Eptifibatide 0.75 mg/ml, solution for infusion
Eptifibatide 2 mg/ml, solution for injection

PL 20117/0115-0116

UKPAR

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LAY SUMMARY

Eptifibatide 0.75 mg/ml, solution for infusion
Eptifibatide 2 mg/ml, solution for injection

This is a summary of the Public Assessment Report (PAR) for Eptifibatide 0.75 mg/ml, solution for infusion (PL 20117/0115) and Eptifibatide 2 mg/ml, solution for injection (PL 20117/0116). It explains how Eptifibatide 0.75 mg/ml, solution for infusion and Eptifibatide 2 mg/ml, solution for injection were assessed and their authorisation recommended, as well as their conditions of use. It is not intended to provide practical advice on how to use Eptifibatide 0.75 mg/ml, solution for infusion and Eptifibatide 2 mg/ml, solution for injection.

For practical information about using Eptifibatide 0.75 mg/ml, solution for infusion and Eptifibatide 2 mg/ml solution for injection, patients should read the package leaflet or contact their doctor or pharmacist.

The products may be referred to as ‘Eptifibatide’ or ‘Eptifibatide 0.75 mg/ml and 2 mg/ml’ in this report.

What is Eptifibatide and what is it used for?

Eptifibatide solution for infusion and Eptifibatide 2 mg/ml solution for injection are ‘generic’ medicines. This means that Eptifibatide 0.75 mg/ml solution for infusion and Eptifibatide 2 mg/ml solution for injection are similar to reference medicines already authorised in the European Union (EU) called Integrilin 0.75 mg/ml Solution for Infusion and Integrilin 2.00 mg/ml Solution for Injection (Glaxo Group Limited).

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

How does Eptifibatide work?

Eptifibatide, the active substance, is an inhibitor of platelet aggregation. This means that it helps to prevent blood clots from forming.

How is Eptifibatide used?

Eptifibatide is available as a solution for infusion and as a solution for injection. Eptifibatide is given by a health professional into a vein by direct injection and is followed by an infusion (drip solution) of eptifibatide.

The dose given is based on the patient’s weight. The recommended dose is 180 micrograms/kg administered as a bolus (rapid intravenous injection), followed by an infusion (drip solution) of 2 micrograms/kg/minute for up to 72 hours. The infusion dose may be reduced to 1 microgram/kg/minute in patients with kidney disease.

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

The patient may also be given doses of aspirin and heparin (if not contraindicated).

Eptifibatide can only be obtained on prescription and is for hospital use only.
For further information on how Eptifibatide 0.75 mg/ml solution for infusion and Eptifibatide 2 mg/ml solution for injection are used, please refer to the respective package leaflet and Summary of Product Characteristics available on the Medicines and Healthcare products Regulatory Agency (MHRA) website.

**What benefits of Eptifibatide have been shown in studies?**
No additional studies were needed as Eptifibatide 0.75 mg/ml and 2 mg/ml are generic medicines that are given by injection or by infusion that contain the same active substance as the reference medicines, Integrilin 0.75 mg/ml, solution for infusion and Integrilin 2.00 mg/ml, solution for injection (Glaxo Group Limited).

**What are possible side effects of Eptifibatide?**
Because Eptifibatide 0.75 mg/ml and 2 mg/ml are generic medicines of the reference medicines Integrilin 0.75 mg/ml, solution for infusion and Integrilin 2.00 mg/ml, solution for injection (Glaxo Group Limited), the possible side effects are taken as being the same as those of the reference medicines.

For the full list of restrictions, see the package leaflets available on the MHRA website.

**Why is Eptifibatide approved?**
It was concluded that, in accordance with EU requirements, Eptifibatide 0.75 mg/ml and 2 mg/ml have been shown to have comparable quality and to be generic equivalents of Integrilin 0.75 mg/ml, solution for infusion and Integrilin 2.00 mg/ml solution for injection (Glaxo Group Limited), respectively. Therefore, the view was that, as for Integrilin 0.75 mg/ml, solution for infusion and Integrilin 2.00 mg/ml solution for injection (Glaxo Group Limited), the benefits outweigh the identified risks.

**What measures are being taken to ensure the safe and effective use of Eptifibatide?**
A risk management plan has been developed to ensure that Eptifibatide 0.75 mg/ml and 2 mg/ml are used as safely as possible. Based on this plan, safety information has been included in the Summaries of Product Characteristics and the package leaflets for Eptifibatide 0.75 mg/ml and 2 mg/ml, including the appropriate precautions to be followed by healthcare professionals and patients.

**Other information about Eptifibatide.**
Marketing Authorisations were granted in the UK on 03 September 2014.

The full PAR for Eptifibatide 0.75 mg/ml and 2 mg/ml follows this summary.

For more information about treatment with Eptifibatide 0.75 mg/ml and 2 mg/ml, read the package leaflets, or contact your doctor or pharmacist.

This summary was last updated in October 2014.
Eptifibatide 0.75 mg/ml, solution for infusion
Eptifibatide 2 mg/ml, solution for injection

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SCIENTIFIC DISCUSSION

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INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the Medicines and Healthcare products Regulatory Agency (MHRA) granted Morningside Healthcare Limited Marketing Authorisations for the medicinal products Eptifibatide 0.75 mg/ml solution for infusion (PL 20117/0115) and 2 mg/ml, solution for injection (PL 20117/0116) on 03 September 2014. The products are prescription only medicines (POM). The products may be referred to as Eptifibatide in this report.

Eptifibatide is intended for use with acetylsalicylic acid and unfractionated heparin. Eptifibatide 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 eptifibatide 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).

The applications were submitted under Article 10(1) of Directive 2001/83/EC, as amended, claiming to be generic medicinal products of Integrilin 0.75 mg/ml, solution for infusion and Integrilin 2.00 mg/ml, solution for injection, currently authorised in the European Economic Area (EEA) to the Glaxo Group Limited. The reference medicinal products were first authorised to Schering-Plough on 01 July 1999, following a centralised procedure application (EMEA/H/C/000230) for a new chemical entity, submitted as a complete dossier under Article 8(3) of Directive 2001/83/EC, as amended and subsequently transferred to the Glaxo Group Limited in 2004.

The active ingredient, eptifibatide, is an antithrombotic agent. It is a synthetic cyclic heptapeptide and is an inhibitor of platelet aggregation. It 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.

No new non-clinical studies were performed, which is acceptable given that the applications were based on being generic medicinal products of originator products that have been in clinical use for over 10 years.

No new clinical data have been submitted and none are required for applications of this type. A bioequivalence study was not necessary to support these applications for aqueous parenteral products, containing the same active substance as the reference products.

No new or unexpected safety concerns arose during review of information provided by the Marketing Authorisation Holder and it was, therefore, judged that the benefits of Eptifibatide 0.75 mg/ml, solution for infusion and Eptifibatide 2 mg/ml, solution for injection outweigh the risks, and Marketing Authorisations were granted.
ACTIVE SUBSTANCE

INN: Eptifibatide
Chemical Name: N^6-(aminoaminomethyl)-N^2-(3-mercapto-1-oxopropyl)-L-lysylglycyl-L-α-aspartyl)-L-tryptophyl-L-prolyl-L-cysteinamide, cyclic (1→6)-disulphide
Molecular formula: C_{35}H_{49}N_{11}O_{9}S_{2}

Molecular mass: 831.96 g/mol
Appearance: A white to off-white powder.
Solubility: Soluble in water and in 1% acetic acid at a concentration of 1 mg/ml to give a clear colourless solution.

Eptifibatide is not the subject of a European Pharmacopoeia monograph.

Synthesis of the active substance from the designated starting materials has been adequately described and appropriate in-process controls and intermediate specifications are applied. Satisfactory specification tests are in place for all starting materials and reagents and these are supported by relevant Certificates of Analysis. Appropriate proof-of-structure data have been supplied. All potential known impurities have been identified and characterised.

An appropriate specification is provided for the active substance. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications. Batch analysis data are provided that comply with the proposed specification.

Satisfactory Certificates of Analysis have been provided for all working standards.

Suitable specifications have been provided for all packaging used. The primary packaging has been shown to comply with current guidelines concerning contact with foodstuff.

Appropriate stability data have been generated to support a suitable retest period when stored in the proposed packaging.
DRUG PRODUCT
Other Ingredients
Other ingredients consist of the pharmaceutical excipients citric acid monohydrate, sodium hydroxide (for pH adjustment) and water for injections. Appropriate justification for the inclusion of each excipient has been provided.

All excipients comply with their respective European Pharmacopoeia monographs. Satisfactory Certificates of Analysis have been provided for all excipients, showing compliance with the proposed specifications.

None of the excipients contains material of animal or human origin. No genetically modified organisms (GMO) have been used in the preparation of these excipients.

Pharmaceutical Development
The objective of the development programme was to formulate safe, efficacious, stable, solutions for infusion and for injection containing 0.75 mg/ml and 2 mg/ml eptifibatide, respectively, comparable in performance to the reference products, Integrilin 0.75 mg/ml solution for infusion and Integrilin 2 mg/ml solution for injection (Glaxo Group Limited), respectively.

Suitable pharmaceutical development data have been provided for these applications.

Manufacturing Process
Satisfactory batch formulae have been provided for the manufacture of the products, along with an appropriate account of the manufacturing process. The manufacturing process has been validated with production-scale batches and has shown satisfactory results.

Control of Finished Product
The finished product specifications are satisfactory. Test methods have been described and adequately validated, as appropriate. Batch data have been provided that comply with the release specifications.

Container Closure System
Eptifibatide 0.75 mg/ml, solution for infusion is packaged in 100 ml clear Type I glass vials with bromobutyl rubber stoppers, sealed with flip off aluminium seals, in a pack size of 1 vial.

Eptifibatide 2 mg/ml, solution for injection is packed in 10 ml clear Tubular Type I glass vials with bromobutyl rubber stoppers, sealed with flip off aluminium seals, in a pack size of 1 vial.

Satisfactory specifications and Certificates of Analysis have been provided for all packaging components. All primary packaging complies with the current European regulations concerning materials for parenteral use.

Stability of the product
Finished product stability studies were performed in accordance with current guidelines on batches of finished product packed in the packaging proposed for marketing. The data from these studies support a shelf-life of 2 years for the unopened products, with the storage conditions ‘Store in a refrigerator (2°C - 8°C). Store in the original package in order to protect from light.’

Following dilution with either normal saline or PlasmaLyte 148 and 5 % Glucose, a shelf life of 24 hours is proposed. Dilutions should be stored below 25°C but do not need to be protected from light.

From a microbiological point of view, unless the method of opening/reconstitution/ dilution precludes the risk of microbial contamination, the product should be used immediately.
Suitable post approval stability commitments have been provided to continue stability studies on batches of finished product.

Bioequivalence
A bioequivalence study was not necessary to support these applications.

Summary of Product Characteristics (SmPCs), Patient Information Leaflet (PILs) and Labelling
The SmPCs, PILs and labelling are satisfactory from a pharmaceutical perspective.

A package leaflet has been submitted to the MHRA along with results of consultations with target patient groups (‘user testing’), in accordance with Article 59 of Council Directive 2001/83/EC, as amended. The leaflet conforms to the requirements. The test shows that the patients/users are able to act upon the information that the leaflet contains.

MAA (Marketing Authorisation Application) Forms
The MAA forms are satisfactory from a pharmaceutical perspective.

Expert Report (Quality Overall Summary)
The quality overall summary is written by an appropriately qualified person and is a suitable summary of the pharmaceutical aspects of the dossier.

Conclusion
The grant of Marketing Authorisations is recommended.
NON-CLINICAL ASSESSMENT

PHARMACODYNAMICS, PHARMACOKINETICS AND TOXICOLOGY
As the pharmacodynamic, pharmacokinetic and toxicological properties of eptifibatide are well-known, no further non-clinical studies are required and none have been provided.

NON-CLINICAL EXPERT REPORT (NON-CLINICAL OVERVIEW)
The applicant’s non-clinical overview has been written by an appropriately qualified person and is satisfactory, providing an appropriate review of the relevant non-clinical pharmacology, pharmacokinetics and toxicology.

ENVIRONMENTAL RISK ASSESSMENT
Suitable justification has been provided for non-submission of an Environmental Risk Assessment. As the applications are for generic versions of already authorised products, no increase in environmental burden is anticipated following approval of the Marketing Authorisations for the proposed products. Thus, non-submission of an Environmental Risk Assessment is accepted.

CONCLUSION
The grant of Marketing Authorisations is recommended.
CLINICAL ASSESSMENT

CLINICAL PHARMACOLOGY
The clinical pharmacology of eptifibatide is well-known. No new clinical pharmacology data have been submitted and none are required for this type of application. A bioequivalence study was not necessary to support these applications for aqueous parenteral products. According to CPMP guidelines, bioequivalence studies are not generally required for parenteral aqueous solutions (CPMP/EWP/QWP/1401/98 Rev. 1/Corr**, Guideline on the Investigation of Bioequivalence).

EFFICACY
The efficacy of eptifibatide is well-known. No new efficacy data have been submitted and none are required for applications of this type.

SAFETY
No new safety data were submitted and none are required for applications of this type. No new or unexpected safety concerns arose from these applications. The safety profile of eptifibatide is well-known.

PHARMACOVIGILANCE SYSTEM AND RISK MANAGEMENT PLAN
The Applicant provided a Pharmacovigilance System Master File Summary (version 1.0, September 2012) stating that they have at their service a Qualified Person for Pharmacovigilance (QPPV) responsible for Pharmacovigilance who is suitably trained and aware of the responsibilities outlined in the current applicable European Union (EU) legislation. The QPPV has the necessary means for collection and notification of any adverse drug reaction occurring either in the Community or in a third country, and the means to fulfil all other requirements of current European Pharmacovigilance legislation.

An acceptable Risk Management Plan has been provided. Routine risk minimisation is provided through the Summaries of Product Characteristics and the Patient Information Leaflets and this is sufficient.

SUMMARY OF PRODUCT CHARACTERISTICS (SmPCs), PATIENT INFORMATION LEAFLETS (PILs) AND LABELLING
The SmPCs, PILs and labelling are acceptable from a clinical perspective. The SmPCs are consistent with those for the reference products. The PILs are consistent with the details in the SmPCs and in line with current guidance. The labelling is also in line with current guidance.

CLINICAL EXPERT REPORT (CLINICAL OVERVIEW)
The clinical overview is written by an appropriately qualified physician and is a suitable summary of the clinical aspects of the dossier.

CONCLUSION
The grant of Marketing Authorisations is recommended.
OVERALL CONCLUSION AND BENEFIT/RISK ASSESSMENT

QUALITY
The important quality characteristics of Eptifibatide 0.75 mg/ml, solution for infusion and Eptifibatide 2 mg/ml, solution for injection are well-defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

NON-CLINICAL
No new non-clinical data were submitted and none are required for applications of this type. As the pharmacokinetics, pharmacodynamics and toxicology of eptifibatide are well-known, no additional data were required.

EFFICACY
No new clinical data were submitted for these applications. No bioequivalence studies were submitted or required for these applications.

SAFETY
The safety profile of eptifibatide is well-known. No new or unexpected safety issues or concerns arose from these applications.

PRODUCT LITERATURE
The SmPCs, PILs and labelling are satisfactory and consistent with those for the reference products, where appropriate, and in line with current guidance.

BENEFIT/RISK ASSESSMENT
The quality of the products is acceptable, and no new non-clinical or clinical safety concerns have been identified. Extensive clinical experience with eptifibatide is considered to have demonstrated the therapeutic value of the compound. The benefit/risk balance is therefore considered to be positive.
Eptifibatide 0.75 mg/ml, solution for infusion
Eptifibatide 2 mg/ml, solution for injection
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STEPS TAKEN FOR ASSESSMENT

1. The MHRA received the Marketing Authorisation applications on 11 February 2013 and 13 February 2013.

2. Following standard checks and communication with the applicant the MHRA considered the applications valid on 19 February 2013.

3. Following assessment of the applications, the MHRA requested further information relating to the dossier on 30 May 2013, 07 March 2014 and 16 July 2014.

4. The applicant responded to the MHRA’s requests, providing further information on the dossier on 18 December 2013, 16 June 2014 and 30 July 2014.

5. The applications were granted on 03 September 2014.
SUMMARY OF PRODUCT CHARACTERISTICS

In accordance with Directive 2010/84/EU, the Summaries of Product Characteristics (SmPCs) for products granted Marketing Authorisations at a national level are available on the MHRA website.
PATIENT INFORMATION LEAFLET

In accordance with Directive 2010/84/EU, the Patient Information Leaflets (PILs) for products granted Marketing Authorisations at a national level are available on the MHRA website.
LABELLING

Each ml of solution for infusion contains 0.75 mg of eptifibatide. One ml of solution for infusion contains 25 mg of eptifibatide. Also contains citric acid monohydrate, sodium hydroxide and water for injection. Read the package leaflet for further information.

Simple use: For intravenous use only. Do not use if particulate matter or discoloration is present. Do not re-administer. Store in the original package in order to protect from light. Do not administer any unused medicinal product after opening.

Keep out of the sight and reach of children. This product is for hospital use only.

Store in a refrigerator (2°C - 8°C).

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PL 20117/0115
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