CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-260

MEDICAL REVIEW(S)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF CARDIO-RENAL DRUG PRODUCTS
HFD 110

Medical Review of NDA 22-260 (serial 000)

Reviewer: **A.O.Williams, M.D.**

Application Type	NDA
Submission Number	22-260
Submission Code	000
Letter Date	August 24, 2007
Stamp Date	August 25, 2007
PDUFA Goal Date	June 27, 2008
Review Completion Date	May 1 2008
Established Names	Epoprostenol for injection
Trade Name	[redacted] b(4)
Therapeutic Class	Prostaglandin (PG12, PGX prostacyclin)
Applicant	GeneraMedix
Priority Designation	S
Formulation (New)	Solution for Injection
Dosing Regimen	Individualized [redacted] b(4)
Indication	Primary pulmonary Hypertension (PPH)
Intended Population	Patients with PPH

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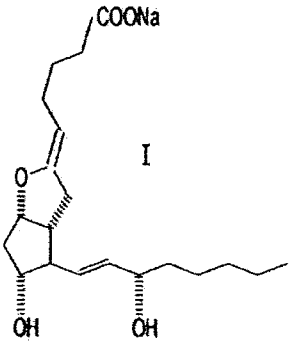
1 EXECUTIVE SUMMARY

The product that is the subject of this submission is a new formulation of Epoprostenol Sodium for Injection. This formulation is deemed by the sponsor to be an advantage for the patient population because it is substantially more stable upon reconstitution and administration than the currently marketed epoprostenol product, Flolan®, made by GlaxoSmithKline. The increased stability allows the product to be prepared up to [redacted] in advance when stored at refrigerated temperatures, and allows for delivery over a 48-hour period when dosed at 25oC. This is in contrast to Flolan, which has only a 40-hour shelf life at refrigerated temperatures and an 8-hour delivery time. The chemical structure is below: b(4)

Figure 1: Molecular Structure of Flolan

Molecular Structure:	
Molecular Formula:	$C_{20}H_{31}NaO_5$
Molecular Weight:	374.45 (sodium salt, as shown above)

The solution used to administer the compound for the Flolan® product is a special diluent sold exclusively for the reconstitution and dilution of this product. The solution intended for use for the GeneraMedix Epoprostenol Sodium for Injection may be Sterile Water for Injection, USP, 0.9% Sodium Chloride Injection, USP, [redacted] b(4)

The commercially available epoprostenol injection product, approved by the FDA in 1995 and used for the treatment of primary pulmonary hypertension, is manufactured by Glaxo-Smith Kline under the trade name of Flolan®. Flolan is supplied as lyophilized vials containing either 0.5 mg or 1.5 mg epoprostenol with a companion vial which consists of 50 mL of a special diluent [redacted] with glycine and [redacted] sodium chloride. The pH of the [redacted] solution is adjusted to a range of 10.2 to 10.8 with sodium hydroxide. b(4)

The rationale for the development of a new epoprostenol injection formula is to minimize the shortcomings of the currently marketed product, Flolan.
In particular:

- The formula should have a better stability profile both during the manufacturing process and upon reconstitution. An improved stability profile would make the use easier for the patient.

- The lyophilized product should be able to be reconstituted with commercially available IV fluids such as sterile Water for Injection, rather than a specially made diluent.
- Upon dilution for delivery, the drug solution should be able to be infused under ambient conditions, rather than requiring ice packs for prolonged delivery.
- The formula should be self-preserving without the addition of antimicrobial agents, to allow for extended shelf life after reconstitution.

1.1 RECOMMENDATION ON REGULATORY ACTION

The proposed formulation is not identical to the Flolan for Injection currently on the market; however, both formulations are solutions at the time of use and both are injected via the central venous catheter. However, the pharmacokinetics are expected to be identical.

A new epoprostenol injection product has been developed that, in the presence of a buffering agent, and high pH (>11), is very stable when compared to the currently available epoprostenol injection product, Flolan. The composition of this new formulation is characterized by improved stability upon reconstitution with commercially available intravenous (IV) fluids.

It is recommended that the proposed formulation be "approvable" subject to submission of a safety study that will characterize any adverse events particularly the potential for phlebitis.

1.2 RECOMMENDATIONS ON POSTMARKETING ACTIONS

Pharmacovigilance for phlebitis should be instituted.

1.2.1 Risk management Activity

Phlebitis should be identified in patients who develop this adverse event and clinically managed.

1.2.2 Required Phase 4 commitments

Not applicable

1.2.3 Other phase 4 requests

Not applicable

1.3 SUMMARY OF CLINICAL FINDINGS

No clinical study has been carried out but the report of an ongoing safety study is expected to be submitted.

1.3.1 Brief overview of clinical program

No study has been carried out.

1.3.2 Efficacy

(See section 6 of this review).

1.3.3 Safety

(See section 7 of this review).

1.3.4 Dosing Regimen and Administration

- Epoprostenol sodium is administered by continuous intravenous infusion via a central venous catheter using an ambulatory infusion pump.
- During initiation of treatment, epoprostenol sodium may be administered peripherally.
- Chronic infusion of epoprostenol should be done via venous catheter. Peripheral infusion may be used temporarily.
- Chronic infusion of epoprostenol sodium should be initiated at 2 ng/kg/min and increased in increments of 2 ng/kg/min every 15 minutes or longer until dose-limiting pharmacologic effects are elicited or until a tolerance limit to the drug is established.
- If symptoms of pulmonary hypertension persist or recur after improving - the infusion should be increased by 1- to 2-ng/kg/min increments at intervals sufficient to allow assessment of clinical response; these intervals should be at least 15 minutes.

1.3.5 Drug –Drug Interactions

Additional reductions in blood pressure may occur when epoprostenol sodium is administered with diuretics, antihypertensive agents, or other vasodilators. When other antiplatelet agents or anticoagulants are used concomitantly, there is the potential for epoprostenol sodium to increase the risk of bleeding. However, patients receiving infusions of epoprostenol sodium in clinical trials were maintained on anticoagulants without evidence of increased bleeding. In clinical trials, epoprostenol sodium was used with digoxin, diuretics, anticoagulants, oral vasodilators, and supplemental oxygen.

In a pharmacokinetic substudy in patients with congestive heart failure receiving furosemide or digoxin in whom therapy with epoprostenol sodium was initiated, apparent

oral clearance values for furosemide (n = 23) and digoxin (n = 30) were decreased by 13% and 15%, respectively, on the second day of therapy and had returned to baseline values by day 87. The change in furosemide clearance value is not likely to be clinically significant. However, patients on digoxin may show elevations of digoxin concentrations after initiation of therapy with epoprostenol sodium, which may be clinically significant in patients prone to digoxin toxicity.

1.3.6 Special populations

Not applicable.

2 INTRODUCTION AND BACKGROUND

2.1 Product information

Epoprostenol (PGI2, PGX, prostacyclin), a metabolite of arachidonic acid, is a naturally occurring prostaglandin with potent vasodilatory activity and inhibitory activity of platelet aggregation.

Epoprostenol Sodium for Injection is a white to off-white lyophilized material that may be translucent. It is reconstituted with Sterile Water for Injection, USP, Sodium Chloride 0.9% Injection, USP. [redacted] The reconstituted solution of Epoprostenol Sodium for Injection has a pH of >11.0 and is increasingly unstable at a lower pH. b(4)

Epoprostenol Sodium for Injection is a sterile sodium salt formulated for intravenous (IV) administration. Each vial of Epoprostenol Sodium for Injection contains epoprostenol sodium equivalent to 1.5 mg (1,500,000 ng) epoprostenol, 50 mg arginine, and 50 mg mannitol. Sodium hydroxide is added to adjust pH.

Flolan must be reconstituted only with the sterile diluent for Flolan. Reconstituted solutions of Flolan must not be diluted or administered with other parenteral solutions or medications. The reconstituted solutions of Flolan must be protected from light and must be refrigerated at 2° to 8°C (36° to 46°F) if not used immediately. The refrigerated solution, however, can be held for only two days and must be discarded thereafter. Additionally, the reconstituted solution cannot be frozen, and the solution must be discarded if it is frozen.

At the start of this development program, simulated Flolan was manufactured following the outline of the formula given in the Physician's Desk Reference (PDR). These simulated Flolan products were then studied for their various stability characteristics. The approach of using simulated Flolan was deemed necessary since the actual product itself is tightly controlled in the marketplace and difficult to obtain.

The data obtained confirmed much of the information readily available in the product insert. The pH of this Flolan product is not sufficient to maintain stability at refrigerated conditions for more than 40 hours or room temperature conditions for longer than 8 hours. The data generated on the simulated Flolan suggested that a limit of — potency was used to obtain these limits for dosing. b(4)

The rationale for the development of a new epoprostenol injection formula is to minimize the shortcomings of the currently marketed product, Flolan. In particular:

a) The formula should have a better stability profile both during the manufacturing process and upon reconstitution. An improved stability profile would make the use easier for the patient. b) The lyophilized product should be able to be reconstituted with commercially available IV fluids such as sterile Water for Injection, rather than a specially made diluent. c) Upon dilution for delivery, the drug solution should be able to be infused under ambient conditions, rather than requiring ice packs for prolonged delivery. d) The formula should be self-preserving without the addition of antimicrobial agents, to allow for extended shelf life after reconstitution.

A new epoprostenol injection product has been developed that, in the presence of a buffering agent, and high pH (>11), is very stable when compared to the currently available epoprostenol injection product, Flolan. The composition of this new formulation is characterized by improved stability upon reconstitution with commercially available intravenous (IV) fluids. When reconstituted and/or diluted in commercially available IV fluids, the stability of the present formulation is characterized by > 90% of the original epoprostenol remaining after 24 hours at 25°C. Moreover, this product can also be prepared in the vial and kept at refrigerated conditions for as long as 5 days, which allows the patient or caregiver to prepare doses well in advance of their need.

This extended 5-day refrigerated shelf life is due in part to the self-preservation of the reconstituted product, preventing the growth of microorganisms that may be introduced into the product. This has been shown by challenging the product to a USP Preservative Effectiveness Test.

In addition, the admixtures diluted for delivery are hemocompatible. The literature contains references that suggest high pH formulations may be incompatible with blood. Because the proposed epoprostenol formulation is administered at high pH (>11), one might expect similar incompatibility. However, epoprostenol is dosed in very small quantities, allowing for much more dilution in the blood, with much less potential for the types of reactions associated in the literature with high pH formulations. Nonetheless, a hemocompatibility study was performed and the results indicate that next to no blood cell lysis does occurs when the proposed epoprostenol formulation is present in a ratio comparable to the rate of delivery as compared with the volume of blood flow

This formulation was arrived at after several various formulation prototypes were explored. These prototypes included excipients such as — They also included various — b(4)

[redacted] Several batches were made with various ratios of these excipients. Vials from these batches were placed on limited stability, primarily at the accelerated temperature of 40°C. b(4)

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

NON-CLINICAL TOXICOLOGY

Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term studies in animals have not been performed to evaluate carcinogenic potential. A micronucleus test in rats revealed no evidence of mutagenicity. The Ames test and DNA elution tests were also negative, although the instability of epoprostenol makes the significance of these tests uncertain. Fertility was not impaired in rats given epoprostenol sodium by subcutaneous injection at doses up to 100 mcg/kg/day (600 mcg/m2/day, 2.5 times the recommended human dose [4.6 ng/kg/min or 245.1 mcg/m2/day, IV] based on body surface area).

Long-term studies in animals have not been performed to evaluate carcinogenic potential. A micronucleus test in rats revealed no evidence of mutagenicity. The Ames test and DNA elution tests were also negative, although the instability of epoprostenol makes the significance of these tests uncertain. Fertility was not impaired in rats given epoprostenol sodium by subcutaneous injection at doses up to 100 mcg/kg/day (600 mcg/m2/day, 2.5 times the recommended human dose [4.6 ng/kg/min or 245.1 mcg/m2/day, IV] based on body surface area).

Pregnancy

Pregnancy Category B. Reproductive studies have been performed in pregnant rats and rabbits at doses up to 100 mcg/kg/day (600 mcg/m2/day in rats, 2.5 times the recommended human dose, and 1,180 mcg/m2/day in rabbits, 4.8 times the recommended human dose based on body surface area) and have revealed no evidence of impaired fertility or harm to the fetus due to epoprostenol sodium. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Labor and Delivery

The use of epoprostenol sodium during labor, vaginal delivery, or cesarean section has not been adequately studied in humans.

4 DATA SOURCES, REVIEW STRATEGY AND DATA INTEGRITY

The data reviewed are from electronic submission. The review strategy was to justify the 505 (b) (2) pathway applied for filing the application and to verify bioequivalence and that all the ingredients for this pathway are acceptable.

5 CLINICAL PHARMACOLOGY

Mechanism of Action

Epoprostenol has 2 major pharmacological actions: (1) direct vasodilation of pulmonary and systemic arterial vascular beds, and (2) inhibition of platelet aggregation.

General

Epoprostenol has 2 major pharmacological actions: (1) direct vasodilation of pulmonary and systemic arterial vascular beds, and (2) inhibition of platelet aggregation. In animals, the vasodilatory effects reduce right- and left-ventricular afterload and increase cardiac output and stroke volume. The effect of epoprostenol on heart rate in animals varies with dose. At low doses, there is vagally mediated bradycardia, but at higher doses, epoprostenol causes reflex tachycardia in response to direct vasodilation and hypotension. No major effects on cardiac conduction have been observed. Additional pharmacologic effects of epoprostenol in animals include bronchodilation, inhibition of gastric acid secretion, and decreased gastric emptying.

5.1 Pharmacokinetics

Epoprostenol is rapidly hydrolyzed at neutral pH in blood and is also subject to enzymatic degradation. Animal studies using tritium-labeled epoprostenol have indicated a high clearance (93 mL/kg/min), small volume of distribution (357 mL/kg), and a short half-life (2.7 minutes). During infusions in animals, steady-state plasma concentrations of tritium-labeled epoprostenol were reached within 15 minutes and were proportional to infusion rates.

No available chemical assay is sufficiently sensitive and specific to assess the in vivo human pharmacokinetics of epoprostenol. The in vitro half-life of epoprostenol in human blood at 37°C and pH 7.4 is approximately 6 minutes; therefore, the in vivo half-life of epoprostenol in humans is expected to be no greater than 6 minutes. The in vitro pharmacologic half-life of epoprostenol in human plasma, based on inhibition of platelet aggregation, was similar for males (n = 954) and females (n = 1,024).

Tritium-labeled epoprostenol has been administered to humans in order to identify the metabolic products of epoprostenol. Epoprostenol is metabolized to 2 primary metabolites: 6-keto-PGF1a (formed by spontaneous degradation) and 6,15-diketo-13,14-dihydro-PGF1a (enzymatically formed), both of which have pharmacological activity orders of magnitude less than epoprostenol in animal test systems. The recovery of radioactivity in urine and feces over a 1-week period was 82% and 4% of the administered dose, respectively. Fourteen additional minor metabolites have been isolated from urine, indicating that epoprostenol is extensively metabolized in humans.

5.2 Pharmacodynamics

In animals, the vasodilatory effects reduce right- and left-ventricular afterload and increase cardiac output and stroke volume. The effect of epoprostenol on heart rate in animals varies with dose. At low doses, there is vagally mediated bradycardia, but at

higher doses, epoprostenol causes reflex tachycardia in response to direct vasodilation and hypotension. No major effects on cardiac conduction have been observed. Additional pharmacologic effects of epoprostenol in animals include bronchodilation, inhibition of gastric acid secretion, and decreased gastric emptying.

5.3 Exposure relationship

In the interest of due diligence for patients using this product, a study was carried out to examine the effect of the proposed formulation and other prototypes on hemolysis of blood.

In this study the hemocompatibility of the proposed mannitol/arginine was examined, using Sterile Water for Injection, 0.9% Sodium Chloride Injection , ——— ———as the admixture diluents. Samples were diluted to a concentration of ~15µg/mL in each of the large volume parenteral diluents. Then 70 uL of diluted admixture were added to 5mL fresh blood and incubated for ~20 minutes at 37oC. b(4)

A ratio of 70 µL diluted product to 5 mL blood was chosen for the exposure of blood to product. This ratio was chosen based on the estimates of the pumping rate of this product and the blood flow rate at the location in which it is delivered. The pumping rate of this product is estimated to be ~0.05 mL (50µL) per pulse of the pump (per the vendor). Thus, a value slightly higher of 70 µL was chosen as a worst case.

The blood flow rate is published to be 3 to 30 mL/minute in a forearm vein. Approximately one pulse is given every 30 seconds at the highest dosing rates through the pump. Therefore, at the slowest blood flow rates above, 50 µ L would be exposed to ~1.5 mL blood. However, this product is generally delivered via a central venous catheter. Therefore, the volumetric blood flow rate would be much higher than 3 mL/ minute. Nonetheless, 5 mL of blood was estimated as a worst case volume to simulate delivery into a vein based on overall blood flow rate in the peripheral vein that might be used to start the patient on the drug.

After incubation, the plasma was recovered and the optical density (OD) absorbance at ——— was measured to establish the level of hemolysis. The 0.9% Sodium Chloride Injection was used as the non-hemolytic control and de-ionized water was used as the hemolytic control. Untreated blood samples were also examined to confirm the background levels of hemolysis based on the handling of the samples. The relative hemolysis of each sample was determined using the following equation: b(4)

Relative Hemolysis = (OD Sample – OD NaCl) / (OD DI water – OD NaCl)

The results showed that the mannitol/arginine/epoprostenol formulation showed nearly no measurable hemolysis (0.0 to 0.3%) when compared to the saline and blood controls. The analysis was also conducted using a cyanmethemoglobin reagent to reduce all the forms of hemoglobin. The total concentration o free hemoglobin was then compared to the total concentration of hemoglobin in the blood. The results were similar in that nearly no measureable hemolysis was observed (0.0 to 0.3%).

Epoprostenol Sodium for Injection, 1.5 mg/vial is compatible with parenteral diluents such as Water for Injection, USP, 0.9% Sodium Chloride Injection USP, ——— b(4)
: ——————— '. When diluted to as little as 15 µg/mL, the potency of the epoprostenol is ~90% or better in all the diluents when held at 25°C for 24 hours. Moreover, the potency of the epoprostenol is — or better in all the diluents when held at 25°C for 48 hours.

Because the dilution data for the simulated Flolan solutions suggest that Flolan is dosed to a level of — potency, a similar potency requirement can be applied to the Epoprostenol Sodium for Injection, 1.5mg/vial. Therefore, Epoprostenol Sodium for b(4)
Injection may be diluted and dosed for up to 48 hours at 25°C.

These data, in conjunction with the stability of the reconstituted concentrate discussed in Section 3.2.P.2. Pharmaceutical Development in the Container Closure System section, show that the product can be reconstituted with 5mL of the chosen diluent, kept refrigerated for as long as 5 days, then dosed at room temperature over the course of up to b(4)
48 hours and still deliver — of the potency at the end of the time of delivery.

The data also show that the drug product, when reconstituted with 5mL diluent, is chemically stable at 2-8°C for as long as 5 days. Moreover, the drug product diluted in this fashion is also self preserving, so that no microbial growth is of concern. This product can then be further diluted with the same diluent to a delivery concentration as low as 15 µg/mL and dosed over 24 -48 hours when held up to 25°C.

6 CLINICAL STUDIES-EFFICACY

6.1.1 Methodology

Study design described above for Flolan as no clinical study was carried out.

6.1.2 Efficacy findings - Clinical Trials in Pulmonary Hypertension

Acute Hemodynamic Effects: Acute intravenous infusions of epoprostenol sodium for up to 15 minutes in patients with secondary and primary pulmonary hypertension 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 sodium on mean pulmonary artery pressure (PAPm) were variable and minor.

Chronic Infusion in Primary Pulmonary Hypertension (PPH):

Hemodynamic Effects: Chronic continuous infusions of epoprostenol sodium in patients with PPH were studied in 2 prospective, open, randomized trials of 8 and 12 weeks' duration comparing epoprostenol sodium 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.

Chronic hemodynamic effects were generally similar to acute effects. Increases in CI, SV, and arterial oxygen saturation and decreases in PAPm, mean right atrial pressure (RAPm), TPR, and systemic vascular resistance (SVR) were observed in patients who received epoprostenol sodium chronically compared to those who did not. Table 1 illustrates the treatment-related hemodynamic changes in these patients after 8 or 12 weeks of treatment.

Table 1: Hemodynamics during chronic administration of Epoprostenol Sodium in patients with PPH

Hemodynamic Parameter	Baseline		Mean Change from Baseline at End of Treatment Period*	
	Epoprostenol Sodium (N = 52)	Standard Therapy (N = 54)	Epoprostenol Sodium (N = 48)	Standard Therapy (N = 41)
CI (L/min/m2)	2.0	2.0	0.3†	-0.1
PAPm (mm Hg)	60	60	-5†	1
PVR (Wood U)	16	17	-4†	1
SAPm (mm Hg)	89	91	-4	-3
SV (mL/beat)	44	43	6†	-1
TPR (Wood U)	20	21	-5†	1

+ denotes statistically significant difference between Epoprostenol Sodium and conventional therapy. CI= Cardiac index; PAPm = mean pulmonary arterial pressure; PVR= pulmonary vascular resistance; SAPm=mean systemic arterial pressure; SV = stroke volume; TPR = total pulmonary resistance.

These hemodynamic improvements appeared to persist when epoprostenol sodium was administered for at least 36 months in an open, nonrandomized study.

Clinical Effects: Statistically significant improvement was observed in exercise capacity, as measured by the 6-minute walk test in patients receiving continuous intravenous epoprostenol sodium plus conventional therapy (N = 52) for 8 or 12 weeks compared to those receiving conventional therapy alone (N = 54). Improvements were apparent as early as the first week of therapy. Increases in exercise capacity were accompanied by

statistically significant improvement in dyspnea and fatigue, as measured by the Chronic Heart Failure Questionnaire and the Dyspnea Fatigue Index.

Survival was improved in NYHA functional Class III and Class IV PPH patients treated with epoprostenol sodium for 12 weeks in a multicenter, open, randomized, parallel study. At the end of the treatment period, 8 of 40 (20%) patients receiving conventional therapy alone died, whereas none of the 41 patients receiving epoprostenol sodium died ($p = 0.003$).

Chronic Infusion in Pulmonary Hypertension Associated with the Scleroderma Spectrum of Diseases (PH/SSD):

Hemodynamic Effects: Chronic continuous infusions of epoprostenol sodium in patients with PH/SSD were studied in a prospective, open, randomized trial of 12 weeks' duration comparing epoprostenol sodium 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. 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 sodium chronically compared to those who did not. Table 10 illustrates the treatment-related hemodynamic changes in these patients after 12 weeks of treatment.

Table 2: Hemodynamics during chronic administration of Epoprostenol sodium in patients with PH/SSD

Hemodynamics During Chronic Administration of Epoprostenol Sodium in Patients With PH/SSD

Hemodynamic Parameter	Baseline		Mean Change from Baseline at 12 Weeks	
	Epoprostenol Sodium (N = 56)	Conventional Therapy (N = 55)	Epoprostenol Sodium (N = 50)	Conventional Therapy (N = 48)
CI (L/min/m2)	1.9	2.2	0.5*	-0.1
PAPm (mm Hg)	51	49	-5*	1
RAPm (mm Hg)	13	11	-1*	1
PVR (Wood U)	14	11	-5*	1
SAPm (mm Hg)	93	89	-8*	-1

* Denotes statistically significant difference between epoprostenol sodium and conventional therapy groups (N is the number of patients with hemodynamic data).
CI = cardiac index, PAPm = mean pulmonary arterial pressure, RAPm = mean right

arterial pressure, PVR = pulmonary vascular resistance, SAPm = mean systemic arterial pressure.

Clinical Effects: Statistically significant improvement was observed in exercise capacity, as measured by the 6-minute walk, in patients receiving continuous intravenous epoprostenol sodium plus conventional therapy for 12 weeks compared to those receiving conventional therapy alone. 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 dyspnea and fatigue, as measured by the Borg Dyspnea Index and Dyspnea Fatigue Index. At week 12, NYHA functional class improved in 21 of 51 (41%) patients treated with epoprostenol sodium compared to none of the 48 patients treated with conventional therapy alone. However, more patients in both treatment groups (28/51 [55%] with epoprostenol sodium and 35/48 [73%] with conventional therapy alone) showed no change in functional class, and 2/51 (4%) with epoprostenol sodium and 13/48 (27%) with conventional therapy alone worsened. Of the patients randomized, NYHA functional class data at 12 weeks were not available for 5 patients treated with epoprostenol sodium and 7 patients treated with conventional therapy alone.

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

No controlled clinical trials with epoprostenol sodium have been performed in patients with pulmonary hypertension associated with other diseases.

6.1.3 Efficacy findings - CLINICAL TRIALS in pulmonary hypertension

Acute Hemodynamic Effects:

Acute intravenous infusions of epoprostenol sodium for up to 15 minutes in patients with secondary and primary pulmonary hypertension 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 sodium on mean pulmonary artery pressure (PAPm) were variable and minor.

Chronic Infusion in Primary Pulmonary Hypertension (PPH)
Hemodynamic Effects

Chronic continuous infusions of epoprostenol sodium in patients with PPH were studied in 2 prospective, open, randomized trials of 8 and 12 weeks' duration comparing epoprostenol sodium 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.

Chronic hemodynamic effects were generally similar to acute effects. Increases in CI, SV, and arterial oxygen saturation and decreases in PAPm, mean right atrial pressure (RAPm), TPR, and systemic vascular resistance (SVR) were observed in patients who received epoprostenol sodium chronically compared to those who did not. Table 1 illustrates the treatment-related hemodynamic changes in these patients after 8 or 12 weeks of treatment.

Table 3: Hemodynamics During Chronic Administration of Epoprostenol Sodium in Patients With PPH

	Baseline		Mean Change from Baseline at End of Treatment Period*	
HemodynamicParameter	Epoprostenol Sodium(N = 52)	StandardTherapy(N = 54)	Epoprostenol Sodium(N = 48)	StandardTherapy(N = 41)
CI (L/min/m2)	2.0	2.0	0.3†	-0.1
PAPm (mm Hg)	60	60	-5†	1
PVR (Wood U)	16	17	-4†	1
SAPm (mm Hg)	89	91	-4	-3
SV (mL/beat)	44	43	6†	-1
TPR (Wood U)	20	21	-5†	1

* At 8 weeks: Epoprostenol Sodium N = 10, conventional therapy N = 11 (N is the number of patients with hemodynamic data). At 12 weeks: Epoprostenol Sodium N = 38, conventional therapy N = 30 (N is the number of patients with hemodynamic data).

† Denotes statistically significant difference between Epoprostenol Sodium and conventional therapy groups. CI = cardiac index, PAPm = mean pulmonary arterial pressure, PVR = pulmonary vascular resistance, SAPm = mean systemic arterial pressure, SV = stroke volume, TPR = total pulmonary resistance.

These hemodynamic improvements appeared to persist when epoprostenol sodium was administered for at least 36 months in an open, nonrandomized study.

6.1.4 Efficacy - Clinical Effects

Statistically significant improvement was observed in exercise capacity, as measured by the 6-minute walk test in patients receiving continuous intravenous epoprostenol sodium plus conventional therapy (N = 52) for 8 or 12 weeks compared to those receiving conventional therapy alone (N = 54). Improvements were apparent as early as the first week of therapy. Increases in exercise capacity were accompanied by statistically significant improvement in dyspnea and fatigue, as measured by the Chronic Heart Failure Questionnaire and the Dyspnea Fatigue Index.

Survival was improved in NYHA functional Class III and Class IV PPH patients treated with epoprostenol sodium for 12 weeks in a multicenter, open, randomized, parallel study. At the end of the treatment period, 8 of 40 (20%) patients receiving conventional

therapy alone died, whereas none of the 41 patients receiving epoprostenol sodium died ($p = 0.003$).

Chronic Infusion in Pulmonary Hypertension Associated with the Scleroderma Spectrum of Diseases (PH/SSD)

Hemodynamic Effects

Chronic continuous infusions of epoprostenol sodium in patients with PH/SSD were studied in a prospective, open, randomized trial of 12 weeks' duration comparing epoprostenol sodium 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. 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 sodium chronically compared to those who did not. Table 2 illustrates the treatment-related hemodynamic changes in these patients after 12 weeks of treatment.

Table 4; Hemodynamics During Chronic Administration of Epoprostenol Sodium in Patients With PH/SSD

HemodynamicParameter	Baseline		Mean Change from Baseline at 12 Weeks	
	Epoprostenol Sodium(N = 56)	Conventional Therapy(N = 55)	Epoprostenol Sodium(N = 50)	Conventional Therapy(N = 48)
CI (L/min/m2)	1.9	2.2	0.5*	-0.1
PAPm (mm Hg)	51	49	-5*	1
RAPm (mm Hg)	13	11	-1*	1
PVR (Wood U)	14	11	-5*	1
SAPm (mm Hg)	93	89	-8*	-1

* Denotes statistically significant difference between epoprostenol sodium and conventional therapy groups (N is the number of patients with hemodynamic data). CI = cardiac index, PAPm = mean pulmonary arterial pressure, RAPm = mean right arterial pressure, PVR = pulmonary vascular resistance, SAPm = mean systemic arterial pressure.

6.1.5 Clinical Microbiology

Not applicable.

6.1.6 Efficacy Conclusions - Clinical Effects

Statistically significant improvement was observed in exercise capacity, as measured by the 6-minute walk, in patients receiving continuous intravenous epoprostenol sodium plus

conventional therapy for 12 weeks compared to those receiving conventional therapy alone. 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 dyspnea and fatigue, as measured by the Borg Dyspnea Index and Dyspnea Fatigue Index. At week 12, NYHA functional class improved in 21 of 51 (41%) patients treated with epoprostenol sodium compared to none of the 48 patients treated with conventional therapy alone. However, more patients in both treatment groups (28/51 [55%] with epoprostenol sodium and 35/48 [73%] with conventional therapy alone) showed no change in functional class, and 2/51 (4%) with epoprostenol sodium and 13/48 (27%) with conventional therapy alone worsened. Of the patients randomized, NYHA functional class data at 12 weeks were not available for 5 patients treated with epoprostenol sodium and 7 patients treated with conventional therapy alone.

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

No controlled clinical trials with epoprostenol sodium have been performed in patients with pulmonary hypertension associated with other diseases.

7 Review of Safety

7.1.1 Deaths

No deaths

7.1.2 Adverse reactions

During clinical trials of Flolan, adverse events were classified as follows: (1) adverse events during dose initiation and escalation, (2) adverse events during chronic dosing, and (3) adverse events associated with the drug delivery system.

Adverse Events During Dose Initiation and Escalation

During early clinical trials, epoprostenol sodium was increased in 2-ng/kg/min increments until the patients developed symptomatic intolerance. The most common adverse events and the adverse events that limited further increases in dose were generally related to vasodilation, the major pharmacologic effect of epoprostenol sodium. The most common dose-limiting adverse events (occurring in ≥1% of patients) were nausea, vomiting, headache, hypotension, and flushing, but also include chest pain, anxiety, dizziness, bradycardia, dyspnea, abdominal pain, musculoskeletal pain, and tachycardia. Table 3 lists the adverse events reported during dose initiation and escalation in decreasing order of frequency.

Table 5:Adverse Events During Dose Initiation and Escalation

Adverse Events Occurring in ≥1% of Patients	Epoprostenol Sodium(n = 391)
Flushing	58%

Headache	49%
Nausea/vomiting	32%
Hypotension	16%
Anxiety, nervousness, agitation	11%
Chest pain	11%
Dizziness	8%
Bradycardia	5%
Abdominal pain	5%
Musculoskeletal pain	3%
Dyspnea	2%
Back pain	2%
Sweating	1%
Dyspepsia	1%
Hypoesthesia/paresthesia	1%
Tachycardia	1%

Adverse Events During Chronic Administration

Interpretation of adverse events is complicated by the clinical features of PPH and PH/SSD, which are similar to some of the pharmacologic effects of epoprostenol sodium (e.g., dizziness, syncope). Adverse events probably related to the underlying disease include dyspnea, fatigue, chest pain, edema, hypoxia, right ventricular failure, and pallor. Several adverse events, on the other hand, can clearly be attributed to epoprostenol sodium. These include headache, jaw pain, flushing, diarrhea, nausea and vomiting, flu-like symptoms, and anxiety/nervousness.

Adverse Events During Chronic Administration for PPH

In an effort to separate the adverse effects of the drug from the adverse effects of the underlying disease, Table 6 lists adverse events that occurred at a rate at least 10% different in the 2 groups in controlled trials for PPH.

Table 6: Adverse Events Regardless of Attribution Occurring the Patients with PPH With ≥10% Difference Between Epoprostenol Sodium and Conventional Therapy Alone

Adverse Event	Epoprostenol Sodium (n = 52)	Conventional Therapy (n = 54)
Occurrence More Common With Epoprostenol Sodium		

General		
Chills/fever/sepsis/flu-like symptoms	25%	11%
Cardiovascular		
Tachycardia	35%	24%
Flushing	42%	2%
Gastrointestinal		
Diarrhea	37%	6%
Nausea/vomiting	67%	48%
Musculoskeletal		
Jaw pain	54%	0%
Myalgia	44%	31%
Nonspecific musculoskeletal pain	35%	15%
Neurological		
Anxiety/nervousness/tremor	21%	9%
Dizziness	83%	70%
Headache	83%	33%
Hypoesthesia, hyperesthesia, paresthesia	12%	2%
Occurrence More Common With Standard Therapy		
Cardiovascular		
Heart failure	31%	52%
Syncope	13%	24%
Shock	0%	13%
Respiratory		
Hypoxia	25	37%

Thrombocytopenia has been reported during uncontrolled clinical trials in patients receiving epoprostenol sodium.

Table 7: Adverse Events Regardless of Attribution Occurring in Patients with PPH With <10% Difference Between Epoprostenol Sodium and Conventional Therapy Alone

Adverse Event	Epoprostenol Sodium (n = 52)	Conventional Therapy (n = 54)
General		
Asthenia	87%	81%
Cardiovascular		

Angina pectoris	19%	20%
Arrhythmia	27%	20%
Bradycardia	15%	9%
Supraventricular tachycardia	8%	0%
Pallor	21%	30%
Cyanosis	31%	39%
Palpitation	63%	61%
Cerebrovascular accident	4%	0%
Hemorrhage	19%	11%
Hypotension	27%	31%
Myocardial ischemia	2%	6%
Gastrointestinal		
Abdominal pain	27%	31%
Anorexia	25%	30%
Ascites	12%	17%
Constipation	6%	2%
Metabolic		
Edema	60%	63%
Hypokalemia	6%	4%
Weight reduction	27%	24%
Weight gain	6%	4%
Musculoskeletal		
Arthralgia	6%	0%
Bone pain	0%	4%
Chest pain	67%	65%
Neurological		
Confusion	6%	11%
Convulsion	4%	0%
Depression	37%	44%
Insomnia	4%	4%
Respiratory		
Cough increase	38%	46%
Dyspnea	90%	85%
Epistaxis	4%	2%
Pleural effusion	4%	2%
Skin and Appendages		
Pruritus	4%	0%
Rash	10%	13%
Sweating	15%	20%

Special Senses		
Amblyopia	8%	4%
Vision abnormality	%	0%

Adverse Events During Chronic Administration for PH/SSD

In an effort to separate the adverse effects of the drug from the adverse effects of the underlying disease, Table 9 lists adverse events that occurred at a rate at least 10% different in the 2 groups in the controlled trial for patients with PH/SSD.

Table 8: Adverse Events Regardless of Attribution Occurring in Patients With PH/SSD With ≥10 Difference Between Epoprostenol Sodium and Conventional Therapy Alone

Adverse Event	Epoprostenol Sodium (n = 56)	Conventional Therapy (n = 55)
Occurrence More Common With Epoprostenol Sodium		
Cardiovascular		
Flushing	23%	0%
Hypotension	13%	0%
Gastrointestinal		
Anorexia	66%	47%
Nausea/vomiting	41%	16%
Diarrhea	50%	5%
Musculoskeletal		
Jaw pain	75%	0%
Pain/neck pain/arthralgia	84%	65%
Neurological		
Headache	46%	5%
Skin and Appendages		
Skin ulcer	39%	24%
Eczema/rash/urticaria	25%	4%
Occurrence More Common With Conventional Therapy		
Cardiovascular		
Cyanosis	54%	80%
Pallor	32%	53%
Syncope	7%	20%
Gastrointestinal		
Ascites	23%	33%
Esophageal reflux/gastritis	61%	73%
Metabolic		
Weight decrease	45%	56%

Neurological		
Dizziness	59%	76%
Respiratory		
Hypoxia	55%	65%

Table 9: Adverse Events Regardless of Attribution Occurring in Patients With PH/SSD With <10% Difference Between Epoprostenol Sodium and Conventional Therapy Alone

Adverse Event*	Epoprostenol Sodium (n = 56)	Conventional Therapy (n = 55)
General		
Asthenia	100%	98%
Hemorrhage/hemorrhage injection site/hemorrhage rectal	11%	2%
Infection/rhinitis	21%	20%
Chills/fever/sepsis/flu-like symptoms	13%	11%
Blood and Lymphatic		
Thrombocytopenia	4%	0%
Cardiovascular		
Heart failure/heart failure right	11%	13%
Myocardial Infarction	4%	0%
Palpitation	63%	71%
Shock	5%	5%
Tachycardia	43%	42%
Vascular disorder peripheral	96%	100%
Vascular disorder	95%	89%
Gastrointestinal		
Abdominal enlargement	4%	0%
Abdominal pain	14%	7%
Constipation	4%	2%
Flatulence	5%	4%
Metabolic		
Edema/edema peripheral/edema genital	79%	87%
Hypercalcemia	48%	51%
Hyperkalemia	4%	0%
Thirst	0%	4%
Musculoskeletal		
Arthritis	52%	45%
Back pain	13%	5%
Chest pain	52%	45%

Cramps leg	5%	7%
Respiratory		
Cough increase	82%	82%
Dyspnea	100%	100%
Epistaxis	9%	7%
Pharyngitis	5%	2%
Pleural effusion	7%	0%
Pneumonia	5%	0%
Pneumothorax	4%	0%
Pulmonary edema	4%	2%
Respiratory disorder	7%	4%
Neurological		
Anxiety/hyperkinesia/nervousness/tremor	7%	5%
Depression/depression psychotic	13%	4%
Hyperesthesia/hypoesthesia/paresthesia	5%	0%
Insomnia	9%	0%
Somnolence	4%	2%
Skin and Appendages		
Collagen disease	82%	84%
Pruritus	4%	2%
Sweat	41%	36%
Urogenital		
Hematuria	5%	0%
Urinary tract infection	7%	0%

*Adverse events that occurred in at least 2 patients in either treatment group.

Although the relationship to epoprostenol sodium administration has not been established, pulmonary embolism has been reported in several patients taking epoprostenol sodium and there have been reports of hepatic failure.

Adverse Events Attributable to the Drug Delivery System

Chronic infusions of epoprostenol sodium are delivered using a small, portable infusion pump through an indwelling central venous catheter. During controlled PPH trials of up to 12 weeks' duration, up to 21 % of patients reported a local infection and up to 13% of patients reported pain at the injection site. During a controlled PH/SSD trial of 12 weeks' duration, 14% of patients reported a local infection and 9% of patients reported pain at the injection site. During long-term follow-up in the clinical trial of PPH, sepsis was reported at least once in 14% of patients and occurred at a rate of 0.32 infections/patient per year in patients treated with epoprostenol sodium. This rate was higher than reported in patients using chronic indwelling central venous catheters to administer parenteral nutrition, but lower than reported in oncology patients using these catheters. Malfunctions in the delivery system resulting in an inadvertent bolus of or a reduction in

epoprostenol sodium were associated with symptoms related to excess or insufficient epoprostenol sodium, respectively

Observed During Clinical Practice

In addition to adverse reactions reported from clinical trials, the following events have been identified during post-approval use of epoprostenol sodium. Because they are reported voluntarily from a population of unknown size, estimates of frequency cannot be made. These events have been chosen for inclusion due to a combination of their seriousness, frequency of reporting, or potential causal connection to epoprostenol sodium.

- Blood and Lymphatic: Anemia, hypersplenism, pancytopenia, splenomegaly.
- Endocrine and Metabolic: Hyperthyroidism.

7.1.3 OVERDOSE EXPERIENCE

Signs and symptoms of excessive doses of epoprostenol sodium during clinical trials are the expected dose-limiting pharmacologic effects of epoprostenol sodium, including flushing, headache, hypotension, tachycardia, nausea, vomiting, and diarrhea. Treatment will ordinarily require dose reduction of epoprostenol sodium.

One patient with secondary pulmonary hypertension accidentally received 50 mL of an unspecified concentration of epoprostenol sodium. The patient vomited and became unconscious with an initially unrecordable blood pressure. Epoprostenol sodium was discontinued and the patient regained consciousness within seconds. In clinical practice, fatal occurrences of hypoxemia, hypotension, and respiratory arrest have been reported following overdosage of epoprostenol sodium.

Single intravenous doses of epoprostenol sodium at 10 and 50 mg/kg (2,703 and 27,027 times the recommended acute phase human dose based on body surface area) were lethal to mice and rats, respectively. Symptoms of acute toxicity were hypoactivity, ataxia, loss of righting reflex, deep slow breathing, and hypothermia.

8 ADDITIONAL CLINICAL STUDIES

Awaited.

9 OVERALL ASSESSMENTS

9.1 CONCLUSIONS

Approvable but awaiting report of safety study.

10 LABEL

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