··Revised: August 2017

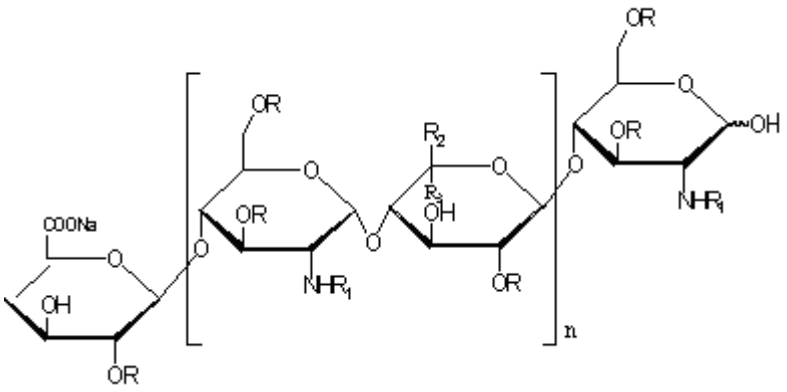
Enoxaparin Sodium Injection

Please read carefully and use under guidance of physicians.

WARNING: Intraspinal Hematomas. It should be attention that when intraspinal anesthesia (spinal anesthesia and epidural anesthesia) or spinal puncture, the use of low molecular weight heparins (LMWH) or heparinoids for thrombus complications prevention may induce intraspinal hematomas. These hematomas may result in long-term or permanent paralysis, nevertheless, it happen very rarely. Epidural catheter insertion, or repeated epidural puncture, or the concomitant use of the drugs affecting hemostasis such as non-steroidal anti-inflammatory drugs (NSAIDs), platelet inhibitors or other anticoagulants, may have a higher incidence rate of intraspinal hematomas. In this case it is necessary to monitor the signs and symptoms caused by neural injury. In case of possible nerve injuries found, emergency treatment is needed. Consider the benefits and risks when the doctor implements the intraspinal intervention (anesthesia or puncture).

[Drug Names]
Generic Name: Enoxaparin Sodium Injection
English Name: Enoxaparin Sodium Injection
Chinese Pinyin: Yinuo Gansuna Zhusheye

[Active ingredient]
Chemical name: enoxaparin sodium. It is a kind of low molecular weight heparin sodium. It is the sodium salt of sulphated glucosaminoglycans, obtained by alkaline degradation of the benzyl ester derivative of heparin from porcine intestinal mucosa.
Structural Formula:



In which, n= 1~21; R= -H or -SO_3Na; R1= -H or -SO_3Na or $COCH_3$;
R2 = -H, R3= -CO_2Na or R2= -CO_2Na, R3 = -H.

Molecular Weight: Weight-average molecular weight ranges between 3500~5500

Dalton.

[Properties]
Clear, colorless to pale yellow solution.

[Indications]

- Prophylaxis of venous thromboembolic diseases (prevention of blood clot formation in veins) in particular those which may be associated with orthopedic or general surgery.
- Treatment of established deep vein thrombosis, with or without pulmonary embolism (PE), not with severe medical symptoms, excluding PE likely to require thrombolytic therapy or surgery.
- Treatment of unstable angina and non-Q-wave myocardial infarction, administered concurrently with aspirin.
- Prevention of thrombus formation in the extra-corporeal circulation during hemodialysis.
- Treatment of acute ST-segment elevation myocardial infarction, receiving thrombolysis or with percutaneous coronary intervention (PCI).

[Strength]
0.4ml: 4000AxaIU; 0.6ml: 6000AxaIU

[Administration and Dosage]
1 mg (0.01 ml) of enoxaparin sodium corresponds approximately to 100 I.U. anti-Xa activity (100 AXa IU).
Enoxaparin sodium should be injected by deep subcutaneous route in prophylaxis of venous thromboembolic diseases, treatment of deep vein thrombosis, treatment of unstable angina and non-Q-wave myocardial infarction, and by intravascular route during hemodialysis in the extra-corporeal circulation; for treatment of acute ST-segment elevation myocardial infarction, enoxaparin sodium is injected initially by intravenous route and followed by deep subcutaneous route.
Do not inject via intramuscular route.
Subcutaneous injection technique:
The pre-filled syringes are ready-to-use. The air bubble from the syringe should not be expelled before the injection. The subcutaneous injection should preferably be made with the patient supine. Enoxaparin sodium is administered in the subcutaneous tissue of the anterolateral or posterolateral abdominal wall, alternately on the left and the right side. The whole length of the needle should be introduced perpendicularly, not tangentially, into a skin fold created between the thumb and index finger. This skin fold should be held throughout the injection.
Intravenous injection technique only for treatment of acute ST-segment elevation myocardial infarction:
When Enoxaparin sodium is administered through an intravenous line, it should not

be mixed or coadministered with other medications. To avoid the possible mixture of enoxaparin 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 to clear the port of drug. Enoxaparin may be safely administered with normal saline solution (0.9%) or 5% dextrose in water.

Initial 3000 AXa IU intravenous administration:

Hold 3000 AXa IU (0.3 ml) of enoxaparin in the syringe, and expel the redundant liquid. Inject the 3000 AXa IU bolus directly into the intravenous vein.

Additional intravenous bolus for percutaneous coronary intervention (PCI):

For patients managed with percutaneous coronary intervention (PCI), if the last enoxaparin subcutaneous administration was given more than 8 hours before balloon inflation, an additional intravenous bolus of 30 AXa IU/kg of enoxaparin should be administered.

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

To obtain a 300 AXa IU/ml solution, using a 6000 AXa IU enoxaparin sodium pre-filled syringe, it is recommended to use a 50 ml infusion bag (i.e. using either 0.9% normal saline solution or 5% dextrose in water) as follows:

Withdraw 30 ml from the infusion bag with a syringe and discard the liquid. Inject the complete contents of the 6000 AXa IU enoxaparin sodium pre-filled syringe into the 20 ml remaining in the bag. Mix the contents of the bag gently. Withdraw the required volume of diluted solution with a syringe for intravenous injection.

After dilution is completed, the volume to be injected can be calculated using the following formula [volume of diluted solution (ml) = patient's weight (kg) × 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

Weight	Required dose (30 IU/kg)	Volume to inject when diluted to a final concentration of 300 IU/ml
(kg)	IU	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:

As there is a risk of heparin-induced thrombocytopenia also occurring with low molecular weight heparins, regular platelet count monitoring should be considered during the therapy.

- **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 AXa IU (0.2 ml) or 4000 AXa IU (0.4 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 thromboembolism (e.g. orthopedic surgery), the recommended dose of enoxaparin sodium given by subcutaneous injection is 4000 AXa IU (0.4 ml) once daily, initiated 12 hours preoperatively.

For special recommendations concerning dosing intervals for spinal/epidural anesthesia and percutaneous coronary revascularization 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. Continued therapy with 4000 AXa IU once daily for 3 weeks has been proven to be beneficial in orthopedic surgery.

- **Prophylaxis of venous thromboembolic disease in medical patients**

The recommended dose of enoxaparin sodium is 4000 AXa 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 deep vein thrombosis, with or without pulmonary embolism, not with severe medical symptoms**

The uncertain reasons for deep vein thrombosis should be identified by appropriate examinations.

Posology and method of administration:

Enoxaparin sodium should be administered subcutaneously either as a single daily injection of 150 AXa IU/kg or as twice daily injections of 100 AXa IU/kg. In patients with complicated thromboembolic disorders, a dose of 100 AXa IU/kg twice daily is recommended.

The posology of enoxaparin sodium has not been assessed in patients with body weight more than 100 kg or lower than 40 kg. The therapeutic effect of enoxaparin sodium may decrease slightly in patients with body weight > 100 kg. The bleeding risk may increase in patients with body weight < 40 kg. All such patients should be observed carefully.

During the treatment of deep vein thrombosis, enoxaparin sodium should be replaced by oral anticoagulant therapy as early as possible, unless there is a specific contraindication. Enoxaparin sodium treatment is usually prescribed for a maximum of 10 days, including the days required to achieve a therapeutic anticoagulant effect, unless it cannot be established (see section *Precautions: platelet monitoring*).

Therefore, oral anticoagulant therapy should be initiated at early stage.

- **Prevention of thrombus formation in extracorporeal circulation during hemodialysis**

The recommended dose of enoxaparin sodium is 100 Axa IU/kg. During hemodialysis enoxaparin sodium should be introduced into the arterial line of the circuit at the beginning of the dialysis session. The effect of this dose is usually sufficient for a 4-hours session. However, if fibrin rings are found in the dialysis device, a further dose of 50 to 100 Axa IU/kg should be given.

- **Treatment of unstable angina and non-Q wave myocardial infarction**

The recommended dose of enoxaparin sodium is 100 Axa IU/kg every 12 hours by subcutaneous injection, administered concurrently with oral aspirin (100 to 325 mg once daily). The usual duration of treatment is 2 to 8 days, till clinical stabilization.

- **Treatment of acute ST-segment elevation myocardial infarction, receiving thrombolysis or with percutaneous coronary intervention (PCI)**

The recommended dose of enoxaparin sodium is a single IV bolus of 3000 AXa IU at the beginning and a 100 AXa IU/kg SC dose after 15 minutes, followed by 100 AXa IU/kg administered SC every 12 hours (max 10000 AXa IU for the first two SC doses only).

When administered in conjunction with a thrombolytic (fibrin specific or nonfibrin specific) enoxaparin sodium should be given between 15 minutes before and 30 minutes after the start of fibrinolytic therapy.

The recommended duration of enoxaparin sodium treatment is 8 days or until hospital discharge, whichever comes first.

Concomitant therapy: All patients should receive acetylsalicylic acid (ASA) as soon as they are identified as having STEMI and maintained under 75 to 325 mg once daily unless contraindicated.

For patients managed with Percutaneous Coronary Intervention (PCI):

If the last enoxaparin sodium SC administration was given less than 8 hours before balloon inflation, no additional dosing is needed. If the last SC administration was given more than 8 hours before balloon inflation, an IV bolus of 30 AXa IU/kg of enoxaparin sodium should be administered. To enhance the accuracy of injection dose, it is recommended to dilute the drug to 300 AXa IU/ml (see section *Administration and Dosage: Intravenous injection technique only for treatment of acute ST-segment elevation myocardial infarction*).

For treatment of acute ST-segment elevation myocardial infarction in elderly patients ≥75 years of age, do not use an initial IV bolus. Initiate dosing with 75 AXa IU/kg SC every 12 hours (maximum 7500 AXa IU for the first two doses only).

- Renal failure: For prophylactic objective the dose adjustment is not needed, but for treatment the dose should be adjusted and the anti-Xa activity should be monitored.
- For patients of body weight lower than 40 kg or higher than 100 kg: the dose should be adjusted according to clinical monitoring.

[Adverse reactions]

Like other drugs, the product may induce undesirable effects to a greater or lesser degree.

– Hemorrhage (bleeding):

Associated risk factors: age, renal impairment, low body weight, variance from the therapeutic advice, especially no dose adjustment according to body weight.

This may occur during treatment with any anticoagulant: organic lesions liable to bleed, the concomitant use of medications affecting hemostasis (see section *Precautions*), or retroperitoneal and intracranial bleeding. Some of these cases have been fatal. If it happens, your physician should be informed immediately to use low molecular weight heparins during spinal/epidural anaesthesia with very few reports of intraspinal hematomas. These reactions have resulted in varying degrees of neurologic injuries including long-term or permanent paralysis.

– Hematomas may occur at injection sites after subcutaneous injection.

The risk may be increased if the recommended injection route is not followed or reasonable injection supplies are not used. Petechia and ecchymosis were found in part of the injection sites. Rarely, hard inflammatory nodules have been observed at the injection site. They resolve after a few days and should not cause treatment discontinuation. Exceptional cases of skin necrosis (skin lesion including irreversible damages) at the injection site have been reported. These phenomena are usually preceded by purpura (small hemorragia in the skin) or erythematous plaques (red inflammatory rash), infiltrated and painful. Treatment must be discontinued.

– Localized or general allergic reactions. Although rare, cutaneous (bullous eruptions) or systemic allergic reactions may occur.
– Thrombocytopenia (abnormally low platelet count level):

In rare cases, immno-allergic thrombocytopenia with thrombosis (formation of clot in the veins). In some cases, thrombosis was complicated by organ infarction (tissue death by lack of oxygen) or limb ischemia (deficiency of blood supply). Your physician should be informed immediately.

– Asymptomatic and Reversible thrombocytosis may occur.
– Risk of Osteoporosis (bone dernineralization leading to bone fragility): may occur after several months' therapy.
– Increased blood level of certain enzymes (transaminases).
– Cases of hyperkalemia have been reported.
– Rare cutaneous vasculitis occurs due to hypersensitivity.

Do not hesitate to ask your physician or pharmacist for advice and to report any undesirable effect not mentioned in this leaflet.

[Contraindications]

This medicine should not be used in the following situations:

– Hypersensitivity to either enoxaparin sodium, heparin or its derivatives including other Low molecular weight heparins;
– Hemorrhage or bleeding associated with major clotting disorders (except for diffuse intravascular coagulation unrelated to heparin therapy);
– History of type II heparin-induced thrombocytopenia (obvious decrease of platelet

count in the past) induced by heparins or low molecular weight heparins;
- Active gastro-intestinal ulcer or organic lesion likely to bleed;
- Clinical significant active hemorrhage;
- Cerebral hemorrhage;
- Due to the lack of relevant data, except the special cases requiring dialysis, patients with severe renal impairment (measuring body weight, according to Cockcroft formula, creatinine clearance 30 ml/min);

For patients with severe renal impairment, unfractionated heparin should be used.
- Patients receiving therapeutic low molecular weight heparins should not undergo spinal anesthesia or epidural anesthesia;

This medicine is not recommended in the following situations:
- Acute large-area ischemic stroke with or without disorder of consciousness;

If the stroke is due to embolism, enoxaparin should not be injected within 72 hours.
Regardless of the cause of stroke, infarct size or clinical severity, the efficacy of enoxaparin and other low molecular heparins treatment doses have not been established.
- Mild to moderate renal impairment (creatinine clearance 30-60 ml/min);
- Uncontrolled arterial hypertension;
- Acute infectious endocarditis, except for some embolized heart diseases.

In addition, the medicine should be used with caution when used in combination with other medicines.
In case of doubt you must consult your physician or pharmacist.

[Precautions]
Enoxaparin should be used with caution in the following cases: patients with hemostasis disorder and renal or hepatic dysfunction, history of peptic ulcer, or any organic lesion likely to bleed, recent ischaemic stroke, uncontrolled severe arterial hypertension, diabetic retinopathy, shortly after neural or ophthalmologic surgery and spinal or epidural anesthesia. As with other anticoagulants, bleeding may occur at any site (see section *Adverse reactions*). If bleeding occurs, the origin of the haemorrhage should be investigated and appropriate treatment instituted.
· No increase in bleeding is observed in the elderly at prophylactic doses while at therapeutic doses bleeding complications may be observed particularly in patients ≥ 80 years of age. Careful monitoring is recommended.
· Renal impairment:
Renal function needs to be assessed before treatment with low molecular weight heparin, especially for patients ≥ 75 years of age, mainly using the Cockcroft formula and the recently determined body weight to determine creatinine clearance (Clcr).
Male patients: Clcr=(140-age)×body weight/(0.814×serum creatinine). Where, age is "years old", body weight is kg, serum creatinine is μmol/l. For femal patients, the result of the formula should be multiplied by 0.85. When the serum creatinine unit is mg/ml, the value should be multiplied by 8.8. In patients with renal impairment, there is an increase in exposure of low molecular weight heparin which increases the risk of bleeding. Therefore, in patients with severe renal impairment (creatinine clearance 30

ml/min), a dosage adjustment is recommended. The following dosage adjustments are recommended:
Prophylactic dose ranges: 2000 Axa IU once daily; therapeutic dose ranges: 100 Axa IU/kg once daily.
Although no dosage adjustments are recommended in patients with moderate and mild renal impairment, careful clinical monitoring is advised.
· Hepatic impairment: Caution should be used in hepatically impaired patients.
· In low-weight women (< 45 kg) and low-weight men (< 57 kg), an increase in low molecular weight heparin exposure has been observed within the prophylactic dosage ranges (non-weight adjusted), which may lead to a higher risk of bleeding. Therefore, careful clinical monitoring is advised in these patients.
· Laboratory examination
– Platelet monitoring
Heparin-induced thrombocytopenia (HIT)
There is a risk of severe, sometimes thrombotic, heparin-induced thrombocytopenia (the main report is unfractionated heparin, which is less common in low molecular weight heparin) during treatment, which is mainly immunogenic, known as type II HIT.
As the risk of thrombocytopenia occurring with low molecular weight heparins, regular platelet count monitoring should be considered regardless of the therapeutic indication and the dosage administrated. It is recommended that the platelet counts should be measured before administration or within 24 hours after initiation of therapy and twice a week during the treatment. If the platelet count falls below 100,000/mm^3 and/or decreased by 30%-50% between two consecutive counts, heparin-induced thrombocytopenia should be suspected. Thrombocytopenia, should it occur, usually appears between the 5th and the 21st day following the beginning of therapy (about 10 days after treatment as the peak period).
Thrombocytopenia may occur earlier if patients has a history of heparin-induced thrombocytopenia, but there are a few reports that occurred after 21 days of treatment. Therefore, before starting treatment, patients need to be asked about the relevant medical history in detail and systematically. Moreover, when heparin is used again, the risk of recurrent thrombocytopenia may persist for several years or even longer.
In all cases, heparin-induced thrombocytopenia is an emergency and requires expert's advice.
The significant decrease of the platelet count (30 to 50 % of the initial value) is a warning, which makes the previous platelet count reach a critical level. If a decrease in platelet count is observed, all cases need to be examined:
1) Immediate confirmation of platelet count;
2) If it is confirmed that the number of platelets has decreased, or even the decrease in platelets has increased, heparin treatment must be immediately discontinued in the absence of other clear reasons.
In order to perform platelet aggregation assay and immunologic test in vitro, citrate test tube was used to collect samples. But, in this case, the immediate measures are not based on the in vitro platelet aggregation rate or the results of the immunologic

test, because only some special laboratories can routinely perform these tests, and ideally in a few hours to obtain the results. However, these examinations are necessary to aid in the diagnosis of complications, as the risk of thrombosis will be high if heparin therapy is continued.

3) Prevention and treatment of thrombotic complications associated with HIT.

If continued anticoagulant therapy is necessary, heparin should be replaced with other types of anticoagulant drugs, such as danaparoid sodium or hirudin, but the dose of both treatment and prevention should be individualized.

– Replacement of heparin with oral anticoagulant

Clinical observations and laboratory tests will enhance the monitoring of the efficacy of oral anticoagulants.

Since oral anticoagulant therapy has a segmental interval before its optimal efficacy, heparin therapy should continue at a fixed dose, in order to maintain the international normalized ratio (INR) value within the expected treatment range during two consecutive examinations.

– Monitoring of anti-Xa activity

Since many clinical studies have shown that for the adjustment of low molecular weight heparin dose according to body weight, the efficacy is not specifically monitored in the laboratory. And laboratory tests for evaluating the efficacy of low molecular weight heparin have not been established. However, laboratory tests, such as monitoring of anti-Xa activity, may play a role in the management of bleeding risk in some clinical situations with a risk of drug overdose.

These conditions mainly occur when low molecular weight heparin is administered to the following patients:

1) Patients with mild to moderate renal impairment (calculated by Cockroft formula, creatinine clearance 30-60 ml/min). Because low molecular weight heparin is different from unfractionated heparin, mainly through renal clearance, and any renal impairment disease can lead to relative drug overdose (see section *Contraindications*);

2) Overweight or underweight (emaciation or even cachexia, obesity);

3) Unexplained bleeding.

Conversely, if low molecular weight heparin treatment follows treatment recommendations (especially for treatment course), laboratory monitoring may not be recommended for prophylactic medication or hemodialysis.

To determine the possible cumulative effect of heparin after repeated administration, it is recommended that blood samples should be collected at peak blood concentration (based on collected data), such as subcutaneous injection twice daily, and about 4 hours after the third injection.

By repeating the activity of factor Xa to determine the level of serum heparin, such as every 2 to 3 days, the dose of low molecular weight heparin should be adjusted based on individual condition and previous result.

The anti-Xa activity of each low molecular weight heparin and each administration method is different.

According to the collected data, the mean value (±standard deviation) was 1.20 ± 0.17 AXa IU/ml measured at 4 hours after the 7th injection of 100 Axa IU/kg of

enoxaparin twice daily.
The average value of the anti-Xa activity during clinical trials was determined by fluorescence assay (amide decomposition method).
– Activated partial thromboplastin time (aPTT)
Some low molecular weight heparins increase aPTT moderately. Since no clinical correlation has been established, it is meaningless to monitor the therapeutic effect with the test.
The following conditions require therapeutic monitoring:
1) Hepatic dysfunction
2) History of peptic ulcer or any organic lesion likely to bleed
3) Choroidal retinal vascular disease
4) After brain or spinal cord surgery
5) Lumbar puncture: mainly considering the possible risk of spinal cord hemorrhage, so postpone as much as possible
6) Combination with drugs that affect blood clotting (see section *Interactions*)
In all cases, the doctor's advice should be strictly observed.
Special warning:
Do not inject intramuscularly.
Keep out of reach of children.

Low molecular weight heparins should not be used interchangeably since they differ in their manufacturing process, molecular weights, anti-Xa activities and dosage.
Special attention and compliance with the instructions for use specific to each proprietary medicinal product are therefore required. Enoxaparin is to be used with extreme caution in patients with a history of heparin-induced thrombocytopenia.

· Bleeding risk
Recommended medications (therapeutic doses and course) must be followed. Failure to follow these recommendations completely may result in bleeding, especially in patients at high risk (elderly, with renal impairment, etc.).
The following serious bleeding events have been reported:
- Elderly subjects, especially those with age-related renal impairment
- Patients with renal failure
- Body Weight < 40 kg
- Treatment time exceeds the recommended average of 10 days course
- Failure to follow recommended medication method (especially during the treatment period and at the time of treatment, the dose was not adjusted according to body weight)
- Combination with drugs that increase the risk of bleeding (see section *Interactions*)
Close monitoring of elderly patients and/or patients with renal impairment, as well as patients with a prolonged treatment period of more than 10 days is required.
When detecting drug accumulation, anti-Xa activity should be determined in some cases.
· Heparin-induced thrombocytopenia (HIT) risk :

When the following thrombosis complications occur in patients treated with low molecular weight heparin (therapeutic dose or prophylactic dose):
- The thrombus treated is aggravated
- Phlebitis
- Pulmonary embolism
- Acute ischemia of lower extremities
- or myocardial infarction or ischemic stroke

Heparin-induced thrombocytopenia should be suspected and platelet counts should be examined urgently.

· Spinal/epidural anesthesia:

As with other anticoagulants, there have been cases of neuraxial hematomas reported with the concurrent use of enoxaparin sodium and spinal/epidural anesthesia, resulting in long-term or permanent paralysis. The above events are very rare with enoxaparin sodium dosage regimens of 4000 Axa IU once daily or lower. The risk of these events may be higher with prolonged use of post-operative epidural catheters. Neurological monitoring is required. Trauma or repeated puncture can also increase the occurrence of the above events. During epidural or spinal anesthesia, the placement and removal of the catheter is best performed when the anticoagulant effect of enoxaparin sodium is low: 10-12 hours after administration of 4000 IU or less daily doses of enoxaparin sodium or 24 hours following the administration of higher doses (100 Axa IU/kg twice daily or 150 Axa IU/kg once daily) .

The subsequent administration should be given no sooner than 2 hours after catheter removal. Extreme vigilance and frequent monitoring of the patient's neurological status is required. If signs of neuraxial hematoma are suspected urgent diagnosis and treatment including spinal cord decompression are necessary.

· Prosthetic heart valves

There have been no adequate studies to assess the safe and effective use of enoxaparin sodium in preventing thromboembolism in patients with prosthetic heart valves. The use of enoxaparin sodium can not be recommended for this purpose.

· Percutaneous coronary revascularisation procedures

To minimise the risk of bleeding following vascular instrumentation during the treatment of unstable angina, non-Q-wave myocardial infarction and acute ST-segment elevation myocardial infarction, adhere precisely to the intervals recommended between enoxaparin sodium doses. It is important to achieve homeostasis 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 haematoma formation.

This drug should only be taken under the medical supervision.
Never suddenly discontinue treatment without consulting a your physician.

[Pregnancy and lactation]

Pregnancy

Animal studies have not shown any evidence of teratogenicity due to enoxaparin.

Since there is no teratogenicity in animals, it is expected that there will be no similar effect in humans. At present, comparative studies between two lines have found that substances that have teratogenic effects on humans have been confirmed to have teratogenic effects on animals.

At present, there was insufficient clinical data to determine its possible teratogenic effects or fetotoxicity of enoxaparin with therapeutic dose during pregnancy.

Currently, the use of therapeutic dose of enoxaparin during pregnancy is not recommended as a precaution.

Spinal anesthesia or epidural anesthesia should not be performed during the treatment with low molecular weight heparins.

In humans, there is no evidence that enoxaparin crosses the placental barrier. Enoxaparin sodium should be used during pregnancy only if the physician has established a clear need.

Lactation

In principle, it is impossible for newborns to absorb this drug through gastrointestinal tract, so there is no contraindication for lactating women to use enoxaparin.

Lactating women are suggested to stop lactation during administration.

[Pediatric Use]

Safety and effectiveness in pediatric patients have not been established, so low molecular weight heparins are not recommended in children.

[Geriatric Use]

In elderly subjects renal function is physiologically decreased, and elimination is slightly slower. This change does not require adjustment of the dose or frequency of injections in preventive treatment as long as the renal function of these patients remains within acceptable limits, i.e. only slightly impaired.

Renal function needs to be assessed before treatment with low molecular weight heparin, especially for patients ≥ 75 years of age, mainly using Cockcroft formula (see section *Precautions*).

Patients with mild to moderate renal impairment (creatinine clearance > 30 ml/min)：

In some cases, in order to prevent overdosage of enoxaparin at therapeutic doses, in curative treatment anti-Xa activity should be measured (see section *Precautions*).

[Interactions]

In order to avoid possible interaction with other drugs, you must inform your physician or pharmacist about any other current treatment.

Certain medications or treatment categories may increase the incidence of hyperkalemia:

Potassium salts, potassium-preserving diuretics, conversion enzyme inhibitors, angiotensin II inhibitors, non-steroidal anti-inflammatory drugs, heparin (low

molecular weight heparin or **unfractionated heparin**), cyclosporine and tacrolimus, trimethoprim.
There is a potential risk when used in combination with the above drugs.

Not recommended medicines (combination increasing hemorrhagic tendency): acetylsalicylic acid (and derivatives) at analgesic and antipyretic doses, non steroidal anti-inflammatory drugs (general route), dextran 40 (parenteral use).
When using this product together with the following drugs, attention should be paid: oral anticoagulant, glucocorticoid (systemic medication).
Combinations to be used with caution: anticoagulant, acetylsalicylic acid at anticoagulant platelet doses (in the treatment of unstable angina and non-Q-wave myocardial infarction), clopidogrel, glucocorticoids (general route).
Anticoagulant, abciximab, for antiplatelet agglutination doses of acetylsalicylic acid (for the treatment of unstable angina and non-Q-wave myocardial infarction), beraprost, clopidogrel, eptifibatide, iloprost, ticlopidine, tirofiban.

[Overdose]
Overdosage after subcutaneous injection of massive doses of enoxaparin could lead to bleeding complication.
Neutralization can be obtained by slow intravenous injection of protamine (1 mg protamine can be used to neutralize the anticoagulant effect of 1 mg enoxaparin).
In case of overdosage or accidental intoxication you must inform your physician.

[Pharmacology and Toxicology]
Enoxaparin is a low molecular weight heparin with high anti-Xa activity (100 I.U./mg), and low anti-IIa or anti-thrombin activity (about 28 I.U./mg). At doses required for the various indications, it does not increase bleeding time. At preventive doses, enoxaparin has no significant effect on APTT. It neither influences platelet aggregation nor binding of fibrinogen to platelets.

[Pharmacokinetics]
The pharmacokinetic parameters have been studied in terms of the time course of plasma anti-Xa activity.
Bioavailability: After subcutaneous injection, enoxaparin sodium is absorbed rapidly and completely, and its bioavailability is approximately 95%.
Distribution: Three hours after subcutaneous injection, the blood drug concentration reaches its maximum. Anti-Xa activity exists in veins.
Biotransformation: Enoxaparin is primarily metabolized in liver.
Elimination: The half time of anti-Xa activity is about 4.4 hours after administration of 4000 Axa IU (0.4 ml), while it is about 4 hours after administration of 6000 Axa IU (0.6 ml) or 8000 Axa IU (0.8 ml). The elimination half-time is prolonged slightly in elder patients.
Excretion: Enoxaparin is excreted by urine.

[Storage]
Store in dark and cool place (avoid light, at temperature not more than 25℃).

[Package]
Pre-filled syringe, 2 syringes/pack; Pre-filled syringe, 10 syringes/pack; Ampoule, 10 ampoules/pack

[Shelf life]
24 months

[Specification]
National Pharmaceutical Standard YBH04982006

[Approval Number]
GYZZ H20064066 (0.4 ml)
GYZZ H20064067 (0.6 ml)

[Manufacturer]
Name: Hangzhou Jiuyuan Gene Engineering Co., Ltd.
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