

PRODUCT MONOGRAPH

PrFONDAPARINUX SODIUM INJECTION

2.5 mg/0.5 mL , 5.0 mg/0.4 mL, 7.5 mg/0.6 mL, and 10.0 mg/0.8 mL

Sterile

2.5 mg/0.5 mL (5 mg/mL)
5.0 mg/0.4 mL (12.5 mg/mL)
7.5 mg/0.6 mL (12.5 mg/mL)
10.0 mg/0.8 mL (12.5 mg/mL)

Synthetic Antithrombotic

DIN Owner:
Dr. Reddy's Laboratories Limited
Bachupally – 500 090 INDIA

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Innomar Strategies Inc.
3470 Superior Court-
Oakville, Ontario L6L 0C4
CANADA

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PrFONDAPARINUX SODIUM INJECTION
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PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	All Nonmedicinal Ingredients
Subcutaneous	Injection/ 2.5 mg/0.5 mL 5.0 mg/0.4 mL 7.5 mg/0.6 mL 10.0 mg/0.8 mL	Isotonic solution of sodium chloride and water for injection. Also contains sodium hydroxide or hydrochloric acid for pH adjusters.
Intravenous	2.5 mg/0.5 mL	

INDICATIONS AND CLINICAL USE

Fondaparinux Sodium Injection is indicated for:

- Prophylaxis of venous thromboembolic events (VTE) for up to one month post-surgery in patients undergoing orthopedic surgeries of the lower limbs such as hip fracture, knee surgery or hip replacement surgery.
- Prophylaxis of venous thromboembolic events (VTE) in patients undergoing abdominal surgery who are at high risk of thromboembolic complications, such as patients undergoing abdominal cancer surgery.
- Treatment of Acute Deep Vein Thrombosis (DVT) and treatment of Acute Pulmonary Embolism (PE).
- Management of unstable angina or non-ST segment elevation myocardial infarction (UA/NSTEMI) for the prevention of death and subsequent myocardial infarction.
- Management of ST segment elevation myocardial infarction (STEMI) for the prevention of death and myocardial reinfarction in patients who are managed with thrombolytics or who initially are to receive no form of reperfusion therapy.

Geriatrics (> 65 years of age):

Fondaparinux Sodium Injection should be used with caution in elderly patients due to the risk of hemorrhage.

Pediatrics (< 17 years of age):

The safety and effectiveness of Fondaparinux Sodium Injection in children has not been established.

CONTRAINDICATIONS

- Patients who are hypersensitive to Fondaparinux Sodium Injection or to any ingredient in the formulation.
- Thrombocytopenia associated with a positive *in vitro* test for anti-platelet antibody in the presence of fondaparinux sodium.
- Active clinically significant bleeding.
- Acute bacterial endocarditis.

WARNINGS AND PRECAUTIONS

General

Fondaparinux Sodium Injection must be administered only by the subcutaneous (SC) or intravenous (IV) route. **Fondaparinux Sodium Injection must not be administered intramuscularly.**

Carcinogenesis and Mutagenesis

See TOXICOLOGY, Carcinogenicity and Mutagenicity.

Cardiovascular

Risk of catheter thrombosis during PCI

In patients undergoing any percutaneous coronary intervention (PCI), the use of Fondaparinux Sodium Injection as the sole anticoagulant during PCI is not recommended because of an increased risk of guiding catheter thrombosis. An effective anti-thrombin regimen such as unfractionated heparin (UFH) should be used as an adjunct to PCI, according to standard practice (see DOSAGE AND ADMINISTRATION, and DETAILED PHARMACOLOGY).

In STEMI patients undergoing primary PCI for reperfusion, the use of Fondaparinux Sodium Injection prior to and during PCI is not recommended (see ADVERSE REACTIONS, *Management of STEMI*, Risk of catheter thrombosis during PCI, and DOSAGE AND ADMINISTRATION).

Clinical trials have shown a low but increased risk of guiding catheter thrombosis in patients treated solely with fondaparinux sodium for anticoagulation during PCI compared to control (see ADVERSE REACTIONS, *Management of UA/NSTEMI and Management of STEMI*, Risk of catheter thrombosis during PCI). Incidences during PCI in UA/NSTEMI were 1.00% with fondaparinux sodium, 0.32% with enoxaparin alone, and 0.16% with enoxaparin with adjunctive UFH. In fondaparinux-treated UA/NSTEMI patients randomized to receive one of two dosing regimens of adjunctive UFH during PCI, the incidences of catheter thrombus were reported to range from 0.1% to 0.5%, depending on the UFH dose administered (For further details, see

ADVERSE REACTIONS, *Management of UA/NSTEMI, Risk of catheter thrombosis during PCI*). In patients with STEMI undergoing primary PCI, incidences were 1.18% with fondaparinux sodium and 0% with UFH. Use of Fondaparinux Sodium Injection during primary PCI is not recommended.

It is to be expected that the risk of peri-procedural myocardial infarction (MI) may be increased in patients who develop guiding catheter thrombosis, irrespective of anticoagulant used (see **ADVERSE REACTIONS, *Management of UA/NSTEMI and Management of STEMI, Risk of catheter thrombosis during PCI***).

Hematologic

Hemorrhage

Fondaparinux Sodium Injection, like other antithrombotic drugs, should be used with caution in patients who have an increased risk of hemorrhage, such as those with congenital or acquired bleeding disorders, active ulcerative gastrointestinal disease and recent intracranial hemorrhage or shortly after brain, spinal, or ophthalmological surgery.

Risk of hemorrhage is expected to increase with decreasing renal function (see **ADVERSE REACTIONS**). Appropriate caution should be exercised in patients with moderate to severe renal impairment (see **WARNINGS AND PRECAUTIONS, Renal**).

Prophylaxis and Treatment of VTE

Agents that may enhance the risk of hemorrhage, with the exception of vitamin K antagonists used concomitantly for treatment of VTE, should be discontinued prior to initiation of Fondaparinux Sodium Injection therapy. If co-administration is necessary, close monitoring may be appropriate (see **DRUG INTERACTIONS**).

Prophylaxis of VTE following orthopedic or abdominal surgery (timing of first fondaparinux injection)

The timing of the first dose of Fondaparinux Sodium Injection following surgery requires strict adherence. The first dose should be given no earlier than 6 hours following surgical closure, and only after hemostasis has been established. Administration before 6 hours has been associated with an increased risk of major bleeding (see **DOSAGE and ADMINISTRATION**).

Patient groups at particular risk are those older than 75 years of age, body weight of less than 50 kg or renal impairment with creatinine clearance less than 50 mL/min.

Management of UA/NSTEMI, STEMI

Fondaparinux Sodium Injection should be used with caution in patients who are being treated concomitantly with other therapies that increase the risk of hemorrhage (such as GPIIb/IIIa inhibitors or thrombolytics).

Thrombocytopenia

Thrombocytopenia of any degree should be monitored closely. If the platelet count falls below 50,000/mm³, Fondaparinux Sodium Injection should be discontinued. Fondaparinux sodium is

contraindicated in patients with thrombocytopenia associated with a positive *in vitro* test for anti-platelet antibody in the presence of fondaparinux.

Rare spontaneous reports of heparin-induced thrombocytopenia (HIT) in patients treated with fondaparinux have been received.

Prophylaxis of VTE following orthopedic or abdominal surgery

Thrombocytopenia can occur with the administration of Fondaparinux Sodium Injection following any major surgical procedure. Moderate thrombocytopenia (platelet counts between 100,000/mm³ and 50,000/mm³) occurred at a rate of 3.0% in patients given fondaparinux sodium 2.5 mg in the peri-operative orthopedic and abdominal surgery clinical trials. Severe thrombocytopenia (platelet counts less than 50,000/mm³) occurred at a rate of 0.2% in patients given 2.5 mg in peri-operative clinical trials.

Treatment of DVT and PE

Moderate thrombocytopenia occurred at a rate of 0.5% in patients given the fondaparinux sodium treatment regimen in the DVT and PE treatment clinical trials. Severe thrombocytopenia occurred at a rate of 0.04% in patients given the fondaparinux sodium treatment regimen.

Hepatic

There is no evidence that fondaparinux is metabolized or eliminated hepatically.

Following a single subcutaneous dose of 7.5 mg of fondaparinux sodium in patients with moderate hepatic impairment (Child-Pugh Category B) compared to subjects with normal liver function, changes from baseline in aPTT, PT/INR, and antithrombin III were similar in the two groups (see **ACTION AND CLINICAL PHARMACOLOGY, Special Populations and Conditions, Hepatic Insufficiency**). However, a higher incidence of hemorrhage was observed in subjects with moderate hepatic impairment than in normal subjects, especially mild hematomas at the blood sampling or injection site. The pharmacokinetics of fondaparinux have not been studied in patients with severe hepatic impairment. The use of Fondaparinux Sodium Injection should be considered with caution because of an increased risk of bleeding due to a deficiency of coagulation factors in patients with severe hepatic insufficiency. Thus, in patients with severe hepatic insufficiency, Fondaparinux Sodium Injection should be used only with care.

Peri-Operative Considerations

There have been cases of intra-spinal hematomas with the concurrent use of antithrombotics (i.e. low molecular weight heparins) and spinal/epidural anaesthesia resulting in long-term or permanent paralysis. The risk of these events may be higher with the use of post-operative indwelling epidural catheters or by the concomitant use of drugs affecting hemostasis: nonsteroidal anti-inflammatory drugs (NSAIDs), platelet inhibitors, or other drugs affecting coagulation. The risk also appears to be increased by traumatic or repeated epidural or spinal procedure. **Fondaparinux Sodium Injection should only be used concurrently with spinal/epidural anaesthesia when the therapeutic benefits to the patients outweigh the possible risks.** Careful vigilance for neurological signs is recommended with rapid diagnosis and treatment, if signs occur.

Renal

The plasma clearance of fondaparinux decreases with the severity of renal impairment, and is associated with an increased risk of hemorrhage (see **ACTION AND CLINICAL PHARMACOLOGY, Renal Insufficiency**). This has also been observed with all low molecular weight heparins (LMWH).

In patients with severe renal impairment, i.e., creatinine clearance (CrCl) < 30 mL/min, use of Fondaparinux Sodium Injection should generally be avoided, due to increased risk of bleeding (see **DOSAGE AND ADMINISTRATION, Use in Patients with Renal Insufficiency**).

Prophylaxis of VTE following orthopedic or abdominal surgery

Occurrences of major bleeding in patients receiving prophylactic therapy following orthopedic surgery with normal renal function, mild renal insufficiency, moderate renal insufficiency and severe renal insufficiency have been found to be 1.6% (25/1565), 2.4% (31/1288), 3.8% (19/504) and 4.8% (4/83) respectively.

Major bleeding in patients receiving prophylactic therapy in abdominal surgery in an active-controlled trial with dalteparin sodium, occurred in 2.1% (13/606) of patients with normal renal function, in 3.6% (22/613) with mild renal impairment, in 6.7% (12/179) with moderate renal impairment, and in 7.1% (1/14) with severe renal impairment.

Therefore, Fondaparinux Sodium Injection prophylactic therapy following orthopedic or abdominal surgery is not recommended in patients with severe renal insufficiency (CrCl < 30 mL/min) and should be used with caution in patients with moderate renal insufficiency (CrCl 30-50 mL/min) (see **ACTION AND CLINICAL PHARMACOLOGY, Renal Insufficiency**).

Renal function should be assessed periodically in orthopedic and abdominal surgery patients receiving prophylactic therapy. Consideration of immediate discontinuation of Fondaparinux Sodium Injection should be undertaken for patients who develop severe renal insufficiency or labile renal function while on prophylactic therapy. After discontinuation of Fondaparinux Sodium Injection prophylactic therapy, its anticoagulant effects may persist for 2-4 days in patients with normal renal function (i.e. at least 3-5 half-lives). The anticoagulant effects of Fondaparinux Sodium Injection prophylactic therapy may persist even longer in patients with renal insufficiency.

Treatment of DVT and PE

No dosing adjustment is generally necessary in patients with mild to moderate renal insufficiency, however, close monitoring of these patients is recommended. In patients with severe renal impairment (creatinine clearance \leq 30 mL/min) use is not recommended due to risk of hemorrhage.

Management of UA/NSTEMI, STEMI

There are limited clinical data available on the use of fondaparinux 2.5 mg once daily in patients with creatinine clearance \leq 30 mL/min (see **DOSAGE AND ADMINISTRATION, and ACTION AND CLINICAL PHARMACOLOGY, Renal Insufficiency**).

Special Populations

Low Body Weight

Patients with body weight < 50 kg are at increased risk of bleeding due to reduced clearance of Fondaparinux Sodium Injection.

Prophylaxis of VTE following orthopedic or abdominal surgery

Fondaparinux Sodium Injection prophylactic therapy should be used with caution in patients with body weight < 50 kg undergoing orthopedic surgery.

Treatment of DVT and PE

For DVT and PE treatment, in patients with body weight < 50 kg, a daily dose of 5 mg is recommended. In patients with body weight > 100 kg, a daily dose of 10 mg is recommended (see **DOSAGE AND ADMINISTRATION**).

Management of UA/NSTEMI, STEMI

Fondaparinux Sodium Injection should be used with caution in patients weighing < 50 kg.

Pregnant Women: There are very limited clinical data available on the use of fondaparinux sodium in pregnant women. Caution should be exercised when prescribing Fondaparinux Sodium Injection to pregnant women. Fondaparinux Sodium Injection should not be prescribed to pregnant women unless the potential benefit outweighs the risk. Animal studies do not indicate either direct or indirect harmful effects with respect to pregnancy, embryonal/fetal development, parturition or post-natal development (see **TOXICOLOGY**).

Nursing Women: Although it is not known whether fondaparinux is excreted in human milk, it has been shown to be excreted in the milk of lactating rat dams. Because many drugs may be excreted in human milk, breast feeding is not recommended during treatment with Fondaparinux Sodium Injection.

Pediatrics: The safety and effectiveness of Fondaparinux Sodium Injection in children under the age of 17 years has not been established.

Geriatrics (> 65 years of age): Fondaparinux Sodium Injection should be used with caution in elderly patients because of increased risk of hemorrhage (see **ADVERSE REACTIONS**). Since fondaparinux sodium is substantially excreted by the kidney, risks associated with its use may be expected to be greater in patients with impaired renal function, including the elderly (see **ADVERSE REACTIONS, and DOSAGE AND ADMINISTRATION**). Because elderly patients are more likely to have decreased renal function, renal function should be monitored, as clinically warranted (see **WARNINGS AND PRECAUTIONS, Renal**).

Monitoring, Laboratory and Coagulation Tests

Since the international standards of heparin or low molecular weight heparins (LMWH) are not appropriate calibrators, the activity of fondaparinux sodium is expressed in milligrams (mg) of the fondaparinux and cannot be compared with activities of heparin or LMWH.

At the 2.5 mg dose, fondaparinux sodium does not have a clinically relevant effect on routine coagulation tests such as activated partial thromboplastin time (aPTT), activated clotting time (ACT) or prothrombin time (PT)/International Normalized Ratio (INR) tests in plasma. When administered at the recommended prophylactic dose, routine coagulation tests such as PT and aPTT are relatively insensitive measures of fondaparinux sodium activity, and therefore unsuitable for monitoring. Although monitoring of fondaparinux sodium is generally not required, the anti-Factor Xa assay is the preferred test to measure the anti-coagulant activity of fondaparinux sodium. Only fondaparinux can be used to calibrate the anti-Xa assay (see **ACTION AND CLINICAL PHARMACOLOGY, Mechanism of Action**).

If during Fondaparinux Sodium Injection therapy, unexpected changes in coagulation parameters or major bleeding occurs, Fondaparinux Sodium Injection should be discontinued and a search for other causes such as concomitant medications that could interfere with coagulation, should be undertaken.

ADVERSE REACTIONS

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

The data described below reflect experience in over 25,000 patients randomized to fondaparinux sodium injection in controlled trials of hip fracture, hip replacement, major knee, or abdominal surgeries, treatment of DVT and PE, and the management of UA/NSTEMI and STEMI. Patients received fondaparinux sodium primarily in two large peri-operative dose-response trials (n=989), four active-controlled peri-operative VTE prophylaxis trials with enoxaparin sodium (n=3,616), an extended VTE prophylaxis trial (n=327), an active-controlled VTE prophylaxis trial with dalteparin sodium (n=1,425) in abdominal surgery, a dose-response trial (n=111) and an active-controlled trial with enoxaparin sodium in DVT treatment (n=1,091), an active-controlled trial with heparin in PE treatment (n=1,092), an active-controlled trial (OASIS 5) with enoxaparin in the treatment of UA/NSTEMI (n=9,979), and an active and placebo-controlled trial (OASIS 6) with standard of care in the treatment of STEMI (n=5,954), (see **CLINICAL TRIALS**).

Additionally, safety data were obtained from the FUTURA/OASIS 8 trial, comparing two adjunctive UFH regimens during non-primary PCI in UA/NSTEMI patients treated with fondaparinux sodium (n=2,026).

Hemorrhage

As with any antithrombotic treatment, hemorrhagic manifestations can occur. The incidence of major hemorrhagic complications during fondaparinux sodium treatment has been low and generally did not differ from that observed with other antithrombotics. In clinical trials or in post-marketing experience, rare cases of intracranial/ intracerebral or retroperitoneal bleedings have been reported.

Prophylaxis of VTE following orthopedic surgery

The rates of major bleeding events reported during the orthopedic surgery clinical trials with fondaparinux sodium 2.5 mg injection are provided in Table 1, Table 2 and Table 3 below.

Table 1 Summary of bleeding results from first injection up to Day 11 – Percentage of Patients

Surgery Type		Bleeding	Fondaparinux sodium 2.5 mg daily (%)	Enoxaparin (%)
Hip Fracture		Major bleeding ¹	18/831 (2.2)	19/842 (2.3)
		Minor bleeding ²	34/831 (4.1)	18/842 (2.1)
Knee Replacement		Major bleeding	11/517 (2.1 ⁵)	1/517 (0.2)
		Minor bleeding	14/517 (2.7)	19/517 (3.7)
Hip Replacement	Study 1 ⁴	Major bleeding	20/1128 (1.8)	11/1129 (1.0)
		Minor bleeding	17/1128 (1.5)	24/1129 (2.1)
	Study 2 ³	Major bleeding	47/1140 (4.1)	32/1133 (2.8)
		Minor bleeding	44/1140 (3.9)	38/1133 (3.4)

¹ Major bleeding was defined as clinically overt bleeding that was (1) fatal, (2) at a critical site (e.g. Intracranial, retroperitoneal, intra-ocular, pericardial, spinal or into adrenal gland), (3) associated with re-operation or (4) Bleeding Index (BI) ≥ 2 i.e. BI = drop in hemoglobin (Hb) pre-bleed minus post-bleed + number of units transfused. There were no fatal bleeds or bleeds at a critical site in the fondaparinux sodium group, and one fatal bleed and one bleed into a critical site in the enoxaparin group.

² Minor bleeding was clinically overt bleeding that was not major.

³ Comparator was Enoxaparin 40 mg o.d.

⁴ Comparator was Enoxaparin 30 mg b.i.d.

⁵ p-value versus enoxaparin is 0.0081.

Table 2 Bleeding across Hip Fracture, Hip Replacement and Knee Replacement Surgery Studies

	Fondaparinux sodium 2.5 mg SC once daily	Comparator: Enoxaparin Sodium ¹
	N = 3616	N = 3956
Major bleeding ²	96 (2.7%)	75 (1.9%)
Fatal bleeding	0 (0.0%)	1 (< 0.1%)
Non-fatal bleeding at critical site	0 (0.0%)	1 (< 0.1%)

Re-operation due to bleeding	12 (0.3%)	10 (0.3%)
Bleeding Index (BI) ≥ 2 ^{3,5}	84 (2.3%)	63 (1.6%)
Minor bleeding ⁴	109 (3.0%)	116 (2.9%)

¹ Enoxaparin Sodium dosing regimen: 30 mg every 12 hours or 40 mg once daily (see Clinical Trials).

² Major bleeding was defined as clinically overt bleeding that was (1) fatal, (2) bleeding at critical site (e.g. intracranial, retroperitoneal, intra-ocular, pericardial, spinal or into adrenal gland), (3) associated with reoperation at operative site, or (4) with a bleeding index (BI) ≥ 2 .

³ BI ≥ 2 : overt bleeding associated only with a bleeding index ≥ 2 [calculated as number of whole blood or packed red blood cells units transfused + [(pre-bleeding) - (post-bleeding)] hemoglobin (g/dL) values].

⁴ Minor bleeding was defined as clinically overt bleeding that was not major.

⁵ Incidence of BI ≥ 2 with fondaparinux sodium across the 4 phase III studies decreased when the first dose was given ≥ 6 hours after surgical closure.

Table 3 Number (Percentage) of patients with adjudicated bleeding events in hip fracture surgery

	Pre-randomization Open-Label Period (Day 1 to Day 7 \pm 1 post-surgery)	Randomized Double-Blind Extended Prophylaxis Period (Day 8 to Day 28 \pm 2 post-surgery)	
	Fondaparinux sodium N = 737	Fondaparinux sodium N = 327	Placebo N = 329
Any bleeding	37 (5.0%)	13 (4.0%)	4 (1.2%)
Minor bleeding only ¹	15 (2.0%)	5 (1.5%)	2 (0.6%)
Any major bleeding ²	22 (3.0%)	8 (2.4%)	2 (0.6%)
Fatal bleeding	2 (0.3%)	0 (0.0%)	0 (0.0%)
Non-fatal bleeding	1 (0.1%)	0 (0.0%)	0 (0.0%)
Other non-fatal major bleeding	19 (2.6%)	8 (2.4%)	2 (0.6%)
At surgical site leading to re-operation	3 (0.4%)	2 (0.6%)	2 (0.6%)
Only bleeding index (BI) ≥ 2 ³	16 (2.2%)	6 (1.8%)	0 (0.0%)

¹ Minor bleeding was defined as clinically overt bleeding that was not major.

² Major bleeding was defined as clinically overt bleeding that was (1) fatal, (2) bleeding at critical site (e.g. intracranial, retroperitoneal, intra-ocular, pericardial, spinal or into adrenal gland), (3) associated with reoperation at operative site, or (4) with a bleeding index (BI) ≥ 2 .

³ Adjudicated as major and with BI ≥ 2 and/or decrease of hemoglobin ≥ 2 g/dL and/or number of units transfused ≥ 2 .

Major bleeding from the first active fondaparinux sodium dose decreased by 26% if the first dose was given 6 hours after surgical closure: major bleeding with fondaparinux sodium started < 6 hours after surgical closure was 2.6% (n=1,337) versus major bleeding with fondaparinux sodium started 6 hours after surgical closure which was 1.9% (n=2,230).

Geriatrics: Over 2,300 patients, 65 years and older, have received fondaparinux sodium 2.5 mg in randomized clinical trials in the orthopedic surgery program. In the peri-operative, orthopedic

surgery, clinical trials with patients receiving fondaparinux sodium 2.5 mg, the risk of fondaparinux sodium-associated non-fatal major bleeding increased with age: 1.8% (23/1,253) in patients < 65 years, 2.2% (24/1,111) in those 65-74 years, and 2.7% (33/1,227) in those ≥ 75 years. Serious adverse events increased with age for patients receiving fondaparinux sodium.

In patients undergoing extended prophylaxis following the first week of therapy, the incidence of fondaparinux sodium-associated non-fatal major bleeding was: 1.9% (1/52) in patients < 65 years, 1.4% (1/71) in those 65-74 years, and 2.9% (6/204) in those ≥ 75 years.

Prophylaxis of VTE following abdominal surgery

The rates of major bleeding reported during an abdominal surgery clinical trial with fondaparinux sodium 2.5 mg are provided in Table 4 below.

Table 4 Major and non-major Bleeding Episodes¹ in a Randomized, Controlled, Abdominal Surgery Study

	Study 1	
	Fondaparinux sodium 2.5 mg SC once daily	Dalteparin Sodium 5,000 IU SC once daily
	N = 1433	N = 1425
Major bleeding ¹	49 (3.4%)	34 (2.4%)
Fatal bleeding	2 (0.1%)	2 (0.1%)
Non-fatal bleeding at critical site	0 (0.0%)	0 (0.0%)
Other non-fatal major bleeding		
Surgical site	38 (2.7%)	26 (1.8%)
Non-surgical site	9 (0.6%)	6 (0.4%)
Minor bleeding ²	31 (2.2%)	23 (1.6%)

¹ Major bleeding was defined as bleeding that was (1) fatal, (2) bleeding at the surgical site leading to intervention, (3) non-surgical bleeding at a critical site (eg. intracranial, retroperitoneal, intra-ocular, pericardial, spinal, or into adrenal gland), or leading to an intervention, and/or with a bleeding index (BI ≥2 calculated as [number of whole blood or packed red blood cell unites transfused + [(pre-bleeding) – (post-bleeding)] hemoglobin (g/dL) values]).

² Minor bleeding was defined as clinically overt bleeding that was not major.

Geriatrics: In the abdominal surgery active-controlled clinical trial with dalteparin sodium, the risk of major bleeding associated with use of fondaparinux sodium increased with age: 3.0% (19/644) in patients < 65 years, 3.2% (16/507) in those 65-74 years, and 5.0% (14/282) in those ≥ 75 years.

Treatment of DVT and PE

The rates of major bleeding events reported during the DVT and PE clinical trials with the fondaparinux sodium injection treatment regimen are provided in Table 5 below.

Table 5 Major Bleeding Episodes^{1,2} in DVT and PE Treatment Studies

Indications	Fondaparinux sodium Treatment Regimen	Enoxaparin Sodium ¹ mg/kg SC q 12h	Heparin IV aPTT adjusted
	N = 2294	N = 1101	N = 1092
DVT and PE Treatment	28 (1.2%)	13 (1.2%)	12 (1.1%)

¹ Major bleeding was defined as clinically overt - and/or contributing to death - and/or in a critical organ including intracranial, retroperitoneal, intraocular, spinal, pericardial or adrenal gland - and/or associated with a fall in hemoglobin level = 2 g/dL - and/or leading to a transfusion \geq 2 units of packed red blood cells or whole blood.

² Bleeding rates are during the study drug treatment period (approximately 7 days). Patients were also treated with vitamin K antagonists initiated within 72 hours after the first study drug administration.

Geriatrics: Over 1,200 patients, 65 years and older, have received the fondaparinux sodium treatment regimen in the DVT and PE treatment clinical trials. In the DVT and PE treatment clinical trials with patients receiving the fondaparinux sodium treatment regimen, the risk of fondaparinux sodium-associated non-fatal major bleeding increased with age: 0.6% (7/1,151) in patients < 65 years, 1.6% (9/560) in those 65-74 years, and 2.1% (12/583) in those \geq 75 years. Careful attention to dosing directions and concomitant medications (especially antiplatelet medication) is advised (see **DRUG INTERACTIONS**).

Management of UA/NSTEMI

The rates of major bleeding events reported during the management of UA/NSTEMI clinical trials with fondaparinux sodium 2.5 mg injection are provided in Table 6 and Table 7 below.

Table 6 Bleeding Episodes in OASIS 5, a Randomized, Controlled Study in UA/NSTEMI⁵

	Up to 9 days after presenting with UA/NSTEMI	
	Fondaparinux sodium ⁵ N = 9979	Enoxaparin ⁶ N = 9969
Investigator Reported Major Bleeding ¹	205 (2.1%)	410 (4.1%)
Fatal bleeding	7 (<0.1%)	22 (0.2%)
Intracranial	7 (<0.1%)	7 (<0.1%)
Retroperitoneal	9 (<0.1%)	36 (0.4%)
Requiring surgical intervention	39 (0.4%)	78 (0.8%)
Drop in hemoglobin \geq 3 g/dL	189 (1.9%)	385 (3.9%)
Blood transfusion \geq 2 units	156 (1.6%)	280 (2.8%)
Modified TIMI Severe Hemorrhage ²	148 (1.5%)	260 (2.6%)
Minor Bleeding ³	115 (1.2%)	320 (3.2%)
PCI-related bleed ⁴	82 (0.8%)	183 (1.8%)
CABG-related bleed ⁴	86 (0.9%)	72 (0.7%)

¹ Major bleeding was defined as clinically overt bleeding with at least one of the following criteria: fatal, symptomatic intracranial hemorrhage, retroperitoneal hemorrhage, intraocular hemorrhage leading to significant vision loss, bleeding requiring surgical intervention, decrease in Hb of \geq 3 g/dL, or blood transfusion \geq 2 units.

² Modified TIMI severe hemorrhage was defined as fatal hemorrhage, intracranial hemorrhage, cardiac tamponade, or a clinically significant hemorrhage with a decrease in Hb of > 5 g/dL.

³ Minor bleeding was defined as clinically overt bleeding that was not major and that led to interruption of study drug for at least 24 hours, or transfusion of one unit of blood.

- 4 The number of patients undergoing PCI was 3,422 for fondaparinux sodium and 3,410 for enoxaparin and the number of patients undergoing CABG was 956 for fondaparinux sodium and 886 for enoxaparin.
- 5 Patients randomized to fondaparinux sodium received 2.5 mg fondaparinux SC once daily for up to 8 days or discharge.
- 6 Patients randomized to enoxaparin sodium received 1 mg/kg enoxaparin SC twice daily (once daily if creatinine clearance was between 20 mL/min and 30 mL/min) for 2-8 days or until clinically stable.

Table 7 Incidence of Adjudicated Major Bleeding in OASIS 5 at Day 9 in UA/NSTEMI Patients Treated with Fondaparinux sodium by Renal Function Status at baseline

Covariate Endpoint/ Timepoint	Number Events / Number Analyzed		OR/HR ¹ (95% CI)	Interaction p-value ⁴
	Fondaparinux sodium ²	Enoxaparin ³		
On therapy	183/9943 (1.8%)	388/9928 (3.9%)	0.46 (0.38, 0.55)	0.343
<20 mL/min	1/40 (2.5%)	5/43 (11.6%)	0.19 (0.02, 1.75)	
≥20 - <30 mL/min	4/240 (1.7%)	19/239 (7.9%)	0.20 (0.07, 0.59)	
≥30 - <50 mL/min	47/1649 (2.9%)	104/1715 (6.1%)	0.45 (0.32, 0.65)	
≥50 - <80 mL/min	93/4,257 (2.2%)	185/4,188 (4.4%)	0.48 (0.38, 0.62)	
≥80 mL/min	38/3,757 (1.0%)	75/3,743 (2.0%)	0.50 (0.34, 0.74)	
Creatinine clearance not recorded	0/36	1/41 (2.4%)		
Day 9	209/9979 (2.1%)	405/9969 (4.1%)	0.51 (0.43, 0.60)	0.248
<20 mL/min	2/40 (5.0%)	5/43 (11.6%)	0.41 (0.08, 2.11)	
≥20 - <30 mL/min	4/240 (1.7%)	21/239 (8.8%)	0.19 (0.06, 0.54)	
≥30 - <50 mL/min	54/1649 (3.3%)	107/1715 (6.2%)	0.52 (0.37, 0.71)	
≥50 - <80 mL/min	103/4257 (2.4%)	193/4188 (4.6%)	0.52 (0.41, 0.66)	
≥80 mL/min	46/3757 (1.2%)	79/3743 (2.1%)	0.58 (0.40, 0.83)	
Creatinine clearance not recorded	0/36	1/41 (2.4%)		

Note: Creatinine clearance was included as a continuous variable in the estimate of the overall hazard/odds ratio and covariate p-value.

¹ Odds ratio for the on-therapy analysis; hazard ratio for the Day 9 analysis.

² Patients randomized to fondaparinux sodium received 2.5 mg fondaparinux SC once daily for up to 8 days or discharge.

³ Patients randomized to enoxaparin sodium received 1 mg/kg enoxaparin SC twice daily (once daily if creatinine clearance was between 20 mL/min and 30 mL/min) for 2-8 days or until clinically stable.

⁴ Treatment by Covariate Interaction (test for homogeneity of treatment effect).

In a study of 3,235 high-risk UA/NSTEMI patients scheduled for angiography and treated with open-label fondaparinux (FUTURA/OASIS 8), the 2,026 patients indicated for PCI were randomized to receive one of two double-blind dose regimens of adjunctive unfractionated heparin (UFH). All enrolled patients received fondaparinux 2.5 mg subcutaneously, once daily for up to 8 days, or until hospital discharge. Randomized patients received either “low dose” UFH regimen (50 U/kg irrespective of planned GPIIb/IIIa use; non ACT-guided) or “standard dose” UFH regimen (85 U/kg, ACT-guided, if no GPIIb/IIIa use; or 60 U/kg, ACT-guided, if planned GPIIb/IIIa use), immediately prior to the start of the PCI.

The primary endpoint was a composite of peri-PCI (defined as time of randomization up to 48 hours post-PCI) adjudicated major or minor bleeding, or non-adjudicated major vascular access site complications. It is noteworthy that FUTURA/OASIS 8 was underpowered to conclusively rule out any statistically significant differences between both UFH groups.

Table 8 Incidence of Peri-PCI Major or Minor Bleeding, or Major Vascular Access Site Complications, in High-Risk UA/NSTEMI Patients in FUTURA/OASIS 8 Receiving Fondaparinux sodium with either Low-Dose or Standard-Dose⁵ Adjunctive UFH during PCI

Endpoints, n (%)	Incidence		Odds Ratio ¹ (95% CI)	p-value
	Low-Dose UFH N = 1,024	Standard Dose UFH N = 1,002		
<u>Primary</u> Peri-PCI major ² or minor ³ bleeding, or major vascular access site complications ⁴	48 (4.7%)	58 (5.8%)	0.80 (0.54, 1.19)	0.267
<u>Secondary</u> Peri-PCI major bleeding	14 (1.4%)	12 (1.2%)	1.14 (0.53, 2.49)	0.734
Peri-PCI minor bleeding	7 (0.7%)	17 (1.7%)	0.40 (0.16, 0.97)	0.042
Major vascular access site complications	33 (3.2%)	43 (4.3%)	0.74 (0.47, 1.18)	0.207
Peri-PCI major bleeding, or death, MI or TVR up to Day 30.	59 (5.8%)	39 (3.9%)	1.51 (1.00, 2.28)	0.051
Death, MI or TVR up to Day 30.	46 (4.5%)	29 (2.9%)	1.58 (0.98, 2.53)	0.059
Death up to Day 30	8 (0.8%)	6 (0.6%)	1.31 (0.45, 3.78)	0.621
MI up to Day 30	31 (3.0%)	25 (2.5%)	1.22 (0.72, 2.08)	0.466
TVR up to Day 30	9 (0.9%)	3 (0.3%)	2.95 (0.80, 10.93)	0.105

TVR, Target Vessel Revascularisation; MI, Myocardial Infarction

¹ Odds ratio: Low Dose/Standard Dose

² Major bleeding was defined as clinically overt bleeding with at least one of the following criteria: fatal, symptomatic intracranial hemorrhage, retroperitoneal hemorrhage, intraocular hemorrhage leading to significant vision loss, bleeding requiring surgical intervention, decrease in Hb of ≥ 3 g/dL, or blood transfusion ≥ 2 units. Peri-PCI includes the time of randomization up to 48 hours post-PCI.

³ Minor bleeding was defined as clinically overt bleeding that was not major and that led to interruption of study drug for at least 24 hours, or transfusion of one unit of blood.

⁴ Major vascular access site complications include large hematoma, pseudoaneurysm requiring treatment, arteriovenous fistula, or other vascular procedures related to the access site.

⁵ For description of low-dose or standard dose, see narrative text, two paragraphs above this Table

Risk of catheter thrombosis during PCI

Clinical trials have shown an increased risk of guiding catheter thrombosis in patients treated solely with fondaparinux sodium for anticoagulation during percutaneous coronary intervention (PCI) compared to control (see **WARNINGS AND PRECAUTIONS, Cardiovascular**). The incidence of catheter thrombosis in UA/NSTEMI patients undergoing PCI in OASIS 5 were 0.9% (29/3173) with fondaparinux sodium, 0.3% (6/1,883) with enoxaparin alone, and 0.2% (2/1,286) with enoxaparin with adjunctive UFH. In OASIS 5, patients randomized to fondaparinux sodium received fondaparinux sodium as the sole adjunctive therapy during PCI whereas enoxaparin subjects received enoxaparin with or without UFH during PCI based on the timing since the last subcutaneous injection of enoxaparin.

In fondaparinux sodium-treated high risk UA/NSTEMI patients randomized to receive low-dose or standard regimens of UFH during non-primary PCI (see FUTURA/OASIS 8 trial description above), the incidences of adjudicated catheter thrombus were 0.5% (5/1,024), and 0.1%

(1/1,002), respectively (see **WARNINGS AND PRECAUTIONS**, Cardiovascular). In addition, in non-randomized patients, four (0.3%) cases of confirmed catheter thrombus occurred during diagnostic angiography. Of the 3,235 patients enrolled in the trial, thirteen (0.40%) in total experienced thrombus in the arterial sheath, with 7 cases of sheath thrombosis during angiography and 6 during PCI.

Fondaparinux Sodium Injection should not be used as the sole anticoagulant during PCI because of an increased risk of guiding catheter thrombosis. An effective anti-thrombin regimen such as unfractionated heparin (UFH) should be administered as an adjunct to PCI according to standard practice (see WARNINGS AND PRECAUTIONS, Cardiovascular).

Geriatrics: Nearly 8,000 UA/NSTEMI patients, 65 years or older, received treatment with fondaparinux sodium in OASIS 5 AND FUTURA/OASIS 8. In the OASIS-5 study, the rate of major bleeding at Day 9 was: 1.3% (50/3,885) in patients < 65 years, 2.4% (89/3,644) in those 65-74 years, and 2.9% (71/2,450) in those ≥ 75 years.

Management of STEMI

The rates of major bleeding events reported during the management of STEMI clinical trials with fondaparinux sodium 2.5 mg injection are provided in Table 9 below.

Table 9 Bleeding Episodes^{1,2} in OASIS 6, Randomized, Controlled Study in STEMI³

	Up to 9 days after presenting with STEMI (Number (%) Subjects)					
	Overall		Stratum 1		Stratum 2	
Investigator reported bleeding events	Fondaparinux sodium ³ N = 5954	Control (UFH/placebo) N = 5947	Fondaparinux sodium ³ N = 2808	Placebo N=2818	Fondaparinux sodium ³ N = 3146	UFH N=3129
Modified TIMI Severe Hemorrhage ¹	78 (1.3%)	94 (1.6%)	34 (1.2%)	48 (1.7%)	44 (1.4%)	46 (1.5%)
Fatal	35 (0.6%)	48 (0.8%)	19 (0.7%)	32 (1.1%)	16 (0.5%)	16 (0.5%)
Intracranial	12 (0.2%)	12 (0.2%)	6 (0.2%)	7 (0.2%)	6 (0.2%)	5 (0.2%)
Cardiac tamponade	26 (0.4%)	47 (0.8%)	15 (0.5%)	30 (1.1%)	11 (0.3%)	17 (0.5%)
Drop in Hgb ≥ 5 g/dL	37 (0.6%)	34 (0.6%)	12 (0.4%)	10 (0.4%)	25 (0.8%)	24 (0.8%)
By Reperfusion strategy						
No reperfusion	13/1415 (0.9%)	20/1367 (1.5%)	3/620 (0.5%)	5/599 (0.8%)	10/795 (1.3%)	15/768 (2.0%)
Thrombolytic group	34/2676 (1.3%)	55/2711 (2.0%)	25/2182 (1.1%)	41/2214 (1.9%)	9/494 (1.8%)	14/497 (2.8%)
Primary PCI	17/1863 (0.9%)	8/1869 (0.4%)	0/6	0/5	17/1857 (0.9%)	8/1864 (0.4%)
Major Bleeding ²	104 (1.7%)	131 (2.2%)	40 (1.4%)	61 (2.2%)	64 (2.0%)	70 (2.2%)
Minor Bleeding	37 (0.6%)	23 (0.4%)	19 (0.7%)	6 (0.2%)	18 (0.6%)	17 (0.5%)
PCI related bleeding	45 (0.8%)	47 (0.8%)	7 (0.2%)	3 (0.1%)	38 (1.2%)	44 (1.4%)
CABG related bleeding	3 (<0.1%)	6 (0.1%)	1 (<0.1%)	3 (0.1%)	2 (<0.1%)	3 (<0.1%)

1 Severe hemorrhage was defined according to a modified TIMI criteria as: fatal hemorrhage, intracranial hemorrhage, cardiac tamponade, or a clinically significant hemorrhage with a decrease in Hb of >5 g/dL.

2 Major bleeding was defined as clinically overt bleeding with at least one of the following criteria: fatal, symptomatic intracranial hemorrhage, retroperitoneal hemorrhage, intraocular hemorrhage leading to significant vision loss, bleeding requiring surgical intervention, decrease in Hb of >3.0 g/dL, or blood transfusion ≥2 units.

3 Patients randomized to fondaparinux sodium received an IV bolus injection of 2.5 mg followed by 2.5 mg by SC injection daily for up to 8 days or discharge.

In those patients who underwent non-primary PCI < 6 hours after the last dose of fondaparinux, the median dose of UFH used was 5000 IU and the incidence of major bleeding was 4.1% (2/49).

In those patients who underwent non-primary PCI 6-24 hours after the last dose of fondaparinux, the median dose of UFH was 8000 IU and the incidence of major bleeding was 2% (2/98).

The relative effects of fondaparinux sodium compared to control on severe hemorrhage or any hemorrhage up to Day 9 by clopidogrel use were consistent with that observed for the overall population.

Risk of catheter thrombosis during PCI

Clinical trials have shown an increased risk of guiding catheter thrombosis in patients treated solely with fondaparinux sodium for anticoagulation during percutaneous coronary intervention (PCI) compared to control (see **WARNINGS AND PRECAUTIONS, Cardiovascular**). The incidence of catheter thrombus in STEMI patients undergoing primary PCI were 1.18% (22/1,862) for fondaparinux sodium, when fondaparinux sodium was used as the sole adjunctive therapy, compared to 0% for UFH (0/1,853). In STEMI patients treated with fondaparinux sodium undergoing non-primary PCI (234 patients, 238 procedures) who received UFH as an adjunct to the procedure, no cases of guiding catheter thrombus occurred.

In STEMI patients undergoing primary percutaneous coronary intervention (PCI) for reperfusion, the use of Fondaparinux Sodium Injection prior to and during PCI is not recommended (see WARNINGS AND PRECAUTIONS, Cardiovascular, and DOSAGE AND ADMINISTRATION).

Geriatrics: Over 2,300 STEMI patients, 65 years or older, received treatment with fondaparinux sodium in OASIS 6. In the STEMI clinical trials with patients receiving fondaparinux sodium, the risk of severe hemorrhage was: 0.6% (22/3,565) in patients < 65 years, 1.5% (23/1,518) in those 65-74 years, and 2.2% (19/871) in those ≥ 75 years.

Non-hemorrhagic adverse events

Other adverse events that occurred during treatment with fondaparinux sodium or enoxaparin sodium in clinical trials with patients undergoing hip fracture surgery, hip replacement surgery, or knee replacement surgery and that occurred at a rate of at least 2% in either treatment group, are provided in Table 10 and Table 11 below.

Other adverse events that occurred during treatment with fondaparinux sodium or dalteparin sodium in a clinical trial with patients undergoing abdominal surgery that occurred at a rate of at least 2% in either treatment group are provided in Table 12 below.

Table 10 Adverse events occurring in greater than or equal to 2 percent of Fondaparinux Sodium or Enoxaparin Sodium Treated Patients Regardless of Relationship to Study Drug Across Hip Fracture, Hip Replacement Surgery, or Knee Replacement Surgery Studies

Adverse Events	Fondaparinux sodium 2.5 mg SC once daily N = 3616	Comparator: Low Molecular Weight Heparin or Enoxaparin Sodium¹ N = 3956
Anemia	19.6%	16.9%
Fever	13.6%	15.4%
Nausea	11.3%	12.2%
Edema	8.7%	8.8%
Constipation	8.5%	10.5%
Rash	7.5%	8.3%
Vomiting	5.9%	6.0%
Insomnia	5.0%	5.4%
Wound drainage increased	4.5%	4.7%
Hypokalemia	4.2%	4.1%
Urinary tract infection	3.8%	3.4%
Dizziness	3.6%	4.2%
Purpura	3.5%	3.5%
Hypotension	3.5%	3.2%
Confusion	3.1%	3.3%
Bullous eruption	3.1%	2.6%
Urinary retention	2.9%	3.0%
Hematoma	2.8%	2.8%
Diarrhea	2.5%	2.6%
Dyspepsia	2.4%	2.6%
Post-operative hemorrhage	2.4%	1.7%
Headache	2.0%	2.5%
Pain	1.7%	2.6%

¹ Enoxaparin Sodium dosing regimen: 30 mg every 12 hours or 40 mg once daily.

Table 11 Adverse events occurring in greater than or equal to 2 percent of Fondaparinux Sodium or Placebo Treated Patients Regardless of Relationship to Study Drug During Pre-randomization open label period and Extended prophylaxis period after Hip Fracture Surgery

	Pre-randomization Open-Label Period (Day 1 to Day 7 ± 1 post- surgery)	Randomized Double-Blind Extended Prophylaxis Period (Day 8 to Day 28 ± 2 post-surgery)	
Adverse Events	Fondaparinux sodium N = 737	Fondaparinux sodium N =327	Placebo SC N = 329
Constipation	7.1%	1.8%	2.1%
Anemia	5.8%	1.5%	1.2%
Nausea	4.6%	0.3%	1.2%
Confusion	4.1%	1.2%	0.3%
Fever	4.1%	0.3%	1.2%
Urinary tract infection	3.1%	4.0%	4.0%
Vomiting	2.7%	0.6%	1.2%
Post-operative hemorrhage	2.4%	0.6%	0.6%
Hematoma	1.2%	2.1%	0.3%
Surgical site reaction	0.7%	1.5%	2.4%
Diarrhea	0.5%	1.8%	2.4%

Table 12 Adverse Events Occurring in greater than or equal to 2 percent of Patients Treated With Fondaparinux Sodium or Dalteparin Sodium Undergoing Abdominal Surgery Regardless of Relationship to Study Drug

	Fondaparinux sodium 2.5 mg SC once daily N = 1433	Dalteparin Sodium 5000 IU SC once daily N = 1425
Adverse Events		
Post-operative wound infection	4.9%	4.8%
Post-operative hemorrhage	4.3%	2.9%
Fever	3.7%	3.8%
Surgical site reaction	3.2%	2.8%
Anaemia	2.4%	1.8%
Hypertension	2.4%	2.9%
Pneumonia	2.3%	1.6%
Vomiting	2.2%	1.8%

Other adverse events that occurred during treatment with fondaparinux sodium, enoxaparin sodium or heparin in the DVT and PE treatment clinical trials and that occurred at a rate of at least 2% in any treatment group are provided in Table 13 below.

Table 13 Adverse events occurring in greater than or equal to 2 percent of Fondaparinux Sodium or Enoxaparin Sodium or Heparin Treated Patients Regardless of Relationship to Study Drug Across VTE Treatment Studies

Adverse Events	Fondaparinux sodium Treatment Regimen	Enoxaparin Sodium 1 mg/kg SC q 12h	Heparin IV aPTT adjusted
	N = 2294	N = 1101	N = 1092
Constipation	106 (4.6%)	32 (2.9%)	93 (8.5%)
Headache	104 (4.5%)	37 (3.4%)	65 (6.0%)
Insomnia	86 (3.7%)	19 (1.7%)	75 (6.9%)
Fever	81 (3.5%)	32 (2.9%)	47 (4.3%)
Nausea	76 (3.3%)	29 (2.6%)	53 (4.9%)
Urinary Tract Infection	53 (2.3%)	20 (1.8%)	24 (2.2%)
Coughing	48 (2.1%)	7 (0.6%)	26 (2.4%)
Diarrhea	43 (1.9%)	22 (2.0%)	27 (2.5%)
Abdominal Pain	33 (1.4%)	14 (1.3%)	28 (2.6%)
Chest Pain	33 (1.4%)	8 (0.7%)	26 (2.4%)
Leg Pain	31 (1.4%)	10 (0.9%)	22 (2.0%)
Back Pain	30 (1.3%)	11 (1.0%)	34 (3.1%)
Epistaxis	30 (1.3%)	12 (1.1%)	41 (3.8%)
Prothrombin decreased	30 (1.3%)	3 (0.3%)	34 (3.1%)
Anemia	28 (1.2%)	3 (0.3%)	23 (2.1%)
Vomiting	26 (1.1%)	14 (1.3%)	27 (2.5%)
Hypokalemia	25 (1.1%)	2 (0.2%)	23 (2.1%)
Bruise	24 (1.0%)	24 (2.2%)	14 (1.3%)
Anxiety	18 (0.8%)	8 (0.7%)	22 (2.0%)
Hepatic Function abnormal	10 (0.4%)	14 (1.3%)	24 (2.2%)
Hepatic Enzymes increased	7 (0.3%)	52 (4.7%)	30 (2.7%)
ALT increased	7 (0.3%)	47 (4.3%)	8 (0.7%)
AST increased	4 (0.2%)	31 (2.8%)	3 (0.3%)

Other adverse events that occurred during treatment with fondaparinux sodium, enoxaparin, UFH or placebo in clinical trials with acute coronary syndrome patients and that occurred at a rate of at least 2% in any treatment group, are described in Table 14 below.

Table 14 Adverse Events Occurring in $\geq 2\%$ of Fondaparinux sodium or Control¹ Treated Patients Regardless of Relationship to Study Drug Across Studies of UA/NSTEMI (OASIS 5) and STEMI (OASIS 6)

	Number (%) Subjects							
	OASIS 5		OASIS 6					
	Fondaparinux sodium N=9979	Enoxaparin N=9969	Overall		Stratum 1		Stratum 2	
Fondaparinux sodium N=5954			Control ¹ N=5947	Fondaparinux sodium N=2808	Placebo N=2818	Fondaparinux sodium N=3146	UFH N=3129	
Any AE²	2426 (24)	2785 (28)	1933 (32)	1959 (33)	922 (33)	954 (34)	1011 (32)	1005 (32)
Headache	227 (2)	226 (2)	105 (2)	118 (2)	60 (2)	63 (2)	45 (1)	55 (2)
Atrial fibrillation	103 (1)	124 (1)	164 (3)	126 (2)	69 (2)	57 (2)	95 (3)	69 (2)
Pyrexia	96 (<1)	110 (1)	189 (3)	200 (3)	119 (4)	125 (4)	70 (2)	75 (2)
Chest pain	148 (1)	147 (1)	108 (2)	79 (1)	50 (2)	42 (1)	58 (2)	37 (1)
Vomiting	50 (<1)	62 (<1)	74 (1)	74 (1)	47 (2)	42 (1)	27 (1)	32 (1)
Ventricular tachycardia	35 (<1)	28 (<1)	76 (1)	81 (1)	26 (<1)	29 (1)	50 (2)	52 (2)

1 OASIS 5 is a study in UA/NSTEMI and OASIS 6 is a study in STEMI. Control for the OASIS 5 study was enoxaparin and for the OASIS 6 study was placebo or UFH.

2 Includes any efficacy outcomes (except hemorrhagic stroke), non-fatal cardiac arrest and heart failure reported as AEs by the investigator in contravention of the protocol.

Other adverse events reported in greater than or equal to 1% of high-risk UA/NSTEMI patients treated with fondaparinux sodium and receiving either “low-dose” or “standard dose” of adjunctive intravenous UFH during non-primary PCI in FUTURA/OASIS 8, included headache, pyrexia, post-procedural discharge, hypotension, cough and dizziness. No individual AE occurred in greater than 3% of subjects. For those high-risk UA/NSTEMI patients in the same trial, who were not indicated for PCI and were treated with fondaparinux sodium only, the other adverse events occurring in greater than or equal to 1% of patients, included headache (1.5%), gastritis (1.2%), urinary tract infection (1.2%), asthenia (1.1%) and pyrexia (1.1%).

Thrombocytopenia: See WARNINGS AND PRECAUTIONS, Hematologic, *Thrombocytopenia*.

Liver Function Tests

Prophylaxis of VTE following orthopedic surgery

Transient elevation of liver transaminases (AST and ALT) to > 3 times the upper limit of laboratory range have been observed with the peri-operative prophylactic use of fondaparinux sodium as have been seen with other antithrombotics such as low molecular weight heparins. Such elevations are fully reversible and are rarely associated with increases in bilirubin. Transient transaminase increases > 3 times upper limit of laboratory range during the extended prophylaxis clinical trial were as follows: ALT - 4 /272 (1.5%) fondaparinux sodium vs. 2 /274 (0.7%) placebo; AST - 2 /268 (0.7%) fondaparinux sodium vs. 1/ 271 (0.4%) placebo. However, these increases were reversible and there was no significant difference in the change in the hepatic enzymes between the two treatment groups from the baseline post-randomization period to the last value on double blind treatment.

Treatment of DVT and PE

In the DVT and PE treatment clinical trials asymptomatic increases in AST and ALT levels > 3 times the upper limit of normal of the laboratory reference range have been reported in 0.7% and 1.3% of patients, respectively, during the fondaparinux sodium injection treatment regimen.

In comparison, these increases have been reported in 4.8% and 12.3% of patients, respectively, in the DVT treatment trial during treatment with enoxaparin sodium 1 mg/kg every 12 hours, and in 2.9% and 8.7% of patients, respectively, in the PE treatment trial during treatment with aPTT adjusted heparin.

Allergic Reaction

Skin rash and allergic reactions have been observed with fondaparinux sodium use, but are uncommon. As with any subcutaneous injection, mild local irritation (injection site bleeding, rash and pruritis) may occur following subcutaneous injection of Fondaparinux Sodium Injection. Very rare reports of angioedema and anaphylactoid/anaphylactic reactions (< 0.01%) have been received.

Other Adverse Reactions

Other adverse reactions that occurred during treatment with fondaparinux sodium in clinical trials with patients undergoing hip fracture surgery, hip replacement surgery, knee replacement surgery or abdominal surgery and that occurred at a rate of less than 1.0%, include the following: thrombocytopenia, thrombocythemia, abnormal platelets, and coagulation disorder. Adverse reactions events that have occurred at a rate of less than 0.1% in patients during clinical trials include: somnolence, vertigo, dyspnea, fatigue, flushing, and syncope.

Post-Marketing Adverse Drug Reactions

The following adverse reactions have been identified during post-approval use of fondaparinux sodium.

Rare spontaneous reports of elevated aPTT have been received at the 2.5 mg dose. A causal association between treatment with fondaparinux and the occurrence of elevated aPTT has not been established.

DRUG INTERACTIONS

Drug-Drug Interactions

In clinical studies performed with fondaparinux sodium, the concomitant use of oral anticoagulants (warfarin), platelet inhibitors (acetylsalicylic acid), NSAIDs (piroxicam) and digoxin did not interact with the pharmacokinetics/pharmacodynamics of fondaparinux sodium. In addition, fondaparinux sodium neither influenced the pharmacodynamics of warfarin, acetylsalicylic acid, piroxicam and digoxin, nor the pharmacokinetics of digoxin at steady state.

Agents that may enhance the risk of hemorrhage should be discontinued prior to initiation of fondaparinux sodium therapy unless indicated for the management of the underlying condition, such as vitamin K antagonists for the treatment of venous thromboembolism (VTE). If co-administration is necessary, close monitoring may be appropriate.

Since fondaparinux does not inhibit isozymes of the CYP P450 system *in vitro* (CYP 1A2, CYP 2A6, CYP 2C9, CYP 2C19, CYP 2D6, CYP 2E1 or CYP 3A4), fondaparinux sodium is not expected to interact with other drugs metabolized *in vivo* via these isozymes.

Fondaparinux sodium does not bind significantly to plasma proteins other than ATIII, therefore, drug interactions by protein binding displacement are not expected.

Drug-Food Interactions

Interactions with food have not been established.

Drug-Herb Interactions

Interactions with herbal products have not been established.

Drug-Laboratory Interactions

See WARNINGS AND PRECAUTIONS - Monitoring, Laboratory and Coagulation Tests.

DOSAGE AND ADMINISTRATION

Recommended Dose and Dosage Adjustment

Prophylaxis of VTE following orthopedic surgery

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

After hemostasis has been established, the initial dose should be given no earlier than 6 hours after surgical closure. In clinical studies, 99% of the patients had received the initial dose of fondaparinux sodium by 18 hours after surgical closure. **Administration before 6 hours after orthopedic surgery has been associated with an increased risk of major bleeding.** The timing of the first dose of Fondaparinux Sodium Injection following surgery requires strict adherence (see **WARNING AND PRECAUTIONS, Hemorrhage, and Peri-Operative Considerations; ACTION AND CLINICAL PHARMACOLOGY**).

The usual duration of prophylactic therapy with Fondaparinux Sodium Injection is 7 ± 2 days. Treatment should be continued for as long as the risk of VTE persists. In patients for whom extended prophylaxis is indicated, administration of Fondaparinux Sodium Injection in or out of the hospital up to an additional 24 days is recommended. In clinical trials of extended prophylaxis, a total of 32 days (peri-operative and extended prophylaxis) has been tolerated.

Prophylaxis of VTE following abdominal surgery

The recommended dose of Fondaparinux Sodium Injection is 2.5 mg once daily administered post-operatively by subcutaneous injection after hemostasis has been established.

The initial dose should be given 6 to 8 hours after surgery. **Administration before 6 hours after abdominal surgery has been associated with an increased risk of major bleeding.** The timing of the first dose of Fondaparinux Sodium Injection following surgery requires strict adherence

(see **WARNING AND PRECAUTIONS, Hemorrhage, and Peri-Operative Considerations; ACTION AND CLINICAL PHARMACOLOGY**).

The usual duration of administration is 5 to 9 days, and up to 10 days of Fondaparinux Sodium Injection has been administered.

Treatment of DVT and PE

The recommended dose of Fondaparinux Sodium Injection is 5 mg (body weight < 50 kg), 7.5 mg (body weight 50-100 kg) or 10 mg (body weight > 100 kg) by subcutaneous injection once daily.

Concomitant oral anticoagulation treatment should be initiated as soon as possible, usually within 72 hours. Fondaparinux Sodium Injection treatment should be continued for at least 5 days and until a therapeutic oral anticoagulant effect is established (INR 2.0 to 3.0).

The average duration of administration is 7 days. In controlled clinical trials administration of Fondaparinux Sodium Injection for up to 26 days to a small number of patients has been well tolerated.

Management of Unstable Angina/Non-ST Segment Elevation Myocardial Infarction (UA/NSTEMI)

The recommended dose of Fondaparinux Sodium Injection is 2.5 mg once daily, administered by subcutaneous injection. Treatment should be initiated as soon as possible following diagnosis and may be continued for up to 8 days or until hospital discharge.

If a patient is to undergo percutaneous coronary intervention (PCI) while being treated with Fondaparinux Sodium Injection, an effective anti-thrombin regimen such as unfractionated heparin (UFH) should be administered as an adjunct to PCI, as per standard practice, taking into account the patient's potential risk of bleeding, including the time since the last dose of Fondaparinux Sodium Injection (see **WARNINGS AND PRECAUTIONS, Risk of catheter thrombosis during PCI, and Hemorrhage**).

The timing of the next dose of subcutaneous Fondaparinux Sodium Injection after sheath removal should be based on clinical judgment. In the UA/NSTEMI clinical trials treatment with fondaparinux sodium was restarted no earlier than 2 hours after sheath removal.

In patients who are to undergo coronary artery bypass graft (CABG) surgery—Fondaparinux Sodium Injection where possible, should not be given during the 24 hours before surgery and may be restarted 48 hours post-operatively.

Management of ST Segment Elevation Myocardial Infarction (STEMI)

The recommended dose of Fondaparinux Sodium Injection is 2.5 mg once daily. The first dose of Fondaparinux Sodium Injection 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 8 days or until hospital discharge.

Fondaparinux Sodium Injection should not be used if primary PCI is the planned reperfusion therapy (see **INDICATIONS, WARNINGS AND PRECAUTIONS, Risk of catheter thrombosis during PCI**). Fondaparinux Sodium Injection is indicated for use in patients who are managed with thrombolytics or who initially are to receive no form of reperfusion therapy.

If a patient is to undergo subsequent PCI while being treated with Fondaparinux Sodium Injection, an effective anti-thrombin regimen such as unfractionated heparin (UFH) should be administered as an adjunct to PCI as per standard practice, taking into account the patient's potential risk of bleeding, including the time since the last dose of Fondaparinux Sodium Injection (see **WARNINGS AND PRECAUTIONS, Risk of catheter thrombosis during PCI, and Hemorrhage**).

There are limited data on the use of UFH during non-primary PCI in STEMI patients treated with fondaparinux (see **CLINICAL TRIALS**). In those patients with STEMI who underwent non-primary PCI in OASIS-6 less than 6 hours after the last dose of fondaparinux, the median dose of UFH was 5000 IU and the incidence of major bleeding was 4.1% (2/49). In those patients who underwent non-primary PCI 6-24 hours after the last dose of fondaparinux, the median dose of UFH was 8000 IU and the incidence of major bleeding was 2% (2/98).

The timing of the next dose of subcutaneous fondaparinux after sheath removal should be based on clinical judgment. In the STEMI clinical trials treatment with fondaparinux was restarted no earlier than 3 hours after sheath removal.

In 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.

General Dosing Considerations

Use in Patients with Renal Insufficiency

The risk of hemorrhage increases with increasing renal insufficiency. Fondaparinux Sodium Injection should be used with caution in patients with moderate renal insufficiency (creatinine clearance 30–50 mL/min) (see **ACTION AND CLINICAL PHARMACOLOGY, Renal Insufficiency**). In severe renal impairment, the use of Fondaparinux Sodium Injection should be avoided or, if the physician determines that the benefit outweighs the risk, Fondaparinux Sodium Injection should only be used with caution.

Renal function should be assessed periodically in patients receiving the drug. For prophylactic use following orthopedic surgery, Fondaparinux Sodium Injection should be discontinued immediately in patients who develop severe renal insufficiency or labile renal function while on therapy. After discontinuation of Fondaparinux Sodium Injection, its anticoagulant effects may persist for 2-4 days in patients with normal renal function (i.e. at least 3-5 half-lives).

The anticoagulant effects of Fondaparinux Sodium Injection may persist even longer in patients with renal insufficiency.

Use in Patients with Hepatic Insufficiency

No dose adjustment is recommended in patients with mild to moderate hepatic impairment, based upon single-dose pharmacokinetic data. Pharmacokinetic data are not available for patients with severe hepatic impairment. Patients with hepatic impairment may be particularly vulnerable to bleeding during Fondaparinux Sodium Injection therapy. Observe these patients closely for signs and symptoms of bleeding (see **WARNINGS AND PRECAUTIONS**).

Use in Geriatric Patients

Use with caution in elderly patients (see **WARNINGS AND PRECAUTIONS, Geriatrics, and ADVERSE REACTIONS, Geriatrics**).

Use in Patients with Low Body Weight

For patients of body weight < 50 kg, Fondaparinux Sodium Injection should be used with caution (see **WARNINGS AND PRECAUTIONS, Low Body Weight**).

Administration

Fondaparinux Sodium Injection is intended for use under a physician's guidance. Patients may self-inject only if their physician determines that it is appropriate, and with medical follow-up as necessary. Proper training in subcutaneous injection technique should be provided.

Subcutaneous administration:

Administration is by subcutaneous injection only. **Do not inject Fondaparinux Sodium Injection intramuscularly.**

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. For step-by-step instructions for use, please see **CONSUMER INFORMATION**.

Intravenous administration:

For STEMI patients treated with Fondaparinux Sodium Injection, the initial dose is to be administered intravenously. Administration should be through an existing intravenous line either directly or using a small volume (25 mL or 50 mL) 0.9% saline minibag as the first dose in the treatment of STEMI.

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 the administration of Fondaparinux Sodium 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.

If Fondaparinux Sodium Injection is added to a 0.9% saline minibag it should be infused immediately, but can be stored between 15°C-30°C for up to 24 hours. Minibags are typically composed of a variety of polymers including PVC, polyethylene, polypropylene, or styrene-ethylene-butadiene, individually or in combination.

In the absence of compatibility studies, Fondaparinux Sodium Injection must not be mixed with other medicinal products.

OVERDOSAGE

Hemorrhage is the major clinical sign of overdose.

Overdosage of Fondaparinux Sodium Injection, associated with bleeding complications, should lead to treatment discontinuation, a search for the primary cause of bleeding, and initiation of appropriate therapy, which may include surgical hemostasis, blood replacement, fresh plasma transfusion, or plasmapheresis.

Minor bleeding rarely requires specific therapy, and reducing or delaying subsequent doses of Fondaparinux Sodium Injection is usually sufficient.

For management of a suspected drug overdose, contact your regional Poison Control Centre immediately.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

Fondaparinux sodium Injection is a synthetic and specific inhibitor of activated Factor X (Xa). As fondaparinux sodium has no animal-sourced components, there is no risk of animal contamination such as transmissible spongiform encephalitis (TSE).

The mechanism of action of fondaparinux sodium is the potentiation of antithrombin III (ATIII) which selectively inhibits Factor Xa. By selectively binding to ATIII, fondaparinux sodium potentiates approximately 300 times the neutralization of Factor Xa. Neutralization of Factor Xa interrupts the blood coagulation cascade and thus inhibits thrombin formation and thrombus development.

Fondaparinux sodium does not inactivate thrombin (activated Factor II) and has no effect on platelets. At the recommended dose, fondaparinux sodium does not affect fibrinolytic activity or bleeding time.

At equivalent antithrombotic concentrations, experimental bleeding models demonstrate that fondaparinux sodium induces less bleeding than unfractionated heparin.

Fondaparinux sodium does not bind to Human Platelet Factor 4 (unlike heparin) and does not cross-react with sera from patients with heparin-induced thrombocytopenia. No thrombocytopenia with suspected immuno-allergic pathophysiology was documented in the overall clinical development program or in post-marketing experience.

Anti-Xa Activity: The pharmacodynamics/pharmacokinetics of fondaparinux sodium are derived from fondaparinux plasma concentrations quantified via anti-Factor Xa activity. Only fondaparinux can be used to calibrate the anti-Xa assay. (The international standards of heparin

or Low Molecular Weight Heparin [LMWH] are not appropriate for this use). As a result, the activity of fondaparinux sodium is expressed as milligram (mg) of the fondaparinux calibrator. The anti-Xa activity of the drug increases with increasing drug concentration, reaching maximum values in approximately 3 hours.

Pharmacokinetics

Absorption: Following a single 4 mg i.v. bolus administration to normal healthy subjects, mean peak fondaparinux plasma concentration is approximately 0.81 mg/L at the first sampling time point of 5 minutes. After subcutaneous dosing, fondaparinux is completely and rapidly absorbed, with an absolute bioavailability of 100%. Following a single subcutaneous injection of 2.5 mg, peak plasma concentration (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.

Pharmacokinetics of fondaparinux are linear in the range of 2 to 8 mg by the subcutaneous route. At steady state, mean plasma concentrations 2 hours post dosing ranged between 0.32 and 0.47 mg/L in patients undergoing orthopedic surgeries receiving fondaparinux sodium 2.5 mg.

In patients with symptomatic deep vein thrombosis and pulmonary embolism undergoing treatment with fondaparinux sodium injection 5 mg (body weight < 50 kg), 7.5 mg (body weight 50-100 kg) and 10 mg (body weight > 100 kg) once daily, the body-weight-adjusted doses provide similar exposure across all body weight categories. The peak steady-state plasma concentration is, on average, 1.20-1.26 mg/L. In these patients, the minimum steady-state plasma concentration is 0.46-0.62 mg/L.

Distribution: In healthy adults, intravenously or subcutaneously administered fondaparinux distributes mainly in blood as evidenced by steady state and non-steady state apparent volume of distribution of 7 to 11 L.

In vitro fondaparinux is highly (at least 94% in the concentration range from 0.5 to 2 mg/L) and specifically bound to ATIII and does not bind significantly to other plasma proteins, including Platelet Factor 4 (PF4).

Metabolism: There is no evidence that fondaparinux is metabolized since most of the administered dose is eliminated unchanged in urine.

Excretion: The elimination half life ($T_{1/2}$) is 17 to 21 hours in healthy subjects.

Up to 77% of a single subcutaneous dose of fondaparinux is excreted in urine as unchanged compound in 72 hours in healthy individuals up to 75 years of age.

Special Populations and Conditions

Geriatrics: Fondaparinux elimination is prolonged in patients over 75 years old. In studies evaluating fondaparinux sodium 2.5 mg prophylaxis in hip fracture surgery or elective hip surgery, the total clearance of fondaparinux was approximately 25% lower in patients over 75

years old as compared to patients less than 65 years old. A similar pattern is observed in DVT and PE treatment patients.

Following a single intravenous dose of fondaparinux 4 mg in healthy elderly subjects, a mean C_{max} of 0.86 mg/L was observed at the first sampling timepoint of 5 minutes. Other pharmacokinetic parameters following intravenous administration were similar to those observed for subcutaneous administration.

Renal Insufficiency: Fondaparinux elimination is prolonged in patients with renal insufficiency since the major route of elimination is urinary excretion of unchanged drug.

In patients undergoing prophylaxis following elective hip surgery or hip fracture surgery, the total clearance of fondaparinux is approximately 25% lower in patients with mild renal insufficiency (creatinine clearance 50 to 80 mL/min), approximately 40% lower in patients with moderate renal insufficiency (creatinine clearance 30 to 50 mL/min) and approximately 55% lower in patients with severe renal insufficiency (< 30 mL/min) compared to patients with normal renal function. The associated terminal half-life values were 29 hours in moderate and 72 hours in patients with severe renal insufficiency. A similar pattern is observed in DVT and PE treatment patients (see **WARNINGS AND PRECAUTIONS, Renal**).

Hepatic Insufficiency: Unbound concentrations of fondaparinux are expected to be unchanged in patients with mild to moderate hepatic insufficiency, and therefore, no dose adjustment is necessary based on pharmacokinetics. Following a single, subcutaneous dose of fondaparinux in subjects with moderate hepatic insufficiency (Child-Pugh Category B), 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 insufficiency thereby resulting in increased renal clearance of fondaparinux. There were no clinically relevant differences in the pharmacodynamic measures as assessed by aPTT, PT and ATIII concentrations, indicating that the effect of fondaparinux in subjects with hepatic impairment was similar to that in individuals with normal liver function.

The pharmacokinetics of fondaparinux have not been studied in patients with severe hepatic insufficiency (see **DOSAGE AND ADMINISTRATION, Use in Patients with Hepatic Insufficiency and WARNINGS AND PRECAUTIONS**).

Patients Weighing Less Than 50 kg: Total clearance of fondaparinux sodium is decreased by approximately 30% in patients weighing less than 50 kg (see **WARNINGS AND PRECAUTIONS, Low Body Weight**, and **DOSAGE AND ADMINISTRATION, Use in Patients with Low Body Weight**).

Pediatrics: The pharmacokinetics of fondaparinux have not been investigated in pediatric patients.

STORAGE AND STABILITY

Store at controlled room temperature 15°C - 30°C. Do not freeze.

If Fondaparinux Sodium Injection is added to a 0.9% saline minibag it should be infused immediately, but can be stored between 15°C-30°C for up to 24 hours. Minibags are typically composed of a variety of polymers including PVC, polyethylene, polypropylene, or styrene-ethylene-butadiene, individually or in combination.

SPECIAL HANDLING INSTRUCTIONS

Keep out of the sight and reach of children. Single dose syringes. Discard unused portion.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Fondaparinux Sodium Injection is supplied as a sterile injectable solution for subcutaneous and intravenous use, is available in the following strengths and package sizes:

Package of 10:

2.5 mg Fondaparinux Sodium Injection in 0.5 mL single dose prefilled syringe, affixed with a 27-gauge x ½-inch needle with a blue plunger rod.

5 mg Fondaparinux Sodium Injection in 0.4 mL single dose prefilled syringe, affixed with a 27-gauge x ½-inch needle with an orange plunger rod.

7.5 mg Fondaparinux Sodium Injection in 0.6 mL single dose prefilled syringe, affixed with a 27-gauge x ½-inch needle with a magenta plunger rod.

10 mg Fondaparinux Sodium Injection in 0.8 mL single dose prefilled syringe, affixed with a 27-gauge x ½-inch needle with a violet plunger rod.

As with all parenteral drug products, syringes should be inspected visually for clarity, particulate matter, precipitate, discoloration and leakage prior to administration.

Solutions showing haziness, particulate matter, precipitate, discoloration or leakage should not be used.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

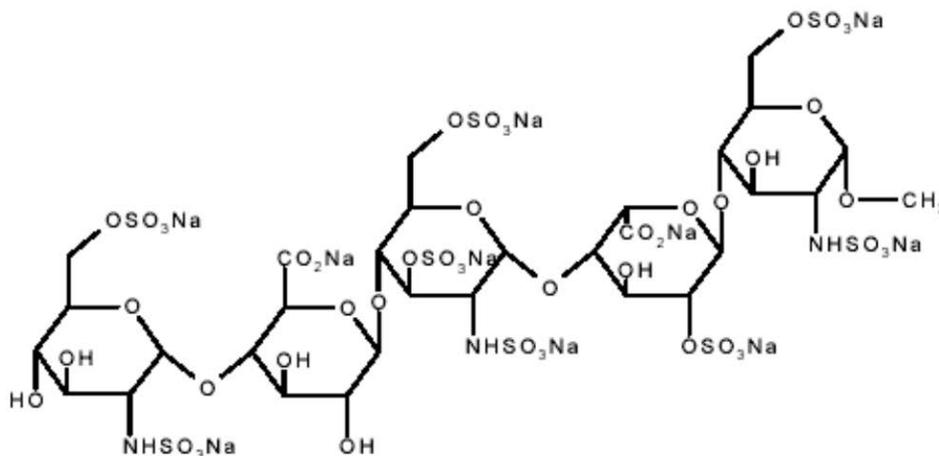
Drug Substance

Proper name: fondaparinux sodium

Chemical name: methyl O-2-deoxy-6-O-sulfo-2-(sulfoamino)- α -D-glucopyranosyl-(1 \rightarrow 4)-O- β -D-glucopyranuronosyl-(1 \rightarrow 4)-O-2-deoxy-3,6-di-O-sulfo-2-(sulfoamino)- α -D-glucopyranosyl-(1 \rightarrow 4)-O-2-O-sulfo- α -L-idopyranuronosyl-(1 \rightarrow 4)-2-deoxy-6-O-sulfo-2-(sulfoamino)- α -D-glucopyranoside, decasodium salt

Molecular formula and molecular mass: C₃₁H₄₃N₃Na₁₀O₄₉S₈

Structural formula:



Molecular weight: 1728 (g/mol).

Physicochemical properties: pH between 5.5 and 7.0 (1.25% w/v in water)

Solubility: Freely soluble in water, 2.0 M Sodium chloride and 0.5 M Sodium hydroxide and insoluble in ethanol

Composition: Each single-dose, prefilled syringe of fondaparinux sodium, affixed with an active needle protection system, contains 2.5 mg of fondaparinux sodium in 0.5 mL, 5.0 mg of fondaparinux sodium in 0.4 mL, 7.5 mg of fondaparinux sodium in 0.6 mL, or 10.0 mg of fondaparinux sodium in 0.8 mL of an isotonic solution of sodium chloride, water for injection. Also contains sodium hydroxide or

hydrochloric acid for pH adjusters. The final drug product is a clear and colorless to slightly yellow liquid with a pH between 5.5 and 8.0.

CLINICAL TRIALS

Prophylaxis of Thromboembolic Events Following Hip Fracture Surgery

Table 15 Summary of patient demographics for clinical trials in the prophylaxis of thromboembolic events following hip fracture surgery

Trial design	Dosage, route of administration and duration	Study subjects (n=number)	Mean age (Range)	Gender
Randomized, double-blind	2.5 mg subcutaneous once daily	1711	77 (17-101)	25% men 75% women

In a randomized, double-blind, clinical trial in patients undergoing hip fracture surgery, fondaparinux sodium 2.5 mg subcutaneous (SC) once daily was compared to enoxaparin 40 mg SC once daily (the dose of enoxaparin sodium approved for use in prophylaxis in conjunction with orthopedic surgery in Canada is 30 mg SC twice daily).

A total of 1711 patients were randomized and 1673 were treated. Patients ranged in age from 17-101 years (mean age 77 years) with 25% men and 75% women. Patients were 99% Caucasian, 1% other races. Patients with multiple trauma affecting more than one organ system, serum creatinine level more than 180 µmol/L (2 mg/dL), or platelet count less than 100,000/mm³ were excluded from the trial. Fondaparinux sodium was initiated 6 hours after surgery in 88% of patients and the comparator was initiated an average of 18 hours after surgery in 74% of patients. For both drugs, treatment was continued for 7 ± 2 days. Efficacy results are provided in Table 16 below. Major bleeding episodes for both drugs are provided in Table 1 and Table 2 (see **ADVERSE REACTIONS**).

Table 16 Efficacy Results of study in the prophylaxis of thromboembolic events following hip fracture surgery

Endpoint	Associated value and statistical significance for fondaparinux sodium 2.5 mg SC once daily ¹	Associated value and statistical significance for Enoxaparin 40 mg SC once daily ¹
All treated Hip Fracture Surgery Patients	N=831	N=840
All Evaluable ² Hip Fracture Surgery Patients		
Venous Thromboembolic Event (VTE ³)	52/626 8.3% ⁴ (6.3, 10.8) ⁵	119/624 19.1% (16.1, 22.4)
All Deep Vein Thrombosis (DVT)	49/624 7.9% ⁴ (5.9, 10.2)	117/623 18.8% (15.8, 22.1)
Proximal DVT	6/650 0.9% ⁴ (0.3, 2.0)	28/646 4.3% (2.9, 6.2)
Symptomatic Pulmonary Embolism (PE)	3/831 0.4% ⁶ (0.1, 1.1)	3/840 0.4% (0.1, 1.0)

- 1 Fondaparinux sodium was initiated 6 hours after surgery in 88% of patients and the enoxaparin was initiated an average of 18 hours after surgery in 74% of patients.
- 2 Evaluable patients were those who were treated and underwent the appropriate surgery (i.e. hip fracture surgery of the upper third of the femur), with an adequate efficacy assessment up to Day 11.
- 3 VTE was a composite of documented DVT and/or documented symptomatic PE reported up to Day 11.
- 4 p-value <0.001
- 5 Number in parentheses indicates 95% confidence interval
- 6 p-value: Not Significant (NS)

Extended Prophylaxis of Thromboembolic Events

Table 17 Summary of patient demographics for clinical trials in the extended prophylaxis of thromboembolic events following orthopedic surgery

Trial design	Dosage, route of administration and duration	Study subjects (n=number)	Mean age (Range)	Gender
Randomized	2.5 mg subcutaneous once daily for 7 ± 1 days. At the end of this period, randomized to receive either fondaparinux sodium 2.5 mg od or placebo, for 21 ± 2 days.	Fondaparinux sodium: n=737 open period Fondaparinux sodium: n=326 Placebo: n=330	75 (23-96)	29% men 71% women

In an unblinded manner, 737 patients undergoing hip fracture surgery were initially treated with fondaparinux sodium 2.5 mg once daily for 7 ± 1 days. At the end of this period, 326 patients were randomized to receive fondaparinux sodium 2.5 mg once daily and 330 to placebo in a double-blind trial for 21 ± 2 days; 81 patients were not eligible for randomization. Patients ranged in age from 23 to 96 years (mean age 75 years) and were 29% men and 71% women. Patients were 99% Caucasian and 1% other races. Patients undergoing standard surgery for fracture of the upper third of the femur or the femoral head and neck not more than 48 hours after admission were entered unless they had, mainly, active and significant bleeding, bleeding disorders, creatinine level above 180 mol/L (2.0 mg/dL), received other anticoagulants between admission and surgery and diagnosed deep vein thrombus or pulmonary emboli (PE) during screening or prerandomization period.

The primary efficacy endpoint was the composite of the following adjudicated VTE outcomes, evaluated during the randomization period up to day 24: symptomatic DVT and/or adjudicated non-fatal PE, and mandatory venogram positive for VTE. The efficacy data are provided in Table 18 below and demonstrate that extended prophylaxis with fondaparinux sodium was associated with a VTE rate of 1.4% compared with a VTE rate of 35.0% for placebo for a relative risk reduction of 95.9% (95% CI=[-99.7; -87.2], $p < 0.0001$). Major bleeding episodes for non-randomized and randomized patients are provided in Table 3 (see **ADVERSE REACTIONS, Hemorrhage**).

Table 18 Efficacy of Fondaparinux sodium Injection In the Extended Prophylaxis Period (Day 7 ± 1 to Day 28 ± 2) Number and Percentage of thromboembolic events in patients who had undergone hip fracture surgery one week earlier.¹

Endpoint	Fondaparinux sodium 2.5 mg SC once daily	Placebo SC once daily
All Randomized Treated Hip Fracture Surgery Patients	N=326	N=330
All Randomized Evaluable Hip Fracture Surgery Patients²		
VTE ³	3/208 1.4% ⁴ (0.3, 4.2) ⁵	77/220 35.0% (28.7, 41.7)
All DVT	3/208 1.4% ⁴ (0.3, 4.2)	74/218 33.9% (27.7, 40.6)
Proximal DVT	2/221 0.9% ⁴ (0.1, 3.2)	35/222 15.8% (11.2, 21.2)
Symptomatic VTE	1/326 0.3% ⁶ (0.1, 1.7)	9/330 2.7% (1.3, 5.1)

¹ During the one week pre-randomization period preceding the Extended Prophylaxis Period all patients had been treated with open-label fondaparinux sodium 2.5 mg SC once daily.

² Evaluable patients were those who were treated in the post-randomization period, with an adequate efficacy assessment up to Day 24 following randomization.

³ VTE was a composite of documented DVT and/or documented symptomatic PE reported up to Day 24 following randomization.

⁴ p-value <0.001

⁵ Number in parentheses indicates 95% confidence interval

⁶ p-value = 0.021

Prophylaxis of Thromboembolic Events following Hip Replacement Surgery

Table 19 Summary of patient demographics for clinical trials in the prophylaxis of thromboembolic events following hip replacement surgery

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n=number)	Mean age (Range)	Gender
1	Randomized, double-blind	2.5 mg fondaparinux subcutaneous once daily vs. 30 mg enoxaparin bid.	2275	65 (18-92)	48% men 52% women
2	Randomized, double-blind	2.5 mg fondaparinux subcutaneous once daily vs. 40 mg enoxaparin once daily	2309	65 (24-97)	42% men 58% women

In two randomized, double-blind, clinical trials in patients undergoing hip replacement surgery, fondaparinux sodium 2.5 mg SC once daily was compared to either enoxaparin sodium 30 mg SC every 12 hours (Study 1) or to enoxaparin sodium 40 mg SC once a day (Study 2). The dose of enoxaparin sodium approved for prophylaxis in conjunction with orthopedic surgery in Canada is 30 mg SC twice daily. In Study 1, a total of 2,275 patients were randomized and 2,257 were treated. Patients ranged in age from 18 to 92 years (mean age 65 years) with 48% men and 52% women. Patients were 94% Caucasian, 4% Black, <1% Asian, and 2% others. In Study 2, a total of 2,309 patients were randomized and 2,273 were treated. Patients ranged in age from 24 to 97 years (mean age 65 years) with 42% men and 58% women. Patients were 99% Caucasian, and 1% other races. Patients with serum creatinine level more than 180 µmol/L (2 mg/dL), or platelet count less than 100,000/mm³ were excluded from both trials.

In Study 1, fondaparinux sodium was initiated 6 ± 2 hours (mean 6.5 hrs) after surgery in 92% of patients and enoxaparin sodium was initiated 12 to 24 hours (mean 20.25 hrs) after surgery in 97% of patients. In Study 2, fondaparinux sodium was initiated 6 ± 2 hours (mean 6.25 hrs) after surgery in 86% of patients and enoxaparin sodium was initiated 12 hours before surgery in 78% of patients. The first post-operative enoxaparin sodium dose was given before 12 hours after surgery in 60% of patients and 12 to 24 hours after surgery in 35% of patients with a mean of 13 hrs. For both studies, both study treatments were continued for 7 ± 2 days. Efficacy results are provided in Table 20 below. Major bleeding episodes for both drugs are provided in Table 1 and Table 2 (see **ADVERSE REACTIONS**).

Table 20 Efficacy Results of study in the prophylaxis of thromboembolic events following hip replacement surgery

Endpoint	Study 1		Study 2	
	Fondaparinux sodium 2.5 mg SC once daily ¹	Enoxaparin 30 mg SC every 12 hr ²	Fondaparinux sodium 2.5 mg SC once daily ¹	Enoxaparin 40 mg SC once daily ³
All Treated Hip Replacement Surgery Patients				
	N=1126	N=1128	N=1129	N=1123
All Evaluable ⁴ Hip Replacement Surgery Patients				
VTE ⁵	48/787 6.1% ⁶ (4.5, 8.0) ⁷	66/797 8.3% (6.5, 10.4)	37/908 4.1% ⁹ (2.9, 5.6)	85/919 9.2% (7.5, 11.3)
All DVT	44/784 5.6% ⁸ (4.1, 7.5)	65/796 8.2% (6.4, 10.3)	36/908 4.0% ⁹ (2.8, 5.4)	83/918 9.0% (7.3, 11.1)
Proximal DVT	14/816 1.7% ⁶ (0.9, 2.9)	10/830 1.2% (0.6, 2.2)	6/922 0.7% ⁹ (0.2, 1.4)	23/927 2.5% (1.6, 3.7)
Symptomatic PE	5/1126 0.4% ⁶ (0.1, 1.0)	1/1128 0.1% (0.0, 0.5)	2/1129 0.2% ⁶ (0.0, 0.6)	2/1123 0.2% (0.0, 0.6)

¹ Patients randomized to fondaparinux sodium 2.5 mg were to receive the first injection 6 ± 2 hours after surgery providing that hemostasis had been achieved.

² Patients randomized to enoxaparin sodium were to receive the first injection between 12 and 24 hours after surgery.

³ Patients randomized to enoxaparin sodium were to receive the first injection 12 hours prior to surgery except in the case of spinal anesthesia. The first post-operative enoxaparin sodium dose was to be given between 12 to 24 hours after surgery.

⁴ Evaluable patients were those who were treated and underwent the appropriate surgery (i.e. elective hip replacement surgery), with an adequate efficacy assessment up to Day 11.

⁵ VTE was a composite of documented DVT and/or documented symptomatic PE reported up to Day 11.

⁶ p-value versus enoxaparin sodium: NS

⁷ Number in parentheses indicates 95% confidence interval

⁸ p-value versus enoxaparin sodium in study 1: <0.05

⁹ p-value versus enoxaparin sodium in study 2: <0.01

Prophylaxis of Thromboembolic Events following Knee Replacement Surgery

Table 21 Summary of patient demographics for clinical trials in the prophylaxis of thromboembolic events following knee replacement surgery

Trial design	Dosage, route of administration and duration	Study subjects (n=number)	Mean age (Range)	Gender
Randomized, double-blind	2.5 mg fondaparinux subcutaneous once daily vs. 30 mg enoxaparin SC bid.	1049	68 (19-94)	41% men 59% women

In a randomized, double-blind, clinical trial in patients undergoing knee replacement surgery (i.e., surgery requiring resection of the distal end of the femur or proximal end of the tibia),

fondaparinux sodium 2.5 mg SC once daily was compared to enoxaparin sodium 30 mg SC every 12 hours. A total of 1,049 patients were randomized and 1,034 were treated.

Patients ranged in age from 19 to 94 years (mean age 68 years) with 41% men and 59% women. Patients were 88% Caucasian, 8% Black, <1% Asian, and 3% others. Patients with serum creatinine level more than 180 µmol/L (2 mg/dL), or platelet count less than 100,000/mm³ were excluded from the trial. Fondaparinux sodium was initiated 6 ± 2 hours (mean 6.25 hrs) after surgery in 94% of patients and enoxaparin sodium was initiated 12 to 24 hours (mean 21 hrs) after surgery in 96% of patients. For both drugs, treatment was continued to 7 ± 2 days. Efficacy results are provided in Table 22 below. Major bleeding episodes for both drugs are provided in Table 1 and Table 2 (see **ADVERSE REACTIONS**).

Table 22 Efficacy Results of study in the prophylaxis of thromboembolic events following knee replacement surgery

Endpoint	Fondaparinux sodium ¹	Enoxaparin ²
All treated Knee Replacement Surgery Patients	N=517	N=517
All Evaluable³ Knee Replacement Surgery Patients		
VTE ⁴	45/361 12.5% ⁵ (9.2, 16.3) ⁶	101/363 27.8% (23.3, 32.7)
All DVT	45/361 12.5% ⁵ (9.2, 16.3)	98/361 27.1% (22.6, 32.0)
Proximal DVT	9/368 2.4% ⁷ (1.1, 4.6)	20/372 5.4% (3.3, 8.2)
Symptomatic PE	1/517 0.2% ⁷ (0.0, 1.1)	4/517 0.8% (0.2, 2.0)

¹ Patients randomized to fondaparinux sodium 2.5 mg received the first injection 6 ± 2 hours after surgery providing that hemostasis had been achieved.

² Patients randomized to enoxaparin sodium received the first injection at 21 ± 2 hours after surgery closure providing that hemostasis had been achieved.

³ Evaluable patients were those who were treated and underwent the appropriate surgery (i.e. knee replacement surgery), with an adequate efficacy assessment up to Day 11.

⁴ VTE was a composite of documented DVT and/or documented symptomatic PE reported up to Day 11.

⁵ p-value <0.001

⁶ Number in parentheses indicates 95% confidence interval

⁷ p-value: NS

Prophylaxis of Thromboembolic Events following Abdominal Surgery

In a double-blind, double-dummy clinical trial, 2,927 patients at high risk of thromboembolic complication while undergoing abdominal surgery were randomized to fondaparinux sodium 2.5 mg SC once daily started 6 hours postoperatively or dalteparin sodium 5,000 IU SC once daily (2,500 IU SC 2 hours before and a 2,500 IU SC 12 hours after operation on the first day). Both treatments were given for 5 to 9 days to 2,858 patients who were then followed-up for one

month. Patients were 17 to 93 years (mean age 65 years), 55% were men and 97% were Caucasian. Patients undergoing urological (other than kidney), gynaecological, vascular, or laparoscopic surgery were excluded.

While it had been originally planned to include any patients at high risk of venous thromboembolic events (VTE) when undergoing abdominal surgery, it was noted during a blinded review of the data that VTE rate was lower than expected. It was then decided to recruit mainly cancer patients as these patients have a higher risk of VTE. Sixty-nine percent (69%) of study patients underwent cancer-related abdominal surgery.

The study was initially designed to show superiority of fondaparinux sodium over dalteparin. Assuming a frequency of VTE of 7% with dalteparin, 1,000 evaluable patients per treatment group would give a power greater than 75% to detect a targeted relative risk reduction of 40%. However, it was observed early after the start of the study that the VTE rate was much lower than anticipated and that since this trend continued until the end, it became evident that superiority could not be demonstrated. The Steering Committee decided at the very end, but before database lock-up and un-blinding, to also perform a non-inferiority analysis. The results of two meta-analyses were used to determine the non-inferiority margin. One meta-analysis evaluated the effects of perioperative administration of subcutaneous heparin compared to placebo on VTE and pulmonary embolism. The other and more pertinent meta-analysis used the results of studies comparing the effects of low molecular weight heparins and heparin on VTE in patients undergoing general and cancer surgery. An indirect confidence interval method was used to select a non-inferiority margin of 1.7 (odds ratio) which corresponds to preserving 63% of the minimal effect expected with low molecular weight heparins.

In all evaluable patients (N=2,058), the incidence of total venous thromboembolic events with fondaparinux sodium was 4.6% (47/1,027) and with dalteparin was 6.1% (62/1,021) for an absolute risk reduction of 1.5% and odds ratio reduction of 25.8% (95% CI: -9.5%, +49.7%). The difference in total VTE between the two groups was not statistically significant and was mainly due to a reduction in asymptomatic distal deep vein thrombosis (DVT). The incidence of symptomatic DVT was similar between the groups: 6/1,027 (0.4%) in the fondaparinux sodium group and 5/1,021 (0.3%) in the dalteparin group. In patients undergoing cancer surgery, 69% of the 2058 evaluable patients, the VTE rate was 4.7% in the fondaparinux sodium group and 7.7% in the dalteparin group.

Major bleeding was observed in 3.4% (49/1,433) of the fondaparinux sodium treated patients and 2.4% (34/1,425) of the dalteparin-treated patients. For other bleeding events see Table 4 under ADVERSE REACTIONS - Prophylaxis of VTE following abdominal surgery. See also **WARNINGS AND PRECAUTIONS** - Renal - *Prophylaxis of VTE following orthopedic or abdominal surgery*.

Treatment of Deep Vein Thrombosis and Pulmonary Embolism

The fondaparinux sodium clinical program in treatment of venous thromboembolism was designed to demonstrate the efficacy of fondaparinux sodium for the treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE). Over 4,874 patients were studied in controlled Phase II and III clinical studies.

Treatment of Deep Vein Thrombosis

Table 23 Summary of patient demographics for clinical trial in the treatment of Deep Vein Thrombosis

Trial design	Dosage, route of administration and duration	Study subjects (n=number)	Mean age (Range)	Gender
Randomized, double-blind	5 mg (body wt < 50 kg) 7.5 mg (body wt 50 -100 kg) 10 mg (body wt > 100 kg) fondaparinux subcutaneous once daily vs. 1 mg/kg enoxaparin SC every 12 hours	2205	61 (18-95)	53% men 47% women

In a randomized, double-blind, clinical trial in patients with a confirmed diagnosis of acute symptomatic DVT, fondaparinux sodium 5 mg (body weight < 50 kg), 7.5 mg (body weight 50-100 kg) or 10 mg (body weight > 100 kg) SC once daily (fondaparinux sodium treatment regimen) was compared to enoxaparin sodium 1 mg/kg SC every 12 hours in both hospitalized and non-hospitalized patients. Outpatient and home treatment of fondaparinux sodium was permitted, and approximately 32% of patients were discharged home from the hospital while receiving fondaparinux therapy.

A total of 2,205 patients were randomized and 2,192 were treated. Patients ranged in age from 18-95 years (mean age 61 years) with 53% men and 47% women. Patients were 97% Caucasian, 2% Black and 1% other races. For both groups, treatment continued for at least 5 days, and both treatment groups received Vitamin K antagonist therapy initiated within 72 hours after the first study drug administration and continued for 90 ± 7 days, with regular dose adjustments to achieve an INR of 2-3. The primary efficacy endpoint was confirmed, symptomatic, recurrent VTE reported up to Day 97. Treatment with fondaparinux sodium was associated with a VTE rate of 3.9% compared with a VTE rate of 4.1% for enoxaparin sodium. The efficacy data are provided in Table 24 below.

Table 24 Efficacy of Fondaparinux sodium Injection In the Treatment of Deep Vein Thrombosis

Endpoint	Fondaparinux sodium ¹ 5, 7.5 or 10 mg SC once daily (Treatment Regimen)	Enoxaparin Sodium ¹ 1 mg/kg SC q 12h
All Randomized DVT Patients	N=1098	N=1107
Total VTE ²	43 ³ (3.9%)	45 (4.1%)
DVT only	18 (1.6%)	28 (2.5%)
Non-fatal PE	20 (1.8%)	12 (1.1%)
Fatal VTE	5 (0.5%)	5 (0.5%)

¹ Patients were also treated with vitamin K antagonists initiated within 72 hours after the first study drug administration.

² VTE was a composite of symptomatic recurrent VTE or fatal VTE reported up to Day 97.

³ The 95% confidence interval for the treatment difference for total VTE was: -1.8% to 1.5%.

Treatment of Pulmonary Embolism

Table 25 Summary of patient demographics for clinical trial in the treatment of Pulmonary Embolism

Trial design	Dosage, route of administration and duration	Study subjects (n=number)	Mean age (Range)	Gender
Randomized, open label	5 mg (body wt < 50 kg) 7.5 mg (body wt 50 -100 kg) 10 mg (body wt > 100 kg) fondaparinux subcutaneous once daily vs. heparin IV bolus (5000 units) followed by aPPT adjusted continuous IV infusion	2213	62 (18-97)	44% men 56% women

In a randomized, open-label, clinical trial in patients with a confirmed diagnosis of acute symptomatic PE, with or without DVT, fondaparinux sodium 5 mg (body weight < 50 kg), 7.5 mg (body weight 50-100 kg) or 10 mg (body weight > 100 kg) SC once daily (fondaparinux sodium treatment regimen) was compared to heparin IV bolus (5,000 units) followed by a continuous IV infusion adjusted to maintain 1.5-2.5 times aPTT control value.

Outpatient and home treatment of fondaparinux sodium was permitted, and approximately 15% of patients were discharged home from the hospital while receiving fondaparinux therapy.

A total of 2,213 patients were randomized and 2,184 were treated. Patients ranged in age from 18-97 years (mean age 62 years) with 44% men and 56% women. Patients were 94% Caucasian, 5% Black and 1% other races. For both groups, treatment continued for at least 5 days, and both treatment groups received Vitamin K antagonist therapy initiated within 72 hours after the first study drug administration and continued for 90 ± 7 days, with regular dose adjustments to achieve an INR of 2-3. The primary efficacy endpoint was confirmed, symptomatic, recurrent

VTE reported up to Day 97. Treatment with fondaparinux sodium was associated with a VTE rate of 3.8% compared with a VTE rate of 5.0% for unfractionated heparin. The efficacy data are provided in Table 26 below.

Table 26 Efficacy of Fondaparinux sodium Injection In the Treatment of Pulmonary Embolism

Endpoint	Fondaparinux sodium ¹ 5, 7.5 or 10 mg SC once daily (Treatment Regimen)	Heparin ¹ aPTT adjusted IV
All Randomized PE Patients	N=1103	N=1110
Total VTE ²	42 ³ (3.8%)	56 (5.0%)
DVT only	12 (1.1%)	17 (1.5%)
Non-fatal PE	14 (1.3%)	24 (2.2%)
Fatal VTE	16 (1.5%)	15 (1.4%)

¹ Patients were also treated with vitamin K antagonists initiated within 72 hours after the first study drug administration.

² VTE was a composite of symptomatic recurrent VTE or fatal VTE reported up to Day 97.

³ The 95% confidence interval for the treatment difference for total VTE was: -3.0% to 0.5%.

Management of Unstable Angina or Non-ST Segment Elevation Myocardial Infarction (UA/NSTEMI)

In a randomized, double-blind, outcome trial, OASIS 5, 20,078 subjects presenting to hospital with suspected UA/NSTEMI acute coronary syndrome and at least 2 of 3 risk criteria (aged ≥60 years, troponin T or I or CK-MB above the upper limit of normal, or ECG changes compatible with ischemia) were randomized to fondaparinux sodium (n=10,057) or enoxaparin (n=10,021) within 24 hours of the most recent episode of symptoms. Patients were to be eligible for anticoagulation treatment.

Table 27 Summary of Patient Demographics in OASIS 5^{1,2}

Trial design	Dosage, route of administration and duration	Study subjects (n=number)	Mean age (Range)	Gender
Randomized, double-blind, non-inferiority outcome trial	2.5 mg fondaparinux SC once daily for up to 8 days or discharge 1 mg/kg enoxaparin SC twice daily (once daily if creatinine clearance was between 20 mL/min and 30 mL/min) for 2-8 days or until clinically stable	20078	67 (21-98)	62% men 38% women

¹ 45% of subjects had UA, and 55% had NSTEMI.

² 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 insufficiency, respectively, at randomization.

Patients received standard medical care for UA/NSTEMI including acetylsalicylic acid, clopidogrel/ ticlopidine, GPIIb/IIIa inhibitors, as well as percutaneous coronary intervention (PCI) or coronary artery bypass graft (CABG) surgery, where appropriate. Patients undergoing PCI received either a single pre-procedural dose of fondaparinux sodium intravenously (fondaparinux sodium treatment arm) or unfractionated heparin intravenously (enoxaparin treatment arm) using an algorithm based on the time of the previous subcutaneous dose and whether GPIIb/IIIa inhibitors were planned. Subcutaneous study drug was resumed after PCI if possible. Patients undergoing CABG surgery had study drug temporarily stopped 24 hours prior to surgery and restarted 48 hours post surgery, if possible.

The objective of the study was to determine whether fondaparinux sodium was non-inferior to enoxaparin within 9 days of randomization based on the primary composite endpoint of death, myocardial infarction (MI) and refractory ischemia (RI) (see Table 28).

Table 28 Efficacy of Fondaparinux sodium in the Treatment of UA/NSTEMI up to Day 9 in OASIS 5 (All Randomized Patients)

Endpoint	Fondaparinux sodium ¹ N=10 057	Enoxaparin ² N=10 021	Hazard Ratio (95% CI)
Death or MI or RI ³	579 (5.8%)	574 (5.7%)	1.01 (0.90, 1.13) ⁴
Death	177 (1.8%)	186 (1.9%)	0.95 (0.77, 1.17)
MI	263 (2.6%)	264 (2.6%)	0.99 (0.84, 1.18)
RI	194 (1.9%)	189 (1.7%)	1.02 (0.84, 1.25)

¹ Patients randomized to fondaparinux sodium received 2.5 mg fondaparinux SC once daily for up to 8 days or discharge.

² Patients randomized to enoxaparin sodium received 1 mg/kg enoxaparin SC twice daily (once daily if creatinine clearance was between 20 mL/min and 30 mL/min) for 2-8 days or until clinically stable.

³ The primary endpoint was a composite of death, myocardial infarction (MI) and refractory ischemia (RI) within 9 days of randomization.

⁴ p=0.003, one-sided non-inferiority.

Fondaparinux sodium was as effective as enoxaparin in reducing the risk of death, MI or refractory ischemia at Day 9 (see Table 28 and Table 29). The treatment effect observed for the components was consistent with that for the overall composite endpoint (see Table 28).

At 6 month follow-up, the benefit of fondaparinux sodium was maintained (Table 29).

Table 29 Efficacy of Fondaparinux sodium for the Prevention of Death, MI or RI in UA/NSTEMI up to Day 180 in OASIS 5 (All Randomized Patients)

Endpoint	Fondaparinux sodium ¹ N=10 057	Enoxaparin ² N=10 021	Hazard Ratio (95% CI)	P-value
Day 9 ³	579 (5.8%)	574 (5.7%)	1.019 (0.90, 1.13)	p=0.923 ⁴
Day 14	658 (6.5%)	701 (7.0%)	0.94 (0.84, 1.04)	p=0.222
Day 30	806 (8.0%)	865 (8.6%)	0.93 (0.84, 1.02)	p=0.127
Day 90	1044 (10.4%)	1112 (11.1%)	0.93 (0.86, 1.02)	p=0.110
Day 180	1223 (12.2%)	1309 (13.1%)	0.93 (0.86, 1.00)	p=0.063

¹ Patients randomized to fondaparinux sodium received 2.5 mg fondaparinux SC once daily for up to 8 days or discharge.

² Patients randomized to enoxaparin sodium received 1 mg/kg enoxaparin SC twice daily (once daily if creatinine clearance was between 20 mL/min and 30 mL/min) for 2-8 days or until clinically stable.

³ The primary endpoint was a composite of death, myocardial infarction (MI) and refractory ischemia (RI) within 9 days of randomization.

⁴ p=0.003, one-sided non-inferiority.

In the management of UA/NSTEMI with fondaparinux sodium, the risk of all cause mortality up to Day 180 is reported in Table 30.

Table 30 Efficacy of Fondaparinux sodium for the Prevention of All Cause Mortality in UA/NSTEMI up to Day 180 in OASIS 5 (All Randomized Patients)

Endpoint	Fondaparinux sodium ¹ N=10 057	Enoxaparin ² N=10 021	Hazard Ratio (95% CI)	P-value
Day 9	177 (1.8%)	186 (1.9%)	0.95 (0.77, 1.17)	0.614
Day 14	211 (2.1%)	242 (2.4%)	0.87 (0.72, 1.04)	0.135
Day 30	295 (2.9%)	352 (3.5%)	0.83 (0.71, 0.97)	0.022
Day 90	460 (4.6%)	510 (5.1%)	0.90 (0.79, 1.02)	0.089
Day 180	574 (5.7%)	638 (6.4%)	0.89 (0.80, 1.00)	0.052

¹ Patients randomized to fondaparinux sodium received 2.5 mg fondaparinux SC once daily for up to 8 days or discharge.

² Patients randomized to enoxaparin sodium received 1 mg/kg enoxaparin SC twice daily (once daily if creatinine clearance was between 20 mL/min and 30 mL/min) for 2-8 days or until clinically stable.

The rates of major bleeding episodes for UA/NSTEMI patients treated with fondaparinux sodium vs. enoxaparin are provided in Table 6 and Table 7 (see **ADVERSE REACTIONS**).

In patients undergoing PCI during the initial hospitalization, the relative effects of fondaparinux sodium and enoxaparin on death, MI or refractory ischemia and on major bleeding at Day 9 were consistent with that observed for the overall population (see Table 31 and Table 32). However, in patients undergoing PCI, the incidence of guiding catheter thrombosis, although rare, was higher in patients treated with fondaparinux sodium compared to enoxaparin (see **WARNINGS AND PRECAUTIONS, Cardiovascular, and ADVERSE REACTIONS, Management of UA/NSTEMI, Risk of catheter thrombosis during PCI**).

Table 31 Efficacy of Fondaparinux sodium by PCI Usage during Initial Hospitalisation up to Day 9 and Day 180 in OASIS 5 (All Randomized Patients)

		Fondaparinux sodium			Enoxaparin			HR (95% CI)
Death/MI/RI*		n	N	%	n	N	%	
Day 9	Overall	579	10057	5.8	574	10021	5.7	1.01 (0.90, 1.13)
PCI use:	Yes	305	3454	8.8	282	3435	8.2	1.08 (0.92, 1.27)
	No	274	6597	4.2	292	6585	4.4	0.94 (0.79, 1.10)
Day 180	Overall	1223	10057	12.2	1309	10021	13.1	0.93 (0.86, 1.00)
PCI use:	Yes	448	3454	13.0	438	3435	12.8	1.02 (0.89, 1.16)
	No	775	6597	11.7	871	6585	13.2	0.88 (0.80, 0.97)
Death/MI								
Day 9	Overall	409	10057	4.1	412	10021	4.1	0.99 (0.86, 1.13)
PCI use:	Yes	196	3454	5.7	185	3435	5.4	1.05 (0.86, 1.29)
	No	213	6597	3.2	227	6585	3.4	0.94 (0.78, 1.13)
Day 180	Overall	1042	10057	10.4	1127	10021	11.2	0.92 (0.84, 1.00)
PCI use:	Yes	332	3454	9.6	333	3435	9.7	0.99 (0.85, 1.16)
	No	710	6597	10.8	794	6585	12.1	0.89 (0.80, 0.98)
Death alone								
Day 9	Overall	177	10057	1.8	186	10021	1.9	0.95 (0.77, 1.17)
PCI use:	Yes	37	3454	1.1	38	3435	1.1	0.97 (0.62, 1.52)
	No	140	6597	2.1	148	6585	2.2	0.94 (0.75, 1.19)
Day 180	Overall	574	10057	5.7	638	10021	6.4	0.89 (0.80, 1.00)
PCI use:	Yes	113	3454	3.3	121	3435	3.5	0.93 (0.72, 1.20)
	No	461	6597	7.0	517	6585	7.9	0.89 (0.78, 1.01)

* The primary endpoint was a composite of death, myocardial infarction (MI) and refractory ischemia (RI) up to and including Day 9

Table 32 Adjudicated Major Bleeding by PCI Usage during Initial Hospitalisation (As Treated Patients) in OASIS 5

		Fondaparinux sodium			Enoxaparin			HR (95% CI)	P-value
		n	N	%	n	N	%		
On Therapy¹	Overall	183	9979	1.8	389	9969	3.9	0.38 (0.29, 0.49)	<0.001
PCI use:	Yes	66	3422	1.9	165	3410	4.8	0.39 (0.29, 0.52)	
	No	117	6555	1.8	224	6559	3.4	0.51 (0.41, 0.64)	
Day 9	Overall	209	9979	2.1	406	9969	4.1	0.51 (0.43, 0.60)	<0.001
PCI use:	Yes	74	3422	2.2	169	3410	5.0	0.43 (0.33, 0.57)	
	No	135	6555	2.1	237	6559	3.6	0.57 (0.46, 0.70)	

¹ The on therapy period was from the start of dosing at randomization until 2 days post the last injection.

Management of ST segment Elevation Myocardial Infarction (STEMI)

In OASIS 6 a randomized, double-blind, outcome trial, fondaparinux sodium was compared to usual care (placebo or UFH) in 12,092 subjects presenting to hospital with STEMI acute coronary syndrome within 12 hours of symptom onset. Randomization was stratified according to whether UFH was indicated based on the judgement of the investigator. A total of 5,658 patients were enrolled in Stratum 1 who received fondaparinux sodium (n=2,823) or placebo (n=2,835) and 6,434 patients were enrolled in Stratum 2 who received fondaparinux sodium (n=3,213) or UFH (n=3,221).

Table 33 Summary of Patient Demographics in OASIS 6¹

Trial design	Dosage, route of administration and duration	Study subjects (n=number)	Mean age (Range)	Gender
Randomized, double-blind, superiority outcome trial	2.5 mg fondaparinux SC once daily for up to 8 days or discharge, initial dose 2.5 mg IV bolus Usual care Stratum 1: placebo Stratum 2: UFH 60 IU/kg IV bolus followed by 12 IU/kg/hr infusion for 24-48 hours (IV bolus only in primary PCI patients)	12 092	61 (22-96)	72% men 28% women

¹ 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 insufficiency, respectively, at randomization.

The primary adjudicated endpoint was a composite of death and reinfarction (recurrent myocardial infarction) within 30 days of randomization. The results for fondaparinux sodium compared to control (UFH or placebo combined) at Day 30 were 9.7% vs. 11.1% for death or myocardial reinfarction (p=0.008), 7.8% vs. 8.9% for death (all cause mortality) (p=0.023), and 2.3% vs. 2.8% for myocardial reinfarction (p=0.069) (see Table 34).

Table 34 Efficacy of Fondaparinux sodium in the treatment of STEMI up to Day 30 in OASIS 6 (All Randomized Patients)

Endpoint	Overall			Stratum 1			Stratum 2		
	Fondaparinux sodium ¹ N=6036	Control ² N=6056	Hazard Ratio ³ (95% CI)	Fondaparinux sodium N=2823	Placebo ⁵ N=2835	Hazard Ratio ³ (95% CI)	Fondaparinux sodium N=3213	UFH N=3221	Hazard Ratio ³ (95% CI)
Death/ Reinfarction ⁴	584 (9.7%)	675 (11.1%)	0.86 (0.77, 0.96)	318 (11.3%)	396 (14.0%)	0.80 (0.60, 0.93)	266 (8.3%)	279 (8.7%)	0.94 (0.79, 1.11)
Death	470 (7.8%)	541 (8.9%)	0.87 (0.77, 0.98)	257 (9.1%)	321 (11.3%)	0.80 (0.68, 0.94)	213 (6.6%)	220 (6.8%)	0.95 (0.79, 1.15)
Reinfarction	141 (2.3%)	172 (2.8%)	0.81 (0.65, 1.02)	74 (2.6%)	92 (3.2%)	0.79 (0.58, 1.07)	67 (2.1%)	80 (2.5%)	0.83 (0.60, 1.15)

¹ Patients randomized to fondaparinux sodium received an IV bolus injection of 2.5 mg followed by 2.5 mg by SC injection daily for up to 8 days or discharge.

² Patients randomized to UFH received an IV bolus injection 60 IU/kg followed by an infusion of 12 IU/kg/hr for 24 to 48 hours.

³ The hazard ratio, fondaparinux sodium versus control, was adjusted for treatment group and strata.

⁴ The primary endpoint was a composite of death and reinfarction within 30 days of randomization.

⁵ Placebo patients did not receive unfractionated heparin as an anticoagulant.

The treatment effect was greater with fondaparinux sodium than with control (UFH or placebo combined) in reducing the risk of death or reinfarction at Day 30 (see Table 34). The treatment effect observed for the components was consistent with that for the overall composite endpoint (see Table 34). At 6 month follow-up, the benefit of fondaparinux sodium was maintained (see Table 35).

Table 35 Efficacy of Fondaparinux sodium for the Prevention of Death or Reinfarction in STEMI up to 6 months in OASIS 6 (All Randomized Patients)

Endpoint	Overall			Stratum 1			Stratum 2		
	Fondaparinux sodium ¹ N=6036	Control ² N=6056	Hazard Ratio ³ (95% CI)	Fondaparinux sodium N=2823	Placebo ⁴ N=2835	Hazard Ratio ³ (95% CI)	Fondaparinux sodium N=3213	UFH ² N=3221	Hazard Ratio ³ (95% CI)
Day 9	443 (7.3%)	536 (8.9%)	0.82 (0.73, 0.93)	240 (8.5%)	314 (11.1%)	0.76 (0.64, 0.90)	203 (6.3%)	222 (6.9%)	0.91 (0.75, 1.10)
Day 30	584 (9.7%)	675 (11.1%)	0.86 (0.77, 0.96)	318 (11.3%)	396 (14.0%)	0.80 (0.69, 0.93)	266 (8.3%)	279 (8.7%)	0.94 (0.79, 1.11)
Day 90	683 (11.3%)	796 (13.1%)	0.85 (0.77, 0.94)	369 (13.1%)	441 (15.6%)	0.83 (0.72, 0.95)	314 (9.8%)	355 (11.0%)	0.87 (0.75, 1.02)
Day 180	756 (12.5%)	855 (14.1%)	0.88 (0.79, 0.97)	414 (14.7%)	469 (16.5%)	0.87 (0.77, 1.00)	342 (10.6%)	386 (12.0%)	0.87 (0.75, 1.01)

¹ Patients randomized to fondaparinux sodium received an IV bolus injection of 2.5 mg followed by 2.5 mg by SC injection daily for up to 8 days or discharge.

² Patients randomized to UFH received an IV bolus injection 60 IU/kg followed by an infusion of 12 IU/kg/hr for 24 to 48 hours.

³ The hazard ratio, fondaparinux sodium versus control, was adjusted for treatment group and strata.

⁴ Placebo patients did not receive unfractionated heparin as an anticoagulant.

In the management of STEMI with fondaparinux sodium, the risk of all cause mortality up to Day 180 is reported in Table 36.

Table 36 Efficacy of Fondaparinux sodium for the Prevention of Adjudicated Death (All Cause Mortality) in STEMI up to 6 months in OASIS 6 (All Randomized Patients)

Endpoint	Overall			Stratum 1			Stratum 2		
	Fondaparinux sodium ¹ N=6036	Control ² N=6056	Hazard Ratio ³ (95% CI)	Fondaparinux sodium N=2823	Placebo ⁴ N=2835	Hazard Ratio ³ (95% CI)	Fondaparinux sodium N=3213	UFH N=3221	Hazard Ratio ³ (95% CI)
Day 9	368 (6.1%)	426 (7.0%)	0.86 (0.75, 0.99)	202 (7.2%)	252 (8.9%)	0.80 (0.66, 0.96)	166 (5.2%)	174 (5.4%)	0.95 (0.77, 1.17)
Day 30	470 (7.8%)	541 (8.9%)	0.87 (0.77, .98) ⁶	257 (9.1%)	321 (11.3%)	0.80 (0.68, 0.94)	213 (6.6%)	220 (6.8%)	0.95 (0.79, 1.15)
Day 90	545 (9.0%)	634 (10.5%)	0.86 (0.76, 0.96)	301 (10.7%)	354 (12.5%)	0.85 (0.73, 0.99)	244 (7.6%)	280 (8.7%)	0.86 (0.72, 1.02)
Day 180	599 (9.9%)	675 (11.1%)	0.88 (0.79, 0.99)	336 (11.9%)	375 (13.2%)	0.89 (0.77, 1.04)	263 (8.2%)	300 (9.3%)	0.87 (0.73, 1.02)

¹ Patients randomized to fondaparinux sodium received an IV bolus injection of 2.5 mg followed by 2.5 mg by SC injection daily for up to 8 days or discharge.

² Patients randomized to UFH received an IV bolus injection 60 IU/kg followed by an infusion of 12 IU/kg/hr for 24 to 48 hours.

³ The hazard ratio, fondaparinux sodium versus control, was adjusted for treatment group and strata.

⁴ Placebo patients did not receive unfractionated heparin as an anticoagulant.

The results for the primary endpoint (death or reinfarction) at Day 30 by reperfusion strategy are presented in Table 37.

Table 37 Efficacy of Fondaparinux sodium for the Prevention of Adjudicated Death or Reinfarction in STEMI up to Day 30 in OASIS 6 by Initial Reperfusion Strategy (All Randomized Patients)

Endpoint	Fondaparinux sodium (N=6036)	Control (N=6056)	Hazard Ratio (95% CI)
Overall (primary endpoint)	584 (9.7%)	675 (11.1%)	0.86 (0.77, 0.96) ¹
Reperfusion Strategy			
No reperfusion	176/1452 (12.1%)	211/1405 (15.0%)	0.79 (0.65, 0.97)
Thrombolytic Agent	295/2695 (10.9%)	373/2742 (13.6%)	0.79 (0.68, 0.93)
- Fibrin specific	50/425 (11.8%)	54/443 (12.2%)	0.98 (0.67, 1.44)
- Non-fibrin specific	244/2267 (10.8%)	318/2298 (13.8%)	0.77 (0.65, 0.90)
Primary PCI	113/1889 (6.0%)	91/1909 (4.8%)	1.26 (0.96, 1.66)
Patients receiving Thrombolytics or No reperfusion ²			
Overall	471/4147 (11.4%)	584/4147 (14.1%)	0.80 (0.70, 0.90)
- Stratum 1 ³ :	318/2813 (11.3%)	395/2828 (14.0%)	0.80 (0.69, 0.92)
- Stratum 2 ⁴	153/1334 (11.5%)	189/1319 (14.3%)	0.79 (0.64, 0.98)

¹ p-value versus control: 0.008

² Patients not undergoing primary PCI

³ UFH Not Indicated

⁴ UFH Indicated

The rates of major bleeding episodes for STEMI patients treated with fondaparinux sodium vs. control (UFH/placebo) are provided in Table 9 (see **ADVERSE REACTIONS**).

The results for major bleeding by initial reperfusion strategy are presented in Table 38.

Table 38 Major Bleeding in the OASIS 6 study by Initial Reperfusion Strategy (As Treated Patients)

Endpoint	Fondaparinux sodium	Control	Hazard Ratio (95% CI)
On-therapy			
Overall	99/5954 (1.7)	120/5947 (2.0)	0.82 (0.63, 1.07)
Reperfusion Strategy			
No reperfusion	16/1415 (1.1)	24/1367 (1.8)	0.64 (0.34, 1.20)
Thrombolytic Agent	47/2676 (1.8)	66/2711 (2.4)	0.72 (0.49, 1.04)
- Fibrin specific	10/420 (2.47)	18/443 (4.2)	0.58 (0.27, 1.26)
- Non-fibrin specific	37/2253 (1.6)	48/2277 (2.1)	0.77 (0.50, 1.18)
Primary PCI	36/1863 (1.9)	30/1869 (1.6)	1.21 (0.74, 1.96)
Patients receiving Thombolytics or No reperfusion ¹			
Overall	63/4091 (1.5)	90/4078 (2.2)	0.69 (0.50, 0.95)
- Stratum 1 ²	40/2802 (1.4)	53/2813 (1.9)	0.75 (0.50, 1.13)
- Stratum 2 ³	23/1289 (1.8)	37/1265 (2.9)	0.61 (0.36, 1.02)
By Day 9			
Overall	104/5954 (1.7)	128/5947 (2.1)	0.81 (0.62, 1.05)
Reperfusion Strategy			
No reperfusion	17/1415 (1.2)	24/1367 (1.8)	0.68 (0.36, 1.26)
Thrombolytic Agent	47/2676 (1.8)	73/2711 (2.7)	0.65 (0.45, 0.93)
- Fibrin specific	10/420 (2.4)	18/433 (4.2)	0.58 (0.27, 1.26)
- Non-fibrin specific	37/2253 (1.6)	55/2277 (2.4)	0.67 (0.44, 1.01)
Primary PCI	40/1863 (2.1)	31/1869 (1.7)	1.30 (0.81, 2.08)
Patients receiving Thombolytics or No reperfusion ¹			
Overall	64/4091 (1.6)	97/4078 (2.4)	0.65 (0.47, 0.89)
- Stratum 1 ²	39/2802 (1.4)	58/2813 (2.1)	0.67 (0.45, 1.00)
- Stratum 2 ³	25/1289 (1.9)	39/1265 (3.1)	0.63 (0.38, 1.03)

¹ Patients not undergoing primary PCI

² UFH Not Indicated

³ UFH Indicated

DETAILED PHARMACOLOGY

Effect on thrombosis in animal models

Fondaparinux has potent dose-dependent antithrombotic activity in a variety of models of experimental thrombosis.

The inhibitory activity varies according to the nature of the thrombotic stimulus and the location of the thrombus i.e. venous (low shear) and arterial (high shear).

Antithrombotic activity is generally achieved at concentrations below those required to saturate plasma ATIII concentrations, with the exception of the inhibition of the thromboplastin-induced thromboembolism which occurs at doses far above antithrombin III-saturating levels. The duration of the antithrombotic activity is correlated with that of anti-factor Xa activity.

Safety Pharmacology

Fondaparinux sodium:

- Showed no relevant effects on the central nervous system
- Did not affect body weight, body temperature and gastro-intestinal motility
- Had no significant effect on electrolyte balance
- Did not induce relevant changes in cardiovascular and respiration parameters
- Did not affect coagulation time, defined as aPTT and PT (see **PRECAUTIONS - Coagulation Tests**), blood cell counts, hemoglobin concentration and hematocrit in animals
- Had little effect on bleeding in the subdermal bleeding model in the rat and in the ear bleeding model in the rabbit at doses that are 25 times higher than the dose resulting in the saturation of antithrombin III (0.8 mg/kg)
- Did not bind to Human Platelet Factor 4 (unlike heparin) and did not cross-react with Heparin Induced Thrombocytopenic (HIT) sera from HIT-patients.
- Did not influence lipid metabolism through the release of triglyceride lipase activity in rats (unlike heparin)

TOXICOLOGY

Acute Toxicity

Single subcutaneous or intravenous doses of 40 mg/kg were well tolerated in mice, rats and monkeys. No lethal effects were observed. This dose represents up to 1200 times the recommended human dose.

Long Term Toxicity

Repeated dose toxicity studies were performed in rats and monkeys at dose levels of 0.4, 2 and 10 mg/kg/d, up to 12, 60 and 300 times the recommended human doses. Fondaparinux had low toxicity and induced mainly an increase of the trauma-related hemorrhage.

Small numbers of animal deaths were due to hemorrhage and hematomas. These were primarily attributed to repeated injection traumas and to the pharmacological activity of the compound.

In monkey studies, some large hematomas were also observed at handling sites, blood puncture and anaesthetic injection sites.

Carcinogenicity

Fondaparinux has not been tested for its carcinogenic potential in long-term animal studies.

Mutagenicity

Fondaparinux was not mutagenic in the *in vitro* Ames Test nor the mouse lymphoma cell (L5178Y/TK^{+/+}) forward mutation test. Fondaparinux was not clastogenic in the human lymphocyte chromosomal aberration test, rat hepatocyte unscheduled DNA synthesis (UDS) test or in the *in vivo* rat micronucleus test.

Reproduction and Teratology

Fondaparinux at doses up to 10 mg/kg/day (i.e. doses up to 280 times the human daily doses) did not impair the reproduction parameters studied: rat mating performance and fertility, rat and rabbit gestation and embryo-fetal development and rat parturition, lactation, new-born viability and growth, F1 behaviour and reproduction and F2 fetal development.

The main treatment-related findings were hematomas and hemorrhage at the injection site. The only other treatment-related finding noted was one fatality associated with hematoma and changes in liver and lungs.

Very low placental transfer and very limited excretion in the milk were demonstrated in rats.

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IMPORTANT: PLEASE READ

PART III: CONSUMER INFORMATION

PrFONDAPARINUX SODIUM INJECTION
2.5 mg/0.5 mL, 5.0 mg/0.4 mL, 7.5 mg/0.6 mL, and
10.0 mg/0.8 mL

This leaflet is part III of a three-part "Product Monograph" published when Fondaparinux Sodium Injection was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about Fondaparinux Sodium Injection. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:

Fondaparinux Sodium Injection is a synthetic antithrombotic agent (against blood clotting). An antithrombotic drug helps prevent clots from forming in the blood. Fondaparinux Sodium Injection sodium is used:

- to prevent the occurrence of venous thromboembolic events (blood clots in the blood vessels of the legs or lungs) for up to one month post-surgery in patients undergoing orthopedic surgery of the lower limbs (hip fracture, knee surgery or hip replacement surgery);
- to prevent the occurrence of venous thromboembolic events (blood clots in the blood vessels of the legs or lungs) in patients undergoing abdominal surgery;
- to treat acute deep vein thrombosis (blood clots in a deep vein of the legs) and acute pulmonary embolism (blood clots in the blood vessels of the lungs);
- for the management of unstable angina or non-ST segment elevation myocardial infarction (severe chest pain and a type of heart attack);
- for the management ST segment elevation myocardial infarction (severe heart attack).

What it does:

Fondaparinux Sodium Injection contains fondaparinux sodium, a synthetic compound, that inhibits specifically a clotting factor and plays an important role in blood coagulation. It helps to prevent the development of unwanted blood clots (thrombosis) in blood vessels and is useful in dissolving existing blood clots.

When it should not be used:

Do not take Fondaparinux Sodium Injection if:

- You are allergic to fondaparinux sodium or to any non-medicinal ingredient in the formulation;
- You have thrombocytopenia (an abnormally small number of platelets in the circulating blood) associated with a positive lab test for anti-platelet protective protein in the presence of fondaparinux sodium (see your doctor);
- You are bleeding excessively;
- You suffer from bacterial infection of the heart.

What the medicinal ingredient is:

Fondaparinux sodium

What the nonmedicinal ingredients are:

Isotonic solution of sodium chloride and water for injection. Also contain sodium hydroxide or hydrochloric acid for pH adjustment (pH 5.5-8).

What dosage forms it comes in:

Fondaparinux Sodium Injection is a solution for injection supplied in a sterile prefilled syringe affixed with an active needle protection to help prevent needle injuries after use.

Package of 10:

Single-dose, prefilled syringes containing either 2.5 mg/0.5 mL, 5 mg/0.4 mL, 7.5 mg/0.6 mL or 10 mg/0.8 mL of fondaparinux.

IMPORTANT: PLEASE READ

WARNINGS AND PRECAUTIONS

It is important that you provide your doctor with an accurate history of any serious illnesses you may have had in the past or any current medical conditions, as these may influence the action of Fondaparinux Sodium Injection.

BEFORE you use Fondaparinux Sodium Injection, talk to your doctor or pharmacist if:

- You weigh less than 50 kg or are 65 years of age or older.
- You have had or currently suffer from any of the following conditions listed below, it is necessary that you inform your doctor before starting treatment.
 - You suffer from bacterial infection of the heart;
 - You are bleeding excessively;
 - You have a risk of hemorrhage (uncontrolled bleeding), such as:
 - stomach ulcer;
 - bleeding disorders;
 - recent intracranial bleeding;
 - You have had recent brain, spinal column or eye surgery;
 - You have liver disease;
 - You have kidney disease.

Pregnancy and Breast-feeding

If you are pregnant or breast-feeding, you should tell your doctor so that the possible risks to you and your child can be assessed.

Pediatrics

The safety and effectiveness of Fondaparinux Sodium Injection in children under the age of 17 has not been established.

It is necessary that you follow the instructions of your doctor or nurse carefully. Only give yourself the injections prescribed and do so the entire time period specified by your doctor.

INTERACTIONS WITH THIS MEDICATION

Some other medicines may affect the way Fondaparinux Sodium Injection works or vice versa. Please tell your doctor or pharmacist what medicine you have recently taken, are taking or intend to take since these medicines might affect blood clotting, even those available without prescription such as acetylsalicylic acid (i.e. ASPIRIN®). If you should see another doctor or a dentist while you are using Fondaparinux Sodium Injection, you should inform/tell them that you are using Fondaparinux Sodium Injection.

PROPER USE OF THIS MEDICATION

Usual dose:

Fondaparinux Sodium Injection is a prescription drug and must be used as directed. Fondaparinux Sodium Injection is given by injection under the skin (subcutaneously) into a skin fold of the lower stomach area. For a step-by-step 'Instructions for use' please see below. Do not inject Fondaparinux Sodium Injection into muscle (intramuscularly).

While you are in the hospital, your doctor or a nurse will give your first injection. It is possible that after you go home, you may need to continue your injections of Fondaparinux Sodium Injection for a few days.

For prevention of blood clots following orthopedic or abdominal surgery:

The usual dose of Fondaparinux Sodium Injection is 2.5 mg once a day.

For treatment of blood clots:

The usual dose of Fondaparinux Sodium Injection is 5 mg (body weight < 50 kg), 7.5 mg (body weight 50-100 kg) or 10 mg (body weight > 100 kg) once daily.

IMPORTANT: PLEASE READ

In the management of heart attacks or severe angina:

The usual dose of Fondaparinux Sodium Injection is 2.5 mg once daily.

You should continue Fondaparinux Sodium Injection treatment for as long as your doctor has told you, since Fondaparinux Sodium Injection decreases the risk of developing more serious conditions.

Always use Fondaparinux Sodium Injection exactly as your doctor has instructed you. You should check with your doctor or pharmacist if you are unsure.

The different parts of Fondaparinux Sodium Injection safety syringe are:

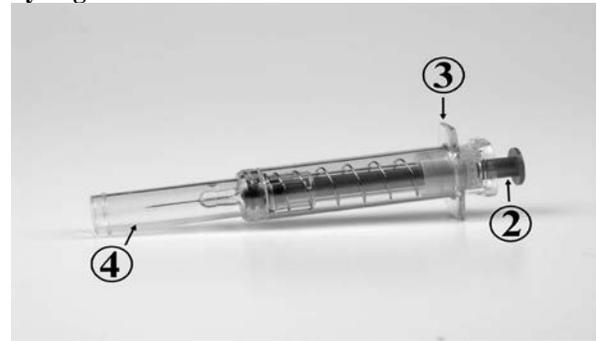
- 1. Rigid needle Shield**
- 2. Plunger**
- 3. Finger-grip**
- 4. Security sleeve**



Syringe BEFORE USE



Syringe AFTER USE



IMPORTANT: PLEASE READ

Instructions for self-injection of fondaparinux sodium:

1. Wash your hands thoroughly with soap and water. Towel dry. When at home, there is nothing for you to prepare. The syringe is pre-filled with the exact amount of drug required. Do not press on the plunger prior to injection.



Figure A

2. Sit or lie down in a comfortable position. Choose a spot on the lower stomach area (abdomen), at least 5 centimeters below your belly button (Figure A). Change (alternate) between using the left and right side of the lower abdomen for each injection. If injecting in the stomach area is not possible or you have any questions, consult your nurse or doctor for instruction.

3. Clean the injection area with an alcohol swab.

4. Remove the needle shield by pulling it straight off the syringe (Figure B). Discard the rigid needle shield.

To prevent infection, do not touch the needle or let it come in contact with any surface before the injection. A small air bubble in the syringe is normal. To be sure that you do not lose any medicine from the syringe, do not try to remove air bubbles from the syringe before giving the injection.

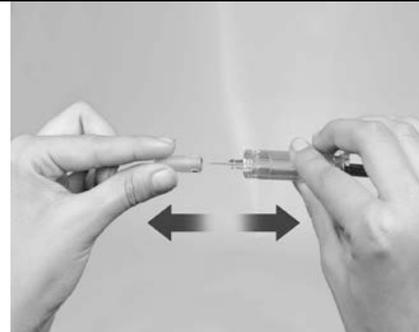


Figure B

5. Gently pinch the skin that has been cleaned to make a fold. Hold the fold between the thumb and the forefinger of one hand during the entire injection (Figure C).



Figure C

6. Hold the syringe firmly in your other hand using the finger-grip. Insert the full length of the needle directly up and down (at an angle of 90°) into the skin fold (Figure D).



Figure D

IMPORTANT: PLEASE READ

Instructions for self-injection of fondaparinux sodium:

7. Inject all of the medicine in the syringe by pressing down on the plunger as far as it goes. (Figure E).



Figure E

8. Remove the syringe from the injection site keeping your finger on the plunger.



Figure F

9. Orient the needle away from you and others, and activate the safety shield by firmly pushing the plunger. The protective sleeve will automatically cover the needle and an audible "click" will be heard to confirm shield activation.



Figure G

Discard the used syringe into a sharps container as your nurse or doctor has instructed you.

Follow the instructions given to you by your nurse or doctor about the right way to throw away used syringes and needles. There may be laws about the right way to dispose of used syringes, needles, and disposal containers.

NOTE:

- The safety system can only be activated once the syringe has been emptied.
- Activation of the safety system must be done only after removing the needle from the patient's skin.
- Do not replace the needle shield after injection.
- The safety system should not be sterilized.
- Activation of the safety system may cause minimal splatter of fluid. For optimal safety activate the system while orienting it downwards away from yourself and others.

IMPORTANT: PLEASE READ

Overdose:

If you think you have taken too much Fondaparinux Sodium Injection, contact your healthcare professional, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

Missed Dose:

NEVER inject a double dose to make up for forgotten individual doses. If you are not sure what to do, ask your doctor or pharmacist before you take any action.

If you stop treatment before your doctor told you to, you are at risk of developing a blood clot in a vein of your leg or in the lung. Contact your doctor or pharmacist before stopping treatment if for any reason you feel you need to stop the treatment.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Fondaparinux Sodium Injection helps most people in the prevention of blood clots. However, like all medicines it may have unwanted effects on some people.

The most common side effect that may occur in up to one in every 10 people is bleeding. Any bleeding can be serious, if this occurs you should contact your doctor urgently. Other common side effects are edema (swelling) and insomnia (trouble sleeping).

Uncommon side effects that may occur in up to one in every 100 people are: Headache, nausea (feeling sick), vomiting, rash, itchy skin, wound secretion (oozing) blood coagulation disorders, low platelet count and fever.

Rare side effects that may occur in up to one in every 1,000 people are: Anxiety, confusion, dizziness, coughing, indigestion, stomach pain, constipation, diarrhea, skin reactions at injection site (mild irritation, pain, bruising and redness), tiredness, flushing, somnolence (drowsiness), vertigo (feeling of spinning), dyspnea (shortness of breath), fatigue, and syncope (loss of consciousness).

If you notice any unwanted effects not mentioned, please inform your doctor or pharmacist.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect	Talk with your doctor or pharmacist		Stop taking drug and seek immediate emergency medical attention
	Only if severe	In all cases	
Common	A low number of red blood cells which can cause tiredness, weakness, shortness of breath and feeling generally unwell	√	
	Bleeding from various sites (i.e., from an operation site, bruising, blood in urine and stool, an existing stomach ulcer, nosebleed, etc.)		√
	Bruises that are joining together	√	
	Urinary tract infection (pain or burning sensation during urination, frequent urge to urinate)		√
Uncommon	Liver problems (symptoms include nausea, vomiting, loss of appetite, yellowing of the skin or eyes, dark urine and unusual tiredness)		√
Rare	Wound infection at site of surgery (oozing of fluid, swelling around the wound)		√
	Allergic reactions such as rash or itching, swelling (usually of the face, lips, tongue or throat) which may cause difficulty breathing or swallowing or collapse		√ immediately

IMPORTANT: PLEASE READ

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect		Talk with your doctor or pharmacist		Stop taking drug and seek immediate emergency medical attention
		Only if severe	In all cases	
Rare	Reduction of potassium in the blood (hypokalemia) which can cause muscular weakness and cramping		√	
	Low blood pressure (if measured) which can result in lightheadedness, dizziness or fainting		√	
	Chest pain		√	
	Leg pain		√	

Additionally, Fondaparinux Sodium Injection may also cause some side effects which can only be diagnosed by your health care provider and may require blood tests, for example: reduction or increase in the number of platelets (blood cells necessary for blood clotting), abnormal blood clotting (coagulation disorder) or bleeding around the brain or internal organs.

This is not a complete list of side effects. For any unexpected effects while taking Fondaparinux Sodium Injection, contact your doctor or pharmacist.

HOW TO STORE IT

Fondaparinux Sodium Injection should be stored at 15°C - 30°C. Do not freeze. Keep out of the reach and sight of children.

Do not use Fondaparinux Sodium Injection under the following conditions:

- after the expiry date stated on the label and carton;
- if you notice that particulate matter or discoloration is present in the solution;
- if you notice that the syringe is damaged;
- if you have opened a syringe and do not intend to use it straight away.

Any unused syringe should be disposed of in a safe manner.

Reporting Side Effects

You can help improve the safe use of health products for Canadians by reporting serious and unexpected side effects to Health Canada. Your report may help to identify new side effects and change the product safety information.

3 ways to report:

- Online at MedEffect (<http://hc-sc.gc.ca/dhp-mps/medeff/index-eng.php>);
- By calling 1-866-234-2345 (toll-free);
- By completing a Consumer Side Effect Reporting Form and sending it by:
 - Fax to 1-866-678-6789 (toll-free), or
 - Mail to: Canada Vigilance Program
Health Canada, Postal Locator
0701E
Ottawa, ON
K1A 0K9

Postage paid labels and the Consumer Side Effect Reporting Form are available at MedEffect (<http://hc-sc.gc.ca/dhp-mps/medeff/index-eng.php>).

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

IMPORTANT: PLEASE READ

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be found at:

DIN Owner:

Dr. Reddy's Laboratories Limited

Bachupally – 500 090 INDIA

1-855-845-1739

Canadian Importer/Distributor:

Innomar Strategies Inc.

3470 Superior Court

Oakville, Ontario L6L 0C4

CANADA

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