Diviti
Solution for injection

Composition:
Each 0.5 ml contains
Fondaparinux sodium 2.5 mg

List of Excipients:
Sodium chloride, hydrochloric acid, water for injection

Product Description:
Clear, colorless to slightly yellow solution.

Pharmacodynamics:
ATC code: B01AX05
Fondaparinux is a synthetic and selective inhibitor of activated factor X (Xa). The antithrombotic activity of fondaparinux is the result of antithrombin III (ATIII) mediated selective inhibition of factor Xa. By binding selectively to ATIII, fondaparinux potentiates (about 300 times) the innate neutralization of factor Xa by ATIII. Neutralization of factor Xa interrupts the blood coagulation cascade and inhibits both thrombin formation and thrombus development.

Fondaparinux does not inactivate thrombin (activated factor II) and has no known effect on platelet function.

At the 2.5 mg dose, fondaparinux does not affect routine coagulation tests, such as activated partial thromboplastin time (aPTT), activated clotting time (ACT) or prothrombin time (PT)/international 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/liter.

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

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

In patients undergoing hip replacement surgery receiving fondaparinux 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 postdose. In these patients, the minimum steady-state plasma concentration is 0.14 to 0.19 mg/L.

In patients with symptomatic deep vein thrombosis and pulmonary embolism undergoing treatment with fondaparinux 5 mg (body weight less than 50 kg), 7.5 mg (body weight 50 to 100 kg) and 10 mg (body weight greater than 100 kg) subcutaneously once daily, the body-weight-adjusted doses provide similar mean steady-state peaks and minimum plasma concentrations across all body weight categories. The mean peak steady-state plasma concentration is in the range of 1.20 to 1.26 mg/L. In these patients, the mean minimum steady-state plasma concentration is in the range of 0.46 to 0.62 mg/L.

Distribution
In healthy adults, 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 (ATIII) 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. In healthy individuals, 64 to 77% of a single subcutaneous or intravenous dose is eliminated in urine in 72 hours. The elimination half-life is about 17 hours in healthy young subjects and about 21 hours in healthy elderly subjects. 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.

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

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

Elderly
Fondaparinux elimination is prolonged in patients over 75 years old. In studies evaluating fondaparinux 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 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. However, studies performed in Asian (Japanese) healthy subjects did not reveal a different pharmacokinetic profile compared to Caucasian healthy subjects. 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**).

Clinical Studies:
***Prevention of venous thromboembolic events (VTE) in patients undergoing major* orthopedic surgery of the lower limbs treated up to 9 days**
The fondaparinux clinical program was designed to demonstrate the efficacy of fondaparinux for the prevention of venous thromboembolic events (VTE), i.e. proximal and distal deep vein thrombosis (DVT) and pulmonary embolism (PE) in patients undergoing major orthopedic surgery of the lower limbs such as hip fracture, major knee surgery or hip replacement surgery. Over 8,000 patients (hip fracture - 1,711, hip replacement - 5,829, major knee surgery - 1,367) were studied in controlled phase II and III clinical studies. Fondaparinux 2.5 mg once daily started 6-8 hours postoperatively was compared with enoxaparin 40 mg once daily started 12 hours before surgery, or 30 mg twice daily started 12-24 hours after surgery.
In a pooled analysis of these studies, the recommended dose regimen of fondaparinux versus enoxaparin was associated with a significant decrease (54%-95% CI, 44 %; 63%) in the rate of VTE evaluated up to day 11 after surgery, irrespective of the type of surgery performed. The majority of endpoint events were diagnosed by a prescheduled venography and consisted mainly of distal DVT, but the incidence of proximal DVT was also significantly reduced. The incidence of symptomatic VTE, including PE was not significantly different between treatment groups.
In studies versus enoxaparin 40 mg once daily started 12 hours before surgery, major bleeding was observed in 2.8% of fondaparinux patients treated with the recommended dose, compared to 2.6% with enoxaparin.

Prevention of venous thromboembolic events (VTE) in patients undergoing hip fracture surgery treated for up to 24 days following an initial prophylaxis of 1 week
In a randomized double-blind clinical trial, 737 patients were treated with fondaparinux 2.5 mg once daily for 7±1 days following hip fracture surgery. At the end of this period, 656 patients were randomized to receive fondaparinux 2.5 mg once daily or placebo for an additional 21±2 days. Fondaparinux provided a significant reduction in the overall rate of VTE compared with placebo [3 patients (1.4%) vs 77 patients (35%), respectively]. The majority (70/80) of the recorded VTE events were venographically detected nonsymptomatic cases of DVT. Fondaparinux also provided a significant reduction in the rate of symptomatic VTE (DVT, and/or PE) [1 (0.3%) vs 9 (2.7%) patients, respectively] including two fatal PE reported in the placebo group. Major bleedings, all at surgical site and none fatal, were observed in 8 patients (2.4%) treated with fondaparinux 2.5 mg compared to 2 (0.6%) with placebo.

Prevention of VTE in patients undergoing abdominal surgery at risk of thromboembolic events
Patients were randomized to receive either fondaparinux 2.5 mg once daily or dalteparin 5,000 IU once daily, with one 2,500 IU preoperative injection and a first 2,500 IU postoperative injection, for 7±2 days following abdominal surgery.
Fondaparinux was noninferior to dalteparin (VTE rates 4.6% versus 6.1%, respectively). The incidence of symptomatic VTE was similar between treatment groups (0.4% on fondaparinux versus 0.3% on dalteparin).

In patients undergoing cancer surgery, representing the major subgroup of the clinical study (69% of the population) the VTE rate was 4.7% in the fondaparinux group versus 7.7% in the dalteparin group.
Major bleeding was observed in 3.4% of the patients in the fondaparinux group and in 2.4% of the dalteparin group. In patients treated with fondaparinux according to the recommended regimen (6 hours after surgery), the rate of major bleeding was 2.8%.

Treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE)
DVT
In patients with a confirmed diagnosis of acute symptomatic DVT, fondaparinux 5 mg (body weight less than 50 kg), 7.5 mg (body weight 50 kg to 100 kg) or 10 mg (body weight greater than 100 kg) once daily, was compared to enoxaparin 1 mg/kg subcutaneously twice daily. Patients were treated for at least 5 days in conjunction with a vitamin K antagonist which was continued for 90±7 days, with regular dose adjustments to achieve an INR of 2 to 3.
Fondaparinux was demonstrated to be noninferior to enoxaparin (VTE rates 3.9% and 4.1% at day 97, respectively). Major bleeding during the initial treatment period was observed in 1.1% of fondaparinux patients, compared to 1.2% with enoxaparin.

PE
In patients with a confirmed diagnosis of acute symptomatic PE, fondaparinux 5 mg (body weight less than 50 kg), 7.5 mg (body weight 50 kg to 100 kg) or 10 mg (body weight greater than 100 kg) once daily, was compared to unfractionated heparin (UFH) IV bolus (5,000 IU), followed by a continuous IV infusion adjusted to maintain 1.5 to 2.5 times aPTT control value. Patients were treated for at least 5 days in conjunction with a vitamin K antagonist which was continued for 90±7 days, with regular dose adjustments to achieve an INR of 2 to 3.
Fondaparinux was demonstrated to be noninferior to UFH (VTE rates 3.8% and 5.0% at day 97, respectively). Major bleeding during the initial treatment period was observed in 1.3% of fondaparinux patients, compared to 1.1% with UFH.

Treatment of unstable angina or non-ST segment elevation myocardial infarction (UA/NSTEMI)
A double-blind, randomized, non-inferiority study (OASIS 5) assessed the safety and efficacy of fondaparinux 2.5 mg subcutaneously once daily versus enoxaparin 1 mg/kg subcutaneously twice daily in approximately 20,000 patients with UA/NSTEMI. The median treatment duration was 6 days in the fondaparinux treatment group and 5 days in the enoxaparin treatment group. The mean age of the patients was 67 years, and approximately 60% were aged at least 65 years. Approximately 40% and 17% of patients had mild (creatinine clearance 50 to less than 80 ml/minute) or moderate (creatinine clearance 30 to less than 50 ml/minute) renal impairment, respectively.

The primary adjudicated endpoint was a composite of death, myocardial infarction (MI) and refractory ischemia (RI) within 9 days of randomization. Fondaparinux was as effective as enoxaparin on the primary endpoint. Of the patients treated with fondaparinux or enoxaparin, 5.8% and 5.7% of patients, respectively experienced an event by day 9 (hazard ratio 1.01, 95% CI, 0.90, 1.13, one-sided non-inferiority p value = 0.003).

There was a 17% reduction in the risk of all-cause mortality in favor of fondaparinux by day 30 (fondaparinux, 2.9%, enoxaparin, 3.5%, hazard ratio 0.83, 95% CI, 0.71, 0.97, p=0.02) that was apparent by day 14 (fondaparinux, 2.1%, enoxaparin, 2.4%, hazard ratio 0.86, 95% CI, 0.72, 1.04, p=0.14) and sustained to day 180 (fondaparinux, 5.7%, enoxaparin, 6.4%, hazard ratio 0.89, 95% CI, 0.80, 1.00, p=0.05). The effects of fondaparinux and enoxaparin on the incidence of MI and RI were similar at all-time points. The efficacy findings were consistent across demographic subgroups, including elderly and renally impaired patients, and across the range of concomitant medications and interventions.

Treatment with fondaparinux was associated with a statistically and clinically significant reduction in the incidence of major bleeding compared to enoxaparin. At day 9 the incidence of major bleeding on fondaparinux and enoxaparin was 2.1% and 4.1%, respectively (hazard ratio 0.52, 95% CI, 0.44, 0.61, p<0.001). The lower incidence of major bleeding on fondaparinux compared to enoxaparin was also observed consistently across demographic subgroups, including elderly and renally impaired patients, and when fondaparinux was used concomitantly with aspirin, thienopyridines or GPIIb/IIIa inhibitors.
In patients undergoing CABG surgery, the incidence of major bleeding at day 9 was similar on fondaparinux and enoxaparin (9.7% and 9.8% respectively).

Treatment of ST segment elevation myocardial infarction (STEMI)
A double blind, randomized study (OASIS 6) assessed the safety and efficacy of fondaparinux 2.5 mg once daily up to 8 days, or until hospital discharge, versus usual care (placebo or UFH) in approximately 12,000 patients with STEMI. All patients received standard treatments for STEMI at the investigators discretion, including reperfusion with primary PCI (31%), thrombolytics (45%) or no reperfusion (24%). The mean age of the patients was 61 years, and approximately 40% were aged at least 65 years. Approximately 40% and 14% of patients had mild (creatinine clearance 50 to less than 80 ml/minute) or moderate (creatinine clearance 30 to less than 50 ml/minute) renal impairment, respectively.

The primary adjudicated endpoint was a composite of death and recurrent myocardial infarction (re-MI) within 30 days of randomization. Fondaparinux was superior to control on the primary endpoint. Of the patients treated with fondaparinux or control, 9.7% and 11.1% respectively experienced an event by day 30 (hazard ratio 0.86, 95% CI, 0.77, 0.96, p=0.008). This statistically significant benefit was observed as early as day 9 and was maintained through day 180.

There was a 13% reduction in the risk of all-cause mortality in favor of fondaparinux at day 30 (fondaparinux, 7.8%, control, 8.9%, hazard ratio 0.87, 95% CI, 0.77, 0.98, p=0.02) that was apparent by day 9 (fondaparinux, 6.1%, control, 7.0%, hazard ratio 0.86, 95% CI, 0.75, 0.99, p=0.04) and sustained to day 180 (fondaparinux, 9.9%, control, 11.1%, hazard ratio 0.88, 95% CI, 0.79, 0.99, p=0.03).

In patients for whom a thrombolytic was chosen as the reperfusion strategy, fondaparinux reduced the risk of death and re-MI at day 30. Of the patients receiving thrombolytics treated with fondaparinux or control, 10.9% and 13.6%, respectively experienced an event by day 30 (hazard ratio 0.79, 95% CI, 0.68, 0.93, p=0.003).

In patients for whom primary PCI was chosen as the reperfusion strategy, there was no efficacy benefit with fondaparinux. The incidence of death and re-MI at day 30 in patients treated with fondaparinux and control were 6.0% and 4.8%, respectively (hazard ratio 1.26, 95% CI, 0.96, 1.66, p=0.1).

In patients who were treated without primary PCI or thrombolytic, fondaparinux reduced the risk of death and re-MI at day 30. Of the patients treated with fondaparinux or control, 12.1% and 15.0% respectively experienced an event by day 30 (hazard ratio 0.79, 95% CI, 0.65, 0.97, p=0.023). The efficacy findings were consistent across demographic subgroups, including elderly and renally impaired patients, and across the range of concomitant medications.

Treatment with fondaparinux was not associated with an increased risk of bleeding in the overall population or in demographic subgroups, including the elderly and renally impaired, and when used concomitantly with aspirin and thienopyridines. Overall, 1.1% of patients treated with fondaparinux and 1.4% of control patients experienced a severe hemorrhage, defined according to modified thrombolysis in myocardial infarction criteria (TIMI), by day 9.

In patients for whom a thrombolytic was chosen as the reperfusion strategy, the incidence of severe hemorrhage at day 9 was 1.3% on fondaparinux and 2.0% on control. In patients for whom primary PCI was chosen as the reperfusion strategy, the incidence of severe hemorrhage at day 9 was 1.0% on fondaparinux and 0.4% on control. In patients who were treated without primary PCI or thrombolytic, the incidence of severe hemorrhage at day 9 was 1.2% on fondaparinux and 1.5% on control.

In patients (n=222) undergoing non-primary PCI, where it was recorded that they received adjunct UFH for anticoagulation during the procedure (238 procedures), the incidence of severe hemorrhage occurring postPCI was low and similar for fondaparinux (1.7%; 4 cases) and control (1.3%; 3 cases) at day 9.

In fondaparinux-treated STEMI patients undergoing non-primary PCI [n=229 (318 procedures)], in whom UFH was recommended for anticoagulation during the procedure, one event of guiding catheter thrombus was reported. However, this patient received UFH as treatment for the event of catheter thrombus rather than prePCI.
Approximately 1% of patients underwent CABG surgery. In these patients the incidence of severe hemorrhage at day 9 was 6.9% on fondaparinux and 17.1% on control.

Preclinical Safety Data:
Preclinical data reveal no special risk for humans based on conventional studies of safety pharmacology, repeated dose toxicity, and genotoxicity. Animal studies are insufficient with respect to effects on toxicity to reproduction because of limited exposure.

Indications:
- Prevention of venous thromboembolic events (VTE) in patients undergoing major orthopedic surgery of the lower limbs such as:
  a. hip fracture,
  b. major knee surgery,
  c. hip replacement surgery.
- Prevention of venous thromboembolic events (VTE) in patients undergoing abdominal surgery who are at risk of thromboembolic complications.
- Treatment of deep vein thrombosis (DVT) and treatment of acute pulmonary embolism (PE) except in hemodynamically unstable patients or patients who require thrombolysis or pulmonary embolectomy.
- Treatment of unstable angina or non-ST segment elevation myocardial infarction (UA/NSTEMI) acute coronary syndrome for the prevention of death, myocardial infarction and refractory ischemia (see **Warnings and Precautions**).
- Treatment of ST segment elevation myocardial infarction (STEMI) acute coronary syndrome for the prevention of death and myocardial reinfarction in patients who are managed with thrombolytics or who initially are to receive no other form of reperfusion therapy (see **Warnings and Precautions**).

Recommended Dosage:
Adults
Prevention of VTE
The recommended dose of DIVITI 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 DIVITI should be considered for up to an additional 24 days.

Treatment of DVT and PE
The recommended dose of DIVITI to be administered by subcutaneous injection once daily is:
- 5 mg for body weight less than 50 kg;
- 7.5 mg for body weight 50 to 100 kg;
- 10 mg for body weight greater than 100 kg.

Treatment should be continued for at least 5 days and until adequate oral anticoagulation is established (international normalized ratio 2 to 3). Concomitant treatment with vitamin K antagonists should be initiated as soon as possible, usually within 72 hours. The usual duration of DIVITI treatment is 5 to 9 days.

Treatment of unstable angina/non-ST segment elevation myocardial infarction (UA/NSTEMI)
The recommended dose of DIVITI is 2.5 mg once daily, administered by subcutaneous injection. Treatment should be initiated as soon as possible following diagnosis and continued for up to 8 days or until hospital discharge. If a patient is to undergo percutaneous coronary intervention (PCI) while on DIVITI, unfractionated heparin (UFH) as per standard practice should be administered during PCI, taking into account the patient's potential risk of bleeding, including the time since the last dose of DIVITI (see **Warnings and Precautions**).

The timing of restarting subcutaneous DIVITI after sheath removal should be based on clinical judgment. In the UA/NSTEMI clinical trial treatment with fondaparinux was restarted no earlier than 2 hours after sheath removal.

In patients who are to undergo coronary artery bypass graft (CABG) surgery, DIVITI where possible, should not be given during the 24 hours before surgery and may be restarted 48 hours postoperatively.

Treatment of ST segment elevation myocardial infarction (STEMI)
The recommended dose of DIVITI is 2.5 mg once daily. The first dose of DIVITI 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. If a patient is to undergo non-primary percutaneous coronary intervention (PCI) while on DIVITI, unfractionated heparin (UFH) as per standard practice should be administered during PCI, taking into account the patient's potential risk of bleeding, including the time since the last dose of DIVITI (see **Warnings and Precautions**).

The timing of restarting subcutaneous DIVITI after sheath removal should be based on clinical judgment. In the STEMI clinical trial 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, DIVITI where possible, should not be given during the 24 hours before surgery and may be restarted 48 hours postoperatively.

Special Populations
The first DIVITI administration should be given not earlier than 6 hours following surgical closure. The injection should not be given unless hemostasis has been established.
- Children
  The safety and efficacy of DIVITI in patients under the age of 17 has not been established.
- Elderly (from 75 years)
  DIVITI 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 DIVITI 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 DIVITI requires strict adherence (see **Warnings and Precautions**).
- Renal impairment
  a. Prevention and treatment of VTE
  In patients undergoing surgery, the timing of the first dose of DIVITI requires strict adherence. DIVITI should be used with caution in patients with moderate renal impairment (creatinine clearance 30-50 ml/minute). DIVITI should not be used in patients with severe (creatinine clearance less than 30 ml/minute) renal impairment (see **Warnings and Precautions**).

68791-00XX-YY
Last revised: dd/mm/yyyy

b. Treatment of UA/NSTEMI and STEMI
DIVITI is not recommended for use in patients with a creatinine clearance of less than 20 ml/minute (see **Warnings and Precautions**). No dosage reduction is required for patients with a creatinine clearance greater than or equal to 20 ml/minute.

- Hepatic impairment
No dosing adjustment of DIVITI is necessary (see **Pharmacokinetics**). In patients with severe hepatic impairment, DIVITI should be used with caution (see **Warnings and Precautions**).

Route of Administrations:
Subcutaneous administration
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.

DIVITI 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 and Disposal**).

Intravenous administration (first dose in STEMI patients only)
Intravenous administration should be through an existing intravenous line either directly or using a small volume (25 or 50 ml) 0.9% saline minibag. 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 intravenous tubing should be well flushed with saline after injection to ensure that all of the medicinal product is administered. If administered via a minibag, the infusion should be given over 1 to 2 minutes.

Contraindications:
- Known hypersensitivity to fondaparinux or any of the excipients.
- Active clinically significant bleeding.
- Acute bacterial endocarditis.
- Severe renal impairment defined by creatinine clearance <30 ml/minute.

Warnings and Precautions:
Route of administration
DIVITI must not be administered intramuscularly (see **Recommended Dosage**)**.** There is limited experience from treatment with fondaparinux in hemodynamically unstable patients and no experience in patients requiring thrombolysis, embolectomy or insertion of a vena cava filter.

PCI and risk of guiding catheter thrombus
In STEMI patients undergoing primary PCI for reperfusion, the use of DIVITI prior to and during PCI is not recommended. In UA/NSTEMI and STEMI patients undergoing non-primary PCI, the use of DIVITI as the sole anticoagulant during PCI is not recommended, therefore UFH should be used according to local practice (see **Recommended Dosage**). There are limited data on the use of UFH during non-primary PCI in patients treated with DIVITI. In those patients who underwent non-primary PCI 6-24 hours after the last dose of fondaparinux, the median dose of UFH was 8,000 IU and the incidence of major bleeding was 2% (2/98). In those patients who underwent non-primary PCI <6 hours after the last dose of fondaparinux, the median dose of UFH was 5,000 IU and the incidence of major bleeding was 4.1% (2/49).

Clinical trials have shown a low but increased risk of guiding catheter thrombus in patients treated solely with fondaparinux for anticoagulation during PCI compared to control. Incidences in non-primary PCI in UA/NSTEMI were 1.0% vs 0.3% (fondaparinux vs enoxaparin) and in primary PCI in STEMI were 1.2% vs 0% (fondaparinux vs control).

Hemorrhage
DIVITI, like other anticoagulants must 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, or in patients treated concomitantly with agents that may enhance the risk of hemorrhage).
- Prevention and treatment of VTE
Other medicinal products enhancing the risk of hemorrhage, with the exception of vitamin K antagonists used concomitantly for treatment of VTE, should not be administered with DIVITI. If coadministration is essential, close monitoring is recommended (see **Interactions with Other Medicines and Other Forms of Interaction**).
- Prevention of VTE following surgery (timing of first DIVITI 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.
- Treatment of UA/NSTEMI and STEMI
DIVITI should be used with caution in patients who are being treated concomitantly with other medicinal products that increase the risk of hemorrhage (such as GPIIb/IIIa inhibitors or thrombolytics).

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 DIVITI. DIVITI should be used with caution in elderly patients (see **Recommended Dosage**).

Low body weight
Patients with body weight less than 50 kg are at increased risk of bleeding. Elimination of DIVITI decreases with weight decrease. DIVITI should be used with caution in these patients (see **Recommended Dosage**).

Renal impairment
The plasma clearance of fondaparinux decreases with the severity of renal impairment, and is associated with an increased risk of hemorrhage (see **Pharmacokinetics**). Due to the limited data available, DIVITI should not be used in patients with a creatinine clearance less than 30 ml/minute. For the treatment of UA/NSTEMI and STEMI, there are limited data available on the use of DIVITI 2.5 mg once daily in patients with creatinine clearance between 20 to 30 ml/minute. Therefore the physician should determine if the benefit of treatment outweighs the risk (see **Recommended Dosage** and **Pharmacokinetics**). DIVITI is not recommended in patients with a creatinine clearance of less than 20 ml/minute.

Severe hepatic impairment
In patients with an elevation in prothrombin time, the use of DIVITI 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 **Recommended Dosage**).

Heparin induced thrombocytopenia
DIVITI does not bind to platelet factor 4 and does not cross-react with sera from patients with heparin induced thrombocytopenia (HIT)-type II. It should be used with caution in patients with a history of HIT. The efficacy and safety of DIVITI have not been formally studied in HIT-type II.

Latex allergy
The needle guard of the prefilled syringe contains dry natural latex rubber that has the potential to cause allergic reactions in latex sensitive individuals.

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.

Interactions with Other Medicines and Other Forms of Interaction:
Fondaparinux does not markedly inhibit CYP450s (CYP1A2, CYP2A6, CYP2C9, CYP2C19, CYP2D6, CYP2E1 or CYP3A4) *in vitro*. Thus, DIVITI 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 ATIII, no interaction with other medicinal products by protein binding displacement are expected.

In clinical studies performed with fondaparinux, 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 DIVITI injection. If follow up treatment with Vitamin K antagonist is required, treatment with fondaparinux should be continued until the target INR value has been reached.

Use during Pregnancy and Lactation:
Pregnancy
There are no adequate data from the use of DIVITI in pregnant women. DIVITI 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 DIVITI.

Adverse Effects:
Adverse reactions are listed below by system organ class and frequency and indication. Frequencies are defined as: very common (≥1/10), common (≥1/100, <1/10), uncommon (≥1/1,000, <1/100), rare (≥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.

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, thrombocythemia, 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 hepatic function, hepatic enzymes increased.
Rare: bilirubinemia.

Skin and subcutaneous tissue disorders
Uncommon: rash, pruritus.

General disorders and administration site conditions
Common: edema.
Uncommon: fever, wound secretion.
Rare: reaction at injection site, chest pain, leg pain, fatigue, flushing, syncope.

Overdose and Treatment:
Symptoms and signs
DIVITI 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.

Incompatibilities:
In the absence of compatibility studies, DIVITI must not be mixed with other medicinal products.

Shelf Life After Reconstitution:
DIVITI solution for injection 2.5 mg/0.5 ml is compatible with 0.9% sodium chloride solution. Chemical and physical in-use stability has been demonstrated for 24 hours at 30°C. From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2 to 8°C, unless dilution has taken place in controlled and validated aseptic conditions.

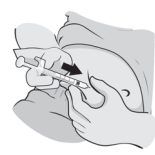
Instructions for Use, Handling and Disposal:
Parenteral solutions should be inspected visually for particulate matter and discoloration prior to administration.
DIVITI is administered by subcutaneous or intravenous injection. It must not be administered by intramuscular injections.
The subcutaneous injection 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 DIVITI 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. Plunger
3. Finger-grip
4. Security sleeve

***Instructions 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.

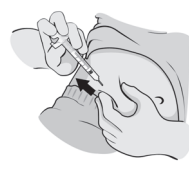
4. Clean the injection area with an alcohol wipe.
5. Gently pinch the skin that has been cleaned to make a fold. Hold the fold between the thumb and the forefinger during the entire injection.

6. Hold the syringe firmly by the finger grip. Insert the full length of the needle at right angles into the skin fold.

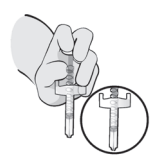


7. Inject all of the contents of the syringe by pressing down on the plunger as far as it goes.

8. After the injection process is complete, pull the syringe from the patient's body and keep the plunger fully depressed.



9. Release the plunger and the needle will automatically go back into the security sleeve where it will be locked permanently.



Do not dispose of the used syringe in the household waste. Dispose of it as your doctor or pharmacist has instructed.

Presentation and Registration Number:
Box, 2 prefilled syringes x 0.5 ml; SINXXXXXX

ON MEDICAL PRESCRIPTION ONLY.

STORE AT OR BELOW 30ºC.

Manufactured by
PT Ferron Par Pharmaceuticals
Cikarang-Indonesia

For
PT Dexa Medica
Jl. Jend. Bambang Utoyo No. 138
Palembang-Indonesia

Date of Review**:** 14 July 2022