

PRESCRIBING INFORMATION

FLOLAN[®] (epoprostenol sodium) for Injection

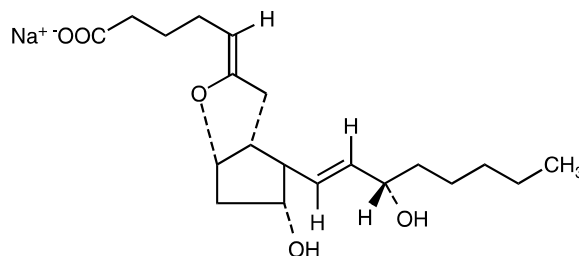
DESCRIPTION

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 (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 (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 C₂₀H₃₁NaO₅. 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_{1α} (formed by spontaneous degradation) and 6,15-diketo-13,14-dihydro-PGF_{1α}
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 ARTERIAL HYPERTENSION (PAH)**

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

62 **Chronic Infusion in Idiopathic or Heritable PAH: Hemodynamic Effects:** Chronic
63 continuous infusions of FLOLAN in patients with idiopathic or heritable PAH 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 **Idiopathic or Heritable PAH**

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

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 [†] 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 patients with idiopathic or
100 heritable PAH treated with FLOLAN for 12 weeks in a multicenter, open, randomized, parallel
101 study. At the end of the treatment period, 8 of 40 (20%) patients receiving conventional therapy
102 alone died, whereas none of the 41 patients receiving FLOLAN died (p = 0.003).

103 **Chronic Infusion in PAH/Scleroderma Spectrum of Diseases (SSD):**

104 **Hemodynamic Effects:** Chronic continuous infusions of FLOLAN in patients with PAH/SSD
105 were studied in a prospective, open, randomized trial of 12 weeks' duration comparing FLOLAN
106 plus conventional therapy (N = 56) to conventional therapy alone (N = 55). Except for 5 NYHA
107 functional Class II patients, all patients were either functional Class III or Class IV. Dosage of
108 FLOLAN was determined as described in DOSAGE AND ADMINISTRATION and averaged
109 11.2 ng/kg/min at study's end. Conventional therapy varied among patients and included some or
110 all of the following: anticoagulants in essentially all patients, supplemental oxygen and diuretics
111 in two thirds of the patients, oral vasodilators in 40% of the patients, and digoxin in a third of the
112 patients. A statistically significant increase in CI, and statistically significant decreases in PAPm,
113 RAPm, PVR, and SAPm after 12 weeks of treatment were observed in patients who received
114 FLOLAN chronically compared to those who did not. Table 2 illustrates the treatment-related
115 hemodynamic changes in these patients after 12 weeks of treatment.

116

117 **Table 2. Hemodynamics During Chronic Administration of FLOLAN in Patients With**
118 **PAH/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

119 * Denotes statistically significant difference between FLOLAN and conventional therapy
120 groups (N is the number of patients with hemodynamic data).
121 CI = cardiac index, PAPm = mean pulmonary arterial pressure, RAPm = mean right arterial
122 pressure, PVR = pulmonary vascular resistance, SAPm = mean systemic arterial pressure.
123

124 **Clinical Effects:** Statistically significant improvement was observed in exercise capacity, as
125 measured by the 6-minute walk, in patients receiving continuous intravenous FLOLAN plus
126 conventional therapy for 12 weeks compared to those receiving conventional therapy alone.
127 Improvements were apparent in some patients at the end of the first week of therapy. Increases in
128 exercise capacity were accompanied by statistically significant improvements in dyspnea and
129 fatigue, as measured by the Borg Dyspnea Index and Dyspnea Fatigue Index. At week 12,
130 NYHA functional class improved in 21 of 51 (41%) patients treated with FLOLAN compared to
131 none of the 48 patients treated with conventional therapy alone. However, more patients in both
132 treatment groups (28/51 [55%] with FLOLAN and 35/48 [73%] with conventional therapy alone)
133 showed no change in functional class, and 2/51 (4%) with FLOLAN and 13/48 (27%) with
134 conventional therapy alone worsened. Of the patients randomized, NYHA functional class data
135 at 12 weeks were not available for 5 patients treated with FLOLAN and 7 patients treated with
136 conventional therapy alone.

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

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

143 **INDICATIONS AND USAGE**

144 FLOLAN is indicated for the treatment of pulmonary arterial hypertension (WHO
145 Group 1) to improve exercise capacity. Studies establishing effectiveness included
146 predominantly patients with NYHA Functional Class III-IV symptoms and etiologies of
147 idiopathic or heritable PAH or PAH associated with connective tissue diseases.

148 **CONTRAINDICATIONS**

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

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

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

160 **WARNINGS**

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

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

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

171 **PRECAUTIONS**

172 **General:** FLOLAN should be used only by clinicians experienced in the diagnosis and
173 treatment of pulmonary hypertension. Carefully establish the diagnosis of idiopathic or heritable
174 PAH or PAH/CTD.

175 FLOLAN is a potent pulmonary and systemic vasodilator. Initiate FLOLAN in a setting with
176 adequate personnel and equipment for physiologic monitoring and emergency care. Dose
177 initiation has been performed during right heart catheterization and without cardiac

178 catheterization. During dose initiation, asymptomatic increases in pulmonary artery pressure
179 coincident with increases in cardiac output occurred rarely. In such cases, consider dose
180 reduction, but such an increase does not imply that chronic treatment is contraindicated.

181 FLOLAN is a potent inhibitor of platelet aggregation. Therefore, expect an increased risk for
182 hemorrhagic complications, particularly for patients with other risk factors for bleeding (see
183 PRECAUTIONS: Drug Interactions).

184 During chronic use, deliver FLOLAN continuously on an ambulatory basis through a
185 permanent indwelling central venous catheter. Unless contraindicated, administer anticoagulant
186 therapy to patients receiving FLOLAN to reduce the risk of pulmonary thromboembolism or
187 systemic embolism through a patent foramen ovale. To reduce the risk of infection, use aseptic
188 technique in the reconstitution and administration of FLOLAN and in routine catheter care.

189 Because FLOLAN is metabolized rapidly, even brief interruptions in the delivery of FLOLAN
190 may result in symptoms associated with rebound pulmonary hypertension including dyspnea,
191 dizziness, and asthenia. Intravenous therapy with FLOLAN will likely be needed for prolonged
192 periods, possibly years, so consider the patient's ability to accept and care for a permanent
193 intravenous catheter and infusion pump.

194 Based on clinical trials, the acute hemodynamic response to FLOLAN did not correlate well
195 with improvement in exercise tolerance or survival during chronic use of FLOLAN. Adjust
196 dosage of FLOLAN during chronic use at the first sign of recurrence or worsening of symptoms
197 attributable to pulmonary hypertension or the occurrence of adverse events associated with
198 FLOLAN (see DOSAGE AND ADMINISTRATION). Following dosage adjustments, monitor
199 standing and supine blood pressure and heart rate closely for several hours.

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

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

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

225 **Carcinogenesis, Mutagenesis, Impairment of Fertility:** Long-term studies in animals
226 have not been performed to evaluate carcinogenic potential. A micronucleus test in rats revealed
227 no evidence of mutagenicity. The Ames test and DNA elution tests were also negative, although
228 the instability of epoprostenol makes the significance of these tests uncertain. Fertility was not
229 impaired in rats given FLOLAN by subcutaneous injection at doses up to 100 mcg/kg/day
230 (600 mcg/m²/day, 2.5 times the recommended human dose [4.6 ng/kg/min or 245.1 mcg/m²/day,
231 IV] based on body surface area).

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

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

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

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

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

252 **ADVERSE REACTIONS**

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

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

265
266

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%

267

268 **Adverse Events During Chronic Administration:** Interpretation of adverse events is
269 complicated by the clinical features of PAH, which are similar to some of the pharmacologic
270 effects of FLOLAN (e.g., dizziness, syncope). Adverse events which may be related to the
271 underlying disease include dyspnea, fatigue, chest pain, edema, hypoxia, right ventricular failure,
272 and pallor. Several adverse events, on the other hand, can clearly be attributed to FLOLAN.
273 These include hypotension, bradycardia, tachycardia, pulmonary edema, bleeding at various
274 sites, thrombocytopenia, headache, abdominal pain, pain (unspecified), sweating, rash,
275 arthralgia, jaw pain, flushing, diarrhea, nausea and vomiting, flu-like symptoms,
276 anxiety/nervousness, and agitation. In addition, chest pain, fatigue, and pallor have been reported
277 during FLOLAN therapy, and a role for the drug in these events cannot be excluded.

278 **Adverse Events During Chronic Administration for Idiopathic or Heritable PAH:** In
279 an effort to separate the adverse effects of the drug from the adverse effects of the underlying
280 disease, Table 4 lists adverse events that occurred at a rate at least 10% greater on FLOLAN in
281 controlled trials.

282

283 **Table 4. Adverse Events Regardless of Attribution Occurring in Patients With Idiopathic**
284 **or Heritable PAH With $\geq 10\%$ Difference Between FLOLAN and Conventional Therapy**
285 **Alone**

Adverse Event	FLOLAN (n = 52)	Conventional Therapy (n = 54)
Occurrence 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%
Nonspecific musculoskeletal pain	35%	15%
Neurological		
Anxiety/nervousness/tremor	21%	9%
Dizziness	83%	70%
Headache	83%	33%
Hypesthesia, hyperesthesia, paresthesia	12%	2%

286

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

289 **Adverse Events During Chronic Administration for PAH/SSD:** In an effort to separate
290 the adverse effects of the drug from the adverse effects of the underlying disease, Table 5 lists
291 adverse events that occurred at a rate at least 10% greater on FLOLAN in the controlled trial.

292

293 **Table 5. Adverse Events Regardless of Attribution Occurring in Patients with PAH/SSD**
294 **With $\geq 10\%$ Difference Between FLOLAN and Conventional Therapy Alone**

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

295

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

299 **Adverse Events Attributable to the Drug Delivery System:** Chronic infusions of
300 FLOLAN are delivered using a small, portable infusion pump through an indwelling central
301 venous catheter. During controlled PAH trials of up to 12 weeks' duration, the local infection
302 rate was about 18%, and the rate for pain was about 11%. During long-term follow-up, sepsis
303 was reported at a rate of 0.3 infections/patient per year in patients treated with FLOLAN. This
304 rate was higher than reported in patients using chronic indwelling central venous catheters to
305 administer parenteral nutrition, but lower than reported in oncology patients using these
306 catheters. Malfunctions in the delivery system resulting in an inadvertent bolus of or a reduction
307 in FLOLAN were associated with symptoms related to excess or insufficient FLOLAN,
308 respectively (see ADVERSE REACTIONS: Adverse Events During Chronic Administration).

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

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

315 **Endocrine and Metabolic:** Hyperthyroidism.

316 **OVERDOSAGE**

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

321 One patient with PAH/CTD accidentally received 50 mL of an unspecified concentration of
322 FLOLAN. The patient vomited and became unconscious with an initially unrecordable blood
323 pressure. FLOLAN was discontinued and the patient regained consciousness within seconds. In
324 clinical practice, fatal occurrences of hypoxemia, hypotension, and respiratory arrest have been
325 reported following overdosage of FLOLAN.

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

330 **DOSAGE AND ADMINISTRATION**

331 **Important Note: FLOLAN must be reconstituted only with STERILE DILUENT for**
332 **FLOLAN.** Do not dilute reconstituted solutions of FLOLAN or administer with other parenteral
333 solutions or medications (see WARNINGS).

334 **Dosage:** Administer continuous chronic infusion of FLOLAN through a central venous
335 catheter. Temporary peripheral intravenous infusion may be used until central access is
336 established. Initiate chronic infusion of FLOLAN at 2 ng/kg/min and increase in increments of
337 2 ng/kg/min every 15 minutes or longer until dose-limiting pharmacologic effects are elicited or
338 until a tolerance limit to the drug is established or further increases in the infusion rate are not
339 clinically warranted (see Dosage Adjustments). If dose-limiting pharmacologic effects occur,
340 then decrease the infusion rate until FLOLAN is tolerated. In clinical trials, the most common
341 dose-limiting adverse events were nausea, vomiting, hypotension, sepsis, headache, abdominal
342 pain, or respiratory disorder (most treatment-limiting adverse events were not serious). If the
343 initial infusion rate of 2 ng/kg/min is not tolerated, identify a lower dose that is tolerated by the
344 patient.

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

349 **Dosage Adjustments:** Base changes in the chronic infusion rate on persistence,
350 recurrence, or worsening of the patient's symptoms of pulmonary hypertension and the
351 occurrence of adverse events due to excessive doses of FLOLAN. In general, expect increases in
352 dose from the initial chronic dose.

353 Consider increments in dose if symptoms of PAH persist or recur. Increase the infusion by 1-
354 to 2-ng/kg/min increments at intervals sufficient to allow assessment of clinical response; these
355 intervals should be at least 15 minutes. In clinical trials, incremental increases in dose occurred
356 at intervals of 24 to 48 hours or longer. Following establishment of a new chronic infusion rate,
357 observe the patient, and monitor standing and supine blood pressure and heart rate for several
358 hours to ensure that the new dose is tolerated.

359 During chronic infusion, the occurrence of dose-limiting pharmacological events may
360 necessitate a decrease in infusion rate, but the adverse event may occasionally resolve without
361 dosage adjustment. Make dosage decreases gradually in 2-ng/kg/min decrements every
362 15 minutes or longer until the dose-limiting effects resolve. Avoid abrupt withdrawal of
363 FLOLAN or sudden large reductions in infusion rates. Except in life-threatening situations (e.g.,
364 unconsciousness, collapse, etc.), adjust infusion rates of FLOLAN only under the direction of a
365 physician.

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

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

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

380 To avoid interruptions in drug delivery, the patient should have access to a backup infusion
381 pump and intravenous infusion sets. Consider a multi-lumen catheter if other intravenous
382 therapies are routinely administered.

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

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

391 Select a concentration for the solution of FLOLAN that is compatible with the infusion pump
392 being used with respect to minimum and maximum flow rates, reservoir capacity, and the

393 infusion pump criteria listed above. When administered chronically, prepare FLOLAN in a drug
394 delivery reservoir appropriate for the infusion pump with a total reservoir volume of at least 100
395 mL, using 2 vials of STERILE DILUENT for FLOLAN for use during a 24-hour period. Table 6
396 gives directions for preparing several different concentrations of FLOLAN.

397

398 **Table 6. 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.

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

400

401 Generally, 3,000 ng/mL and 10,000 ng/mL are satisfactory concentrations to deliver between
402 2 to 16 ng/kg/min in adults. Infusion rates may be calculated using the following formula:

403

$$404 \quad \text{Infusion Rate (mL/hr)} = \frac{[\text{Dose (ng/kg/min)} \times \text{Weight (kg)} \times \text{60 min/hr}]}{\text{Final Concentration (ng/mL)}} \\ 405$$

406

407 Tables 7 through 10 provide infusion delivery rates for doses up to 16 ng/kg/min based upon
408 patient weight, drug delivery rate, and concentration of the solution of FLOLAN to be used.
409 These tables may be used to select the most appropriate concentration of FLOLAN that will
410 result in an infusion rate between the minimum and maximum flow rates of the infusion pump
411 and that will allow the desired duration of infusion from a given reservoir volume. Higher
412 infusion rates, and therefore, more concentrated solutions may be necessary with long-term
413 administration of FLOLAN.

414

415 **Table 7. 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

416

417 **Table 8. 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

418

419 **Table 9. 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

420

421 **Table 10. 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

422

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

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

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

431 During use, a single reservoir of reconstituted solution of FLOLAN can be administered at
432 room temperature for a total duration of 8 hours, or it can be used with a cold pouch and
433 administered up to 24 hours with the use of 2 frozen 6-oz gel packs in a cold pouch. When stored
434 or in use, insulate reconstituted FLOLAN from temperatures greater than 25°C (77°F) and less
435 than 0°C (32°F), and do not expose to direct sunlight.

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

442 **Use with a Cold Pouch:** Prior to infusion with the use of a cold pouch, solutions may be
443 stored refrigerated at 2° to 8°C (36° to 46°F) for up to 24 hours. When a cold pouch is employed
444 during the infusion, reconstituted solutions of FLOLAN may be used for no longer than
445 24 hours. Change gel packs every 12 hours. Reconstituted solutions may be kept at 2° to 8°C
446 (36° to 46°F), either in refrigerated storage or in a cold pouch or a combination of the two, for no
447 more than 48 hours.

448 Inspect parenteral drug products for particulate matter and discoloration prior to
449 administration whenever solution and container permit. If either occurs, do not administer.

450 **HOW SUPPLIED**

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

453 17-mL vial containing epoprostenol sodium equivalent to 0.5 mg (500,000 ng), carton of 1
454 (NDC 0173-0517-00).

455 17-mL vial containing epoprostenol sodium equivalent to 1.5 mg (1,500,000 ng), carton of 1
456 (NDC 0173-0519-00).

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

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

460 50-mL of STERILE DILUENT for FLOLAN, tray of 2 vials (NDC 0173-0518-01).

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

463



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GlaxoSmithKline

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Research Triangle Park, NC 27709

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