ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

INTEGRILIN 0.75 mg/ml solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml of solution for infusion contains 0.75 mg of eptifibatide.

One vial of 100 ml of solution for infusion contains 75 mg of eptifibatide.

Excipients with known effect
Contains 161 mg of sodium per 100 ml vial

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for infusion.

Clear, colourless solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

INTEGRILIN is intended for use with acetylsalicylic acid and unfractionated heparin.

INTEGRILIN is indicated for the prevention of early myocardial infarction in adults presenting with unstable angina or non-Q-wave myocardial infarction, with the last episode of chest pain occurring within 24 hours and with electrocardiogram (ECG) changes and/or elevated cardiac enzymes.

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 symptoms including for instance those that are likely to undergo an early PTCA (Percutaneous Transluminal Coronary Angioplasty) (see section 5.1).

4.2 Posology and method of administration

This product is for hospital use only. It should be administered by specialist physicians experienced in the management of acute coronary syndromes.

INTEGRILIN solution for infusion must be used in conjunction with INTEGRILIN solution for injection.

Concurrent administration of heparin is recommended unless this is contraindicated for reasons such as a history of thrombocytopenia associated with use of heparin (see ‘Heparin administration’, section 4.4). INTEGRILIN is also intended for concurrent use with acetylsalicylic acid, as it is part of standard management of patients with acute coronary syndromes, unless its use is contraindicated.

Posology

Adults (≥ 18 years of age) presenting with unstable angina (UA) or non-Q-wave myocardial infarction (NQMI)
The recommended dosage is an intravenous bolus of 180 microgram/kg administered as soon as possible following diagnosis, followed by a continuous infusion of 2 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 Percutaneous Coronary Intervention (PCI) is performed during eptifibatide therapy, continue the infusion for 20-24 hours post-PCI for an overall maximum duration of therapy of 96 hours.

Emergency or semi-elective surgery
If the patient requires emergency or urgent cardiac surgery during the course of eptifibatide therapy, terminate the infusion immediately. If the patient requires semi-elective surgery, stop the eptifibatide infusion at an appropriate time to allow time for platelet function to return towards normal.

Hepatic impairment
Experience in patients with hepatic impairment is very limited. Administer with caution to patients with hepatic impairment in whom coagulation could be affected (see section 4.3, prothrombin time). It is contraindicated in patients with clinically significant hepatic impairment.

Renal impairment
In patients with moderate renal impairment (creatinine clearance ≥ 30 - < 50 ml/min**)**, an intravenous bolus of 180 microgram/kg should be administered followed by a continuous infusion dose of 1.0 microgram/kg/min for the duration of therapy. This recommendation is based on pharmacodynamic and pharmacokinetic data. The available clinical evidence cannot however confirm that this dose modification results in a preserved benefit (see section 5.1). Use in patients with more severe renal impairment is contraindicated (see section 4.3).

Paediatric population
It is not recommended for use in children and adolescents below 18 years of age, due to a lack of data on safety and efficacy.

4.3 Contraindications

INTEGRILIN must not be used to treat patients with:
- hypersensitivity to the active substance or to any of the excipients listed in section 6.1
- evidence of gastrointestinal bleeding, gross genitourinary bleeding or other active abnormal bleeding within the previous 30 days of treatment
- history of stroke within 30 days or any history of haemorrhagic stroke
- known history of intracranial disease (neoplasm, arteriovenous malformation, aneurysm)
- major surgery or severe trauma within past 6 weeks
- a history of bleeding diathesis
- thrombocytopenia (< 100,000 cells/mm^3)
- prothrombin time > 1.2 times control, or International Normalized Ratio (INR) ≥ 2.0
- severe hypertension (systolic blood pressure > 200 mm Hg or diastolic blood pressure > 110 mm Hg on antihypertensive therapy)
- severe renal impairment (creatinine clearance < 30 ml/min) or dependency on renal dialysis
- clinically significant hepatic impairment
- concomitant or planned administration of another parenteral glycoprotein (GP) IIb/IIIa inhibitor

4.4 Special warnings and precautions for use

Bleeding
INTEGRILIN is an antithrombotic agent that acts by inhibition of platelet aggregation; therefore the patient must be observed carefully for indications of bleeding during treatment (see section 4.8). Women, the elderly, patients with low body weight or with moderate renal impairment (creatinine

clearance ≥ 30 - < 50 ml/min) may have an increased risk of bleeding. Monitor these patients closely with regard to bleeding.

An increased risk of bleeding may also be observed in patients who receive early administration of INTEGRILIN (e.g. upon diagnosis) compared to receiving it immediately prior to PCI, as seen in the Early ACS trial. Unlike the approved posology in the EU, all patients in this trial were administered a double bolus before the infusion (see section 5.1).

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 and genitourinary tracts) must be observed carefully. Other potential bleeding sites such as central and peripheral nervous system and retroperitoneal sites, must be carefully considered too.

Because INTEGRILIN inhibits platelet aggregation, caution must be employed when it is used with other medicinal products that affect haemostasis, including ticlopidine, clopidogrel, thrombolytics, oral anticoagulants, dextran solutions, adenosine, sulfinpyrazone, prostacyclin, non-steroidal anti-inflammatory agents, or dypyridamole (see section 4.5).

There is no experience with INTEGRILIN and low molecular weight heparins.

There is limited therapeutic experience with INTEGRILIN in patients for whom thrombolytic therapy is generally indicated (e.g. acute transmural myocardial infarction with new pathological Q-waves or elevated ST-segments or left bundle branch block in the ECG). Consequently the use of INTEGRILIN is not recommended in these circumstances (see section 4.5).

INTEGRILIN infusion should be stopped immediately if circumstances arise that necessitate thrombolytic therapy or if the patient must undergo an emergency CABG surgery or requires an intraortic balloon pump.

If serious bleeding occurs that is not controllable with pressure, the INTEGRILIN infusion should be stopped immediately and any unfractionated heparin that is given concomitantly.

Arterial procedures
During treatment with eptifibatide there is a significant increase in bleeding rates, especially in the femoral artery area, where the catheter sheath is introduced. Take care to ensure that only the anterior wall of the femoral artery is punctured. Arterial sheaths may be removed when coagulation has returned to normal (e.g. when activated clotting time (ACT) is less than 180 seconds (usually 2-6 hours after discontinuation of heparin). After removal of the introducer sheath, careful haemostasis must be ensured under close observation.

Thrombocytopenia and Immunogencity related to GP IIb/IIIa inhibitors
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 eptifibatide or placebo. Thrombocytopaenia, including acute profound thrombocytopaenia, has been observed with eptifibatide administration post-marketing (see section 4.8)

The mechanism, whether immune- and/or non-immune-mediated, by which eptifibatide may induce thrombocytopaenia is not fully understood. However, treatment with eptifibatide was associated with antibodies that recognise GPIIb/IIIa occupied by eptifibatide, suggesting an immune-mediated mechanism. Thrombocytopaenia occurring after first exposure to a GPIIb/IIIa inhibitor may be explained by the fact that antibodies are naturally present in some normal individuals.

Since either repeat exposure with any GP IIb/IIIa ligand-mimetic agent (like abciximab or eptifibatide) or first-time exposure to a GP IIb/IIIa inhibitor may be associated with immune-mediated thrombocytopenic responses, monitoring is required, i.e. platelet counts should be monitored prior to

treatment, within 6 hours of administration, and at least once daily thereafter while on therapy and immediately at clinical signs of unexpected bleeding tendency.

If either a confirmed platelet decrease to < 100,000/mm^3 or acute profound thrombocytopaenia is observed, discontinuation of each treatment medication having known or suspected thrombocytopenic effects, including eptifibatide, heparin and clopidogrel, should be considered immediately. The decision to use platelet transfusions should be based upon clinical judgment on an individual basis.

In patients with previous immune-mediated thrombocytopaenia from other parenteral GP IIb/IIIa inhibitors, there are no data with the use of INTEGRILIN. Therefore, it is not recommended to administer eptifibatide in patients who have previously experienced immune mediated thrombocytopenia with GP IIb/IIIa inhibitors, including eptifibatide.

Heparin administration
Heparin administration is recommended unless a contraindication (such as a history of thrombocytopenia associated with use of heparin) is present.

UA/NQMI: For a patient who weighs ≥ 70 kg, it is recommended that a bolus dose of 5,000 units is given, followed by a constant intravenous infusion of 1,000 units/hr. If the patient weighs < 70 kg, a bolus dose of 60 units/kg is recommended, followed by an infusion of 12 units/kg/hr. The activated partial thromboplastin time (aPTT) must be monitored in order to maintain a value between 50 and 70 seconds, above 70 seconds there may be an increased risk of bleeding.

If PCI is to be performed in the setting of UA/NQMI, monitor the activated clotting time (ACT) to maintain a value between 300-350 seconds. Stop heparin administration if the ACT exceeds 300 seconds; do not administer until the ACT falls below 300 seconds.

Monitoring of laboratory values
Before infusion of INTEGRILIN, the following laboratory tests are recommended to identify pre-existing haemostatic abnormalities: prothrombin time (PT) and aPTT, serum creatinine, platelet count, haemoglobin and haematocrit levels. Haemoglobin, haematocrit, and platelet count are to be monitored as well within 6 hours after start of therapy and at least once daily thereafter while on therapy (or more often if there is evidence of a marked decrease). If the platelet count falls below 100,000/mm^3, further platelet counts are required to rule out pseudothrombocytopenia. Discontinue unfractionated heparin. In patients undergoing PCI, measure the ACT also.

Sodium
This medicinal product contains 161 mg sodium per 100 ml vial, equivalent to 8.1% of the WHO recommended maximum daily intake of 2 g sodium for an adult.

4.5 Interaction with other medicinal products and other forms of interaction

Warfarin and dipyridamole
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.

INTEGRILIN and thrombolytic agents
Data are limited on the use of INTEGRILIN in patients receiving thrombolytic agents. There was no consistent evidence that eptifibatide increased the risk of major or minor bleeding associated with tissue plasminogen activator in either a PCI or an acute myocardial infarction study. Eptifibatide appeared to increase the risk of bleeding when administered with streptokinase in an acute myocardial infarction study. The combination of reduced dose tenecteplase and eptifibatide compared to placebo and eptifibatide significantly increased the risk of both major and minor bleeding when administered concomitantly in an acute ST-elevation myocardial infarction study.

In an acute myocardial infarction study involving 181 patients, eptifibatide (in regimens up to a bolus injection of 180 microgram/kg, followed by an infusion up to 2 microgram/kg/min for up to 72 hours) was administered concomitantly with streptokinase (1.5 million units over 60 minutes). At the highest infusion rates (1.3 microgram/kg/min and 2.0 microgram/kg/min) studied, eptifibatide was associated with an increased incidence of bleeding and transfusions compared to the incidence seen when streptokinase was given alone.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no adequate data from the use of eptifibatide in pregnant women.

Animal studies are insufficient with respect to effects on pregnancy, embryonal/foetal development, parturition or postnatal development (see section 5.3). The potential risk for humans is unknown. INTEGRILIN should not be used during pregnancy unless clearly necessary.

Breast-feeding

It is not known whether eptifibatide is excreted in human milk. Interruption of breast-feeding during the treatment period is recommended.

4.7 Effects on ability to drive and use machines

Not relevant, as INTEGRILIN is intended for use only in hospitalised patients.

4.8 Undesirable effects

The majority of adverse reactions experienced by patients treated with eptifibatide were generally related to bleeding or to cardiovascular events that occur frequently in this patient population.

Clinical Trials
The data sources used to determine adverse reaction frequency descriptors included two phase III clinical studies (PURSUIT and ESPRIT). These trials are briefly described below.

PURSUIT: This was a randomised, double-blind evaluation of the efficacy and safety of Integrilin versus placebo for reducing mortality and myocardial (re)infarction in patients with unstable angina or non-Q-wave myocardial infarction.

ESPRIT: This was a double-blind, multicentre, randomised, parallel-group, placebo-controlled trial evaluating the safety and efficacy of eptifibatide therapy in patients scheduled to undergo non-emergent percutaneous coronary intervention (PCI) with stent implantation.

In PURSUIT, bleeding and non-bleeding events were collected from hospital discharge to the 30 day visit. In ESPRIT, bleeding events were reported at 48 hours, and non-bleeding events were reported at 30 days. While Thrombolysis in Myocardial Infarction TIMI bleeding criteria were used to categorize the incidence of major and minor bleeding in both the PURSUIT and the ESPRIT trials, PURSUIT data was collected within 30 days while ESPRIT data was limited to events within 48 hours or discharge, whichever came first.

The undesirable effects are listed by body system and frequency. Frequencies are defined as very common (≥1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (< 1/10,000). These are absolute reporting frequencies without taking into account placebo rates. For a particular adverse reaction, if data was available from both PURSUIT and ESPRIT, then the highest reported incidence was used to assign adverse reaction frequency.

Note that causality has not been determined for all adverse reactions.

Blood and Lymphatic System Disorder	
Very common	Bleeding (major and minor bleeding including femoral artery access, CABG-related, gastrointestinal, genitourinary, retroperitoneal, intracranial, haematemesis, haematuria, oral/oropharyngeal, haemoglobin/haematocrit decreased and other).
Uncommon	Thrombocytopenia.
Nervous System disorders	
Uncommon	Cerebral ischaemia.
Cardiac Disorders	
Common	Cardiac arrest, ventricular fibrillation, ventricular tachycardia, congestive heart failure, atrioventricular block, atrial fibrillation.
Vascular Disorders	
Common	Shock, hypotension, phlebitis.

Cardiac arrest, congestive heart failure, atrial fibrillation, hypotension, and shock, which are commonly reported events from the PURSUIT trial, were events related to the underlying disease.

Administration of eptifibatide is associated with an increase in major and minor bleeding as classified by the criteria of the TIMI study group. At the recommended therapeutic dose, as administered in the PURSUIT trial involving nearly 11,000 patients, bleeding was the most common complication encountered during eptifibatide therapy. The most common bleeding complications were associated with cardiac invasive procedures (coronary artery bypass grafting (CABG)-related or at femoral artery access site).

Minor bleeding was defined in the PURSUIT trial as spontaneous gross haematuria, spontaneous haematemesis, observed blood loss with a haemoglobin decrease of more than 3 g/dl, or a haemoglobin decrease of more than 4 g/dl in the absence of an observed bleeding site. During treatment with Integrilin in this study, minor bleeding was a very common complication (>1/10, or 13.1% for Integrilin versus 7.6% for placebo). Bleeding events were more frequent in patients receiving concurrent heparin while undergoing PCI, when ACT exceeded 350 seconds (see section 4.4, heparin use).

Major bleeding was defined in the PURSUIT trial as either an intracranial haemorrhage or a decrease in haemoglobin concentrations of more than 5 g/dl. Major bleeding was also very common and reported more frequently with Integrilin than with placebo in the PURSUIT study ($\geq$1/10 or 10.8% versus 9.3%), but it was infrequent in the vast majority of patients who did not undergo CABG within 30 days of inclusion in the study. In patients undergoing CABG, the incidence of bleeding was not increased by Integrilin compared to the patients treated with placebo. In the subgroup of patients undergoing PCI, major bleeding was observed commonly, in 9.7 % of Integrilin-treated patients vs. 4.6 % of placebo-treated patients.

The incidence of severe or life threatening bleeding events with Integrilin was 1.9% compared to 1.1% with placebo. The need for blood transfusions was increased modestly by Integrilin treatment (11.8% versus 9.3% for placebo).

Changes during eptifibatide treatment result from its known pharmacological 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 eptifibatide or with placebo in values for liver function (SGOT/AST, SGPT/ALT, bilirubin, alkaline phosphatase) or renal function (serum creatinine, blood urea nitrogen).

Post-marketing experience

Blood and lymphatic system disorders	
Very rare	Fatal bleeding (the majority involved central and peripheral nervous system disorders: cerebral or intracranial haemorrhages); pulmonary haemorrhage, acute profound thrombocytopenia, haematoma.
Immune system disorders	
Very rare	Anaphylactic reactions.
Skin and subcutaneous tissue disorders	
Very rare	Rash, application site disorders such as urticaria.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

The experience in humans with overdose of eptifibatide is extremely limited. There was no indication of severe adverse reactions 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 the recommended dose, 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 surgery was reported as having had a moderate bleed. Specifically, no patients experienced an intracranial bleed.

Potentially, an overdose of eptifibatide could result in bleeding. Because of its short half-life and rapid clearance, the activity of eptifibatide may be halted readily by discontinuing the infusion. Thus, although eptifibatide can be dialysed, the need for dialysis is unlikely.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antithrombotic agent (platelet aggregation inhibitors excl. heparin), ATC code: B01AC16

Mechanism of action

Eptifibatide, a synthetic cyclic heptapeptide containing six amino acids, including one cysteine amide and one mercaptopropionyl (desamino cysteinyl) residue, is an inhibitor of platelet aggregation and belongs to the class of RGD (arginine-glycine-aspartate)-mimetics.

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.

Pharmacodynamic effects

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.

Platelet inhibition was readily reversed, with a return of platelet function towards baseline (> 50 % platelet aggregation) 4 hours after stopping a continuous infusion of 2.0 microgram/kg/min. Measurements of ADP-induced *ex vivo* platelet aggregation at physiologic calcium concentrations (D-phenylalanyl-L-prolyl-L-arginine chloromethyl ketone 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 approximately 550 ng/ml and an IC_{80} (80 % inhibitory concentration) of approximately 1,100 ng/ml.

There is limited data with regards to platelet inhibition in patients with renal impairment. In patients with moderate renal impairment, (creatinine clearance 30 – 50mL/min) 100% inhibition was achieved at 24 hours following administration of 2 microgram/kg/min. In patients with severe renal impairment (creatinine clearance <30mL/min) administered 1microgram/kg/min , 80% inhibition was achieved in more than 80% of patients at 24 hours.

Clinical efficacy and safety

PURSUIT trial
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, randomised, placebo-controlled study in 10,948 patients presenting with UA or NQMI. Patients could be enrolled only if they had experienced cardiac ischemia at rest (≥ 10 minutes) within the previous 24 hours and had:

- either ST-segment changes: 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 randomised to either placebo, eptifibatide 180 microgram/kg bolus followed by a 2.0 microgram/kg/min infusion (180/2.0), or eptifibatide 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 eptifibatide 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 eptifibatide infusion, of whom approximately 50 % received intracoronary stents; 87 % were managed medically (without PCI during eptifibatide infusion).

The vast majority of patients received acetylsalicylic acid (75-325 mg once daily).
Unfractionated heparin was administered intravenously or subcutaneously at the physician's discretion, most commonly as an intravenous bolus of 5,000 U followed by a continuous infusion of 1,000 U/h. A target aPTT of 50-70 seconds was recommended. A total of 1,250 patients underwent PCI within 72 hours after randomisation, 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 randomisation. The component MI could be defined as asymptomatic with enzymatic elevation of CK-MB or new Q wave.

Compared to placebo, eptifibatide 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 Randomised» Population)

Time	Placebo	Eptifibatide	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 eptifibatide.

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 eptifibatide 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 eptifibatide 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

PURSUIT was conducted at a time when the standard of care of managing acute coronary syndromes was different from that of present times in terms of thienopyridine use and the routine use of intracoronary stents.

ESPRIT trial
ESPRIT (Enhanced Suppression of the Platelet IIb/IIIa Receptor with eptifibatide Therapy) was a double-blind, randomised, placebo-controlled trial (n= 2,064) for nonurgent PCI with intracoronary stenting.

All patients received routine standard of care and were randomised to either placebo or eptifibatide (2 bolus doses of 180 microgram/kg and a continuous infusion until discharge from hospital or a maximum of 18-24 hours).

The first bolus and the infusion were started simultaneously, immediately before the PCI procedure and were followed by a second bolus 10 minutes after the first. The rate of infusion was 2.0 microgram/kg/min for patients with serum creatinine ≤ 175 micromols/l or 1.0 microgram/kg/min for serum creatinine > 175 up to 350 micromols/l.

In the eptifibatide arm of the trial, virtually all patients received aspirin (99.7 %), and 98.1 % received a thienopyridine, (clopidogrel in 95.4 % and ticlopidine in 2.7 %). On the day of PCI, prior to catheterization, 53.2 % received a thienopyridine (clopidogrel 52.7 %; ticlopidine 0.5 %) – mostly as a

loading dose (300 mg or more). The placebo arm was comparable (aspirin 99.7 %, clopidogrel 95.9 %, ticlopidin 2.6 %).

The ESPRIT trial used a simplified regimen of heparin during PCI that consisted of an initial bolus of 60 units/kg, with a target ACT of 200 - 300 seconds. The primary endpoint of the trial was death (D), MI, urgent target vessel revascularisation (UTVR), and acute antithrombotic rescue with GP IIb/IIIa inhibitor therapy (RT) within 48 hours of randomisation.

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 ≥ 3 x the upper limit of normal; thus, validation by the CEC was not required. MI could also be reported following CEC adjudication of an investigator report.

The primary endpoint analysis [quadruple composite of death, MI, urgent target vessel revascularisation (UTVR) and thrombolytic bail-out (TBO) at 48 hours] showed a 37 % relative and 3.9 % absolute reduction in the eptifibatide group (6.6 % events versus 10.5 %, p = 0.0015). Results on the primary endpoint were mainly attributed to the reduction of enzymatic MI occurrence, identified as the occurrence of early elevation of cardiac enzymes after PCI (80 out of 92 MIs in the placebo group vs. 47 out of 56 MIs in the eptifibatide group). The clinical relevance of such enzymatic MIs is still controversial.

Similar results were also obtained for the 2 secondary endpoints assessed at 30 days: a triple composite of death, MI and UTVR, and the more robust combination of death and MI.

The reduction in the incidence of endpoint events in patients receiving eptifibatide appeared early during treatment. There was no increased benefit thereafter, up to 1 year.

Prolongation of bleeding time
Administration of eptifibatide 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 in approximately 6 (2-8) hours. When administered alone, eptifibatide has no measurable effect on prothrombin time (PT) or activated partial thromboplastin time (aPTT).

EARLY-ACS trial
EARLY ACS (Early Glycoprotein IIb/IIIa Inhibition in Non-ST-segment Elevation Acute Coronary Syndrome) was a study of early routine eptifibatide versus placebo (with delayed provisional use of eptifibatide in the catheterization laboratory) used in combination with antithrombotic therapies (ASA, UFH, bivalirudin, fondaparinux or low molecular weight heparin), in subjects with high-risk NSTE ACS. Patients were to undergo an invasive strategy for further management after receiving study drug for 12 to 96 hours. Patients could be medically managed, proceed to coronary artery bypass graft (CABG), or undergo percutaneous coronary intervention (PCI). Unlike the approved posology in the EU, the study used a double bolus of study drug (separated by 10 minutes) before the infusion.

Early routine eptifibatide in this high-risk NSTE-ACS optimally-treated population who were managed with an invasive strategy did not result in a statistically significant reduction in the composite primary endpoint of rate of death, MI, RI-UR, and TBO within 96 hours compared with a regimen of delayed provisional eptifibatide (9.3% in early eptifibatide patients vs. 10.0% in patients assigned to delayed provisional eptifibatide; odds ratio=0.920; 95% CI=0.802-1.055; p=0.234). GUSTO severe/life threatening bleeding was uncommon and comparable in both treatment groups (0.8%). GUSTO moderate or severe/life threatening bleeding occurred significantly more often with early routine eptifibatide (7.4% vs. 5.0% in delayed provisional eptifibatide group; p <0.001). Similar

differences were noted for TIMI major haemorrhage (118 [2.5%] in early routine use vs. 83 [1.8%] in delayed provisional use; p=0.016).

No statistically significant benefit of early routine eptifibatide strategy was demonstrated in the subgroup of patients who were managed medically or during the medical management periods prior to PCI or CABG.

In a post hoc analysis of the EARLY ACS trial the risk benefit of dose reduction in patients with moderate renal impairment is inconclusive. The primary endpoint event rate was 11.9 % in patients who received a reduced dose (1microgram/kg/min) vs 11.2% in patients who received the standard dose (2microgram/kg/min) when eptifibatide was administered in the early routine fashion (p=0.81). With delayed provisional eptifibatide administration, the event rates were 10% vs 11.5% in patients who received reduced dose and standard dose respectively (p=0.61). TIMI major bleeding occurred in 2.7 % of patients who received a reduced dose (1microgram/kg/min) vs 4.2% of patients who received the standard dose (2microgram/kg/min) when eptifibatide was administered in the early routine fashion (p=0.36). With delayed provisional eptifibatide administration, the TIMI major events were 1.4% vs 2.0% in patients who received reduced dose and standard dose respectively (p=0.54). There were no notable differences observed with GUSTO severe bleeding rates.

5.2 Pharmacokinetic properties

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. In patients with moderate to severe renal insufficiency (creatinine clearance < 50 ml/min), the clearance of eptifibatide is reduced by approximately 50% and steady-state plasma levels are approximately doubled.

No formal pharmacokinetic interaction studies have been conducted. However, in a population pharmacokinetic study there was no evidence of a pharmacokinetic interaction between eptifibatide and the following concomitant medicinal products: amlodipine, atenolol, atropine, captopril, cefazolin, diazepam, digoxin, diltiazem, diphenhydramine, enalapril, fentanyl, furosemide, heparin, lidocaine, lisinopril, metoprolol, midazolam, morphine, nitrates, nifedipine, and warfarin.

5.3 Preclinical safety data

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 genotoxic effects were observed with eptifibatide.

Teratology studies have been performed by continuous intravenous infusion of eptifibatide in pregnant rats at total daily doses of up to 72 mg/kg/day (about 4 times the recommended maximum daily human dose on a body surface area basis) and in pregnant rabbits at total daily doses of up to 36 mg/kg/day (about 4 times the recommended maximum daily human dose on a body surface area basis). These studies revealed no evidence of impaired fertility or harm to the foetus due to eptifibatide. Reproduction studies in animal species where eptifibatide shows a similar pharmacologic activity as in

humans are not available. Consequently these studies are not suitable to evaluate the toxicity of eptifibatide on reproductive function (see section 4.6).

The carcinogenic potential of eptifibatide has not been evaluated in long-term studies.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Citric acid monohydrate
Sodium hydroxide
Water for injections

6.2 Incompatibilities

INTEGRILIN is not compatible with furosemide.

In the absence of compatibility studies, INTEGRILIN must not be mixed with other medicinal products except those mentioned in 6.6.

6.3 Shelf life

3 years

6.4 Special precautions for storage

Store in a refrigerator (2°C - 8°C).
Store in the original package in order to protect from light.

6.5 Nature and contents of container

One 100 ml Type I glass vial, closed with a butyl rubber stopper and sealed with a crimped aluminium seal.

6.6 Special precautions for disposal and other handling

Physical and chemical compatibility testing indicate that INTEGRILIN 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 solution for infusion and with dextrose 5 % in Normosol R with or without potassium chloride. Please refer to the Normosol R Summary of Product Characteristics for details on its composition.

Before using, inspect the vial contents. Do not use if particulate matter or discolouration is present. Protection of INTEGRILIN solution from light is not necessary during administration.

Discard any unused medicinal product after opening.

7. MARKETING AUTHORISATION HOLDER

GlaxoSmithKline (Ireland) Limited
12 Riverwalk
Citywest Business Campus
Dublin 24
Ireland

8. MARKETING AUTHORISATION NUMBER

EU/1/99/109/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 01.07.1999
Date of latest renewal: 09.07.2009

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu

1. NAME OF THE MEDICINAL PRODUCT

INTEGRILIN 2 mg/ml solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml of solution for injection contains 2 mg of eptifibatide.

One vial of 10 ml of solution for injection contains 20 mg of eptifibatide.

Excipients with known effect
Contains 13.8 mg of sodium per 10 ml vial

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection.

Clear, colourless solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

INTEGRILIN is intended for use with acetylsalicylic acid and unfractionated heparin.

INTEGRILIN is indicated for the prevention of early myocardial infarction in adults presenting with unstable angina or non-Q-wave myocardial infarction, with the last episode of chest pain occurring within 24 hours and with electrocardiogram (ECG) changes and/or elevated cardiac enzymes.

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 symptoms including for instance those that are likely to undergo an early PTCA (Percutaneous Transluminal Coronary Angioplasty) (see section 5.1).

4.2 Posology and method of administration

This product is for hospital use only. It should be administered by specialist physicians experienced in the management of acute coronary syndromes.

INTEGRILIN solution for injection must be used in conjunction with INTEGRILIN solution for infusion.

Concurrent administration of heparin is recommended unless this is contraindicated for reasons such as a history of thrombocytopenia associated with use of heparin (see ‘Heparin administration’, section 4.4). INTEGRILIN is also intended for concurrent use with acetylsalicylic acid, as it is part of standard management of patients with acute coronary syndromes, unless its use is contraindicated.

Posology

Adults (≥ 18 years of age) presenting with unstable angina (UA) or non-Q-wave myocardial infarction (NQMI)
The recommended dosage is an intravenous bolus of 180 microgram/kg administered as soon as possible following diagnosis, followed by a continuous infusion of 2 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 Percutaneous Coronary Intervention (PCI) is performed during eptifibatide therapy, continue the infusion for 20-24 hours post-PCI for an overall maximum duration of therapy of 96 hours.

Emergency or semi-elective surgery
If the patient requires emergency or urgent cardiac surgery during the course of eptifibatide therapy, terminate the infusion immediately. If the patient requires semi-elective surgery, stop the eptifibatide infusion at an appropriate time to allow time for platelet function to return towards normal.

Hepatic impairment
Experience in patients with hepatic impairment is very limited. Administer with caution to patients with hepatic impairment in whom coagulation could be affected (see section 4.3, prothrombin time). It is contraindicated in patients with clinically significant hepatic impairment.

Renal impairment
In patients with moderate renal impairment (creatinine clearance ≥ 30 - < 50 ml/min**)**, an intravenous bolus of 180 microgram/kg should be administered followed by a continuous infusion dose of 1.0 microgram/kg/min for the duration of therapy. This recommendation is based on pharmacodynamic and pharmacokinetic data. The available clinical evidence cannot however confirm that this dose modification results in a preserved benefit (see section 5.1). Use in patients with more severe renal impairment is contraindicated (see section 4.3).

Paediatric population
It is not recommended for use in children and adolescents below 18 years of age, due to a lack of data on safety and efficacy.

4.3 Contraindications

INTEGRILIN must not be used to treat patients with:
- hypersensitivity to the active substance or to any of the excipients listed in section 6.1
- evidence of gastrointestinal bleeding, gross genitourinary bleeding or other active abnormal bleeding within the previous 30 days of treatment
- history of stroke within 30 days or any history of haemorrhagic stroke
- known history of intracranial disease (neoplasm, arteriovenous malformation, aneurysm)
- major surgery or severe trauma within past 6 weeks
- a history of bleeding diathesis
- thrombocytopenia (< 100,000 cells/mm^3)
- prothrombin time > 1.2 times control, or International Normalized Ratio (INR) ≥ 2.0
- severe hypertension (systolic blood pressure > 200 mm Hg or diastolic blood pressure > 110 mm Hg on antihypertensive therapy)
- severe renal impairment (creatinine clearance < 30 ml/min) or dependency on renal dialysis
- clinically significant hepatic impairment
- concomitant or planned administration of another parenteral glycoprotein (GP) IIb/IIIa inhibitor

4.4 Special warnings and precautions for use

Bleeding
INTEGRILIN is an antithrombotic agent that acts by inhibition of platelet aggregation; therefore the patient must be observed carefully for indications of bleeding during treatment (see section 4.8). Women, the elderly, patients with low body weight or with moderate renal impairment (creatinine

clearance > 30 - < 50 ml/min) may have an increased risk of bleeding. Monitor these patients closely with regard to bleeding.

An increased risk of bleeding may also be observed in patients who receive early administration of INTEGRILIN (e.g. upon diagnosis) compared to receiving it immediately prior to PCI, as seen in the Early ACS trial. Unlike the approved posology in the EU, all patients in this trial were administered a double bolus before the infusion (see section 5.1).

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 and genitourinary tracts) must be observed carefully. Other potential bleeding sites such as central and peripheral nervous system and retroperitoneal sites, must be carefully considered too.

Because INTEGRILIN inhibits platelet aggregation, caution must be employed when it is used with other medicinal products that affect haemostasis, including ticlopidine, clopidogrel, thrombolytics, oral anticoagulants, dextran solutions, adenosine, sulfinpyrazone, prostacyclin, non-steroidal anti-inflammatory agents, or dypyridamole (see section 4.5).

There is no experience with INTEGRILIN and low molecular weight heparins.

There is limited therapeutic experience with INTEGRILIN in patients for whom thrombolytic therapy is generally indicated (e.g. acute transmural myocardial infarction with new pathological Q-waves or elevated ST-segments or left bundle branch block in the ECG). Consequently the use of INTEGRILIN is not recommended in these circumstances (see section 4.5).

INTEGRILIN infusion should be stopped immediately if circumstances arise that necessitate thrombolytic therapy or if the patient must undergo an emergency CABG surgery or requires an intraortic balloon pump.

If serious bleeding occurs that is not controllable with pressure, the INTEGRILIN infusion should be stopped immediately and any unfractionated heparin that is given concomitantly.

Arterial procedures
During treatment with eptifibatide there is a significant increase in bleeding rates, especially in the femoral artery area, where the catheter sheath is introduced. Take care to ensure that only the anterior wall of the femoral artery is punctured. Arterial sheaths may be removed when coagulation has returned to normal (e.g. when activated clotting time (ACT) is less than 180 seconds (usually 2-6 hours after discontinuation of heparin). After removal of the introducer sheath, careful haemostasis must be ensured under close observation.

Thrombocytopenia and Immunogencity related to GP IIb/IIIa inhibitors
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 eptifibatide or placebo. Thrombocytopaenia, including acute profound thrombocytopaenia, has been observed with eptifibatide administration post-marketing (see section 4.8).

The mechanism, whether immune- and/or non-immune-mediated, by which eptifibatide may induce thrombocytopaenia is not fully understood. However, treatment with eptifibatide was associated with antibodies that recognise GPIIb/IIIa occupied by eptifibatide, suggesting an immune-mediated mechanism. Thrombocytopaenia occurring after first exposure to a GPIIb/IIIa inhibitor may be explained by the fact that antibodies are naturally present in some normal individuals.

Since either repeat exposure with any GP IIb/IIIa ligand-mimetic agent (like abciximab or eptifibatide) or first-time exposure to a GP IIb/IIIa inhibitor may be associated with immune-mediated thrombocytopenic responses, monitoring is required, i.e. platelet counts should be monitored prior to

treatment, within 6 hours of administration, and at least once daily thereafter while on therapy and immediately at clinical signs of unexpected bleeding tendency.

If either a confirmed platelet decrease to < 100,000/mm^3 or acute profound thrombocytopaenia is observed, discontinuation of each treatment medication having known or suspected thrombocytopenic effects, including eptifibatide, heparin and clopidogrel, should be considered immediately. The decision to use platelet transfusions should be based upon clinical judgment on an individual basis.

In patients with previous immune-mediated thrombocytopaenia from other parenteral GP IIb/IIIa inhibitors, there are no data with the use of INTEGRILIN. Therefore, it is not recommended to administer eptifibatide in patients who have previously experienced immune mediated thrombocytopenia with GP IIb/IIIa inhibitors, including eptifibatide.

Heparin administration
Heparin administration is recommended unless a contraindication (such as a history of thrombocytopenia associated with use of heparin) is present.

UA/NQMI: For a patient who weighs ≥ 70 kg, it is recommended that a bolus dose of 5,000 units is given, followed by a constant intravenous infusion of 1,000 units/hr. If the patient weighs < 70 kg, a bolus dose of 60 units/kg is recommended, followed by an infusion of 12 units/kg/hr. The activated partial thromboplastin time (aPTT) must be monitored in order to maintain a value between 50 and 70 seconds, above 70 seconds there may be an increased risk of bleeding.

If PCI is to be performed in the setting of UA/NQMI, monitor the activated clotting time (ACT) to maintain a value between 300-350 seconds. Stop heparin administration if the ACT exceeds 300 seconds; do not administer until the ACT falls below 300 seconds.

Monitoring of laboratory values
Before infusion of INTEGRILIN, the following laboratory tests are recommended to identify pre-existing haemostatic abnormalities: prothrombin time (PT) and aPTT, serum creatinine, platelet count, haemoglobin and haematocrit levels. Haemoglobin, haematocrit, and platelet count are to be monitored as well within 6 hours after start of therapy and at least once daily thereafter while on therapy (or more often if there is evidence of a marked decrease). If the platelet count falls below 100,000/mm^3, further platelet counts are required to rule out pseudothrombocytopenia. Discontinue unfractionated heparin. In patients undergoing PCI, measure the ACT also.

Sodium
This medicinal product contains 13.8 mg sodium per 10 ml vial, equivalent to 0.69% of the WHO recommended maximum daily intake of 2 g sodium for an adult.

4.5 Interaction with other medicinal products and other forms of interaction

Warfarin and dipyridamole
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.

INTEGRILIN and thrombolytic agents
Data are limited on the use of INTEGRILIN in patients receiving thrombolytic agents. There was no consistent evidence that eptifibatide increased the risk of major or minor bleeding associated with tissue plasminogen activator in either a PCI or an acute myocardial infarction study. Eptifibatide appeared to increase the risk of bleeding when administered with streptokinase in an acute myocardial infarction study. The combination of reduced dose tenecteplase and eptifibatide compared to placebo

and eptifibatide significantly increased the risk of both major and minor bleeding when administered concomitantly in an acute ST-elevation myocardial infarction study.

In an acute myocardial infarction study involving 181 patients, eptifibatide (in regimens up to a bolus injection of 180 microgram/kg, followed by an infusion up to 2 microgram/kg/min for up to 72 hours) was administered concomitantly with streptokinase (1.5 million units over 60 minutes). At the highest infusion rates (1.3 microgram/kg/min and 2.0 microgram/kg/min) studied, eptifibatide was associated with an increased incidence of bleeding and transfusions compared to the incidence seen when streptokinase was given alone.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no adequate data from the use of eptifibatide in pregnant women.

Animal studies are insufficient with respect to effects on pregnancy, embryonal/foetal development, parturition or postnatal development (see section 5.3). The potential risk for humans is unknown. INTEGRILIN should not be used during pregnancy unless clearly necessary.

Breast-feeding

It is not known whether eptifibatide is excreted in human milk. Interruption of breast-feeding during the treatment period is recommended.

4.7 Effects on ability to drive and use machines

Not relevant, as INTEGRILIN is intended for use only in hospitalised patients.

4.8 Undesirable effects

The majority of adverse reactions experienced by patients treated with eptifibatide were generally related to bleeding or to cardiovascular events that occur frequently in this patient population.

Clinical Trials
The data sources used to determine adverse reaction frequency descriptors included two phase III clinical studies (PURSUIT and ESPRIT). These trials are briefly described below.

PURSUIT: This was a randomised, double-blind evaluation of the efficacy and safety of Integrilin versus placebo for reducing mortality and myocardial (re)infarction in patients with unstable angina or non-Q-wave myocardial infarction.

ESPRIT: This was a double-blind, multicentre, randomised, parallel-group, placebo-controlled trial evaluating the safety and efficacy of eptifibatide therapy in patients scheduled to undergo non-emergent percutaneous coronary intervention (PCI) with stent implantation.

In PURSUIT, bleeding and non-bleeding events were collected from hospital discharge to the 30 day visit. In ESPRIT, bleeding events were reported at 48 hours, and non-bleeding events were reported at 30 days. While Thrombolysis in Myocardial Infarction TIMI bleeding criteria were used to categorize the incidence of major and minor bleeding in both the PURSUIT and the ESPRIT trials, PURSUIT data was collected within 30 days while ESPRIT data was limited to events within 48 hours or discharge, whichever came first.

The undesirable effects are listed by body system and frequency. Frequencies are defined as very common (≥1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (< 1/10,000). These are absolute reporting frequencies without taking into

account placebo rates. For a particular adverse reaction, if data was available from both PURSUIT and ESPRIT, then the highest reported incidence was used to assign adverse reaction frequency.

Note that causality has not been determined for all adverse reactions.

Blood and Lymphatic System Disorder	
Very common	Bleeding (major and minor bleeding including femoral artery access, CABG-related, gastrointestinal, genitourinary, retroperitoneal, intracranial, haematemesis, haematuria, oral/oropharyngeal, haemoglobin/haematocrit decreased and other).
Uncommon	Thrombocytopenia.
Nervous System disorders	
Uncommon	Cerebral ischaemia.
Cardiac Disorders	
Common	Cardiac arrest, ventricular fibrillation, ventricular tachycardia, congestive heart failure, atrioventricular block, atrial fibrillation.
Vascular Disorders	
Common	Shock, hypotension, phlebitis.

Cardiac arrest, congestive heart failure, atrial fibrillation, hypotension, and shock, which are commonly reported events from the PURSUIT trial, were events related to the underlying disease.

Administration of eptifibatide is associated with an increase in major and minor bleeding as classified by the criteria of the TIMI study group. At the recommended therapeutic dose, as administered in the PURSUIT trial involving nearly 11,000 patients, bleeding was the most common complication encountered during eptifibatide therapy. The most common bleeding complications were associated with cardiac invasive procedures (coronary artery bypass grafting (CABG)-related or at femoral artery access site).

Minor bleeding was defined in the PURSUIT trial as spontaneous gross haematuria, spontaneous haematemesis, observed blood loss with a haemoglobin decrease of more than 3 g/dl, or a haemoglobin decrease of more than 4 g/dl in the absence of an observed bleeding site. During treatment with Integrilin in this study, minor bleeding was a very common complication (>1/10, or 13.1% for Integrilin versus 7.6% for placebo). Bleeding events were more frequent in patients receiving concurrent heparin while undergoing PCI, when ACT exceeded 350 seconds (see section 4.4, heparin use).

Major bleeding was defined in the PURSUIT trial as either an intracranial haemorrhage or a decrease in haemoglobin concentrations of more than 5 g/dl. Major bleeding was also very common and reported more frequently with Integrilin than with placebo in the PURSUIT study ($\geq$1/10 or 10.8% versus 9.3%), but it was infrequent in the vast majority of patients who did not undergo CABG within 30 days of inclusion in the study. In patients undergoing CABG, the incidence of bleeding was not increased by Integrilin compared to the patients treated with placebo. In the subgroup of patients undergoing PCI, major bleeding was observed commonly, in 9.7 % of Integrilin-treated patients vs. 4.6 % of placebo-treated patients.

The incidence of severe or life threatening bleeding events with Integrilin was 1.9% compared to 1.1% with placebo. The need for blood transfusions was increased modestly by Integrilin treatment (11.8% versus 9.3% for placebo).

Changes during eptifibatide treatment result from its known pharmacological 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 eptifibatide or with placebo in values for liver function (SGOT/AST, SGPT/ALT, bilirubin, alkaline phosphatase) or renal function (serum creatinine, blood urea nitrogen).

Post-marketing experience

Blood and lymphatic system disorders	
Very rare	Fatal bleeding (the majority involved central and peripheral nervous system disorders: cerebral or intracranial haemorrhages); pulmonary haemorrhage, acute profound thrombocytopenia, haematoma.
Immune system disorders	
Very rare	Anaphylactic reactions.
Skin and subcutaneous tissue disorders	
Very rare	Rash, application site disorders such as urticaria.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

The experience in humans with overdose of eptifibatide is extremely limited. There was no indication of severe adverse reactions 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 the recommended dose, 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 surgery was reported as having had a moderate bleed. Specifically, no patients experienced an intracranial bleed.

Potentially, an overdose of eptifibatide could result in bleeding. Because of its short half-life and rapid clearance, the activity of eptifibatide may be halted readily by discontinuing the infusion. Thus, although eptifibatide can be dialysed, the need for dialysis is unlikely.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antithrombotic agent (platelet aggregation inhibitors excl. heparin), ATC code: B01AC16

Mechanism of action

Eptifibatide, a synthetic cyclic heptapeptide containing six amino acids, including one cysteine amide and one mercaptopropionyl (desamino cysteinyl) residue, is an inhibitor of platelet aggregation and belongs to the class of RGD (arginine-glycine-aspartate)-mimetics.

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.

Pharmacodynamic effects

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.

Platelet inhibition was readily reversed, with a return of platelet function towards baseline (> 50 % platelet aggregation) 4 hours after stopping a continuous infusion of 2.0 microgram/kg/min. Measurements of ADP-induced *ex vivo* platelet aggregation at physiologic calcium concentrations (D-phenylalanyl-L-prolyl-L-arginine chloromethyl ketone 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 approximately 550 ng/ml and an IC_{80} (80 % inhibitory concentration) of approximately 1,100 ng/ml.

There is limited data with regards to platelet inhibition in patients with renal impairment. In patients with moderate renal impairment, (creatinine clearance 30 – 50mL/min) 100% inhibition was achieved at 24 hours following administration of 2 microgram/kg/min. In patients with severe renal impairment (creatinine clearance <30mL/min) administered 1microgram/kg/min , 80% inhibition was achieved in more than 80% of patients at 24 hours.

Clinical efficacy and safety

PURSUIT trial

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, randomised, placebo-controlled study in 10,948 patients presenting with UA or NQMI. Patients could be enrolled only if they had experienced cardiac ischemia at rest (≥ 10 minutes) within the previous 24 hours and had:

- either ST-segment changes: 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 randomised to either placebo, eptifibatide 180 microgram/kg bolus followed by a 2.0 microgram/kg/min infusion (180/2.0), or eptifibatide 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 eptifibatide

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

The vast majority of patients received acetylsalicylic acid (75-325 mg once daily).
Unfractionated heparin was administered intravenously or subcutaneously at the physician's discretion, most commonly as an intravenous bolus of 5,000 U followed by a continuous infusion of 1,000 U/h. A target aPTT of 50-70 seconds was recommended. A total of 1,250 patients underwent PCI within 72 hours after randomisation, 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 randomisation. The component MI could be defined as asymptomatic with enzymatic elevation of CK-MB or new Q wave.

Compared to placebo, eptifibatide 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 Randomised» Population)

Time	Placebo	Eptifibatide	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 eptifibatide.

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 eptifibatide 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 eptifibatide 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

PURSUIT was conducted at a time when the standard of care of managing acute coronary syndromes was different from that of present times in terms of thienopyridine use and the routine use of intracoronary stents.

ESPRIT trial
ESPRIT (Enhanced Suppression of the Platelet IIb/IIIa Receptor with eptifibatide Therapy) was a double-blind, randomised, placebo-controlled trial (n= 2,064) for nonurgent PCI with intracoronary stenting.

All patients received routine standard of care and were randomised to either placebo or eptifibatide (2 bolus doses of 180 microgram/kg and a continuous infusion until discharge from hospital or a maximum of 18-24 hours).

The first bolus and the infusion were started simultaneously, immediately before the PCI procedure and were followed by a second bolus 10 minutes after the first. The rate of infusion was 2.0 microgram/kg/min for patients with serum creatinine ≤ 175 micromols/l or 1.0 microgram/kg/min for serum creatinine > 175 up to 350 micromols/l.

In the eptifibatide arm of the trial, virtually all patients received aspirin (99.7 %), and 98.1 % received a thienopyridine, (clopidogrel in 95.4 % and ticlopidine in 2.7 %). On the day of PCI, prior to catheterization, 53.2 % received a thienopyridine (clopidogrel 52.7 %; ticlopidine 0.5 %) – mostly as a loading dose (300 mg or more). The placebo arm was comparable (aspirin 99.7 %, clopidogrel 95.9 %, ticlopidin 2.6 %).

The ESPRIT trial used a simplified regimen of heparin during PCI that consisted of an initial bolus of 60 units/kg, with a target ACT of 200 - 300 seconds. The primary endpoint of the trial was death (D), MI, urgent target vessel revascularisation (UTVR), and acute antithrombotic rescue with GP IIb/IIIa inhibitor therapy (RT) within 48 hours of randomisation.

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 ≥ 3 x the upper limit of normal; thus, validation by the CEC was not required. MI could also be reported following CEC adjudication of an investigator report.

The primary endpoint analysis [quadruple composite of death, MI, urgent target vessel revascularisation (UTVR) and thrombolytic bail-out (TBO) at 48 hours] showed a 37 % relative and 3.9 % absolute reduction in the eptifibatide group (6.6 % events versus 10.5 %, p = 0.0015). Results on the primary endpoint were mainly attributed to the reduction of enzymatic MI occurrence, identified as the occurrence of early elevation of cardiac enzymes after PCI (80 out of 92 MIs in the placebo group vs. 47 out of 56 MIs in the eptifibatide group). The clinical relevance of such enzymatic MIs is still controversial.

Similar results were also obtained for the 2 secondary endpoints assessed at 30 days: a triple composite of death, MI and UTVR, and the more robust combination of death and MI.

The reduction in the incidence of endpoint events in patients receiving eptifibatide appeared early during treatment. There was no increased benefit thereafter, up to 1 year.

Prolongation of bleeding time
Administration of eptifibatide 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 in approximately 6 (2-8) hours. When administered alone, eptifibatide has no measurable effect on prothrombin time (PT) or activated partial thromboplastin time (aPTT).

EARLY-ACS trial
EARLY ACS (Early Glycoprotein IIb/IIIa Inhibition in Non-ST-segment Elevation Acute Coronary Syndrome) was a study of early routine eptifibatide versus placebo (with delayed provisional use of eptifibatide in the catheterization laboratory) used in combination with antithrombotic therapies (ASA, UFH, bivalirudin, fondaparinux or low molecular weight heparin), in subjects with high-risk NSTE ACS. Patients were to undergo an invasive strategy for further management after receiving study drug for 12 to 96 hours. Patients could be medically managed, proceed to coronary artery bypass graft (CABG), or undergo percutaneous coronary intervention (PCI). Unlike the approved posology in the EU, the study used a double bolus of study drug (separated by 10 minutes) before the infusion.

Early routine eptifibatide in this high-risk NSTE-ACS optimally-treated population who were managed with an invasive strategy did not result in a statistically significant reduction in the composite primary endpoint of rate of death, MI, RI-UR, and TBO within 96 hours compared with a regimen of delayed provisional eptifibatide (9.3% in early eptifibatide patients vs. 10.0% in patients assigned to delayed provisional eptifibatide; odds ratio=0.920; 95% CI=0.802-1.055; p=0.234). GUSTO severe/life threatening bleeding was uncommon and comparable in both treatment groups (0.8%). GUSTO moderate or severe/life threatening bleeding occurred significantly more often with early routine eptifibatide (7.4% vs. 5.0% in delayed provisional eptifibatide group; p <0.001). Similar differences were noted for TIMI major haemorrhage (118 [2.5%] in early routine use vs. 83 [1.8%] in delayed provisional use; p=0.016).

No statistically significant benefit of early routine eptifibatide strategy was demonstrated in the subgroup of patients who were managed medically or during the medical management periods prior to PCI or CABG.

In a post hoc analysis of the EARLY ACS trial the risk benefit of dose reduction in patients with moderate renal impairment is inconclusive. The primary endpoint event rate was 11.9 % in patients who received a reduced dose (1microgram/kg/min) vs 11.2% in patients who received the standard dose (2microgram/kg/min) when eptifibatide was administered in the early routine fashion (p=0.81). With delayed provisional eptifibatide administration, the event rates were 10% vs 11.5% in patients who received reduced dose and standard dose respectively (p=0.61). TIMI major bleeding occurred in 2.7 % of patients who received a reduced dose (1microgram/kg/min) vs 4.2% of patients who received the standard dose (2microgram/kg/min) when eptifibatide was administered in the early routine fashion (p=0.36). With delayed provisional eptifibatide administration, the TIMI major events were 1.4% vs 2.0% in patients who received reduced dose and standard dose respectively (p=0.54). There were no notable differences observed with GUSTO severe bleeding rates.

5.2 Pharmacokinetic properties

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. In patients with moderate to severe renal insufficiency (creatinine clearance < 50 ml/min), the clearance of eptifibatide is reduced by approximately 50% and steady-state plasma levels are approximately doubled.

No formal pharmacokinetic interaction studies have been conducted. However, in a population pharmacokinetic study there was no evidence of a pharmacokinetic interaction between eptifibatide and the following concomitant medicinal products: amlodipine, atenolol, atropine, captopril, cefazolin,

diazepam, digoxin, diltiazem, diphenhydramine, enalapril, fentanyl, furosemide, heparin, lidocaine, lisinopril, metoprolol, midazolam, morphine, nitrates, nifedipine, and warfarin.

5.3 Preclinical safety data

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 genotoxic effects were observed with eptifibatide.

Teratology studies have been performed by continuous intravenous infusion of eptifibatide in pregnant rats at total daily doses of up to 72 mg/kg/day (about 4 times the recommended maximum daily human dose on a body surface area basis) and in pregnant rabbits at total daily doses of up to 36 mg/kg/day (about 4 times the recommended maximum daily human dose on a body surface area basis). These studies revealed no evidence of impaired fertility or harm to the foetus due to eptifibatide. Reproduction studies in animal species where eptifibatide shows a similar pharmacologic activity as in humans are not available. Consequently these studies are not suitable to evaluate the toxicity of eptifibatide on reproductive function (see section 4.6).

The carcinogenic potential of eptifibatide has not been evaluated in long-term studies.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Citric acid monohydrate
Sodium hydroxide
Water for injections

6.2 Incompatibilities

INTEGRILIN is not compatible with furosemide.

In the absence of compatibility studies, INTEGRILIN must not be mixed with other medicinal products except those mentioned in 6.6.

6.3 Shelf life

3 years

6.4 Special precautions for storage

Store in a refrigerator (2°C - 8°C). Store in the original package in order to protect from light.

6.5 Nature and contents of container

One 10 ml Type I glass vial, closed with a butyl rubber stopper and sealed with a crimped aluminium seal.

6.6 Special precautions for disposal and other handling

Physical and chemical compatibility testing indicate that INTEGRILIN 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 solution for injection and with dextrose 5 % in Normosol R with or without potassium chloride. Please refer to the Normosol R Summary of Product Characteristics for details on its composition.

Before using, inspect the vial contents. Do not use if particulate matter or discolouration is present. Protection of INTEGRILIN solution from light is not necessary during administration.

Discard any unused medicinal product after opening.

7. MARKETING AUTHORISATION HOLDER

GlaxoSmithKline (Ireland) Limited
12 Riverwalk
Citywest Business Campus
Dublin 24
Ireland

8. MARKETING AUTHORISATION NUMBER

EU/1/99/109/002

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 01.07.1999
Date of latest renewal: 09.07.2009

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu

ANNEX II

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer responsible for batch release

GlaxoSmithKline Manufacturing S.P.A.
Strada Provinciale Asolana No. 90
San Polo di Torrile 43056
Parma
Italy

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (See Annex I: Summary of Product Characteristics, 4.2)

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON

1. NAME OF THE MEDICINAL PRODUCT

INTEGRILIN 0.75 mg/ml solution for infusion
eptifibatide

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each ml of solution for infusion contains 0.75 mg of eptifibatide.

One 100 ml vial contains 75 mg of eptifibatide.

3. LIST OF EXCIPIENTS

Citric acid monohydrate, sodium hydroxide, water for injections

This medicine contains sodium (see package leaflet for further information)

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for infusion

1 vial of 100 ml

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Intravenous use
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Inspect the vial content. Do not use if particulate matter or discolouration is present.

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.

Store in the original package in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Discard any unused material after opening.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

GlaxoSmithKline (Ireland) Limited, 12 Riverwalk, Citywest Business Campus, Dublin 24, Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/99/109/001

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC:
SN:
NN:

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

INTEGRILIN 0.75 mg/ml solution for infusion
eptifibatide

Intravenous use

2. METHOD OF ADMINISTRATION

Read the package leaflet before use

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Batch

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

1 vial of 100 ml

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON

1. NAME OF THE MEDICINAL PRODUCT

INTEGRILIN 2 mg/ml solution for injection
eptifibatide

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each ml of solution for injection contains 2 mg of eptifibatide.

One 10 ml vial contains 20 mg of eptifibatide.

3. LIST OF EXCIPIENTS

Citric acid monohydrate, sodium hydroxide, water for injections

This medicine contains sodium (see package leaflet for further information)

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection

1 vial of 10 ml

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Intravenous use

Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Inspect the vial content. Do not use if particulate matter or discolouration is present.

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.

Store in the original package in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Discard any unused material after opening.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

GlaxoSmithKline (Ireland) Limited, 12 Riverwalk, Citywest Business Campus, Dublin 24, Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/99/109/002

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC:
SN:
NN:

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

INTEGRILIN 2 mg/ml solution for injection
eptifibatide

Intravenous use

2. METHOD OF ADMINISTRATION

Read the package leaflet before use

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Batch

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

1 vial of 10 ml

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

Integrilin 0.75 mg/ml solution for infusion
eptifibatide

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or hospital pharmacist or nurse.
- If you get any side effects talk to your doctor or hospital pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet:

1. What Integrilin is and what it is used for

Integrilin is an inhibitor of platelet aggregation. This means that it helps to prevent blood clots from forming.

It is used in adults with manifestation of severe coronary insufficiency defined as spontaneous and recent chest pain with electrocardiographic abnormalities or biological changes. It is usually given with aspirin and unfractionated heparin.

2. What you need to know before you are given Integrilin

You must not be given Integrilin:
- if you are allergic to eptifibatide or any of the other ingredients of this medicine (listed in section 6).
- if you have recently had bleeding from your stomach, intestines, bladder or other organs, for example if you have seen abnormal blood in your stool or urine (except from menstrual bleeding) in the past 30 days.
- if you have had a stroke within the past 30 days or any haemorrhagic stroke (also, be sure your doctor knows if you ever had a stroke).
- if you have had a brain tumour or a condition that affects the blood vessels around the brain.
- if you had a major operation or severe injury during the past 6 weeks.
- if you have or have had bleeding problems.
- if you have or have had difficulty with your blood clotting or a low blood platelet count.
- if you have or have had severe hypertension (high blood pressure).
- if you have or have had severe kidney or liver problems.
- if you have been treated with another medicineof the same type as Integrilin.

Please tell your doctor if you have had any of these conditions. If you have any questions, ask your doctor or hospital pharmacist or nurse.

Take special care with Integrilin:
- Integrilin is recommended for use only in adult, hospitalised patients in coronary care units.
- Integrilin is not intended for use in children or adolescents less than 18 years of age.

– Before and during your treatment with Integrilin, samples of your blood will be tested as a safety measure to limit the possibility of unexpected bleeding.
  During use of Integrilin, you will be checked carefully for any signs of unusual or unexpected bleeding.

Other medicines and Integrilin
To avoid the possibility of interactions with other medicines please tell your doctor or hospital pharmacist or nurse if you are taking or have recently taken or might take any other medicines, including medicines obtained without a prescription. Particularly:
– blood thinners (oral anticoagulants) or
– medicines that prevent blood clots, including warfarin, dipyridamole, ticlopidine, aspirin (except those that you may be given as part of Integrilin treatment).

Pregnancy and breast-feeding
Integrilin is not usually recommended for use during pregnancy. Tell your doctor if you are pregnant, think you might be pregnant or are planning to have a baby. Your doctor will weigh up the benefit to you against the risk to your baby of using Integrilin while you are pregnant.

If you are breast-feeding a baby, breast-feeding should be interrupted during the treatment period.

Integrilin contains sodium
– This medicine contains 161 mg sodium (main component of cooking/table salt) in each 100 ml vial. This is equivalent to 8.1% of the recommended maximum daily dietary intake of sodium for an adult.

3. How to use Integrilin

Integrilin is given into the vein by direct injection followed by an infusion (drip solution). The dose given is based on your weight. The recommended dose is 180 microgram/kg administered as a bolus (rapid intravenous injection), followed by an infusion (drip solution) of 2 microgram/kg/minute for up to 72 hours. If you have kidney disease, the infusion dose may be reduced to 1 microgram/kg/minute.

If percutaneous coronary intervention (PCI) is performed during Integrilin therapy, the intravenous solution may be continued for up to 96 hours.

You must also be given doses of aspirin and heparin (if not contraindicated in your case).

If you have any further questions on the use of this product, ask your doctor or hospital pharmacist or nurse.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Very common side effects
These may affect more than 1 in 10 people
– minor or major bleeding, (for example, blood in urine, blood in stool, vomiting blood, or bleeding with surgical procedures).
– anaemia (decreased number of red blood cells).

Common side effects
These may affect up to 1 in 10 people
– inflammation of a vein.

Uncommon side effects
These may affect up to 1 in 100 people

– reduction in the number of platelets (blood cells necessary for blood clotting).
– reduced blood flow to the brain.

Very rare side effects
These may affect up to 1 in 10,000 people
– serious bleeding (for example, bleeding inside the abdomen, inside the brain, and into the lungs).
– fatal bleeding.
– severe reduction in the number of platelets (blood cells necessary for blood clotting).
– skin rash (such as hives).
– sudden, severe allergic reaction.

If you notice any signs of bleeding, notify your doctor or hospital pharmacist or nurse immediately. Very rarely, bleeding has become severe and even fatal. Safety measures to prevent this from happening include blood tests and careful checking by the healthcare professionals taking care of you.

If you develop severe allergic reaction or hives, notify your doctor or hospital pharmacist or nurse immediately.

Other events that may occur in patients, who require this type of treatment, include those that are related to the condition you are having treated, such as rapid or irregular heartbeat, low blood pressure, shock or cardiac arrest.

Reporting of side effects
If you get any side effects, talk to your doctor, hospital pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Integrilin

Keep this medicine out of the sight and reach of children

Do not use this medicine after the expiry date (EXP) stated on the package and the vial. The expiry date refers to the last day of that month.

Store in a refrigerator (2°C – 8°C).

Keep the vial in the outer package in order to protect from light. However, protection of Integrilin solution from light is not necessary during administration.

Before using, the vial contents should be inspected.
Integrilin should not be used if it is noticed that particulate matter or discoloration is present.

Any unused medicine after opening should be thrown away.

Do not throw away any medicines via wastewater or household waste. Ask your hospital pharmacist how to throw away medicines you no longer use.

6. Contents of the pack and other information

What Integrilin contains

- The active substance is eptifibatide. Each ml of solution for infusion contains 0.75 mg of eptifibatide. One vial of 100 ml of solution for infusion contains 75 mg of eptifibatide.
- The other ingredients are citric acid monohydrate, sodium hydroxide and water for injections.

What Integrilin looks like and contents of the pack

Integrilin solution for infusion: 100 ml vial, pack of one vial.

The clear, colourless solution is contained in a 100 ml glass vial, which is closed with a butyl rubber stopper and sealed with a crimped aluminium seal.

Marketing Authorisation Holder and manufacturer

Marketing Authorisation Holder:

GlaxoSmithKline (Ireland) Limited, 12 Riverwalk, Citywest Business Campus, Dublin 24, Ireland

Manufacturer:

GlaxoSmithKline Manufacturing S.P.A., Strada Provinciale Asolana No. 90, San Polo di Torrile 43056, Parma, Italy

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder.

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customercontactuk@gsk.com

This leaflet was last revised in

Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu

Package leaflet: Information for the patient

Integrilin 2 mg/ml solution for injection
eptifibatide

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or hospital pharmacist or nurse.
- If you get side effects talk to your doctor or hospital pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet:

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2. What you need to know before you are given Integrilin

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- if you have recently had bleeding from your stomach, intestines, bladder or other organs, for example if you have seen abnormal blood in your stool or urine (except from menstrual bleeding) in the past 30 days.
- if you have had a stroke within the past 30 days or any haemorrhagic stroke (also, be sure your doctor knows if you ever had a stroke).
- if you have had a brain tumour or a condition that affects the blood vessels around the brain.
- if you had a major operation or severe injury during the past 6 weeks.
- if you have or have had bleeding problems.
- if you have or have had difficulty with your blood clotting or a low blood platelet count.
- if you have or have had severe hypertension (high blood pressure).
- if you have or have had severe kidney or liver problems.
- if you have been treated with another medicine of the same type as Integrilin.

Please tell your doctor if you have had any of these conditions. If you have any questions, ask your doctor or hospital pharmacist or nurse.

Take special care with Integrilin:
- Integrilin is recommended for use only in adult, hospitalised patients in coronary care units.
- Integrilin is not intended for use in children or adolescents less than 18 years of age.

– Before and during your treatment with Integrilin, samples of your blood will be tested as a safety measure to limit the possibility of unexpected bleeding.
  During use of Integrilin, you will be checked carefully for any signs of unusual or unexpected bleeding.

Other medicines and Integrilin
To avoid the possibility of interactions with other medicines please tell your doctor or hospital pharmacist if you are taking or have recently taken or might take any other medicines, including medicines obtained without a prescription. Particularly:
– blood thinners (oral anticoagulants) or
– medicines that prevent blood clots, including warfarin, dipyridamole, ticlopidine, aspirin (except those that you may be given as part of Integrilin treatment).

Pregnancy and breast-feeding
Integrilin is not usually recommended for use during pregnancy. Tell your doctor if you are pregnant, think you might be pregnant or are planning to have a baby. Your doctor will weigh up the benefit to you against the risk to your baby of using Integrilin while you are pregnant.

If you are breast-feeding a baby, breast-feeding should be interrupted during the treatment period.

Integrilin contains sodium
– This medicine contains 13.8 mg sodium (main component of cooking/table salt) in each 10 ml vial. This is equivalent to 0.69% of the recommended maximum daily dietary intake of sodium for an adult.

3. How to use Integrilin

Integrilin is given into the vein by direct injection followed by an infusion (drip solution). The dose given is based on your weight. The recommended dose is 180 microgram/kg administered as a bolus (rapid intravenous injection), followed by an infusion (drip solution) of 2 microgram/kg/minute for up to 72 hours. If you have kidney disease, the infusion dose may be reduced to 1 microgram/kg/minute.

If percutaneous coronary intervention (PCI) is performed during Integrilin therapy, the intravenous solution may be continued for up to 96 hours.

You must also be given doses of aspirin and heparin (if not contraindicated in your case).

If you have any further questions on the use of this product, ask your doctor or hospital pharmacist or nurse.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Very common side effects
These may affect more than 1 in 10 people
– minor or major bleeding, (for example, blood in urine, blood in stool, vomiting blood, or bleeding with surgical procedures).
– anaemia (decreased number of red blood cells).

Common side effects
These may affect up to 1 in 10 people
– inflammation of a vein.

Uncommon side effects
These may affect up to 1 in 100 people

– reduction in the number of platelets (blood cells necessary for blood clotting).
– reduced blood flow to the brain.

Very rare side effects
These may affect up to 1 in 10,000 people
– serious bleeding (for example, bleeding inside the abdomen, inside the brain, and into the lungs)
– fatal bleeding.
– severe reduction in the number of platelets (blood cells necessary for blood clotting).
– skin rash (such as hives).
– sudden, severe allergic reaction.

If you notice any signs of bleeding, notify your doctor or hospital pharmacist or nurse immediately. Very rarely, bleeding has become severe and even fatal. Safety measures to prevent this from happening include blood tests and careful checking by the healthcare professionals taking care of you.

If you develop severe allergic reaction or hives, notify your doctor or hospital pharmacist or nurse immediately.

Other events that may occur in patients, who require this type of treatment, include those that are related to the condition you are having treated, such as rapid or irregular heartbeat, low blood pressure, shock or cardiac arrest.

Reporting of side effects
If you get any side effects, talk to your doctor, hospital pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Integrilin

Keep this medicine out of the sight and reach of children

Do not use this medicine after the expiry date (EXP) stated on the package and the vial. The expiry date refers to the last day of that month.

Store in a refrigerator (2°C – 8°C).

Keep the vial in the outer package in order to protect from light. However, protection of Integrilin solution from light is not necessary during administration.

Before using, the vial contents should be inspected.

Integrilin should not be used if it is noticed that particulate matter or discoloration is present.

Any unused medicine after opening should be thrown away.

Do not throw away any medicines via wastewater or household waste. Ask your hospital pharmacist how to throw away medicines you no longer use.

6. Contents of the pack and other information

What Integrilin contains
- The active substance is eptifibatide. Each ml of solution for injection contains 2 mg of eptifibatide. One vial of 10 ml solution for injection contains 20 mg of eptifibatide.
- The other ingredients are citric acid monohydrate, sodium hydroxide and water for injections.

What Integrilin looks like and contents of the pack
Integrilin solution for injection: 10 ml vial, pack of one vial.

The clear, colourless solution is contained in a 10 ml glass vial, which is closed with a butyl rubber stopper and sealed with a crimped aluminium seal.
Marketing Authorisation Holder and manufacturer

Marketing Authorisation Holder:

GlaxoSmithKline (Ireland) Limited, 12 Riverwalk, Citywest Business Campus, Dublin 24, Ireland

Manufacturer:

GlaxoSmithKline Manufacturing S.P.A., Strada Provinciale Asolana No. 90, San Polo di Torrile 43056, Parma, Italy

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder.

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Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu