CENTER FOR DRUG EVALUATION AND RESEARCH

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FINAL PRINTED LABELING

SPINAL/EPIDURAL HEMATOMAS

When neuraxial anesthesia (epidural/spinal anesthesia) or spinal puncture is employed, patients anticoagulated or scheduled to be anticoagulated with low molecular weight heparins, heparinoids or fondaparinux sodium for prevention of thromboembolic complications are at risk of developing an epidural or spinal hematoma which can result in long-term or permanent paralysis.

The risk of these events is increased by the use of indwelling epidural catheters for administration of analgesia or by the concomitant use of drugs affecting hemostasis such as non steroidal anti-inflammatory drugs (NSAIDs), platelet inhibitors, or other anticoagulants. The risk also appears to be increased by traumatic or repeated epidural or spinal puncture.

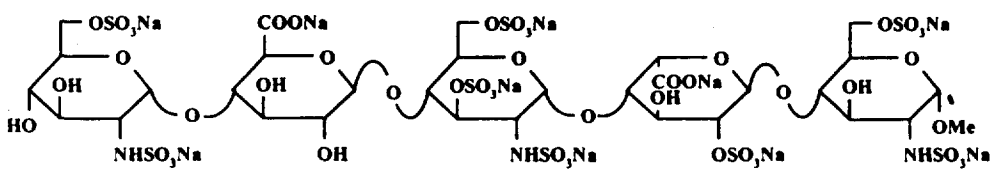
Patients should be frequently monitored for signs and symptoms of neurological impairment. If neurologic compromise is noted, urgent treatment is necessary.

The physician should consider the potential benefit versus risk before neuraxial intervention in patients anticoagulated or to be anticoagulated for thromboprophylaxis (see also **WARNINGS: Hemorrhage** and **PRECAUTIONS: Drug Interactions**).

DESCRIPTION

ARIXTRA™ Injection is a sterile solution containing fondaparinux sodium. It is a synthetic and specific inhibitor of activated Factor X (Xa). Fondaparinux sodium is methyl O-2-deoxy-6-O-sulfo-2-(sulfoamino)- α-D-glucopyranosyl-(1→4)-O-β-D-glucopyranuronosyl-(1→4)-O-2-deoxy-3,6-di-O-sulfo-2-(sulfoamino)-α-D-glucopyranosyl-(1→4)-O-2-O-sulfo-α-L-idopyranuronosyl-(1→4)-2-deoxy-6-O-sulfo-2-(sulfoamino)- α-D-glucopyranoside, decasodium salt.

The molecular formula of fondaparinux sodium is $C_{31}H_{43}N_3\ Na_{10}O_{49}S_8$ and its molecular weight is 1728. The structural formula is provided below.



ARIXTRA is supplied as a sterile, preservative-free injectable solution for subcutaneous use.

Each single dose, prefilled syringe of ARIXTRA, affixed with an automatic needle protection system, contains 2.5 mg of fondaparinux sodium in 0.5 mL of an isotonic solution of sodium chloride and water for injection. The final drug product is a clear and colorless liquid with a pH between 5.0 and 8.0.

CLINICAL PHARMACOLOGY

Pharmacodynamics

Mechanism of Action: The antithrombotic activity of fondaparinux sodium is the result of antithrombin III (ATIII)-mediated selective inhibition of Factor Xa. By selectively binding to ATIII, fondaparinux sodium potentiates (about 300 times) the innate neutralization of Factor Xa by ATIII. 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 known effect on platelet function. At the recommended dose, fondaparinux sodium does not affect fibrinolytic activity or bleeding time.

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 LMWH are not appropriate for this use). As a result, the activity of fondaparinux sodium is expressed as milligrams (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: Fondaparinux sodium administered by subcutaneous injection is rapidly and completely absorbed (absolute bioavailability is 100%). Following a single subcutaneous dose of fondaparinux sodium 2.5 mg in young male subjects, C_{max} of 0.34 mg/L is reached in approximately 2 hours. In patients undergoing treatment with fondaparinux sodium injection 2.5 mg, once daily, the peak steady state plasma concentration is on average 0.39-0.50 mg/L and is reached approximately 3 hours post dose. In these patients, the minimum steady state plasma concentration is 0.14-0.19 mg/L.

Distribution: In healthy adults, intravenously or subcutaneously administered fondaparinux sodium distributes mainly in blood and only to a minor extent in extravascular fluid as evidenced by steady state and non-steady state apparent volume of distribution of 7-11 L. Similar fondaparinux distribution occurs in patients undergoing elective hip surgery or hip fracture surgery. *In vitro*, fondaparinux sodium 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: In individuals with normal kidney function fondaparinux is eliminated in urine mainly as unchanged drug. In healthy individuals up to 75 years of age, up to 77% of a single subcutaneous or intravenous dose fondaparinux is eliminated in urine as unchanged drug in 72 hours. The elimination half-life is 17-21 hours.

Special 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 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/min), approximately 40% lower in patients with moderate renal impairment (creatinine clearance 30 to 50 mL/min) and approximately 55% lower in patients with severe renal impairment (<30 mL/min) compared to patients with normal renal function see **CONTRAINDICATIONS** and **WARNINGS: Renal Impairment**).

Hepatic Impairment: The pharmacokinetic properties of fondaparinux have not been studied in patients with hepatic impairment.

Elderly Patients: Fondaparinux elimination is prolonged in patients over 75 years old. In studies evaluating fondaparinux sodium 2.5 mg 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.

Patients Weighing Less than 50 kg: Total clearance of fondaparinux sodium is decreased by approximately 30% in patients weighing less than 50 kg (see **CONTRAINDICATIONS**).

Gender: The pharmacokinetic properties of fondaparinux sodium are not significantly affected by gender.

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

Drug Interactions: see **PRECAUTIONS: Drug Interactions.**

CLINICAL STUDIES

Prophylaxis of Thromboembolic Events Following Hip Fracture Surgery

In a randomized, double-blind, clinical trial in patients undergoing hip fracture surgery, ARIXTRA 2.5 mg SC once daily was compared to a low molecular weight heparin unapproved for use in the United States for this patient population. 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 2 mg/dL (180 µmol/L), or platelet count less than 100,000/mm^3 were excluded

from the trial. ARIXTRA 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. The efficacy data are provided in Table 1 below. Major bleeding episodes for both drugs are provided in Tables 4 and 5 (see **ADVERSE REACTIONS: Hemorrhage).**

Differences in efficacy and safety between ARIXTRA and the comparator may have been influenced by factors such as the timing of the first dose of drug after surgery (see above).

Table 1. Efficacy of ARIXTRA Injection In the Prophylaxis of Thromboembolic Events Following Hip Fracture Surgery

Endpoint	**Fondaparinux Sodium 2.5 mg SC once daily[1]**	**Comparator[1]**
All Treated Hip Fracture Surgery Patients	N = 831	N = 840
All Evaluable[2] Hip Fracture Surgery Patients		
VTE[3]	52/626 8.3%[4] (6.3, 10.8)[5]	119/624 19.1% (16.1, 22.4)
All 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 PE	3/831 0.4%[6] (0.1, 1.1)	3/840 0.4% (0.1, 1.0)

[1]ARIXTRA 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.
[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: NS

Prophylaxis of Thromboembolic Events Following Hip Replacement Surgery

In two randomized, double-blind, clinical trials in patients undergoing hip replacement surgery, ARIXTRA 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). In Study 1, a total of 2275 patients were randomized and 2257 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 2309 patients were randomized and 2273 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 2 mg/dL (180 µmol/L), or platelet count less than 100,000/mm^3 were excluded from both trials. In Study 1, ARIXTRA 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, ARIXTRA 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. The efficacy data are provided in Table 2 below. Major bleeding episodes for both drugs are provided in Tables 4 and 5 (see **ADVERSE REACTIONS: Hemorrhage**).

Differences in efficacy and safety between ARIXTRA and enoxaparin may have been influenced by factors such as the timing of the first dose of drug after surgery (see above).

Table 2. Efficacy of ARIXTRA Injection 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 Sodium 30 mg SC every12hr [2]**	**Fondaparinux Sodium 2.5 mg SC once daily [1]**	**Enoxaparin Sodium 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% [10] (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 ARIXTRA 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 active comparator 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 active enoxaparin sodium in study 1: < 0.05
9. p value versus active enoxaparin sodium in study 2: < 0.01
10. p value versus active enoxaparin sodium in study 2: < 0.01

Prophylaxis of Thromboembolic Events Following Knee Replacement Surgery

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), ARIXTRA 2.5 mg SC once daily was compared to enoxaparin sodium 30 mg SC every 12 hours. A total of 1049 patients were randomized and 1034 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 2 mg/dL (180 µmol/L), or platelet count less than 100,000/mm^3 were excluded from the trial. ARIXTRA was initiated 6 ± 2 hours (mean 6.25 hrs) after surgery in 94% of patients and active comparator was initiated 12 to 24 hours (mean 21 hrs) after

surgery in 96% of patients. For both drugs, treatment was continued for 7 ± 2 days. The efficacy data are provided in Table 3 below. Major bleeding was significantly greater in ARIXTRA-treated patients as compared to active comparator-treated patients (see **ADVERSE REACTIONS: Hemorrhage**)

Differences in efficacy and safety between ARIXTRA and enoxaparin may have been influenced by factors such as the timing of the first dose of drug after surgery (see above).

Table 3. Efficacy of ARIXTRA Injection in the Prophylaxis of Thromboembolic Events Following Knee Replacement Surgery

Endpoint	**Fondaparinux Sodium 2.5 mg SC once daily[1]**	**Enoxaparin Sodium 30 mg SC every 12 hours[2]**
All Treated Knee Replacement Surgery Patients	N = 517	N = 517
All Evaluable[3] 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 ARIXTRA 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 hemostatis 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

INDICATIONS AND USAGE

ARIXTRA is indicated for the prophylaxis of deep vein thrombosis, which may lead to pulmonary embolism:

- in patients undergoing hip fracture surgery;
- in patients undergoing hip replacement surgery;
- in patients undergoing knee replacement surgery.

CONTRAINDICATIONS

ARIXTRA is contraindicated in patients with severe renal impairment (creatinine clearance < 30 mL/min). ARIXTRA is eliminated primarily by the kidneys, and such patients are at increased risk for major bleeding episodes (see WARNINGS: Renal Impairment).

ARIXTRA is contraindicated in patients with body weight <50 kg. In clinical trials, occurrence of major bleeding was doubled in patients with body weight <50 kg compared with those with body weight ≥50 kg (5.4% vs. 2.1%).

The use of ARIXTRA is contraindicated in patients with active major bleeding, bacterial endocarditis, in patients with thrombocytopenia associated with a positive *in vitro* test for anti-platelet antibody in the presence of fondaparinux sodium, or in patients with known hypersensitivity to fondaparinux sodium.

WARNINGS

ARIXTRA is not intended for intramuscular administration.

ARIXTRA cannot be used interchangeably (unit for unit) with heparin, low molecular weight heparins or heparinoids, as they differ in manufacturing process, anti-Xa and anti-IIa activity, units, and dosage. Each of these medicines has its own instructions for use.

Renal Impairment

The risk of hemorrhage increases with increasing renal impairment. Occurrences of major bleeding in patients with normal renal function, mild renal impairment, moderate renal impairment and severe renal impairment have been found to be 1.6% (25/1565), 2.4% (31/1288), 3.8% (19/504) and 4.8% (4/83), respectively (see **CLINICAL PHARMACOLOGY: Special Populations, *Renal Impairment*** and **CONTRAINDICATIONS**).

Therefore, ARIXTRA is contraindicated in patients with severe renal impairment (creatinine clearance < 30 mL/min) and should be used with caution in patients with moderate renal impairment creatinine clearance 30 - 50 mL/min).

Renal function should be assessed periodically in patients receiving the drug. ARIXTRA should be discontinued immediately in patients who develop severe renal impairment or labile renal function while on therapy. After discontinuation of ARIXTRA, 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 ARIXTRA may persist even longer in patients with renal impairment (see **CLINICAL PHARMACOLOGY**).

Hemorrhage

ARIXTRA Injection, like other anticoagulants, should be used with extreme caution in conditions with increased risk of hemorrhage, such as congenital or acquired bleeding disorders, active ulcerative and angiodysplastic gastrointestinal disease, hemorrhagic stroke, or shortly after brain, spinal, or ophthalmological surgery, or in patients treated concomitantly with platelet inhibitors.

Laboratory Testing

Because routine coagulation tests such as Prothrombin time (PT) and Activated Partial Thromboplastin Time (aPTT) are relatively insensitive measures of ARIXTRA activity and international standards of heparin or LMWH are not calibrators to measure anti-Factor Xa activity of ARIXTRA, if during ARIXTRA therapy unexpected changes in coagulation parameters or major bleeding occurs, ARIXTRA should be discontinued (see **PRECAUTIONS: Laboratory Tests**).

Neuraxial Anesthesia and Post-operative Indwelling Epidural Catheter Use

Spinal or epidural hematomas, which may result in long-term or permanent paralysis, can occur with the use of anticoagulants and neuraxial (spinal/epidural) anesthesia or spinal puncture. The risk of these events may be higher with post-operative use of indwelling epidural catheters or concomitant use of other drugs affecting hemostasis such as NSAIDs (see **Boxed Warning for Spinal/Epidural Hematomas**).

Thrombocytopenia: Thrombocytopenia can occur with the administration of ARIXTRA. Moderate thrombocytopenia (platelet counts between 100,000/mm^3 and 50,000/mm^3) occurred at a rate of 2.9% in patients given ARIXTRA 2.5 mg in clinical trials. Severe thrombocytopenia platelet counts less than 50,000/ mm^3) occurred at a rate of 0.2% in patients given ARIXTRA 2.5 mg in clinical trials.

Thrombocytopenia of any degree should be monitored closely. If the platelet count falls below 100,000/mm^3, ARIXTRA should be discontinued.

PRECAUTIONS

General

ARIXTRA should be used with caution in elderly patients (see **PRECAUTIONS: Geriatric Use**).

ARIXTRA should be used with caution in patients with a history of heparin-induced thrombocytopenia.

ARIXTRA Injection should not be mixed with other injections or infusions.

ARIXTRA Injection should be used with care in patients with a bleeding diathesis, uncontrolled arterial hypertension or a history of recent gastrointestinal ulceration, diabetic retinopathy, and hemorrhage.

If thrombotic events occur despite ARIXTRA prophylaxis, appropriate therapy should be initiated.

Laboratory Tests

Periodic routine complete blood counts (including platelet count), serum creatinine level, and stool occult blood tests are recommended during the course of treatment with ARIXTRA Injection.

When administered at the recommended prophylaxis dose, routine coagulation tests such as Prothrombin time (PT) and Activated Partial Thromboplastin Time (aPTT) are relatively insensitive measures of ARIXTRA activity, and are therefore, unsuitable for monitoring.

The anti-factor Xa activity of fondaparinux sodium can be measured by anti-Xa assay using the appropriate calibrator (fondaparinux). Since the international standards of heparin or 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 low molecular weight heparins. (see **CLINICAL PHARMACOLOGY : Pharmacodynamics and Pharmacokinetics** and **WARNINGS: Laboratory Testing**).

Drug Interactions

In clinical studies performed with ARIXTRA™, the concomitant use of oral anticoagulants (warfarin), platelet inhibitors (acetylsalicylic acid), NSAIDs (piroxicam) and digoxin did not significantly affect the pharmacokinetics/pharmacodynamics of fondaparinux sodium. In addition, 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 ARIXTRA therapy. If co-administration is essential, close monitoring may be appropriate.

In an *in vitro* study in human liver microsomes, inhibition of CYP2A6 hydroxylation of coumarin by fondaparinux (200 μM i.e. 350 mg/L) was 17-28%. Inhibition of the other isozymes evaluated (CYPs 2A1, 2C9, 2C19, 2D6, 3A4, and 3E1) was 0-16%. Since fondaparinux does not markedly inhibit CYP450s (CYP1A2, CYP2A6, CYP2C9, CYP2C19, CYP2D6, CYP2E1 or CYP3A4) *in vitro*, fondaparinux sodium is not expected to significantly interact with other drugs *in vivo* by inhibition of metabolism mediated by these isozymes.

Since fondaparinux sodium does not bind significantly to plasma proteins other than ATIII, no drug interactions by protein binding displacement are expected.

Carcinogenesis, Mutagenesis, Impairment of Fertility

No long-term studies in animals have been performed to evaluate the carcinogenic potential of fondaparinux sodium.

Fondaparinux sodium was not genotoxic in the Ames test, the mouse lymphoma cell (L5178Y/TK$^{+/}$) forward mutation test, the human lymphocyte chromosome aberration test, the rat hepatocyte unscheduled DNA synthesis (UDS) test, or the rat micronucleus test.

At subcutaneous doses up to 10 mg/kg/day (about 32 times the recommended human dose based on body surface area) fondaparinux sodium found to have no effect on fertility and reproductive performance of male and female rats.

Pregnancy

Teratogenic Effects

Pregnancy Category B. Reproduction studies have been performed in pregnant rats at subcutaneous doses up to 10 mg/kg/day (about 32 times the recommended human dose based on body surface area) and pregnant rabbits at subcutaneous doses up to 10 mg/kg/day (about 65 times the recommended human dose based on body surface area) and have revealed no evidence of impaired fertility or harm to the fetus due to fondaparinux sodium. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers

Fondaparinux was found to be excreted in the milk of lactating rats. However, it is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when fondaparinux sodium is administered to a nursing woman.

Pediatric Use

Safety and effectiveness of ARIXTRA in pediatric patients have not been established.

Geriatric Use

ARIXTRA should be used with caution in elderly patients. Over 2300 patients, 65 years and older, have received fondaparinux sodium 2.5 mg in randomized clinical trials in the orthopedic surgery program. The efficacy of ARIXTRA in the elderly (equal or older than 65 years) was similar to that seen in younger patients (younger than 65 years). The risk of ARIXTRA-associated major bleeding increased with age: 1.8% (23/1253) in patients < 65 years, 2.2% (24/1111) in those 65-74 years, and 2.7% (33/1227) in those ≥75 years. Serious adverse events increased with age for patients receiving ARIXTRA. Careful attention to dosing directions and concomitant medications (especially antiplatelet medication) is advised. (see **CLINICAL PHARMACOLOGY** and **PRECAUTIONS: General**)

Fondaparinux sodium is substantially excreted by the kidney, and the risk of toxic reactions to ARIXTRA may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, it may be useful to monitor renal function. (see **CONTRAINDICATIONS** and **WARNINGS: Renal Impairment**).

ADVERSE REACTIONS

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. The adverse reaction information from clinical trials does, however, provide a basis for identifying possible adverse events and for approximating rates.

The data described below reflect exposure to ARIXTRA in 4823 patients undergoing hip fracture, hip replacement, or major knee surgeries. ARIXTRA was studied primarily in two large dose-response [n=989] and four active-controlled trials with enoxaparin sodium [n=3616] (see **CLINICAL STUDIES**). The population ranged in age from 17 to 97 years and in body weight between 30 and 169 kg. The population included 58% females and 42% males, and 95 % Caucasian, 3% Black, 1% Asian, 1% other races. Over 3,500 patients received ARIXTRA 2.5 mg once daily with treatment ranging up to 11 days while over 90% of patients were treated between 5 and 9 days. Patients with serum creatinine >2.0 mg/dL were excluded from these clinical trials.

Hemorrhage:

During ARIXTRA administration, the most common adverse reactions were bleeding complications (see **WARNINGS**). In knee replacement surgery, major bleeding was significantly greater in ARIXTRA treated patients than enoxaparin sodium treated patients.

The rates of major bleeding events reported during clinical trials with ARIXTRA 2.5 mg Injection are provided in Tables 4 and 5 below.

Table 4. Major Bleeding[1] Episodes Following Hip Fracture, Hip Replacement, and Knee Replacement Surgeries

Indications	Fondaparinux Sodium 2.5mg SC once daily	Comparator: Low Molecular Weight Heparin or Enoxaparin Sodium[2]
Hip Fracture	8/831 (2.2%)	19/842 (2.3%)
Hip Replacement	67/2268 (3.0%)	55/2597 (2.1%)
Knee Replacement	11/517 (2.1%)[3]	1/517 (0.2%)

[1] 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.
BI ≥ 2 : overt bleeding associated only with a bleeding index (BI) ≥ 2 [calculated as number of whole blood or packed red blood cells units transfused + [(pre-bleeding) - (post-bleeding)] hemoglobin (g/dL) values].
2 Enoxaparin Sodium dosing regimen: 30 mg every 12 hours or 40 mg once daily.
[3]p value versus enoxaparin sodium: 0.0061; 95% confidence interval: [1.1%, 3.8%] in ARIXTRA group versus [0.0%, 1.1%] in enoxaparin sodium group.

Table 5. Bleeding across Hip Fracture, Hip replacement, and Knee Replacement Surgery Studies

	Fondaparinux Sodium 2.5mg SC once daily	Comparator: Low Molecular Weight Heparin or Enoxaparin Sodium[2]
	N = 3616	N = 3956
Major bleeding[1,2]	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%)
BI≥2[4,3]	84 (2.3%)	63 (1.6%)
Minor bleeding[3,4]	109 (3.0%)	116 (2.9%)

[1] Enoxaparin Sodium dosing regimen: 30 mg every 12 hours or 40 mg once daily.
[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 (BI) ≥ 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.

Thrombocytopenia: see **WARNINGS: Thrombocytopenia.**

Local Reactions: Mild local irritation (injection site bleeding, rash and pruritus) may occur following subcutaneous injection of ARIXTRA.

Elevations of Serum Aminotransferases: Asymptomatic increases in aspartate (AST [SGOT]) and alanine (ALT [SGPT]) aminiotransferase levels greater than three times the upper limit of normal of the laboratory reference range have been reported in 1.7% and 2.6% of patients, respectively, during treatment with ARIXTRA 2.5 mg Injection versus 3.2% and 3.9% of patients, respectively during treatment with enoxaparin sodium 30 mg every 12 hours or 40 mg once daily or a low molecular weight comparator. Such elevations are fully reversible and are rarely associated with increases in bilirubin.

Since aminotransferase determinations are important in the differential diagnosis of myocardial infarction, liver disease, and pulmonary emboli, elevations that might be caused by drugs like ARIXTRA should be interpreted with caution.

Other: Other adverse events that occurred during treatment with ARIXTRA, low molecular weight comparator, 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 6 below.

Table 6 Adverse events occurring in ≥ 2% of ARIXTRA or Enoxaparin Sodium Treated Patients Regardless of Relationship to Study Drug Across Hip Fracture Surgery, 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 Sodium[1] **N = 3956**
Anemia	707 (19.6%)	670 (16.9%)
Fever	491 (13.6%)	610 (15.4%)
Nausea	409 (11.3%)	484 (12.2%)
Edema	313 (8.7%)	348 (8.8%)
Constipation	309 (8.5%)	416 (10.5%)
Rash	273 (7.5%)	329 (8.3%)
Vomiting	212 (5.9%)	236 (6.0%)
Insomnia	179 (5.0%)	214 (5.4%)
Wound drainage increased	161 (4.5%)	184 (4.7%)
Hypokalemia	152 (4.2%)	164 (4.1%)
Urinary tract infection	136 (3.8%)	135 (3.4%)
Dizziness	131 (3.6%)	165 (4.2%)
Purpura	128 (3.5%)	137 (3.5%)
Hypotension	126 (3.5%)	125 (3.2%)
Confusion	113 (3.1%)	132 (3.3%)
Bullous eruption	112 (3.1%)	102 (2.6%)
Urinary retention	106 (2.9%)	117 (3.0%)
Hematoma	103 (2.8%)	109 (2.8%)
Diarrhea	90 (2.5%)	102 (2.6%)
Dyspepsia	87 (2.4%)	102 (2.6%)
Post-operative hemorrhage	85 (2.4%)	69 (1.7%)
Headache	72 (2.0%)	97 (2.5%)
Pain	62 (1.7%)	101 (2.6%)

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

In ongoing studies for other indications, major bleeding events include intracranial hemorrhage, cerebral hemorrhage, and retroperitoneal hemorrhage.

OVERDOSAGE

Symptoms/Treatment

There is no known antidote for ARIXTRA. Overdose of ARIXTRA may lead to hemorrhagic complications. Overdosage associated with bleeding complications should lead to treatment discontinuation and initiation of appropriate therapy.

Data obtained in patients undergoing chronic intermittent hemodialysis suggest that ARIXTRA clearance can increase by 20% during hemodialysis.

DOSAGE AND ADMINISTRATION

ARIXTRA is administered by subcutaneous injection.

In patients undergoing hip fracture, hip replacement, or knee replacement surgery, the recommended dose of ARIXTRA is 2.5 mg administered by subcutaneous injection once daily. After hemostasis has been established, the initial dose should be given 6 to 8 hours after surgery. Administration before 6 hours after surgery has been associated with an increased risk of major bleeding. The usual duration of administration is 5 to 9 days; and up to 11 days administration has been tolerated. (see **CLINICAL STUDIES** and **WARNINGS: Laboratory Testing**).

INSTRUCTIONS FOR USE

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration.

ARIXTRA (fondaparinux sodium) Injection is provided in a single dose, prefilled syringe affixed with an automatic needle protection system. ARIXTRA is administered by subcutaneous injection. It must not be administered by intramuscular injections.

To avoid the loss of drug when using the pre-filled syringe do not expel the air bubble from the syringe before the injection. Administration should be made in the fatty tissue, alternating injection sites (e.g. between the left and right anterolateral or the left and right posterolateral abdominal wall).

To administer ARIXTRA:

1. Wipe the surface of the injection site with an alcohol swab.
2. Twist the plunger cap and remove it.

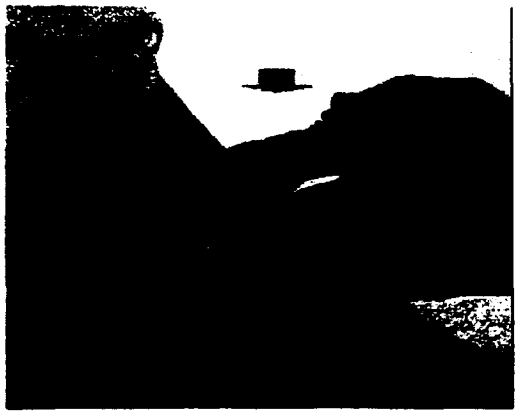
3. Hold the syringe with either hand and use your other hand to twist the rigid needle guard (covers the needle). Pull the rigid needle guard straight off the needle.

4. Pinch a fold of skin at the injection site between your thumb and forefinger and hold it throughout the injection.

5. Hold the syringe with your thumb on the top pad of the plunger rod and your next two fingers on the finger grips on the syringe barrel. Pay attention to avoid sticking yourself with the exposed needle.

6. Insert the full length of the syringe needle perpendicularly into the skin fold held between the thumb and forefinger.

7. Push the plunger rod firmly with your thumb as far as it will go. This will ensure you have injected all the contents of the syringe



8. When you have injected all the contents of the syringe, the plunger should be released. The plunger will then rise automatically while the needle withdraws from the skin and retracts into the security sleeve. Discard the syringe into the sharps container without replacing the rigid needle guard.

9. You will know that the syringe has worked when:
   - The needle is pulled back into the security sleeve and the white safety indicator appears above the blue upper body.
   - You may also hear or feel a soft click when the plunger rod is released fully.

HOW SUPPLIED

ARIXTRA™ (fondaparinux sodium) Injection is available in the following strength and package size:

Package of 10:

2.5 mg ARIXTRA in 0.5 mL single dose prefilled syringe, affixed with a 27-gauge x ½ inch needle with an automatic needle protection system

NDC (##### ### #) ARIXTRA™

Store at 25°C (77°F); excursions permitted to 15°C-30°C (59°C-86°F) [See USP Controlled Room Temperature].

Keep out of the reach of children.

Rx only.

Distributed by: Organon Sanofi-Synthelabo LLC, West Orange, NJ 07052.

Made in: France

Date of labeling approval

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Florence Houn
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