19 November 2015
EMA/851528/2015
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Eptifibatide Accord

International non-proprietary name: eptifibatide

Procedure No. EMEA/H/C/004104/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

AP	Applicant's Part (or Open Part) of a ASMF
AS	Active substance
API	Active Pharmaceutical Ingredient
ASMF	Active Substance Master File = Drug Master File
CABG	Coronary arteries bypass grafting
Cltotal	Total body clearance
DE	Deamidated eptifibatide
EP	European Pharmacopoeia
GC	Gas Chromatography
GC-MS	Gas chromatography mass spectrometry
GP	Glycoprotein
h	Hour (s)
HDPE	High Density Polyethylene
HPLC	High performance liquid chromatography
HPLC/MS	High-performance liquid chromatography- mass spectrometry
IC	Ion exchange chromatography
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
ICP-OES	Inductively coupled plasma optical emission spectrometry
kg	Kilograms
LC-MS	Liquid chromatography mass spectrometry
LOQ	Limit of Quantitation
MAA	Marketing Authorization Application
Mg	Milligrams
MI	Myocardial infarction
Min	Minute (s)
NMR	Nuclear Magnetic Resonance
NMT	Not more than
NQMI	Non-Q-wave myocardial infarction
PCI	Percutaneous coronary intervention
Ph. Eur.	European Pharmacopoeia
RH	Relative Humidity
SmPC	Summary of product characteristics
SMs	Starting materials
STEMI	ST-segment elevation myocardial infarction
RMP	Risk management plan
UA	Unstable angina
UV	Ultraviolet

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Accord Healthcare Limited submitted on 2 December 2014 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Eptifibatide Accord, through the centralised procedure under Article 3 (3) of Regulation (EC) No. 726/2004– 'Generic of a centrally authorised product'. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 23/10/2014.

The application concerns a generic medicinal product as defined in Article 10(2)(b) of Directive 2001/83/EC and refers to a reference product for which a Marketing Authorisation is or has been granted in the Union on the basis of a complete dossier in accordance with Article 8(3) of Directive 2001/83/EC.

The applicant applied for the following indication:

Eptifibatide Accord is intended for use with acetylsalicylic acid and unfractionated heparin. Eptifibatide Accord 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 Accord 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 legal basis for this application refers to:

Generic application (Article 10(1) of Directive No 2001/83/EC).

The application submitted is composed of administrative information and complete quality data. There is no requirement for bioequivalence testing according to cf.CPMP/QWP/EWP/1401/98 Rev. 1.

Information on paediatric requirements

Not applicable.

The chosen reference product is:

- Medicinal product which is or has been authorised in accordance with Community provisions in accordance with Community provisions in force for not less than 6/10 years in the EEA:

  - Product name, strength, pharmaceutical form: INTEGRILIN 0.75 mg/ml solution for infusion and INTEGRILIN 2 mg/ml solution for injection
  - Marketing authorisation holder: Glaxo Group Ltd, United Kingdom
  - Date of authorisation: 01-07-1999
  - Marketing authorisation granted by:
    - Community
  - Marketing authorisation number: EU/1/99/109/001 (0.75 mg/ml) & EU/1/99/109/002 (2 mg/ml)

- Medicinal product authorised in the Community/Members State where the application is made or

European reference medicinal product:

- Product name, strength, pharmaceutical form: INTEGRILIN 0.75 mg/ml solution for infusion and INTEGRILIN 2 mg/ml solution for injection
- Marketing authorisation holder: Glaxo Group Ltd, United Kingdom
- Date of authorisation: 01-07-1999
- Marketing authorisation granted by:
  - Community
    - Marketing authorisation number: EU/1/99/109/001 (0.75 mg/ml) & EU/1/99/109/002 (2 mg/ml)

■ Medicinal product which is or has been authorised in accordance with Community provisions in force and to which bioequivalence has been demonstrated by appropriate bioavailability studies:

This medicinal product is a parenteral preparation. Therefore bioequivalence study is not applicable according to CPMP/EWP/QWP/1401/98 Rev.1.

Scientific advice

The applicant did not seek scientific advice at the CHMP.

Licensing status

The product was not licensed in any country at the time of submission of the application.

1.2. Steps taken for the assessment of the product

The Rapporteur appointed by the CHMP was:

Rapporteur: David Lyons Co-Rapporteur: N/A

- The application was received by the EMA on 2 December 2014.
- The procedure started on 24 December 2014.
- The Rapporteur's Assessment Report was circulated to all CHMP members on 13 March 2015.
- The PRAC RMP advice and assessment overview adopted by PRAC on 10 April 2015.
- During the meeting on 23 April 2015, the CHMP agreed on the consolidated List of Questions to be sent to the applicant.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 18 July 2015.
- The Rapporteur circulated the Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 28 August 2015.
- During the CHMP meeting on 24 September 2015, the CHMP agreed on a list of outstanding issues to be addressed in writing by the applicant.
- The applicant submitted the responses to the CHMP consolidated List of Outstanding Issues on 19 October 2015.

- The Rapporteur circulated the Assessment Report on the applicant's responses to the List of outstanding issues to all CHMP members on 28 October 2015.
- During the meeting on 19 November 2015, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a Marketing Authorisation to Eptifibatide Accord.

2. Scientific discussion

2.1. Introduction

This procedure concerns an application for the marketing authorisation of Eptifibatide Accord 0.75 mg/ml solution for infusion and 2 mg/ml solution for injection by Accord Healthcare via the centralised procedure.

Eptifibatide is approved in the EU since the 01/07/1999 under the trade name Integrilin 0.75 mg/ml solution for infusion and Integrilin 2 mg/ml solution for injection.

Eptifibatide Accord 0.75 mg/ml solution for infusion and 2 mg/ml solution for injection has the same qualitative and similar quantitative composition as the reference product, Integrilin 0.75 mg/ml solution for infusion and Integrilin 2 mg/ml solution for injection.

INTEGRILIN is indicated for:

use with acetylsalicylic acid and unfractionated heparin 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).

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. Eptifibatide is a highly specific GP IIb/IIIa receptor antagonist that competes with fibrinogen, vWF and other adhesive ligands for the binding site on GP IIb/IIIa, thereby preventing their ability to bind to the activated platelet. Eptifibatide binds to GP IIb/IIIa with low affinity (dissociation constant of 120 nM) and dissociates from the receptor rapidly. Therefore, platelet aggregation inhibition with eptifibatide is reversible following the cessation of the treatment. The binding location of eptifibatide is in the binding pocket between the IIb and IIIa arms of GP IIb/IIIa, thereby blocking the binding domain for fibrinogen and inhibiting the formation of thrombi.

Although eptifibatide is highly specific for the GP IIb/IIIa receptors, eptifibatide at higher concentrations may have the ability to interfere with vitronectin binding, the ligand for αvβ3 in vascular cells, which may provide additional antithrombotic benefits.

Eptifibatide is intended for use with acetylsalicylic acid and heparin (unless the use of acetylsalicylic acid or heparin is contraindicated).

In 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, the infusion should be continued for 20-24 hours post-PCI for an overall maximum duration of therapy of 96 hours.

If the patient requires emergency or urgent cardiac surgery during the course of eptifibatide therapy, the infusion should be terminated immediately. If the patient requires semi-elective surgery, the eptifibatide infusion should be stopped 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. Eptifibatide should be administered with caution to patients with hepatic impairment in whom coagulation could be affected. 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. Use in patients with more severe renal impairment is contraindicated.

Paediatric population

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

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. Eptifibatide Accord solution for infusion must be used in conjunction with Eptifibatide Accord 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. Eptifibatide Accord 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.

2.2. Quality aspects

2.2.1. Introduction

The finished product is presented as a solution for infusion and a solution for injection containing respectively 0.75 mg/ml and 2 mg/ml of eptifibatide as active substance.

Other ingredients are: citric acid monohydrate, sodium hydroxide and water for injections as described in section 6.1 of the SmPC.

Eptifibatide Accord solution for infusion and solution for injection are available in Type I clear glass vials with butyl rubber stoppers and flip-off aluminium seals, as described in section 6.5 of the SmPC.

2.2.2. Active substance

General information

The chemical name of the active substance eptifibatide is cyclo(*S*-*S*)-mercaptopropionyl-(L)homoarginyl-glycyl-(L)aspartyl-(L)tryptophanyl-(L)propyl-(L)cysteinamide, corresponding to the molecular formula $C_{35}H_{49}N_{11}O_9S_2$ and has a relative molecular mass 831.32 g/mol. The active substance has the structure shown in figure 1:

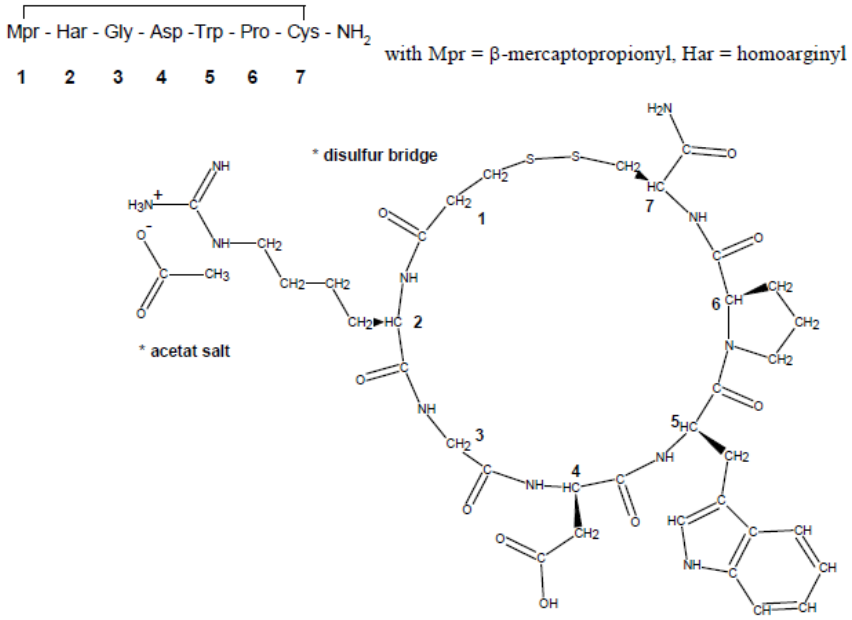

Figure 1: Eptifibatide structure

The structure of the active substance (AS) has been confirmed by one and two dimensional ^{1}H- and ^{13}C-NMR, sequencing by LC-MS and enantiomeric purity via chiral GC-MS, all of which support the chemical structure.

It appears as a white, hygroscopic, amorphous powder. It is sparingly soluble in water and methanol, slightly soluble in ethanol and insoluble in non-polar solvents. The pH of a 0.1% solution in water is 4.44 and of a 1% solution in water is 4.36. No crystalline structure has been identified for eptifibatide and therefore, it does not exhibit polymorphism.

Five of the amino acids present in eptifibatide are chiral, each existing in their natural L-configuration. Thus, there are 32 (2^5) potential optical isomers, 30 of which are diastereomers and 1 of which is an enantiomer of the active substance.

The stereochemistry of the AS is controlled via the specification of the starting materials which include tests for enantiomers, and is further controlled by appropriate specifications on key synthesis intermediates. In addition the five diastereomers of the AS that each containing one D-amino acid, have been synthesized and it has been shown chromatographically that none is present in the AS at a level greater than 0.5 %. The probability of the pure enantiomer (all five amino acids in their D-configuration) being present is virtually nil.

Finally, the optical purity of the amino acids in eptifibatide has been determined in one batch which was hydrolysed into the free amino acids. The enantiomers are separated using a chiral column and detected by mass spectrometry. The results obtained in this study confirm the theoretical stereochemistry of eptifibatide active substance.

Thus, although there is the potential for the presence of many optical isomers, the specifications and tests on the starting materials, intermediates and the final drug substance provides assurance that they are not present in significant amounts.

Manufacture, characterisation and process controls

The information on the active substance is provided according to the Active Substance Master File (ASMF) procedure.

Eptifibatide is synthesised in a convergent approach in six main synthetic steps whereby fragments are joined together in a specific order to produce the final peptide. The peptide is then purified in two steps and it is finally lyophilised and packaged. The originally proposed starting materials (SMs) have been redefined and the finally selected six SMs are considered acceptable in line with the principles of ICH Q11. Following the redefinition of the starting materials, not all analytical methods have been fully validated. However the validation protocol has been provided and the ASMF holder has also provided batch data for 3 historical batches of all the redefined starting materials and for the intermediate thus providing sufficient reassurance regarding the adequacy of the proposed controls and the quality of the AS. Nevertheless, although this is not considered as a quality concern that would prevent approval at this time, the HPLC methods for the identification, purity and levels of impurities in the recently redefined starting materials and the redefined intermediate should be validated as soon as possible and tabulated summaries of the validation results should be registered by way of an appropriate variation within 3 months of the finalisation of this procedure.

The chemistry is well described and various combinations of routine protecting groups are used throughout the synthesis to ensure the desired final structure is obtained. The reaction conditions and parameters used in the synthetic and purification steps were described in sufficient detail. The lyophilisation process has been validated. The critical process parameters for the freeze-drying steps are well described and controlled. The purification steps involve standard methods for purifying peptides. The filtration and lyophilisation steps were also sufficiently described. Although the AS is not required to be sterile, a bioburden reducing filter is used given that the AS will ultimately be used to manufacture a sterile parenteral medicinal product.

The active substance and its impurities have been sufficiently characterised. Potential and actual impurities were characterised and are well discussed with regards to their origin and fate.

The active substance is packaged in high density polyethylene (HDPE) bottles closed with polypropylene screw caps. The bottles are labeled and then sealed with an adhesive tape before being placed in a low

density polyethylene bag sealed with a heat sealing system. The primary container complies with EU regulations and conforms to the Ph. Eur. monograph for plastic containers for parenteral aqueous solutions.

Specification

The active substance specification includes tests and limits for appearance (visual), identity (NMR, HPLC), specific optical rotation (Ph. Eur.), water content (Ph. Eur), assay (HPLC), chromatographic purity (HPLC), acetate content (IC), residual solvents (GC), palladium (ICP-OES), microbial limits (Ph. Eur.) and bacterial endotoxins (Ph. Eur.).
The omission of testing for heavy metals other than palladium is acceptable based on batch data showing that heavy metals have not been detected above the LOQ in the last 18 batches, and considering the fact that no other heavy metal is actually used in the manufacturing process. Tests for optical rotation and enantiomeric purity are included for those SMs where isomerism is possible. Since no epimerisation of the chiral centres occur during manufacture, no test for stereoisomers is included in the AS specification. The analytical methods used have been adequately described and (non-compendial methods) appropriately validated in accordance with the ICH guidelines. Satisfactory information on the reference standards has been provided.

Batch analysis results for ten commercial scale batches manufactured by the proposed manufacturer were presented. The certificates of analysis of the AS from finished product manufacturer were also presented. The results comply with the proposed specification.

Stability

Stability data from more than 16 commercial scale batches packaged in the proposed packaging and stored under the long term storage condition (-25 ± 7 °C) for up to 72 months and under accelerated conditions (25 ± 2 °C / 60% ± 5% RH) for up to 36 months were presented.
The following parameters were tested: appearance, purity, assay, water content, microbial quality and acetate content. Analytical procedures used in stability studies are the same as described for release which were shown to be stability indicating. All tested parameters remained within the specification except for a noticeable upward trend in water content under long term storage conditions (-25 ± 7 °C) in earlier batches which resulted in some out of specification results. In more recent batches, such a trend in water content was not observed, with the exception of one batch. This finding is not unexpected as eptifibatide is a hydroscopic active substance. The results at accelerated storage conditions where water content is out of specification already after 2 months showed that degradation impurities increase and there are out of specification impurity results from 9 months onwards.
Nevertheless it has been further shown that higher water content does not adversely affect the overall quality of the active substance i.e. assay, impurities or microbial purity when stored under the long term conditions. Furthermore, it has been demonstrated that the upward trend in water content observed in historical batches has not been seen in five additional more recent commercial scale batches stored under long term storage conditions.

A photostability study on one commercial scale batch conducted as per ICH showed that the substance is stable under natural light and exhibited some degradation under UV light. As the AS is packaged in a non-transparent HDPE bottle, there is no concern relating to its photostability.

A forced degradation study was conducted using stress conditions of acid, alkali, water, heat, UV and H_2O_2. Various levels of degradation were observed under each of the above stress conditions. Mass balance between the main eptifibatide peak and sum of impurity peaks has been demonstrated.

In conclusion, a re-test period of 36 months at -25 ± 7 °C when the active substance is stored in the proposed packaging is adequately supported by the stability data provided and is accepted.

2.2.3. Finished medicinal product

Description of the product and pharmaceutical development

The development activities were aimed towards achieving a generic, stable formulations of eptifibatide solution for infusion 0.75 mg/ml and solution for injection 2 mg/ml in glass vials which are equivalent to those of the reference product Integrilin solution for infusion 0.75 mg/ml, and Integrilin solution for injection 2 mg/ml. Eptifibatide Accord has qualitatively the same composition as the reference product, a comparable impurity profile and similar physicochemical properties. The compositions of the solution for infusion and solution for injection are identical in terms of content per ml for the AS and each of the excipients.

The excipients selected are commonly used in parenteral formulations. Eptifibatide Accord does not contain any preservatives or antioxidants.

The manufacturing process has been optimised with regard to the conditions of AS solubilisation, pH of solution and order of addition of excipients in order to minimise the possible degradation of eptifibatide. The exact amounts of excipients have been also optimised to ensure the robustness of formulation. It was shown that slight variation in excipient quantities does not affect the quality of the final formulation (e.g. pH). Finally the pH of the formulation was optimised with regard to the stability of the product over its shelf life.

Terminal sterilization was shown not to be an appropriate method of sterilization because the product is sensitive to heat. Hence sterilisation by filtration and aseptic processing is used.The choice of the sterilisation method has been well described and is considered acceptable. The suitability of the filters was demonstrated and the filtration step has been validated with regard to integrity, chemical compatibility, bacterial viability and challenge, and extractables. The bulk solution holding time has been sufficiently justified by data and the compatibility of the product with the equipment has been sufficiently demonstrated. Finally, the impact of headspace gas on AS degradation was investigated. Although inert gas sparging / headspace flushing did not show any obvious advantage over air, nitrogen was selected as an extra precaution.

The product has been found to be light sensitive (see stability below) and precautions are taken to prevent exposure to light during manufacturing.

A freeze thaw study was carried out to study the effects of temperature variations on the product when cycled through temperature conditions that simulate the short-term excursions outside of the proposed labeled storage conditions likely to be encountered by the drug product during distribution. Based on the review of this data, it was concluded that there is no significant impact on product quality which will remain acceptable upon unexpected exposure to very low temperature or high temperature which could occur during transit.

The product does not require reconstitution or further dilution in appropriate dilution fluid prior to administration. Although the data presented confirm the physical and chemical stability of Eptifibatide Accord solution for injection after in-use storage at 20-25 °C for 12 hours, it is considered acceptable not to

include any statement in this regard in section 6.3 because the proposed warning “Discard any unused medicinal product after opening” in the section 6.6 is deemed sufficient.

Compatibility studies have been submitted confirming the compatibility of Eptifibatide Accord solution for infusion with sodium chloride injection and dextrose 5% in Normasol R with KCl. Physical and chemical stability of these mixtures have been shown up to 92 hours when stored at 20-25 °C. The submitted compatibility studies support the reference to these compatible diluents in the SmPC section 6.6.
Since Eptifibatide Accord is a generic of Integrilin containing the same active substance and excipients, the wording of the SmPC Section 6.6. regarding the physical and chemical compatibility of Eptifibatide Accord when administered through an intravenous line with atropine sulfate, dobutamine, heparin, lidocaine, meperidine, metoprolol, midazolam, morphine, nitroglycerin, tissue plasminogen activator, or verapamil, is considered acceptable as well.

Eptifibatide Accord is packaged in Type I glass containers with butyl rubber stoppers. The Type I glass complies with Ph. Eur. requirements. The stopper complies with Ph. Eur. requirements and appropriate compatibility studies have been carried out with the drug product.

Manufacture of the product and process controls

The main steps of the manufacturing process are cleaning and sterilisation of equipment, vials, stoppers and seals, preparation of bulk solution, pre-filtration, sterile filtration of the bulk solution, aseptic filling of vials and stoppering, sealing of the vials, visual inspection and packaging.

Critical steps and process parameters that are considered critical for the quality of the product were identified. The following process steps and respective process control parameters are defined as critical: aseptic filtration, sterilisation of materials, vial filling and sealing. Adequate in-process controls are in place for this type of manufacturing process including bioburden limit prior to aseptic filtration solution pH, filter integrity pre- and post-filtration, fill weight and assay.

As the manufacturing process is a non-standard one as per the Annex II to the guideline on process validation one full process validation on three batches of each strength/ pharmaceutical form of the product at the proposed batch size has already been carried out and results have been presented. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner.

Product specification

The finished product release and shelf life specifications include appropriate tests and limits for this kind of dosage form including appearance (visual), identification (HPLC, UV), pH (Ph. Eur.), extractable volume (Ph. Eur.), particulate matter (Ph. Eur.), clarity and colour of solution (Ph. Eur.), assay (Ph. Eur.), related substances (HPLC), sterility (Ph. Eur.) and bacterial endotoxins (Ph. Eur.).

The proposed limits in the finished product specification are in line with Ph. Eur. general monograph #0502 for Parenteral Preparations and the ICH Q6A guideline. The proposed limits of impurities have been set in line with the Ph. Eur. general monograph #2034 Substances for Pharmaceutical Use and are considered appropriate.
The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards of active substance and impurities has been presented.

Batch analysis data was provided on three commercial scale batches of each strength manufactured at the proposed manufacturing site. Results were in line with proposed specifications and confirm the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

Stability of the product

Stability studies have been conducted on three commercial scale batches per strength manufactured at the proposed manufacturing site and packaged in the proposed commercial packaging in accordance with ICH requirements. Stability results were provided for samples stored in inverted position for up to 24 months under long-term conditions (2-8 °C) and for six months under accelerated conditions (25±2 °C, 60%±5% RH).

Parameters tested as per the stability protocol were: appearance, colour and clarity of the solution, pH of the solution, assay, related substances, particulate matter, sterility and bacterial endotoxins. Analytical methods used in stability studies are the same as described for release which were shown to be stability indicating. All the results under long term storage conditions met the specification and showed only a slight upward trend in individual and total impurities. However, the levels of these impurities don't approach the specification limits after 24 months. Under accelerated conditions, the upward trend in impurity levels are more pronounced. There are, however, no significant changes (i.e. no out of spec results) observed between 0 and 6 months under these conditions. Based on the 6 month data submitted, it could be considered that the drug product could be stable when stored at 25°C. However as the applicant has not continued these studies past the 6 month time-points, it is not possible to conclude on this point. The choice of the more restrictive storage condition of 2-8 °C is considered acceptable.

In addition, one pilot batch was exposed to light as defined in the ICH Guideline on Photostability Testing. The results showed that the product failed to meet the specification for description, assay and related compounds thus indicating that the product is highly sensitive when exposed to light conditions (UV & visible) as per ICH guidance. As this product is highly sensitive to light, it was required to establish the impact of normal room light on product stability. Based on the latter study, it can be concluded that the product Eptifibatide Accord 0.75 mg/ml and 2.0 mg/ml is very sensitive even at room light exposure. Hence the product should be protected from light within its opaque secondary packaging material until its use.

Forced degradation studies were performed where samples were stress tested under acid, alkali, water, heat, UV, and oxidative conditions. Various levels of degradation were observed at each of the above stress conditions. Mass balance between the main eptifibatide peak and sum of impurity peaks has been demonstrated. Based on this study, the analytical methods were shown to be stability indicating.

On the basis of the overall available stability data, the shelf life of 24 months when stored at 2-8°C in the original package in order to protect from light as stated in sections 6.3 and 6.4 of the SmPC is accepted.

Adventitious agents

No excipients of human or animal origin are used.

2.2.4. Discussion on chemical, and pharmaceutical aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The proposed starting materials have been re-defined and the overall control strategy for the active substance is acceptable. The finished product is manufactured by

aseptic processing which is considered a non-standard process and therefore full process validation data have been provided confirming the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner. The choice of the sterilisation method has been sufficiently justified and supported by data. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

2.2.6. Recommendation for future quality development

In the context of the obligation of the MAHs to take due account of technical and scientific progress, the CHMP recommends the following points for investigation:

-the validation of the HPLC methods for the identification, purity and levels of impurities in the recently redefined starting materials and the recently defined intermediate should be performed as soon as possible and the tabulated summaries of the validation results should be registered by way of an appropriate variation.

2.3. Non-clinical aspects

2.3.1. Introduction

A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which is based on up-to-date and adequate scientific literature.

The pharmacological, pharmacokinetic and toxicological properties of eptifibatide are well known and have been adequately summarised in the Non-clinical Overview. As the applicant considered this application an abridged application claiming essential similarity in accordance with article 10.1.a.iii of Directive 2001/83/EC to an existing product (Integrilin 0.75 mg/ml and 2 mg/ml solution for injection), no additional studies have been provided. The non-clinical aspects of the SmPC are in line with the SmPC of the reference product. The impurity profile has been discussed and was considered acceptable.

Overall, it is considered that the non-clinical overview is based on up-to-date and adequate scientific literature. It is agreed that no further non-clinical studies are required.

2.3.2. Ecotoxicity/environmental risk assessment

No Environmental Risk Assessment was submitted. This was justified by the applicant as the introduction of Eptifibatide Accord 0.75 mg/ml & 2 mg/ml solution for injection manufactured by Accord Healthcare Limited is considered unlikely to result in any significant increase in the combined sales volumes for all eptifibatide containing products and the exposure of the environment to the active substance. Thus, the ERA is

expected to be similar and not increased.

2.3.3. Conclusion on the non-clinical aspects

No new nonclinical studies were provided. The pharmacological, pharmacokinetic and toxicological properties of eptifibatide are well known and have been adequately summarised in the Non-clinical overview. The non-clinical aspects of the product information are in line with the product information of the reference medicinal product. Therefore the CHMP considered the approval of Eptifibatide Accord 0.75 mg/ml & 2 mg/ml solution for injection from a non-clinical point of view acceptale.

2.4. Clinical aspects

2.4.1. Introduction

This is an application for 0.75 mg/ml solution for infusion and 2 mg/ml solution for injection containing eptifibatide. The applicant provided a clinical overview outlining the pharmacokinetics and pharmacodynamics as well as efficacy and safety of eptifibatide based on published literature. The SmPC is in line with the SmPC of the reference product.

No CHMP scientific advice pertinent to the clinical development was given for this medicinal product.

For the clinical assessment the Guideline on the Investigation of Bioequivalence CPMP/EWP/QWP/1401/98) is of particular relevance.

Exemption

According to the *Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98)*, bioequivalence studies are generally not required for intravenous solution if:

- the test product contains the same active substance as the currently approved product.
- no excipients interact with the drug substance, i.e. do not affect the disposition of the drug substance.

Eptifibatide Accord is to be administered as an aqueous intravenous solution that contains the same active substance eptifibatide as the marketed product Integrilin. Excipients used in the 0.75 mg/ml and 2 mg/ml formulations are qualitatively the same as in the Originator. Any potential differences in the quantitative content of excipients (e.g citric acid monohydrate or sodium hydroxide) are unlikely to have any impact (please refer to the quality assessment for more information). This was considered acceptable by the CHMP.

2.4.2. Pharmacokinetics

No new PK studies were presented. Reference was made to the SmPC of the reference product Integrilin. This was considered acceptable.

2.4.3. Pharmacodynamics

No new pharmacodynamic studies were presented and no such studies are required for this application.

2.4.4. Post marketing experience

No post-marketing data are available. The medicinal product has not been marketed in any country.

2.4.5. Discussion on clinical aspects

The applicant has not conducted any clinical studies for the application. Instead appropriate data were provided to support the claim that the proposed product is essentially similar to the originator. The qualitative composition of Eptifibatide Accord is identical with that of the originator and the applicant's proposed SmPCs are compliant with the reference product with no novel claims or dose recommendations.

2.4.6. Conclusions on clinical aspects

The application contains an adequate review of published clinical data concerning the clinical use of eptifibatide for the proposed indication. All data regarding safety and efficacy available for the reference medicinal product also apply for this application. The clinical sections of the proposed SmPCs are in line with that of Integrilin and were considered acceptable to the CHMP.

In accordance to the *Guideline on the investigation of Bioequivalence (CPMP/EWP/QWP/1401/98)* and in the case of aqueous intravenous solution, no bioequivalence studies are requested because:

- the test product contains the same active substance as the currently approved product Integrilin.
- no excipients interact with the drug substance, i.e. do not affect the disposition of the drug substance.

The CHMP agreed with this conclusion and considered Eptifibatide Accord 0.75 mg/ml solution for infusion & 2 mg/ml solution for injection approvable from a clinical point of view.

2.5. Risk management plan

The PRAC considered that the risk management plan version 2.0 could be acceptable if the applicant implements the changes to the RMP as described in the PRAC advice.

The applicant implemented the changes in the RMP as requested by PRAC.

The CHMP endorsed the Risk Management Plan version 3.0 with the following content:

Safety concerns

Important identified risk	• Bleeding including increased risk of haemorrhage in patients with moderate renal impairment [(1)] • Thrombocytopenia [(1)]
Important potential risk	• None identified
Missing information	• None identified

Pharmacovigilance plan

Not applicable

Risk minimisation measures

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Important Identified Risks: Bleeding including increased risk of haemorrhage in patients with moderate renal impairment	Accord proposed product information (meant for prescribing physicians) for eptifibatide shall have the following information on this safety concern: Section 4.2 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.	Currently available data does not support the need for additional risk minimization activities.

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	Section 4.4 *Bleeding* Eptifibatide Accord 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. Section 5.1: There is limited data with regards to platelet inhibition in patients with renal impairment. In patients with moderate renal impairment, (creatinine clearance 30 - 50 ml/min) 100 % inhibition was	

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	achieved at 24 hours following administration of 2 microgram/kg/min. In a post hoc analysis of the EARLY ACS (Early Glycoprotein IIb/IIIa Inhibition in Non-ST-segment Elevation Acute Coronary Syndrome) trial the risk benefit of dose reduction in patients with moderate renal impairment is inconclusive. Additionally, targeted follow up questionnaire is prepared by MAH.	
Important Identified Risks: Thrombocytopenia	Accord proposed product information (meant for prescribing physicians) for eptifibatide shall have the following information on this safety concern: Section 4.3: Eptifibatide Accord must not be used to treat patients with thrombocytopenia (< 100,000 cells/mm^3) Section 4.4 *Thrombocytopenia and*	Currently available data does not support the need for additional risk minimization activities.

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	Immunogencity related to GP IIb/IIIa inhibitors Eptifibatide Accord 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. Thrombocytopenia, including acute profound thrombocytopenia, has been observed with eptifibatide administration post-marketing. The mechanism, whether immune- and/or non-immune-mediated, by which eptifibatide may induce thrombocytopenia is not fully understood. However, treatment with eptifibatide was associated with antibodies that recognise GPIIb/IIIa occupied by eptifibatide, suggesting an immune-mediated mechanism. Thrombocytopenia occurring after first exposure to a GPIIb/IIIa inhibitor may be explained by the fact that antibodies	

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	are naturally present in some normal individuals. If either a confirmed platelet decrease to < 100,000/mm3 or acute profound thrombocytopenia 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 thrombocytopenia from other parenteral GP IIb/IIIa inhibitors, there are no data with the use of eptifibatide. Therefore, it is not recommended to administer eptifibatide in patients who have previously experienced immune mediated thrombocytopenia with GP IIb/IIIa inhibitors, including eptifibatide.	

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	Section 4.8 *Blood and Lymphatic System Disorder* Uncommon: Thrombocytopenia Very rare: acute profound thrombocytopenia	

2.6. PSUR submission

The requirements for submission of periodic safety update reports 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 updates published on the European medicines web-portal.

2.7. Pharmacovigilance

Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

3. Benefit-risk balance

This application concerns a generic version of eptifibatide 0.75 mg/ml solution for infusion and 2 mg/ml solution for injection. The reference product Integrilin is indicated for

use with acetylsalicylic acid and unfractionated heparin 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).

No nonclinical studies have been provided for this application but an adequate summary of the available nonclinical information for the active substance was presented and considered sufficient. From a clinical perspective, this application does not contain new data on the pharmacokinetics and pharmacodynamics as

well as the efficacy and safety of the active substance; the applicant's clinical overview on these clinical aspects based on information from published literature was considered sufficient.

In accordance to the *Guideline on the investigation of Bioequivalence (CPMP/EWP/QWP/1401/98)* and in the case of aqueous intravenous solution, no bioequivalence studies were requested because:

- the test product contains the same active substance as the currently approved product Integrilin.
- no excipients interact with the drug substance, i.e. do not affect the disposition of the drug substance.

A benefit/risk ratio comparable to the reference product can therefore be concluded.

The CHMP, having considered the data submitted in the application and available on the chosen reference medicinal product, is of the opinion that no additional risk minimisation activities are required beyond those included in the product information.

4. Recommendation

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Eptifibatide Accord in the following indication:

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

Eptifibatide Accord 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 Accord 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).
is favourable and therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

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

Conditions and requirements of the Marketing Authorisation

- **Periodic Safety Update Reports**

The requirements for submission of periodic safety update reports 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 updates published on the European medicines web-portal.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk Management Plan (RMP)**

The 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.

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States.

Not applicable.