PACKAGE INSERT/PROFESSIONAL BROCHURE

INTEGRILIN[**] Solution for Injection

Brand of eptifibatide

FOR INJECTABLE ADMINISTRATION (Bolus for intravenous injection; Intravenous infusion)

DESCRIPTION: INTEGRILIN Solution for Injection is a clear, colorless solution which contains the active ingredient, eptifibatide, a synthetic cyclic heptapeptide containing six amino acids, including one cysteine amide, and one mercaptopropionyl (des-amino cysteinyl) residue. INTEGRILIN is formulated as a sterile solution for injection in two dosage administration forms, bolus and intravenous infusion. **The bolus injection** is a single dose 10 ml vial containing eptifibatide 2 mg/ml, and the **solution for intravenous infusion** is a single dose 100 ml vial containing eptifibatide 0.75 mg/ml. Inactive ingredients: Monohydrate citric acid, sodium hydroxide, and water for injection.

ACTIONS: Eptifibatide is an inhibitor of platelet aggregation and belongs to the class of RGD (arginine-glycine-aspartate)-mimetics.[1]

Eptifibatide reversibly inhibits platelet aggregation by preventing the binding of fibrinogen, von Willebrand factor and other adhesive ligands to the glycoprotein (GP) IIb/IIIa receptors.[2]

Eptifibatide inhibits platelet aggregation in a dose- and concentration-dependent manner as demonstrated by *ex vivo* platelet aggregation using adenosine diphosphate (ADP) and other agonists to induce platelet aggregation. The effect of eptifibatide is observed immediately after administration of a 180 microgram/kg intravenous bolus. When followed by a 2.0 microgram/kg-min continuous infusion, this regimen produces a >80% inhibition of ADP-induced *ex vivo* platelet aggregation, at physiologic calcium concentrations, in more than 80% of patients.[2]

Platelet inhibition was reversed readily, with a >50% return of platelet function towards baseline 4 hours after stopping a continuous infusion of 2.0 microgram/kg-min.[3] Measurements of ADP-induced *ex vivo* platelet aggregation at physiologic calcium concentrations (D-phenylalanyl-L-prolyl-L-arginine chloromethyl ketone [PPACK] anticoagulant) in patients presenting with unstable angina and non-Q-wave myocardial infarction showed a concentration-dependent inhibition with an IC_{50} (50% inhibitory concentration) of 557 ng/ml and an IC_{80} (80% inhibitory concentration) of 1107 ng/ml.[2,4]

Administration of INTEGRILIN by intravenous bolus and infusion causes up to a 5-fold increase in bleeding time. When administered alone, eptifibatide has no measurable effect on prothrombin time (PT) or activated partial thromboplastin time (aPTT).

PRECLINICAL PHARMACOLOGY AND TOXICOLOGY[2]: Toxicology studies conducted with eptifibatide include single and repeated dose studies in the rat, rabbit and monkey, reproduction studies in the rat and rabbit, *in vitro* and *in vivo* genetic toxicity studies, and irritation, hypersensitivity and antigenicity studies. No unexpected toxic effects for an agent with this pharmacologic profile were observed and findings were predictive of clinical experience, with bleeding effects being the principal adverse event. No genetic liability was observed with eptifibatide.

Reproductive toxicity studies in rabbits which did not show susceptibility to the pharmacologic action of eptifibitide even at high doses were negative.

The carcinogenic potential of INTEGRILIN Solution for Injection has not been evaluated in long-term studies.

CLINICAL PHARMACOLOGY[3,5]: The pharmacokinetics of eptifibatide are linear and dose proportional for bolus doses ranging from 90 to 250 microgram/kg and infusion rates from 0.5 to 3.0 microgram/kg/min. For a 2.0 microgram/kg/min infusion, mean steady-state plasma eptifibatide concentrations range from 1.5 to 2.2 microgram/ml in patients with coronary artery disease. These plasma concentrations are achieved rapidly when the infusion is preceded by a 180 microgram/kg bolus. The extent of eptifibatide binding to human plasma protein is about 25%. In the same population, plasma elimination half-life is approximately 2.5 hours, plasma clearance 55 to 80 ml/kg/hr and volume of distribution of approximately 185 to 260 ml/kg. In healthy subjects, renal excretion accounted for approximately 50% of total body clearance; approximately 50% of the amount cleared is excreted unchanged.

A modest increase in half-life and volume of distribution is seen with increased age, decreased weight (<74 kg) and/or decreased creatinine clearance (CrCl). The pharmacokinetics are unaffected by dose and gender. No dose adjustment of the bolus or infusion is required in the case of mild renal impairment (CrCl ≥50 ml/min using the Cockcroft-Gault equation*). Dose adjustment is recommended for cases of moderate to severe renal impairment (CrCl <50 mL/min using the Cockcroft-Gault equation*). In patients with moderate to severe renal insufficiency (CrCl <50 mL/min), the clearance of eptifibatide is reduced by approximately 50% and steady-state plasma levels are approximately doubled (see PRECAUTIONS, DOSAGE AND ADMINISTRATION).

PURSUIT trial[6]

The pivotal clinical trial for Unstable Angina (UA)/Non-Q Wave Myocardial Infarction (NQMI) was PURSUIT. This study 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 ($\geq$ 10 minutes) within the previous 24 hours and had:

- either ST-segment changes: ST depression > 0.5 mm of less than 30 minutes or persistent ST elevation > 0.5 mm not requiring reperfusion therapy or thrombolytic agents, T-wave inversion (> 1 mm).
- or increased CK-MB.

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

The infusion was continued until hospital discharge, until the time of coronary artery bypass grafting (CABG) or for up to 72 hours, whichever occurred first. If PCI was performed, the INTEGRILIN infusion was continued for 24 hours after the procedure, allowing for a duration of infusion up to 96 hours.

The 180/1.3 arm was stopped after an interim analysis, as prespecified in the protocol, when the two active-treatment arms appeared to have a similar incidence of bleeding.

Patients were 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 INTEGRILIN infusion, of whom approximately 50% received intracoronary stents; 87% were managed medically (without PCI during INTEGRILIN infusion).

The vast majority of patients received acetylsalicylic acid (75-325 mg once daily).

Unfractionated heparin was administered intravenously or subcutaneously at the physicians discretion, most commonly as an intravenous bolus of 5,000 units followed by a continuous infusion of 1,000 units/h. A target aPTT of 50-70 seconds was recommended. A total of 1,250 patients underwent PCI within 72 hours after randomization, in which case they received intravenous unfractionated 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 Events Committee) within 30 days of randomization. The component MI could be defined as asymptomatic with enzymatic elevation of CK-MB or new Q wave.

Compared to placebo, INTEGRILIN administered as 180/2.0 significantly reduced the incidence of the primary endpoint events (Table 1): this represents around 15 events avoided for 1,000 patients treated.

Table 1
Incidence of Death/CEC-Assessed MI («Treated as Randomized» Population)

Time	Placebo	INTEGRILIN	p-Value
30 days	743/4,697 (15.8%)	667/4,680 (14.3%)	0.034[a]

[a] Pearson's chi-square test of difference between placebo and INTEGRILIN.

Results on the primary endpoint were principally attributed to the occurrence of myocardial infarction. The reduction in the incidence of endpoint events in patients receiving INTEGRILIN appeared early during treatment (within the first 72-96 hours) and this reduction was maintained through 6 months, without any significant effect on mortality.

Patients most likely to benefit from INTEGRILIN treatment are those at high risk of developing myocardial infarction within the first 3-4 days after onset of acute angina.

According to epidemiological findings, a higher incidence of cardiovascular events has been associated with certain indicators, for instance:

- age
- elevated heart rate or blood pressure
- persistent or recurrent ischemic cardiac pain
- marked ECG changes (in particular ST-segment abnormalities)
- raised cardiac enzymes or markers (e.g., CK-MB, troponins), and
- heart failure

ESPRIT Trial[7]

ESPRIT (Enhanced Suppression of the Platelet IIb/IIIa Receptor with INTEGRILIN Therapy) was a pivotal trial for nonurgent PCI with intracoronary stenting. This was a 92 center, double-blind, randomized, placebo-controlled trial conducted in the United States and Canada in 2,064 patients scheduled to undergo nonurgent PCI with stent implantation in native coronary vessels. Patients were excluded from the trial if treatment had been planned with a GP IIb/IIIa inhibitor prior to the PCI. Other reasons for exclusion were: if the patient had a myocardial infarction within the previous 24 hours before randomization, ongoing chest pain (or anginal

equivalent) leading to urgent referral, PCI within the previous 90 days before randomization, or prior stent in the target lesion.

All patients received routine standard of care. Patients were randomized to either placebo or INTEGRILIN. The INTEGRILIN dosage regimen used in ESPRIT was two bolus doses of 180 microgram/kg and a continuous infusion until discharge from hospital or a maximum of 18-24 hours. This regimen was developed from mathematical modeling of patient data from PERIGEE and PRIDE, two smaller pharmacokinetic/pharmacodynamic trials: PERIGEE was a subtrial of PURSUIT, and PRIDE evaluated patients who were undergoing elective PCI. Some patients from PERIGEE and PRIDE had INTEGRILIN plasma concentrations above the concentration of 2.65 μg/ml, which the modeling represented as the theoretical mean peak concentration in a stabilized patient population. The knowledge of eptifibatide pharmacokinetics and its variability between and within patients is limited, and it is not known whether individual variability implies a higher hemorrhaging risk for some patients.

The first bolus injection and the infusion were started simultaneously, immediately before the PCI procedure. The second bolus was administered 10 minutes after the first bolus. The rate of infusion was 2.0 microgram/kg/min for patients with serum creatinine $\leq$ 175 micromols/1 or 1.0 microgram/kg/min for serum creatinine > 175 up to 350 micromols/1. Additionally, for any patient considered to be at high risk of bleeding, the infusion rate was allowed to be decreased to 0.5 microgram/kg/min; however the standard infusion dose was to have been continued for at least 12 hours. In addition, investigators had the option to discontinue study medication and start open-label INTEGRILIN in the event of procedural complications, such as abrupt closure, no reflow, or coronary thrombosis (defined as acute antithrombotic rescue therapy). A kit was provided that contained blinded trial drug for bolus administration, enabling investigators to switch their patients to open-label INTEGRILIN without unblinding the initial treatment regimen.

In the INTEGRILIN arm of the trial, virtually all patients received aspirin (99.7%), and 97.1% received a thienopyridine, (clopidogrel in 95.4% and ticlopidine in 2.7%). On the day of PCI, prior to catheterization, 53.1% received a thienopyridine (clopidogrel 52.7%; ticlopidine 0.5%) – mostly as a loading dose (bolus of 300 mg or more). The number of placebo-treated patients who received these agents was similar [aspirin 99.8%, clopidogrel 96%, ticlopidine 2.6%].

The ESPRIT trial used a simplified regimen of heparin dosing during PCI as compared to the PURSUIT trial where urgent PCI was performed. For those patients not treated with heparin in the 6 hours before PCI, an initial bolus of 60 units/kg was recommended. The target ACT during the procedure was 200 – 300 seconds. A heparin infusion regimen after the PCI was discouraged, and the early removal of the vascular access sheath (approximately 4 hours after PCI) was suggested. In patients requiring a heparin infusion after PCI however,

heparin was administered at a rate of 10 units/kg/hour or 800 units/hour, whichever was less. An aPTT was obtained within 4 hours of starting the heparin infusion with an aPTT target of 50 – 70 seconds.

The primary endpoint of the trial was death (D), MI, urgent target vessel revascularization (UTVR), and acute antithrombotic rescue with GP IIb/IIIa inhibitor therapy (RT) within 48 hours of randomization. An independent, blinded Clinical Events Committee was responsible for adjucating suspected endpoint events, including MI, UTVR, and acute antithrombotic rescue therapy (RT).

During this trial, MI was defined as an "enzymatic" or "adjudicated investigator" MI>
Enzymatic MI was identified per the CK-MB core laboratory criteria. For this diagnosis, within 24 hours after the index PCI procedure, there had to be at least two CK-MB values $\geq$ 3 x the upper limit of normal; thus, validation by the CEC was not required. Adjudicated MI is an investigator reported MI, confirmed as MI after adjudication by the CEC.

An independent data safety monitoring committee (DSMC) for the ESPRIT Trial recommended that the trial be terminated prematurely because the data demonstrated overwhelming efficacy in the absence of a safety concern. Overall, the trial showed a significant reduction in the quadruple endpoint at 48 hours, 7 days, and 30 days (Table 2). In addition, a similar benefit was seen in the important secondary endpoints of the double and triple composite endpoints, and was attributed predominately to MI.

Table 2. Selected Endpoint Components at 48 hours, 7 days, 30 days, 6 months and 1 year[7]

Time	Placebo† (N=1024)	INTEGRILIN† (N=1040)	Odds ratio		Risk difference	
			Estimate	95% CI*	Estimate	95% CI*
Death/MI/UTVR/RT						
48 hours	108 (10.5%)	69 (6.6%)	0.603	(0.440,0.826)	-3.9	(-6.3,-1.5)
7 days	114 (11.1%)	75 7.2%)	0.620	(0.457,0.842)	-3.9	(-6.4,-1.4)
30 days	120 (11.7%)	78 (7.25%)	0.611	(0.453,0.824)	-4.2	(-6.8,-1.7)
Death and MI						
48 hours	94 (9.2%)	57 (5.5%)	0.574	(0.48,0.807)	-3.7	(-5.9,-1.5)
7 days	99 (9.7%)	63 (6.1%)	0.602	(0.434,0.837)	-3.6	(-5.9,-1.3)
30 days	104 (10.2%)	66 (6.3%)	0.599	(0.435,0827)	-3.8	(-6.2,-1.4)
6 months	117 (11.5%)	77 (7.4)	0.631+	(0.473 ⎮,0.841)+	NA	NA
1 year	126 (12.4%)	83 (8.0%)	0.630+	(0.478,0.832)+	NA	NA
Death/MI/UTVR						
30 days	107 (10.4%)	71 (6.8%)	0.628	(0.459,0.859)	-3.6	(-6.0,-1.2)
Death						
30 days	6 (0.6%)	4 (0.4%)	0.655	(0.184,2.328)	NA	NA
6 months	14 (1.4%)	8 (0.8%)	0.562+	(0.236,1.339)+	NA	NA

1 year	20 (2.0%)	14 (1.4%)	0.688+	(0.348,1.362)+	NA	NA

†Raw percentages are presented at 48 hours, 7 days and 30 days. Kaplan Meier estimates are presented at 6 months and 1 year*
*Confidence limits use the Normal approximation
+6 months and 1 year data reports Hazards ratio (HR); HR and CI estimated by Cox proportional hazards model

Results on the primary endpoint were mainly attributed to the reduction of enzymatic MI occurrence, identified as the occurrence of early asymptomatic elevation of cardiac enzymes after PCI (80 out of 92 MIs in the eptifibitide group versus 47 out of 56 MIs in the placebo group). The reduction in the incidence of endpoint events in patients receiving INTEGRILIN appeared early during treatment and this reduction was maintained through 1 year.

INDICATIONS AND USAGE: INTEGRILIN Solution for Injection is indicated:

- For the prevention of death and myocardial infarction in patients presenting with unstable angina or non-Q-wave myocardial infarction (chest pain with ST segment depression >0.5 mm or definitive T-wave inversion >1 mm or transient ST segment elevation >0.5 mm of less than 30 minutes or persistent ST segment elevation >0.5 mm not requiring reperfusion therapy or thrombolytic agents, or chest pain in patients without persistent ST segment elevation with CK-MB greater than the upper limit of normal). INTEGRILIN Solution for Injection is indicated in patients who are managed with standard medical therapies and/or with percutaneous coronary intervention. (PURSUIT TRIAL)
- As an adjunct to percutaneous transluminal coronary angioplasty [PTCA] balloon angioplasty with or without stent, directional atherectomy, transluminal extraction catheter atherectomy, rotational ablation angioplasty, or excimer laser angioplasty) for the prevention of abrupt closure of the treated coronary vessel and related acute ischemic cardiac complications (death, myocardial infarction, need for urgent intervention). (ESPRIT TRIAL)

INTEGRILIN Solution for Injection is intended for use with aspirin and heparin

DOSAGE AND ADMINISTRATION: INTEGRILIN Solution for Injection must be used in conjunction with INTEGRILIN Solution for Infusion. INTEGRILIN treatment is for use in adults ≥ 18 years of age.

Acute Coronary Syndrome (Patients presenting with Unstable Angina (UA) or Non-Q-wave Myocardial Infarction (NQMI)): The recommended adult dosage of eptifibatide in patients with a creatinine clearance (CrCl) ≥50 mL/min (using the Cockcroft-Gault equation)* is an intravenous bolus of 180 microgram/kg administered as soon as possible following diagnosis, followed by a continuous infusion of 2.0 microgram/kg-min for up to 72 hours until initiation of coronary artery bypass graft (CABG) surgery or until discharge from the hospital (whichever occurs first). If PTCA is performed during INTEGRILIN therapy, the infusion should be continued for 20-24 hours post-PTCA for an overall maximum duration of therapy of 96 hours.

Acute Coronary Syndrome (UA or NQMI) patients with Creatinine Clearance <50 mL/min: The recommended adult dosage of eptifibatide in patients with Acute Coronary Syndrome with an estimated creatinine clearance <50 mL/min (using the Cockcroft-Gault equation)* is an intravenous bolus of 180 microgram/kg administered as soon as possible following diagnosis, immediately followed by a continuous infusion of 1.0 microgram/kg/min for up to 72 hours until initiation of coronary artery bypass graft (CABG) surgery or until discharge from the hospital (whichever occurs first). If PTCA is performed during Integrilin therapy, the infusion should be continued for 20 -24 hours post-PTCA for an overall maximum duration of therapy of 96 hours.

Patients undergoing Percutaneous Coronary Intervention (PCI): The recommended adult dosage of eptifibatide in patients with a creatinine clearance ≥50 mL/min (using the Cockcroft-Gault equation)* is an intravenous bolus of 180 microgram/kg administered immediately prior to the procedure, followed by a second bolus of 180 microgram/kg 10 minutes after the first bolus injection. Simultaneously with the first bolus, a continuous infusion should be started at a dose of 2.0 microgram/kg/min. Continue the infusion until hospital discharge or up to a maximum of 18-24 hours post PCI. A minimum of 12 hours of infusion is recommended.

Patients undergoing PCI with Creatinine Clearance <50 mL/min: The recommended adult dosage of eptifibatide in patients with an estimated creatinine clearance <50 mL/min (using the Cockcroft-Gault equation)* is an intravenous bolus of 180 microgram/kg administered immediately before the initiation of the procedure, followed by a second 180 microgram/kg bolus administered 10 minutes after the first bolus injection. Simultaneously with the first bolus dose, a continuous infusion should be started at a dose of 1.0 microgram/kg/min. Continue the infusion until hospital discharge or up to a maximum of 18 - 24 hours post PCI. A minimum of 12 hours of infusion is recommended.

Before using, inspect the vial contents. Do not use if particulate matter is present. Protection of INTEGRILIN Solution for Injection from light is not necessary during administration. Do not administer INTEGRILIN Solution for Injection in an intravenous line concomitantly with furosemide (frusemide).

If the patient requires emergency or urgent cardiac surgery during the course of INTEGRILIN therapy, the infusion should be terminated immediately. If the patient requires semi-elective surgery, INTEGRILIN infusion should be stopped to allow time for platelet function to return towards normal.

*Use the Cockcroft-Gault equation with actual body weight to calculate the estimated creatinine clearance in mL/min:

$$\text{Males: } \frac{(140 - \text{age in years}) \times (\text{actual body weight in kg})}{72 \times (\text{serum creatine in mg/dL})}$$

Females: $\frac{(140 - \text{age in years}) \times \text{actual body weight in kg}) \times (0.85)}{72 \times (\text{serum creatinine in mg/dL})}$

DRUG INTERACTIONS/CONCOMITANT THERAPY: No formal pharmacokinetic interaction studies have been conducted. However, in a population pharmacokinetic study, there was no evidence of a pharmacokinetic interaction between INTEGRILIN Solution for Injection and the following concomitant medications: amlodipine, atenolol, atropine, captopril, cefazolin, diazepam, digoxin, diltiazem, diphenhydramine, enalapril, fentanyl, furosemide, heparin, lidocaine, lisinopril, metoprolol, midazolam, morphine, nitrates, nifedipine, and warfarin suggesting a low potential for a pharmacokinetic drug interaction between INTEGRILIN and these commonly used agents in patients with cardiac conditions.[5]

Because INTEGRILIN inhibits platelet aggregation, it should be used cautiously with other medications that affect hemostasis, including oral anticoagulants, dextran solutions, adenosine, sulfinpyrazone, prostacyclin, non-steroidal anti-inflammatory agents, or dipyridamole, ticlopidine and clopidogrel. INTEGRILIN did not appear to increase the risk of major and minor bleeding associated with concomitant use of warfarin and dipyridamole. INTEGRILIN-treated patients who had a prothrombin time (PT)>14.5 seconds and received warfarin concomitantly did not appear to be at an increased risk of bleeding.

In a trial in patients undergoing nonurgent PCI with stenting, 95% received clopidogrel concomitantly with aspirin before or within 48 hours after PCI and daily therafter.[7]

There is very limited experience with INTEGRILIN and low molecular weight heparins. Thus, co-administration of low molecular weight heparins with INTEGRILIN must be done with caution.

Data are limited on the use of INTEGRILIN in patients receiving thrombolytic agents. There was no consistent evidence that INTEGRILIN increased the risk of major and minor bleeding associated with tissue plasminogen activator in either a PTCA or an acute myocardial infarction study; however, INTEGRILIN appeared to increase the risk of bleeding when administered with steptokinase in an acute myocardial infarction study.[8,9]

Bleeding events were more frequent in patients receiving concurrent heparin while undergoing PTCA, when ACT exceeded 350 seconds. (see Precautions; Heparin use.)[7,10]

PHYSICAL AND CHEMICAL COMPATIBILITY: Testing indicates that INTEGRILIN Solution for Injection may be administered through an intravenous line with atropine sulfate, dobutamine, heparin, lidocaine, meperidine, metoprolol, midazolam, morphine, nitroglycerin, tissue plasminogen activator, or verapamil.

INTEGRILIN is compatible with 0.9% Sodium Chloride Injection and with Dextrose 5% in Normosol R, in the presence or absence of potassium chloride.[11]

INTEGRILIN is not compatible with furosemide.[11] In the absence of data, INTEGRILIN should not be mixed with drugs other than those tested and found to be compatible.

ADVERSE EFFECTS: The majority of adverse events experienced by patients treated with INTEGRILIN Solution for Injection were generally related to bleeding, or to cardiac or cardiovascular events that occur frequently in this patient population.

Bleeding

Bleeding was classified in clinical trials as major or minor by TIMI criteria.[12]

Major bleeding was defined as either an intracranial hemorrhage or clinically significant overt hemorrhage (bleeding at an observed site) associated with a drop in hematocrit of 15% or more or a decrease in hemoglobin concentrations of 5 g/dl or more.

Minor bleeding was defined as gross hematuria or hematemesis that does not meet the criteria for a major bleed; or observed blood loss with a drop in hematocrit of 10% or more, or a hemoglobin decrease of 3 g/dl or more.

PURSUIT TRIAL (UA/NQMI)

At the recommended therapeutic dose, as administered in the PURSUIT trial involving nearly 11,000 patients, bleeding was the most common undesirable effect.

Minor bleeding was the most common complication of INTEGRILIN administration (13.1% INTEGRILIN vs 7.6% placebo).

The most common bleeding complications were associated with cardiac invasive procedures (CABG or at femoral artery access site). Major bleeding was infrequent in the PURSUIT trial in the large majority of patients who did not undergo CABG within 30 days of enrollment.

Minor bleeding (TIMI criteria) was the most common complication of INTEGRILIN administration (13.1% INTEGRILIN vs 7.6% placebo at 30 days). CABG related events were the most common (2.8% INTEGRILIN vs 2.7% placebo). Minor bleeding (>1% INTEGRILIN) included genitourinary, femoral artery access, oral/oropharyngeal, and gastrointestinal; hemoglobin/hematocrit decreases were reported. Bleeding events were more frequent in patients receiving concurrent heparin while undergoing PCI, when ACT exceeded 350 seconds (see Heparin use).

Major bleeding (TIMI criteria) was reported more frequently in patients treated with INTEGRILIN (10.8% INTEGRILIN vs 9.3% placebo). Major bleeding (>1% INTEGRILIN) included femoral artery access, oral/oropharyngeal, and gastrointestinal; hemoglobin/hematocrit decreases were reported. Genitourinary, retroperitoneal, and intracranial bleeding was less common.

The incidence of severe or life-threatening bleeding events with INTEGRILIN was 1.9% vs 1.1% with placebo. INTEGRILIN treatment increased the need for blood transfusions modestly (11.8% vs 9.3% placebo).

In the subgroup of patients in the PURSUIT trial undergoing PCI, major bleeding was observed in 9.7% of INTEGRILIN-treated patients vs 4.6% treated with placebo.

ESPRIT TRIAL (non-urgent PCI with intracoronary stenting)
Minor bleeding was the most common complication of INTEGRILIN administration (2.8% INTEGRILIN vs 1.8% placebo, at 48 hours). Minor bleeding events (>1% INTEGRILIN Group) included femoral artery access and hematuria. Less frequently occurring (<1% INTEGRILIN Group) were hematemesis and other gastrointestinal related events.

Major bleeding events were higher with INTEGRILIN than placebo (1.3% vs 0.4%, at 48 hours). INTEGRILIN did not significantly increase the risk of intracranial bleeding, which was uncommon (0.2% INTEGRILIN vs 0.1% placebo). Bleeding incidence was not significantly increased with INTEGRILIN as compared with placebo in patients who underwent CABG surgery (33% vs 50% placebo). Major bleeding sites included femoral artery access, retroperitoneal, intracranial, hematuria, hematemesis and genitourinary sites.

The incidence of severe or life-threatening bleeding events in patients was 0.7% INTEGRILIN vs 0.5% placebo. INTEGRILIN treatment modestly increased the need for red blood cell transfusions (1.4% INTEGRILIN vs 1.0% placebo).

Other undesirable effects

Overall, serious non-bleeding adverse events were reported at a similar rate in patients treated with INTEGRILIN Solution for Injection and those treated with placebo.

Commonly reported events in the PURSUIT trial (occurring in $\geq$ 2% across all group) were events related to the underlying disease, such as atrial fibrillation, hypotension, congestive heart failure, cardiac arrest, shock, ventricular tachycardia or fibrillation.

Additional adverse events reported during use of INTEGRILIN include anaphylaxis, rash, and application site disorders such as urticaria.

Very rare cases of fatal bleeding have been reported. Cases of pulmonary hemorrhage have also been reported very rarely.

In post marketing experience cases of acute profound thrombocytopenia have been reported very rarely..

Laboratory values

Changes during INTEGRILIN Solution for Injection treatment result from its known pharmacologic action, i.e., inhibition of platelet aggregation. Thus, changes in laboratory parameters associated with bleeding (e.g., bleeding time) are common and expected. No apparent differences were observed between patients treated with INTEGRILIN or with placebo in value for hemoglobin, hematocrit, platelet counts, liver function (SGOT/AST, SGPT/ALT, bilirubin, alkaline phosphatase), or renal function (serum creatinine, blood urea nitrogen).

CONTRAINDICATIONS:

INTEGRILIN Solution for Injection must not be used to treat patients with:

- evidence of gastrointestinal bleeding, gross genitourinary bleeding or other active abnormal bleeding (except menstrual bleeding) within the previous 30 days of treatment;
- history of stroke within 30 days or any history of hemorrhagic stroke;
- major surgery within past 6 weeks;
- a history of bleeding diathesis;
- thrombocytopenia (<100,000 cells/mm^3);
- prothrombin time >1.2 times control or INR $\geq$2.0;
- severe hypertension (systolic blood pressure >200 mm Hg or diastolic blood pressure >110 mm Hg on antihypertensive therapy);
- clinically significant hepatic impairment
- Dependency on renal dialysis

- concomitant or planned administration of another parenteral GP IIb/IIIa inhibitor;
- hypersensitivity to any component of the product.

PRECAUTIONS: **Bleeding**: INTEGRILIN Solution for Injection is an antithrombotic agent that acts by inhibition of platelet aggregation; therefore the patient should be observed carefully for indications of bleeding during treatment. (see Adverse Effects) Women, the elderly and patients with low body weight appear to have an increased risk of bleeding. Monitor these patients closely with regard to bleeding.

The risk of bleeding is most common at the arterial access site in patients undergoing percutaneous arterial procedures. All potential bleeding sites, e.g., catheter insertion sites; arterial, venous, or needle puncture sites; cutdown sites; gastrointestinal, genitourinary and retroperitoneal sites, must be observed carefully. Other potential sites of bleeding include central and peripheral nervous system.

If serious bleeding occurs that is not controllable with pressure, the INTEGRILIN infusion and any heparin that is given concomitantly should be stopped immediately. During the marketing of INTEGRILIN, very rare cases of fatal bleeding have been reported.

Thrombocytopenia

INTEGRILIN inhibits platelet aggregation, but does not appear to affect the viability of platelets. As demonstrated in clinical trials, the incidence of thrombocytopenia was low, and similar in patients treated with INTEGRILIN or placebo. If the patient experiences a confirmed platelet decrease to $<100{,}000/mm^3$, discontinue TRA DEMARK and unfractionated heparin and monitor and treat the patient appropriately.

Prolongation of bleeding time

Administration of INTEGRILIN by intravenous bolus and infusion causes up to a 5-fold increase in bleeding time. This increase is readily reversible upon discontinuation of the infusion with bleeding times returning towards baseline within 2 to 6 hours. When administered alone, INTEGRILIN has no measurable effect on prothrombin time (PT) or activated partial thromboplastin time (aPTT).

Immunogenicity

Immunogenic response or anti-integrilin antibodies have not been observed. Thus, if treatment with Integrilin is repeated, no diminished therapeutic response is expected. Neither immunogenic response nor anti-Integrilin antibodies have been observed in individuals who received multiple doses of Integrilin

Heparin use

UA/NQMI: Heparin should be administered to patients unless a contraindication (such as a history of thrombocytopenia associated with use of heparin) is present. For a patient who weighs $\geq$70 kg, it is recommended that a bolus dose of 5000 units is given, followed by a constant intravenous infusion of 1000 units/hr. If the patient weighs < 70 kg, a bolus dose of 60 units/kg should be given, followed by an infusion of 12 units/kg-hr.. The aPTT should be monitored in order to maintain a value between 50 and 70 seconds.

Coronary Angioplasty: If coronary angioplasty is to be performed, the activated clotting time (ACT) should be monitored to maintain a value between 300-350 seconds. Heparin administration should be stopped if the ACT exceeds 300 seconds, and it should not be administered until the ACT falls below 300 seconds.

Nonurgent coronary angioplasty with intracoronary stenting: In patients who have not been treated with heparin within 6 hours before intervention, an initial heparin bolus of 60 U/kg is recommended. The target ACT during the procedure is 200-300 seconds. Additional bolus of heparin may be administered during the PCI procedure to maintain the ACT within this range.

Hepatic impairment

Experience in patients with hepatic impairment is very limited (see CONTRAINDICATIONS). Administer with caution to patients with hepatic impairment in whom coagulation could be affected.

Renal impairment

Integrilin may be administered safely at the standard dose to patients with mild renal impairment (CrCl ≥50 ml/min using the Cockcroft-Gault equation)*. In patients with moderate to severe renal insufficiency (creatinine clearance <50 mL/min using the Cockcroft-Gault equation)*, the clearance of eptifibatide is reduced by approximately 50% and steady state plasma levels are approximately doubled. Patients with moderate to severe renal insufficiency who receive the usual infusion dose of 2 microgram/kg/min have an increased risk of bleeding. Therefore, the infusion dose should be reduced to 1 microgram/kg/min in such patients (see DOSAGE AND ADMINISTRATION section). There has been no clinical experience in patients dependent on renal dialysis.

PEDIATRIC USE: Safety and effectiveness of INTEGRILIN Solution for Injection in children have not been established.

USAGE DURING PREGNANCY AND LACTATION: No clinical studies with INTEGRILIN Solution for Injection have been conducted in pregnant women. However, reproduction studies have been performed in rats and rabbits at doses up to 8 and 4 times the human dose, respectively, and have revealed no evidence of impaired fertility or harm to the fetus due to eptifibatide. Because animal reproduction studies are not always predictive of human response, INTEGRILIN should be used during pregnancy only if the benefit to the mother outweighs the potential risk to the fetus.

It is not known whether INTEGRILIN is excreted in human milk. Breast feeding should be interrupted during the treatment period.

OVERDOSAGE INFORMATION:

The experience in humans with overdosage of INTEGRILIN Solution for Injection is extremely limited. There was no indication of severe adverse events associated with administration of accidental large bolus doses, rapid infusion reported as overdose, or large cumulative doses. In the PURSUIT trial, there were 9 patients who received bolus and/or infusion doses more than double that specified in the protocol, or who were identified by the investigator as having received an overdose. There was no excessive bleeding in any of these patients, although one patient undergoing CABG was reported as having had a moderate bleed. Specifically, no patients experienced an intracranial bleed.

Potentially, an overdose of INTEGRILIN could result in bleeding. Because of its short half-life and rapid clearance, the activity of INTEGRILIN may be halted readily by discontinuing the infusion. INTEGRILIN can also be dialyzed. In certain cases, treatment of overdose may require transfusion.

HOW SUPPLIED: INTEGRILIN* IV Bolus Sterile solution in 10 ml vials containing 20mg of eptifibatide; INTEGRILIN* IV Infusion Sterile solution in 100ml vials containing 75mg of eptifibatide.

STORAGE: Store at 2° to 8°C (Refrigerate). Protect from light. Discard any material unused after opening. Keep out of reach of children.

Shelf life information can be found on the inner and outer labels of the products.

Further information can be obtained from the doctor or the pharmacist.

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