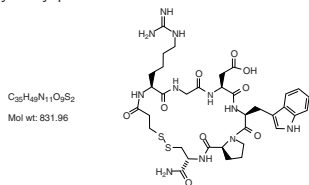


# INTEGRILIN® (eptifibatid) INJECTION

## For Intravenous Administration

**DESCRIPTION** Eptifibatid is a cyclic heptapeptide containing six amino acids and one mercaptopyrionyl (des-amino cysteinyl) residue. An interchain disulfide bridge is formed between the cysteine amide and the mercaptopyrionyl moieties. Chemically it is N<sup>6</sup>-(aminoiminomethyl)-N<sup>7</sup>-(3-mercapto-1-oxopropyl-L-lysylglycyl-L- $\alpha$ -aspartyl-L-tryptophyl-L-prolyl-L-cysteinamide, cyclic (1→6)-disulfide. Eptifibatid binds to the platelet receptor glycoprotein (GP) IIb/IIIa of human platelets and inhibits platelet aggregation.

The eptifibatid peptide is produced by solution-phase peptide synthesis, and is purified by preparative reverse-phase liquid chromatography and lyophilized. The structural formula is:



INTEGRILIN® (eptifibatid) Injection is a clear, colorless, sterile, non-pyrogenic solution for intravenous (IV) use. Each 10-mL vial contains 2 mg/mL of eptifibatid and each 100-mL vial contains either 0.75 mg/mL of eptifibatid or 2 mg/mL of eptifibatid. Each vial of either size also contains 5.25 mg/mL citric acid and sodium hydroxide to adjust the pH to 5.35.

**CLINICAL PHARMACOLOGY Mechanism of Action.** Eptifibatid reversibly inhibits platelet aggregation by preventing the binding of fibrinogen, von Willebrand factor, and other adhesive ligands to GP IIb/IIIa. When administered intravenously, eptifibatid inhibits *ex vivo* platelet aggregation in a dose- and concentration-dependent manner. Platelet aggregation inhibition is reversible following cessation of the eptifibatid infusion; this is thought to result from dissociation of eptifibatid from the platelet.

**Pharmacodynamics.** Infusion of eptifibatid into baboons caused a dose-dependent inhibition of *ex vivo* platelet aggregation, with complete inhibition of aggregation achieved at infusion rates greater than 5.0  $\mu$ g/kg/min. In a baboon model that is refractory to aspirin and heparin, doses of eptifibatid that inhibit aggregation prevented acute thrombosis with only a modest prolongation (2- to 3-fold) of the bleeding time. Platelet aggregation in dogs was also inhibited by infusions of eptifibatid, with complete inhibition at 2.0  $\mu$ g/kg/min. This infusion dose completely inhibited canine coronary thrombosis induced by coronary artery injury (Folts model).

Human pharmacodynamic data were obtained in healthy subjects and in patients presenting with unstable angina (UA) or non-ST-segment elevation myocardial infarction (NSTEMI) and/or undergoing percutaneous coronary interventions. Studies in healthy subjects enrolled only males; patient studies enrolled approximately one third women. In these studies, eptifibatid inhibited *ex vivo* platelet aggregation induced by adenosine diphosphate (ADP) and other agonists in a dose- and concentration-dependent manner. The effect of eptifibatid was observed immediately after administration of a 180  $\mu$ g/kg intravenous bolus. Table 1 shows the effects of dosing regimens of eptifibatid used in the IMPACT II and PURSUIT studies on *ex vivo* platelet aggregation induced by 20  $\mu$ M ADP in PPACK-anticoagulated platelet-rich plasma and on bleeding time. The effects of the dosing regimen used in ESPRIT on platelet aggregation have not been studied.

**Table 1**  
Platelet Inhibition and Bleeding Time

	IMPACT II 135/0.5*	PURSUIT 180/2.0**
Inhibition of platelet aggregation 15 min. after bolus	69%	84%
Inhibition of platelet aggregation at steady state	40-50%	>90%
Bleeding-time prolongation at steady state	<5x	<5x
Inhibition of platelet aggregation 4h after infusion discontinuation	<30%	<50%
Bleeding-time prolongation 6h after infusion discontinuation	1x	1.4x

\* 135  $\mu$ g/kg bolus followed by a continuous infusion of 0.5 mg/kg/min  
\*\* 180  $\mu$ g/kg bolus followed by a continuous infusion of 2.0 mg/kg/min

The eptifibatid dosing regimen used in the ESPRIT study included two 180  $\mu$ g/kg bolus doses given ten minutes apart combined with a continuous 2.0  $\mu$ g/kg/min infusion.

When administered alone, eptifibatid has no measurable effect on prothrombin time (PT) or activated partial thromboplastin time (aPTT). (See also **PRECAUTIONS: Drug Interactions**).

There were no important differences between men and women or between age groups in the pharmacodynamic properties of eptifibatid. Differences among ethnic groups have not been assessed.

**Pharmacokinetics.** The pharmacokinetics of eptifibatid are linear and dose-proportional for bolus doses ranging from 90 to 250  $\mu$ g/kg and infusion rates from 0.5 to 3.0  $\mu$ g/kg/min. Plasma elimination half-life is approximately 2.5 hours. Administration of a single 180  $\mu$ g/kg bolus combined with an infusion produces an early peak level, followed by a small decline prior to attaining steady state (within 4-6 hours). This decline can be prevented by administering a second 180  $\mu$ g/kg bolus ten minutes after the first. The extent of eptifibatid binding to human plasma protein is about 25%. Clearance in patients with coronary artery disease is about 55 mL/kg/h. In healthy subjects, renal clearance accounts for approximately 50% of total body clearance, with the majority of the drug excreted in the urine as eptifibatid, deaminated eptifibatid, and other, more polar metabolites. No major metabolites have been detected in human plasma.

In patients with moderate to severe renal insufficiency (creatinine clearance <50 mL/min using the Cockcroft-Gault equation), the clearance of eptifibatid is reduced by approximately 50% and steady-state plasma levels approximately doubled (see **WARNINGS, DOSAGE AND ADMINISTRATION**).

**Special Populations.** Patients in clinical studies were older (range 20 to 94 years) than those in the clinical pharmacology studies. Elderly patients with coronary artery disease demonstrated higher plasma levels and lower total body clearance of eptifibatid when given the same dose as younger patients. Limited data are available on lighter weight (<50 kg) patients over 75 years of age.

No studies have been conducted in patients with hepatic impairment.

Males and females have not demonstrated any clinically significant differences in the pharmacokinetics of eptifibatid.

**CLINICAL STUDIES** Eptifibatid was studied in three placebo-controlled, randomized studies. PURSUIT evaluated patients with acute coronary syndromes: unstable angina (UA) or non-ST-segment elevation MI (NSTEMI). Two other studies, ESPRIT and IMPACT II, evaluated patients about to undergo a percutaneous coronary intervention (PCI). Patients underwent primarily balloon angioplasty in IMPACT II and intracoronary stent placement, with or without angioplasty, in ESPRIT.

**Non-ST-segment Elevation Acute Coronary Syndrome** Non-ST-segment elevation acute coronary syndrome is defined as prolonged ( $\geq 10$  minutes) symptoms of cardiac ischemia within the previous 24 hours associated with either ST-segment changes (elevation between 0.6 mm and 1 mm or depression >0.5 mm), T-wave inversion (>1 mm), or positive CK-MB. This definition includes "unstable angina" and "NSTEMI" but excludes myocardial infarction that is associated with Q waves or greater degrees of ST-segment elevation.

**PURSUIT (Platelet Glycoprotein IIb/IIIa in Unstable Angina: Receptor Suppression Using INTEGRILIN® Therapy)** PURSUIT was a 726-center, 27-country, double-blind, randomized, placebo-controlled study in 10,948 patients presenting with UA or NSTEMI. Patients could be enrolled only if they had experienced cardiac ischemia at rest ( $\geq 10$  minutes) within the previous 24 hours and had either ST-segment changes (elevations between 0.6 mm and 1 mm or depression >0.5 mm), T-wave inversion (>1 mm), or increased CK-MB. Important exclusion criteria included a history of bleeding diathesis, evidence of abnormal bleeding within the previous 30 days, uncontrolled hypertension, major surgery within the previous 6 weeks, stroke within the previous 30 days, any history of hemorrhagic stroke, serum creatinine >2.0 mg/dL, dependency on renal dialysis, or platelet count <100,000/mm<sup>3</sup>.

Patients were randomized to either placebo, eptifibatid 180  $\mu$ g/kg bolus followed by a 2.0  $\mu$ g/kg/min infusion (180/2.0), or eptifibatid 180  $\mu$ g/kg bolus followed by a 1.3  $\mu$ g/kg/min infusion (180/1.3). The infusion was continued for 72 hours, until hospital discharge, or until the time of coronary artery bypass grafting (CABG), whichever occurred first, except that if PCI was performed, the eptifibatid infusion was continued for 24 hours after the procedure, allowing for a duration of infusion up to 96 hours.

The lower-infusion-rate arm was stopped after the first interim analysis when the two active-treatment arms appeared to have the same incidence of bleeding.

Patient age ranged from 20 to 94 (mean 63) years, and 65% were male. The patients were 89% Caucasian, 6% Hispanic, and

5% Black, recruited in the United States and Canada (40%), Western Europe (39%), Eastern Europe (16%), and Latin America (5%).

This was a "real world" study; each patient was managed according to the usual standards of the investigational site; frequencies of angiography, PCI, and CABG therefore differed widely from site to site and from country to country. Of the patients in PURSUIT, 13% were managed with PCI during drug infusion, of whom 50% received intracoronary stents; 87% were managed medically (without PCI during drug infusion).

The majority of patients received aspirin (75-325 mg once daily). Heparin was administered intravenously or subcutaneously, at the physician's discretion, most commonly as an intravenous bolus of 5000 U followed by a continuous infusion of 1000 U/h. For patients weighing less than 70 kg, the recommended heparin bolus dose was 60 U/kg followed by a continuous infusion of 12 U/kg/h. A target aPTT of 50-70 seconds was recommended. A total of 1250 patients underwent PCI within 72 hours after randomization, in which case they received intravenous heparin to maintain an activated clotting time (ACT) of 300-350 seconds.

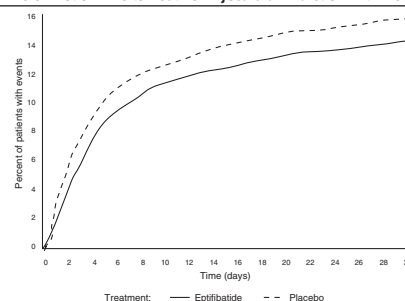
The primary endpoint of the study was the occurrence of death from any cause or new myocardial infarction (MI) (evaluated by a blinded Clinical Endpoints Committee) within 30 days of randomization.

Compared to placebo, eptifibatid administered as a 180  $\mu$ g/kg bolus followed by a 2.0  $\mu$ g/kg/min infusion significantly ( $p=0.042$ ) reduced the incidence of endpoint events (see Table 2). The reduction in the incidence of endpoint events in patients receiving eptifibatid was evident early during treatment, and this reduction was maintained through at least 30 days (see Figure 1). Table 2 also shows the incidence of the components of the primary endpoint, death (whether or not preceded by an MI) and new MI in surviving patients at 30 days.

**Table 2**  
Clinical Events In The PURSUIT Study

	Placebo (n = 4739) n	Eptifibatid (180/2.0) (n = 4722) (%)	p-value
<b>Death or MI</b>			
3 days	359 (7.6%)	279 (5.9%)	0.001
7 days	552 (11.6%)	477 (10.1%)	0.016
30 days			
Death or MI (Primary Endpoint)	745 (15.7%)	672 (14.2%)	0.042
Death	177 (3.7%)	165 (3.5%)	
Nonfatal MI	568 (12.0%)	507 (10.7%)	

**Figure 1: Kaplan-Meier Plot of Time to Death or Myocardial Infarction Within 30 Days of Randomization**



Treatment with eptifibatid prior to determination of patient management strategy reduced clinical events regardless of whether patients ultimately underwent diagnostic catheterization, revascularization (i.e., PCI or CABG surgery) or continued to receive medical management alone. Table 3 shows the incidence of death or MI within 72 hours.

**Table 3**  
Clinical Events (Death or MI) in the PURSUIT Study Within 72 Hours of Randomization

	Placebo n=4739	Eptifibatid 180/2.0 n=4722
<b>Overall Patient Population</b>		
- At 72 hours	7.6%	5.9%
<b>Patients undergoing early PCI</b>		
- Pre-procedure (nonfatal MI only)	5.5%	1.8%
- At 72 hours	14.4%	9.0%
<b>Patients not undergoing early PCI</b>		
- At 72 hours	6.5%	5.4%

All of the effect of eptifibatid was established within 72 hours (during the period of drug infusion), regardless of management strategy. Moreover, for patients undergoing early PCI, a reduction in events was evident prior to the procedure.

Follow-up data were available through 165 days for 10,611 patients enrolled in the PURSUIT trial (96.9 percent of the initial enrollment). This follow-up included 4566 patients who received eptifibatid at the 180/2.0 dose. As reported by the investigators, the occurrence of death from any cause or new myocardial infarction for patients followed for at least 165 days was reduced from 13.6 percent with placebo to 12.1 percent with eptifibatid 180/2.0.

### Percutaneous Coronary Intervention

#### IMPACT II (INTEGRILIN® to Minimize Platelet Aggregation and Prevent Coronary Thrombosis II)

IMPACT II was a multi-center, double-blind, randomized, placebo-controlled study conducted in the United States in 4010 patients undergoing PCI. Major exclusion criteria included a history of bleeding diathesis, major surgery within 6 weeks of treatment, gastrointestinal bleeding within 30 days, any stroke or structural CNS abnormality, uncontrolled hypertension, PT >1.2 times control, hematocrit <30%, platelet count <100,000/mm<sup>3</sup>, and pregnancy.

Patient age ranged from 24 to 89 (mean 60) years, and 75% were male. The patients were 92% Caucasian, 5% Black, and 3% Hispanic. Forty-one percent of the patients underwent PCI for ongoing ACS. Patients were randomly assigned to one of three treatment regimens, each incorporating a bolus dose initiated immediately prior to PCI followed by a continuous infusion lasting 20-24 hours: 1) 135  $\mu$ g/kg bolus followed by a continuous infusion of 0.5  $\mu$ g/kg/min of eptifibatid (135/0.5); 2) 135  $\mu$ g/kg bolus followed by a continuous infusion of 0.75  $\mu$ g/kg/min of eptifibatid (135/0.75); or 3) a matching placebo bolus followed by a matching placebo continuous infusion. Each patient received aspirin and an intravenous heparin bolus of 100 U/kg, with additional bolus infusions of up to 2000 additional units of heparin every 15 minutes to maintain an activated clotting time (ACT) of 300-350 seconds.

The primary endpoint was the composite of death, MI, or urgent revascularization, analyzed at 30 days after randomization in all patients who received at least one dose of study drug.

As shown in Table 4, each eptifibatid regimen reduced the rate of death, MI, or urgent intervention, although at 30 days, this finding was statistically significant only in the lowerdose eptifibatid group. As in the PURSUIT study, the effects of eptifibatid were seen early and persisted throughout the 30-day period.

**Table 4**  
Clinical Events in the IMPACT II Study

	Placebo n(%)	Eptifibatid (135/0.5) n(%)	Eptifibatid (135/0.75) n(%)
<b>Patients</b>	1285	1300	1286
<b>Abrupt Closure</b>	65 (5.1%)	36 (2.8%)	43 (3.3%)
p-value vs. placebo		0.003	0.030
<b>Death, MI, or Urgent Intervention</b>			
24 hours	123 (9.6%)	86 (6.6%)	89 (6.9%)
p-value vs. placebo		0.006	0.014
48 hours	131 (10.2%)	99 (7.6%)	102 (7.9%)
p-value vs. placebo		0.021	0.045
30 days (primary endpoint)	149 (11.6%)	118 (9.1%)	128 (10.0%)
p-value vs. placebo		0.035	0.179
<b>Death or MI</b>			
30 days	110 (8.6%)	89 (6.8%)	95 (7.4%)
p-value vs. placebo		0.102	0.272
6 months	151 (11.9%)*	136 (10.6%)*	130 (10.3%)*
p-value vs. placebo		0.297	0.182

\* Kaplan-Meier estimate of event rate

**ESPRIT (Enhanced Suppression of the Platelet IIb/IIIa Receptor with INTEGRILIN® Therapy)** The ESPRIT study was a multi-center, double-blind, randomized, placebo-controlled study conducted in the United States and Canada that enrolled 2064 patients undergoing elective or urgent PCI with intended intracoronary stent placement. Exclusion criteria included MI within the previous 24 hours, ongoing chest pain, administration of any oral antiplatelet or oral anticoagulant other than aspirin within 30 days of PCI (although loading doses of thienopyridine on the day of PCI were encouraged), planned PCI of a saphenous vein graft or subsequent "staged" PCI, prior stent placement in the target lesion, PCI within the previous 90 days, a history of bleeding diathesis, major surgery within 6 weeks of treatment, gastrointestinal bleeding within 30 days, any stroke or structural CNS abnormality, uncontrolled hypertension, PT >1.2 times control, hematocrit <30%, platelet count <100,000/mm<sup>3</sup>, and pregnancy.

Patient age ranged from 24 to 93 (mean 62 years) and 73% of patients were male. The study enrolled 90% Caucasian, 5% African American, 2% Hispanic and 1% Asian patients. Patients received a wide variety of stents. Patients were randomized either to placebo or eptifibatid administered as an intravenous bolus of 180 µg/kg followed immediately by a continuous infusion of 2.0 µg/kg/min, and a second bolus of 180 µg/kg administered 10 minutes later (180/2.0/180). Eptifibatid infusion was continued for 18-24 hours after PCI or until hospital discharge, whichever came first. Each patient received at least one dose of aspirin (162-325 mg) and 60 U/kg of heparin as a bolus (not to exceed 6000 Units) if not already receiving a heparin infusion. Additional boluses of heparin (10-40 U/kg) could be administered in order to reach a target ACT between 200 and 300 seconds.

The primary endpoint of the ESPRIT study was the composite of death, MI, urgent target vessel revascularization (UTVR) and "bailout" to open label eptifibatid due to a thrombotic complication of PCI (TBO) (e.g., visible thrombus, "no reflow", or abrupt closure) at 48 hours. MI, UTVR and TBO were evaluated by a blinded Clinical Events Committee.

As shown in Table 5, the incidence of the primary endpoint and selected secondary endpoints was significantly reduced in patients who received eptifibatid. A treatment benefit in patients who received eptifibatid was seen by 48 hours and at the end of the 30-day observation period.

**Table 5  
Clinical Events in the ESPRIT Study**

	Placebo (n=1024)	Eptifibatid 180/2.0/180 (n=1040)	Relative Risk (95% CI)	p-Value
<b>Death, MI, Urgent Target Vessel Revascularization, or Thrombotic "Bailout"</b>				
48 Hours (primary endpoint)	108 (10.5%)	69 (6.6%)	0.629 (0.471, 0.840)	0.0015
30 Days	120 (11.7%)	78 (7.5%)	0.640 (0.488, 0.840)	0.0011
<b>Death, MI, or Urgent Target Vessel Revascularization</b>				
48 Hours	95 (9.3%)	62 (6.0%)	0.643 (0.472, 0.875)	0.0045
30 Days (key secondary endpoint)	107 (10.4%)	71 (6.8%)	0.653 (0.490, 0.871)	0.0034
<b>Death or MI</b>				
48 Hours	94 (9.2%)	57 (5.5%)	0.597 (0.435, 0.820)	0.0013
30 Days	104 (10.2%)	66 (6.3%)	0.625 (0.465, 0.840)	0.0016

The need for thrombotic "bailout" was significantly reduced with eptifibatid at 48 hours (2.1% for placebo, 1.0% for eptifibatid; p=0.029). Consistent with previous studies of GP IIb/IIIa inhibitors, most of the benefit achieved acutely with eptifibatid was in the reduction of MI. Eptifibatid reduced the occurrence of MI at 48 hours from 9.0% for placebo to 5.4% (p=0.0015) and maintained that effect with significance at 30 days.

Follow-up (12 month) mortality data were available for 2024 patients (1017 on eptifibatid) enrolled in the ESPRIT trial (98.1% of the initial enrollment). Twelve-month clinical event data were available for 1964 patients (98% on eptifibatid) representing 95.2% of the initial enrollment. As shown in Table 6, the treatment effect of eptifibatid seen at 48 hours and 30 days appeared preserved at 6 months and 1 year. Most of the benefit was in reduction of MI.

**Table 6  
Clinical Events at 6 months and 1 year in the ESPRIT Study**

	Placebo (n=1024)	Eptifibatid 180/2.0/180 (n=1040)	Hazard Ratio (95% CI)
<b>Death, MI, or Target Vessel Revascularization</b>			
6 Months	187 (18.5%)	146 (14.3%)	0.744 (0.599, 0.924)
1 Year	222 (22.1%)	178 (17.5%)	0.762 (0.626, 0.929)
<b>Death, MI</b>			
6 Months	117 (11.5%)	77 (7.4%)	0.631 (0.473, 0.841)
1 Year	126 (12.4%)	83 (8.0%)	0.630 (0.478, 0.832)

Percentages are Kaplan-Meier event rates.

**INDICATIONS AND USAGE** INTEGRILIN® is indicated:

- For the treatment of patients with acute coronary syndrome (unstable angina/non-ST-segment elevation myocardial infarction), including patients who are to be managed medically and those undergoing percutaneous coronary intervention (PCI). In this setting, INTEGRILIN has been shown to decrease the rate of a combined endpoint of death or new myocardial infarction.
- For the treatment of patients undergoing PCI, including those undergoing intracoronary stenting. In this setting, INTEGRILIN has been shown to decrease the rate of a combined endpoint of death, new myocardial infarction, or need for urgent intervention.

In the IMPACT II, PURSUIT and ESPRIT studies of eptifibatid, most patients received heparin and aspirin, as described in CLINICAL TRIALS.

**CONTRAINDICATIONS** Treatment with eptifibatid is contraindicated in patients with:

- A history of bleeding diathesis, or evidence of active abnormal bleeding within the previous 30 days.
- Severe hypertension (systolic blood pressure >200 mm Hg or diastolic blood pressure >110 mm Hg) not adequately controlled on antihypertensive therapy.
- Major surgery within the preceding 6 weeks.
- History of stroke within 30 days or any history of hemorrhagic stroke.
- Current or planned administration of another parenteral GP IIb/IIIa inhibitor.
- Dependency on renal dialysis.
- Known hypersensitivity to any component of the product.

**WARNINGS** Bleeding. Bleeding is the most common complication encountered during eptifibatid therapy. Administration of eptifibatid is associated with an increase in major and minor bleeding, as classified by the criteria of the Thrombolysis in Myocardial Infarction Study group (TIMI), (see **ADVERSE REACTIONS**). Most major bleeding associated with eptifibatid has been at the arterial access site for cardiac catheterization or from the gastrointestinal or genitourinary tract.

In patients undergoing percutaneous coronary interventions, patients receiving eptifibatid experience an increased incidence of major bleeding compared to those receiving placebo without a significant increase in transfusion requirement. Special care should be employed to minimize the risk of bleeding among these patients (see **PRECAUTIONS**). If bleeding cannot be controlled with pressure, infusion of eptifibatid and concomitant heparin should be stopped immediately.

**Renal Insufficiency.** Approximately 50% of eptifibatid is cleared by the kidney in patients with normal renal function. Total drug clearance is decreased by approximately 50% and steady-state plasma eptifibatid concentrations are doubled in patients with an estimated creatinine clearance <50 mL/min (using the Cockcroft-Gault equation). Therefore, the infusion dose should be reduced to 1 µg/kg/min in such patients (see **DOSE AND ADMINISTRATION** section). There has been no clinical experience in patients dependent on dialysis.

**Platelet Count <100,000/mm<sup>3</sup>.** Because it is an inhibitor of platelet aggregation, caution should be exercised when administering eptifibatid to patients with a platelet count <100,000/mm<sup>3</sup>; there has been no clinical experience with eptifibatid initiated in patients with a platelet count <100,000/mm<sup>3</sup>.

**PRECAUTIONS** Bleeding Precautions Care of the Femoral Artery Access Site in Patients Undergoing Percutaneous Coronary Intervention (PCI). In patients undergoing PCI, treatment with eptifibatid is associated with an increase in major and minor bleeding at the site of arterial sheath placement. After PCI, eptifibatid infusion should be continued until hospital discharge or up to 18-24 hours, whichever comes first. Heparin use is discouraged after the PCI procedure. Early sheath removal is encouraged while eptifibatid is being infused. Prior to removing the sheath, it is recommended that heparin be discontinued for 3-4 hours and an aPTT of <45 seconds or ACT <150 seconds be achieved. In any case, both heparin and eptifibatid should be discontinued and sheath hemostasis should be achieved at least 2-4 hours before hospital discharge.

**Use of Thrombolytics, Anticoagulants, and Other Antiplatelet Agents.** In the IMPACT II, PURSUIT and ESPRIT studies, eptifibatid was used concomitantly with unfractionated heparin and aspirin (see **CLINICAL STUDIES**). In the ESPRIT study, clopidogrel or ticlopidine were used routinely starting the day of PCI. Because eptifibatid inhibits platelet aggregation, caution should be employed when it is used with other drugs that affect hemostasis, including thrombolytics, oral anticoagulants, non-steroidal anti-inflammatory drugs, and dipyridamol. To avoid potentially additive pharmacologic effects, concomitant treatment with other inhibitors of platelet receptor GP IIb/IIIa should be avoided.

There is only a small experience with concomitant use of eptifibatid and thrombolytics. In a study of 180 patients with acute myocardial infarction (AMI), eptifibatid (in regimens up to a bolus of 180 µg/kg followed by a continuous infusion of 0.75 µg/kg/min for 24 hours) was administered concomitantly with the approved "accelerated" regimen of alteplase, a thrombolytic agent. The studied regimens of eptifibatid did not increase the incidence of major bleeding or transfusion compared to the incidence seen when alteplase was given alone.

In the IMPACT II study, 15 patients received a thrombolytic agent in conjunction with the 135/0.5 dosing regimen, 2 of whom experienced a major bleed. In the PURSUIT study, 40 patients who received eptifibatid at the 180/2.0 dosing regimen received a thrombolytic agent, 10 of whom experienced a major bleed.

In another AMI study involving 181 patients, eptifibatid (in regimens up to a bolus of 180 µg/kg followed by a continuous infusion of up to 2.0 µg/kg/min for up to 72 hours) was administered concomitantly with streptokinase (1.5 million units over 60 minutes), another thrombolytic agent. At the highest studied infusion rates (1.3 µg/kg/min and 2.0 µg/kg/min), eptifibatid was associated with an increase in the incidence of bleeding and transfusions compared to the incidence seen when streptokinase was given alone.

These limited data on the use of eptifibatid in patients receiving thrombolytic agents do not allow an estimate of the bleeding risk associated with concomitant use of thrombolytics. Systemic thrombolytic therapy should be used with caution in patients who have received eptifibatid.

**Minimization of Vascular and Other Trauma.** Arterial and venous punctures, intramuscular injections, and the use of urinary catheters, nasotracheal intubation, and nasogastric tubes should be minimized. When obtaining intravenous access, non-compressible sites (e.g., subclavian or jugular veins) should be avoided.

**Laboratory Tests.** Before infusion of eptifibatid, the following laboratory tests should be performed to identify pre-existing hemostatic abnormalities: hematocrit or hemoglobin, platelet count, serum creatinine, and PT/aPTT. In patients undergoing PCI, the activated clotting time (ACT) should also be measured.

**Maintaining Target aPTT and ACT.** The aPTT should be maintained between 50 and 70 seconds unless PCI is to be performed. In patients treated with heparin, bleeding can be minimized by close monitoring of the aPTT. Table 7 displays the risk of major bleeding according to the maximum aPTT attained within 72 hours in the PURSUIT study.

**Table 7  
Major Bleeding by Maximal aPTT Within 72 Hours in the PURSUIT Study**

	Placebo n(%)	Eptifibatid 180/1.3* n(%)	Eptifibatid 180/2.0 n(%)
Maximum aPTT (seconds)			
< 50	44/721 (6.1%)	21/244 (8.6%)	44/743 (5.9%)
50 - 70 (recommended)	92/908 (10.1%)	28/259 (10.8%)	99/883 (11.2%)
> 70	281/2786 (10.1%)	99/891 (11.1%)	345/2811 (12.3%)

\* Administered only until the first interim analysis

The ESPRIT study stipulated a target ACT of 200 to 300 seconds during PCI. Patients receiving eptifibatid 180/2.0/180 (mean ACT 284 seconds) experienced an increased incidence of bleeding relative to placebo (mean ACT 276 seconds), primarily at the femoral artery access site. At these lower ACTs, bleeding was less than previously reported with eptifibatid in the PURSUIT and IMPACT II studies.

The aPTT or ACT should be checked prior to arterial sheath removal. The sheath should not be removed unless the aPTT is <45 seconds or the ACT is <150 seconds.

**Thrombocytopenia.** If the patient experiences a confirmed platelet decrease to <100,000/mm<sup>3</sup>, INTEGRILIN® and heparin should be discontinued and the condition appropriately monitored and treated.

**Drug Interactions.** Enoxaparin dosed as a 1.0 mg/kg subcutaneous injection q12h for four doses did not alter the pharmacokinetics of eptifibatid or the level of platelet aggregation in healthy adults.

**Geriatric Use.** The PURSUIT and IMPACT II clinical studies enrolled patients up to the age of 94 years (45% were age 65 and over; 12% were age 75 and older). There was no apparent difference in efficacy between older and younger patients treated with eptifibatid. The incidence of bleeding complications was higher in the elderly in both placebo and eptifibatid groups, and the incremental risk of eptifibatid-associated bleeding was greater in the older patients. No dose adjustment was made for elderly patients, but patients over 75 years of age had to weigh at least 50 kg to be enrolled in the PURSUIT study; no such limitation was stipulated in the ESPRIT study (see also **ADVERSE REACTIONS**).

**Carcinogenesis, Mutagenesis, Impairment of Fertility.** No long-term studies in animals have been performed to evaluate the carcinogenic potential of eptifibatid. Eptifibatid was not genotoxic in the Ames test, the mouse lymphoma cell (L 5178Y, TK+/-) forward mutation test, the human lymphocyte chromosome aberration test, or the mouse micronucleus test. Administered by continuous intravenous infusion at total daily doses up to 72 mg/kg/day (about 4 times the recommended maximum daily human dose on a body surface area basis), eptifibatid had no effect on fertility and reproductive performance of male and female rats.

**Pregnancy.** Pregnancy Category B. Teratology studies have been performed by continuous intravenous infusion of eptifibatid in pregnant rats at total daily doses of up to 72 mg/kg/day (about 4 times the recommended maximum daily human dose on a body surface area basis) and in pregnant rabbits at total daily doses of up to 36 mg/kg/day (also about 4 times the recommended maximum daily human dose on a body surface area basis). These studies revealed no evidence of harm to the fetus due to eptifibatid. There are, however, no adequate and well-controlled studies in pregnant women with eptifibatid. Because animal reproduction studies are not always predictive of human response, eptifibatid should be used during pregnancy only if clearly needed.

**Pediatric Use.** Safety and effectiveness of eptifibatid in pediatric patients have not been studied.

**Nursing Mothers.** It is not known whether eptifibatid is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when eptifibatid is administered to a nursing mother.

**ADVERSE REACTIONS** A total of 16,782 patients were treated in the Phase III clinical trials (PURSUIT, ESPRIT and IMPACT II). These 16,782 patients had a mean age of 62 years (range 20 to 94 years). Eighty-nine percent of the patients were Caucasian, with the remainder being predominantly Black (5%) and Hispanic (5%). Sixty-eight percent were men. Because of the different regimens used in PURSUIT, IMPACT II and ESPRIT, data from the three studies were not pooled.

**Bleeding.** The incidences of bleeding events and transfusions in the PURSUIT, IMPACT II and ESPRIT studies are shown in Table 8. Bleeding was classified as major or minor by the criteria of the TIMI study group. Major bleeding events consisted of intracranial hemorrhage and other bleeding that led to decreases in hemoglobin greater than 5 g/dL. Minor bleeding events included spontaneous gross hematuria, spontaneous hematemesis, other observed blood loss with a hemoglobin decrease of more than 3 g/dL, and other hemoglobin decreases that were greater than 4 g/dL but less than 5 g/dL. In patients who received transfusions, the corresponding loss in hemoglobin was estimated through an adaptation of the method of Landefeld *et al.*

**Table 8  
Bleeding Events and Transfusions in the PURSUIT, ESPRIT and IMPACT II Studies**

	PURSUIT		
	Placebo n (%)	Eptifibatid 180/1.3* n (%)	Eptifibatid 180/2.0 n (%)
Patients	4696	1472	4679
Major bleeding <sup>a</sup>	425 (9.3%)	152 (10.5%)	498 (10.8%)
Minor bleeding <sup>a</sup>	347 (7.6%)	152 (10.5%)	604 (13.1%)
Requiring Transfusions <sup>b</sup>	490 (10.4%)	188 (12.8%)	601 (12.8%)
	ESPRIT		
	Placebo n (%)	Eptifibatid 180/2.0/180 n (%)	
Patients	1024	1040	
Major bleeding <sup>a</sup>	4 (0.4%)	13 (1.3%)	
Minor bleeding <sup>a</sup>	18 (2.0%)	29 (3.0%)	
Requiring Transfusions <sup>b</sup>	11 (1.1%)	16 (1.5%)	
	IMPACT II		
	Placebo n (%)	Eptifibatid 135/0.5 n (%)	Eptifibatid 135/0.75 n (%)
Patients	1285	1300	1286
Major bleeding <sup>a</sup>	55 (4.5%)	55 (4.4%)	58 (4.7%)
Minor bleeding <sup>a</sup>	115 (9.3%)	146 (11.7%)	177 (14.2%)
Requiring Transfusions <sup>b</sup>	66 (5.1%)	71 (5.5%)	74 (5.8%)

Note: denominator is based on patients for whom data are available

\* Administered only until the first interim analysis

<sup>a</sup> For major and minor bleeding, patients are counted only once according to the most severe classification.

<sup>b</sup> Includes transfusions of whole blood, packed red blood cells, fresh frozen plasma, cryoprecipitate, platelets, and autotransfusion during the initial hospitalization.

The majority of major bleeding events in the ESPRIT study occurred at the vascular access site (1 and 8 patients, or 0.1% and 0.8% in the placebo and eptifibatid groups, respectively). Bleeding at "other" locations occurred in 0.2% and 0.4% of patients, respectively.

In the PURSUIT study, the greatest increase in major bleeding in eptifibatid-treated patients compared to placebo-treated patients was associated with bleeding at the femoral artery access site (2.8% versus 1.3%). Oropharyngeal (primarily gingival), genito-urinary, gastrointestinal, and retroperitoneal bleeding were also seen more commonly in eptifibatid-treated patients compared to placebo-treated patients.

Among patients experiencing a major bleed in the IMPACT II study, an increase in bleeding on eptifibatid versus placebo was observed only for the femoral artery access site (3.2% versus 2.8%).

Table 9 displays the incidence of TIMI major bleeding according to the cardiac procedures carried out in the PURSUIT study. The most common bleeding complications were related to cardiac revascularization (CABG-related or femoral artery access site bleeding). A corresponding table for ESPRIT is not presented as every patient underwent PCI in the ESPRIT study and only 11 patients underwent CABG.

**Table 9**  
**Major Bleeding by Procedures in the PURSUIT Study**

	Placebo n(%)	Eptifibatid 180/1.3* n(%)	Eptifibatid 180/2.0 n(%)
Patients	4577	1451	4604
Overall Incidence of Major Bleeding	425 (9.3%)	152 (10.5%)	498 (10.8%)
Breakdown by Procedure:			
CABG	375 (8.2%)	123 (8.5%)	377 (8.2%)
Angioplasty without CABG	27 (0.6%)	16 (1.1%)	64 (1.4%)
Angiography without Angioplasty or CABG	11 (0.2%)	7 (0.5%)	29 (0.6%)
Medical Therapy Only	12 (0.3%)	6 (0.4%)	28 (0.6%)

Denominators are based on the total number of patients whose TIMI classification was resolved.

\*Administered only until the first interim analysis

In the PURSUIT and ESPRIT studies, the risk of major bleeding with eptifibatid increased as patient weight decreased. This relationship was most apparent for patients weighing less than 70 kg.

Bleeding adverse events resulting in discontinuation of study drug were more frequent among patients receiving eptifibatid than placebo (4.6% versus 0.9% in ESPRIT, 8% versus 1% in PURSUIT, 3.5% versus 1.9% in IMPACT II).

**Intracranial Hemorrhage and Stroke.** Intracranial hemorrhage was rare in the PURSUIT, IMPACT II and ESPRIT clinical studies. In the PURSUIT study, 3 patients in the placebo group, 1 patient in the group treated with eptifibatid 180/1.3 and 5 patients in the group treated with eptifibatid 180/2.0 experienced a hemorrhagic stroke. The overall incidence of stroke was 0.5% in patients receiving eptifibatid 180/1.3, 0.7% in patients receiving eptifibatid 180/2.0, and 0.8% in placebo patients.

In the IMPACT II study, intracranial hemorrhage was experienced by 1 patient treated with eptifibatid 135/0.5, 2 patients treated with eptifibatid 135/0.75 and 2 patients in the placebo group. The overall incidence of stroke was 0.5% in patients receiving 135/0.5 eptifibatid, 0.7% in patients receiving eptifibatid 135/0.75 and 0.7% in the placebo group.

In the ESPRIT study, there were 3 hemorrhagic strokes, 1 in the placebo group and 2 in the eptifibatid group. In addition there was 1 case of cerebral infarction in the eptifibatid group.

**Thrombocytopenia.** In the PURSUIT and IMPACT II studies, the incidence of thrombocytopenia (<100,000/mm<sup>3</sup> or ≥50% reduction from baseline) and the incidence of platelet transfusions were similar between patients treated with eptifibatid and placebo. In the ESPRIT study, the incidence was 0.6% in the placebo group and 1.2% in the eptifibatid group.

**Allergic Reactions.** In the PURSUIT study, anaphylaxis was reported in 7 patients receiving placebo (0.15%) and 7 patients receiving eptifibatid 180/2.0 (0.16%). In the IMPACT II study, anaphylaxis was reported in 1 patient (0.08%) on placebo and in no patients on eptifibatid. In the IMPACT II study, 2 patients (1 patient (0.04%) receiving eptifibatid and 1 patient (0.08%) receiving placebo) discontinued study drug because of allergic reactions. In the ESPRIT study, there were no cases of anaphylaxis reported. There were 3 patients who suffered an allergic reaction, 1 on placebo and 2 on eptifibatid. In addition, 1 patient in the placebo group was diagnosed with urticaria.

The potential for development of antibodies to eptifibatid has been studied in 433 subjects. Eptifibatid was non-antigenic in 412 patients receiving a single administration of eptifibatid (135 µg/kg bolus followed by a continuous infusion of either 0.5 µg/kg/min or 0.75 µg/kg/min), and in 21 subjects to whom eptifibatid (135 µg/kg bolus followed by a continuous infusion of 0.75 µg/kg/min) was administered twice, 28 days apart. In both cases, plasma for antibody detection was collected approximately 30 days after each dose. The development of antibodies to eptifibatid at higher doses has not been evaluated.

**Other Adverse Reactions.** In the PURSUIT and ESPRIT studies, the incidence of serious non-bleeding adverse events was similar in patients receiving placebo or eptifibatid (19% and 19%, respectively in PURSUIT, 6% and 7%, respectively in ESPRIT). In PURSUIT, the only serious non-bleeding adverse event that occurred at a rate of at least 1% and was more common with eptifibatid than placebo (7% versus 6%) was hypotension. Most of the serious non-bleeding events consisted of cardiovascular events typical of an unstable angina population. In the IMPACT II study, serious non-bleeding events that occurred in greater than 1% of patients were uncommon and similar in incidence between placebo- and eptifibatid-treated patients.

Discontinuation of study drug due to adverse events other than bleeding was uncommon in the PURSUIT, IMPACT II and ESPRIT studies, with no single event occurring in >0.5% of the study population (except for "other" in the ESPRIT study). In the PURSUIT study, non-bleeding adverse events leading to discontinuation occurred in the eptifibatid and placebo groups in the following body systems with an incidence of ≥0.1%: cardiovascular system (0.3% and 0.3%), digestive system (0.1% and 0.1%), hemic/lymphatic system (0.1% and 0.1%), nervous system (0.3% and 0.4%), urogenital system (0.1% and 0.1%), and whole body system (0.2% and 0.2%). In the ESPRIT study, the following non-bleeding adverse events leading to discontinuation occurred in the eptifibatid and placebo groups with an incidence of ≥0.1%: "other" (1.2% and 1.1%). In the IMPACT II study, non-bleeding adverse events leading to discontinuation occurred in the 135/0.5 eptifibatid and placebo groups in the following body systems with an incidence of ≥0.1%: whole body (0.3% and 0.1%), cardiovascular system (1.4% and 1.4%), digestive system (0.2% and 0%), hemic/lymphatic system (0.2% and 0%), nervous system (0.3% and 0.2%), and respiratory system (0.1% and 0.1%).

**Post-Marketing Experience.** The following adverse events have been reported in post-marketing experience, primarily with eptifibatid in combination with heparin and aspirin: cerebral, GI and pulmonary hemorrhage. Fatal bleeding events have been reported. Acute profound thrombocytopenia has been reported.

**OVERDOSAGE** There has been only limited experience with overdosage of eptifibatid. There were 8 patients in the IMPACT II study, 9 patients in the PURSUIT study and no patient in the ESPRIT study who received bolus doses and/or infusion doses more than double those called for in the protocols. None of these patients experienced an intracranial bleed or other major bleeding.

Eptifibatid was not lethal to rats, rabbits, or monkeys when administered by continuous intravenous infusion for 90 minutes at a total dose of 45 mg/kg (about 2 to 5 times the recommended maximum daily human dose on a body surface area basis). Symptoms of acute toxicity were loss of righting reflex, dyspnea, ptosis, and decreased muscle tone in rabbits and petechial hemorrhages in the femoral and abdominal areas of monkeys.

From *in vitro* studies, eptifibatid is not extensively bound to plasma proteins and thus may be cleared from plasma by dialysis.

**DOSE AND ADMINISTRATION** The safety and efficacy of eptifibatid has been established in clinical studies that employed concomitant use of heparin and aspirin. Different dose regimens of eptifibatid were used in the major clinical studies. (See **CLINICAL STUDIES**.)

**Acute Coronary Syndrome** The recommended adult dosage of eptifibatid in patients with acute coronary syndrome and normal renal function is an intravenous bolus of 180 µg/kg as soon as possible following diagnosis, followed by a continuous infusion of 2.0 µg/kg/min until hospital discharge or initiation of CABG surgery, up to 72 hours. If a patient is to undergo a percutaneous coronary intervention (PCI) while receiving eptifibatid, the infusion should be continued up to hospital discharge, or for up to 18-24 hours after the procedure, whichever comes first, allowing for up to 96 hours of therapy.

**Patients with Creatinine Clearance less than 50 mL/min**

The recommended adult dosage of eptifibatid in patients with acute coronary syndrome with an estimated creatinine clearance (using the Cockcroft-Gault equation) <50 mL/min is an intravenous bolus of 180 µg/kg as soon as possible following diagnosis, immediately followed by a continuous infusion of 1.0 µg/kg/min.

**Percutaneous Coronary Intervention (PCI)** The recommended adult dosage of eptifibatid in patients with normal

renal function is an intravenous bolus of 180 µg/kg administered immediately before the initiation of PCI followed by a continuous infusion of 2.0 µg/kg/min and a second 180 µg/kg bolus 10 minutes after the first bolus. Infusion should be continued until hospital discharge, or for up to 18 to 24 hours, whichever comes first. A minimum of 12 hours of infusion is recommended.

**Patients with Creatinine Clearance less than 50 mL/min**

The recommended adult dose of eptifibatid in patients with an estimated creatinine clearance (using the Cockcroft-Gault equation) <50 mL/min is an intravenous bolus of 180 µg/kg administered immediately before the initiation of the procedure, immediately followed by a continuous infusion of 1.0 µg/kg/min and a second 180 µg/kg bolus administered 10 minutes after the first.

In patients who undergo coronary artery bypass graft surgery, eptifibatid infusion should be discontinued prior to surgery.

\*Use the Cockcroft-Gault equation with actual body weight to calculate creatinine clearance is calculated as:

**Males:**  $(140 - \text{age}) \times (\text{actual body wt in kg}) / 72 \times (\text{serum creatinine})$  **Females:**  $(140 - \text{age}) \times (\text{actual body wt in kg}) \times (0.85) / 72 \times (\text{serum creatinine})$

**Aspirin and Heparin Dosing Recommendations**

In the clinical trials that showed eptifibatid to be effective, most patients received concomitant aspirin and heparin. The recommended aspirin and heparin doses to be used are as follows:

**Acute Coronary Syndrome**

**Aspirin:**

160 – 325 mg orally initially and daily thereafter

**Heparin:**

Target aPTT 50 – 70 seconds during medical management

- If weight ≥70 kg, 5000 U bolus followed by infusion of 1000 U/hr.
- If weight <70 kg, 60 U/kg bolus followed by infusion of 12 U/kg/hr.

Target ACT 200 – 300 seconds during PCI

- If heparin is initiated prior to PCI, additional boluses during PCI to maintain an ACT target of 200 – 300 seconds.
- Heparin infusion after the PCI is discouraged.

**PCI**

**Aspirin:**

160 – 325 mg orally 1 – 24 hours prior to PCI and daily thereafter

**Heparin:**

Target ACT 200 – 300 seconds

- 60 U/kg bolus initially in patients not treated with heparin within 6 hours prior to PCI.
- Additional boluses during PCI to maintain ACT within target.
- Heparin infusion after the PCI is strongly discouraged.

Patients requiring thrombolytic therapy should have eptifibatid infusions stopped.

**Instructions for Administration**

1. Like other parenteral drug products, INTEGRILIN® solutions should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.
2. INTEGRILIN may be administered in the same intravenous line as alteplase, atropine, dobutamine, heparin, lidocaine, meperidine, metoprolol, midazolam, morphine, nitroglycerin, or verapamil. INTEGRILIN should not be administered through the same intravenous line as furosemide.
3. INTEGRILIN may be administered in the same IV line with 0.9% NaCl or 0.9% NaCl/5% dextrose. With either vehicle, the infusion may also contain up to 60 mcg/L of potassium chloride. No incompatibilities have been observed with intravenous administration sets. No compatibility studies have been performed with PVC bags.
4. The bolus dose(s) of INTEGRILIN should be withdrawn from the 10-mL vial into a syringe. The bolus dose(s) should be administered by IV push.
5. Immediately following the bolus dose administration, a continuous infusion of INTEGRILIN should be initiated. When using an intravenous infusion pump, INTEGRILIN should be administered undiluted directly from the 100-mL vial. The 100-mL vial should be spiked with a vented infusion set. Care should be taken to center the spike within the circle on the stopper top.

INTEGRILIN is to be administered by volume according to patient weight. Patients should receive INTEGRILIN according to the following table:

**INTEGRILIN Dosing Charts by Weight**

Patient Weight		180 µg/kg Bolus Volume	2.0 µg/kg/min Infusion Volume	1.0 µg/kg/min Infusion Volume
(kg)	(lb)	(from 2 mg/mL vial)	(from 0.75 mg/mL 100-mL vial)	(from 0.75 mg/mL 100-mL vial)
37-41	81-91	3.4 mL	2.0 mL/h	6.0 mL/h
42-46	92-102	4.0 mL	2.5 mL/h	7.0 mL/h
47-53	103-117	4.5 mL	3.0 mL/h	8.0 mL/h
54-59	118-130	5.0 mL	3.5 mL/h	9.0 mL/h
60-65	131-143	5.6 mL	3.8 mL/h	10.0 mL/h
66-71	144-157	6.2 mL	4.0 mL/h	11.0 mL/h
72-78	158-172	6.8 mL	4.5 mL/h	12.0 mL/h
79-84	173-185	7.3 mL	5.0 mL/h	13.0 mL/h
85-90	186-198	7.9 mL	5.3 mL/h	14.0 mL/h
91-96	199-212	8.5 mL	5.6 mL/h	15.0 mL/h
97-103	213-227	9.0 mL	6.0 mL/h	16.0 mL/h
104-109	228-240	9.5 mL	6.4 mL/h	17.0 mL/h
110-115	241-253	10.2 mL	6.8 mL/h	18.0 mL/h
116-121	254-267	10.7 mL	7.0 mL/h	19.0 mL/h
>121	>267	11.3 mL	7.5 mL/h	20.0 mL/h

**HOW SUPPLIED** INTEGRILIN® (eptifibatid) Injection is supplied as a sterile solution in 10-mL vials containing 20 mg of eptifibatid (NDC 0085-1177-01) and 100-mL vials containing either 75 mg of eptifibatid (NDC 0085-1136-01) or 200 mg of eptifibatid (NDC 0085-1177-02).

Vials should be stored refrigerated at 2-8°C (36-46°F). Vials may be transferred to room temperature storage\* for a period not to exceed 2 months. Upon transfer, vial cartons must be marked by the dispensing pharmacist with a "DISCARD BY" date (2 months from the transfer date or the labeled expiration date, whichever comes first).

Do not use beyond the labeled expiration date. Protect from light until administration. Discard any unused portion left in the vial.

\* USP controlled Room Temperature: 25°C (77°F) with excursions permitted between 15-30°C (59-86°F).

**Rx only**



INTEGRILIN is a registered trademark of Millennium Pharmaceuticals, Inc. Manufactured for Schering Corporation, Kenilworth, NJ 07033 USA. U.S. Patent Nos. 5,686,570; 5,747,447; 5,756,451; 5,807,825; and 5,968,902.