COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Danaparoid Aspen 750 anti-Xa E/0.6 ml, solution for injection (danaparoid sodium)

NL/H/5208/001/DC

Date: 15 November 2021

This module reflects the scientific discussion for the approval of Danaparoid Aspen. The procedure was finalised at 27 May 2021. 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 Danaparoid Aspen, 750 anti-Xa E/0,6 ml, solution for injection from Aspen Pharma Trading Limited.

The product is indicated for the prevention of deep vein thrombosis (DVT) in situations where heparin should not be used, including patients with heparin-induced thrombocytopenia (HIT), and the treatment of thrombo-embolic disorders in patients who require urgent parenteral anticoagulation because of the development or a history of HIT in adults and children.

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

This decentralised procedure concerns a similar biological application claiming essential similarity with the innovator product Orgaran 750 anti-Xa E, solution for injection which has been registered in Ireland by Aspen Pharma Trading Limited since 1991 (original product). In the Netherlands, Orgaran (NL RVG 15006) has been registered by a mutual recognition procedure with procedure number NL/H/0142/001.

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

Danaparoid Aspen is a biological product as it is manufactured from a biological source (porcine intestinal mucosa). Furthermore, it is manufactured at the same site by the same company using the same sources and procedures as the reference product Orgaran, therefore, it should be submitted with legal basis article 10(4) of Directive 2001/83/EC, as amended:

'a biological medicinal product which is similar to a reference biological product does not meet the conditions in the definition of generic medicinal products, owing to, in particular, differences relating to raw materials or differences in manufacturing processes of the biological medicinal product and the reference biological medicinal product'

The marketing authorisation has been granted pursuant to Article 10(4) of Directive 2001/83/EC.

II. QUALITY ASPECTS

II.1 Introduction

Danaparoid Aspen is a clear/colourless to pale yellow aqueous solution for injection.

Danaparoid Aspen contains as active substance 750 anti-factor Xa E of danaparoid sodium per 0.6 ml ampoule, corresponding to 1250 anti-factor Xa E per ml. The anti-Xa unit is derived from the international heparin standard in an antithrombin containing buffer system.

The solution for injection is packed in glass ampoules stored in boxes.

The excipients are sodium sulphite, sodium chloride, water for injections and hydrochloric acid (to adjust the pH).

II.2 Drug Substance

The active substance is danaparoid sodium, an established active substance described in the European Pharmacopoeia (Ph.Eur.). Danaparoid sodium is a white or almost white powder and is freely soluble in water. Danaparoid sodium is considered to be a hygroscopic compound. Danaparoid sodium consists of a mixture of the low molecular weight (LMW) sulphated glycosaminoglycuronans heparan, dermatan and chondroitin sulphates that does not contain heparin and is derived from animal mucosa.

Manufacturing process

The manufacturing process consists of the following steps: isolation of the active substance, preparation of the first intermediate product by filtration, concentration, adsorption, desorption, precipitation, purification and oxidation. The manufacturing process is identical to Orgaran and is adequately described.

Quality control of drug substance

The active substance specifications used by manufacturer I and II are considered adequate to control the quality and meets the requirements of the monograph in the Ph.Eur. Batch analytical data demonstrating compliance with this specification have been provided for 40 batches.

Stability of drug substance

Stability data on the active substance has been provided for three batches (25°C ± 2°C / 60% RH ± 5% RH, up to 60 months), one batch (25°C ± 2°C / 60% RH ± 5% RH, up to 36 months), one batch (25°C ± 2°C / 60% RH ± 5% RH, up to 24 months), one batch (25°C ± 2°C / 60% RH ± 5% RH, up to 12 months) and three batches (40°C ± 2°C / 75% RH ± 5% RH, up to six months) in accordance with applicable European guidelines demonstrating the stability of the active substance for 60 months. Based on the data submitted, a retest period could be granted of 60 months when stored at temperatures up to 25 °C.

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 validity of the current formulation has been demonstrated retrospectively through many years of experience of the product. For the formulation of Danaparoid Aspen 750 anti-Xa E/0.6mL solution for injection sodium sulfite is added as anti-oxidant, sodium chloride is added for tonicity adjustment and hydrochloric acid is necessary for pH adjustment.

Manufacturing process

The manufacturing process has been validated according to relevant European/ICH guidelines. Process validation data on the product have been presented for three batches in accordance with the relevant European guidelines. The validity of the current formulation has been demonstrated retrospectively through many years of experience with the product. A detailed validation report is provided, the report includes the validation protocol, a detailed manufacturing process description, details of in process operational parameters and analytical results, a drug product bulk solution hold study (up to 72 hrs), and filter validation studies.

Control of excipients

The excipients used with the drug product comply with the appropriate monograph of the European Pharmacopoeia (Ph. Eur.). These specifications are acceptable.

Quality control of drug product

The finished product specifications are adequate to control the relevant parameters for the dosage form. The specification is based on the monographs of the Ph.Eur. and contains tests for appearance, identification, danaparoid sodium assay, sodium sulfite assay, pH, extractable volume, relative osmotic pressure, clarity, visible particles, particulate matter, colour, sterility and bacterial endotoxins. The tests in the end of life specification are identical to those in the release specification. 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 of six batches from the proposed production sites have been provided, demonstrating compliance with the specification.

Stability of drug product

Stability data on the product have been provided for three batches which we were tested under the following conditions: 25°C ± 2°C / 60% RH ± 5% up to 36 months, 30°C ± 2°C / 35% RH ± 5% up to 18 months, 40°C ± 2°C / 75% RH ± 5% up to 18 months and 2 - 8°C up to six months in accordance with applicable European guidelines demonstrating the stability of the product for 36 months. On basis of the data submitted, a shelf life of 36 months was granted when stored at 25 °C. Furthermore, chemical and physical in-use stability of danaparoid sodium diluted in common infusion fluids has been demonstrated for up to 48 hours at 25°C.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies

Scientific data and/or certificates of suitability issued by the EDQM have been provided and compliance with the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via medicinal products has been satisfactorily demonstrated.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Danaparoid Aspen 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 Danaparoid Aspen 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 biological generic formulation of Orgaran which is available on the European market. Pharmacodynamic, pharmacokinetic and toxicological properties of danaparoid sodium are well known. As danaparoid sodium is a widely used, well-known active substance, the applicant has not provided additional studies and further studies are not required. The submitted non-clinical overview on the pre-clinical pharmacology, pharmacokinetics and toxicology is adequate.

IV. CLINICAL ASPECTS

IV.1 Introduction

Danaparoid sodium is a well-known active substance with established efficacy and tolerability. A clinical overview has been provided. The overview justifies why there is no need to generate additional clinical data. Therefore, the member state agreed that no further clinical studies are required. Danaparoid Aspen is manufactured at the same site by the same company using the same sources and procedures as the reference product Orgaran. In summary, there is no discernible difference between the reference product and Danaparoid Aspen. The proposed SmPC of Danaparoid Aspen is the same as the SmPC for Orgaran.

Danaparoid Aspen, 750 anti-Xa E/0,6 ml, solution for injection/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 authorized reference medicinal product (NfG CPMP/EWP/QWP 1401/98). The quantitative composition of

Danaparoid Aspen, 750 anti-Xa E/0,6 ml 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.2 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 Danaparoid Aspen.

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

Important identified risks	- Hematoma / haemorrhage / bleeding - Danaparoid worsening of thrombocytopenia - Skin and subcutaneous tissue disorders
Important potential risks	- Medication error
Missing information	None

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

IV.3 Discussion on the clinical aspects

For this authorisation, reference is made to experience with the innovator product Orgaran. As the product applied for is identical to the reference product it is agreed that no clinical studies have been performed. 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 language used for the purpose of user testing the PL was English. The test consisted of two rounds with ten 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

Danaparoid Aspen, 750 anti-Xa E/0,6 ml, solution for injection has a proven chemical-pharmaceutical quality and is a generic form of Orgaran 750 anti-Xa E, solution for injection. Orgaran is a well-known medicinal product with an established favourable efficacy and safety profile.

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 state, on the basis of the data submitted, considered that essential similarity has been demonstrated for Danaparoid Aspen with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 27 May 2021.

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