



There have been cases of neuraxial haematomas reported with the concurrent use of enoxaparin sodium and spinal/epidural anaesthesia. These may result in long-term or permanent paralysis. These events are rare with enoxaparin sodium dosage regimens of 4000 anti-Xa IU once daily or lower. The risk of these events is higher with higher enoxaparin sodium dosage regimens, the use of post-operative indwelling epidural catheters or with concomitant use of drugs affecting hemostasis such as NSAIDs, platelet inhibitors or other anticoagulants (see Section 4.5 Interactions with other Medicaments and other forms of Interactions). The risk also appears to be increased by traumatic or repeated neuraxial puncture or in patients with a history of spinal surgery or spinal deformity.

To reduce the potential risk of bleeding during epidural or spinal anesthesia, the placement and removal of the catheter is best performed when the anticoagulant effect of enoxaparin sodium is low; however, the exact timing to reach a sufficiently low anticoagulant effect in each patient is not known.

Placement or removal of a catheter should be delayed for at least 12 hours after administration of lower doses (2000 anti-Xa IU once daily, 3000 anti-Xa IU once or twice daily or 4000 anti-Xa IU once daily) of enoxaparin, and at least 24 hours after the administration of higher doses (75 anti-Xa IU/kg twice daily, 100 anti-Xa IU/kg twice daily, or 150 anti-Xa IU/kg once daily) of enoxaparin. Anti-Xa levels are still detectable at these time points, and these delays are not a guarantee that neuraxial haematoma will be avoided. Patients receiving the 75 anti-Xa IU/kg twice daily dose or the 100 anti-Xa IU/kg twice daily dose should not receive the second enoxaparin dose in the twice daily regimen to allow a longer delay before catheter placement or removal. Likewise, although a specific recommendation for timing of a subsequent enoxaparin dose after catheter removal cannot be made, consider delaying this next dose for at least four hours, based on a benefit-risk assessment considering both the risk for thrombosis and the risk for bleeding in the context of the procedure and patient risk factors. For patients with creatinine clearance < 30ml/min, additional considerations are necessary because elimination of enoxaparin is more prolonged; consider doubling the timing of removal of a catheter, at least 24 hours for the lower prescribed dose of enoxaparin (3000 anti-Xa IU once daily) and at least 48 hours for the higher dose (100 anti-Xa IU/kg/day).

Should the physician decide to administer enoxaparin in the context of epidural/spinal anesthesia or lumbar puncture, frequent monitoring must be exercised to detect any signs and symptoms of neurological impairment such as midline back pain, sensory and motor deficits (numbness or weakness in lower limbs), bowel and/or bladder dysfunction. Patients should be instructed to inform their physician immediately if they experience any of the above signs or symptoms. If signs or symptoms of spinal haematoma are suspected, urgent diagnosis and treatment including spinal cord decompression should be initiated.

Practitioners should consider fully the potential benefit versus risks before neuraxial intervention in patients anticoagulated or to be anticoagulated for thromboprophylaxis.

Inhixa is a biosimilar product. The prescribing physician should be involved in any decision regarding its interchangeability. In order to improve the traceability of biological medicinal products, the trademark and the batch number of the administered product should be clearly recorded (or stated) in the patient file.

4.5 Interaction with other medicinal products and other forms of interaction

It is recommended that agents which affect hemostasis should be discontinued prior to enoxaparin sodium therapy unless strictly indicated. These agents include medications such as: acetylsalicylic acid (and derivatives), NSAIDs (general route) including ketorolac, ticlopididine, clopidogrel, dextran 40 (parenteral use), glucocorticoids (general route), thrombolytics and anticoagulants, other anti platelet aggregation agents including glycoprotein IIa/IIIb antagonists. As with other Low Molecular Weight Heparins, if the combination is indicated, enoxaparin sodium should be used with careful clinical and laboratory monitoring when appropriate.



4.6 Pregnancy and lactation

Pregnancy: Animal studies have not shown any evidence of foetotoxicity or teratogenicity. In the pregnant rat, the transfer of 35S-enoxaparin cross the maternal placenta to the foetus is minimal.

In humans, there is no evidence that enoxaparin sodium crosses the placental barrier during the second trimester of pregnancy. There is no information available concerning the first and the third trimesters.

As there are no adequate and well-controlled studies in pregnant women and because animal studies are not always predictive of human response, this drug should be used during pregnancy only if the physician has established a clear need.

Pregnant women with mechanical prosthetic heart valves may be at higher risk for thromboembolism (see Special Warnings and Precautions for Use).

Lactation: In lactating rats, the concentration of 35S-enoxaparin or its labelled metabolites in milk is very low.

It is not known whether unchanged enoxaparin sodium is excreted in human breast milk. The oral absorption of enoxaparin is unlikely. However, as a precaution, lactating mothers receiving enoxaparin sodium should be advised to avoid breastfeeding.

4.7 Effects on ability to drive and use machines

Enoxaparin sodium has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Enoxaparin has been evaluated in more than 15000 patients who received enoxaparin in clinical trials. These included 1776 for prophylaxis of deep vein thrombosis following orthopaedic or abdominal surgery in patients at risk for thromboembolic complications, 1169 for prophylaxis of deep vein thrombosis in acutely ill medical patients with severely restricted mobility, 559 for treatment of deep vein thrombosis with or without pulmonary embolism, 1578 for treatment of unstable angina and non-Q-wave myocardial infarction and 10176 for treatment of acute ST-elevation myocardial infarction.

The adverse reactions observed in these clinical studies and reported in post-marketing experience are detailed below. Frequencies are defined as follows: very common ($\geq$ 1/10); common ($\geq$ 1/100 to < 1/10); uncommon ($\geq$ 1/1000 to < 1/100); rare ($\geq$ 1/10,000 to <1/1,000); and very rare (< 1/10,000) or not known (cannot be estimated from available data). Post-marketing adverse reactions are designated with a frequency “not known”.

Very rarely, hypereosinophilia, occurring in isolated cases or along with skin reactions, resolving on treatment discontinuation.

Asymptomatic and reversible increases in platelet counts and liver enzymes have been reported.

Long term therapy with heparin has been associated with a risk of osteoporosis. Although this has not been observed with enoxaparin sodium the risk of osteoporosis cannot be excluded.

Heparin products can cause hypoaldosteronism which may result in an increase in plasma potassium. Rarely, clinically significant hyperkalemia may occur particularly in patient with chronic renal failure and diabetes mellitus.

Haemorrhages

In clinical studies, haemorrhages were the most commonly reported reaction. These included major haemorrhages, reported at most in 4.2 % of the patients (surgical patients¹). Some of these cases have been fatal. As with other anticoagulants, haemorrhage may occur in the presence of associated risk factors such as: organic lesions liable to bleed, invasive procedures or the concomitant use of medications affecting haemostasis (see Section 4.4 Precautions and Section 4.5 Interactions).

MedDRA system organ class	Prophylaxis in Surgical patients	Prophylaxis in medical patients	Treatment in patients with DVT with or without PE	Treatment in patients with unstable angina and non-Q-wave MI	Treatment in patients with acute STEMI
<i>Vascular disorders</i>	<i>Very common:</i> Haemorrhage* <i>Rare:</i> Retroperitoneal haemorrhage	Haemorrhage*	<i>Very common:</i> Haemorrhage* <i>Uncommon:</i> Intracranial haemorrhage, Retroperitoneal haemorrhage	<i>Common:</i> Haemorrhage* <i>Rare:</i> Retroperitoneal haemorrhage	<i>Common:</i> Haemorrhage* <i>Uncommon:</i> Intracranial haemorrhage, Retroperitoneal haemorrhage

*: such as haematoma, ecchymosis other than at injection site, wound haematoma, haematuria, epistaxis and gastro-intestinal haemorrhage.

¹ In surgical patients, haemorrhage complications were considered major: (1) if the haemorrhage caused a significant clinical event, or (2) if accompanied by an haemoglobin decrease $\geq$ 2 g/dL or transfusion of 2 or more units of blood products. Retroperitoneal and intracranial haemorrhages were always considered major.

Thrombocytopenia and thrombocytosis

MedDRA system organ class	Prophylaxis in Surgical patients	Prophylaxis in medical patients	Treatment in patients with DVT with or without PE	Treatment in patients with unstable angina and non-Q-wave MI	Treatment in patients with acute STEMI
<i>Blood and lymphatic system disorders</i>	<i>Very common:</i> Thrombocytosis* <i>Common:</i> Thrombocytopenia	<i>Uncommon:</i> Thrombocytopenia	<i>Very common:</i> Thrombocytosis* <i>Common:</i> Thrombocytopenia	<i>Uncommon:</i> Thrombocytopenia	<i>Common:</i> Thrombocytosis* <i>Very rare:</i> Immuno-allergic thrombocytopenia

*: Platelet increased > 400 G/L

Other clinically relevant adverse reactions

These reactions are presented below, whatever the indications, by system organ class, frequency grouping and decreasing order of seriousness.

MedDRA system organ class	All indications
Immune system disorders	<i>Common:</i> Allergic reaction <i>Rare:</i> Anaphylactic / anaphylactoid reaction (see also Post marketing experience)
Hepatobiliary disorders	<i>Very common:</i> Hepatic enzymes increase (mainly transaminases**)
Skin and subcutaneous tissue disorders	<i>Common:</i> Urticaria, pruritus, erythema, <i>Uncommon:</i> Bullous dermatitis
General disorders and administration site conditions	<i>Common:</i> Injection site haematoma, injection site pain, other injection site reaction* <i>Uncommon:</i> Local irritation; skin necrosis at injection site
Investigations	<i>Rare:</i> Hyperkalaemia

*: such as injection site oedema, haemorrhage, hypersensitivity, inflammation, mass, pain, or reaction (NOS)

***: transaminases levels > 3 times the upper limit of normality

Post marketing experience

The following adverse reactions have been identified during post-approval use of enoxaparin. The adverse reactions are derived from spontaneous reports and therefore, the frequency is “not known” (cannot be estimated from the available data).

- Immune System Disorders
- Anaphylactic / anaphylactoid reaction including shock
- Nervous System Disorders

- Headache

• Vascular Disorders

- Cases of spinal haematoma (or neuraxial haematoma) have been reported with the concurrent use of enoxaparin sodium as well as spinal/epidural anesthesia or spinal puncture. These reactions have resulted in varying degrees of neurologic injuries including long-term or permanent paralysis (see Section 4.4 Warnings: Spinal/epidural anesthesia).

• Blood and Lymphatic System Disorders

- Haemorrhagic anemia
- Cases of immuno-allergic thrombocytopenia with thrombosis; in some of them thrombosis was complicated by organ infarction or limb ischaemia (see Section 4.4 Precautions: Monitoring of platelet counts).
- Eosinophilia

• Skin and subcutaneous disorders

- Cutaneous vasculitis, skin necrosis usually occurring at the injection site (these phenomena have been usually preceded by purpura or erythematous plaques, infiltrated and painful). Treatment with enoxaparin sodium must be discontinued.
- Injection site nodules (inflammatory nodules, which were not cystic enclosure of enoxaparin). They resolve after a few days and should not cause treatment discontinuation.
- Alopecia

• Hepatobiliary disorders

- Hepatocellular liver injury
- Cholestatic liver injury

• Musculoskeletal and connective tissue disorders

- Osteoporosis following long-term therapy (greater than 3 months)

4.9 Overdose

Orally administered enoxaparin sodium is poorly absorbed and even large oral doses should not lead to any serious consequences. This may be checked by plasma assays of anti-Xa and anti-IIa activities. Accidental overdosage after intravenous, extra corporeal or subcutaneous administration of massive doses of enoxaparin sodium may lead to bleeding complications. Neutralization can be obtained by slow intravenous injection of protamine; however the anti-Xa activity of enoxaparin sodium is never completely neutralized (maximum about 60%). 1 mg protamine sodium can be used to neutralize the anticoagulant effect of about 1 mg enoxaparin sodium, if enoxaparin sodium was administered in the previous 8 hours. An infusion of 0.5 mg protamine per 1 mg of enoxaparin sodium may be administered if enoxaparin sodium was administered greater than 8 hours previous to the protamine administration, or if it has been determined that a second dose of protamine is required. After 12 hours of the enoxaparin sodium injections, protamine administration may not be required.

Pharmacological Properties

5.1 Pharmacodynamic Properties

Pharmaco-therapeutic group: antithrombotic agent, heparin group. ATC code B01A B05. Enoxaparin sodium is a low molecular weight heparin which has antithrombotic activity. It is characterised by a higher ratio of antithrombotic activity to anticoagulant activity than unfractionated heparin. At recommended doses, it does not significantly influence platelet aggregation, binding of fibrinogen to platelets or global clotting tests such as APTT and prothrombin time.

Treatment of acute ST-segment elevation myocardial infarction, in combination with a thrombolytic agent in patients who are eligible or not for subsequent PCI.

In a large multicenter study, 20 479 patients with acute ST-segment elevation myocardial infarction having received fibrinolytic treatment were randomized to receive either: enoxaparin as an IV bolus injection of 3000 anti-Xa IU immediately followed by a dose of 100 anti-Xa IU/kg SC, then by an SC injection of 100 anti-Xa IU/kg every 12 hours,

or unfractionated heparin by the IV route as a bolus injection of 60 IU/kg (maximum 4000 IU) followed by a continuous infusion at a dose adjusted to the activated partial thromboplastin time. The SC injections of enoxaparin were administered until discharge from hospital or for a maximum period of 8 days (in 75% of cases for at least 6 days). Half the patients receiving heparin were administered the drug for less than 48 hours (in 89.5% of cases $\geq$ 36 hours). All the patients were also treated with aspirin for at least 30 days. The enoxaparin dosage was adjusted for patients aged 75 years or more: 75 IU/kg as an SC injection every 12 hours, without an initial IV bolus injection.

During the study, 4 716 (23%) patients underwent PCI under antithrombotic treatment using blinded study drugs. Patients did not receive an additional dose if the last SC injection of enoxaparin had been given less than 8 hours before balloon inflation, or, received an IV bolus injection of 30 anti-Xa IU/kg if the last SC injection of enoxaparin had been given more than 8 hours before balloon inflation.

Enoxaparin significantly reduced the incidence of primary end point events (composite end point consisting of myocardial infarction relapse and all-cause mortality within 30 days after inclusion: 9.9% in the enoxaparin group versus 12.0% in the unfractionated heparin group (relative risk reduction of 17% (p<0.001)). The incidence of myocardial infarction relapse was significantly lower in the enoxaparin group (3.4% versus 5%, p<0.001, relative risk reduction 31%). The incidence of deaths was lower in the enoxaparin group, with no statistically significant difference between the groups (6.9% versus 7.5%, p=0.11).

The benefit of enoxaparin in terms of the primary endpoint was consistent, irrespective of sub-group: age, sex, location of myocardial infarction, history of diabetes or myocardial infarction, type of thrombolytic administered and interval between the first clinical signs and treatment initiation.

Enoxaparin demonstrated a significant benefit versus unfractionated heparin in terms of the primary efficacy criterion, both in patients who had undergone PCI within 30 days after inclusion (10.8% versus 13.9%, 23% reduction in relative risk) and in patients who did not have PCI (9.7% versus 11.4%, 15% reduction in relative risk).

The incidence of major bleeding at 30 days was significantly higher (p<0.0001) in the enoxaparin group (2.1%) versus the heparin group (1.4%). There was a higher incidence of gastrointestinal bleeding in the enoxaparin group (0.5%) versus the heparin group (0.1%), while the incidence of intracranial bleeding was similar in both groups (0.8% with enoxaparin versus 0.7% with heparin).

The analysis of the composite criteria measuring overall clinical benefit showed statistically significant superiority (p<0.0001) for enoxaparin versus unfractionated heparin: a relative risk reduction of 14% in favor of enoxaparin (11.0% versus 12.8%) for the composite criteria consisting of death, myocardial infarction relapse, or major bleeding (TIMI criteria) at 30 days, and of 17% (10.1% versus 12.2%) for the composite criteria consisting of death, myocardial infarction relapse or intracranial bleeding at 30 days.

5.2 Pharmacokinetic Properties

The pharmacokinetic parameters have been studied in terms of the time course of plasma anti-Xa activity and also by anti-IIa activity at the recommended dosage ranges. The absolute bioavailability of enoxaparin sodium after subcutaneous administration is close to 100%. The mean maximum plasma anti-Xa activity is observed 3 to 5 hours after subcutaneous injection.

An IV bolus injection of 3000 anti-Xa IU followed by 100 anti-Xa IU/kg by the SC route every 12 hours leads to a first peak in anti-Factor Xa levels of 1.16 IU/ml (n=16) and a mean exposure corresponding to 88% of the steady state level. Steady state is reached as of the second day of treatment.

Enoxaparin sodium pharmacokinetics appear to be linear over the

recommended dosage ranges. Even if a difference in steady-state has been reported between single or repeated administration, this difference is expected and within the therapeutic range. The mean maximum plasma anti-IIa activity is approximately 3 to 4 hours following subcutaneous injection. Enoxaparin sodium is primarily metabolized in the liver. The elimination half-life of anti-Xa activity is approximately 4 hours after a single administration to about 7 hours after repeated administration. Renal clearance of active fragments represents about 10% of the administered dose and total renal excretion 40% of the dose. In the elderly, since renal function is known to decline with age, the elimination may be reduced. In patients with severe renal impairment (creatinine clearance < 30 ml/min), the AUC is significantly increased after repeated subcutaneous administration of 4000 anti-Xa IU once daily. In a single study, elimination rate appeared similar in patients undergoing dialysis.

Enoxaparin sodium, as detected by anti-Xa activity, does not cross the placental barrier during the second trimester of pregnancy.

5.3 Preclinical Safety Data

No long-term studies in animals have been performed to evaluate the carcinogenic potential of enoxaparin. Enoxaparin was not mutagenic in in vitro tests, including the Ames test, the forward mutation test at the thymidine kinase (TK) locus of L5178Y mouse lymphoma cells, and human lymphocyte chromosomal aberration test, and the in vivo rat bone marrow chromosomal aberration test. Enoxaparin was found to have no effect on fertility or reproductive performance of male and female rats at SC doses less than 20 mg/kg/day. Teratogenicity studies have been conducted in gravid rats and rabbits at SC doses of enoxaparin less than 30 mg/kg/day. There was no evidence of teratogenic effects or fetotoxicity due to enoxaparin. Besides the anticoagulant effects of enoxaparin, there was no evidence of adverse effects during the following toxicity studies:

- 15 mg/kg/day in 13-week subcutaneous toxicity studies in rats and dogs
- 10 mg/kg/day in 26-week subcutaneous and intravenous toxicity studies in rats and monkeys.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Water for injections Ph.Eur.

6.2 Incompatibilities

Inhixa should not be mixed with any other injections or infusions.

6.3 Shelf life

24 months

6.4 Special precautions for storage

Store below 30°C. Do not freeze.

6.5 Nature and contents of container

solution in a clear, colourless type I neutral glass syringe barrel with fixed needle and needle shield closed by chlorobutyl rubber stopper and a red polypropylene plunger rod for prefilled syringe (PFS) without needle guard and PFS with BD Preventis or West Nova Guard SA Pro or Hengyu needle guard and white polycarbonate plunger rod for PFS with UltraSafe Passive needle guard.

Packs of:

- 2, 10, 50 pre filled syringes
- 2, 10, 50 pre filled syringes with needle guard

6.6 Manufacturer

Shenzhen Techdow Pharmaceutical Co., Ltd
No. 19 Gaoxinzhongyi Road, High-tech Industrial Park, Nanshan District, Guangdong Province, Shenzhen 518057, China

6.7 Date of Revision of Text

Aug 2021