for Infusion.

- Should a patient be transitioned from FLOLAN prepared with the reformulated Solvent for Solution for Infusion to another intravenous prostanoid therapy in the future, please ensure that the patient understands any differences in reconstitution, storage, and administration occurring as a result of that change.

Revised Labeling

Full product labeling including information for FLOLAN solution reconstituted with either Solvent for Solution for Infusion or reformulated Solvent for Solution for Infusion is enclosed for your information and reference.

Further Information

Details of how to report adverse reaction (including the formulation of diluent in use at the time of the event) including regulatory authority contact information and company contact information for reporting adverse events.

Contact(s) for Further Information/Questions:

Should you have any questions or require additional information, please contact

Name, title, and contact information for the most appropriate GSK person(s) to address questions

With regards,
PPD , MD PhD
PPD , GSK Global Clinical Safety and Pharmacovigilance, Safety Evaluation and Risk Management

Attached: Revised product labeling for FLOLAN

ANNEX 12. OTHER SUPPORTING DATA (INCLUDING REFERENCED MATERIAL)

The following references are included below, otherwise the reference is available upon request.

- Bedard E et al. Has there been any progress made on pregnancy outcomes among women with pulmonary arterial hypertension? Eur Heart J 2009;30:256–265.
- Doran AK et al. Guidelines for the prevention of central venous catheter related blood stream infections with prostanoid therapy for pulmonary arterial hypertension. Int J Clin Pract 2008:62(S160):5–9.
- Galie N et al. Guidelines for the diagnosis and treatment of pulmonary hypertension: the task force for the diagnosis and treatment of pulmonary hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS), endorsed by the International Society of Heart and Lung Transplantation (ISHLT). Eur Heart J 2009;30:2493–2537.
- Kingman MS et al. Prostacyclin administration errors in pulmonary arterial hypertension patients admitted to hospitals in the United States: a national survey. J Heart Lung Transplant 2010;29 (8):841-846.
- Lammers AE et al. Epoprostenol treatment in children with severe pulmonary hypertension. Heart 2007;93:739-743.
- Pieper PG et al. Pregnancy and pulmonary hypertension. Best Pract Res Clin Obstet Gynaecol 2014;28(4):579-591.
- Rich JD et al. The effect of diluent pH on bloodstream infection rates in patients receiving IV treprostinil for pulmonary arterial hypertension. Chest 2012;141(1):36–42.