COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Danaparoid natrium Aspen 750 anti-Xa units/0.6 ml, solution for injection

(danaparoid sodium)

NL/H/3998/001/DC

Date: 4 January 2021

This module reflects the scientific discussion for the approval of Danaparoid natrium Aspen 750 anti-Xa units/0.6 ml, solution for injection. The procedure was finalised at 30 September 2020. 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 natrium Aspen 750 anti-Xa units/0.6 ml, solution for injection, from Aspen Pharma Trading Limited.

The product is indicated for:

- Prevention of deep vein thrombosis (DVT) in situations where heparin should not be used, including patients with heparin-induced thrombocytopenia (HIT).
- Treatment of thrombo-embolic disorders in patients who require urgent parenteral anticoagulation because of the development or a history of HIT.

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 Orgaran, 750 anti-Xa units, solution for injection which has been registered in Ireland by Aspen Pharma Trading Limited since 11 June 1991 (original product). In the Netherlands, Orgaran (NL RVG 15006) has been registered by a mutual recognition procedure NL/H/0142/001.

The concerned member states (CMS) involved in this procedure were Denmark and Italy.

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

Legal basis

Danaparoid is considered a biological as it is manufactured from a biological source (porcine intestinal mucosa). In general, generic applications for biologicals do not qualify for submission with legal basis Article 10(1) and these applications 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…'*

However in this case the product concerns a so-called "auto-generic", i.e. starting materials, the manufacturing process and manufacturers and the proposed MAH are the same as for the reference product Orgaran. Differences between the product at issue and the reference product can therefore be excluded and the medicinal product complies with article 10(1)2(b)

'a medicinal product which has the same qualitative and quantitative composition in active substances and the same pharmaceutical form as the reference medicinal product'.

The RMS considers that the legal basis Article 10(1) of Directive 2001/83 for this "auto-generic" application is acceptable. This was confirmed by the Coordination group for Mutual recognition and Decentralised procedure for human medicinal products (CMDh) in their meeting in May 2017.

II. QUALITY ASPECTS

II.1 Introduction

Danaparoid natrium Aspen is a clear/colourless to pale yellow aqueous solution for injection. The product contains danaparoid sodium, which is a non-heparin mixture of low molecular weight sulphated glycosaminoglycuronans derived from animal mucosa. The mixture comprises heparan sulphate, dermatan sulphate and a minor amount of chondroitin sulphates.

One ampoule (0.6 ml) contains 750 anti-factor Xa units danaparoid sodium corresponding to 1250 anti-factor Xa units 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 a box with ten 1-ml glass ampoules, containing 750 anti-factor Xa units (0.6 ml) danaparoid sodium per ampoule (1250 anti-factor Xa units/ml).

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 is derived from animal mucosa and does not contain heparin.

Manufacturing process

A long experience exists with the manufacture of the drug substance. Adequate specifications have been adopted for starting materials, solvents and reagents. The active substance has been adequately characterised.

Quality control of drug substance

The active substance specification is 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 three batches.

Stability of drug substance
The stability sections have been updated to include the latest available stability information. New results do not raise any issues. It is noted that for three batches already data covering the entire shelf life claim (60 months at 15°C to 25°C) are available.

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 validity of the current formulation has been demonstrated retrospectively through many years of experience of the product.

Manufacturing process
The manufacturing process has been validated according to relevant guidelines. Process validation data on the product have been presented for multiple batches in accordance with the relevant European guidelines.

Control of excipients
The information regarding excipients is acceptable. 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 includes tests for appearance, colour, identification, impurities, physicochemical tests and microbial quality. 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 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 batches stored at 5°C (up to 36 months), 25°C/60% RH (up to 36 months), 30°C/35% RH (up to 36 months) and 40°C/75% RH (6 months). On basis of the data submitted, a shelf life was granted of 3 years. The storage conditions are: 'Do not store above 30°C. Store in the original package in order to protect from light. Do not refrigerate or freeze.' Chemical and physical in-use stability of danaparoid sodium diluted in common infusion fluids has been demonstrated for up to 48 hours at 15 to 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.

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

Danaparoid sodium is manufactured using starting material of animal origin, therefore a TSE statement concerning the TSE risk during the manufacturing of danaparoid sodium is provided.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Danaparoid natrium 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 natrium 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 generic formulation of Orgaran 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

Danaparoid sodium 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.

No clinical studies have been performed for this application. Danaparoid sodium 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 sodium Aspen.

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 natrium 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 the clinical studies and experience with the innovator product Orgaran. No new clinical studies were conducted. 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 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

Danaparoid natrium Aspen 750 anti-Xa units/0.6 ml, solution for injection has a proven chemical-pharmaceutical quality and is a generic form of Orgaran, 750 anti-Xa units, solution for injection. Orgaran is a well-known medicinal product with an established favourable efficacy and safety profile.

Since both the reference and current product are manufactured at the same site by the same company using the same sources and procedures, no clinical studies were performed.

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 Danaparoid natrium Aspen with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 30 September 2020.

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