

## PRESCRIBING INFORMATION

# FLOLAN<sup>®</sup> (epoprostenol sodium) for Injection

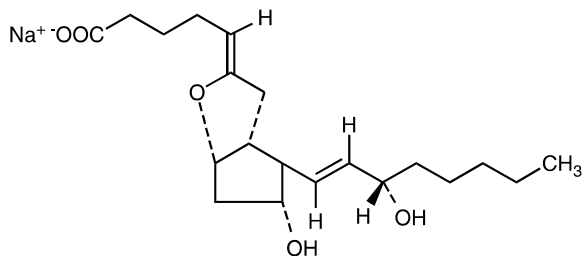
### DESCRIPTION

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<sub>2</sub>, 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*,9*α*,11*α*,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<sub>20</sub>H<sub>31</sub>NaO<sub>5</sub>. 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

33 animals include bronchodilation, inhibition of gastric acid secretion, and decreased gastric  
34 emptying.

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

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

47 Tritium-labeled epoprostenol has been administered to humans in order to identify the  
48 metabolic products of epoprostenol. Epoprostenol is metabolized to 2 primary metabolites:  
49 6-keto-PGF<sub>1α</sub> (formed by spontaneous degradation) and 6,15-diketo-13,14-dihydro-PGF<sub>1α</sub>  
50 (enzymatically formed), both of which have pharmacological activity orders of magnitude less  
51 than epoprostenol in animal test systems. The recovery of radioactivity in urine and feces over a  
52 1-week period was 82% and 4% of the administered dose, respectively. Fourteen additional  
53 minor metabolites have been isolated from urine, indicating that epoprostenol is extensively  
54 metabolized in humans.

## 55 **CLINICAL TRIALS IN PULMONARY HYPERTENSION**

56 **Acute Hemodynamic Effects:** Acute intravenous infusions of FLOLAN for up to 15 minutes  
57 in patients with secondary and primary pulmonary hypertension produce dose-related increases  
58 in cardiac index (CI) and stroke volume (SV) and dose-related decreases in pulmonary vascular  
59 resistance (PVR), total pulmonary resistance (TPR), and mean systemic arterial pressure  
60 (SAPm). The effects of FLOLAN on mean pulmonary artery pressure (PAPm) were variable and  
61 minor.

62 **Chronic Infusion in Primary Pulmonary Hypertension (PPH): Hemodynamic**  
63 **Effects:** Chronic continuous infusions of FLOLAN in patients with PPH were studied in  
64 2 prospective, open, randomized trials of 8 and 12 weeks' duration comparing FLOLAN plus  
65 conventional therapy to conventional therapy alone. Dosage of FLOLAN was determined as  
66 described in DOSAGE AND ADMINISTRATION and averaged 9.2 ng/kg/min at study's end.  
67 Conventional therapy varied among patients and included some or all of the following:  
68 anticoagulants in essentially all patients; oral vasodilators, diuretics, and digoxin in one half to  
69 two thirds of patients; and supplemental oxygen in about half the patients. Except for 2 New  
70 York Heart Association (NYHA) functional Class II patients, all patients were either functional  
71 Class III or Class IV. As results were similar in the 2 studies, the pooled results are described.

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

77

78 **Table 1. Hemodynamics During Chronic Administration of FLOLAN in Patients With**  
 79 **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 <sup>2</sup> )	2.0	2.0	0.3 <sup>†</sup>	-0.1
PAPm (mm Hg)	60	60	-5 <sup>†</sup>	1
PVR (Wood U)	16	17	-4 <sup>†</sup>	1
SAPm (mm Hg)	89	91	-4	-3
SV (mL/beat)	44	43	6 <sup>†</sup>	-1
TPR (Wood U)	20	21	-5 <sup>†</sup>	1

80 \* At 8 weeks: FLOLAN N = 10, conventional therapy N = 11 (N is the number of patients with  
 81 hemodynamic data).

82 At 12 weeks: FLOLAN N = 38, conventional therapy N = 30 (N is the number of patients  
 83 with hemodynamic data).

84 <sup>†</sup> Denotes statistically significant difference between FLOLAN and conventional therapy  
 85 groups.

86 CI = cardiac index, PAPm = mean pulmonary arterial pressure, PVR = pulmonary vascular  
 87 resistance, SAPm = mean systemic arterial pressure, SV = stroke volume, TPR = total  
 88 pulmonary resistance.

89

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

92 **Clinical Effects:** Statistically significant improvement was observed in exercise capacity, as  
 93 measured by the 6-minute walk test in patients receiving continuous intravenous FLOLAN plus  
 94 conventional therapy (N = 52) for 8 or 12 weeks compared to those receiving conventional

95 therapy alone (N = 54). Improvements were apparent as early as the first week of therapy.  
96 Increases in exercise capacity were accompanied by statistically significant improvement in  
97 dyspnea and fatigue, as measured by the Chronic Heart Failure Questionnaire and the Dyspnea  
98 Fatigue Index.

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

103 **Chronic Infusion in Pulmonary Hypertension Associated with the Scleroderma**

104 **Spectrum of Diseases (PH/SSD): Hemodynamic Effects:**

105 Chronic continuous infusions of FLOLAN in patients with PH/SSD were studied in a prospective, open, randomized trial of  
106 12 weeks' duration comparing FLOLAN plus conventional therapy (N = 56) to conventional  
107 therapy alone (N = 55). Except for 5 NYHA functional Class II patients, all patients were either  
108 functional Class III or Class IV. Dosage of FLOLAN was determined as described in DOSAGE  
109 AND ADMINISTRATION and averaged 11.2 ng/kg/min at study's end. Conventional therapy  
110 varied among patients and included some or all of the following: anticoagulants in essentially all  
111 patients, supplemental oxygen and diuretics in two thirds of the patients, oral vasodilators in 40%  
112 of the patients, and digoxin in a third of the patients. A statistically significant increase in CI, and  
113 statistically significant decreases in PAPm, RAPm, PVR, and SAPm after 12 weeks of treatment  
114 were observed in patients who received FLOLAN chronically compared to those who did not.

115 Table 2 illustrates the treatment-related hemodynamic changes in these patients after 12 weeks of  
116 treatment.

117

118 **Table 2. Hemodynamics During Chronic Administration of FLOLAN in Patients With**  
 119 **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 <sup>2</sup> )	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.

142 No controlled clinical trials with FLOLAN have been performed in patients with pulmonary  
143 hypertension associated with other diseases.

#### 144 **INDICATIONS AND USAGE**

145 FLOLAN is indicated for the long-term intravenous treatment of primary pulmonary  
146 hypertension and pulmonary hypertension associated with the scleroderma spectrum of disease  
147 in NYHA Class III and Class IV patients who do not respond adequately to conventional therapy  
148 (see CLINICAL TRIALS IN PULMONARY HYPERTENSION).

#### 149 **CONTRAINDICATIONS**

150 A large study evaluating the effect of FLOLAN on survival in NYHA Class III and IV  
151 patients with congestive heart failure due to severe left ventricular systolic dysfunction was  
152 terminated after an interim analysis of 471 patients revealed a higher mortality in patients  
153 receiving FLOLAN plus conventional therapy than in those receiving conventional therapy  
154 alone. The chronic use of FLOLAN in patients with congestive heart failure due to severe left  
155 ventricular systolic dysfunction is therefore contraindicated.

156 Some patients with pulmonary hypertension have developed pulmonary edema during dose  
157 initiation, which may be associated with pulmonary veno-occlusive disease. FLOLAN should  
158 not be used chronically in patients who develop pulmonary edema during dose initiation.

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

#### 161 **WARNINGS**

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

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

170 **Sepsis:** See ADVERSE REACTIONS: Adverse Events Attributable to the Drug Delivery  
171 System.

#### 172 **PRECAUTIONS**

173 **General:** FLOLAN should be used only by clinicians experienced in the diagnosis and  
174 treatment of pulmonary hypertension. The diagnosis of PPH or PH/SSD should be carefully  
175 established.

176 FLOLAN is a potent pulmonary and systemic vasodilator. Dose initiation with FLOLAN must  
177 be performed in a setting with adequate personnel and equipment for physiologic monitoring and  
178 emergency care. Dose initiation in controlled PPH clinical trials was performed during right

179 heart catheterization. In uncontrolled PPH and controlled PH/SSD clinical trials, dose initiation  
180 was performed without cardiac catheterization. The risk of cardiac catheterization in patients  
181 with pulmonary hypertension should be carefully weighed against the potential benefits. During  
182 dose initiation, asymptomatic increases in pulmonary artery pressure coincident with increases in  
183 cardiac output occurred rarely. In such cases, dose reduction should be considered, but such an  
184 increase does not imply that chronic treatment is contraindicated.

185 **FLOLAN is a potent inhibitor of platelet aggregation.** Therefore, an increased risk for  
186 hemorrhagic complications should be considered, particularly for patients with other risk factors  
187 for bleeding (see PRECAUTIONS: Drug Interactions).

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

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

206 **Information for Patients:** Patients receiving FLOLAN should receive the following  
207 information. **FLOLAN must be reconstituted only with STERILE DILUENT for FLOLAN.**  
208 FLOLAN is infused continuously through a permanent indwelling central venous catheter via a  
209 small, portable infusion pump. Thus, therapy with FLOLAN requires commitment by the patient  
210 to drug reconstitution, drug administration, and care of the permanent central venous catheter.  
211 Sterile technique must be adhered to in preparing the drug and in the care of the catheter, and  
212 even brief interruptions in the delivery of FLOLAN may result in rapid symptomatic  
213 deterioration. A patient's decision to receive FLOLAN should be based upon the understanding  
214 that there is a high likelihood that therapy with FLOLAN will be needed for prolonged periods,  
215 possibly years. The patient's ability to accept and care for a permanent intravenous catheter and  
216 infusion pump should also be carefully considered.

217 **Drug Interactions:** Additional reductions in blood pressure may occur when FLOLAN is  
218 administered with diuretics, antihypertensive agents, or other vasodilators. When other

219 antiplatelet agents or anticoagulants are used concomitantly, there is the potential for FLOLAN  
220 to increase the risk of bleeding. However, patients receiving infusions of FLOLAN in clinical  
221 trials were maintained on anticoagulants without evidence of increased bleeding. In clinical  
222 trials, FLOLAN was used with digoxin, diuretics, anticoagulants, oral vasodilators, and  
223 supplemental oxygen.

224 In a pharmacokinetic substudy in patients with congestive heart failure receiving furosemide  
225 or digoxin in whom therapy with FLOLAN was initiated, apparent oral clearance values for  
226 furosemide (n = 23) and digoxin (n = 30) were decreased by 13% and 15%, respectively, on the  
227 second day of therapy and had returned to baseline values by day 87. The change in furosemide  
228 clearance value is not likely to be clinically significant. However, patients on digoxin may show  
229 elevations of digoxin concentrations after initiation of therapy with FLOLAN, which may be  
230 clinically significant in patients prone to digoxin toxicity.

231 **Carcinogenesis, Mutagenesis, Impairment of Fertility:** Long-term studies in animals  
232 have not been performed to evaluate carcinogenic potential. A micronucleus test in rats revealed  
233 no evidence of mutagenicity. The Ames test and DNA elution tests were also negative, although  
234 the instability of epoprostenol makes the significance of these tests uncertain. Fertility was not  
235 impaired in rats given FLOLAN by subcutaneous injection at doses up to 100 mcg/kg/day  
236 (600 mcg/m<sup>2</sup>/day, 2.5 times the recommended human dose [4.6 ng/kg/min or 245.1 mcg/m<sup>2</sup>/day,  
237 IV] based on body surface area).

238 **Pregnancy:** Pregnancy Category B. Reproductive studies have been performed in pregnant rats  
239 and rabbits at doses up to 100 mcg/kg/day (600 mcg/m<sup>2</sup>/day in rats, 2.5 times the recommended  
240 human dose, and 1,180 mcg/m<sup>2</sup>/day in rabbits, 4.8 times the recommended human dose based on  
241 body surface area) and have revealed no evidence of impaired fertility or harm to the fetus due to  
242 FLOLAN. There are, however, no adequate and well-controlled studies in pregnant women.  
243 Because animal reproduction studies are not always predictive of human response, this drug  
244 should be used during pregnancy only if clearly needed.

245 **Labor and Delivery:** The use of FLOLAN during labor, vaginal delivery, or cesarean section  
246 has not been adequately studied in humans.

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

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

251 **Geriatric Use:** Clinical studies of FLOLAN in pulmonary hypertension did not include  
252 sufficient numbers of subjects aged 65 and over to determine whether they respond differently  
253 from younger patients. Other reported clinical experience has not identified differences in  
254 responses between the elderly and younger patients. In general, dose selection for an elderly  
255 patient should be cautious, usually starting at the low end of the dosing range, reflecting the  
256 greater frequency of decreased hepatic, renal, or cardiac function and of concomitant disease or  
257 other drug therapy.



258 **ADVERSE REACTIONS**

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

262 **Adverse Events During Dose Initiation and Escalation:** During early clinical trials,  
 263 FLOLAN was increased in 2-ng/kg/min increments until the patients developed symptomatic  
 264 intolerance. The most common adverse events and the adverse events that limited further  
 265 increases in dose were generally related to vasodilation, the major pharmacologic effect of  
 266 FLOLAN. The most common dose-limiting adverse events (occurring in  $\geq 1\%$  of patients) were  
 267 nausea, vomiting, headache, hypotension, and flushing, but also include chest pain, anxiety,  
 268 dizziness, bradycardia, dyspnea, abdominal pain, musculoskeletal pain, and tachycardia. Table 3  
 269 lists the adverse events reported during dose initiation and escalation in decreasing order of  
 270 frequency.

271  
 272

**Table 3. Adverse Events During Dose Initiation and Escalation**

Adverse Events Occurring in $\geq 1\%$ of Patients	FLOLAN (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%
Hypesthesia/paresthesia	1%
Tachycardia	1%

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**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 FLOLAN (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

279 FLOLAN. These include headache, jaw pain, flushing, diarrhea, nausea and vomiting, flu-like  
 280 symptoms, and anxiety/nervousness.

281 **Adverse Events During Chronic Administration for PPH:** In an effort to separate the  
 282 adverse effects of the drug from the adverse effects of the underlying disease, Table 4 lists  
 283 adverse events that occurred at a rate at least 10% different in the 2 groups in controlled trials for  
 284 PPH.

285  
 286 **Table 4. Adverse Events Regardless of Attribution Occurring in Patients With PPH With**  
 287 **≥10% Difference Between FLOLAN and Conventional Therapy Alone**

Adverse Event	FLOLAN (n = 52)	Conventional Therapy (n = 54)
<b>Occurrence More Common With FLOLAN</b>		
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%
Hypesthesia, hyperesthesia, paresthesia	12%	2%
<b>Occurrence More Common With Standard Therapy</b>		
Cardiovascular		
Heart failure	31%	52%
Syncope	13%	24%
Shock	0%	13%
Respiratory		
Hypoxia	25%	37%

288  
 289 Thrombocytopenia has been reported during uncontrolled clinical trials in patients receiving  
 290 FLOLAN.

291 Table 5 lists additional adverse events reported in PPH patients receiving FLOLAN plus  
 292 conventional therapy or conventional therapy alone during controlled clinical trials.

293

294 **Table 5. Adverse Events Regardless of Attribution Occurring in Patients With PPH With**  
 295 **<10% Difference Between FLOLAN and Conventional Therapy Alone**

Adverse Event	FLOLAN (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	4%	0%

296

297 **Adverse Events During Chronic Administration for PH/SSD:** In an effort to separate  
298 the adverse effects of the drug from the adverse effects of the underlying disease, Table 6 lists  
299 adverse events that occurred at a rate at least 10% different in the 2 groups in the controlled trial  
300 for patients with PH/SSD.

301

302 **Table 6. Adverse Events Regardless of Attribution Occurring in Patients With PH/SSD**  
303 **With  $\geq 10\%$  Difference Between FLOLAN and Conventional Therapy Alone**

Adverse Event	FLOLAN (n = 56)	Conventional Therapy (n = 55)
<b>Occurrence More Common With FLOLAN</b>		
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%
<b>Occurrence More Common With Conventional Therapy</b>		
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%

304

305 Table 7 lists additional adverse events reported in PH/SSD patients receiving FLOLAN plus  
306 conventional therapy or conventional therapy alone during controlled clinical trials.

307

308 **Table 7. Adverse Events Regardless of Attribution Occurring in Patients With PH/SSD**  
309 **With <10% Difference Between FLOLAN and Conventional Therapy Alone**

Adverse Event*	FLOLAN (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%
<b>Metabolic</b>		
Edema/edema peripheral/edema genital	79%	87%
Hypercalcemia	48%	51%
Hyperkalemia	4%	0%
Thirst	0%	4%
<b>Musculoskeletal</b>		
Arthritis	52%	45%
Back pain	13%	5%
Chest pain	52%	45%
Cramps leg	5%	7%
<b>Respiratory</b>		
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%
Sinusitis	4%	4%
<b>Neurological</b>		
Anxiety/hyperkinesia/nervousness/tremor	7%	5%
Depression/depression psychotic	13%	4%
Hyperesthesia/hypesthesia/paresthesia	5%	0%
Insomnia	9%	0%
Somnolence	4%	2%
<b>Skin and Appendages</b>		
Collagen disease	82%	84%
Pruritus	4%	2%
Sweat	41%	36%
<b>Urogenital</b>		
Hematuria	5%	0%
Urinary tract infection	7%	0%

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

310  
311

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

315 **Adverse Events Attributable to the Drug Delivery System:** Chronic infusions of  
316 FLOLAN are delivered using a small, portable infusion pump through an indwelling central  
317 venous catheter. During controlled PPH trials of up to 12 weeks' duration, up to 21% of patients  
318 reported a local infection and up to 13% of patients reported pain at the injection site. During a  
319 controlled PH/SSD trial of 12 weeks' duration, 14% of patients reported a local infection and 9%  
320 of patients reported pain at the injection site. During long-term follow-up in the clinical trial of  
321 PPH, sepsis was reported at least once in 14% of patients and occurred at a rate of  
322 0.32 infections/patient per year in patients treated with FLOLAN. This rate was higher than  
323 reported in patients using chronic indwelling central venous catheters to administer parenteral  
324 nutrition, but lower than reported in oncology patients using these catheters. Malfunctions in the  
325 delivery system resulting in an inadvertent bolus of or a reduction in FLOLAN were associated  
326 with symptoms related to excess or insufficient FLOLAN, respectively (see ADVERSE  
327 REACTIONS: Adverse Events During Chronic Administration).

328 **Observed During Clinical Practice:** In addition to adverse reactions reported from clinical  
329 trials, the following events have been identified during post-approval use of FLOLAN. Because  
330 they are reported voluntarily from a population of unknown size, estimates of frequency cannot  
331 be made. These events have been chosen for inclusion due to a combination of their seriousness,  
332 frequency of reporting, or potential causal connection to FLOLAN.

333 **Blood and Lymphatic:** Anemia, hypersplenism, pancytopenia, splenomegaly.

334 **Endocrine and Metabolic:** Hyperthyroidism.

### 335 **OVERDOSAGE**

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

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

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

### 349 **DOSAGE AND ADMINISTRATION**

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

353 **Dosage:** Continuous chronic infusion of FLOLAN should be administered through a central  
354 venous catheter. Temporary peripheral intravenous infusion may be used until central access is  
355 established. Chronic infusion of FLOLAN should be initiated at 2 ng/kg/min and increased in  
356 increments of 2 ng/kg/min every 15 minutes or longer until dose-limiting pharmacologic effects  
357 are elicited or until a tolerance limit to the drug is established and further increases in the  
358 infusion rate are not clinically warranted (see Dosage Adjustments). If dose-limiting  
359 pharmacologic effects occur, then the infusion rate should be decreased to an appropriate chronic  
360 infusion rate whereby the pharmacologic effects of FLOLAN are tolerated. In clinical trials, the  
361 most common dose-limiting adverse events were nausea, vomiting, hypotension, sepsis,  
362 headache, abdominal pain, or respiratory disorder (most treatment-limiting adverse events were  
363 not serious). If the initial infusion rate of 2 ng/kg/min is not tolerated, a lower dose that is  
364 tolerated by the patient should be identified.

365 In the controlled 12-week trial in PH/SSD, for example, the dose increased from a mean  
366 starting dose of 2.2 ng/kg/min. During the first 7 days of treatment, the dose was increased daily  
367 to a mean dose of 4.1 ng/kg/min on day 7 of treatment. At the end of week 12, the mean dose  
368 was 11.2 ng/kg/min. The mean incremental increase was 2 to 3 ng/kg/min every 3 weeks.

369 **Dosage Adjustments:** Changes in the chronic infusion rate should be based on persistence,  
370 recurrence, or worsening of the patient's symptoms of pulmonary hypertension and the  
371 occurrence of adverse events due to excessive doses of FLOLAN. In general, increases in dose  
372 from the initial chronic dose should be expected.

373 Increments in dose should be considered if symptoms of pulmonary hypertension persist or  
374 recur after improving. The infusion should be increased by 1- to 2-ng/kg/min increments at  
375 intervals sufficient to allow assessment of clinical response; these intervals should be at least  
376 15 minutes. In clinical trials, incremental increases in dose occurred at intervals of 24 to 48 hours  
377 or longer. Following establishment of a new chronic infusion rate, the patient should be  
378 observed, and standing and supine blood pressure and heart rate monitored for several hours to  
379 ensure that the new dose is tolerated.

380 During chronic infusion, the occurrence of dose-limiting pharmacological events may  
381 necessitate a decrease in infusion rate, but the adverse event may occasionally resolve without  
382 dosage adjustment. Dosage decreases should be made gradually in 2-ng/kg/min decrements  
383 every 15 minutes or longer until the dose-limiting effects resolve. Abrupt withdrawal of  
384 FLOLAN or sudden large reductions in infusion rates should be avoided. Except in  
385 life-threatening situations (e.g., unconsciousness, collapse, etc.), infusion rates of FLOLAN  
386 should be adjusted only under the direction of a physician.

387 In patients receiving lung transplants, doses of FLOLAN were tapered after the initiation of  
388 cardiopulmonary bypass.

389 **Administration:** FLOLAN is administered by continuous intravenous infusion via a central  
390 venous catheter using an ambulatory infusion pump. During initiation of treatment, FLOLAN  
391 may be administered peripherally.



392 The ambulatory infusion pump used to administer FLOLAN should: (1) be small and  
393 lightweight, (2) be able to adjust infusion rates in 2-ng/kg/min increments, (3) have occlusion,  
394 end-of-infusion, and low-battery alarms, (4) be accurate to  $\pm 6\%$  of the programmed rate, and  
395 (5) be positive pressure-driven (continuous or pulsatile) with intervals between pulses not  
396 exceeding 3 minutes at infusion rates used to deliver FLOLAN. The reservoir should be made of  
397 polyvinyl chloride, polypropylene, or glass. The infusion pump used in the most recent clinical  
398 trials was the CADD-1 HFX 5100 (SIMS Deltec). A 60-inch microbore non-DEHP extension set  
399 with proximal antisiphon valve, low priming volume (0.9 mL), and in-line 0.22 micron filter  
400 was used during clinical trials.

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

404 To facilitate extended use at ambient temperatures exceeding 25°C (77°F), a cold pouch with  
405 frozen gel packs was used in clinical trials (see DOSAGE AND ADMINISTRATION: Storage  
406 and Stability). The cold pouches and gel packs used in clinical trials were obtained from Palco  
407 Labs, Palo Alto, California. Any cold pouch used must be capable of maintaining the  
408 temperature of reconstituted FLOLAN between 2° and 8°C for 12 hours.

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

412 A concentration for the solution of FLOLAN should be selected that is compatible with the  
413 infusion pump being used with respect to minimum and maximum flow rates, reservoir capacity,  
414 and the infusion pump criteria listed above. FLOLAN, when administered chronically, should be  
415 prepared in a drug delivery reservoir appropriate for the infusion pump with a total reservoir  
416 volume of at least 100 mL. FLOLAN should be prepared using 2 vials of STERILE DILUENT  
417 for FLOLAN for use during a 24-hour period. Table 8 gives directions for preparing several  
418 different concentrations of FLOLAN.

419

420 **Table 8. Reconstitution and Dilution Instructions**

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.

421 \* Higher concentrations may be required for patients who receive FLOLAN long-term.

422

423 Generally, 3,000 ng/mL and 10,000 ng/mL are satisfactory concentrations to deliver between  
 424 2 to 16 ng/kg/min in adults. Infusion rates may be calculated using the following formula:

425

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

427

428

429 Tables 9 through 12 provide infusion delivery rates for doses up to 16 ng/kg/min based upon  
 430 patient weight, drug delivery rate, and concentration of the solution of FLOLAN to be used.

431 These tables may be used to select the most appropriate concentration of FLOLAN that will

432 result in an infusion rate between the minimum and maximum flow rates of the infusion pump

433 and that will allow the desired duration of infusion from a given reservoir volume. Higher

434 infusion rates, and therefore, more concentrated solutions may be necessary with long-term  
 435 administration of FLOLAN.

436

437 **Table 9. Infusion Rates for FLOLAN at a Concentration of 3,000 ng/mL**

Patient Weight (kg)	Dose or Drug Delivery Rate (ng/kg/min)							
	2	4	6	8	10	12	14	16
	Infusion Delivery Rate (mL/h)							
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

438

439 **Table 10. Infusion Rates for FLOLAN at a Concentration of 5,000 ng/mL**

Patient Weight (kg)	Dose or Drug Delivery Rate (ng/kg/min)							
	2	4	6	8	10	12	14	16
	Infusion Delivery Rate (mL/h)							
10	---	---	---	1.0	1.2	1.4	1.7	1.9
20	---	1.0	1.4	1.9	2.4	2.9	3.4	3.8
30	---	1.4	2.2	2.9	3.6	4.3	5.0	5.8
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	5.8	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

440

441 **Table 11. Infusion Rates for FLOLAN at a Concentration of 10,000 ng/mL**

Patient Weight (kg)	Dose or Drug Delivery Rate (ng/kg/min)						
	4	6	8	10	12	14	16
	Infusion Delivery Rate (mL/h)						
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

442

443 **Table 12. Infusion Rates for FLOLAN at a Concentration of 15,000 ng/mL**

Patient Weight (kg)	Dose or Drug Delivery Rate (ng/kg/min)						
	4	6	8	10	12	14	16
	Infusion Delivery Rate (mL/h)						
30	---	---	1.0	1.2	1.4	1.7	1.9
40	---	1.0	1.3	1.6	1.9	2.2	2.6
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

444

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

447 Unopened vials of STERILE DILUENT for FLOLAN are stable until the date indicated on the  
 448 package when stored at 15° to 25°C (59° to 77°F).

449 Prior to use, reconstituted solutions of FLOLAN must be protected from light and must be  
 450 refrigerated at 2° to 8°C (36° to 46°F) if not used immediately. **Do not freeze reconstituted**  
 451 **solutions of FLOLAN. Discard any reconstituted solution that has been frozen. Discard any**  
 452 **reconstituted solution if it has been refrigerated for more than 48 hours.**

453 During use, a single reservoir of reconstituted solution of FLOLAN can be administered at  
454 room temperature for a total duration of 8 hours, or it can be used with a cold pouch and  
455 administered up to 24 hours with the use of 2 frozen 6-oz gel packs in a cold pouch. When stored  
456 or in use, reconstituted FLOLAN must be insulated from temperatures greater than 25°C (77°F)  
457 and less than 0°C (32°F), and must not be exposed to direct sunlight.

458 **Use at Room Temperature:** Prior to use at room temperature, 15° to 25°C (59° to 77°F),  
459 reconstituted solutions of FLOLAN may be stored refrigerated at 2° to 8°C (36° to 46°F) for no  
460 longer than 40 hours. When administered at room temperature, reconstituted solutions may be  
461 used for no longer than 8 hours. This 48-hour period allows the patient to reconstitute a 2-day  
462 supply (200 mL) of FLOLAN. Each 100-mL daily supply may be divided into 3 equal portions.  
463 Two of the portions are stored refrigerated at 2° to 8°C (36° to 46°F) until they are used.

464 **Use with a Cold Pouch:** Prior to infusion with the use of a cold pouch, solutions may be  
465 stored refrigerated at 2° to 8°C (36° to 46°F) for up to 24 hours. When a cold pouch is employed  
466 during the infusion, reconstituted solutions of FLOLAN may be used for no longer than  
467 24 hours. The gel packs should be changed every 12 hours. Reconstituted solutions may be kept  
468 at 2° to 8°C (36° to 46°F), either in refrigerated storage or in a cold pouch or a combination of  
469 the two, for no more than 48 hours.

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

## 473 HOW SUPPLIED

474 FLOLAN for Injection is supplied as a sterile freeze-dried powder in 17-mL flint glass vials  
475 with gray butyl rubber closures, individually packaged in a carton.

476 17-mL vial containing epoprostenol sodium equivalent to 0.5 mg (500,000 ng), carton of 1  
477 (NDC 0173-0517-00).

478 17-mL vial containing epoprostenol sodium equivalent to 1.5 mg (1,500,000 ng), carton of 1  
479 (NDC 0173-0519-00).

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

481 The STERILE DILUENT for FLOLAN is supplied in flint glass vials containing 50-mL  
482 diluent with fluororesin-faced butyl rubber closures.

483 50-mL of STERILE DILUENT for FLOLAN, tray of 2 vials (NDC 0173-0518-01).

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

486



487  
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490

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493 January 2008

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