FLOLAN®
(epoprostenol sodium) for Injection

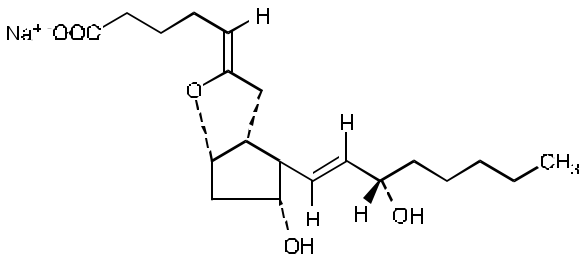
DESCRIPTION

FLOLAN (epoprostenol sodium) for Injection is a sterile sodium salt formulated for intravenous (IV) 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 50 mg mannitol. Sodium hydroxide may have been added to adjust pH.

Epoprostenol (PGI_2, PGX, prostacyclin), a metabolite of arachidonic acid, is a naturally occurring prostaglandin with potent vasodilatory activity and inhibitory activity of platelet aggregation.

Epoprostenol is (5*Z*,9a,11a,13*E*,15*S*)-6,9-epoxy-11,15-dihydroxyprosta-5,13-dien-1-oic acid.

Epoprostenol sodium has a molecular weight of 374.45 and a molecular formula of $C_{20}H_{31}NaO_5$. 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 glass vials containing 50 mL of 94 mg glycine, 73.3 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 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.

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-$PGF_{1\alpha}$ (formed by spontaneous degradation) and 6,15-diketo-13,14-dihydro-$PGF_{1\alpha}$ (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.

CLINICAL TRIALS IN PULMONARY HYPERTENSION

Acute 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) were variable and minor.

Chronic Infusion in Primary Pulmonary Hypertension (PPH): *Hemodynamic Effects:* Chronic continuous infusions of FLOLAN in patients with PPH were studied in 2 prospective, open, randomized trials of 8 and 12 weeks' duration comparing FLOLAN plus conventional therapy to conventional therapy alone. Dosage of FLOLAN was determined as described in DOSAGE AND ADMINISTRATION and averaged 9.2 ng/kg/min at study's end. 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 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 in Patients With PPH

Hemodynamic Parameter	Baseline		Mean Change from Baseline at End of Treatment Period*	
	FLOLAN (N = 52)	Standard Therapy (N = 54)	FLOLAN (N = 48)	Standard Therapy (N = 41)
CI ($L/min/m^2$)	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: FLOLAN N = 10, conventional therapy N = 11 (N is the number of patients with hemodynamic data).
At 12 weeks: FLOLAN N = 38, conventional therapy N = 30 (N is the number of patients with hemodynamic data).

† Denotes statistically significant difference between FLOLAN 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 FLOLAN 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 FLOLAN 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 FLOLAN 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 FLOLAN died (p = 0.003).

Chronic Infusion in Pulmonary Hypertension Associated with the Scleroderma Spectrum of Diseases (PH/SSD): *Hemodynamic Effects:* Chronic continuous infusions of FLOLAN in patients with PH/SSD were studied in a prospective, open, randomized trial of 12 weeks' duration comparing FLOLAN 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. Dosage of FLOLAN was determined as described in DOSAGE AND ADMINISTRATION and averaged 11.2 ng/kg/min at study's end. 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 FLOLAN chronically compared to those who did not. Table 2 illustrates the treatment-related hemodynamic changes in these patients after 12 weeks of treatment.

Table 2. Hemodynamics During Chronic Administration of FLOLAN in Patients With PH/SSD

Hemodynamic Parameter	Baseline		Mean Change from Baseline at 12 Weeks	
	FLOLAN (N = 56)	Conventional Therapy (N = 55)	FLOLAN (N = 50)	Conventional Therapy (N = 48)
CI ($L/min/m^2$)	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 FLOLAN 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 FLOLAN 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 FLOLAN compared to none of the 48 patients treated with conventional therapy alone. However, more patients in both treatment groups (28/51 [55%] with FLOLAN and 35/48 [73%] with conventional therapy alone) showed no change in functional class, and 2/51 (4%) with FLOLAN 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 FLOLAN and 7 patients treated with conventional therapy alone.

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

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