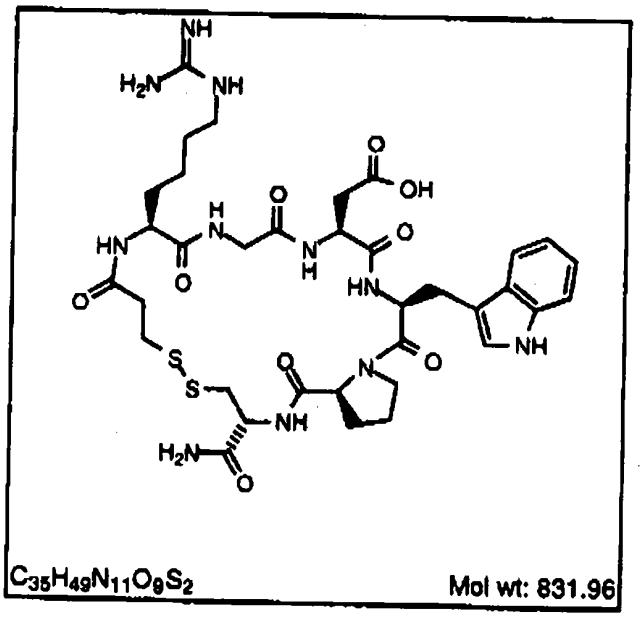
INTEGRILIN® (eptifibatide) INJECTION

For Intravenous Administration

DESCRIPTION

Eptifibatide is a cyclic heptapeptide containing six amino acids and one mercaptopropionyl (des-amino cysteinyl) residue. An interchain disulfide bridge is formed between the cysteine amide and the mercaptopropionyl moieties. Chemically it is N^6-(aminoiminomethyl)-N^2-(3-mercapto-1-oxopropyl-L-lysylglycyl-L-α-aspartyl-L-tryptophyl-L-prolyl-L-cysteinamide, cyclic (1→6)-disulfide. Eptifibatide binds to the platelet receptor glycoprotein (GP) IIb/IIIa of human platelets and inhibits platelet aggregation.

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



$C_{35}H_{49}N_{11}O_9S_2$ Mol wt: 831.96

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

CLINICAL PHARMACOLOGY

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

Pharmacodynamics. Infusion of eptifibatide into baboons caused a dose-dependent inhibition of *ex vivo* platelet aggregation, with complete inhibition of aggregation achieved at infusion rates greater than 5 µg/kg/min. In a baboon model that is refractory to aspirin and heparin, doses of eptifibatide 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 eptifibatide, with complete inhibition at 2 µg/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-Q-wave myocardial infarction (NQMI) and/or undergoing percutaneous coronary interventions. Studies in healthy subjects enrolled only males; patient studies enrolled approximately one third women. In these studies, eptifibatide inhibited *ex vivo* platelet aggregation induced by adenosine diphosphate (ADP) and other agonists in a dose- and concentration-dependent manner. The effect of eptifibatide was observed immediately after administration of a 180 µg/kg intravenous bolus. Table 1 shows

the effects of the two doses of eptifibatide used in the two principal clinical studies on *ex vivo* platelet aggregation induced by 20 µM ADP in PPACK-anticoagulated platelet-rich plasma and on bleeding time.

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 µg/kg bolus followed by a continuous infusion of 0.5 µg/kg/min

** 180 µg/kg bolus followed by a continuous infusion of 2.0 µg/kg/min

When administered alone, eptifibatide 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 eptifibatide. Differences among ethnic groups have not been assessed.

Pharmacokinetics. The pharmacokinetics of eptifibatide are linear and dose-proportional for bolus doses ranging from 90 to 250 µg/kg and infusion rates from 0.5 to 3 µg/kg/min. Plasma elimination half-life is approximately 2.5 hours. The recommended regimens of a bolus followed by an infusion produce an early peak level, followed by a small decline with attainment of steady state within 4-6 hours. The extent of eptifibatide binding to human plasma protein is about 25%.

Excretion and Metabolism. Clearance in patients with coronary artery disease is 55-58 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 eptifibatide, deamidated eptifibatide, and other, more polar metabolites. No major metabolites have been detected in human plasma. Clinical studies have included 2418 patients with serum creatinine between 1 and 2 mg/dL (for the 180 µg/kg bolus and the 2 µg/kg/min infusion) and 7 patients with serum creatinine between 2 and 4 mg/dL (for the 135 µg/kg bolus and the 0.5 µg/kg/min infusion), without dose adjustment. No data are available in patients with more severe degrees of renal impairment, but plasma eptifibatide levels are expected to be higher in such patients (see CONTRAINDICATIONS).

Special Populations. Patients in clinical studies were older than the subjects in clinical pharmacology studies, and they had lower total body eptifibatide clearance and higher eptifibatide plasma levels. Clinical studies were conducted in patients aged 20 to 94 years with coronary artery disease without dose adjustment for age. Because patients over 75 years of age were enrolled into the PURSUIT clinical study only if their body weight exceeded 50 kg, minimal data are available on lighter-weight patients over 75 years of age. Men and women showed no important differences in the pharmacokinetics of eptifibatide.

CLINICAL STUDIES

Eptifibatide was studied in two placebo-controlled, randomized studies, one (PURSUIT) in patients with acute coronary syndrome (unstable angina (UA) or non-Q-wave myocardial infarction (NQMI)), the other (IMPACT II) in patients about to undergo a percutaneous cardiovascular intervention (PCI; balloon angioplasty in most cases, but sometimes directional atherectomy, transluminal extraction catheter atherectomy, rotational ablation atherectomy, or excimer-laser angioplasty).

Acute coronary syndrome is defined as prolonged (≥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 "non-Q-wave myocardial infarction" but excludes myocardial infarction that is associated with Q waves or greater degrees of ST-segment elevation.

PURSUIT was a 726-center, 27-country, double-blind, randomized, placebo-controlled study in 10,948 patients presenting with UA or NQMI. Patients could be enrolled only if they had experienced cardiac ischemia at rest (≥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 mg/dL, dependency on renal dialysis, or platelet count <100,000/mm^3.

Patients were randomized to either placebo, eptifibatide 180 µg/kg bolus followed by a 2 µg/kg/min infusion (180/2.0), or eptifibatide 180 µg/kg bolus followed by a 1.3 µg/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 eptifibatide 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.

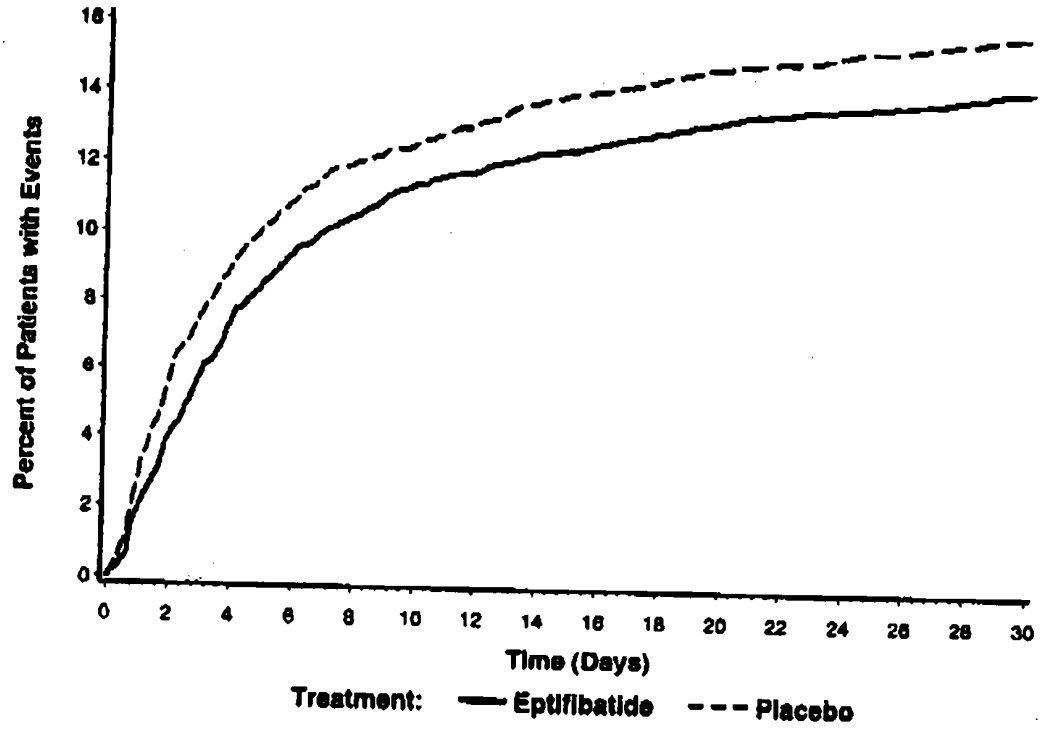
The primary endpoint of the study was the occurrence of death from any cause or new myocardial infarction (MI) (evaluated by a blinded Clinical Endpoints Committee) within 30 days of randomization.

Compared to placebo, eptifibatide administered as a 180 µg/kg bolus followed by a 2 µg/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 eptifibatide 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

Death or MI	Placebo (n = 4739) n (%)	Eptifibatide (180/2.0) (n = 4722) n (%)	p-value
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



The effect of eptifibatide in PURSUIT did not appear to vary with patients' age. There were too few non-Caucasian patients to reach any conclusion as to possible differences related to race. Analysis of the PURSUIT results reveals a complex interaction of treatment, gender, and region. Throughout the world, eptifibatide was significantly less beneficial in women than in men, and in the overall study eptifibatide in women was nonsignificantly worse than placebo. These results were, however, strikingly heterogeneous across the several regions; eptifibatide appeared much worse than placebo in women in Latin America, while effects in men and women were scarcely distinguishable (relative risk reductions of 23% and 18%, respectively) in the U.S. and Canada. These results may reflect (a) genuine biological interactions between eptifibatide and gender, (b) interactions between eptifibatide and unknown international differences in concomitant therapy delivered to men and women, and (c) the play of chance, but the relative contributions of these possible factors are unknown.

Treatment with eptifibatide 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	**Eptifibatide 180/2.0**
Overall Patient Population	n=4739	n=4722
- At 72 hours	7.6%	5.9%
Patients undergoing early PCI	n=631	n=619
- Pre-procedure (nonfatal MI only)	5.5%	1.8%
- At 72 hours	14.4%	9.0%
Patients not undergoing early PCI	n=4108	n=4103
- At 72 hours	6.5%	5.4%

All of the effect of eptifibatide 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 eptifibatide 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 eptifibatide 180/2.0.

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^3, 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. 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 µg/kg bolus followed by a continuous infusion of 0.5 µg/kg/min of eptifibatide (135/0.5); 2) 135 µg/kg bolus followed by a continuous infusion of 0.75 µg/kg/min of eptifibatide (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 eptifibatide regimen reduced the rate of death, MI, or urgent intervention, although at 30 days, this finding was statistically significant only in the lower-dose eptifibatide group. As in the PURSUIT study, the effects of eptifibatide were seen early and persisted throughout the 30-day period.

Table 4
Clinical Events in the IMPACT II Study

	Placebo	**Eptifibatide (135/0.5)**	**Eptifibatide (135/0.75)**
	n (%)	**n (%)**	**n (%)**
Patients	1285	1300	1286
Abrupt Closure	65 (5.1%)	36 (2.8%)	43 (3.3%)
p-value vs. placebo		0.003	0.030
Death, MI, or Urgent Intervention			
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
Death or MI			
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

At the time of randomization, approximately 25% of the IMPACT II patients suffered from only chronic stable angina, or had had no angina at all since a remote (more than 14 days prior) myocardial infarction. At the other extreme, approximately 40% of the IMPACT II patients had ongoing acute coronary syndromes, including patients with rest angina, others with refractory recurrent angina, others with early post-infarction angina, and others about to receive percutaneous interventions during or immediately following acute myocardial infarction. The remaining patients had various histories of recent and remote acute coronary syndromes; data are not available to describe what fraction of these underwent PCI within only a day or two of an acute episode. The IMPACT II study was not powered to obtain stable estimates of efficacy in subpopulations defined by degree of acuity, but (as shown in Table 5) the data suggest that the benefit of eptifibatide was not limited to patients with ongoing acute coronary syndromes.

Table 5

Clinical Events at 30 Days in the IMPACT II Study,
Stratified by Acuity at Time of Randomization

Classification of Patients (%)	Placebo n (%)	Eptifibatide 135/0.5 n (%)	Eptifibatide 135/0.75 n (%)
Ongoing ACS, MI ongoing or within past 24h (41.3%)	538 (11.5%)	532 (10.0%)	527 (10.6%)
Others (58.7%)	747 (11.6%)	768 (8.5%)	759 (9.5%)

INDICATIONS AND USAGE

INTEGRILIN is indicated:

- For the treatment of patients with acute coronary syndrome (UA/NQMI), 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. 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 clinical studies of eptifibatide, most patients received heparin and aspirin, as described in CLINICAL TRIALS.

CONTRAINDICATIONS

Treatment with eptifibatide 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.
- Platelet count <100,000/mm^3.
- Serum creatinine ≥4.0 mg/dL. In patients with serum creatinine levels between 2.0 mg/dL and 4.0 mg/dL, the 135 µg/kg bolus and 0.5 µg/kg/min infusion should be administered.

- Dependency on renal dialysis.
- Known hypersensitivity to any component of the product.

WARNINGS

Bleeding. Bleeding is the most common complication encountered during eptifibatide therapy. Administration of eptifibatide 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 eptifibatide 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 eptifibatide experience an increased incidence of major bleeding compared to those receiving placebo. 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 eptifibatide and concomitant heparin should be stopped immediately.

PRECAUTIONS

Bleeding Precautions

Care of the Femoral Artery Access Site in Patients Undergoing Percutaneous Coronary Intervention (PCI). In patients undergoing PCI, treatment with eptifibatide is associated with an increase in major and minor bleeding at the site of arterial sheath placement. After PCI, eptifibatide infusion should be continued for 20-24 hours. The femoral artery sheath may be removed during treatment with eptifibatide, but only after heparin has been discontinued and its effects largely reversed. In the IMPACT II study, heparin use was discouraged after the PCI procedure if the coronary lesion appeared

angiographically stable. Early sheath removal was encouraged in both the IMPACT II and the PURSUIT studies while study drug was being infused. Prior to removing the sheath, it was recommended that heparin be discontinued for 3-4 hours and that an aPTT of <45 seconds be documented. In any case, both heparin and eptifibatide should be discontinued and sheath hemostasis should be achieved by standard compressive techniques at least 4 hours before hospital discharge.

Use of Thrombolytics, Anticoagulants, and Other Antiplatelet Agents. In the IMPACT II and PURSUIT studies, eptifibatide was used concomitantly with heparin and aspirin (see CLINICAL STUDIES). Because eptifibatide 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, dipyridamole, ticlopidine**, and **clopidogrel**. 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 eptifibatide and **thrombolytics**. In a study of 180 patients with acute myocardial infarction (AMI), eptifibatide (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 eptifibatide 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 eptifibatide 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, eptifibatide (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), eptifibatide 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 eptifibatide 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 eptifibatide.

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 eptifibatide, 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 6 displays the risk of major bleeding according to the maximum aPTT attained within 72 hours in the PURSUIT study.

Table 6
Major Bleeding by Maximal aPTT Within 72 Hours in the PURSUIT Study

	Placebo	Eptifibatide 180/1.3*	Eptifibatide 180/2.0
	n (%)	n (%)	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

During PCI, the PURSUIT study stipulated a target ACT of between 300 and 350 seconds. Patients receiving an eptifibatide 180 µg/kg bolus followed by a 2 µg/kg/min infusion experienced an increased incidence of bleeding relative to placebo, primarily at the femoral artery access site.

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^3, INTEGRILIN and heparin should be discontinued and the condition appropriately monitored and treated.

Renal Insufficiency. Based on results of clinical studies with eptifibatide (which did not adjust dose for renal function) and the fact that the drug is cleared equally by renal and nonrenal mechanisms, dose adjustment is unnecessary for patients with mild to moderate renal impairment (serum creatinine <2 mg/dL for the 180 µg/kg bolus and the 2.0 µg/kg/min infusion and <4 mg/dL for the 135 µg/kg bolus and the 0.5 µg/kg/min infusion). For patients with serum creatinine >2 mg/dL and <4 mg/dL, eptifibatide should be administered as a

135 µg/kg bolus followed by a 0.5 µg/kg/min infusion. Plasma eptifibatide levels are expected to be higher in patients with more severe renal impairment, but no data are available for such patients or for patients on renal dialysis. *In vitro* studies have indicated that eptifibatide may be cleared from plasma by dialysis.

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 eptifibatide. The incidence of bleeding complications was higher in the elderly in both placebo and eptifibatide groups, and the incremental risk of eptifibatide-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 because of concern about an increased risk of bleeding in this subgroup (see also ADVERSE REACTIONS).

Carcinogenesis, Mutagenesis, Impairment of Fertility. No long-term studies in animals have been performed to evaluate the carcinogenic potential of eptifibatide. Eptifibatide 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), eptifibatide 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 eptifibatide 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 eptifibatide. There are, however, no adequate and well-controlled studies in pregnant women with eptifibatide. Because animal reproduction studies are not always predictive of human response, eptifibatide should be used during pregnancy only if clearly needed.

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

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

ADVERSE REACTIONS

A total of 14,718 patients were treated in the two Phase III clinical trials (PURSUIT and IMPACT II). Of these, 8737 received eptifibatide: 1300 at 135/0.5 for up to 24 hours, 1286 at 135/0.75 for up to 24 hours, 1472 at 180/1.3 for up to 72 hours, and 4679 at 180/2.0 for up to 72 hours. The other 5981 patients received placebo. These 14,718 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-seven percent were men.

Because of the different regimens used in PURSUIT and IMPACT II, data from the two studies were not pooled.

Bleeding. The incidences of bleeding events and transfusions in the PURSUIT and IMPACT II studies are shown in Table 7. 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 7
Bleeding Events and Transfusions in the PURSUIT and IMPACT II Studies

	PURSUIT		
	Placebo	**Eptifibatide 180/1.3***	**Eptifibatide 180/2.0**
	n (%)	**n (%)**	**n (%)**
Patients	4696	1472	4679
Major bleeding[a]	425 (9.3%)	152 (10.5%)	498 (10.8%)
Minor bleeding[a]	347 (7.6%)	152 (10.5%)	604 (13.1%)
Requiring Transfusions[b]	490 (10.4%)	188 (12.8%)	601 (12.8%)
	IMPACT II		
	Placebo	**Eptifibatide 135/0.5**	**Eptifibatide 135/0.75**
	n (%)	**n (%)**	**n (%)**
Patients	1285	1300	1286
Major bleeding[a]	55 (4.5%)	55 (4.4%)	58 (4.7%)
Minor bleeding[a]	115 (9.3%)	146 (11.7%)	177 (14.2%)
Requiring Transfusions[b]	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

[a] For major and minor bleeding, patients are counted only once according to the most severe classification.

[b] Includes transfusions of whole blood, packed red blood cells, fresh frozen plasma, cryoprecipitate, platelets, and autotransfusion during the initial hospitalization.

As shown in Tables 8 and 9, the overall incidence of major bleeding in these studies was strongly related to the incidence of coronary artery bypass graft (CABG) surgery; the excess bleeding seen with eptifibatide, however, was seen only among the patients who did not undergo CABG.

In the PURSUIT study, the greatest increase in major bleeding in eptifibatide-treated patients compared to placebo 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 eptifibatide-treated patients compared to placebo. Among patients experiencing a major bleed in the IMPACT II study, an increase in bleeding on eptifibatide versus placebo was observed only for the femoral artery access site (3.2% versus 2.8%).

Tables 8 and 9 display the incidence of TIMI major bleeding according to the cardiac procedures carried out in the PURSUIT and IMPACT II studies, respectively. The most common bleeding complications were related to cardiac revascularization (CABG-related or femoral artery access site bleeding).

Table 8
Major Bleeding by Procedures in the PURSUIT Study

	Placebo	Eptifibatide 180/1.3*	Eptifibatide 180/2.0
	n (%)	n (%)	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

Table 9
Major Bleeding by Procedures in the IMPACT II Study

	Placebo n (%)	Eptifibatide 135/0.5 n (%)	Eptifibatide 135/0.75 n (%)
Patients	1230	1249	1245
Overall Incidence of Major Bleeding	55 (4.5%)	55 (4.4%)	58 (4.7%)
Breakdown of Bleeding by Procedure:			
CABG	35 (2.8%)	23 (1.8%)	26 (2.1%)
Angioplasty without CABG	20 (1.6%)	32 (2.6%)	32 (2.7%)

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

In the PURSUIT study, the risk of major bleeding with eptifibatide increased inversely with patient weight. This relationship was most apparent for patients weighing less than 70 kg. These trends were not apparent in the IMPACT II study.

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

Intracranial Hemorrhage and Stroke. Intracranial hemorrhage was rare in the PURSUIT clinical study, with only 3 patients in the placebo group, 1 patient in the group treated with eptifibatide 180/1.3 and 5 patients in the group treated with eptifibatide 180/2.0 experiencing a hemorrhagic stroke within 30 days of randomization. The overall incidence of stroke was 0.5% in patients receiving eptifibatide 180/1.3, 0.7% in patients receiving eptifibatide 180/2.0, and 0.8% in placebo patients within 30 days of randomization.

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

135/0.5 eptifibatide, 0.7% in patients receiving eptifibatide 135/0.75 and 0.7% in the placebo group.

Thrombocytopenia. In the PURSUIT and IMPACT II studies, the incidence of thrombocytopenia (<100,000/mm^3 or ≥50% reduction from baseline) and the incidence of platelet transfusions were similar between patients treated with eptifibatide and placebo.

Allergic Reactions. In the IMPACT II study, anaphylaxis was reported in 1 patient (0.08%) on placebo and in no patients on eptifibatide. In the PURSUIT study, anaphylaxis was reported in 7 patients receiving placebo (0.15%) and 7 patients receiving eptifibatide 180/2.0 (0.16%). In the IMPACT II study, 2 patients (1 patient (0.04%) receiving eptifibatide and 1 patient (0.08%) receiving placebo) discontinued study drug because of allergic reactions. In the PURSUIT study, anaphylaxis was given as a reason for drug discontinuation in 3 patients (0.05%) who received eptifibatide and in none of the patients who received placebo.

The potential for development of antibodies to eptifibatide has been studied in 433 subjects. Eptifibatide was non-antigenic in 412 patients receiving a single administration of eptifibatide (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 eptifibatide (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 eptifibatide at higher doses has not been evaluated.

Other Adverse Reactions. Serious non-bleeding events occurred in 19% of the eptifibatide and 19% of the placebo patients in the PURSUIT study. The only serious non-bleeding adverse event that occurred at a rate of at least 1% and was more common with eptifibatide 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 eptifibatide-treated patients.

Discontinuation of study drug due to adverse events other than bleeding was uncommon in both the PURSUIT and IMPACT II studies, with no single event occurring in >0.5% of the study population. In the PURSUIT study, non-bleeding adverse events leading to discontinuation occurred in the eptifibatide 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 IMPACT II study, non-bleeding adverse events leading to discontinuation occurred in the 135/0.5 eptifibatide 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%).

OVERDOSAGE

There has been only limited experience with overdosage of eptifibatide. There were 8 patients in the IMPACT II study and 9 patients in the PURSUIT study who received bolus doses and/or infusion doses more than double those called for in the protocols, or who were identified by the investigator as having received an overdose. None of these patients experienced an intracranial bleed or other major bleeding.

Eptifibatide 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.

DOSAGE AND ADMINISTRATION

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

Acute Coronary Syndrome. The recommended adult dosage of eptifibatide in patients with acute coronary syndrome is an intravenous bolus of 180 µg/kg as soon as possible following diagnosis, followed by a continuous infusion of 2 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 eptifibatide, consideration can be given to decreasing the infusion rate to 0.5 µg/kg/min (the infusion rate in IMPACT II) at the time of the procedure. Infusion should be continued for an additional 20-24 hours after the procedure, allowing for up to 96 hours of therapy. In the PURSUIT Study, patients weighing more than 121 kg received a maximum bolus of 22.6 mg (11.3 mL of the 2 mg/mL injection) followed by a maximum infusion rate of 15 mg (20 mL of the 0.75 mg/mL injection) per hour.

Percutaneous Coronary Intervention (PCI) in patients not presenting with an acute coronary syndrome. The recommended adult dosage of eptifibatide in patients undergoing PCI and not presenting with an acute coronary syndrome is an intravenous bolus of 135 µg/kg administered immediately before the initiation of PCI followed by a continuous infusion of 0.5 µg/kg/min for 20-24 hours. In the IMPACT II Study, there was little experience in patients weighing more than 143 kg.

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

In the clinical trials that showed eptifibatide to be effective, most patients received concomitant aspirin and heparin. The aspirin doses used in the clinical studies were as follows:

Acute Coronary Syndrome (PURSUIT Study)	Angioplasty (IMPACT II Study)
160 mg initially, then 75-325 mg daily	75-325 mg 1-24 hours prior to intervention

The initial target aPTT in the PURSUIT study was 50-70 seconds, and the recommended heparin dosing was:

- 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

When these patients were to undergo PCI, the target ACT was 300-350 seconds, and the recommended heparin doses were:

Initial Heparin Bolus

ACT (seconds)	Heparin Bolus
<150	100 U/kg (10,000 U maximum)
151-225	75 U/kg
226-299	50 U/kg
≥300	none

Repeat Heparin Bolus*

ACT (seconds)	Heparin Bolus
<275	50 U/kg
275-299	25 U/kg
≥300	none

* based on hourly ACT determinations

In the IMPACT II study, the target ACT was 300-350 seconds before the procedure and ≤ 350 seconds thereafter. The recommended heparin doses were:

- prior to intervention: 100 U/kg bolus
- during intervention: up to 2000 U bolus q15min
- after intervention: infusion at physician's discretion

Patients requiring thrombolytic therapy had eptifibatide infusions stopped and were discontinued from the studies.

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 mEq/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 of INTEGRILIN should be withdrawn from the 10-mL vial into a syringe. The bolus dose should be administered by IV push over 1-2 minutes.
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:

1. **INTEGRILIN Dosing Chart by Weight for Patients With Acute Coronary Syndrome (180 µg/kg Bolus and 2 µg/kg/min Infusion)**

Patient Weight (kg)	Bolus Volume (2 mg/mL)	Infusion Rate (0.75 mg/mL)
37-41	3.4 mL	6 mL/h
42-46	4	7
47-53	4.5	8
54-59	5	9
60-65	5.6	10
66-71	6.2	11
72-78	6.8	12
79-84	7.3	13
85-90	7.9	14
91-96	8.5	15
97-103	9	16
104-109	9.5	17
110-115	10.2	18
116-121	10.7	19
>121	11.3	20

2. **INTEGRILIN Dosing Chart by Weight for Patients Without Acute Coronary Syndromes Undergoing PCI (135 µg/kg Bolus and 0.5 µg/kg/min Infusion)**

Patient Weight (kg)	Bolus Volume (2 mg/mL)	Infusion Rate (0.75 mg/mL)
40-55	3.4 mL	2 mL/h
56-68	4.2	2.5
69-80	5.1	3
81-93	5.9	3.5
94-105	6.8	4
106-118	7.6	4.5
119-131	8.4	5
132-143	9.2	5.5

HOW SUPPLIED

INTEGRILIN (eptifibatide) Injection is supplied as a sterile solution in 10-mL vials containing 20 mg of eptifibatide (NDC 0085-1177-01) and 100-mL vials containing 75 mg of eptifibatide (NDC 0085-1136-01).

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.

Marketed By: COR Therapeutics, Inc.
South San Francisco, CA 94080

and

Key Pharmaceuticals, Inc.
Kenilworth, NJ 07033

Distributed By: Key Pharmaceuticals, Inc.
Kenilworth, NJ 07033

Issued ~~June~~ August 1999
Rev ~~2~~ 3