

CENTER FOR DRUG EVALUATION AND RESEARCH

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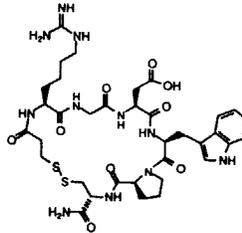
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INTEGRILIN® (eptifibatid) INJECTION
For Intravenous Administration

DESCRIPTION

Eptifibatid 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 N⁶-(aminoiminomethyl)-N⁵-(3-mercapto-1-oxopropyl-L-lysylglycyl-L-α-aspartyl-L-tryptophyl-L-protyl-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:



C₂₃H₄₀N₁₁O₉S₂

Mol wt: 831.96

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 0.75 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 5.25.

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 µg/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 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 (NQM) 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 µg/kg intravenous bolus. Table 1 shows the effects of the two doses of eptifibatid 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, 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 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 eptifibatid 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 eptifibatid, deamidated eptifibatid, 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 eptifibatid 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 eptifibatid clearance and higher eptifibatid 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 eptifibatid.

CLINICAL STUDIES

Eptifibatid 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 (NQM)), 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 NQM. 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

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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/mm³.

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

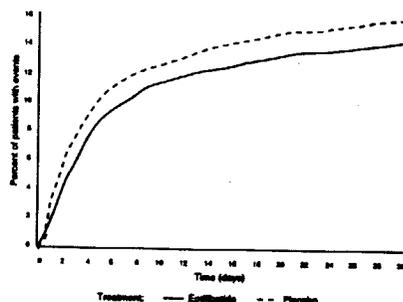
The primary endpoint of the study was the occurrence of death from any cause or new myocardial infarction (MI) (evaluated by a blinded Clinical Endpoints Committee) within 30 days of randomization.

Compared to placebo, eptifibatid administered as a 180 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 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) n (%) | p-value |
|--------------------------------|--------------------------------|---|---------|
| Death or MI | | | |
| 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 eptifibatid 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, eptifibatid was significantly less beneficial in women than in men, and in the overall study eptifibatid in women was nonsignificantly worse than placebo. These results were, however, strikingly heterogeneous across the several regions; eptifibatid 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 eptifibatid and gender, (b) interactions between eptifibatid and unknown interregional 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 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 | Eptifibatid 180/2.0 |
|--|----------------|------------------------|
| Overall Patient Population | | |
| - At 72 hours | n=4739 7.6% | n=4722 5.9% |
| Patients undergoing early PCI | | |
| - Pre-procedure (nonfatal MI only) | n=631 | n=619 |
| - At 72 hours | 5.5% | 1.6% |
| | 14.4% | 9.0% |
| Patients not undergoing early PCI | | |
| - At 72 hours | n=4108 6.5% | n=4103 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 4,566 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.

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/mm³, 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 eptifibatid (135/0.5); 2) 135 µg/kg bolus followed by a continuous infusion of 0.75 µg/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 lower-dose 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 (%) |
|--|------------------|-----------------------------------|------------------------------------|
| 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 eptifibatid 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 (%) | Eptifibatid 135/0.5 n (%) | Eptifibatid 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 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.
- Platelet count <100,000/mm³.
- 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 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. 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.

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 for 20-24 hours. The femoral artery sheath may be removed during treatment with eptifibatid, 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 eptifibatid 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, eptifibatid was used concomitantly with heparin and aspirin (see CLINICAL STUDIES). 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, glycyrrhizic acid, 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 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 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 | Eptifibatid 180/1.3* | Eptifibatid 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%) | 28/258 (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 eptifibatid 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 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/mm³, INTEGRILIN and heparin should be discontinued and the condition appropriately monitored and treated.

Renal Insufficiency. Based on results of clinical studies with eptifibatid (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, eptifibatid should be administered as a 135 µg/kg bolus followed by a 0.5 µg/kg/min infusion. Plasma eptifibatid 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 eptifibatid 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 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 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 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 14,718 patients were treated in the two Phase III clinical trials (PURSUIT and IMPACT II). Of these, 8737 received eptifibatid: 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 | Eptifibatid 180/1.3* | Eptifibatid 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 | Eptifibatid 135/0.5 | Eptifibatid 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%) | 148 (11.7%) | 177 (14.2%) |
| Requiring Transfusions ^b | 68 (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 eptifibatid, however, was seen only among the patients who did not undergo CABG.

In the PURSUIT study, the greatest increase in major bleeding in eptifibatid-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 eptifibatid-treated patients compared to placebo. 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%).

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 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

Table 9
Major Bleeding by Procedures in the IMPACT II Study

| | Placebo n (%) | Eptifibatid 135/0.5 n (%) | Eptifibatid 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 eptifibatid 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 eptifibatid 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 eptifibatid 180/1.3 and 5 patients in the group treated with eptifibatid 180/2.0 experiencing a hemorrhagic stroke within 30 days of randomization. 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 within 30 days randomization.

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.

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

Allergic Reactions. In the IMPACT II study, anaphylaxis was reported in 1 patient (0.08%) on placebo and in no patients on eptifibatid. 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, 2 patients (1 patient (0.04%) receiving eptifibatid 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 eptifibatid and in none of the patients who received placebo.

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 $\mu\text{g}/\text{kg}$ bolus followed by a continuous infusion of either 0.5 $\mu\text{g}/\text{kg}/\text{min}$ or 0.75 $\mu\text{g}/\text{kg}/\text{min}$), and in 21 subjects to whom eptifibatid (135 $\mu\text{g}/\text{kg}$ bolus followed by a continuous infusion of 0.75 $\mu\text{g}/\text{kg}/\text{min}$) 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. Serious non-bleeding events occurred in 19% of the eptifibatid 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 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 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 eptifibatid and placebo groups in the following body systems with an incidence of $\geq 0.1\%$: 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 eptifibatid and placebo groups in the following body systems with an incidence of $\geq 0.1\%$: 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 eptifibatid. There were 6 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.

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.

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 Syndromes. The recommended adult dosage of eptifibatid in patients with acute coronary syndrome is an intravenous bolus of 180 $\mu\text{g}/\text{kg}$ as soon as possible following diagnosis, followed by a continuous infusion of 2 $\mu\text{g}/\text{kg}/\text{min}$ 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, consideration can be given to decreasing the infusion rate to 0.5 $\mu\text{g}/\text{kg}/\text{min}$ (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 eptifibatid in patients undergoing PCI and not presenting with an acute coronary syndrome is an intravenous bolus of 135 $\mu\text{g}/\text{kg}$ administered immediately before the initiation of PCI followed by a continuous infusion of 0.5 $\mu\text{g}/\text{kg}/\text{min}$ 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, eptifibatid infusion should be discontinued prior to surgery.

In the clinical trials that showed eptifibatid 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)
160 mg initially,
then 75-325 mg daily

Angioplasty
(IMPACT II Study)
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:

| ACT (seconds) | Initial Heparin Bolus | Heparin Bolus |
|---------------|-----------------------|-----------------------------|
| <150 | | 100 U/kg (10,000 U maximum) |
| 151-225 | | 75 U/kg |
| 226-299 | | 50 U/kg |
| ≥ 300 | | none |
| ACT (seconds) | Repeat Heparin Bolus* | 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 thrombotic therapy had epifibatid 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 μ g/kg Bolus and 2 μ g/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 μ g/kg Bolus and 0.5 μ g/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 | 7.8 | 4.5 |
| 119-131 | 8.4 | 5 |
| 132-143 | 9.2 | 5.5 |

HOW SUPPLIED

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

R_x only

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