IPAR

Public Assessment Report for a
Medicinal Product for Human Use

Scientific Discussion

Fondaparinux Sodium Aspen 7.5 mg/0.6 ml solution for injection, pre-filled syringe.
Fondaparinux sodium
PA1691/034/004

The Public Assessment Report reflects the scientific conclusion reached by the Health Products Regulatory Authority (HPRA) at the end of the evaluation process and provides a summary of the grounds for approval of a marketing authorisation for a specific medicinal product for human use. It is made available by the HPRA for information to the public, after deletion of commercially sensitive information. The legal basis for its creation and availability is contained in Article 21 of Directive 2001/83/EC, as amended. It is a concise document which highlights the main parts of the documentation submitted by the applicant and the scientific evaluation carried out by the HPRA leading to the approval of the medicinal product for marketing in Ireland.

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I. INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the HPRA has granted a marketing authorisation for Fondaparinux Sodium Aspen 7.5/0.6 mg/ml, Solution for injection, pre-filled syringe from Aspen Pharma Trading Limited on 29th July 2022.

This is a generic product and the legal basis for this application is article 10 (1) of Directive 2001/83/EC as amended.

HPRA was RMS in this decentralised procedure and France was a CMS.

This medicinal product has been approved with the following indications in adults:
Fondaparinux Sodium Aspen 5mg/ml concentration formulations (1.5mg/0.3mL, 2.5mg/0.5ml) are indicated for:
Prevention of Venous Thromboembolic Events (VTE) in adults undergoing major orthopaedic surgery of the lower limbs such as hip fracture, major knee surgery or hip replacement surgery.
Prevention of Venous Thromboembolic Events (VTE) in adults undergoing abdominal surgery who are judged to be at high risk of thromboembolic complications, such as patients undergoing abdominal cancer surgery.
Prevention of Venous Thromboembolic Events (VTE) in adult medical patients who are judged to be at high risk for VTE and who are immobilised due to acute illness such as cardiac insufficiency and/or acute respiratory disorders, and/or acute infectious or inflammatory disease.
Treatment of adults with acute symptomatic spontaneous superficial vein thrombosis of the lower limbs without concomitant deep vein thrombosis.

In addition to the above indications, Fondaparinux Sodium Aspen 2.5mg/0.5ml is indicated for:

- Treatment of unstable angina or non-ST segment elevation myocardial infarction (UA/NSTEMI) in adults for whom urgent (< 120 mins) invasive management (PCI) is not indicated.
- Treatment of ST segment elevation myocardial infarction (STEMI) in adults who are managed with thrombolytics or who initially are to receive no other form of reperfusion therapy.

Fondaparinux Sodium Aspen 12.5mg/ml concentration formulations (5mg/0.4mL, 7.5mg/0.6mL, 10mg/0.8mL) are indicated for the treatment of adults with acute Deep Vein Thrombosis (DVT) and treatment of acute Pulmonary Embolism (PE), except in haemodynamically unstable patients or patients who require thrombolysis or pulmonary embolectomy.

This medicinal product is subject to prescription, which may not be renewed.

The Summary of Product Characteristics for (SmPC) and Patient Information Leaflet for this medicinal product is available on the HPRA's website.

Name of the product	Fondaparinux Sodium Aspen 7.5/0.6 mg/ml, Solution for injection, pre-filled syringe
Name(s) of the active substance(s) (INN)	Fondaparinux sodium
Pharmacotherapeutic classification (ATC code)	B01AX05
Pharmaceutical form and strength(s)	Solution for injection
Marketing Authorisation Number(s) in Ireland (PA)	PA1691/034/004
Marketing Authorisation Holder	Aspen Pharma Trading Limited
MRP/DCP No.	IE/H/1192/004/DC
Reference Member State	IE
Concerned Member State	FR

II. QUALITY ASPECTS

II.1. Introduction

This application is for Fondaparinux Sodium Aspen 7.5/0.6 mg/ml, Solution for injection, pre-filled syringe.

II.2 Drug substance

The active substance is Fondaparinux Sodium, an established active substance not described in the European Pharmacopoeia.

Full information in regard to the active substance is provided by the applicant. The active substance is manufactured in accordance with the principles of Good Manufacturing Practice (GMP).

The drug substance specification has been established in-house. The drug substance specification is considered adequate to control the quality in view of the route of synthesis and the various European guidelines.

Batch analytical data demonstrating compliance with this specification has been provided.

II.3 Medicinal product

P.1 Composition
Fondaparinux sodium solution for Injection is presented in five strengths 1.5 mg/0.3 ml, 2.5 mg/0.5 ml, 5.0mg/0.4ml, 7.5mg/0.6ml and 10.0mg/0.8ml.

Fondaparinux sodium solution for Injection (5mg/ml) is a colourless, clear to practically clear liquid, containing 5mg/mL Fondaparinux Sodium (1.5 mg/0.3 ml and 2.5 mg/0.5 ml).

Fondaparinux sodium solution for Injection (12.5mg/mL) is colorless to slightly yellow, clear to practically clear liquid, containing 12.5mg/mL Fondaparinux Sodium (5.0mg/0.4mL, 7.5mg/0.6mL and 10.0mg/0.8mL).

The excipients in the medicinal product are listed in section 6.1 of the SmPC.
A visual description of the product is included in section 3 of the SmPC.

P.2 Pharmaceutical Development
The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines.
Compatibility between the active substance and the excipients is supported by stability studies. The packaging materials have shown to be suitable by acceptable stability studies.

P.3 Manufacture of the Product

The product is manufactured in accordance with the principles of good manufacturing practice (GMP) at suitably qualified manufacturing sites.

The manufacturing process has been validated according to relevant European/ICH guidelines and the process is considered to be sufficiently validated.

Batch formulae have been provided for the manufacture of the product. In-process controls are appropriate considering the nature of the product and the method of manufacture. Process validation data on the product have been presented for full-scale batches in accordance with the relevant European guidelines. The manufacturing process is considered to be sufficiently validated.

P.4 Control of Other Substances (Excipients/*Ancillary Substances*)
The excipients used in the manufacture of Fondaparinux sodium solution for Injection are standard excipients in manufacturing of parenteral, products and controlled and tested in compliance with the respective Ph. Eur. monograph.

P.5 Control of Finished Product
The Finished Product Specification is based on the pharmacopoeial monograph for parenteral preparations and ICH Q6A.

The tests and control limits in the specifications have been adequately justified and are considered appropriate for adequate quality control of the product. The analytical methods used are described in sufficient detail and are supported by validation data.

Batch analytical data for a number of batches from the proposed production site have been provided, and demonstrate the ability of the manufacturer to produce batches of finished product of consistent quality.

P.6 Packaging material
The approved packaging for this product is described in section 6.5 of the SmPC.

Evidence has been provided that the packaging complies with relevant Ph. Eur requirements and EU legislation on plastic materials and articles intended to come into contact with food.

P.7 Stability of the Finished Product
Stability data on the finished product in the proposed packaging have been provided in accordance with EU guidelines and support the shelf-life and storage conditions listed in sections 6.3 and 6.4 of the SmPC.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
No excipients of animal or human origin are included.

II.4 Discussion on Chemical, Pharmaceutical and Biological Aspects

The important quality characteristics of the product are well-defined and controlled. Satisfactory chemical and pharmaceutical documentation has been provided, assuring consistent quality of Fondaparinux Sodium Aspen 1.5 mg/ 0.3 ml, Solution for injection, Fondaparinux Sodium Aspen 2.5 mg/ 0.5 ml, Solution for injection, Fondaparinux Sodium Aspen 5 mg/ 0.4 ml, Solution for injection, Fondaparinux Sodium Aspen 7.5 mg/ 0.6 ml, Solution for injection, Fondaparinux Sodium Aspen 10 mg/ 0.8 ml, Solution for injection (PA1691/034/001-005).

III. NON-CLINICAL ASPECTS

III.1 Introduction

This active substance is a generic formulation of Arixtra on the European market. No new preclinical data have been submitted. As such, no pre-clinical assessment has been made on the application. This is acceptable for this type of application.

III.2 Ecotoxicity/environmental risk assessment

The active substance is a natural carbohydrate molecule, the use of which will not alter the concentration or distribution of the substance in the environment. Therefore, Fondaparinux sodium is not expected to pose a risk to the environment.

III.3 Discussion on the non-clinical aspects

Pharmacodynamic, pharmacokinetic and toxicological properties of Fondaparinux sodium are well known. As Fondaparinux sodium is a widely used, well-known active substance, the applicant has not provided additional studies and further studies are not required. Overview based on literature review has been provided and is adequate. No new nonclinical data have been provided that would alter the benefit-risk assessment for this product.

IV. CLINICAL ASPECTS

IV.1 Introduction

Fondaparinux sodium is a well-known active substance with established efficacy and tolerability.

The content of the SmPC approved during the decentralised procedure is in accordance with that accepted for the reference product Arixtra (EMEA/H/C/000403) marketed by Mylan IRE Healthcare Limited.

For this generic application, the applicant was not required to perform bioequivalence studies in compliance with the CHMP guideline on the Investigation of Bioequivalence (CPMP/PWP/EWP/1401/98 Rev 1/Corr**) regarding subcutaneous parenteral solutions. The product is an aqueous solution containing the same concentration of the same active substance and the same excipients in similar amounts as the medicinal product currently approved.

IV.2 Pharmacokinetics

The pharmacokinetic profile of fondaparinux is well characterised.

Absorption:
Fondaparinux achieves complete bioavailability (100%) subcutaneously. There is rapid onset of action with peak plasma concentration (Cmax) of 0.34 mg/L after 2 hours post-dose.

Distribution:
Its volume of distribution is limited to 7-11 litres in blood volume and in individuals with normal kidney function. *Invitro*, fondaparinux is highly and specifically bound to antithrombin protein with a dose-dependent plasma concentration binding (98.6% to 97% in the concentration range from 0.5 to 2 mg/l).

Biotransformation:
Although not fully evaluated, there is no evidence of fondaparinux metabolism and in particular no evidence for the formation of active metabolites. Fondaparinux does not inhibit CYP450s *invitro*.

Elimination:
In individuals with normal kidney function fondaparinux is eliminated (64-77%) in urine mainly as unchanged drug. The plasma terminal elimination half-life (t½) of fondaparinux sodium is about 17 hours in healthy young subjects and about 21 hours in elderly subjects.

Additional information on the PK characteristics of cetirizine in renal impairment, hepatic impairment, elderly and low body weight is provided in the product information.

IV.3 Pharmacodynamics

The pharmacodynamics of fondaparinux are well-known. Fondaparinux is a synthetic and selective inhibitor of activated *FactorX(Xa)*.The antithrombotic activity of fondaparinux is the result of antithrombin III (ATIII) mediated selective inhibition of *FactorXa*. By binding selectively to ATIII, fondaparinux potentiates (about 300 times) the innate neutralization of *FactorXa*by ATIII. Neutralisation of *Factor Xa*interrupts the blood coagulation cascade and inhibits both thrombin formation and thrombus development. Fondaparinux does not inactivate thrombin (activated Factor II) and has no effects on platelets.

IV.4 Clinical Efficacy

No clinical efficacy data are provided as this is a generic application.

IV.5 Clinical Safety

As this is a generic application, no other clinical safety data are required.

Risk Management Plan
The risk management plan proposed by the applicant, including the proposed pharmacovigilance activities and risk minimisation measures is considered acceptable. The approved summary of safety concerns is outlined in the table below:

Important identified risks	• Bleeding events • Off-label use • Catheter thrombosis during Percutaneous Coronary Intervention (PCI) when fondaparinux is used as sole anti-coagulant adjunct to PCI
Important potential risks	• Heparin induced thrombocytopenia • Use of higher VTE treatment doses (5mg, 7.5mg, 10mg) for treatment of superficial-vein

	thrombosis • Use of fondaparinux (2.5mg) in superficial-vein thrombosis patients with concomitant DVT
Missing information	• Use in paediatric patients

Routine risk minimisation measures and routine pharmacovigilance activities are proposed to address the safety concerns outlined above and this is considered acceptable.

The Applicant should submit Periodic Safety Update Reports (PSUR) Periodic Safety Update Reports (PSUR) in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

IV.6 Discussion on the clinical aspects

As this approval concerns a generic application, there are no new efficacy or safety studies required, as the applicant can refer to the data of the reference medical products.

V. OVERALL CONCLUSIONS

Fondaparinux Sodium Aspen 7.5/0.6 mg/ml, Solution for injection is a generic form of Arixtra (EMEA/H/C/000403). Arixtra is a well-known medicinal product with a proven chemical-pharmaceutical quality and an established favourable efficacy and safety profile.

Bioequivalence was waived in compliance with the CHMP guidance documents. The SmPC is consistent with that of the reference product.

The MAH has provided written confirmation that systems and services are in place to ensure compliance with their pharmacovigilance obligations.

The HPRA, on the basis of the data submitted considered that Fondaparinux Sodium Aspen demonstrated a satisfactory risk/benefit profile and therefore granted a marketing authorisation.

VI. REVISION DATE

22.06.2027