

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Fondaparinux sodium Aspen 2.5 mg/0.5 ml solution for injection, pre-filled syringe.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each pre-filled syringe (0.5 ml) contains 2.5 mg of fondaparinux sodium.

Excipient(s) with known effect: Contains less than 1 mmol of sodium (23 mg) per dose, and therefore is essentially sodium free.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for injection.

The solution is a clear and colourless liquid.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

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 (see section 5.1).

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 unstable angina or non-ST segment elevation myocardial infarction (UA/NSTEMI) in adults for whom urgent (< 120 mins) invasive management (PCI) is not indicated (see sections 4.4 and 5.1).

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.

Treatment of adults with acute symptomatic spontaneous superficial-vein thrombosis of the lower limbs without concomitant deep-vein thrombosis (see sections 4.2 and 5.1).

4.2 Posology and method of administration

Posology

Patients undergoing major orthopaedic or abdominal surgery

The recommended dose of fondaparinux is 2.5 mg once daily administered post-operatively by subcutaneous injection.

The initial dose should be given 6 hours following surgical closure provided that haemostasis has been established.

Treatment should be continued until the risk of venous thrombo-embolism has diminished, usually until the patient is ambulant, at least 5 to 9 days after surgery. Experience shows that in patients undergoing hip fracture surgery, the risk of VTE continues beyond 9 days after surgery. In these patients the use of prolonged prophylaxis with fondaparinux should be considered for up to an additional 24 days (see section 5.1).

Medical patients who are at high risk for thromboembolic complications based on an individual risk assessment

The recommended dose of fondaparinux is 2.5 mg once daily administered by subcutaneous injection. A treatment duration of 6-14 days has been clinically studied in medical patients (see section 5.1).

Treatment of unstable angina/non- ST segment elevation myocardial infarction (UA/NSTEMI)

The recommended dose of fondaparinux is 2.5 mg once daily, administered by subcutaneous injection. Treatment should be initiated as soon as possible following diagnosis and continued for up to a maximum of 8 days or until hospital discharge if that occurs earlier.

If a patient is to undergo percutaneous coronary intervention (PCI), unfractionated heparin (UFH) as per standard practice should be administered during PCI, taking into account the patient's potential risk of bleeding, including the time since the last dose of fondaparinux (see section 4.4). The timing of restarting subcutaneous fondaparinux after sheath removal should be based on clinical judgment. In the pivotal UA/NSTEMI clinical trial, treatment with fondaparinux was restarted no earlier than 2 hours after sheath removal.

Treatment of ST segment elevation myocardial infarction (STEMI)

The recommended dose of fondaparinux is 2.5 mg once daily. The first dose of fondaparinux is administered intravenously and subsequent doses are administered by subcutaneous injection. Treatment should be initiated as soon as possible following diagnosis and continued for up to a maximum of 8 days or until hospital discharge if that occurs earlier.

If a patient is to undergo non-primary PCI, unfractionated heparin (UFH) as per standard practice should be administered during PCI, taking into account the patient's potential risk of bleeding, including the time since the last dose of fondaparinux (see section 4.4). The timing of restarting subcutaneous fondaparinux after sheath removal should be based on clinical judgment. In the pivotal STEMI clinical trial, treatment with fondaparinux was restarted no earlier than 3 hours after sheath removal.

- *Patients who are to undergo coronary artery bypass graft (CABG) surgery*

In STEMI or UA/NSTEMI patients who are to undergo coronary artery bypass graft (CABG) surgery, fondaparinux where possible, should not be given during the 24 hours before surgery and may be restarted 48 hours post-operatively.

Treatment of superficial-vein thrombosis

The recommended dose of fondaparinux is 2.5 mg once daily, administered by subcutaneous injection. Patients eligible for fondaparinux 2.5 mg treatment should have acute, symptomatic, isolated, spontaneous superficial-vein thrombosis of the lower limbs, at least 5 cm long and documented by ultrasonographic investigation or other objective methods. Treatment should be initiated as soon as possible following diagnosis and after exclusion of concomitant DVT or superficial-vein thrombosis within 3 cm from the sapheno-femoral junction. Treatment should be continued for a minimum of 30 days and up to a maximum of 45 days in patients at high risk of thromboembolic complications (see sections 4.4 and 5.1). Patients could be recommended to self-inject the product when they are judged willing and able to do so. Physicians should provide clear instructions for self-injection.

- *Patients who are to undergo surgery or other invasive procedures*

In superficial vein thrombosis patients who are to undergo surgery or other invasive procedures, fondaparinux, where possible, should not be given during the 24 hours before surgery. Fondaparinux may be restarted at least 6 hours post-operatively provided haemostasis has been achieved.

Special populations

Prevention of VTE following Surgery

In patients undergoing surgery, timing of the first fondaparinux injection requires strict adherence in patients ≥ 75 years, and/or with body weight < 50 kg and/or with renal impairment with creatinine clearance ranging between 20 to 50 ml/min.

The first fondaparinux administration should be given not earlier than 6 hours following surgical closure. The injection should not be given unless haemostasis has been established (see section 4.4).

Renal impairment

- *Prophylaxis of VTE* - Fondaparinux should not be used in patients with creatinine clearance <20 ml/min (see section 4.3). The dose should be reduced to 1.5 mg once daily in patients with creatinine clearance in the range of 20 to 50 ml/min (see sections 4.4 and 5.2). No dosage reduction is required for patients with mild renal impairment (creatinine clearance >50 ml/min).
- *Treatment of UA/NSTEMI and STEMI* - Fondaparinux should not be used in patients with creatinine clearance < 20 ml/min (see section 4.3). No dosage reduction is required for patients with creatinine clearance > 20 ml/min.
- *Treatment of superficial-vein thrombosis* - Fondaparinux should not be used in patients with creatinine clearance <20 ml/min (see section 4.3). The dose should be reduced to 1.5 mg once daily in patients with creatinine clearance in the range of 20 to 50 ml/min (see sections 4.4 and 5.2). No dosage reduction is required for patients with mild renal impairment (creatinine clearance >50 ml/min). The safety and efficacy of 1.5 mg has not been studied (see section 4.4.)

Hepatic impairment

- *Prevention of VTE and Treatment of UA/NSTEMI and STEMI* - No dosing adjustment is necessary in patients with either mild or moderate hepatic impairment. In patients with severe hepatic impairment, fondaparinux should be used with care as this patient group has not been studied (see sections 4.4 and 5.2).
- *Treatment of superficial-vein thrombosis* - The safety and efficacy of fondaparinux in patients with severe hepatic impairment has not been studied, therefore fondaparinux is not recommended for use in these patients (see section 4.4).

Paediatric population - Fondaparinux is not recommended for use in children below 17 years of age due to a lack of data on safety and efficacy.

Low body weight

- *Prevention of VTE and Treatment of UA/NSTEMI and STEMI* - Patients with body weight <50 kg are at increased risk of bleeding. Elimination of fondaparinux decreases with weight. Fondaparinux should be used with caution in these patients (see section 4.4).
- *Treatment of superficial-vein thrombosis* - The safety and efficacy of fondaparinux in patients with body weight less than 50 kg has not been studied, therefore fondaparinux is not recommended for use in these patients (see section 4.4).

Method of administration

- *Subcutaneous administration*

Fondaparinux is administered by deep subcutaneous injection while the patient is lying down. Sites of administration should alternate between the left and the right anterolateral and left and right posterolateral abdominal wall. To avoid the loss of medicinal product when using the pre-filled syringe do not expel the air bubble from the syringe before the injection. The whole length of the needle should be inserted perpendicularly into a skin fold held between the thumb and the forefinger; the skin fold should be held throughout the injection.

- *Intravenous administration (first dose in patients with STEMI only)*

Intravenous administration should be through an existing intravenous line either directly or using a small volume (25 or 50ml) 0.9% saline minibag. To avoid the loss of medicinal product when using the pre-filled syringe do not expel the air bubble from the syringe before the injection. The intravenous tubing should be well flushed with saline after injection to ensure that all of the medicinal product is administered. If administered via a minibag, the infusion should be given over 1 to 2 minutes. For additional instructions for use and handling and disposal see section 6.6.

4.3 Contraindications

- hypersensitivity to the active substance or to any of the excipients listed in section 6.1
- active clinically significant bleeding
- acute bacterial endocarditis
- severe renal impairment defined by creatinine clearance < 20 ml/min.

4.4 Special warnings and precautions for use

Fondaparinux is intended for subcutaneous use only. Do not administer intramuscularly.

Haemorrhage

Fondaparinux should be used with caution in patients who have an increased risk of haemorrhage, such as those with congenital or acquired bleeding disorders (e.g. platelet count <50,000/mm³), active ulcerative gastrointestinal disease and recent intracranial haemorrhage or shortly after brain, spinal or ophthalmic surgery and in special patient groups as outlined below.

For prevention of VTE - Agents that may enhance the risk of haemorrhage should not be administered concomitantly with fondaparinux. These agents include desirudin, fibrinolytic agents, GP IIb/IIIa receptor antagonists, heparin, heparinoids, or Low Molecular Weight Heparin (LMWH). When required, concomitant therapy with vitamin K antagonist should be administered in accordance with the information of Section 4.5. Other antiplatelet medicinal products (acetylsalicylic acid, dipyridamole, sulfipyrazone, ticlopidine or clopidogrel), and NSAIDs should be used with caution. If co-administration is essential, close monitoring is necessary.

For treatment of UA/NSTEMI and STEMI-Fondaparinux should be used with caution in patients who are being treated concomitantly with other agents that increase the risk of haemorrhage (such as GPIIb/IIIa inhibitors or thrombolytics).

For treatment of superficial-vein thrombosis - Fondaparinux should be used with caution in patients who are being treated concomitantly with other medicinal products that increase the risk of haemorrhage.

PCI and risk of guiding catheter thrombus

In STEMI patients undergoing primary PCI, the use of fondaparinux prior to and during PCI is not recommended. Similarly, in UA/NSTEMI patients with life threatening conditions that require urgent revascularisation, the use of fondaparinux prior to and during PCI is not recommended. These are patients with refractory or recurrent angina associated with dynamic ST deviation, heart failure, life-threatening arrhythmias or haemodynamic instability.

In UA/NSTEMI and STEMI patients undergoing non-primary PCI, the use of fondaparinux as the sole anticoagulant during PCI is not recommended due to an increased risk of guiding catheter thrombus (see clinical studies section 5.1). Therefore adjunctive UFH should be used during non-primary PCI according to standard practice (see posology in section 4.2).

Patients with superficial-vein thrombosis

Presence of superficial-vein thrombosis greater than 3 cm from the sapheno-femoral junction should be confirmed and concomitant DVT should be excluded by compression ultrasound or objective methods prior to initiating treatment of fondaparinux. There are no data regarding the use of fondaparinux 2.5 mg in superficial-vein thrombosis patients with concomitant DVT or with superficial-vein thrombosis within 3 cm of the sapheno-femoral junction (see section 4.2 and 5.1).

The safety and efficacy of fondaparinux 2.5 mg has not been studied in the following groups: patients with superficial-vein thrombosis following sclerotherapy or resulting as a complication of an intravenous line, patients with history of superficial-vein thrombosis within the previous 3 months, patients with history of venous thromboembolic disease within the previous 6 months, or patients with active cancer (see section 4.2 and 5.1).

Spinal / Epidural anaesthesia

In patients undergoing major orthopaedic surgery, epidural or spinal haematomas that may result in long-term or permanent paralysis cannot be excluded with the concurrent use of fondaparinux and spinal/epidural anaesthesia or spinal puncture. The risk of these rare events may be higher with post-operative use of indwelling epidural catheters or the concomitant use of other medicinal products affecting haemostasis.

Elderly patients

The elderly population is at increased risk of bleeding. As renal function is generally decreasing with age, elderly patients may show reduced elimination and increased exposure of fondaparinux (see section 5.2). Fondaparinux should be used with caution in elderly patients (see section 4.2).

Low body weight

- *Prevention of VTE* - Patients with body weight <50 kg are at increased risk of bleeding. Elimination of fondaparinux decreases with weight. Fondaparinux should be used with caution in these patients (see section 4.2).
- *Treatment of superficial-vein thrombosis* - There are no clinical data available for the use of fondaparinux for the treatment of superficial-vein thrombosis in patients with body weight less than 50kg. Therefore, fondaparinux is not recommended for treatment of superficial-vein thrombosis in these patients (see section 4.2).

Renal impairment

- *Prevention of VTE* - Fondaparinux is known to be mainly excreted by the kidney. Patients with creatinine clearance <50 ml/min are at increased risk of bleeding and VTE and should be treated with caution (see sections 4.2, 4.3 and 5.2). There are limited clinical data available from patients with creatinine clearance less than 30 ml/min.
- *Treatment of superficial-vein thrombosis* - Fondaparinux should not be used in patients with creatinine clearance <20 ml/min (see section 4.3). The dose should be reduced to 1.5 mg once daily in patients with creatinine clearance in the range of 20 to 50 ml/min (see sections 4.2 and 5.2). The safety and efficacy of 1.5 mg has not been studied.

Severe hepatic impairment

- *Prevention of VTE* - Dosing adjustment of fondaparinux is not necessary. However, the use of fondaparinux should be considered with caution because of an increased risk of bleeding due to a deficiency of coagulation factors in patients with severe hepatic impairment (see section 4.2).
- *Treatment of superficial-vein thrombosis* - There are no clinical data available for the use of fondaparinux for the treatment of superficial-vein thrombosis in patients with severe hepatic impairment. Therefore, fondaparinux is not recommended for the treatment of superficial-vein thrombosis in these patients (see section 4.2).
- *Treatment of UA/NSTEMI and STEMI* - For the treatment of UA/NSTEMI and STEMI, there are limited clinical data available on the use of fondaparinux 2.5mg once daily in patients with creatinine clearance between 20 and 30 ml/min. Therefore the physician should determine if the benefit of treatment outweighs the risk (see sections 4.2 and 4.3).

Patients with Heparin Induced Thrombocytopenia

Fondaparinux **should be used with caution in patients with a history of HIT**. The efficacy and safety of fondaparinux have not been formally studied in patients with HIT type II. Fondaparinux does not bind to platelet factor 4 and does not usually cross-react with sera from patients with Heparin Induced Thrombocytopenia (HIT) type II. However, **rare spontaneous reports of HIT in patients treated with fondaparinux have been received**.

Latex Allergy

The needle shield of the pre-filled syringe contains dry natural latex rubber that may cause severe allergic reactions.

Sodium

This medicine contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

Bleeding risk is increased with concomitant administration of fondaparinux and agents that may enhance the risk of haemorrhage (see section 4.4).

Oral anticoagulants (warfarin), platelet inhibitors (acetylsalicylic acid), NSAIDs (piroxicam) and digoxin did not interact with the pharmacokinetics of fondaparinux. The fondaparinux dose (10 mg) in the interaction studies was higher than the dose recommended for the present indications. Fondaparinux neither influenced the INR activity of warfarin, nor the bleeding time under acetylsalicylic acid or piroxicam treatment, nor the pharmacokinetics of digoxin at steady state.

Follow-up therapy with another anticoagulant medicinal product

If follow-up treatment is to be initiated with heparin or LMWH, the first injection should, as a general rule, be given one day after the last fondaparinux injection.

If follow up treatment with a Vitamin K antagonist is required, treatment with fondaparinux should be continued until the target INR value has been reached.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no adequate data from the use of fondaparinux in pregnant women. Animal studies are insufficient with respect to effects on pregnancy, embryo/foetal development, parturition and postnatal development because of limited exposure. Fondaparinux should not be prescribed to pregnant women unless clearly necessary.

Breast-feeding

Fondaparinux is excreted in rat milk but it is not known whether fondaparinux is excreted in human milk. Breast-feeding is not recommended during treatment with fondaparinux. Oral absorption by the child is however unlikely.

Fertility

There are no data available on the effect of fondaparinux on human fertility. Animal studies do not show any effect on fertility.

4.7 Effects on ability to drive and use machines

No studies on the effect on the ability to drive and to use machines have been performed.

4.8 Undesirable effects

The most commonly reported serious adverse reactions reported with fondaparinux are bleeding complications (various sites including rare cases of intracranial/ intracerebral and retroperitoneal bleedings) and anaemia. Fondaparinux should be used with caution in patients who have an increased risk of haemorrhage (see section 4.4).

The safety of fondaparinux 2.5 mg has been evaluated in:

- 3,595 patients undergoing major orthopaedic surgery of the lower limbs treated up to 9 days
- 327 patients undergoing hip fracture surgery treated for 3 weeks following an initial prophylaxis of 1 week
- 1,407 patients undergoing abdominal surgery treated up to 9 days
- 425 medical patients who are at risk for thromboembolic complications treated up to 14 days
- 10,057 patients undergoing treatment of UA or NSTEMI ACS
- 6,036 patients undergoing treatment of STEMI ACS.

For the prevention of VTE, the adverse reactions reported by the investigator as at least possibly related to fondaparinux are presented within each frequency grouping (very common $\geq 1/10$; common: $\geq 1/100$ to $< 1/10$; uncommon: $\geq 1/1,000$ to $< 1/100$; rare: $\geq 1/10,000$ to $< 1/1,000$; very rare $< 1/10,000$) and system organ class by decreasing order of seriousness; these adverse reactions should be interpreted within the surgical and medical context.

System organ class MedDRA	Adverse reactions in patients undergoing major orthopaedic surgery of lower limbs and/or abdominal surgery	Adverse reactions in medical patients
<i>Infections and infestations</i>	<i>Rare:</i> post-operative wound infection	
<i>Blood and lymphatic system disorders</i>	<i>Common:</i> post-operative haemorrhage,	<i>Common:</i> bleeding

	anaemia <i>Uncommon:</i> bleeding (epistaxis, gastrointestinal, haemoptysis, haematuria, haematoma) thrombocytopenia, purpura, thrombocythaemia, platelet abnormal, coagulation disorder	(haematoma, haematuria, haemoptysis, gingival bleeding) <i>Uncommon:</i> anaemia
<i>Immune system disorders</i>	<i>Rare:</i> allergic reaction (including very rare reports of angioedema, anaphylactoid/anaphylactic reaction)	<i>Rare:</i> allergic reaction (including very rare reports of angioedema, anaphylactoid/anaphylactic reaction)
<i>Metabolism and nutrition disorders</i>	<i>Rare:</i> hypokalaemia	
<i>Nervous system disorders</i>	<i>Rare:</i> anxiety, somnolence, vertigo, dizziness, headache, confusion	
<i>Vascular disorders</i>	<i>Rare:</i> hypotension	
<i>Respiratory, thoracic and mediastinal disorders</i>	<i>Rare:</i> dyspnoea, coughing	<i>Uncommon:</i> dyspnoea
<i>Gastrointestinal disorders</i>	<i>Uncommon:</i> nausea, vomiting <i>Rare:</i> abdominal pain, dyspepsia, gastritis, constipation, diarrhoea	
<i>Hepatobiliary disorders</i>	<i>Uncommon:</i> hepatic enzymes increased, hepatic function abnormal <i>Rare:</i> bilirubinaemia	
<i>Skin and subcutaneous tissue disorders</i>	<i>Uncommon:</i> rash, pruritus	<i>Uncommon:</i> rash, pruritus
<i>General disorders and administration site conditions</i>	<i>Uncommon:</i> oedema, oedema peripheral, fever, wound secretion <i>Rare:</i> chest pain, fatigue, hot flushes, leg pain, oedema genital, flushing, syncope	<i>Uncommon:</i> chest pain

In other studies or in post-marketing experience, rare cases of intracranial / intracerebral and retroperitoneal bleedings have been reported.

The adverse event profile reported in the ACS program is consistent with the adverse drug reactions identified for VTE prophylaxis.

Bleeding was a commonly reported event in patients with UA/NSTEMI and STEMI. The incidence of adjudicated major bleeding was 2.1% (fondaparinux) vs. 4.1% (enoxaparin) up to and including Day 9 in the Phase III UA/NSTEMI study, and the incidence of adjudicated severe haemorrhage by modified TIMI criteria was 1.1% (fondaparinux) vs. 1.4% (control [UFH/placebo]) up to and including Day 9 in the Phase III STEMI study.

In the Phase III UA/NSTEMI study, the most commonly reported non-bleeding adverse events (reported in at least 1% of subjects on fondaparinux) were headache, chest pain and atrial fibrillation.

In the Phase III study in STEMI patients, the most commonly reported non-bleeding adverse events (reported in at least 1% of subjects on fondaparinux) were atrial fibrillation, pyrexia, chest pain, headache, ventricular tachycardia, vomiting, and hypotension.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the HPRA Pharmacovigilance

Website: www.hpra.ie.

4.9 Overdose

Fondaparinux doses above the recommended regimen may lead to an increased risk of bleeding. There is no known antidote to fondaparinux.

Overdose associated with bleeding complications should lead to treatment discontinuation and search for the primary cause. Initiation of appropriate therapy such as surgical haemostasis, blood replacements, fresh plasma transfusion, plasmapheresis should be considered.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: antithrombotic agents.

ATC code: B01AX05

Pharmacodynamic effects

Fondaparinux is a synthetic and selective inhibitor of activated Factor X (Xa). The antithrombotic activity of fondaparinux is the result of antithrombin III (ATIII) mediated selective inhibition of Factor Xa. By binding selectively to ATIII, fondaparinux potentiates (about 300 times) the innate neutralization of Factor Xa 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.

At the 2.5 mg dose, fondaparinux does not affect routine coagulation tests such as activated partial thromboplastin time (aPTT), activated clotting time (ACT) or prothrombin time (PT)/International Normalised Ratio (INR) tests in plasma nor bleeding time or fibrinolytic activity. However, rare spontaneous reports of aPTT prolongation have been received.

Fondaparinux does not usually cross-react with sera from patients with heparin-induced thrombocytopenia (HIT). However, rare spontaneous reports of HIT in patients treated with fondaparinux have been received.

Clinical studies

Prevention of Venous Thromboembolic Events (VTE) in patients undergoing major orthopaedic surgery of the lower limbs treated up to 9 days

The fondaparinux clinical program was designed to demonstrate the efficacy of fondaparinux for the prevention of venous thromboembolic events (VTE), i.e. proximal and distal deep vein thrombosis (DVT) and pulmonary embolism (PE) in patients undergoing major orthopaedic surgery of the lower limbs such as hip fracture, major knee surgery or hip replacement surgery. Over 8,000 patients (hip fracture – 1,711, hip replacement – 5,829, major knee surgery – 1,367) were studied in controlled Phase II and III clinical studies. Fondaparinux 2.5 mg once daily started 6-8 hours postoperatively was compared with enoxaparin 40 mg once daily started 12 hours before surgery, or 30 mg twice daily started 12-24 hours after surgery.

In a pooled analysis of these studies, the recommended dose regimen of fondaparinux versus enoxaparin was associated with a significant decrease (54% [95% CI, 44 %; 63%]) in the rate of VTE evaluated up to day 11 after surgery, irrespective of the type of surgery performed. The majority of endpoint events were diagnosed by a prescheduled venography and consisted mainly of distal DVT, but the incidence of proximal DVT was also significantly reduced. The incidence of symptomatic VTE, including PE was not significantly different between treatment groups.

In studies versus enoxaparin 40 mg once daily started 12 hours before surgery, major bleeding was observed in 2.8% of fondaparinux patients treated with the recommended dose, compared to 2.6% with enoxaparin.

Prevention of Venous Thromboembolic Events (VTE) in patients undergoing hip fracture surgery treated for up to 24 days following an initial prophylaxis of 1 week

In a randomised double-blind clinical trial, 737 patients were treated with fondaparinux 2.5 mg once daily for 7 +/- 1 days following hip fracture surgery. At the end of this period, 656 patients were randomised to receive fondaparinux 2.5 mg once daily or placebo for an additional 21 +/- 2 days. Fondaparinux provided a significant reduction in the overall rate of VTE compared with placebo [3 patients (1.4%) vs 77 patients (35%), respectively]. The majority (70/80) of the recorded VTE events were venographically detected non-symptomatic cases of DVT. Fondaparinux also provided a significant reduction in the rate of symptomatic VTE (DVT, and / or PE) [1 (0.3%) vs 9 (2.7%) patients, respectively] including two fatal PE reported in the placebo group. Major bleedings, all at surgical site and none fatal, were observed in 8 patients (2.4%) treated with fondaparinux 2.5 mg compared to 2 (0.6%) with placebo.

Prevention of Venous Thromboembolic Events (VTE) in patients undergoing abdominal surgery who are judged to be at high risk of thromboembolic complications, such as patients undergoing abdominal cancer surgery

In a double-blind clinical study, 2,927 patients were randomised to receive fondaparinux 2.5mg once daily or dalteparin 5,000 IU once daily, with one 2,500 IU preoperative injection and a first 2,500 IU post-operative injection, for 7±2 days. The main sites of surgery were colonic/rectal, gastric, hepatic, cholecystectomy or other biliary. Sixty-nine percent of the patients underwent surgery for cancer. Patients under-going urological (other than kidney) or gynaecological surgery, laparoscopic surgery or vascular surgery were not included in the study.

In this study, the incidence of total VTE was 4.6% (47/1,027) with fondaparinux, versus 6.1%: (62/1,021) with dalteparin: odds ratio reduction [95%CI] = -25.8% [-49.7%, 9.5%]. The difference in total VTE rates between the treatment groups, which was not statistically significant, was mainly due to a reduction of asymptomatic distal DVT. The incidence of symptomatic DVT was similar between treatment groups: 6 patients (0.4%) in the fondaparinux group vs 5 patients (0.3%) in the dalteparin group. In the large subgroup of patients undergoing cancer surgery (69% of the patient population), the VTE rate was 4.7% in the fondaparinux group, versus 7.7% in the dalteparin group.

Major bleeding was observed in 3.4% of the patients in the fondaparinux group and in 2.4% of the dalteparin group.

Prevention of Venous Thromboembolic Events (VTE) in medical patients who are at high risk for thromboembolic complications due to restricted mobility during acute illness

In a randomised double-blind clinical trial, 839 patients were treated with fondaparinux 2.5 mg once daily or placebo for 6 to 14 days. This study included acutely ill medical patients, aged ≥ 60 years, expected to require bed rest for at least four days, and hospitalized for congestive heart failure NYHA class III/IV and/or acute respiratory illness and/or acute infectious or inflammatory disease. Fondaparinux significantly reduced the overall rate of VTE compared to placebo [18 patients (5.6%) vs 34 patients (10.5%), respectively]. The majority of events were asymptomatic distal DVT. Fondaparinux also significantly reduced the rate of adjudicated fatal PE [0 patients (0.0%) vs 5 patients (1.2%), respectively]. Major bleedings were observed in 1 patient (0.2%) of each group.

Treatment of unstable angina or non-ST segment elevation myocardial infarction (UA/NSTEMI)

OASIS 5 was a double-blind, randomised, non-inferiority study with fondaparinux 2.5 mg subcutaneously once daily versus enoxaparin 1 mg/kg subcutaneously twice daily in approximately 20,000 patients with UA/NSTEMI. All patients received standard medical treatment for UA/NSTEMI, with 34% of patients undergoing PCI and 9% undergoing CABG. The mean treatment duration was 5.5 days in the fondaparinux group and 5.2 days in the enoxaparin group. If PCI was performed, patients received either intravenous fondaparinux (fondaparinux patients) or weight adjusted intravenous UFH (enoxaparin patients) as adjunctive therapy, dependent on the timing of the last subcutaneous dose and planned use of GP IIb/IIIa inhibitor. The mean age of the patients was 67 years, and approximately 60% were at least 65 years old. Approximately 40% and 17% of patients had mild (creatinine clearance ≥50 to <80 ml/min) or moderate (creatinine clearance ≥30 to <50 ml/min) renal impairment, respectively.

The primary adjudicated endpoint was a composite of death, myocardial infarction (MI) and refractory ischaemia (RI) within 9 days of randomisation. Of the patients in the fondaparinux group, 5.8% experienced an event by Day 9 compared to 5.7% for enoxaparin-treated patients (hazard ratio 1.01, 95% CI, 0.90, 1.13, one-sided non-inferiority p value = 0.003).

By Day 30, the incidence of all cause mortality was significantly reduced from 3.5% on enoxaparin to 2.9% on fondaparinux (hazard ratio 0.83, 95% CI, 0.71;0.97, p = 0.02). The effects on the incidence of MI and RI were not statistically different between the fondaparinux and enoxaparin treatment groups.

At Day 9 the incidence of major bleeding on fondaparinux and enoxaparin was 2.1% and 4.1%, respectively (hazard ratio 0.52, 95% CI, 0.44;0.61, $p < 0.001$).

The efficacy findings and results on major bleeding were consistent across prespecified subgroups such as elderly, renally impaired patients, type of concomitant platelet aggregation inhibitors (aspirin, thienopyridines or GP IIb/IIIa inhibitors).

In the subgroup of patients treated with fondaparinux or enoxaparin who underwent PCI, 8.8% and 8.2% of patients respectively, experience death/MI/RI within 9 days of randomisation (hazard ratio 1.08, 95% CI, 0.92;1.27). In this subgroup, the incidence of major bleeding on fondaparinux and enoxaparin at Day 9 was 2.2% and 5.0% respectively (hazard ratio 0.43, 95% CI, 0.33;0.57). In subjects undergoing PCI the incidence of adjudicated guiding catheter thrombus was 1.0% vs. 0.3% in fondaparinux vs. enoxaparin subjects, respectively.

Treatment of unstable angina (UA) or non-ST segment elevation myocardial infarction (NSTEMI) in patients who underwent subsequent PCI with adjunctive UFH

In a study of 3235 high-risk UA/NSTEMI patients scheduled for angiography and treated with open-label fondaparinux (OASIS 8/FUTURA), the 2026 patients indicated for PCI were randomised to receive one of two double-blind dose regimens of adjunctive UFH. All enrolled patients received fondaparinux 2.5 mg subcutaneously, once daily for up to 8 days, or until hospital discharge. Randomised patients received either "low dose" UFH regimen (50 U/kg irrespective of planned GPIIb/IIIa use; non ACT guided) or "standard dose" UFH regimen (no GPIIb/IIIa use: 85 U/kg, ACT guided; planned GPIIb/IIIa use: 60 U/kg, ACT guided) immediately prior to the start of the PCI.

The baseline characteristics and duration of fondaparinux treatment were comparable in both UFH groups. In subjects randomized to the "standard dose UFH" or the "low dose UFH" regimen the median dose of UFH was 85 U/kg and 50 U/kg, respectively.

The primary outcome was a composite of peri-PCI (defined as time of randomisation up to 48 hours post-PCI) adjudicated major or minor bleeding, or major vascular access site complications.

Outcomes	Incidence		Odds Ratio ¹ (95%CI)	p-value
	Low Dose UFH N = 1024	Standard Dose UFH N = 1002		
Primary				
Peri-PCI major or minor bleeding, or major vascular access site complications	4.7%	5.8%	0.80 (0.54, 1.19)	0.267
Secondary				
Peri-PCI major bleeding	1.4%	1.2%	1.14 (0.53, 2.49)	0.734
Peri-PCI minor bleeding	0.7%	1.7%	0.40 (0.16, 0.97)	0.042
Major vascular access site complications	3.2%	4.3%	0.74 (0.47, 1.18)	0.207
Peri-PCI major bleeding or death, MI or TVR at Day 30	5.8%	3.9%	1.51 (1.0, 2.28)	0.051
Death, MI or TVR at Day 30	4.5%	2.9%	1.58 (0.98, 2.53)	0.059
1: Odds ratio: Low Dose/Standard Dose Note: MI - myocardial infarction. TVR - target vessel revascularization				

The incidences of adjudicated guiding catheter thrombus were 0.1% (1/1002) and 0.5% (5/1024), in patients randomised to "standard dose" and "low dose" UFH respectively during PCI.

Four (0.3%) non-randomised patients experienced thrombus in the diagnostic catheter during coronary angiography. Twelve (0.37%) enrolled patients experienced thrombus in the arterial sheath, of these 7 were reported during angiography and 5 were reported during PCI.

Treatment of ST segment elevation myocardial infarction (STEMI)

OASIS 6 was a double blind, randomised study assessing the safety and efficacy of fondaparinux 2.5 mg once daily, versus usual care (placebo (47%) or UFH (53%) in approximately 12,000 patients with STEMI. All patients received standard treatments for STEMI, including primary PCI (31%), thrombolytics (45%) or no reperfusion (24%). Of the patients treated with a thrombolytic, 84% were treated with a non-fibrin specific agent (primarily streptokinase). The mean treatment duration was 6.2

days on fondaparinux. The mean age of the patients was 61 years, and approximately 40% were at least 65 years old. Approximately 40% and 14% of patients had mild (creatinine clearance ≥ 50 to < 80 ml/min) or moderate (creatinine clearance ≥ 30 to < 50 ml/min) renal impairment, respectively.

The primary adjudicated endpoint was a composite of death and recurrent MI (re-MI) within 30 days of randomisation. The incidence of death/re-MI at Day 30 was significantly reduced from 11.1% for the control group to 9.7% for the fondaparinux group (hazard ratio 0.86, 95% CI, 0.77, 0.96, $p = 0.008$). In the predefined stratum comparing fondaparinux to placebo (i.e. patients treated with non-fibrin specific lytics (77.3%), no reperfusion (22%), fibrin-specific lytics (0.3%), primary PCI (0.4%)), the incidence of death/re-MI at Day 30 was significantly reduced from 14.0% on placebo to 11.3% (hazard ratio 0.80, 95% CI, 0.69, 0.93, $p = 0.003$). In the predefined stratum comparing fondaparinux to UFH (patients treated with primary PCI (58.5%), fibrin-specific lytics (13%), non-fibrin-specific lytics (2.6%) and no reperfusion (25.9%)), the effects of fondaparinux and UFH on the incidence of death/re-MI at Day 30 were not statistically different: respectively, 8.3% vs 8.7% (hazard ratio 0.94, 95% CI, 0.79, 1.11 $p = 0.460$). However, in this stratum, in the subgroup of indicated population undergoing thrombolysis or no reperfusion (i.e. patients not undergoing primary PCI), the incidence of death/re-MI at Day 30 was significantly reduced from 14.3% on UFH to 11.5% with fondaparinux (hazard ratio 0.79, 95% CI, 0.64, 0.98, $p = 0.03$).

The incidence of all cause mortality at Day 30 was also significantly reduced from 8.9% for the control group to 7.8% in the fondaparinux group (hazard ratio 0.87, 95% CI, 0.77;0.98, $p = 0.02$). The difference in mortality was statistically significant in stratum 1 (placebo comparator) but not in stratum 2 (UFH comparator). The mortality benefit shown in the fondaparinux group was maintained until the end of follow-up at Day 180.

In patients who were revascularised with a thrombolytic, fondaparinux significantly reduced the incidence of death/re-MI at Day 30 from 13.6% for the control group to 10.9% (hazard ratio 0.79, 95%CI, 0.68;0.93, $p = 0.003$). Among patients initially not reperfused, the incidence of death/re-MI at Day 30 was significantly reduced from 15% for the control group to 12.1% for the fondaparinux group (hazard ratio 0.79, 95% CI, 0.65;0.97, $p = 0.023$). In patients treated with primary PCI, the incidence of death/re-MI at Day 30 was not statistically different between the two groups [6.0% in fondaparinux group vs 4.8% in the control group; hazard ratio 1.26, 95% CI, 0.96, 1.66].

By Day 9, 1.1% of patients treated with fondaparinux and 1.4% of control patients experienced a severe haemorrhage. In patients given a thrombolytic, severe haemorrhage occurred in 1.3% of the fondaparinux patients and in 2.0% of controls. In patients initially not reperfused, the incidence of severe haemorrhage was 1.2% for fondaparinux vs 1.5% for controls. For patients receiving primary PCI, the incidence of severe haemorrhage was 1.0% for fondaparinux and 0.4% for controls.

In subjects undergoing primary PCI the incidence of adjudicated guiding catheter thrombus was 1.2% vs 0% in fondaparinux vs. control subjects, respectively.

The efficacy findings and results on severe haemorrhage were consistent across prespecified subgroups such as elderly, renally impaired patients, type of concomitant platelet aggregation inhibitors (aspirin, thienopyridines).

Treatment of patients with acute symptomatic spontaneous superficial-vein thrombosis without concomitant Deep-Vein Thrombosis (DVT)

A randomised, double blind, clinical trial (CALISTO) included 3002 patients with acute symptomatic isolated, spontaneous superficial-vein thrombosis of the lower limbs, at least 5 cm long, confirmed by compression ultrasonography. Patients were not included if they had concomitant DVT or superficial-vein thrombosis within 3 cm of the sapheno-femoral junction. Patients were excluded if they had severe hepatic impairment, severe renal impairment (creatinine clearance < 30 ml/min), low body weight (< 50 kg), active cancer, symptomatic PE or a recent history of DVT/PE (< 6 months) or superficial-vein thrombosis (< 90 days), or superficial-vein thrombosis associated with sclerotherapy or a complication of an IV line, or they were at high risk of bleeding.

Patients were randomised to receive fondaparinux 2.5 mg once daily or placebo for 45 days in addition to elastic stockings, analgesic and/or topical NSAIDs anti-inflammatory drugs. Follow-up continued up to Day 77. The study population was 64% female, with a median age of 58 years, 4.4% had a creatinine clearance < 50 ml/min.

The primary efficacy outcome, a composite of symptomatic PE, symptomatic DVT, symptomatic superficial-vein thrombosis extension, symptomatic superficial-vein thrombosis recurrence, or Death up to Day 47, was significantly reduced from 5.9% in placebo patients to 0.9% in those receiving fondaparinux 2.5 mg (relative risk reduction: 85.2%; 95% CIs, 73.7% to 91.7% [$p < 0.001$]). The incidence of each thromboembolic component of the primary outcome was also significantly reduced in fondaparinux patients as follows: symptomatic PE [0 (0%) vs 5 (0.3%) ($p = 0.031$)], symptomatic DVT [3 (0.2%) vs 18 (1.2%); relative risk reduction 83.4% ($p < 0.001$)], symptomatic superficial-vein thrombosis extension [4 (0.3%) vs 51 (3.4%); relative risk

reduction 92.2% ($p < 0.001$), symptomatic superficial-vein thrombosis recurrence [5 (0.3%) vs 24 (1.6%); relative risk reduction 79.2% ($p < 0.001$)].

The mortality rates were low and similar between the treatments groups with 2 (0.1%) deaths in the fondaparinux group versus 1 (0.1%) death in the placebo group.

Efficacy was maintained up to Day 77 and was consistent across all predefined subgroups including patients with varicose veins and patients with superficial-vein thrombosis located below the knee.

Major bleeding during treatment occurred in 1 (0.1%) fondaparinux patient and in 1 (0.1%) placebo patient. Clinically relevant non major bleeding occurred in 5 (0.3%) fondaparinux patients and 8 (0.5%) placebo patients.

5.2 Pharmacokinetic properties

Absorption

After subcutaneous dosing, fondaparinux is completely and rapidly absorbed (absolute bioavailability 100%). Following a single subcutaneous injection of fondaparinux 2.5 mg to young healthy subjects, peak plasma concentration (mean C_{max} = 0.34 mg/l) is obtained 2 hours post-dosing. Plasma concentrations of half the mean C_{max} values are reached 25 minutes post-dosing.

In elderly healthy subjects, pharmacokinetics of fondaparinux are linear in the range of 2 to 8 mg by subcutaneous route. Following once daily subcutaneous dosing, steady state of plasma levels is obtained after 3 to 4 days with a 1.3-fold increase in C_{max} and AUC.

Mean (CV%) steady state pharmacokinetic parameters estimates of fondaparinux in patients undergoing hip replacement surgery receiving fondaparinux 2.5 mg once daily are: C_{max} (mg/l) - 0.39 (31%), T_{max} (h) - 2.8 (18%) and C_{min} (mg/l) - 0.14 (56%). In hip fracture patients, associated with their increased age, fondaparinux steady state plasma concentrations are: C_{max} (mg/l) - 0.50 (32%), C_{min} (mg/l) - 0.19 (58%).

Distribution

The distribution volume of fondaparinux is limited (7-11 litres). *In vitro*, fondaparinux is highly and specifically bound to antithrombin protein with a dose-dependant plasma concentration binding (98.6% to 97.0% in the concentration range from 0.5 to 2 mg/l). Fondaparinux does not bind significantly to other plasma proteins, including platelet factor 4 (PF4).

Since fondaparinux does not bind significantly to plasma proteins other than ATIII, no interaction with other medicinal products by protein binding displacement are expected.

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 (CYP1A2, CYP2A6, CYP2C9, CYP2C19, CYP2D6, CYP2E1 or CYP3A4) *in vitro*. Thus, fondaparinux is not expected to interact with other medicinal products *in vivo* by inhibition of CYP-mediated metabolism.

Elimination

The elimination half-life ($t_{1/2}$) is about 17 hours in healthy young subjects and about 21 hours in healthy elderly subjects. Fondaparinux is excreted to 64 – 77 % by the kidney as unchanged compound.

Special populations

Paediatric patients - Fondaparinux has not been investigated in this population for the prevention of VTE or for the treatment of superficial vein thrombosis or acute coronary syndrome (ACS).

Elderly patients - Renal function may decrease with age and thus, the elimination capacity for fondaparinux may be reduced in elderly. In patients >75 years undergoing orthopaedic surgery, the estimated plasma clearance was 1.2 to 1.4 times lower than in patients <65 years.

Renal impairment - Compared with patients with normal renal function (creatinine clearance > 80 ml/min), plasma clearance is 1.2 to 1.4 times lower in patients with mild renal impairment (creatinine clearance 50 to 80 ml/min) and on average 2 times lower in patients with moderate renal impairment (creatinine clearance 30 to 50 ml/min). In severe renal impairment (creatinine clearance < 30 ml/min), plasma clearance is approximately 5 times lower than in normal renal function. Associated terminal half-life values were 29 h in moderate and 72 h in patients with severe renal impairment.

Gender - No gender differences were observed after adjustment for body weight.

Race - Pharmacokinetic differences due to race have not been studied prospectively. However, studies performed in Asian (Japanese) healthy subjects did not reveal a different pharmacokinetic profile compared to Caucasian healthy subjects. Similarly, no plasma clearance differences were observed between black and Caucasian patients undergoing orthopaedic surgery.

Body weight - Plasma clearance of fondaparinux increases with body weight (9% increase per 10 kg).

Hepatic impairment - Following a single, subcutaneous dose of fondaparinux in subjects with moderate hepatic impairment (Child-Pugh Category B), total (i.e., bound and unbound) C_{max} and AUC were decreased by 22% and 39%, respectively, as compared to subjects with normal liver function. The lower plasma concentrations of fondaparinux were attributed to reduced binding to ATIII secondary to the lower ATIII plasma concentrations in subjects with hepatic impairment thereby resulting in increased renal clearance of fondaparinux. Consequently, unbound concentrations of fondaparinux are expected to be unchanged in patients with mild to moderate hepatic impairment, and therefore, no dose adjustment is necessary based on pharmacokinetics.

The pharmacokinetics of fondaparinux has not been studied in patients with severe hepatic impairment (see sections 4.2 and 4.4).

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, and genotoxicity. Animal studies are insufficient with respect to effects on toxicity to reproduction because of limited exposure.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium chloride
Water for injections
Hydrochloric acid (for pH-adjustment)
Sodium hydroxide (for pH-adjustment)

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

3 years.

If fondaparinux sodium is added to a 0.9% saline minibag it should ideally be infused immediately, but can be stored at room temperature for up to 24 hours.

6.4 Special precautions for storage

Store below 25°C. Do not freeze.

6.5 Nature and contents of container

Type I glass barrel (1 ml) affixed with a 27 gauge x 12.7 mm needle and stoppered with a bromobutyl or chlorobutyl elastomer plunger stopper.

Fondaparinux sodium Aspen is available in pack sizes of 2, 7, 10 and 20 pre-filled syringes. There are two types of syringes:

- syringe with a blue plunger and an automatic safety system
- syringe with blue plunger and a manual safety system.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

The subcutaneous injection is administered in the same way as with a classical syringe. Intravenous administration should be through an existing intravenous line either directly or using a small volume (25 or 50ml) 0.9% saline minibag.

Parenteral solutions should be inspected visually for particulate matter and discoloration prior to administration. Only clear, colourless and particle free solution should be used.

Instruction on self-administration by subcutaneous injection is included in the Package Leaflet.

The needle protection system of the Fondaparinux sodium Aspen pre-filled syringes have been designed with a safety system to protect from needle stick injuries following injection.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

This medicinal product is for single use only. Any unused solution should be discarded.

7 MARKETING AUTHORISATION HOLDER

Aspen Pharma Trading Limited
3016 Lake Drive
Citywest Business Campus
Dublin 24
Ireland

8 MARKETING AUTHORISATION NUMBER

PA1691/034/002

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 29th July 2022

10 DATE OF REVISION OF THE TEXT