

DIVITI

Prefilled syringe injection



WARNING: SPINAL/EPIDURAL HEMATOMAS

Epidural or spinal hematomas may occur in patients who are anticoagulated with low molecular weight heparins (LMWH), heparinoids, or fondaparinux sodium and are receiving neuraxial anesthesia or undergoing spinal puncture. These hematomas may result in long-term or permanent paralysis. Consider these risks when scheduling patients for spinal procedures. Factors that can increase the risk developing epidural or spinal hematomas in these patients include:

- use of indwelling epidural catheters,
- concomitant use of other drugs that affect hemostasis, such as nonsteroidal anti-inflammatory drugs (NSAIDs), platelet inhibitors, or other anticoagulants
- a history of traumatic or repeated epidural or spinal puncture
- a history of spinal deformity or spinal surgery

Monitor patients frequently for signs and symptoms of impairment. If neurologic compromise is noted, urgent treatment is necessary. Consider the benefit and risks before neuraxial intervention in patients anticoagulated or to be anticoagulated for thromboprophylaxis (See Warnings and precautions and Drug interactions).

Composition:
Each 0.5 ml injection contains
Fondaparinux sodium 2.5 mg

Pharmacology:
Fondaparinux is a synthetic and selective inhibitor of activated factor X (Xa). The antithrombotic activity of fondaparinux is the result of antithrombin III (AT III) mediated selective inhibition of factor Xa. By binding selectively to AT III, fondaparinux potentiates (about 300 times) the innate neutralization of factor Xa by AT III. Neutralization of factor Xa interrupts the blood coagulation cascade and inhibits both thrombin formation and thrombin development.
Fondaparinux does not inactivate thrombin (activated factor II) and has no known effect on platelet function.
At the 2.5 mg dose, fondaparinux 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, nor bleeding time or fibrinolytic activity.
Fondaparinux does not cross-react with sera from patients with heparin induced thrombocytopenia (HIT) type II.

Anti-Xa Activity

The pharmacodynamics/pharmacokinetics of fondaparinux is 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 concentration of fondaparinux is expressed as milligrams of the fondaparinux calibrator/litre.

Pharmacokinetics:

Absorption

After subcutaneous dosing, fondaparinux is completely and rapidly absorbed (absolute bioavailability 100%). Following a single subcutaneous injection of fondaparinux sodium 2.5 mg, peak plasma concentration, mean C_{max} of 0.34 mg/l is reached in approximately 2 hours. Plasma concentrations of half the mean C_{max} values are reached 25 minutes post-dosing.
In elderly patients, pharmacokinetics of fondaparinux is linear in the range of 2 to 8 mg by subcutaneous route. Following once daily subcutaneous dosing, steady state of plasma levels is obtained after 3 to 4 days with a 1.3-fold increase in C_{max} and AUC.
Following a single intravenous bolus administration to healthy elderly, the pharmacokinetics of fondaparinux is linear over the therapeutic range. In patients undergoing hip replacement surgery receiving fondaparinux sodium 2.5 mg once daily subcutaneously, the peak steady-state plasma concentration is, on average, 0.39 to 0.50 mg/l and is reached approximately 3 hours post-dose. In these patients, the minimum steady-state plasma concentration is 0.14 to 0.19 mg/l.

Distribution

Intravenously or subcutaneously administered fondaparinux distributes mainly in blood and only to a minor extent in extravascular fluid, as demonstrated by steady state and non-steady state apparent volume of distribution of 7 to 11 l. *In vitro*, fondaparinux is highly (at least 94%) and specifically bound to antithrombin III (AT III) and does not bind significantly to other plasma proteins, including platelet factor 4 (PF4) or red blood cells.

Metabolism

In vivo metabolism of fondaparinux has not been investigated since the majority of the administered dose is eliminated unchanged in urine in individuals with normal kidney function.

Elimination

Fondaparinux is eliminated in urine mainly as unchanged drug. The elimination half-life is about 17 hours in young patients and about 21 hours in elderly. In patients with normal renal function, the mean fondaparinux clearance is 7.82 ml/minute.

Special patient populations

Renal impairment

Fondaparinux elimination is prolonged in patients with renal impairment 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 impairment (creatinine clearance 50 to 80 ml/minute), approximately 40% lower in patients with moderate renal impairment (creatinine clearance 30 to 50 ml/minute) and approximately 55% lower in patients with severe renal impairment (less than 30 ml/minute), 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 impairment. A similar relationship between fondaparinux clearance and extent of renal impairment was observed in DVT treatment patients. Due to the limited clinical data available, fondaparinux sodium should not be used in patients with severe renal impairment (see **Warnings and precautions**).

Hepatic impairment

Fondaparinux pharmacokinetics have not been studied in patients with hepatic impairment.

Children

The use of fondaparinux sodium has not been investigated in children under the age of 17 years.

Elderly

Fondaparinux elimination is prolonged in patients over 75 years old. A similar relationship between fondaparinux clearance and age was observed in DVT treatment patients.

Gender

No gender differences were observed after adjustment for body weight.

Race

Pharmacokinetic differences due to race have not been studied prospectively. Similarly, based on the results of population pharmacokinetic analysis conducted in patients undergoing orthopedic surgery, no plasma clearance differences were observed between black and Caucasian patients.

Body weight

In patients weighing less than 50 kg the total clearance of fondaparinux sodium is decreased by approximately 30% (see **Warnings and precautions**).

Indications:

- Prevention of venous thromboembolic events (VTE) in patients undergoing major orthopedic surgery of the lower limbs such as hip fracture including extended prophylaxis, knee replacement surgery, hip replacement surgery.
- Prevention of venous thromboembolic events (VTE) in patients undergoing abdominal surgery who are at risk of thromboembolic complications.
- Prevention of venous thromboembolic events (VTE) in medical patients who are at risk for VTE and who are thromboembolic complications due to restricted mobility during acute illness.

Contraindications:

- Patients with known hypersensitivity to fondaparinux sodium or any of the excipients of this drug.
- Active clinically significant bleeding.
- Acute bacterial endocarditis.
- Severe renal impairment defined by creatinine <20 ml/minute.

Dosage and administrations:

Dosage

Orthopedic and abdominal surgery.
The recommended dose of fondaparinux sodium is 2.5 mg once daily, administered postoperatively by subcutaneous injection. The timing of the first dose should be no earlier than 6 hours following surgical closure, and only after hemostasis has been established (see **Warnings and precautions**).
Treatment should be continued until the risk of venous thromboembolism has diminished, usually until the patient is ambulant, at least 5 to 9 days after surgery.
Experience shows that in patients undergoing hip fracture surgery, the risk of VTE continues beyond 9 days after surgery. In these patients the use of prolonged prophylaxis with fondaparinux sodium should be considered for up to an additional 24 days.

Medical patients at risk of thromboembolic complications:

The recommended dose of fondaparinux sodium is 2.5 mg once daily administered by subcutaneous injection. Treatment duration is about 6 to 14 days.

Special populations

Children

The safety and efficacy of fondaparinux sodium in patients under the age of 17 has not been established.

Elderly (from 75 years)

Fondaparinux sodium should be used with caution in elderly patients as renal function decreases with age (see **renal impairment, Warnings and precautions**). In patients undergoing surgery, the timing of the first dose of fondaparinux sodium requires strict adherence (see **Warnings and precautions**).

Patients with body weight less than 50 kg

Patients with body weight below 50 kg are at increased risk of bleeding (see **Warnings and precautions**). In patients undergoing surgery, the timing of the first dose of fondaparinux sodium requires strict adherence (see **Warnings and precautions**).

Renal impairment

Fondaparinux sodium should not be used in patients with severe (creatinine clearance less than 30 ml/minute) renal impairment (see **Warnings and precautions**). No dosage reduction is required for patients with mild or moderate renal impairment. In patients undergoing surgery, the timing of the first dose of fondaparinux sodium requires strict adherence.

Hepatic impairment

No dosing adjustment of fondaparinux sodium is necessary (see **Pharmacokinetics**). In patients with severe hepatic impairment, fondaparinux sodium should be used with caution (see **Warnings and precautions**).

Administration

Subcutaneous injection

The sites of subcutaneous injection should alternate between the left and the right anterolateral and left and right posterolateral abdominal wall. To avoid the loss of medicinal product when using the prefilled syringe do not expel the air bubble from the syringe before the injection. The whole length of the needle should be inserted perpendicularly into a skin fold held between the thumb and the forefinger. The skin fold should be held throughout the injection.

Fondaparinux sodium 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. Instruction for self-administration is included in the package leaflet (see **Instructions for use/handling**).

Warnings and precautions:

Route of administration

Fondaparinux sodium must not be administered intramuscularly.

Hemorrhage

Fondaparinux sodium, like other anticoagulants should be used with caution in conditions with an increased risk of hemorrhage (such as congenital or acquired bleeding disorders, active ulcerative gastrointestinal disease, recent intracranial hemorrhage, shortly after brain, spinal or ophthalmic surgery).

Agents enhancing the risk of hemorrhage should not be administered concomitantly with fondaparinux. These agents include desirudin, fibrinolytic agents, GP IIb/IIIa receptor antagonists, heparin, heparinoids, or low molecular weight heparin (LMWH). Other antiplatelet medicinal products (acetylsalicylic acid, dipyridamole, sulfapyrazone, ticlopidine or clopidogrel), and NSAIDs should be used with caution. If coadministration is essential, close monitoring is necessary.

Prevention of VTE

Other medicinal products enhancing the risk of hemorrhage, with the exception of vitamin K antagonists used concomitantly for treatment of VTE, other agents enhancing the risk of hemorrhage should not be administered with fondaparinux sodium. If coadministration is essential, close monitoring is recommended (see **Drug Interactions**).

Prevention of VTE following surgery (timing of the first fondaparinux sodium injection)

The timing of the first injection 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. Patient groups at particular risk are those from 75 years of age, body weight of less than 50 kg, or renal impairment with creatinine clearance less than 50 ml/minute.

Spinal/epidural anesthesia/spinal puncture

Epidural or spinal hematomas that may result in long-term or permanent paralysis can occur with the use of anticoagulants and spinal/epidural anesthesia or spinal puncture. The risk of these rare events may be higher with postoperative use of indwelling epidural catheters or the concomitant use of other medicinal products affecting hemostasis.

Elderly patients

The elderly population is at increased risk of bleeding. As renal function generally decreases with age, elderly patients may show reduced elimination and increased exposure of fondaparinux sodium. Fondaparinux sodium should be used with caution in elderly patients (see **Dosage and administration**).

Low body weight

Patients with body weight less than 50 kg are at increased risk of bleeding. Elimination of fondaparinux sodium decreases with weight decrease. For prophylaxis following surgery fondaparinux sodium should be used with caution in these patients (see **Dosage and administration**).

Renal impairment

The plasma clearance time of fondaparinux increases with the severity of renal impairment, and is associated with an increased risk of hemorrhage (see **Pharmacokinetics**). Due to the limited clinical data available for prevention and treatment of VTE, fondaparinux sodium should not be used in patients with severe renal impairment (creatinine clearance less than 30 ml/minute).

Severe hepatic impairment

In patients with an elevation in prothrombin time, the use of fondaparinux sodium should be considered with caution, because of an increased risk of bleeding due to a possible deficiency of coagulation factors in patients with severe hepatic impairment (see **Dosage and administration**).

Heparin induced thrombocytopenia

Fondaparinux sodium does not bind to platelet factor 4 and does not cross-react with sera from patients with heparin induced thrombocytopenia (HIT) type II and fondaparinux sodium should not be used in such patients.

Pregnancy and lactation

Pregnancy
Fondaparinux sodium should not be prescribed to pregnant women unless the benefit outweighs the risk.

Lactation

Fondaparinux is excreted in rat milk but it is not known whether fondaparinux is excreted in human milk. Breastfeeding is not recommended during treatment with fondaparinux sodium.

Adverse reactions:

Adverse reactions are listed below by system organ class and frequency and indication. Frequencies are defined as: very common ($\geq 1/10$), common ($\geq 1/100$, $< 1/10$), uncommon ($\geq 1/1,000$, $< 1/100$), rare ($\geq 1/10,000$, $< 1/1,000$), very rare ($< 1/10,000$). These adverse reactions should be interpreted within the surgical or medical context of the indications.

Undesirable effects in patients undergoing major orthopedic surgery of lower limbs and/or abdominal surgery:

Infections and infestations

Rare: postoperative wound infections.

Blood and lymphatic system disorders

Common: anemia, bleeding (various sites including rare cases of intracranial/ intracerebral and retroperitoneal bleedings), purpura.

Uncommon: thrombocytopenia, thrombocytopenia, abnormal platelets, coagulation disorder.

Immune system disorders

Rare: allergic reaction.

Metabolism and nutrition disorders

Rare: hypokalemia.

Nervous system disorders

Uncommon: headache.

Rare: anxiety, confusion, dizziness, somnolence, vertigo.

Vascular disorders

Rare: hypotension.

Respiratory, thoracic and mediastinal disorders

Rare: dyspnea, coughing.

Gastrointestinal disorders

Uncommon: nausea, vomiting.

Rare: abdominal pain, dyspepsia, gastritis, constipation, diarrhea.

Hepatobiliary disorders

Uncommon: abnormal liver function tests, hepatic enzymes increased.

Rare: bilirubinemia.

Skin and subcutaneous tissue disorders

Uncommon: rash, pruritus, wound secretion.

General disorders and administration site conditions

Common: fever, wound secretion, edema peripheral.

Rare: reaction at injection site, chest pain, leg pain, fatigue, edema genital, flushing, syncope.

Undesirable effects in medical patients:

Blood and lymphatic systems disorders

Common: bleeding (hematoma, hematuria, hemoptysis, gingival bleeding).

Uncommon: anemia.

Respiratory, thoracic and mediastinal disorders

Uncommon: dyspnea.

Skin and subcutaneous tissue disorders

Uncommon: rash, pruritus.

General disorders and administration site conditions

Uncommon: chest pain.

Drug interactions:

Fondaparinux does not markedly inhibit CYP450s (CYP1A2, CYP2A6, CYP2C9, CYP2C19, CYP2D6, CYP2E1 or CYP3A4) *in vitro*. Thus, fondaparinux sodium is not expected to interact with other medicinal products *in vivo* by inhibition of CYP-mediated metabolism.

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

Bleeding risk is increased with concomitant administration of fondaparinux and agents that may enhance the risk of hemorrhage (see **Warnings and precautions**).

The concomitant use of warfarin (oral anticoagulant), acetylsalicylic acid (platelet inhibitor), piroxicam (nonsteroidal anti-inflammatory), and digoxin (cardiac glycoside) did not significantly affect the pharmacokinetics or pharmacodynamics of fondaparinux. In addition fondaparinux neither influenced the INR activity of warfarin, nor the bleeding time under acetylsalicylic acid or piroxicam treatment, nor the pharmacokinetics or pharmacodynamics of digoxin at steady state.

Follow-up therapy with another anticoagulant medicinal product. If follow-up treatment is to be initiated with heparin or LMWH, the first injection should, as a general rule, be given one day after the last fondaparinux injection. If follow up treatment with a vitamin K antagonist is required, treatment with fondaparinux should be continued until the target INR value has been reached.

Effects on ability to drive and use machines

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

Overdose:

Symptoms and signs

Fondaparinux sodium doses above the recommended regimen may lead to an increased risk of bleeding.

Treatment

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

Instructions for use/handling:

Parenteral solutions should be inspected visually for particulate matter and discoloration prior to administration. Fondaparinux sodium is administered by subcutaneous or intravenous injection. It must not be administered by intramuscular injection.

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

The fondaparinux sodium prefilled syringe has been designed with an automatic needle protection system to prevent needle stick injuries following injection.

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

Step by step instructions

Parts of the syringes:

1. Needle shield
2. Finger grip
3. Security sleeve
4. Plunger

Instruction for use:

1. Wash your hands thoroughly with soap and water and dry them with a towel.
2. Remove the syringe from the carton and check that:
 - the expiry date has not passed
 - the solution is clear and colorless and doesn't contain particles
 - the syringe has not been opened or damaged
3. Sit or lie down in a comfortable position. Choose a place in the lower abdominal (tummy) area, at least 5 cm below your belly button. Alternate the left and right side of the lower abdominal area at each injection. This will help to reduce the discomfort at the injection site. If injecting in the lower abdominal area is not possible, ask your nurse or doctor for advice.

