

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER: 20-444/S003

ADMINISTRATIVE DOCUMENTS



NDA 20-444/S-003

Food and Drug Administration
Rockville MD 20857

Glaxo Wellcome, Inc.
Attention: Roger Gaby
Project Director, Regulatory Affairs
Five Moore Drive
Research Triangle Park, NC 27709

MAY 26 1999

Dear Mr. Gaby:

Please refer to your supplemental new drug application dated December 11, 1998, received December 14, 1998, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Flolan (epoprostenol sodium) for Injection.

We acknowledge receipt of your submissions dated April 20, 23, 28, and May 5, and 6, 1999.

This supplement provides for the use of FLOLAN (epoprostenol sodium) for Injection for the treatment of secondary pulmonary hypertension in patients refractory to conventional therapy.

We have completed our review and find the information presented is inadequate, and the supplemental application is not approvable under section 505(d) of the Act and 21 CFR 314.125(b). The deficiencies may be summarized as follows:

Study VA1A4001 was a multicenter, randomized, open-label, parallel group trial of FLOLAN plus conventional therapy versus conventional therapy alone for 12 weeks in patients having pulmonary hypertension due to the scleroderma spectrum of diseases (SSD). The primary objective was to evaluate the effect of continuous FLOLAN infusions plus conventional therapy on exercise capacity compared to conventional therapy alone, and to evaluate the safety of continuous infusions of FLOLAN plus conventional therapy compared to conventional therapy alone. The primary efficacy parameter was exercise capacity as measured by the maximum distance walked in meters during the 6-minute walk test after 12 weeks of study drug treatment.

The evidence provided by Study VA1A4001 is not sufficiently convincing to support approval of FLOLAN for the requested indication: _____

_____ Nor is it sufficiently convincing to support approval of FLOLAN for treatment of patients with secondary pulmonary hypertension due to the scleroderma spectrum of diseases alone.

[]

In addition, Study VA1A4001, as a single trial, fails to adequately support efficacy of FLOLAN for Injection in treatment of secondary pulmonary hypertension for the following reasons:

1. Study VA1A4001 was too small to establish consistency in efficacy results across centers due to the small numbers of patients enrolled at each center.
2. Consistency in efficacy results across subsets of patients (i.e., gender or age) was not established. Because of the small number of patients, especially males and patients 65 years and older, establishing such consistency was difficult.
3. Efficacy results across both primary and secondary efficacy endpoints were inconsistent. Multiple efficacy endpoints were examined in Study VA1A4001, including the 6 Minute Walk Test, Borg Dyspnea Score, Dyspnea Fatigue Index, Raynauds Severity Score, cardiopulmonary hemodynamic parameters, and mortality. Although an improvement was observed in the 6 Minute Walk Test and many of the cardiopulmonary hemodynamic parameters, no benefit was observed for mortality, clinical signs and symptoms of the scleroderma spectrum of diseases, and NYHA Class.
4. Due to the inconsistency of efficacy results across endpoints and subsets of patients, the efficacy results were not statistically persuasive for a single study.

The side effect profile of FLOLAN in this application reflected its considerable morbidity as outlined in the current product labeling. Thus, at present, there is a clearly unfavorable benefit-risk relationship for the use of FLOLAN in treating secondary pulmonary hypertension due to the scleroderma spectrum of diseases.

Within 10 days after the date of this letter, you are required to amend the supplemental application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.120. In the absence of any such action FDA may proceed to withdraw the application. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

In addition, as of April 1, 1999, all applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred (63 FR 66632). Please propose a pediatric development plan for the indication proposed in this supplemental application.

This product may be considered to be misbranded under the Federal Food, Drug, and Cosmetic Act if it is marketed with this change(s) prior to approval of this supplemental application.

If you have any questions, contact Brian Strongin, Project Manager, at (301) 827-7310.

Sincerely,

/S/

Lilia Talarico, M.D.
Director
Division of Gastrointestinal and Coagulation Drug
Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

APPEARS THIS WAY
ON ORIGINAL

WITHHOLD 25 PAGES

Draft

Labeling

NOV -4 1999

Division of Gastrointestinal & Coagulation Drug Products

PROJECT MANAGER REVIEW

Application Number: 20-444/SE1-003

Name of Drug: Flolan (epoprostenol sodium) for Injection

Sponsor: Glaxo Wellcome, Inc.

Material Reviewed

Submission Dates: October 13, 1999; Complete Response to a May 26, 1999 Not Approvable Letter

Receipt Dates: October 14, 1999

Background and Summary Description: NDA 20-444 for Flolan for Injection was approved September 20, 1995 for the long-term intravenous treatment of primary pulmonary hypertension in NYHA Class III and IV patients. Efficacy supplement S-003, submitted December 11, 1998,

Safety and efficacy in S-003 is supported by Study VA1A4001, a multicenter, randomized, open-label, parallel group trial of Flolan plus conventional therapy versus conventional therapy alone for 12 weeks in patients having pulmonary hypertension secondary to the scleroderma spectrum of diseases (SPH/SSD). A Not Approvable action was taken May 26, 1999 with the following reasons cited in the action letter:

1. The population studied (SSD) did not adequately reflect the population for which labeling was sought — Clinical data was provided in SSD patients only. The requested indication, — encompasses pulmonary hypertension secondary to any underlying disease. Because the — subpopulations differ with respect to the underlying disease, the morbidity/mortality consequences and benefit/risk assessment associated with the use of Flolan for Injection may differ in the different subpopulations. Some clinical data in the other — subpopulations is necessary to adequately assess the benefit/risk of Flolan for the requested indication.
2. Study VA1A4001, as a single study, failed to adequately support efficacy because it lacked consistency across centers, subsets of patients, and across primary and secondary endpoints.

In a September 27, 1999 meeting with the Division the firm promised to submit a response to the May 26, 1999 Not Approvable (NA) letter that included the following: (1) a list of patients

showing outcomes for all primary and secondary endpoints for each patient as well as any summary tables and descriptive statistics necessary to demonstrate support for both correlation among the efficacy endpoints and internal consistency over time; and, (2) proposed labeling listing

The firm's response, including revised draft labeling, is compared to the currently approved labeling (554128; December, 1995) and the differences are noted below. The firm's revised draft labeling, including underlined additions to the currently approved labeling, and marked-out deletions, as well as the currently approved labeling are attached.

Review

┌

└

WITHHOLD 3 PAGES

DRAFT

Labeling

┌

└

Conclusions

The Medical Officer will review and comment on these changes. Marked-up draft labeling will be developed to attach to the action letter if necessary.

/S/

11/4/99

Regulatory Health Project Manager

ATTACHMENTS

Currently Approved Labeling NDA 20-444

Firm's Proposed Labeling NDA 20-444/SE1-003

Currently Approved Labeling
NDA 20-444

FLOLAN® (epoprostenol sodium) for Injection
Packaging Insert

SLR-001
AA

554128



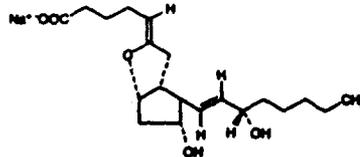
FLOLAN® (epoprostenol sodium) for Injection

DESCRIPTION: FLOLAN (epoprostenol sodium) for Injection is a sterile sodium salt formulated for intravenous administration. Each vial of FLOLAN contains epoprostenol sodium equivalent to either 0.5 mg (500,000 ng) or 1.5 mg (1,500,000 ng) epoprostenol, 3.76 mg glycine, 2.93 mg sodium chloride, and 30 mg marcol. Sodium hydroxide may have been added to adjust pH.

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 is (2Z,8a,11α,13E,15S)-4,8-epoxy-11,15-dihydroprosta-6,13-dien-1-ic acid.

Epoprostenol sodium has a molecular weight of 374.46 and a molecular formula of C₂₀H₃₄NaO₄. The structural formula is:



FLOLAN is a white to off-white powder that must be reconstituted with STERILE DILUENT for FLOLAN. STERILE DILUENT for FLOLAN is supplied in 80 mL glass vials containing 94 mg glycine, 73.5 mg sodium chloride, sodium hydroxide (added to adjust pH), and Water for Injection, USP.

The reconstituted solution of FLOLAN has a pH of 10.2 to 10.8 and is increasingly unstable at a lower pH.

CLINICAL PHARMACOLOGY:

General: Epoprostenol has two 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.

Pharmacokinetics: Epoprostenol is rapidly hydrolyzed at neutral pH in blood and is also subject to enzymatic degradation. Animal studies using tritium-labelled epoprostenol have indicated a high clearance (83 mL/min/kg), 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-labelled 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; the *in vivo* half-life of epoprostenol in man is therefore 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 = 1024).

Tritium-labelled epoprostenol has been administered to humans in order to identify the metabolic products of epoprostenol. Epoprostenol is metabolized to two primary metabolites: 6-keto-PGF_{1α} (formed by spontaneous degradation) and 6,15-dihydro-13,14-dihydro-PGF_{1α} (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 one-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 man.

Clinical Trials in Primary Pulmonary Hypertension (PPH):

Hemodynamic Effects: Acute intravenous infusions of FLOLAN 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 FLOLAN on mean pulmonary artery pressure (PAPm) in patients with PPH were variable and minor.

Chronic continuous infusions of FLOLAN in patients with PPH were studied in two prospective, open, randomized trials of 8 and 12 weeks duration comparing FLOLAN plus standard therapy to standard therapy alone. Dosage of FLOLAN was determined as described in DOSAGE AND ADMINISTRATION and averaged 0.2 ng/kg/min at study end. Standard 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 two 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 two studies, the pooled results are described. Chronic hemodynamic effects were generally similar to acute effects. CI, SV, and arterial oxygen saturation were increased, and PAPm, right atrial pressure (RAP), TPR, and systemic vascular resistance (SVR) were decreased in patients who received FLOLAN 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 FLOLAN

Hemodynamic Parameter	Baseline		Mean change from baseline at end of treatment period*	
	FLOLAN (n = 62)	Standard Therapy (n = 54)	FLOLAN (n = 48)	Standard Therapy (n = 41)
CI (L/min/m ²)	2.0	2.0	0.2**	-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/min/m ²)	44	43	6**	-1
TPR (Wood U)	20	21	-5**	1

*At 8 weeks: FLOLAN n = 10; Standard Therapy n = 11.

At 12 weeks: FLOLAN n = 38; Standard Therapy n = 30.

**Denotes statistically significant change between FLOLAN and Standard Therapy groups.

CI = cardiac index; PAPm = mean pulmonary artery pressure; PVR = pulmonary vascular resistance; SAPm = mean systemic arterial pressure; SV = stroke volume; TPR = total pulmonary resistance.

FLOLANP (epoprostenol sodium) for injection

These hemodynamic improvements appeared to persist when FLOLAN was administered for at least 36 months in an open, non-randomized study.

Clinical Effects: Exercise capacity, as measured by the 6-minute walk test, improved significantly in patients receiving continuous intravenous FLOLAN plus standard therapy for 6 or 12 weeks compared to those receiving standard therapy alone. Improvements were apparent as early as the first week of therapy. Increases in exercise capacity were accompanied by significant improvement in dyspnea and fatigue, as measured by the Congestive Heart Failure Questionnaire and the Dyspnea Fatigue Index.

Survival was improved in NYHA functional Class III and Class IV patients treated with FLOLAN for 12 weeks in a multicenter, open, randomized, parallel study. At the end of the treatment period, 6 of 49 patients receiving standard therapy alone died, whereas none of the 41 patients receiving FLOLAN died (P=0.003).

INDICATIONS AND USAGE: FLOLAN is indicated for the long-term intravenous treatment of primary pulmonary hypertension in NYHA Class III and Class IV patients (see CLINICAL PHARMACOLOGY: Clinical Trials).

CONTRAINDICATIONS: A large study evaluating the effect of FLOLAN on survival in NYHA Class III and IV patients with CHF due to severe left ventricular systolic dysfunction was terminated after an interim analysis of 471 patients revealed a higher mortality in patients receiving FLOLAN plus standard therapy than in those receiving standard therapy alone. The chronic use of FLOLAN in patients with CHF due to severe left ventricular systolic dysfunction is therefore contraindicated.

FLOLAN is also contraindicated in patients with known hypersensitivity to the drug or to structurally-related compounds.

WARNINGS: FLOLAN must be reconstituted only as directed using STERILE DILUENT for FLOLAN. FLOLAN must not be reconstituted or mixed with any other parenteral medications or solutions prior to or during administration.

Abrupt Withdrawal: Abrupt withdrawal (including interruptions in drug delivery) or sudden large reductions in dosage of FLOLAN may result in symptoms associated with rebound pulmonary hypertension, including dyspnea, dizziness, and asthma. In clinical trials, one Class III PPH patient's death was judged attributable to the interruption of FLOLAN. Abrupt withdrawal should be avoided.

Pulmonary Edema: Some patients with primary pulmonary hypertension have developed pulmonary edema during dose ranging, which may be associated with pulmonary vaso-occlusive disease. FLOLAN should not be used chronically in patients who develop pulmonary edema during dose ranging.

Repeals: See ADVERSE REACTIONS: Adverse Events Attributable to the Drug Delivery System.

PRECAUTIONS:

General: FLOLAN should be used only by clinicians experienced in the diagnosis and treatment of PPH. The diagnosis of PPH should be carefully established by standard clinical tests to exclude secondary causes of pulmonary hypertension.

FLOLAN is a potent pulmonary and systemic vasodilator. Dose ranging with FLOLAN must be performed in a setting with adequate personnel and equipment for physiologic monitoring and emergency care. Although dose ranging in clinical trials was performed during right heart catheterization employing a pulmonary artery catheter, in uncontrolled studies utilizing FLOLAN, acute dose ranging was performed without cardiac catheterization. The risk of cardiac catheterization in patients with PPH should be carefully weighed against the potential benefits. During acute dose ranging, asymptomatic increases in pulmonary artery pressure consistent with increases in cardiac output occurred rarely. In such cases, dose reduction should be considered, but such an increase does not imply that chronic treatment is contraindicated.

During chronic use, FLOLAN is delivered continuously on an ambulatory basis through a permanent indwelling central venous catheter. Unless contraindicated, anticoagulant therapy should be administered to PPH patients receiving FLOLAN to reduce the risk of pulmonary thromboembolism or systemic embolism through a patent foramen ovale. In order to reduce the risk of infection, aseptic technique must be used in the reconstitution and administration of FLOLAN as well as in routine catheter care. Because FLOLAN is metabolized rapidly, even brief interruptions in the delivery of FLOLAN may result in symptoms associated with rebound pulmonary hypertension including dyspnea, dizziness, and asthma. The decision to initiate therapy with FLOLAN should be based upon the understanding that there is a high likelihood that intravenous therapy with FLOLAN will be needed for prolonged periods, possibly years, and the patient's ability to accept and care for a permanent intravenous catheter and infusion pump should be carefully considered.

Based on clinical trials, the acute hemodynamic response to FLOLAN did not correlate well with improvement in exercise tolerance or survival during chronic use of FLOLAN. Dosage of FLOLAN during chronic use should be adjusted at the first sign of recurrence or worsening of symptoms attributable to PPH or the occurrence of adverse events associated with FLOLAN (see DOSAGE AND ADMINISTRATION). Following dosage adjustments, standing and supine blood pressure and heart rate should be monitored closely for several hours.

Information for Patients: Patients receiving FLOLAN should receive the following information: FLOLAN must be reconstituted only with STERILE DILUENT for FLOLAN. 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 drug reconstitution, drug administration, and care of the permanent central venous catheter. Sterile technique must be adhered to in preparing the drug and in the care of the catheter, and even brief interruptions in the delivery of FLOLAN may result in rapid symptomatic deterioration. The decision to receive FLOLAN for PPH should be based upon the 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 intravenous catheter and infusion pump should be carefully considered.

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

Cardiogenesis, 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 strand break tests were also negative, although the instability of epoprostenol makes the significance of these tests uncertain. Fertility was not impaired in rats given FLOLAN by subcutaneous injection at doses up to 100 µg/kg/day (800 µg/m²/day), 2.5 times the recommended human dose (4.6 mg/kg/day or 246.1 µg/m²/day, i.v.) based on body surface area.

Pregnancy: Pregnancy Category B. Reproductive studies have been performed in pregnant rats and rabbits at doses up to 100 µg/kg/day (800 µg/m²/day) in rats, 2.5 times the recommended human dose, and 1160 µg/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 FLOLAN. 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 FLOLAN during labor, vaginal delivery, or cesarean section has not been adequately studied in humans.

Nursing Mothers: It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when FLOLAN is administered to a nursing woman.

Pediatric Use: Safety and effectiveness in pediatric patients have not been established.

Geriatric Use: Clinical studies of FLOLAN did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently from younger patients. In general, dose selection for an elderly patient should be cautious, reflecting the greater frequency of decreased hepatic, renal, or cardiac function and of concomitant disease or other drug therapy.

ADVERSE REACTIONS: During clinical trials, adverse events were classified as follows: (1) adverse events during acute dose ranging, (2) adverse events during chronic dosing, and (3) adverse events associated with the drug delivery system.

Adverse Events During Acute Dose Ranging: During acute dose ranging, FLOLAN was administered in 2 mg/kg/day 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 the major pharmacologic effect of FLOLAN, vasodilation. 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 2 lists the adverse events reported during acute dose ranging in decreasing order of frequency.

FLOLANP (epoprostenol sodium) for injection

Table 2
Adverse Events During Acute Dose Ranging

Adverse Events Occurring in ≥1% of Patients	FLOLANP (% of patients) (n = 301)
Flushing	58
Headache	49
Nausea/Vomiting	32
Hypotension	16
Anxiety, nervousness, agitation	11
Chest pain	11
Dizziness	9
Bradycardia	5
Abdominal pain	5
Musculoskeletal pain	5
Dyspnea	3
Back pain	2
Sweating	2
Dyspepsia	1
Hypertension/Parosmia	1
Tachycardia	1

Adverse Events During Chronic Administration: Interpretation of adverse events is complicated by the clinical features of PPH, which are similar to some of the pharmacologic effects of FLOLAN (e.g., dizziness, syncope). Adverse events possibly related to the underlying disease include dyspnea, fatigue, chest pain, right ventricular failure, and panic. Several adverse events, on the other hand, can clearly be attributed to FLOLAN. These include headache, jaw pain, flushing, diarrhea, nausea and vomiting, flu-like symptoms, and anxiety/nervousness. In an effort to separate the adverse effects of the drug from the adverse effects of the underlying disease, table 3 lists adverse events that occurred at a rate of at least 10% different in the two groups in controlled trials.

Table 3
Adverse Events Regardless of Attribution Occurring with ≥10% Difference Between FLOLAN and Standard Therapy Alone

Adverse Event	FLOLANP (% of patients) (n = 52)	Standard therapy (% of patients) (n = 54)
Occurrences More Common with FLOLAN		
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
Non-specific musculoskeletal pain	35	15
NEUROLOGICAL		
Anxiety/nervousness/tremor	21	9
Dizziness	83	70
Headache	83	33
Hypertension, Hypotension, Parosmia	12	2
Occurrences 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 FLOLAN. Table 4 lists additional adverse events reported in PPH patients receiving FLOLAN plus standard therapy or standard therapy alone during controlled clinical trials.

Table 4
Adverse Events Regardless of Attribution Occurring with <10% Difference Between FLOLAN and Standard Therapy Alone

Adverse Event	FLOLANP (% of patients) (n = 52)	Standard therapy (% of patients) (n = 54)
GENERAL		
Asthenia	67	61
CARDIOVASCULAR		
Angina pectoris	19	20
Arrhythmia	27	20
Bradycardia	15	9
Supraventricular tachycardia	8	0
Pallor	21	30
Cyanosis	31	39
Palpitation	63	61
Cardiovascular accident	4	0
Hemorrhage	19	11
Hypotension	27	31
Myocardial ischemia	2	6
GASTROINTESTINAL		
Abdominal pain	27	31
Anorexia	25	30
Acidosis	12	17
Constipation	6	2
METABOLIC		
Edema	60	63
Hypokalemia	6	4
Weight reduction	27	24
Weight gain	6	4
MUSCULOSKELETAL		
Asthenia	6	0
Back pain	0	4
Chest pain	67	65
NEUROLOGICAL		
Confusion	6	11
Convulsion	4	0
Depression	37	44
Insomnia	4	4

(continued)

578
978

NDA 20-444

FLOLAN® (epoprostenol sodium) for injection

Table 4
Adverse Events Regardless of Attribution Occurring with <10% Difference
Between FLOLAN and Standard Therapy Alone (n=14)

Adverse Event	FLOLAN® (% of patients) (n = 52)	Standard therapy (% of patients) (n = 14)
RESPIRATORY		
Cough increase	38	46
Dyspnea	80	86
Epistaxis	4	2
Pleural effusion	4	2
DERMATOLOGIC		
Pruritus	4	0
Rash	10	13
Sweating	15	28
SPECIAL SENSES		
Amblyopia	8	4
Vision abnormality	4	0

Adverse Events Attributable to the Drug Delivery System: Chronic infusions of FLOLAN are delivered using a small, portable infusion pump through an indwelling central venous catheter. During controlled trials of up to 12 weeks duration, 21% of patients reported a local infection and 13% of patients reported pain at the injection site. During long-term follow-up, sepsis was reported at least once in 14% of patients and occurred at a rate of 0.32 infections per patient per year in patients treated with FLOLAN. This rate was higher than reported in oncology 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 FLOLAN was associated with symptoms related to excess or insufficient FLOLAN, respectively (see ADVERSE REACTIONS: Adverse Events During Chronic Administration).

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

One patient with secondary pulmonary hypertension inadvertently received 50 mL of an unspecified concentration of FLOLAN. The patient vomited and became unconscious with an initially unrecordable blood pressure. FLOLAN was discontinued and the patient regained consciousness within seconds. No test events have been reported following overdose of FLOLAN.

Single intravenous doses of FLOLAN at 10 and 50 mg/kg (2,700 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 hypoxia, ataxia, loss of righting reflex, deep slow breathing, and hypothermia.

DOSEAGE AND ADMINISTRATION:

Important Note: FLOLAN must be reconstituted only with STERILE DILUENT for FLOLAN. Reconstituted solutions of FLOLAN must not be diluted or administered with other parenteral solutions or medications (see WARNINGS).

Dosage:

Acute Dose Ranging:

The initial chronic infusion rate of FLOLAN is determined by an acute dose-ranging procedure. During controlled clinical trials, this procedure was performed during cardiac catheterization (see PRECAUTIONS), but in subsequent uncontrolled clinical trials, acute dose ranging was performed without cardiac catheterization. In either case, the infusion rate is 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. The most common dose-limiting pharmacologic effects (occurring in 21% of patients) during dose ranging are nausea, vomiting, headache, hypotension, and flushing, but also include chest pain, weakness, dizziness, bradycardia, dyspnea, abdominal pain, musculoskeletal pain, and tachycardia. During acute dose ranging in clinical trials, the mean maximum dose which did not elicit dose-limiting pharmacologic effects was 6.6 ± 0.3 ng/kg/min.

Continuous Chronic Infusion:

Chronic continuous infusion of FLOLAN should be administered through a central venous catheter. Temporary peripheral intravenous infusions may be used until central access is established. Chronic infusions of FLOLAN should be initiated at 4 ng/kg/min less than the maximum-tolerated infusion rate determined during acute dose ranging. If the maximum-tolerated infusion rate is less than 5 ng/kg/min, the chronic infusion should be started at one-half the maximum-tolerated infusion rate. During clinical trials, the mean initial chronic infusion rate was 5 ng/kg/min.

Dosage Adjustments: Changes in the chronic infusion rate should be based on persistence, recurrence, or worsening of the patient's symptoms of PPH and the occurrence of adverse events due to excessive doses of FLOLAN. In general, increases in dose from the initial chronic dose should be expected. In the controlled 12-week trial, for example, the dose increased from a mean starting dose of 5.2 ng/kg/min (4 ng/kg/min less than the now tolerated dose) to 6.2 ng/kg/min by the end of week 12, just 1.0 ng/kg/min less than the mean non-tolerated dose.

Increases in dose should be considered if symptoms of PPH 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. Following establishment of a new chronic infusion rate, the patient should be observed, and standing and supine blood pressure and heart rate monitored for several hours to ensure that the new dose is tolerated.

During chronic infusion, the occurrence of dose-related pharmacological events similar to those observed during acute dose ranging may necessitate a decrease in infusion rate, but the adverse event may occasionally resolve without dosage adjustment. Dosage decreases should be made gradually in 2 ng/kg/min increments every 15 minutes or longer until the dose-limiting effects resolve. Rapid withdrawal of FLOLAN or sudden large reductions in infusion rates should be avoided. Except in life-threatening situations (e.g., unconsciousness, collapse, etc.), infusion rates of FLOLAN should be adjusted only under the direction of a physician.

In patients receiving long-term therapy, doses of FLOLAN were tapered after the initiation of cardiopulmonary bypass.

Administration: FLOLAN is administered by continuous intravenous infusion via a central venous catheter using an ambulatory infusion pump. During dose-ranging, FLOLAN may be administered peripherally.

The ambulatory infusion pump used to administer FLOLAN should: (1) be small and lightweight, (2) be able to adjust infusion rates in 2 ng/kg/min increments, (3) have an occlusion, end of infusion, and low battery alarm, (4) be accurate to 0.5% of the programmed rate, and (5) be positive pressure driven (continuous or pulsatile) with intervals between pulses not exceeding 3 minutes at infusion rates used to deliver FLOLAN. The reservoir should be made of polypropylene, polycarbonate, or glass. Infusion pumps used in clinical trials were the CAED-1 HFV 5100 (Pharmacia Deltec, Wade-Med 410 C (Medtronic, Inc.), and the Auto Syringe ASZF (Baxter Health Care).

To avoid potential interruptions in drug delivery, the patient should have access to a backup infusion pump and intravenous infusion sets. A multi-lumen catheter should be considered if other intravenous therapies are routinely administered.

To facilitate extended use at ambient temperatures exceeding 20°C (77°F), a cold pouch with frozen gel packs was used in clinical trials (see DOSAGE AND ADMINISTRATION: Storage and Stability). The cold pouches and gel packs used in clinical trials were obtained from Palo Alto Labs, Palo Alto, California. Any cold pouch used must be capable of maintaining the temperature of reconstituted FLOLAN between 2° and 8°C for 12 hours.

Reconstitution: FLOLAN is only stable when reconstituted with STERILE DILUENT for FLOLAN. FLOLAN must not be reconstituted or mixed with any other parenteral medications or solutions prior to or during administration.

A concentration for the solution of FLOLAN for acute dose ranging or chronic therapy should be selected which is compatible with the infusion pump being used with respect to minimum and maximum flow rates, reservoir capacity, and the infusion pump criteria listed above. FLOLAN, when administered chronically, should be prepared in a drug delivery reservoir appropriate for the infusion pump with a total reservoir volume of at least 100 mL. FLOLAN should be prepared using 2 vials of STERILE DILUENT for FLOLAN for use during a 24-

FLOLAN® (epiprostal sodium) for injection

Table 5

To make 100 mL of solution with final concentration (ng/mL) of:	Directions:
3,000 ng/mL	Dissolve contents of one 0.5 mg vial with 5 mL of STERILE DILUENT for FLOLAN. Withdraw 3 mL, and add to sufficient STERILE DILUENT for FLOLAN to make a total of 100 mL.
5,000 ng/mL	Dissolve contents of one 0.5 mg vial with 5 mL of STERILE DILUENT for FLOLAN. Withdraw entire vial contents and add sufficient STERILE DILUENT for FLOLAN to make a total of 100 mL.
10,000 ng/mL	Dissolve contents of two 0.5 mg vials each with 5 mL of STERILE DILUENT for FLOLAN. Withdraw entire vial contents and add sufficient STERILE DILUENT for FLOLAN to make a total of 100 mL.
15,000 ng/mL	Dissolve contents of one 1.5 mg vial with 5 mL of STERILE DILUENT for FLOLAN. Withdraw entire vial contents and add sufficient STERILE DILUENT for FLOLAN to make a total of 100 mL.

*Higher concentrations may be required for patients who receive FLOLAN long-term. More than one solution strength may be required to accommodate the range of infusions anticipated during acute dose-ranging. Generally, 3,000 ng/mL and 10,000 ng/mL are satisfactory concentrations to deliver between 2 to 16 ng/kg/min in adults. Infusion rates may be calculated using the following formula:

$$\text{Infusion Rate (mL/hr)} = \frac{\text{Dose (ng/kg/min)} \times \text{Weight (kg)} \times 60 \text{ min/hr}}{\text{Final Concentration (ng/mL)}}$$

Tables 6 through 9 provide infusion delivery rates for doses up to 16 ng/kg/min based upon patient weight, drug delivery rate, and concentration of the solution of FLOLAN to be used. These tables may be used to select the most appropriate concentration of FLOLAN that will result in an infusion rate between the minimum and maximum flow rates of the infusion pump and which will allow the desired duration of infusion from a given reservoir volume. Higher infusion rates, and therefore, more concentrated solutions may be necessary with long-term administration of FLOLAN.

Table 6

Patient Weight (kg)	Infusion Rates for FLOLAN® at a Concentration of 3,000 ng/mL							
	Dose or Drug Delivery Rate (ng/kg/min)							
	2	4	6	8	10	12	14	16
	Infusion Delivery Rate (mL/hr)							
10	—	—	1.2	1.6	2.0	2.4	2.8	3.2
20	—	1.6	2.4	3.2	4.0	4.8	5.6	6.4
30	1.2	2.4	3.6	4.8	6.0	7.2	8.4	9.6
40	1.6	3.2	4.8	6.4	8.0	9.6	11.2	12.8
50	2.0	4.0	6.0	8.0	10.0	12.0	14.0	16.0
60	2.4	4.8	7.2	9.6	12.0	14.4	16.8	19.2
70	2.8	5.6	8.4	11.2	14.0	16.8	19.6	22.4
80	3.2	6.4	9.6	12.8	16.0	19.2	22.4	25.6
90	3.6	7.2	10.8	14.4	18.0	21.6	25.2	28.8
100	4.0	8.0	12.0	16.0	20.0	24.0	28.0	32.0

Table 7

Patient Weight (kg)	Infusion Rates for FLOLAN® at a Concentration of 5,000 ng/mL							
	Dose or Drug Delivery Rate (ng/kg/min)							
	2	4	6	8	10	12	14	16
	Infusion Delivery Rate (mL/hr)							
10	—	—	—	1.0	1.2	1.4	1.7	1.9
20	—	1.0	1.4	1.8	2.4	2.9	3.4	3.8
30	—	1.4	2.2	2.9	3.6	4.3	5.0	5.6
40	1.0	1.9	2.9	3.8	4.8	5.8	6.7	7.7
50	1.2	2.4	3.6	4.8	6.0	7.2	8.4	9.6
60	1.4	2.9	4.3	5.8	7.2	8.6	10.1	11.5
70	1.7	3.4	5.0	6.7	8.4	10.1	11.8	13.4
80	1.9	3.8	5.6	7.7	9.6	11.5	13.4	15.4
90	2.2	4.3	6.5	8.6	10.8	13.0	15.1	17.3
100	2.4	4.8	7.2	9.6	12.0	14.4	16.8	19.2

Table 8

Patient Weight (kg)	Infusion Rates for FLOLAN® at a Concentration of 10,000 ng/mL						
	Dose or Drug Delivery Rate (ng/kg/min)						
	4	6	8	10	12	14	16
	Infusion Delivery Rate (mL/hr)						
20	—	—	1.0	1.2	1.4	1.7	1.9
30	—	1.1	1.4	1.8	2.2	2.5	2.9
40	1.0	1.4	1.9	2.4	2.9	3.4	3.8
50	1.2	1.8	2.4	3.0	3.6	4.2	4.8
60	1.4	2.2	2.9	3.6	4.3	5.0	5.8
70	1.7	2.5	3.4	4.2	5.0	5.9	6.7
80	1.9	2.9	3.8	4.8	5.8	6.7	7.7
90	2.2	3.2	4.3	5.4	6.5	7.6	8.6
100	2.4	3.6	4.8	6.0	7.2	8.4	9.6

Table 9

Patient Weight (kg)	Infusion Rates for FLOLAN® at a Concentration of 15,000 ng/mL						
	Dose or Drug Delivery Rate (ng/kg/min)						
	4	6	8	10	12	14	16
	Infusion Delivery Rate (mL/hr)						
30	—	—	1.0	1.2	1.4	1.7	1.9
40	—	1.0	1.3	1.6	1.9	2.2	2.5
50	—	1.2	1.6	2.0	2.4	2.8	3.2
60	1.0	1.4	1.9	2.4	2.9	3.4	3.8
70	1.1	1.7	2.2	2.8	3.4	3.9	4.5
80	1.3	1.9	2.6	3.2	3.8	4.5	5.1
90	1.4	2.2	2.9	3.6	4.3	5.0	5.8
100	1.6	2.4	3.2	4.0	4.8	5.6	6.4

FLOLAN® (epiprostal sodium) for injection

Storage and Stability: Unopened vials of FLOLAN are stable until the date indicated on the package when stored at 15° to 25°C (59° to 77°F) and protected from light in the carton. Unopened vials of STERILE DILUENT for FLOLAN are stable until the date indicated on the package when stored at 15° to 25°C (59° to 77°F).

Prior to use, 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. Do not freeze reconstituted solutions of FLOLAN. Discard any reconstituted solution that has been frozen. Discard any reconstituted solution if it has been refrigerated for more than 48 hours.

During use, a single reservoir of reconstituted solution of FLOLAN can be administered at room temperature for a total duration of 8 hours, or it can be used with a cold pouch and administered up to 24 hours with the use of two frozen 6-oz gel packs in a cold pouch. When stored or in use, reconstituted FLOLAN must be insulated from temperatures greater than 25°C (77°F) and less than 0°C (32°F), and must not be exposed to direct sunlight.

Use at Room Temperature: Prior to use at room temperature, 15° to 25°C (59° to 77°F), reconstituted solutions of FLOLAN may be stored refrigerated at 2° to 8°C (36° to 46°F) for no longer than 48 hours. When administered at room temperature, reconstituted solutions may be used for no longer than 8 hours. This 48-hour period allows the patient to reconstitute a 2-day supply (200 mL) of FLOLAN. Each 100 mL daily supply may be divided into three equal portions. Two of the portions are stored refrigerated at 2° to 8°C (36° to 46°F) until they are used.

Use with a Cold Pouch: Prior to infusion with the use of a cold pouch, solutions may be stored refrigerated at 2° to 8°C (36° to 46°F) for up to 24 hours. When a cold pouch is employed during the infusion, reconstituted solutions of FLOLAN may be used for no longer than 24 hours. The gel packs should be changed every 12 hours. Reconstituted solutions may be kept at 2° to 8°C (36° to 46°F), either in refrigerated storage or in a cold pouch or a combination of the two, for no more than 48 hours.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit. If either occurs, FLOLAN should not be administered.

NOW SUPPLIED: FLOLAN for injection is supplied as a sterile freeze-dried powder in 17 mL first glass vial with gray butyl rubber closures, individually packaged in a carton.

17 mL vial containing epiprostal sodium equivalent to 0.5 mg (500,000 ng), carton of 1, (NDC 0081-0480-01).

17 mL vial containing epiprostal sodium equivalent to 1.5 mg (1,500,000 ng), carton of 1, (NDC 0081-0484-01).

Store the vials of FLOLAN at 15° to 25°C (59° to 77°F). Protect from light.

The STERILE DILUENT for FLOLAN is supplied in 90 mL first glass vials with fluorocarbon faced butyl rubber closures.

90 mL vial of STERILE DILUENT for FLOLAN, box of 4 (NDC 0081-0462-01).

Store the vials of STERILE DILUENT for FLOLAN at 15° to 25°C (59° to 77°F). DO NOT FREEZE.

Caution: Federal law prohibits dispensing without prescription.

U.S. Patent Nos. 4335138, 4538333, and 4883812 (Use Patent)

Licensed Under U.S. Patent No. 4338325

Manufactured by
THE WELLCOME FOUNDATION LTD.
London, England NWT 5BP for
BURROUGHS WELLCOME CO.
Research Triangle Park, NC 27709

Printed in U.S.A.

December 1985

PL226

554128

WITHHOLD 76 PAGES

Draft

Labeling

Safety evaluation included all adverse events reported during the study with special reference to disease-related adverse events and treatment-related (Drug delivery system) adverse events.

The number of patients per treatment group needed to provide 80% power to detect a difference of 50 meters average change from baseline for the 6-minute walk test at the 0.05 significance level in a two-tailed t-test was calculated from the results of the study of Flolan administered for 12 weeks to patients with PPH.

A total of 117 patients were randomized, of these, 111 received study drug: 56 patients received Flolan and 55 patients received conventional therapy.

At the end of 12 weeks on study, patients were given the option to continue Flolan therapy in an open-label extension study (VA1A4002).

Efficacy analysis was based on the ITT population defined as all patients who received any amount of study drug or conventional therapy.

The primary efficacy results (treatment comparison of the 6-minute walk test) by nonparametric analysis of covariance showed no treatment difference at week 1 and statistically significantly greater exercise capacity at week 6 (p-value 0.0028) and at week 12 (p-value <0.0001). The parametric analysis of the results showed statistically significant difference in exercise capacity in favor of the Flolan therapy at all time points (week 1, 6 and 12).

Statistically significant improvement in pulmonary arterial pressure, pulmonary vascular resistance, right arterial pressure, cardiac index and mixed venous oxygen saturation were observed in patients in the Flolan group compared to conventional therapy.

No significant improvement was observed in NYHA functional class changes from baseline between treatment groups. Dyspnea Fatigue Rating and Borg Dyspnea Scores showed significant improvement from baseline in the group treated with Flolan.

No significant differences between treatment groups were observed for clinical signs and symptoms of the SSD.

No difference in survival was observed between Flolan (4 deaths) and conventional therapy groups (5 deaths).

More than 80% of patients in each group experienced adverse events likely related to the underlying disease (asthenia, arthralgia, cardiac and pulmonary adverse events, hypercalcemia, dizziness, etc). Flolan therapy was associated with considerable morbidity related to its pharmacologic effect and to its method of administration. The rate of infection, including sepsis, was higher in the Flolan group compared to the conventional therapy (18% vs 9%). Other catheter-associated complications, such as hemorrhage and cellulitis were also reported.

Other adverse events occurring more frequently in the Flolan group than in the conventional therapy group were similar to those described with the use of Flolan for the treatment of PPH. Mortality was essentially similar in the two groups.

In this efficacy supplement to NDA 20-444, the sponsor has requested approval of Flolan "for the long-term treatment of pulmonary hypertension _____ in NYHA Class III and Class IV patients who do not respond to conventional therapy." The sponsor, however, has assessed the efficacy and safety of Flolan only in patients with pulmonary hypertension secondary to SDS. Flolan therapy for pulmonary hypertension associated with other conditions must, therefore, be assessed in an additional clinical trial.

Although the study shows statistically significant difference in primary efficacy endpoint and in some of the secondary efficacy endpoints in favor of the Flolan treatment, the study has numerous limitations for the requirement for approval as single study. The study was open-label and not well controlled, some of the endpoints of efficacy were assessed using inconsistent and unspecified modalities. The study showed no consistency among study centers and patients subsets most likely due to the small size of the study, and inconsistent efficacy across both primary and secondary efficacy endpoints.

The evidence provided by Study VA1A4001 is not sufficiently convincing to support the approval of Flolan for the treatment of patients with secondary pulmonary hypertension due to SDS. The sponsor should perform an additional study enrolling patients with all types of secondary pulmonary hypertension.

/S/
Lilia Talarico, M.D.

cc:
HFD-180
HFD-180/LTalarico
HFD-180/KRobie-Suh
HFD-181/CSO
HFD-180/JChoudary
HFD-180/EDuffy
f/t 5/26/99 jgw

APPEARS THIS WAY
ON ORIGINAL

PATENT INFORMATION

Patent information relevant to the Supplemental NDA 20-444 for FLOLAN is provided on the following pages.

APPEARS THIS WAY
ON ORIGINAL

Time Sensitive Patent Information

Pursuant to 21 C.F.R. § 314.53
for

FLOLAN® (epoprostenol sodium) Injection

Item 13 of Supplemental NDA 20-444

The following is provided in accord with the Drug Price Competition and Patent Term Restoration Act of 1984:

Trade Name: FLOLAN®
Active Ingredient: epoprostenol sodium
Strength(s): Eq. 0.5 mg base/vial and Eq. 1.5 mg base/vial
Dosage Form: Injectable; Injection

<u>U.S. Patent</u>	<u>Expiration Date</u>	<u>Type of Patent</u>	<u>Patent Owner</u>	<u>U.S. Agent</u>
4,335,139	15 June 1999	Drug Product · Composition/ Formulation Method of Use	Glaxo Wellcome Inc.	Glaxo Wellcome Inc.
4,539,333	3 Sept 2002	Drug Method of Use	Glaxo Wellcome Inc.	Glaxo Wellcome Inc.
4,883,812	12 May 2006	Method of Use	Glaxo Wellcome Inc.	Glaxo Wellcome Inc.
4,338,325	6 July 1999	Drug Product · Composition/ Formulation	Upjohn Co.	Glaxo Wellcome Inc. -Licensee

The undersigned declares that U.S. Patent 4,335,139 covers the formulation, composition and/or method of use of FLOLAN® (epoprostenol sodium) Injection. This product is currently approved under section 505 of the Federal Food, Drug, and Cosmetic Act.

The undersigned declares that U.S. Patent 4,539,333 covers the formulation, composition and/or method of use of FLOLAN® (epoprostenol sodium) Injection. This product is currently approved under section 505 of the Federal Food, Drug, and Cosmetic Act.

The undersigned declares that U.S. Patent 4,883,812 covers the formulation, composition and/or method of use of FLOLAN® (epoprostenol sodium) Injection. The expiration date, 12 May 2006, was extended 1347 days from the original expiration date of 3 September 2002 pursuant to 35 U.S.C. §156. This product is currently approved under section 505 of the Federal Food, Drug, and Cosmetic Act.

The undersigned declares that U.S. Patent 4,338,325 covers the formulation, composition and/or method of use of FLOLAN® (epoprostenol sodium) Injection. This patent is licensed to Glaxo Wellcome Inc. from The Upjohn Co. This product is currently approved under section 505 of the Federal Food, Drug, and Cosmetic Act.

Please address all communications to:

David J. Levy, Ph.D.
Patent Counsel
Glaxo Wellcome Inc.
Intellectual Property Department
Five Moore Drive
Research Triangle Park, NC 27709
(919) 483-7656

Respectfully submitted,



Lorie Ann Morgan
Attorney for Applicant
Glaxo Wellcome Inc.

Date: 19 November, 1998

lam:c:\cv\FLOLAN@ndapatinfo.doc

APPEARS THIS WAY
ON ORIGINAL

EXCLUSIVITY SUMMARY FOR NDA # 20-444 SUPPL # SE1-003

Trade Name FLOLAN for Injection _____ Generic Name epoprostenol sodium

Applicant Name Glaxo Wellcome, Inc. HFD - 180 _____

Approval Date If Known _____

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following question about the submission.

a) Is it an original NDA?

YES / / NO / /

b) Is it an effectiveness supplement?

YES / / NO / /

If yes, what type? (SE1, SE2, etc.) SE1

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data. answer "no.")

YES / / NO / /

d) Did the applicant request exclusivity?

YES / / NO / /

e) Has pediatric exclusivity been granted for this Active Moiety?

NO

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule, previously been approved by FDA for the same use? (Rx to OTC switches should be answered NO-please indicate as such)

YES / / NO / /

3. Is this drug product or indication a DESI upgrade?

YES / / NO / /

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES / / NO / /

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# NDA 20-444 FLOLAN (epoprostenol sodium) for Injection

PART III THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES / / NO / /

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

- (a) In light of previously approved applications, is a clinical investigation (either conducted

by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES / / NO / /

- (b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES / / NO / /

- (1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES / / NO / /

- (2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES / / NO / /

- c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

INVESTIGATION #1: Study VA1A4001. "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 Pulmonary Hypertension Secondary to the Scleroderma Spectrum of Diseases: A Twelve-Week Study"

INVESTIGATION #2: Study 35/35: "Multicenter Evaluation of Long-Term flolan Infusions in Patients with Primary Pulmonary Hypertension"

INVESTIGATION #3: Study 46: "A Multicenter, Open-Label, Randomized, Parallel Comparison of the Safety and Efficacy of Chronic Flolan Infusions Plus Conventional Therapy Alone in Patients with Severe primary Pulmonary Hypertension: A Twelve Week Study"

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

- a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a

previously approved drug, answer "no.")

Investigation #1 YES / / NO / /

Investigation #2 YES / / NO / /

Investigation #3 YES / / NO / /

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

INVESTIGATION #2: Study 35/35: "Multicenter Evaluation of Long-Term flolan Infusions in Patients with Primary Pulmonary Hypertension"

INVESTIGATION #3: Study 46: "A Multicenter, Open-Label, Randomized, Parallel Comparison of the Safety and Efficacy of Chronic Flolan Infusions Plus Conventional Therapy Alone in Patients with Severe primary Pulmonary Hypertension: A Twelve Week Study"

Investigation #2 and Investigation #3 both supported the safety and efficacy of NDA 20-444 for FLOLAN (epoprostenol sodium) for Injection, approved September 20, 1995 for long-term intravenous treatment of primary pulmonary hypertension in NYHA Class III and IV adult patients.

- b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES / / NO / /

Investigation #2 YES / / NO / /

Investigation #3 YES / / NO / /

- c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

INVESTIGATION #1: Study VA1A4001. "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 Pulmonary Hypertension Secondary to the Scleroderma Spectrum of Diseases: A Twelve-Week Study"

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial

support will mean providing 50 percent or more of the cost of the study.

- a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1

IND # YES / X / NO / / Explain:

Investigation #2

IND # YES / X / NO / / Explain:

Investigation #3

IND # YES / X / NO / / Explain:

- b) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES / / NO / X /

 / S / 3/30/00
Signature Date
Title: Regulatory - Health
Project Manager

 / S / 3-30-00
Signature of Date
Division Director

cc: Original NDA
Division File
HFD-93 Mary Ann Holovac

DEBARMENT CERTIFICATION

The following is the debarment statement provided by Glaxo Wellcome.

**APPEARS THIS WAY
ON ORIGINAL**

NDA 20-444

FLOLAN®
(epoprostenol sodium for injection)

DEBARMENT CERTIFICATION

Glaxo Wellcome hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act of in connection with this application.



Charles E. Mueller
Head, US Clinical Compliance
World Wide Compliance

13 OCT 98

Date

APPEARS THIS WAY
ON ORIGINAL

PEDIATRIC PAGE

(Complete for all original application and all efficacy supplements)

NDA/BLA Number:	<u>20444</u>	Trade Name:	<u>FLOLAN (EPOFROSTENOL SODIUM) INJ</u>
Supplement Number:	<u>3</u>	Generic Name:	<u>EPOPROSTENOL SODIUM</u>
Supplement Type:	<u>SE1</u>	Dosage Form:	<u>INJ</u>
Regulatory Action:	<u>AP</u>	Proposed Indication:	<u>Long-term intravenous treatment of pulmonary hypertension associated with the scleroderma spectrum of diseases in NYHA Class III and Class IV patients who do not respond adequately to conventional therapy.</u>

ARE THERE PEDIATRIC STUDIES IN THIS SUBMISSION?

NO. No waiver and no pediatric data

What are the INTENDED Pediatric Age Groups for this submission?

NeoNates (0-30 Days) Children (25 Months-12 years)
 Infants (1-24 Months) Adolescents (13-16 years)

Label Adequacy Adequate for ALL pediatric age groups
Formulation Status
Studies Needed
Study Status

Are there any Pediatric Phase 4 Commitments in the Action Letter for the Original Submission? NO

COMMENTS:

This drug indication has Orphan designation and is exempt from the 12/2/98 Pediatric Rule. The Pediatric labeling is acceptable.

This Page was completed based on information from a PROJECT MANAGER/CONSUMER SAFETY OFFICER, BRIAN STRONGIN

Signature /S/ _____ Date 3/30/00

 /S/ 3-30-00