CBG MEB

Public Assessment Report

Scientific discussion

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

(eptifibatide)

NL/H/3888/001-002/DC

Date: 21 February 2018

This module reflects the scientific discussion for the approval of Eptifibatide ADOH. The procedure was finalised on 14 December 2017. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

List of abbreviations

ASMF	Active Substance Master File
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CMS	Concerned Member State
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EEA	European Economic Area
ERA	Environmental Risk Assessment
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
Ph.Eur.	European Pharmacopoeia
PL	Package Leaflet
RH	Relative Humidity
RMP	Risk Management Plan
SmPC	Summary of Product Characteristics
TSE	Transmissible Spongiform Encephalopathy

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Eptifibatide ADOH 0.75 mg/ml, solution for infusion and 2 mg/ml, solution for injection from ADOH B.V.

The product is intended for use with acetylsalicylic acid and unfractionated heparin.

Eptifibatide ADOH 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 ADOH 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).

A comprehensive description of the indications and posology is given in the SmPC.

This decentralised procedure concerns a generic application claiming essential similarity with the innovator products Integrilin 0.75 mg/ml, solution for infusion and Integrilin 2 mg/ml, solution for injection which have been registered in the EEA by Glaxo Group Ltd since 1 July 1999 through centralised procedure EMEA/H/C/000230.

The concerned member state (CMS) involved in this procedure was Germany.

The marketing authorisation has been granted pursuant to Article 10(1) of Directive 2001/83/EC.

II. QUALITY ASPECTS

II.1 Introduction

Eptifibatide ADOH is a clear, colourless or almost colourless solution with pH 5.25-5.75.
Each ml of solution contains 0.75 mg or 2 mg of eptifibatide.

The solution is packed in type I glass vials, closed with a chlorinated butyl stopper and sealed with a crimped aluminium-plastic flip-off seal.

The excipients are citric acid monohydrate, sodium hydroxide and water for injections.
The composition for the both strengths is the same, except for the concentration of the active substance eptifibatide.

II.2 Drug Substance

The active substance is eptifibatide, an established active substance. It is not described in the European Pharmacopoeia (Ph.Eur.) or another pharmacopoeia. It is a white or off-white powder which is freely soluble in 1% acetic acid solution and soluble in water. Eptifibatide is an amorphous powder.
There are four different isomers for eptifibatide. the active substance is a synthetic cyclic heptapeptide containing six amino acids, including one cysteine amide and one mercaptopropionyl (desamino cysteinyl) residue.

The Active Substance Master File (ASMF) procedure is used for the active substance. The main objective of the ASMF procedure, commonly known as the European Drug Master File (EDMF) procedure, is to allow valuable confidential intellectual property or ‘know-how’ of the manufacturer of the active substance (ASM) to be protected, while at the same time allowing the applicant or

marketing authorisation holder (MAH) to take full responsibility for the medicinal product, the quality and quality control of the active substance. Competent Authorities/EMA thus have access to the complete information that is necessary to evaluate the suitability of the use of the active substance in the medicinal product.

Manufacturing process
The manufacturing process of the active substance has been adequately described. The applied control tests are adequate for ensuring the quality of the final drug substance.

Quality control of drug substance
The active substance specification is considered adequate to control the quality. The specifications are in line with the requirements for synthetic peptides as present in Ph. Eur. general monograph Substances for Pharmaceutical Use (2034). Batch analytical data demonstrating co have been provided.

Stability of drug substance
Stability data on the active substance have been provided for six batches stored at 2-8°C (for 3 batches 36 months data are available, for 3 other batches 24 months data) and 25°C/60% RH for 6 months (3 batches).
Based on the provided data, a re-test period of 3 years at 2-8°C, has been granted, when stored protected from light in a tightly closed container.

II.3 Medicinal Product

Pharmaceutical development
The pharmaceutical development is strongly based on the innovator product. The MAH demonstrated that the generic product is similar to the reference product in terms of composition, impurity profile and physicochemical characteristics. A question on the proposed pH range is posed. The heat sensitivity of eptifibatide has been tested, and proper process temperature control range has been established.
Formulation development has been guided on basis of quality target product profile for proposed product (QTPP) and critical quality attributes (CQAs) evaluations. Comparative test results demonstrated that the proposed product and the reference product are very similar, for both solutions.
The manufacturing process development was adequately performed. The choice of sterilizing filtration is adequately justified.

Manufacturing process
The manufacturing process involves seven distinct stages: 1) Treatment of vials and stoppers, 2) Weighing, 3) Preparation of bulk solution and filtering, 4) Filling, 5) Capping, 6) Vial inspection, and 7) Packaging. The preparation (i.e. sterilisation and depyrogenation) of containers, closures, equipment is well described. The dispensing and bulk manufacturing steps are described in sufficient detail; temperature, time and pH controls are described.
Three batches of both solutions have been validated. Sufficient (validation) data are available on the autoclave process (moist heat sterilization) and the dry heat sterilization/depyrogenation process. Also sufficient data are provided on the sterilizing filtration process and performance of the filter materials involved. Media fill tests have been performed for validating the aseptic filling process.

Control of excipients
The excipients citric acid monohydrate, sodium hydroxide and water for injections meet the requirements of the Ph. Eur. These specifications are acceptable.

Quality control of drug product
Drug product specifications are applied for appearance, identification, clarity and colour of solution, pH, extractable volume, assay, related compounds, visible particles and sub-visible particles, sterility and bacterial endotoxins.
The specifications are in line with the requirements for synthetic peptides as present in Ph. Eur. general monograph Substances for Pharmaceutical Use (2034). The drug product specifications and methods are in line with Ph. Eur. requirements for parenteral products.
The HPLC methods for identification/assay and related substances are in-house methods and have been fully validated. The bacterial endotoxins and sterility test methods have been validated. All other

test methods are Ph. Eur. methods. Batch analysis data have been provided for 3 batches of each strength, demonstrating compliance with this specification.

Stability of drug product
Three batches of 0.75 mg/ml and three batches of 2 mg/ml have been put on stability; results are available for 18 months at 2-8°C and 6 months at 25°C/60% RH, at all conditions in upright and inverted position. All stability results meet the set shelf-life specifications, and no clear trends are observed. A photostability study showed that the product is light sensitive.
Based on the provided data, the granted shelf life is 21 months, when stored in the proposed container closure system, with storage conditions 'Store in a refrigerator (2°C - 8°C)' and 'Store in the original package in order to protect from light'.
The proposed product diluted according to the SmPC with 0.9% NaCl or 0.9% NaCl/5% dextrose, at low concentration (0.004 mg/ml eptifibatide) or high level (0.075 mg/ml eptifibatide), is meeting the set requirements up to 5 days (120 hours), and fully comparable with the similarly treated reference product. Eptifibatide ADOH is fully compatible with the infusion liquids as recommended in the SmPC.

Specific measures for the prevention of the transmission of animal spongiform encephalopathies
There are no substances of ruminant animal origin present in the product nor have any been used in the manufacturing of this product, so a theoretical risk of transmitting TSE can be excluded.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Eptifibatide ADOH has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product. No post-approval commitments were made.

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Eptifibatide ADOH is intended for generic substitution, this will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

III.2 Discussion on the non-clinical aspects

This product is a generic formulation of Integrilin, which is available on the European market. Reference is made to the preclinical data obtained with the innovator product. 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 overview justifies why there is no need to generate additional non-clinical pharmacology, pharmacokinetics and toxicology data. Therefore, the member states agreed that no further non-clinical studies are required.

IV. CLINICAL ASPECTS

IV.1 Introduction

Eptifibatide is a well-known active substance with established efficacy and tolerability.
A clinical overview has been provided, which is based on scientific literature. The overview justifies why there is no need to generate additional clinical data. Therefore, the member states agreed that no further clinical studies are required.

IV.2 Pharmacokinetics

Eptifibatide ADOH 0.75 mg/ml, solution for infusion and 2 mg/ml solution for injection are parenteral formulations and therefore fulfil the exemption mentioned in the Note for Guidance on bioequivalence

"5.1.6 parenteral solutions", which states that a bioequivalence study is not required if the product is administered as an aqueous intravenous solution containing the same active substance in the same concentration as the currently authorized reference medicinal product (NfG CPMP/EWP/QWP 1401/98). The qualitative composition of Eptifibatide ADOH 0.75 mg/ml and 2 mg/ml is the same as the originator. It may be considered as therapeutic equivalent, with the same efficacy/safety profile as known for the active substance of the reference medicinal product. The current product can be used instead of its reference product.

IV.3 Risk Management Plan

The MAH has submitted a risk management plan, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Eptifibatide ADOH.

- Summary table of safety concerns as approved in RMP

Important identified risks	Bleeding including increased risk of haemorrhage in patients with moderate renal impairment Thrombocytopenia
Important potential risks	None identified
Missing information	None identified

The member states agreed that routine pharmacovigilance activities and routine risk minimisation measures are sufficient for the risks and areas of missing information.

IV.4 Discussion on the clinical aspects

For this authorisation, reference is made to the clinical studies and experience with the innovator product Integrilin. No new clinical studies were conducted. The MAH demonstrated essential similarity based on quality attributes. Risk management is adequately addressed. This generic medicinal product can be used instead of the reference product.

V. USER CONSULTATION

The package leaflet has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The test consisted of two rounds with 10 participants each. The test consisted out of 12 questions covering specific questions relating to the content of the package leaflet and 5 questions relating to the general impression of the package leaflet and technical layout of the leaflet. The questions covered the following areas sufficiently: traceability, comprehensibility and applicability. The user test was considered acceptable.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Eptifibatide ADOH 0.75 mg/ml, solution for infusion and Eptifibatide ADOH 2 mg/ml, solution for injection have a proven chemical-pharmaceutical quality and are generic forms of Integrilin 0.75 mg/ml and 2 mg/ml. Integrilin is a well-known medicinal product with an established favourable efficacy and safety profile

Since both the reference and current product are intended for parenteral use, no bioequivalence study is deemed necessary.

The Board followed the advice of the assessors.

There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The member states, on the basis of the data submitted, considered that essential

similarity has been demonstrated for Eptifibatide ADOH with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 14 December 2017.

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Procedure number	Scope	Product Information affected	Date of end of the procedure	Approval/ non approval	Summary/ Justification for refuse