APPROVED

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of Health of Ukraine

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Registration certificate

No. UA/13119/01/01

INSTRUCTION

for medical use of medicinal product

FLENOX®

Composition:

active ingredient: enoxaparin sodium;

1 mL of solution contains: 10,000 anti-Ха IU, equivalent to 100 mg of enoxaparin sodium;

2,000 anti-Ха IU/0.2 mL, equivalent to 20 mg of enoxaparin sodium;

4,000 anti-Ха IU/0.4 mL, equivalent to 40 mg of enoxaparin sodium;

6,000 anti-Ха IU/0.6 mL, equivalent to 60 mg of enoxaparin sodium;

8,000 anti-Ха IU/0.8 mL, equivalent to 80 mg of enoxaparin sodium;

excipients: water for injection.

Pharmaceutical form

Solution for injection.

Basic physical and chemical properties: clear, colorless or light yellow liquid.

Pharmacotherapeutical group

Anti-thrombotics. Heparin group. Enoxaparins.

ATC Code В01А В05.

Pharmacological properties

Pharmacodynamics

Enoxaparin is a low-molecular-weight heparin (LMWH) in which the antithrombotic and anticoagulant activities of standard heparin have been dissociated. It is characterized by higher anti-Xa activity than anti-IIa and antithrombin activity (for enoxaparin, the ratio between these two activities is 3.6). At prophylactic doses, it does not significantly affect the aPTT (activated partial thromboplastin time).

At curative doses, aPTT can be prolonged by 1.5-2.2 times the control time at peak activity. This prolongation reflects the residual antithrombin activity.

Treatment of acute ST-segment elevation myocardial infarction, in combination with thrombolytic patients eligible or not for subsequent coronary angioplasty.

In a large-scale multicenter clinical study, 20,479 patients with acute ST-segment elevation myocardial infarction after fibrinolytic therapy were randomised to receive either enoxaparin as a bolus intravenous injection of 3,000 anti-Xa IU, followed by immediate subcutaneous dose of 100 anti-Xa IU/kg, then they were administered subcutaneous injections of 100 anti-Xa IU/kg every 12 hours, or treated with intravenous unfractionated heparin as a bolus injection of 60 IU/kg (up to 4,000 IU/kg) followed by continuous infusion at a dose adjusted according to an activated partial thromboplastin time value. Subcutaneous injections of enoxaparin were administered until discharge from the hospital or for a maximum period of 8 days (in 75% of cases for at least 6 days). Half of patients receiving heparin were administered the drug for at least 48 hours (in 89.5% of cases for ≥ 36 hours). All the patients were also treated with acetylsalicylic acid for at least 30 days. The enoxaparin dosage was adjusted for patients aged 75 years or more: 0.75 mg/kg (75 anti-Xa IU/kg) as a subcutaneous injection every 12 hours, without an initial IV bolus injection.

During the study 4,716 (23%) patients underwent coronary angioplasty with antithrombotic treatment using blinded study drugs. Patients did not receive an additional dose if the last subcutaneous injection of enoxaparin had been given less than 8 hours before balloon inflation, or, received an IV bolus injection of 0.3 mg/kg (30 anti-Xa IU/kg) if the last subcutaneous injection of enoxaparin had been given more than 8 hours before balloon inflation.

Enoxaparin significantly reduced the incidence of primary end point events (the composite end point consisting of myocardial infarction relapse and all-cause mortality within 30 days of follow-up period after the study inclusion: 9.9% in the enoxaparin group versus 12% 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 coronary angioplasty within 30 days after inclusion (10.8% versus 13.9%, 23% reduction in relative risk) and in patients who did not have coronary angioplasty (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% 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.

Pharmacokinetics

The pharmacokinetic parameters of enoxaparin have been evaluated based on the time changes in plasma anti-Xa and anti-IIa activity at the recommended dose ranges.

Bioavailability. Subcutaneously administered enoxaparin is rapidly and almost completely absorbed (nearly 100%). Peak plasma activity is observed between 3 and 4 hours after administration.

This peak activity (expressed as anti-Xa IU) is 0.18 ± 0.04 (after 2,000 anti-Xa IU), 0.43 ± 0.11 (after 4,000 anti-Xa IU) in prophylactic treatment, and 1.01 ± 0.14 (after 10,000 anti-Xa IU).

An IV bolus injection of 30 mg (0.3 mL; 3,000 anti-Xa IU) followed by 1 mg/kg (100 anti-Xa IU/kg) by the subcutaneous route every 12 hours leads to a first peak in anti-Factor Xa levels of 1.16 IU/mL (n=16) and the mean area under the curve corresponding to 88% of the steady state level. Steady state is reached on the second day of treatment.

Enoxaparin pharmacokinetics is linear over the recommended dose range. Intra-patient and inter-patient variability is low. After repeated subcutaneous administration of 40 mg (0.4 mL; 4,000 anti-Xa IU) once daily in healthy volunteers, the steady state is reached on day 2 with mean enoxaparin activity of approximately 15% higher than that obtained after a single dose. Steady-state enoxaparin activity levels are well predicted by single dose pharmacokinetics. After repeated subcutaneous administration of 1 mg/kg (100 anti-Xa IU/kg) b.i.d., the steady state is reached between day 3 and 4 with mean exposure about 65% higher than after a single dose, and with maximum and minimum anti-Xa activity of about 1.2 and 0.52 anti-Xa IU/mL, respectively. Based on enoxaparin sodium pharmacokinetics, this difference in steady state is expected and is within the therapeutic range.

Plasma anti-IIa activity after subcutaneous administration is about 10-fold lower than anti-Xa activity. The mean maximum anti-Xa activity is observed approximately 3 to 4 hours following subcutaneous injection, and reaches 0.13 anti-Xa IU/mL following repeated administration of a 1 mg/kg (100 anti-Xa IU/kg) dose b.i.d.

Distribution. The volume of distribution of enoxaparin anti-Xa activity is about 5 liters and is close to the circulation blood volume.

Metabolism. Enoxaparin is metabolized mainly in the liver (desulfation, depolymerization).

Elimination. Following subcutaneous injection, the apparent anti-Xa activity elimination half-life is higher for low-molecular-weight heparins than for unfractionated heparins.

Enoxaparin exhibits a monophasic elimination pattern with a half-life of about 4 hours after a single subcutaneous dose to about 7 hours after repeated dosing. With low-molecular-weight heparin, plasma decay occurs more quickly for anti-IIa activity than for anti-Xa activity.

Enoxaparin and its metabolites are eliminated via the renal route (nonsaturable mechanism) and by the biliary route.

Renal clearance of fragments with anti-Xa activity accounts for 10% of the administered dose, and total renal excretion of active and non-active metabolites is 40% of the dose.

High-risk populations

Elderly patients. As renal function is physiologically impaired in this population, elimination is slower. This does not affect doses or the administration schedule in prophylactic. It is essential to systematically assess renal function in elderly patients over 75 years of age using the Cockroft formula before initiating treatment with LMWH.

Patients with mild to moderate renal failure (creatinine clearance >30 mL/min). In certain cases, it may be useful to monitor the circulating anti-factor Xa activity to prevent overdose when enoxaparin is used as curative treatment.

Clinical particulars

Indications

* Prevention of venous thromboembolic disease in moderate or high risk surgery;
* Prevention of deep vein thrombosis in patients who are bedridden due to acute medical conditions: heart failure (NYHA class III or IV), acute respiratory failure, acute infection or acute rheumatic disorder associated with at least one other risk factor for venous thromboembolic disease;
* Prevention of clotting in the extra-corporeal circulation during hemodialysis (generally a session of 4 hrs or less);
* Treatment of established deep vein thrombosis, with or without pulmonary embolism, without signs of clinical severity, excluding pulmonary embolism likely to require treatment with a thrombolytic agent or by surgery;
* Treatment of unstable angina and acute non-Q-wave myocardial infarction, in combination with acetylsalicylic acid;
* Treatment of acute ST-segment elevation myocardial infarction, in combination with a thrombolytic agent in patients eligible or not for subsequent coronary angioplasty.

***Contraindications.***

*For 2,000 anti-Ха IU/0.2 mL, equivalent to 20 mg of enoxaparin sodium;*

*For 4,000 anti-Ха IU/0.4 mL, equivalent to 40 mg of enoxaparin sodium;*

*For 6,000 anti-Ха IU/0.6 mL, equivalent to 60 mg of enoxaparin sodium;*

*For 8,000 anti-Ха IU/0.8 mL, equivalent to 80 mg of enoxaparin sodium*

This medicinal product must not be used in the following situations

* hypersensitivity to enoxaparin, heparin or its derivatives, including the other low molecular weight heparins;
* history of severe type-II heparin-induced thrombocytopenia (or HIT) induced by unfractionated heparin or by low molecular weight heparin (see Special warnings and precautions for use);
* hemorrhagic signs or tendencies associated with hemostasis disorders (disseminated intravascular coagulations may be an exception to this rule if these are not related to heparin treatment (see Special warnings and precautions for use);
* organic lesion liable to bleed;
* clinically significant active major bleeding;
* active gastric or duodenal ulcers;
* locoregional anesthesia in elective surgical procedures is contraindicated in patients receiving heparin for treatment other than prophylaxis.

*For 2,000 anti-Ха IU/0.2 mL, equivalent to 20 mg of enoxaparin sodium;*

*For 4,000 anti-Ха IU/0.4 mL, equivalent to 40 mg of enoxaparin sodium*

This medicinal product is not generally recommended in the following situations

* severe renal failure (defined by creatinine clearance of approximately 30 mL/min according to calculation using the Cockroft formula, see Special warnings and precautions for use);
* during the first 24 hours following intracerebral hemorrhage.

*In addition, in patients > 65 years, prophylactic doses of this medicinal product are not advisable when combined with the following (see Interactions with other medicinal products and other forms of interaction):*

1. Acetylsalicylic acid at analgesic, antipyretic and anti-inflammatory doses.
2. Non-steroidal anti-inflammatory drugs (NSAIDs)*(systemic use)*.
3. Dextran 40*(parenteral use).*

*For 6,000 anti-Ха IU/0.6 mL, equivalent to 60 mg of enoxaparin sodium;*

*For 8,000 anti-Ха IU/0.8 mL, equivalent to 80 mg of enoxaparin sodium*

This medicinal product is not generally recommended in the following situations

* Intracerebral hemorrhage.
* In the absence of data, severe renal failure (creatinine clearance of 30 mL/min according to calculation using the Cockroft formula), apart from the specific situation of dialysis. In severe renal failure, use unfractionated heparin.

For calculation of the Cockroft formula, it is necessary to have a recent weight of the patient (see Special warnings and precautions for use).

* Spinal or epidural anesthesia must never be performed in patients treated with LMWH.

This medicinal product is not advisable in the following cases:

* acute extensive ischemic stroke, with or without impaired consciousness. If the stroke is caused by embolism, enoxaparin must not be administered for 72 hours following the event. The efficacy of curative doses of LMWH has however not yet been established, regardless of the cause, extent or clinical severity of cerebral infarction.
* acute infectious endocarditis (except for some emboligenic cardiac conditions);
* mild to moderate renal failure (creatinine clearance between 30 and 60 mL/min).

In addition, this drug is *generally not advisable* when combined with the following (sec. Interactions with other medicinal products and other forms of interaction):

1. Acetylsalicylic acid at analgesic, antipyretic and anti-inflammatory doses.
2. Non-steroidal anti-inflammatory drugs (NSAIDs) (systemic use).
3. Dextran 40 (parenteral use).

Interaction with other medicinal products and other forms of interaction.

Certain drugs or therapeutic classes may promote the occurrence of hyperkalemia: potassium salts, potassium-sparing diuretics, conversion enzyme inhibitors, angiotensin II inhibitors, non-steroidal anti-inflammatory drugs, heparins (low-molecular-weight or unfractionated heparin), cyclosporine and tacrolimus, trimethoprim.

Occurrence of hyperkalemia may depend on possible related risk factors.

This risk is potentiated when the previously mentioned drugs are co-administered.

Elderly (65 years of age and older).

*Adverse combinations.*

Acetylsalicylic acid at analgesic, antipyretic and anti­-inflammatory doses (and, by extrapolation, other salicylates): increased risk of bleeding (salicylate-induced platelet function inhibition and gastroduodenal mucosal damage). Use a non-salicylate antipyretic analgesic (such as paracetamol).

Non-steroidal anti-inflammatory drugs, including ketorolac (systemic use): increased risk of bleeding (NSAID-induced platelet function inhibition and gastroduodenal mucosal damage). If co-administration cannot be avoided, close clinical monitoring is required.

Dextran 40 (parenteral use): increased risk of bleeding (platelet function inhibition by Dextran 40).

Combinations requiring precautions.

*Oral anticoagulants:* potentiation of the anticoagulant effect. Clinical monitoring should be strengthened when switching from heparin to an oral anticoagulant.

*Combinations to be considered.*

*Inhibitors of platelet aggregation (*other than acetylsalicylic acid at analgesic, antipyretic and anti-inflammatory doses; NSAIDs): *abciximab, acetylsalicylic acid at antiaggregant doses used in cardiological and neurological diseases, beraprost, clopidogrel, eptifibatide, iloprost, ticlopidine, tirofiban:* increased risk of bleeding.

*Patients under 65 years of age.*

*Combinations to be considered.*

Combined use of drugs affecting various stages of hemostasis potentiates the risk of bleeding. Therefore, regardless of the age of the patients, co-administration of LMWH at preventive doses with the following drugs must be taken into consideration by continued clinical monitoring and possible laboratory test: oral anticoagulants, platelet aggregation inhibitors *(abciximab, NSAIDs, acetylsalicylic acid at any dose, clopidogrel, systemic glucocorticosteroids, eptifibatide, iloprost, ticlopidine, tirofiban)* and thrombolytic agents.

Special warnings and precautions for use

Do not administer by the intramuscular route.

Low molecular weight heparins differ in molecular weight, specific anti-Xa activity, and dosage; therefore, they are not interchangeable. Particular attention should therefore be paid and the instructions for use of each of the low molecular weight heparins should be observed.

Precautions for use.

*Bleeding.*

As with all anticoagulants, bleeding can occur (see Undesirable effects). If bleeding occurs, the origin of the hemorrhage must be investigated and appropriate treatment instituted.

Renal function.

Before low-molecular-weight heparin treatment is initiated, it is essential to evaluate renal function, particularly in patients 75 years or older, by determining creatinine clearance using the Cockcroft formula and based on a recent bodyweight measurement.

In male patients: creatinine clearance = (140 - age) x weight / (0.814 x serum creatinine) where age is expressed in years, weight in kg and serum creatinine in µmol/l.

This formula must be adjusted for female patients by multiplying the result by 0.85.

When serum creatinine is expressed in mg/mL, the value should be multiplied by a factor of 8.8.

In patients diagnosed with severe renal failure (creatinine clearance of about 30 mL/min) the use of LMWH as curative treatment is contraindicated (see Contraindications).

*Inhibition of aldosterone secretion.*

Heparin can suppress adrenal secretion of aldosterone leading to hyperkalemia, particularly in patients with diabetes mellitus, chronic renal failure, pre-existing metabolic acidosis, raised plasma potassium, and those taking potassium drugs. The risk of hyperkalemia appears to increase with duration of therapy but is usually reversible. The plasma potassium concentration should be measured in patients at risk of hyperkalemia before starting heparin and monitored regularly thereafter, particularly if treatment is to be continued for longer than 7 days.

*Laboratory tests.*

* Platelet monitoring.

Heparin-induced thrombocytopenia (HIT).

There is a risk of serious, occasionally thrombogenic, heparin-induced thrombocytopenia (reported with unfractionated heparin and less often with LMWH) of immunologic origin, called type II HIT (see Undesirable effects).

As a result of this risk, platelet counts must be performed regardless of the therapeutic indication and the dose administered.

Platelet counts must be performed before administration or at the latest within 24 hours of initiating treatment, then twice a week during the usual treatment duration.

Should long-term treatment prove necessary in certain specific cases (eg. hip surgery, second and third trimesters of high-risk pregnancy (see Pregnancy and Lactation)), platelet counts shall be measured twice a week during the first month of treatment (highest risk period) and then once a week until treatment discontinuation.

HIT should be suspected when the platelet count is below 150,000/mm3 and/or when there is a drop of 30% to 50% between two successive platelet counts. HIT mainly develops 5 to 21 days after heparin treatment is instituted (with a peak incidence after about 10 days).

This complication can however occur much earlier in patients with a history of heparin-induced thrombocytopenia. Isolated cases have been also reported after 21 days. This type of patient history must therefore be systematically investigated by means of an in-depth interview before starting treatment.

Furthermore, the risk of recurrence when reinstituting heparin may remain for several years or even indefinitely (see Contraindications).

In all cases, the occurrence of HIT constitutes an emergency situation and requires a specialist opinion.

Any significant drop in the platelet count (30% to 50% vs. baseline) is a warning sign even before values reach a critical level. Should a decrease in platelets be observed, the following must be performed in all cases:

1. an immediate platelet count for verification;
2. discontinuation of heparin treatment, if the drop is confirmed or even increased based on these results and when no other obvious cause is identified.

A blood sample must be taken using a citrate tube in order to perform in vitro platelet aggregation and immunological tests. However, under these conditions, the immediate measures to be taken are not based on in vitro platelet aggregation or immunological test results as only a few specialized laboratories perform these tests routinely and the results are available at best after several hours. These tests are however necessary to assist in diagnosis of the complication as the risk of thrombosis is very high if heparin treatment is continued.

1. prevention or treatment of HIT-related thrombotic complications.

If continued anticoagulant therapy appears to be essential, heparin must be replaced by an antithrombotic agent of a different chemical group such as sodium danaparoid or hirudin, prescribed at curative or preventive doses on a case-by-case basis.

Replacement by oral anticoagulants can only take place after the platelet count has reverted to normal due to the risk of exacerbation of thrombosis by oral anticoagulants.

* Replacement of heparin by oral anticoagulants.

Clinical monitoring and laboratory tests (prothrombin time expressed as the international normalized ratio (INR)) must be intensified to monitor the effect of oral anticoagulants.

As there is an interval before the oral anticoagulant reaches its maximum effect, heparin therapy should be continued at a constant dose for as long as necessary in order to maintain INR within the desired therapeutic range, for the indication in two successive tests.

* Monitoring of anti-factor Xa activity.

As most of the clinical studies which demonstrated the efficacy of LMWH were conducted using a dose based on bodyweight without specific laboratory monitoring, the usefulness of laboratory tests for assessing the efficacy of LMWH treatment has not been established. However, laboratory tests, i.e. monitoring of anti-Xa activity may be useful in managing the risk of bleeding in certain clinical conditions often associated with a risk of overdose.

These situations mainly involve the curative indications of LMWH, due to the doses administered, in patients with:

* mild to moderate renal failure (creatinine clearance of approximately 30 mL/min to 60 mL/min calculated using the Cockroft formula). As LMWH is primarily eliminated by the renal route, unlike standard unfractionated heparin, any renal failure can result in relative overdose. Severe renal failure is a contraindication to the use of LMWH at curative doses (see Contraindications);
* extreme high or low bodyweight (extremely low body weight or even cachexia, obesity);
* unexplained bleeding.

In contrast, laboratory monitoring is not recommended at prophylactic doses if the LMWH treatment complies with the therapeutic recommendations (particularly treatment duration), or during hemodialysis.

To detect possible heparin accumulation following repeated administration, it is recommended, if necessary, to collect a blood sample at peak activity (based on available data), i.e. approximately 4 hours after the third injection when the drug is given as 2 subcutaneous injections per day.

Repeating anti-Xa activity tests to determine blood heparin levels, for example every 2 to 3 days, should be decided on a case-by-case basis, depending on the results of the previous investigation. Possible LMWH dose adjustment should be considered.

The anti-Xa activity observed varies for each LMWH and each dosage regimen.

According to the information, based on available data, the mean value (± standard deviation) observed 4 hours after the 7th injection of enoxaparin given at a dose of 100 anti-Xa IU/kg/injection b.i.d. was 1.2 ± 0.17 anti-Xa IU/mL.

This mean value was observed during clinical studies when anti-Xa activity tests were performed by a chromogenic (amidolytic) method.

* Activated partial thromboplastin time (aPTT) monitoring.

Certain LMWHs moderately prolong APTT. In the absence of any established clinical relevance, any treatment monitoring based on this test is useless.

*Spinal/epidural* anesthesia *in patients under preventive treatment with LMWH.*

* As with other anticoagulants, rare cases of intraspinal hematoma leading to long-term or permanent paralysis have been reported during the administration of LMWH during spinal or epidural anesthesia.

The risk of intraspinal hematoma appears to be higher with an epidural anesthesia using a catheter than with a spinal anesthesia.

The risk of these rare events may be increased by the prolonged use of epidural catheters after surgery.

Should it be decided to administer anticoagulants with epidural/spinal anesthesia, careful vigilance and frequent monitoring should be exercised to detect any signs and symptoms of neurological impairment such as: back pain, sensory and motor deficits (numbness and weakness of the lower limbs), bowel and/or bladder dysfunction. Patients should be instructed to inform immediately their physician or nurse if they experience any of the above symptoms. If signs or symptoms of spinal or epidural hematoma are suspected, urgent diagnosis and treatment including spinal cord decompression should be initiated.

* If pre-surgical treatment with LMWH is necessary (prolonged bed rest, injury) and the benefit of a locoregional spinal anesthesia has been carefully evaluated, this technique may be used in a patient having received an injection of LMWH before surgery, as long as a period of at least 12 hours is left between the heparin injection and administration of the spinal anesthesia.

Careful neurological monitoring is recommended due to the risk of intraspinal hematoma.

In almost all cases, preventive treatment with LMWH can be started within 6 to 8 hours following the technique or removal of the catheter, under neurological monitoring.

Particular caution is required in the event of combination with other drugs interfering with hemostasis (non-steroidal anti-inflammatory drugs, acetylsalicylic acid).

Situations involving particular risk.

Monitoring of treatment should be intensified in the following cases:

* hepatic insufficiency;
* gastro-intestinal ulcer or any other organic lesion likely to bleed;
* chorioretinal vascular disease;
* post-operatively, following cerebral and/or spinal cord surgery;
* spinal (lumbar) puncture: the performance of a lumbar puncture must be discussed, taking into account the risk of intraspinal bleeding and should be postponed whenever possible;
* concomitant use of medicinal products affecting hemostasis (see Interaction with other medicinal products and other forms of interaction).

Although the concentrations of the various low-molecular-weight heparins are all expressed in anti-Xa international units (IU), their efficacy is not only related to their anti-Xa activity. It would be dangerous to replace one LMWH dosage regimen by another as each regimen has been validated by specific clinical studies. Particular care is therefore required and the specific instructions for use of each drug must be followed.

Warnings.

Risk of hemorrhage.

The recommended dosage regimens must be respected (dosage and duration of treatment). Failure to comply with these recommendations can lead to hemorrhage, particularly in high-risk patients (the elderly, patients with renal failure).

Serious hemorrhagic events have been reported in the following situations:

* elderly subjects, particularly due to age-related renal impairment;
* patients with renal failure;
* bodyweight under 40 kg;
* if treatment prolonged beyond the recommended mean duration of 10 days;
* in non-compliance with the recommended treatment conditions (in particular treatment duration and dosage adjustment on the basis of weight for curative treatments);
* concomitant use of other medicinal products (see Interaction with other medicinal products and other forms of interaction).

Like any other anticoagulant, enoxaparin injections should be used with caution in conditions with increased risk of hemorrhage, such as hemostatic disorders, history of peptic ulcer, recent ischemic stroke, uncontrolled hypertension, diabetic retinopathy, recent neurosurgical or ophthalmological surgery.

In any event, special monitoring is essential in the elderly and/or patients with renal failure, as well as during treatment prolonged beyond ten days.

Tests for anti-Xa activity may in certain cases be useful to detect drug accumulation (see Special warnings and special precautions for use).

Risk of heparin-induced thrombocytopenia (HIT):

Should a patient treated with LMWH (at curative or preventive doses) develop thrombotic complications:

* exacerbation of the thrombosis being treated;
* phlebitis;
* pulmonary embolism;
* acute ischemia of the lower limbs;
* or even myocardial infarction or ischemic stroke,

HIT should systematically be suspected and a platelet count performed urgently (see Special warnings and special precautions for use).

Coronary angioplasty revascularization procedures.

To minimize the risk of hemorrhage during coronary angioplasty for unstable angina, non-Q-wave myocardial infarction and acute ST-segment elevation myocardial infarction, it is recommended that the advised intervals between enoxaparin injections be strictly complied with. It is important to achieve hemostasis at the vascular puncture site following coronary angioplasty. If an occlusion device (hemostatic device) is used, the introducer can be removed immediately. If manual compression is performed, the introducer must be removed 6 hours after the last subcutaneous/intravenous injection of enoxaparin. If enoxaparin treatment is continued, the following injection must be performed at the earliest 6 to 8 hours after removal of the introducer. The puncture site must be monitored to detect any signs of bleeding or hematoma. *Mechanical prosthetic heart valves.*

The use of enoxaparin in the prevention of thromboembolic events in patients with mechanical prosthetic heart valves has not been specifically investigated.

However, some isolated cases of thrombosis have been reported in patients with this device who received enoxaparin as prophylactic treatment of thromboembolic events.

*Pregnant women.*

During a clinical study in pregnant women with mechanical prosthetic heart valves receiving 100 anti-Xa IU/kg bodyweight of enoxaparin twice daily to reduce the risk of thromboembolic events, two of eighth women developed thrombosis which led to an obstructed valve with fatal outcome for both the woman and the fetus. In addition, other isolated post-marketing cases of thrombosis have been reported in pregnant women with mechanical prosthetic heart valves who received thromboembolic prophylaxis with enoxaparin. Therefore, the risk of thromboembolic events in this population might be higher.

Hemorrhage in elderly patients

No increased bleeding tendency was observed in the elderly with preventive dosage ranges. Elderly patients (especially patients 80 years of age and older) may be at an increased risk for bleeding complications with the therapeutic dosage ranges. In the treatment of ST-segment elevation acute myocardial infarction increase in bleeding events was observed in patients aged 65 to 75 years, indicating that these patients may be at particular risk of bleeding. Close clinical monitoring is recommended.

*Renal insufficiency*

In patients with renal impairment, there is an increase in exposure of enoxaparin which increases the risk of bleeding. Since exposure of enoxaparin is significantly increased in patients with severe renal impairment (creatinine clearance <30 mL/min), a dosage adjustment is advised for therapeutic and prophylactic dosage ranges. 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 observation is advised. In the treatment of acute myocardial infarction with ST-segment elevation data in patients with creatinine levels above 220 and 175 µmol/L for men and women are respectively limited.

*Low body weight*

An increase in exposure of enoxaparin with prophylactic dosages (non-weight adjusted) has been observed in low-weight women (<45 kg) and low-weight men (<57 kg), which may lead to a higher risk of bleeding. Therefore, careful clinical monitoring is advised in these patients.

*Monitoring.*

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.

Laboratory tests

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 or binding of fibrinogen to platelets. At higher doses, increases in APTT (activated 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 are unsuitable and unreliable for monitoring enoxaparin sodium activity.

Pregnancy and lactation.

For 2,000 anti-Ха IU/0.2 mL, equivalent to 20 mg of enoxaparin sodium;

*For 4,000 anti-Ха IU/0.4 mL, equivalent to 40 mg of enoxaparin sodium*

*Pregnancy.*

Prophylactic treatment during the first trimester.

There are not enough relevant clinical data concerning possible teratogenic or fetotoxic effects of enoxaparin when the drug is administered preventively during the first trimester.

As a precautionary measure, enoxaparin prophylaxis should not be administered during the first trimester.

If epidural anesthesia is planned, preventive heparin treatment should be interrupted whenever possible within 12 hours before the anesthesia at the latest.

Preventive treatment during the second and third trimesters.

Administration of prophylactic doses of enoxaparin to women during the second and third trimesters in a limited number of pregnancies has apparently not resulted in any particular teratogenic or fetotoxic effects. However, additional studies are needed to evaluate the effects of exposure under these conditions.

Therefore, enoxaparin prophylaxis during the second and third trimesters should only be administered if necessary.

If epidural anesthesia is planned, preventive heparin treatment should be interrupted whenever possible within 12 hours before the anesthesia at the latest.

*For 6,000 anti-Ха IU/0.6 mL, equivalent to 60 mg of enoxaparin sodium;*

*For 8,000 anti-Ха IU/0.8 mL, equivalent to 80 mg of enoxaparin sodium*

In a clinical context, there are not yet enough relevant data in order to evaluate a possible teratogenic or fetotoxic effect of enoxaparin when administered at curative doses throughout pregnancy. Consequently, as a precautionary measure, it is preferable to avoid use of enoxaparin at curative doses throughout pregnancy.

In any case spinal or epidural anesthesia should not be performed in patients receiving treatment with LMWH.

*Breast-feeding.*

Since gastro-intestinal absorption by neonates is unlikely in principle, treatment with enoxaparin is not contraindicated in breast-feeding women.

***Effects on ability to drive and use machines.***

Enoxaparin sodium has no effect on the ability to drive and operate machines. However, care should be taken in view of possible adverse reactions (see Undesirable effects).

Posology and method of administration.

1 mg (0.01 mL) of enoxaparin sodium is equivalent to approximately 100 anti-Xa IU. Flenox® should be administered subcutaneously for prophylactic and therapeutic use apart from the following indications:

* administration for anticoagulation in hemodialysis;
* in patients with acute ST-segment elevation myocardial infarction, in whom IV bolus administration is required.

Do not administer **Flenox®** by the intramuscular route. This drug is suitable for adults only.

Subcutaneous injection technique. The prefilled syringe is ready for immediate use. The dose of Flenox® can be adjusted according to patient’s bodyweight if required. Any excess volume can be discarded before administering the injection if required. When there is no excess volume, the air should not be expelled from the syringe before the injection.

Flenox® should be administered by injection into the subcutaneous tissue, preferably with the patient supine. Administration should be alternated between the left and right anterolateral and posterolateral abdominal walls. The whole length of the needle should be inserted vertically, not from the side, into a skin fold held between the thumb and forefinger. This skin fold should be held throughout the injection. Do not rub the injection site after administration.

Intravenous (bolus) injection technique of *Flenox®* for the treatment of acute ST-segment elevation myocardial infarction.

Treatment is initiated with an IV bolus injection, immediately followed by an SC injection. For the intravenous bolus of pre-filled graduated syringe with Flenox® containing 40 mg (0.4 mL, 4,000 anti-Xa IU), 60 mg (0.6 mL, 6,000 anti-Xa IU) or 80 mg (0 8 mL 8,000 anti-Xa IU), remove the excess amount of the drug to leave the dose of 30 mg (0.3 mL, 3,000 anti-Xa IU) in the syringe.

This dose of Flenox® should be injected into a venous line, and must not be mixed or administered with other medicinal products. To avoid any traces of other medicinal products and therefore to prevent them from mixing with Flenox®, the injection line must be rinsed with a sufficient quantity of normal saline or glucose solution before and after IV bolus injection of Flenox®. Enoxaparin can be safely administered with the sufficient amount of 0.9% normal saline solution or 5% glucose solution. Flenox® can be safely administered with 0.9% normal saline solution or 5% glucose solution.

In the hospital setting, Flenox® can be used to:

* obtain the required 1mg/kg (100 anti-Xa IU/kg) dose for the first SC injection, to be given along with the IV bolus, and then the required 1mg/kg (100 anti-Xa IU/kg) doses for SC injection, repeated every 12 hours,
* obtain the 0.3 mg/kg (30 anti-Xa IU/kg) dose for IV bolus injection for patients undergoing subsequent coronary angioplasty.

Regular monitoring of the platelet count is essential throughout the treatment due to the risk of heparin-induced thrombocytopenia (HIT).

Prophylactic treatment of venous thromboembolic disease in surgery associated with moderate to high thrombogenic risk.

As a general rule, these recommendations apply to surgical procedures carried out under general anesthesia.

For spinal and epidural anesthesia techniques, the benefit of a pre-operative injection of enoxaparin should be weighed against the theoretically increased risk of spinal hematoma (see Special warnings and precautions for use).

* Administration schedule. One subcutaneous injection of Flenox® daily.
* Dose. The dose must be determined based on the individual risk related to the patient and the type of surgery.

Surgery involving moderate thrombogenic risk.

In surgery involving moderate thrombogenic risk and in patients who are not at high risk of thromboembolism, effective prevention is achieved by daily injection of Flenox® at 20 mg (0.2 mL; 2,000 anti-Xa IU). The studied dosage regimen involves administration of the first injection 2 hours before surgery.

Surgery involving high thrombogenic risk.

Hip and knee surgery.

The dosage of Flenox® is 40 mg (0.4 mL; 4,000 anti-Xa IU) injected once daily.

The studied dosage regimen involves either administration of the first injection of 4,000 anti-Xa IU (total dose) 12 hours before surgery, or a first injection of 2,000 anti-Xa IU (half dose) 2 hours before surgery.

Other situations.

When there appears to be an increased risk of venous thromboembolism due to the type of surgery (particularly cancer surgery) and/or due to the patient (particularly history of venous thromboembolism), administering a prophylactic dose identical to that for high-risk orthopedic surgery, such as hip or knee surgery, can be considered.

* *Duration of treatment.*

Treatment with LMWH should be maintained, along with the usual methods of elastic support of the legs, until the patient is fully and actively ambulatory:

* in general surgery, the duration of LMWH treatment must be less than 10 days unless there is a patient-specific risk of venous thromboembolism (see Special warnings and precautions for use);
* the therapeutic benefit of prophylactic treatment consisting of an injection of 4,000 anti-Xa IU/day of enoxaparin for 4 to 5 weeks after hip surgery has been established;
* if the patient is still at risk of venous thromboembolism after the recommended treatment duration, continuing prophylactic therapy must be considered, particularly by administration of oral anticoagulants.

However, the clinical benefit of long-term treatment with low-molecular-weight heparins or oral anticoagulants has not yet been evaluated.

Prophylactic treatment of deep vein thrombosis in patients who are bedridden due to acute medical conditions.

The recommended dose of Flenox® is 40 mg (0.4 mL, 4 000 anti-Xa IU) once a day by subcutaneous injection. Flenox® is prescribed for a minimum of 6 days and continued until the full return to deambulation, for a maximum of 14 days. If the patient is still at risk of venous thromboembolism after the recommended treatment duration, continuing prophylactic therapy must be considered by administration of oral anticoagulants.

Prevention of clotting in the extracorporeal circulation during hemodialysis.

Injection is administered by the intravascular route (in the arterial line of the dialysis circuit).

In patients undergoing repeated hemodialysis sessions, prevention of clotting in the extrarenal purification system is obtained by injecting an initial dose of 100 anti-Xa IU/kg in the arterial line of the dialysis circuit at the beginning of the session.

This dose, administered as a single intravascular bolus injection, is only suitable for hemodialysis sessions of 4 hours or less. It may be adjusted subsequently given high inter- and intra-individual variability. The maximum recommended dose is 100 anti-Xa IU/kg.

In hemodialysis patients at high risk of hemorrhage (particularly pre- and post-operative dialysis) or with active hemorrhage, dialysis sessions may be carried out using a dose of 50 anti-Xa IU/kg (double vascular access) or 75 anti-Xa IU/kg (single vascular access).

Treatment of deep vein thrombosis (DVT), with or without pulmonary embolism, without signs of clinical severity.

Any suspected deep vein thrombosis should be quickly confirmed by the appropriate examinations.

Administration schedule.

Flenox® can be administered subcutaneously as twice daily injections of 100 anti-Xa IU/kg every 12 hours.

LMWH dosage has not been evaluated in terms of bodyweight in patients weighing more than 100 kg or less than 40 kg. The efficacy of LMWH treatment may be lower in patients weighing more than 100 kg, and the risk of hemorrhage may be higher in patients weighing less than 40 kg. Specific clinical monitoring must be carried out in these patients.

Deep vein thrombosis treatment duration.

Treatment with low-molecular-weight heparin should be quickly replaced by oral anticoagulant therapy, unless contraindicated. Treatment duration with LMWH should not exceed 10 days, including the time needed to reach the required oral anticoagulant effect, except when this is difficult to achieve. Oral anticoagulant treatment should therefore be initiated as soon as possible.

Treatment of unstable angina/non-Q-wave myocardial infarction.

The recommended dose of 1 mg/kg (100 anti-Xa IU/kg) of Flenox® is administered by subcutaneous injection at 12-hour intervals, in combination with acetylsalicylic acid (recommended doses: 75 to 325 mg orally, following a minimum loading dose of 160 mg).

The duration of treatment is at least 2 to 8 days, until the patient is clinically stable.

Treatment of acute ST-segment elevation myocardial infarction in combination with a thrombolytic agent in patients eligible or not for subsequent coronary angioplasty.

An initial IV bolus injection of 30 mg/kg (0.3 mL; 3,000 anti-Xa IU/kg) of Flenox® followed by an SC injection of 1 mg/kg (100 anti-Xa IU/kg) within 15 minutes, then every 12 hours (a maximum of 10,000 anti-Xa IU for the first two SC doses).

The first dose of Flenox® should be administered at any time between 15 minutes before and 30 minutes after the start of thrombolytic treatment.

The recommended duration of treatment is 8 days, or until the patient is discharged from hospital if the hospitalization period is less than 8 days.

Concomitant treatment: administration of acetylsalicylic acid 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.

Patients treated by coronary angioplasty:

* if the last SC injection of Flenox® 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 0.3 mg/kg (30 anti-Xa IU/kg) of Flenox® must be administered. In order to provide the accuracy of the volumes to be injected, it is recommended to dilute the drug to 300 anti-Xa IU/mL (0.3 mL (3,000 anti-Xa IU) should be diluted in 10 mL of solvent (0.9% sodium chloride or 5% dextrose)) (see. Table).

Volumes to inject when dilution is performed for coronary angioplasty patients

|  |  |  |
| --- | --- | --- |
| Weight, Kg | Required dose, anti-Xa IU | Volume to inject when diluted to final concentration of 300 IU/mL (i.e. 0.3 mL (3,000 anti-Xa IU) of Flenox® diluted in 10 mL of solvent)), 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 |

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 7,500 anti-Xa IU for the first two injections only).

Children.

Due to the lack of relevant data LMWH is not recommended in pediatric patients.

Overdose.

Accidental overdose following subcutaneous administration of massive doses of low-molecular-weight heparin may result in hemorrhagic complications.

In case of hemorrhage, certain patients can be treated with protamine sulfate, taking the following factors into account:

* its efficacy is far lower than that reported in overdoses with unfractionated heparin,
* due to its undesirable effects (particularly anaphylactic shock), the benefit/risk ratio of protamine sulfate should be carefully weighed beforehand.

Neutralization is performed by slow intravenous injection of protamine (sulfate or hydrochloride).

The protamine dose required depends on:

* the heparin dose injected (100 anti-heparin units of protamine neutralizes the activity of 100 anti-Xa IU of low-molecular-weight heparin), if enoxaparin sodium was administered within the last 8 hours.
* the time since the heparin injection:
* an infusion of 50 anti-heparin units of protamine per 100 anti-Xa IU of enoxaparin sodium may be administered if enoxaparin sodium was given more than 8 hours previously, or if a second dose of protamine seems necessary.
* if the injection of enoxaparin sodium was given more than 12 hours previously, it is not necessary to administer protamine.

These recommendations concern patients with normal renal function receiving repeated doses.

Nevertheless, the anti-Xa activity cannot be completely neutralized. Furthermore, the neutralization may be transient due to the absorption pharmacokinetics of low-molecular-weight heparin, which may require dividing the total calculated dose of protamine into several injections (2 to 4) given over 24 hours.

No serious consequences are likely after ingestion of low-molecular-weight heparin, even in massive quantities (no cases reported), due to the very low gastric and intestinal absorption of the drug.

Undesirable effects.

Major hemorrhagic complications including peritoneal and intracranial bleeding have been reported, in rare instances these have been fatal. Hemorrhagic complications (bleeding), such as hematoma, ecchymosis other than at injection site, wound hematoma, hematuria, epistaxis and gastro-intestinal hemorrhage have been reported. Hemorrhagic manifestations were, mainly, related to:

* *associated risk factors:* organic lesions liable to bleed or the concomitant use of medications affecting hemostasis (see Contraindications and Interaction with other medicinal products and other forms of interaction), age, renal insufficiency, low body weight;
* *non-compliance with therapeutic recommendations*, including those relating to the duration of treatment and dose adjustment according to the body weight (see Special warnings and precautions for use).

There have been reports of spinal hematomas after administration of LMWH during spinal anesthesia, analgesia or epidural anesthesia.

These reactions have resulted in varying degrees of neurologic injuries including long-term or permanent paralysis (see Special warnings and precautions for use).

After subcutaneous administration hematoma may appear at the site of injection. There have been reported cases of pain at the injection site, other reactions including irritation, swelling at the injection site, hypersensitivity, inflammation and the nodules. This risk increases if the recommended injection technique is not observed or improper means are used. Inflammatory injection site nodules resolve after a few days and should not cause treatment discontinuation.

Thrombocytopenia was reported. There are two types of thrombocytopenia:

* Type I, the most common cases are usually moderate (platelet count over 100,000/mm3) and occur in the early stages (Day 5) and did not require discontinuation of treatment;
* Type II, uncommon cases of severe immunoallergic thrombocytopenia (heparin-induced thrombocytopenia (HIT) with thrombosis); in some cases thrombosis was complicated by myocardial ischemia of organs or limbs. Its frequency has been studied insufficiently (see Special warnings and precautions for use).

Asymptomatic and reversible increases in platelet counts have been reported.

Skin necrosis has been reported when heparins were used. It has been usually preceded by purpura or erythematous plaques, infiltrated and painful. Treatment must be discontinued in these cases.

Systemic allergic reactions, including anaphylactoid-like reactions and skin reactions (urticaria, pruritus, erythema, bullous rash) may occur. In some cases discontinuation of therapy may be necessary.

As with unfractionated heparins, the risk of osteoporosis cannot be excluded in long term treatment.

Unfractionated heparin products can cause hypoaldosteronism which may result in an increase in plasma potassium. Clinically significant hyperkalemia may occur particularly in patients with chronic renal failure and diabetes mellitus.

Transient transaminase elevations have been observed.

Rare cases of hyperkalemia have been reported.

Hypersensitivity cutaneous vasculitis has been observed.

Hypereosinophilia has been observed alone or with skin reactions which resulted in discontinuation of the treatment.

Shelf life

2 years.

Do no use the drug after the expiry date stated on the package.

Storage

Store in the original package. Store below 25 °С. Do not freeze.

Keep out of reach of children.

Incompatibilities

Do not mix with any other drugs.

Nature and contents of packaging

0.2 mL, 0.4 mL, 0.6 mL or 0.8 mL per syringe.

1 syringe in a blister. 1, 2 and 10 blisters (2,000 anti-Xa IU, 4,000 IU anti-Xa, 6,000 anti-Xa IU drug activity) and 1 or 2 blisters (8,000 anti Xa IU drug activity) inserted into a carton.

2 syringes in a blister. 1 and 5 blisters (2,000 anti-Xa IU, 4,000 anti-Xa IU, 6,000 anti-Xa IU drug activity) and 1 blister (8,000 anti Xa IU drug activity) inserted into a carton.

Prescription status

Prescription only.

Manufacturer

Farmak JSC.

**Location of manufacturer and address of manufacturing site**.

63, Frunze str., Kyiv 04080, Ukraine.

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