Package insert 20210906-01

210 mm

580 mm

Inhixa
Product summary

1. **Trade Name of Medicinal product**
Concentration of 10000 anti-Xa IU equivalent to 100mg enoxaparin sodium in each ml of the solution.
Inhixa 2,000 anti-Xa IU (20 mg)/0.2 mL
Inhixa 4,000 anti-Xa IU (40 mg)/0.4 mL
Inhixa 6,000 anti-Xa IU (60 mg)/0.6 mL
Inhixa 8,000 anti-Xa IU (80 mg)/0.8 mL
Inhixa 10,000 anti-Xa IU (100 mg)/1 mL
Not all presentations may be available locally

2. **Qualitative and Quantitative Composition**
Active Ingredient: Enoxaparin sodium
Solvent: Water for injection

Each ml of the solution contains 10000 anti-Xa IU equivalent to 100 mg enoxaparin sodium. One mg (0.01 ml) of enoxaparin sodium corresponds approximately to 100 anti-Xa IU.
Inhixa 2,000 anti-Xa IU is equivalent to 20 mg, Inhixa 4,000 anti-Xa IU is equivalent to 40 mg, Inhixa 6,000 anti-Xa IU is equivalent to 60 mg, Inhixa 8,000 anti-Xa IU is equivalent to 80 mg, Inhixa 10,000 anti-Xa IU is equivalent to 100 mg.

3. **Pharmaceutical Form**
Solution for injection
Clear, colorless to pale yellow solution

Clinical Particulars

4.1 Inhixa is indicated in adults for:
Prophylaxis of venous thromboembolic disease (prevention of blood clot formation in
the veins), in particular those which may be associated with orthopedic or general surgery.

Prophylaxis of venous thromboembolic disease in medical patients bedridden due to acute illnesses.

Treatment of established deep vein thrombosis.

Prevention of thrombus formation in extracorporeal circulation during haemodialysis.

Treatment of unstable angina and non-Q-wave myocardial infarction, administered concurrently with aspirin.

Treatment of acute ST-segment Elevation Myocardial Infarction (STEMI), in combination with a thrombolytic agent, in patients to be managed medically or with subsequent Percutaneous Coronary Intervention (PCI).

4.2 Posology and Method of Administration

Adults:

Prophylaxis of venous thromboembolic disease in surgical patients:
In patients with a moderate thromboembolism risk (e.g. abdominal surgery) the recommended dose of enoxaparin sodium is 2000 anti-Xa IU (0.2 ml) once daily by subcutaneous injection. In general surgery, the first injection should be given 2 hours before the surgical procedure. In patients with a high risk of thromboembolic (e.g. orthopedic surgery) the recommended dose of enoxaparin sodium given by subcutaneous injection is 4000 anti Xa IU (0.4 ml) once daily initiated 12 hours preoperatively. For special recommendation concerning dosing intervals for spinal/ epidural anesthesia and PCI procedures, see Warnings. Enoxaparin sodium treatment is usually prescribed for an average period of 7 to 10 days. Longer treatment duration may be appropriate in some patients and the treatment should be continued for as long as there is a risk of venous thromboembolism and until the patient is ambulatory. Therapy with 4000 anti-Xa IU once daily for 30 post-operative days has been proved to be beneficial in total hip replacement surgery.

Prophylaxis of venous thromboembolic disease in medical patients:
The recommended dose of enoxaparin sodium is 4000 anti-Xa IU (0.4 ml) once daily by subcutaneous injection. Treatment with enoxaparin sodium is prescribed for a minimum of 6 days and continued until the return to full ambulation, for a maximum of 14 days

Treatment of established deep vein thrombosis:
Enoxaparin sodium is administered subcutaneously at the dose of 100 anti-Xa IU/kg every 12 hours.
The treatment is prescribed until a therapeutic anticoagulant effect has been achieved with oral anticoagulant therapy, usually for an average period of 10 days.

Prevention of extracorporeal thrombus formation during haemodialysis:
A dose equivalent to 100 anti-Xa IU/kg (1mg/kg) introduced into the arterial line at the beginning of a dialysis session is usually sufficient for a 4 hour session. If fibrin rings are found, such as after a longer than normal session, a further dose of 50 to 100 anti-Xa IU/kg (0.5 to 1.0 mg/kg) may be given. For patients at a higher risk of haemorrhage the dose should be reduced to 50 anti-Xa IU/kg (0.5 mg/kg) for double vascular access or 75 anti-Xa IU/kg (0.75 mg/kg) for a single vascular access.

Treatment of unstable angina and non-Q-wave myocardial infarction:
The recommended dose is 100 anti-Xa IU/kg Inhixa every 12 hours by subcutaneous injection, administered concurrently with oral aspirin (100 to 325 mg once daily).
Treatment with Inhixa in these patients should be prescribed for a minimum of 2 days and continued until clinical stabilisation. The usual duration of treatment is 2 to 8 days.

Treatment of acute ST-segment elevation myocardial infarction in combination with a thrombolytic agent in patients eligible or not for subsequent PCI:
An initial IV bolus injection of 3,000 anti-Xa IU (0.3 ml) followed by an SC injection of 100 anti-Xa IU/kg within 15 minutes, then every 12 hours (a maximum of 10000 anti-Xa IU (1.0 ml) for each of the first two SC doses only, followed by 100 anti-Xa IU/kg SC dosing for the remaining doses). For dosage in patients ⩾75 years of age, see sub-section Elderly.
The first dose of enoxaparin should be administered at any time between 15 minutes before 30 minutes after the start of thrombolytic treatment (whether fibrin-specific or not).
Administration of aspirin must be instituted as soon as possible after symptoms appear, and maintained at a dosage of between 75 mg and 325 mg daily for at least 30 days, unless otherwise indicated.
The recommended duration of **enoxaparin** treatment is 8 days, or until the patient is discharged from hospital if the hospitalization period is less than 8 days.

Patients managed with Percutaneous Coronary Intervention (PCI):
If the last SC injection of enoxaparin was performed less than 8 hours before balloon inflation, no additional administration is necessary.
If the last SC injection was performed more than 8 hours before balloon inflation, an IV bolus of 30 anti-Xa IU/kg of enoxaparin must be administered. In order to improve the accuracy of the volumes to be injected, it is recommended to dilute the drug to 300 anti-Xa IU/ml (see sub-section Intravenous (bolus) injection technique for the treatment of acute STEMI only)

Elderly:
Treatment of acute ST-segment elevation myocardial infarction, in combination with a thrombolytic agent in patients eligible or not for subsequent PCI:
In patients aged 75 and over, treated for acute ST-segment elevation myocardial infarction, the initial IV bolus injection should not be administered. A SC dose of 75 anti-Xa IU/kg every 12 hours should be administered (maximum of 7500 anti-Xa IU for each of the first two SC doses only, followed by 75 anti-Xa IU/kg dosing for the remaining doses).

For other therapeutic indications:
No dose adjustment necessary in the elderly, unless kidney functions is impaired.

Children:
Not recommended, a dosage is not established.

Renal impairment:
See Special Warnings & Precautions for Use

Severe renal impairment:
A dosage adjustment is required for patients with severe renal impairment (creatinine clearance < 30 ml/min), since enoxaparin sodium exposure is significantly increased in this patient population.

The following dosage adjustments are recommended for **prophylactic** dose ranges:

Standard Dosing	Severe renal impairment
2000-4000 anti-Xa IU SC once daily	2000 anti-Xa IU SC once daily

The following dosage adjustments are recommended for therapeutic dose ranges:

Standard Dosing	Severe renal impairment
100 anti-Xa IU/kg SC twice daily	100 anti-Xa IU/kg SC once daily
For treatment of acute STEMI in patients <75 years of age	
3000 anti-Xa IU-single IV bolus plus a 100 anti-Xa IU/kg SC dose followed by 100 anti-Xa IU/kg SC twice daily (Max 10000 anti-Xa IU for each of the first two SC doses)	3000 anti-Xa IU-single IV bolus plus a 100 anti-Xa IU/kg SC dose followed by 100 anti-Xa IU/kg SC once daily (Max 10000 anti-Xa IU for first SC dose only)
For treatment of acute STEMI in elderly patients ⩾75 years of age	
75 anti-Xa IU/kg SC twice daily without initial bolus (Max 7500 anti-Xa IU for each of the first two SC doses)	100 anti-Xa IU/kg SC once daily without initial bolus (Max 10000 anti-Xa IU for first SC dose only)

Moderate and mild renal impairment:
Although no dose adjustment is recommended in patients with moderate (creatinine clearance 30-50 ml/min) and mild (creatinine clearance 50-80 ml/min) renal impairment, careful clinical monitoring is recommended.

Hepatic impairment:
In the absence of clinical studies, caution should be exercised.
Administration: Inhixa is administered by subcutaneous injection for the prevention of venous thromboembolic disease, treatment of deep vein thrombosis or for the treatment of unstable angina and non-Q-wave myocardial infarction, and through the arterial line of dialysis circuit for the prevention of thrombus formation in the extracorporeal circulation during haemodialysis. It must not be administered by the intramuscular route.

Spinal/epidural anesthesia
For patients receiving spinal/epidural anesthesia see Section 4.4 Warnings: Spinal/epidural anesthesia.

Subcutaneous injection technique (except for patients with acute ST-segment elevation myocardial infarction, in whom IV bolus administration is required for solution for injection containing 6000, 8000 and 10000 anti-Xa IU):
The prefilled disposable syringe is ready for immediate use. Inhixa should be administered when the patient is lying down by deep subcutaneous injection. The administration should be alternated between the left and right anterolateral or postrolateral abdominal wall. The whole length of the needle should be introduced vertically into a skin fold held between the thumb and index finger. The skin fold should not be released until the injection is complete. Do not rub the injection site after administration.

Intravenous (bolus) injection technique for the treatment of acute ST-segment elevation myocardial infarction only:
Enoxaparin sodium should be administered through intravenous line. It should not be mixed or co-administered with other medications. To avoid the possible mixture of enoxaparin sodium with other drugs, the intravenous access chosen should be flushed with a sufficient amount of saline or dextrose solution prior to and following the intravenous bolus administration of enoxaparin sodium to clear the port of drug. Enoxaparin sodium may be safely administered with normal saline solution (0.9%) or 5% dextrose in water.

- Initial 3000 anti-Xa IU (0.3 ml) bolus

For the initial 3000 anti-Xa IU (0.3 ml) bolus, using an enoxaparin sodium graduated prefilled syringe, expel the excessive volume to retain only 3000 anti-Xa IU (0.3 ml) in the syringe. The 3000 anti-Xa IU (0.3 ml) dose can be directly injected into the intravenous line.

- Additional bolus for patients treated by PCI when last SC administration was given more than 8 hours before balloon inflation

For patients undergoing subsequent PCI an additional IV bolus of 30 anti-Xa IU/kg is to be administered if last SC administration was given more than 8 hours before balloon inflation (see Posology and Method of Administration: Treatment of acute STEMI).

In order to assure the accuracy of the small volume to be injected, it is recommended to dilute the drug to 300 anti Xa-IU/ml.

To obtain a 300 anti-Xa IU/ml solution, using a 6000 anti-Xa IU enoxaparin sodium prefilled syringe, it is recommended to use a 50 ml infusion bag (i.e. using either normal saline solution (0.9%) or 5% dextrose in water) as follows:
Withdraw 30ml from the infusion bag with a syringe and discard the liquid. Inject the complete contents of the 6000 anti-Xa IU (0.6 ml) enoxaparin sodium prefilled syringe into the 20 ml remaining in the bag. Gently mix the contents of the bag. Withdraw the required volume of diluted solution with a syringe for administration into the intravenous line.

After dilution is completed, the volume to be injected can be calculated using the following formula [Volume of diluted solution (ml) = Patient weight (kg) x 0.1) or using the table below. It is recommended to prepare the dilution immediately before use.

Volume to be injected through intravenous line after dilution is completed

Wight [Kg]	Required dose (30 anti-Xa IU/Kg) [IU]	Volume to inject when diluted to final concentration of 300 anti-Xa IU/ml [ml]
45	1350	4.5
50	1500	5
55	1650	5.5
60	1800	6
65	1950	6.5
70	2100	7
75	2250	7.5
80	2400	8
85	2550	8.5
90	2700	9
95	2850	9.5
100	3000	10

General recommendation:
Regular monitoring of the platelet count is essential throughout the treatment due to the risk of heparin-induced thrombocytopenia (HIT) (see Section 4.4 Special Warnings and Precautions for Use).

4.3 Contraindications
Contraindicated in patients with:
- acute bacteria endocarditis;
- active major bleeding disorders and conditions with a high risk of uncontrolled haemorrhage, including recent hemorrhagic stroke (unless due to systemic emboli);
- thrombocytopenia in patients with a positive in-vitro aggregation test in the presence of enoxaparin;
- acute gastric or duodenal ulceration;
- hypersensitivity to either enoxaparin sodium, heparin or other low molecular weight heparins;

4.4 Special warnings and precautions for use
Low Molecular Weight Heparins should not be used interchangeably since they differ
in their manufacturing process, molecular weights, specific anti-Xa activities, units and dosage. Very careful attention and compliance with the specific instructions on use of each product are absolutely essential.

Heparin-induced thrombocytopenia (HIT)
Enoxaparin sodium is to be used with extreme caution in patients with a history of heparin-induced thrombocytopenia with or without thrombosis.

Monitoring of platelet count
As there is a risk of antibody-mediated heparin-induced thrombocytopenia also occurring with a low molecular weight heparins, regular platelet count monitoring should be considered prior to and during therapy with these agents. Thrombocytopenia, should it occur, usually appears between the 5th and the 21st day following the beginning of therapy. Therefore, it is recommended that the platelet counts be measured before the initiation of therapy with enoxaparin sodium and then regularly thereafter during the treatment. In practice, if a confirmed significant decrease of the platelet count is observed (30 to 50% of the initial value), enoxaparin sodium treatment must be discontinued immediately and an alternative therapy initiated.

Monitoring of anti-factor Xa activity
Risk assessment and clinical monitoring are the best predictors of the risk of potential bleeding. Routine anti-Xa activity monitoring is usually not required. However, anti-Xa activity monitoring might be considered in those patients treated with LMWH who also have either an increased risk of bleeding (such as those with renal impairment, elderly and extremes of weight) or are actively bleeding.

Activated partial thromboplastin time (aPTT)
At doses used for prophylaxis of venous thromboembolism, enoxaparin sodium does not influence bleeding time and global blood coagulation tests significantly, nor does it affect platelet aggregation of binding of fibrinogen to platelets. At higher doses, increasing in aPTT (active Partial Thromboplastin Time) and ACT (Activated Clotting Time) may occur. Increases in aPTT and ACT are not linearly correlated with increasing enoxaparin sodium antithrombotic activity and therefore these tests are unsuitable and unreliable for monitoring enoxaparin sodium activity.

PCI/coronary angioplasty revascularization procedures:
To limit the risk of hemorrhage in patients undergoing coronary angioplasty for the treatment of unstable angina, non-Q-wave myocardial infarction and acute ST-segment elevation myocardial infarction, adhere precisely to the intervals recommended between Inhixa Injection doses. It is important to achieve hemostasis at the puncture site after PCI. In case a closure device is used, the sheath can be removed immediately. If a manual compression method is used, sheath should be removed 6 hours after the last IV/SC enoxaparin sodium injection. If the treatment with enoxaparin sodium is to be continued, the next scheduled dose should be given no sooner than 6 to 8 hours after sheath removal. The site of the procedure should be observed for signs of bleeding or hematoma formation.

Bleeding:
As with other anticoagulants, bleeding may occur at any site. If bleeding occurs, the origin of the hemorrhage should be investigated and appropriate treatment instituted. Enoxaparin sodium should be used with caution in conditions with increased potential for bleeding, such as impaired hemostasis, history of peptic ulcer, recent ischemic stroke, uncontrolled severe arterial hypertension, diabetic retinopathy and recent neuro- or ophthalmologic surgery, concomitant use of medications affecting hemostasis (see Interactions).

Heparin can suppress adrenal secretion of aldosterone leading to hyperkalaemia, particularly in patients such as those with diabetes mellitus, chronic renal failure, preexisting metabolic acidosis, a raised plasma potassium or taking potassium sparing drugs. The risk of hyperkalemia appears to increase with duration of therapy but is usually reversible. Plasma potassium should be measured in patients at risk before starting heparin therapy and monitored regularly thereafter particularly if treatment is prolonged beyond 7 days.

Hemorrhage in the elderly:
No increased bleeding tendency is observed in the elderly within the prophylactic dosage ranges. Elderly patients (especially patients aged eighty years and above) may be at an increased risk for bleeding complications within the therapeutic dosage ranges. In the treatment of acute ST-segment Elevation Myocardial Infarction (STEMI), an increase in bleeding events was observed in patients aged 65-75 years suggesting these patients might be at particular risk of bleeding. Careful monitoring is advised.

Renal impairment:
In patients with renal impairment, there is an increase in enoxaparin exposure which increases the risk of bleeding. Therefore, in patients with severe renal impairment, a dosage adjustment is recommended for prophylactic and therapeutic dose ranges (see Posology & Method of Administration). Although no dosage adjustments are recommended in patients with moderate (creatinine clearance 30-50ml/min) and mild (creatinine clearance 50-80 ml/min) renal impairment, careful clinical monitoring is advised. In the treatment of acute ST-segment Elevation Myocardial Infarction (STEMI), the data are limited in patients with creatinine levels above 220 and 175 µmol/L for males and females respectively.

Low weight:
In low weight patients (women < 45 kg and men < 57 kg), an increase in exposure of enoxaparin sodium with prophylactic doses has been observed which may lead to a higher risk of bleeding. Therefore, careful monitoring is recommended.

Obese patients:
Obese patients are at higher risk for thromboembolism. The safety and efficacy of prophylactic doses in obese patients (BMI > 30 kg/m^2) has not been fully determined and there is no consensus for dose adjustment. These patients should be observed carefully for signs and symptoms of thromboembolism.

Mechanical prosthetic heart valves
Use of enoxaparin in the prevention of thromboembolic complications in patients with mechanical prosthetic heart valves has not specifically been studied.

Nevertheless, some isolated cases of thrombosis have been reported in patients with mechanical prosthetic heart valves receiving enoxaparin for the prevention of thromboembolic complications.

Pregnant women with mechanical prosthetic heart valves
In a clinical study in pregnant women with mechanical prosthetic heart valves who received 100 anti-Xa IU/kg enoxaparin b.i.d. to reduce the risk of thromboembolic complications, 2 of 8 women developed thrombosis causing valve obstruction leading to maternal and fetal death. Moreover, isolated cases of prosthetic valve thrombosis in pregnant women receiving enoxaparin for the prevention of thromboembolic complications have been reported as part of post-marketing surveillance of the drug. Therefore, the risk of thromboembolic complications in these patients could be higher.

Spinal/epidural anesthesia in patients given preventive treatment with LMWH

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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 foetoxicity 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 (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1000 to < 1/100); rare (≥ 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 patients†,). 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
Vascular disorders	*Very common:* Haemorrhage* *Rare:* Retroperitoneal haemorrhage	Haemorrhage*	*Very common:* Haemorrhage* *Uncommon:* Intracranial haemorrhage, Retroperitoneal haemorrhage	*Common:* Haemorrhage* Rare: Retroperitoneal haemorrhage	*Common:* Haemorrhage* *Uncommon:* Intracranial haemorrhage, Retroperitoneal haemorrhage

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

† 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 ≥ 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
Blood and lymphatic system disorders	Very common: Thrombocytosis* Common: Thrombocytopenia	Uncommon: Thrombocytopenia	Very common: Thrombocytosis* Common: Thrombocytopenia	Uncommon: Thrombocytopenia	Common: Thrombocytosis* Thrombocytopenia Very rare: 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	Common: Allergic reaction Rare: Anaphylactic / anaphylactoid reaction (see also Post marketing experience)
Hepatobilary disorders	Very common: Hepatic enzymes increase (mainly transaminases**)
Skin and subcutaneous tissue disorders	Common: Urticaria, pruritus, erythema, Uncommon: Bullous dermatitis
General disorders and administration site conditions	Common: Injection site haematoma, injection site pain, other injection site reaction* Uncommon: Local irritation; skin necrosis at injection site
Investigations	Rare: 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 ounts).
- 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

• Hepatobilary 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 > 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, Guandong Province, Shenzhen 518057, China

6.7 Date of Revision of Text
Aug 2021

210 mm

580 mm