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MERCK

Dear Doctor:

Thank you for your interest in the enclosed supplement, "Clinical Update: Managing High-Risk Patients With Acute Coronary Syndrome (ACS)" with Dr. Marc Cohen as published in *Cardiology News,* March, 2011. Merck has paid for and provided input for this supplement.

Indications for INTEGRILIN® (eptifibatide) Injection:

- For the treatment of patients with acute coronary syndrome (UA/NSTEMI), including patients who are to be managed medically and those undergoing percutaneous coronary intervention (PCI)
- For the treatment of patients undergoing PCI, including those undergoing intracoronary stenting

Selected Safety Information

INTEGRILIN 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 preceding 6 weeks
- History of stroke within 30 days or any history of hemorrhagic stroke
- Current or planned administration of another parenteral GP IIb-IIIa inhibitor
- Dependency on renal dialysis
- Known hypersensitivity to any component of the product.

Selected Warnings and Precautions

- Bleeding is the most common complication encountered during INTEGRILIN therapy. The majority of excess major bleeding events were localized at the femoral artery access site. Oropharyngeal, genitourinary, gastrointestinal, and retroperitoneal bleeding were also seen more commonly with INTEGRILIN compared to placebo.
- If bleeding cannot be controlled with pressure, infusion of INTEGRILIN and concomitant heparin should be stopped immediately.
- INTEGRILIN is cleared in part by the kidney and its plasma concentrations are doubled in patients with renal disease (creatinine clearance <50 mL/min). Therefore, the infusion dose of INTEGRILIN needs to be reduced to 1 mcg/kg/min in these patients.
- In the event of acute profound thrombocytopenia or a confirmed platelet decrease to <100,000mm^3, discontinue INTEGRILIN and heparin (UFH or LMWH).
- There has been no clinical experience with INTEGRILIN initiated in patients with a baseline platelet count <100,000mm^3. If a patient with low platelet counts is receiving INTEGRILIN, their platelet count should be monitored closely.
- In patients undergoing PCI, INTEGRILIN is associated with an increase in major and minor bleeding at the site of arterial sheath placement. Special care should be employed to minimize the risk of bleeding among these patients.
- Because INTEGRILIN inhibits platelet aggregation, caution should be employed when it is used with other drugs that affect hemostasis, including thrombolytics, oral anticoagulants, NSAIDs, and dipyridamole.
- Use with other GP IIb-IIIa inhibitors should be avoided.

Before prescribing INTEGRILIN, please read the accompanying Prescribing Information. For additional copies of the Prescribing Information, call 1-800-672-6372, visit Integrilin.com, or contact your Merck representative.

Thank you for your interest in this information about INTEGRILIN®.

Sincerely,

Chris Allen, MD FRCA FFPM
Lead, Global Medical Information and Operations
Global Medical Affairs

Cover letter XX XX/XX

Reprint XXXXXX

Managing High-Risk Patients With Acute Coronary Syndrome

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Determining the appropriate course of action for patients with acute coronary syndrome (ACS) requires careful assessment of each patient's risk of mortality and ischemic events. Patients who present with unstable angina (UA) or non–ST-segment elevation myocardial infarction (NSTEMI) can be evaluated/triaged with the Thrombolysis in Myocardial Infarction (TIMI) risk score.[1] This score helps determine an individual's risk of subsequent adverse events and therefore helps individualize the therapeutic approach. The TIMI risk score takes into account the patient's age, prior aspirin use, the presence of risk factors for coronary artery disease, ST-segment changes on the electrocardiogram (ECG), serum cardiac markers, and presentation with recurring angina.[1] Similarly, the Global Registry of Acute Coronary Events (GRACE) scoring system uses several assessment parameters to determine the patient's risk level, including age, previous myocardial infarction (MI), prior heart failure, increased pulse rate at presentation, lower systolic blood pressure at presentation, an elevated serum creatinine level, elevated serum cardiac marker levels, and ST-segment depression on presenting ECG.[2]

In Dr Marc Cohen's experience, three of the most important factors to weigh in assessing whether a patient with ACS is at high or low risk for adverse outcomes are troponin status, age, and the morphology of the lesions as determined by cardiac catheterization and coronary arteriography. Coronary angiography may reveal evidence of an intraluminal thrombus, for instance, or diffuse or long lesions, for example in a patient with diabetes. Clinicians have learned that these angiographic parameters are associated with a heightened risk of adverse events after coronary angioplasty.

Patients with ACS who are deemed at high risk for adverse outcomes, either by using the demographic parameters or if the angiographic parameters mentioned above are present, may be candidates for a variety of antithrombotic agents. Choosing an agent for each patient requires an in-depth understanding of each drug's advantages and disadvantages.

Balancing the Benefits and Risks of Eptifibatide

Among the drugs to be considered is eptifibatide, which inhibits platelet aggregation by binding to the platelet's glycoprotein (GP) IIb/IIIa receptor. Such binding prevents fibrinogen, von Willebrand factor, and other adhesive ligands from attaching to the platelet, reducing its "stickiness" and ability to form a blood clot.[3]

INTEGRILIN® (eptifibatide) Injection is indicated:

- For the treatment of patients with ACS (UA/NSTEMI), including patients who are to be managed medically and those undergoing percutaneous coronary intervention (PCI)
- For the treatment of patients undergoing PCI, including those undergoing intracoronary stenting[3]

INTEGRILIN is contraindicated in patients with:

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- A history of bleeding diathesis or evidence of active abnormal bleeding within the previous 30 days
- Severe hypertension (systolic blood pressure >200 mm Hg or diastolic blood pressure >110 mm Hg) not adequately controlled on antihypertensive therapy
- Major surgery within the preceding 6 weeks
- History of stroke within 30 days or any history of hemorrhagic stroke
- Current or planned administration of another parenteral GP IIb/IIIa inhibitor
- Dependency on renal dialysis
- Known hypersensitivity to any component of the product[3]

Several controlled, randomized, multicenter trials have demonstrated that eptifibatide reduces the risk of subsequent ischemic events and death. The Enhanced Suppression of the Platelet IIb/IIIa Receptor With INTEGRILIN Therapy (ESPRIT) trial was a multicenter, double-blind, randomized study conducted in the United States and Canada that enrolled 2,064 patients undergoing elective or urgent PCI with intended intracoronary stent placement. Investigators found that the composite of death, MI, urgent target vessel revascularization, or thrombotic "bailout" was lower in eptifibatide-treated patients, compared to those on placebo (eptifibatide 180/2.0/180 vs. placebo, 6.6% vs. 10.5% at 48 hours, P=0.0015).[4]

Similarly, in the Platelet Glycoprotein IIb/IIIa in Unstable Angina: Receptor Suppression Using INTEGRILIN Therapy (PURSUIT) trial, in which half of the patients received eptifibatide and the other half did not receive eptifibatide, the occurrence of death from any cause or new MI within 30 days was lower among patients taking eptifibatide, when compared to those on placebo (P=0.042).[3,5] This international trial included almost 11,000 patients presenting with UA or NSTEMI. Patients were enrolled only if they had experienced cardiac ischemia at rest (≥10 minutes) within the previous 24 hours and had either ST-segment changes, T-wave inversion, or increased levels of creatine kinase MB isoenzyme (CK-MB). Patients were randomized to receive placebo, eptifibatide 180-mcg/kg bolus followed by a 2.0-mcg/kg/min infusion, or eptifibatide 180-mcg/kg bolus followed by a 1.3-mcg/kg/min infusion. The infusion was continued for 72 hours, until hospital discharge, or until the time of coronary artery bypass grafting (CABG), whichever occurred first. If, however, 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.[3,5]

A third major clinical trial to demonstrate the efficacy of eptifibatide was the INTEGRILIN to Minimize Platelet Aggregation and Prevent Coronary Thrombosis II (IMPACT II) trial.[6] This multicenter, double-blind, randomized study included more than 4,000 patients who underwent PCI. Forty-one percent of the patients underwent PCI for ongoing ACS, and 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 to 24 hours. The three arms of the study were:

- 135-mcg/kg bolus followed by a continuous infusion of 0.5 mcg/kg/min of eptifibatide
- 135-mcg/kg bolus followed by a continuous infusion of 0.75 mcg/kg/min of eptifibatide
- A matching placebo bolus followed by a matching placebo continuous infusion

Each patient also received aspirin and an intravenous heparin bolus of 100 U/kg, with additional bolus infusions of up to 2,000 additional units of heparin every 15 minutes to maintain an activated clotting time (ACT) of 300 to 350 seconds.[6]

Eptifibatide 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 where event rates were 6.8% (P=0.102 vs. placebo) compared to 7.4% (P=0.272 vs. placebo) in the higher-dose group.[3]

Of note, these studies reported a risk of bleeding in patients on the antithrombotic agent. The risk of bleeding varied among these trials. Monitoring of the ACT is important. The ESPRIT study stipulated a target ACT of 200 to 300 seconds during PCI, and at these lower ACTs, bleeding was less than previously reported with eptifibatide in the PURSUIT and IMPACT II studies.[3,7]

Selected Warnings and Precautions

- Bleeding is the most common complication encountered during INTEGRILIN therapy. The majority of excess major bleeding events were localized at the femoral artery access site. Oropharyngeal, genitourinary, gastrointestinal, and retroperitoneal bleeding were also seen more commonly with INTEGRILIN compared to placebo.
- If bleeding cannot be controlled with pressure, infusion of INTEGRILIN and concomitant heparin should be stopped immediately.
- INTEGRILIN is cleared in part by the kidney and its plasma concentrations are doubled in patients with renal disease (creatinine clearance <50 mL/min). Therefore, the infusion dose of INTEGRILIN needs to be reduced to 1 mcg/kg/min in these patients.
- In the event of acute profound thrombocytopenia or a confirmed platelet decrease to <100,000mm^3, discontinue INTEGRILIN and heparin (UFH or LMWH).
- There has been no clinical experience with INTEGRILIN initiated in patients with a baseline platelet count <100,000mm^3. If a patient with low platelet counts is receiving INTEGRILIN, their platelet count should be monitored closely.
- In patients undergoing PCI, INTEGRILIN is associated with an increase in major and minor bleeding at the site of arterial sheath placement. Special care should be employed to minimize the risk of bleeding among these patients.
- Because INTEGRILIN inhibits platelet aggregation, caution should be employed when it is used with other drugs that affect hemostasis, including thrombolytics, oral anticoagulants, NSAIDs, and dipyridamole.
- Use with other GP IIb-IIIa inhibitors should be avoided.

The final factor to consider when weighing the benefits and risks of using eptifibatide is the patient's age. Elderly patients are clearly at greater risk of bleeding.[3] One of the ways to reduce the risk of bleeding in this population is to avoid the femoral artery approach to cardiac catheterization and use the radial artery instead.[8]

These factors should be taken into consideration when assessing the risk/benefit ratio.

Adhering to the Correct Dosing Schedule

Adhering to the dosing regimen outlined in the prescribing information and proven effective in the large clinical trials mentioned earlier is important. The recommended adult dosage of eptifibatide in patients with ACS and normal renal function is an intravenous bolus of 180 mcg/kg as soon as possible following diagnosis, followed by a continuous infusion of 2.0 mcg/kg/min until hospital discharge or initiation of CABG surgery, up to 72 hours. If a patient is to undergo PCI while receiving eptifibatide, the infusion should be continued until hospital discharge or for up to 18 to 24 hours after the procedure, whichever comes first, allowing for up to 96 hours of therapy.[3]

Since impaired renal function can reduce the drug's clearance and increase the risk of bleeding, these dosing instructions need to be adjusted in patients with kidney dysfunction. The recommended adult dosage of eptifibatide in patients with

ACS with an estimated creatinine clearance (using the Cockcroft-Gault equation) below 50 mL/min is an intravenous bolus of 180 mcg/kg as soon as possible following diagnosis, immediately followed by a continuous infusion of 1.0 mcg/kg/min.[3]

Since intense heparin therapy has been associated with an increased risk of bleeding in patients on eptifibatide, clinicians should be familiar with the heparin dosing instructions for patients with ACS. The target activated partial thromboplastin time is 50 to 70 seconds during medical management. If a patient weighs 70 kg or more, a 5,000-U bolus of heparin is recommended, followed by an infusion of 1,000 U/h. Patients weighing less than 70 kg should receive a 60-U/kg bolus followed by an infusion of 12 U/kg/h. The target listed in the prescribing information is an ACT of 200 to 300 seconds during PCI. If heparin is initiated prior to PCI, additional boluses during PCI to maintain an ACT target of 200 to 300 seconds are recommended. Heparin infusion after PCI is discouraged.[3]

Before prescribing INTEGRILIN, please read the accompanying Prescribing Information.

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