COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

# Public Assessment Report

# Scientific discussion

# Bivalirudine ADOH 250 mg, powder for concentrate for solution for injection or infusion

# (bivalirudin)

# NL/H/4677/001/DC

# Date: 10 March 2020

**This module reflects the scientific discussion for the approval of Bivalirudine ADOH 250 mg, powder for concentrate for solution for injection or infusion. The procedure was finalised at 14 December 2019. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.**

# List of abbreviations

| | |
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| 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 Bivalirudine ADOH 250 mg, powder for concentrate for solution for injection or infusion, from ADOH B.V.

The product is indicated:

- as an anticoagulant in adult patients undergoing percutaneous coronary intervention (PCI), including patients with ST-segment elevation myocardial infarction (STEMI) undergoing primary PCI;
- for the treatment of adult patients with unstable angina/non-ST segment elevation myocardial infarction (UA/NSTEMI) planned for urgent or early intervention.

The product should be administered with acetylsalicylic and clopidogrel.

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 product Angiox 250 mg, powder for concentrate for solution for injection or infusion which has been registered in the EEA by The Medicines Company UK Ltd. since 20 September 2004. In the Netherlands the product was withdrawn on 1 July 2018.

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

Bivalirudine ADOH is a white to off-white lyophilised powder for concentrate for solution for injection or infusion. Each vial contains 250 mg bivalirudin. After reconstitution 1 ml contains 50 mg bivalirudin. After dilution 1 ml contains 5 mg bivalirudin.

The powder for concentrate for solution for injection or infusion is supplied as a lyophilised cake or powder in 10 ml single use clear glass vial closed with a rubber stopper and sealed with an aluminium-plastic over seal.

The excipients are mannitol (E421), sodium hydroxide (for pH adjustment) (E524) and nitrogen (E941).

## II.2 Drug Substance

The active substance is bivalirudin, an established substance. It is not described in the European Pharmacopoeia (Ph.Eur.), however is published in Pharmacopeial Forum (PF 44(2), Published March 1, 2018). The drug substance is a white or almost white powder, which is hygroscopic and soluble in water or glacial acetic acid but insoluble in acetonitrile or diethyl ether. Bivalirudine is amorphous and exhibits optical isomerism as it contains multiple chiral centres.

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 synthesis of Bivalirudin is performed by solid phase peptide synthesis and consists of 3 steps. The active substance has been adequately characterised and acceptable specifications have been adopted for the starting materials, solvents and reagents.

Quality control of drug substance

The active substance specification is considered adequate to control the quality. The specification is established in-house and is acceptable in view of the route of synthesis and the various European. Batch analytical data demonstrating compliance with this specification have been provided for two batches from the drug product manufacturer and three batches of the ASMF-holder.

Stability of drug substance

Stability data on the active substance have been provided for three consecutive commercial batches stored at -20°C (18 months) and 25°C (6 months). Based on the data submitted, a retest period could be granted of 18 months when stored under the stated conditions.

## II.3 Medicinal Product

Pharmaceutical development

The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines. The choice of excipients is justified and their functions explained. The main development studies concentrated on compounding, filtration, filling and lyophilisation. Chemical-physical properties of the current product are comparable to those of the innovator product.

Manufacturing process

The manufacturing process is a common process for lyophilised product, including the operation units of treatments of packaging components, compounding, filtration, filling, lyophilisation, capping and visual inspection. The process has been validated according to relevant European guidelines. Process validation data on the product have been presented for three commercial scale batches in accordance with the relevant European guidelines. Given the manufacturing process contains a critical lyophilisation step; the manufacturing process is regarded non-standard. The process has been successfully validated on sufficient production bathes.

Control of excipients

The excipients comply with the Ph. Eur. These specifications are acceptable.

Microbiological attributes

The microbiological attributes of the proposed drug product are discussed and assessed from the aspects of raw materials, manufacturing process, integrity of the container closure system and storage after dilution. The assessment shows that the sterility of the proposed drug product can be achieved by current control strategies.

Quality control of drug product

The finished product specifications are adequate to control the relevant parameters for the dosage form. The specification includes tests for appearance, identification, reconstituted solution, appearance of solution, pH, water, uniformity of dosage units, visible particulates, particulate matters, bacterial endotoxins, sterility, related substances and assay. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product. Satisfactory validation data for the analytical methods have been provided. Batch analytical data from three production scale batches from the proposed production site have been provided, demonstrating compliance with the specification.

Stability of drug product

Stability data on the product have been provided for three commercial scale batches stored at 25°C/60% RH (12 months), 30°C/75% RH (12 months) and 40°C/75% RH (6 months). The results of photostability study show that the product is photo stable and no additional protection from light is needed. On basis of the data submitted, a shelf life was granted of 24 months. Chemical and physical in-use stability has been demonstrated for 24 hours for reconstituted solution at 2-8°C when stored in a refrigerator and not frozen and for 24 hours for the diluted solution when stored below 25°C. From a microbiological point of view, the product should be used immediately. If not used immediately, in use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2–8°C unless reconstitution/dilution has taken place in controlled and validated aseptic conditions.

Specific measures concerning 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 Bivalirudine 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 Bivalirudine 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 Angiox 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

Bivalirudin 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

Bivalirudine ADOH 250 mg, powder for concentrate for solution for injection or infusion is a parenteral formulation and therefore fulfils 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 authorised reference medicinal product (NfG CPMP/EWP/QWP 1401/98). The quantitative composition of the product is entirely the same as the originator. Therefore, 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 Angiox.

**Table 1. Summary table of safety concerns as approved in RMP**

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| Important identified risks | - Medication error (including reports describing patients receiving bivalirudin bolus without subsequent infusion)<br>- Serious bleeding events |
| Important potential risks | None |
| Missing information | - Use during pregnancy |

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 Angiox. No new clinical studies were conducted. Risk management is adequately addressed. This generic medicinal product can be used instead of the reference product.

## V. USER CONSULTATION

The package leaflet (PL) 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 questions covered the following areas sufficiently: traceability, comprehensibility and applicability. The results show that the PL meets the

criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

# VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Bivalirudine ADOH 250 mg, powder for concentrate for solution for injection or infusion has a proven chemical-pharmaceutical quality and is a generic form of Angiox 250 mg, powder for concentrate for solution for injection or infusion. Angiox 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. A biowaiver has been granted.

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 Bivalirudine ADOH with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 14 December 2019.

## STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

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