Area for pharmacode

Lovenox®

Enoxaparine sodium
4000anti-Xa IU/0.4 mL

sanofi

The package insert is continually updated: Please read carefully before using a new pack. In case of any question, please contact your physician or pharmacist.

Composition
Active ingredient: enoxaparin sodium.
Solvent : water for injections.
Appearance: Clear, colorless to pale yellow solution
Each ml of the solution contains 10000 anti-Xa IU equivalent to 100 mg enoxaparin sodium. One mg (0.01ml) of enoxaparin sodium corresponds approximately to 100 anti-Xa IU. LOVENOX 4000 anti-Xa IU is equivalent to 40 mg.

PHARMACOLOGICAL PROPERTIES
Pharmacodynamics properties
ANTITHROMBOTIC AGENT (B01AB05)
Enoxaparin is a low molecular weight heparin in which the antithrombotic and anticoagulant activities of standard heparin have been dissociated. It is characterized by a higher ratio of anti-Xa activity to anti-IIa (or antithrombin) activity.
The ratio between these two activities is 3.6.
As with standard heparin, the anti-Xa and anti-IIa activity of enoxaparin results from its effect on antithrombin.
When used as prophylactic treatment, it does not significantly affect the activated partial thromboplastin time (aPTT).
When used as curative treatment, aPTT can be prolonged by 1.5-2.2 times the control time at peak activity.
This prolongation reflects the residual antithrombin activity.

Prophylactic treatment of venous thromboembolism in patients who are bedridden due to an acute medical disorder
A randomized, double-blind, placebo-controlled study (Medenox) was carried out to compare the safety and efficacy of enoxaparin 2000 anti-Xa IU/0.2 ml (20 mg/0.2 ml) and enoxaparin 4000 anti-Xa IU/0.4 ml (40 mg/0.4 ml) in preventing venous thromboembolism. The study medication or placebo were administered once daily for 6 to 14 days to 1102 patients who were bedridden due to an acute medical disorder occurring within the previous three days and who were at moderate risk of venous thromboembolism. The patients were over 40 years of age and had heart failure (NYHA class III or IV), acute respiratory failure revealing or complicating chronic respiratory insufficiency, an acute infectious or rheumatic disease associated with at least one thromboembolic risk factor (age > 75 years, cancer, history of venous thromboembolism, obesity, varicose, hormone therapy, chronic heart or respiratory failure).

Medical patients at high risk of venous thromboembolism complications (acute phase of myocardial infarction, heart disease such as arrhythmia or valvular disease requiring anticoagulant therapy, intubated patients or patients or who had experienced a stroke within the last three months) were not included in the study.

The primary efficacy criterion was the incidence of venous thromboembolic events on treatment day 10 (± 4) defined as:
- deep vein thrombosis (DVT) documented systematically by venography (83.4% of evaluable patients) or by Doppler ultrasound (16.6% of evaluable patients) in patients with symptomatic DVT.
- Non-fatal symptomatic pulmonary embolism confirmed by pulmonary angiography or spiral CT,
- or fatal pulmonary embolism.

A significant decrease in the incidence of venous thromboembolic events was observed in the 866 evaluable patients on day 10 (± 4), 16/291 (5.5%) in the Lovenox 4000 anti-Xa IU/0.4 ml (40 mg/0.4 ml) group versus 43/288 (14.9%) in the placebo group (p=0.0002). This was mainly due to the significant decrease in the incidence of total DVT (proximal and distal), i.e. 16/291 (5.5%) in the Lovenox 4 000 anti-Xa IU/0.4 ml (40 mg/0.4 ml) group versus 41/288 (14.2%) in the placebo group (p=0.0004). Most DVTs were asymptomatic (only 6 were symptomatic). The observed benefit was maintained after 3 months.
Fifty-nine percent (59%) of patients in the Lovenox 4000 anti-Xa iu/0.4 ml (40 mg/0.4 ml) group regained autonomous mobility (> 10 meters) during the treatment period.
Regarding safety, the incidence of hematomas or ecchymoses larger than 5 cm at the injection site was significantly higher in the Lovenox 4000 anti-Xa IU/0.4 ml/day (40 mg/day) group than in the placebo group.
This study showed no significant difference in efficacy between Lovenox 2000 anti-Xa IU/0.2 ml (20 mg/0.2 ml) and the placebo.

Pharmacokinetic properties
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 (11.0% versus 12.85) 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.

Pharmacokinetic properties
The pharmacokinetic parameters of enoxaparin have been evaluated based on the time course of plasma anti-Xa and anti-IIa activity at the recommended doses (validated amidolytic methods) following single and repeated SC administration, and following single IV injection.

Bioavailability
Subcutaneously administered enoxaparin is rapidly and almost completelyabsorbed (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 administration of 2 000 Anti-Xa IU), 0.43±0.11 (after administration of 4 000 Anti-Xa IU) in prophylactic treatment and 1.01±0.14 (after administration of 10 000 Anti-Xa IU) in curative treatment.
Enoxaparin pharmacokinetics appears to be linear over the recommended dose ranges. Intra- and inter-patient variability is low. After repeated SC administration of 4 000 Anti-Xa IU once daily in healthy volunteers, 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 SC administration of 100 Anti-Xa IU/kg twice daily, 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 within the therapeutic range.
Plasma anti-IIa activity after SC administration is about 10-fold lower than anti-Xa activity. The mean maximum anti-IIa activity is observed approximately 3-4 hours following SC injection and reaches 0.13 anti-IIa IU/ml following repeated administration of a 100 Anti-Xa IU/kg dose twice daily.

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

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

Elimination
Following SC injection, the apparent anti-Xa activity elimination half-life is higher for LMWHs than for unfractionated heparins.
Enoxaparin exhibits a monophasic elimination pattern with a half-life of about 4 hours after a single SC dose to about 7 hours after repeated dosing by SC route.
With LMWH, 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 about 10% of the administered dose, and total renal excretion of active and non-active compounds for 40% of the dose.

Special populations
Elderly patients
As kidney function is physiologically impaired in this population, elimination is slower. This does not affect doses or the administration schedule in prophylactic treatment as long as the renal function of these patients remains within acceptable limits, i.e., only slightly impaired.
It is essential to systematically assess renal function in elderly patients aged over 75 years using the Cockcroft formula before initiating treatment with LMWH.

Hemodialysis
LMWH is injected in the arterial line of the dialysis circuit at sufficient doses to avoid coagulation in the circuit.
The pharmacokinetic parameters remain, in principle, unchanged except in cases of overdose or where the drug passes into the general circulation, causing high anti-Xa activity related to end-stage renal failure.

Pregnancy
Low molecular weight heparins are unlikely to cross the placental barrier, but data on the subject remain insufficient.

INDICATIONS
This heparin is a low-molecular-weight heparin (LMWH).
This medicinal product is indicated for:
- Prophylactic treatment of venous thromboembolic disease in moderate or high risk surgery.
- Prophylactic treatment of deep vein thrombosis in patients who are bedridden due to an acute medical condition:
  - heart failure (NYHA class III or IV)
  - acute respiratory failure
  - episode of acute infection or acute rheumatic disorder associated with at least one other risk of venous thromboembolism factor.
- Prevention of clotting in the extracorporeal circulating during hemodialisis (generally a session of 4 hours or less).

DOSAGE AND ADMINISTRATION
SUBCUTANEOUS ROUTE (except in the hemodialysis indication).

This presentation is suitable for adults.
Do not inject via the intramuscular route.
One milliliter of solution for injection is equivalent to approximately 10000 anti-Xa IU of enoxaparin.

Subcutaneous injection technique :
The pre-filled syringe is ready for immediate use; do not press on the plunger to expel any air bubbles before injecting the drug.
Enoxaparin 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 perpendicularly, not from the side, into a skin fold held between the thumb and index finger. This skin fold should be held throughout the injection.

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

Prophylactic treatment of venous thromboembolic disease in surgery
As general rule, these recommendations apply to surgical procedures carried out under general anesthesia.
For spinal and epidural anesthesia techniques, the benefit of pre-operative injection of enoxaparin should be weighed against the theoretically increased risk of spinal hematoma (see
Precautions for use).

Administration schedule:
One injection per day.

Dosage:
The dose must be determined basedon the risk related to the patientand 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 2 000 anti-Xa IU (0.2 ml).
The studied dosage regimen involves administration of the first injection approximately 2 hours before surgery.

Surgery involving high thrombogenic risk :
- Hip and knee surgery:
  The dosage is 4 000 anti-Xa IU (0.4 ml) 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 related to the type of surgery (particularly cancer surgery) and/or related to the patient (particularly history of venous thromboembolism), administering a prophylactic dose identical to that for high risk 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 for 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 Precautions for use, platelet monitoring).
- The therapeutic benefit of prophylactic treatment consisting of a daily 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 an acute medical condition:
Dosage:
The dosage is 40 mg or 4000 anti-Xa IU/0.4 ml injected subcutaneously once daily.

Duration of treatment:
It has been demonstrated that treatment is beneficial for between 6 to 14 days. To date, no efficacy and safety data are available concerning prophylaxis for more than 14 days. If the risk of venous thromboembolism persists, prolonged prophylactic treatment, particularly with oral anticoagulants, must be considered.

Prevention of clotting in extracorporeal circulation/hemodialysis:
Inject by the intravascular route (in the arterial line of the dialysis circuit).
In patients undergoing repeated hemodialysis sessions, preventing 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 session.
This dose, administered as a single intravascular bolus injection, is only suitable for hemodialysis sessions of 4 hours or less. If fibrin rings are found in the dialysis device, an additional dose of 50 to 100 anti-Xa IU/kg may be injected, depending on the time to the end of dialysis.

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).

SPECIAL WARNINGS AND SPECIAL PRECAUTIONS FOR USE
WARNINGS
Quantification: the concentrations of the various low molecular weight heparins are expressed using different systems, i.e. non equivalent units or mg. Special care is therefore required and the specific instructions for each product should be followed exactly.

• Spinal/epidural anesthesia
As with other anticoagulants, therehave been rare reports of spinal haematomas following the administration of enoxaparin during spinal/epidural anesthesia, resulting in long-term or permanent paralysis. The risk of these rare events may be
increased by prolonged use of postoperative indwelling epidural catheters.

• 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, etc.)
Serious hemorrhage events have been reported in the following situations:
- elderly subjects, particularly due to age-related renal impairment,
- patients with renal failure,
- bodyweight below 40 kg,
- treatment lasting longer than the recommended mean duration of ten days,
- non-compliance with therapeutic recommendations.
- co-administration with drug increasing the risk of hemorrhage.

In any event, special monitoring is indispensable in the elderly and/or patients with renal failure, as well as during treatment for more than ten days.
Assay of anti-Xa activity may in certain cases be useful in detecting accumulation.

Risk of heparin-induced thrombocytopenia (HIT):
Should a patient treated with LMWH (curative or preventive dose) develop thromboembolic complications such as:
- 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.

Use in children:
As no relevant data are available, use of LHWH is not recommended in children.

Mechanical prosthetic heart valves :
The use of enoxaparin in the prevention of thromboembolic events in patients with mechanical prosthetic heart has not been specifically investigated. However, some isolated cases of thrombosis have been reported in patients with this devise who received enoxaparin as prophylactic treatment of thrmboembolic 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 eight 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.

Prophylactic treatment in acute medical conditions:
- In the event of an acute episode of infection or bone-joint disease, prophylactic treatment is only justified if the condition is associated with at least one of the following venous thromboembolic risk factor:
  - age > 75 years,
  - cancer
  - history of venous thromboembolism,
  - obesity
  - hormone therapy
  - heart failure
  - chronic respiratory failure.
- In medical prophylaxis, there is very limited clinical experience in elderly patients over 80 years of age whose bodyweight is below 40 kg

PRECAUTIONS FOR USE
Haemorrhage
As with all anticoagulants, bleeding may occur. If the event of bleeding, the cause 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 subjects 75 years or older by determining creatinine clearance (Clcr), using the Cockcroft formula and a recent bodyweight measurement:
In male patients: Clcr = (140 – age) x weight / (0.814 x serum creatinine) where age is expressed in years , weight in kg and serum creatinine in µ mol/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 insufficiency (creatinine clearance of about 30 ml/min) the use of LMWH as curative intent is contraindicated.

Obese patients
Obese patients are at higher risk for thromboembolism. The safety and efficacy of prophylactic doses in obese patients (BMI > 30 kg/m²) 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.

History of HIT (>100 days)
Use of enoxaparin sodium in patients with a history of immune mediated HIT within the past 100 days or in the presence of circulating antibodies is contraindicated (see section 4.3). Circulating antibodies may persist several years.
Enoxaparin sodium is to be used with extreme caution in patients with a history (>100 days) of heparin-induced thrombocytopenia without circulating antibodies. The decision to use enoxaparin sodium in such a case must be made only after a careful benefit risk assessment and after non-heparin alternative treatments are considered.

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.
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 (i.e. hip surgery, second and third trimesters of high-risk pregnancy, the schedule for platelet counts is 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 100 000/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 and extremely rare cases have been 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 years or even indefinitely.
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% versus 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 when no other obvious cause is identified. A sample must be taken using a citrate tube in order to perform in vitro platelet aggregation and immunological assays. 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.
3. Prevention or treatment of HIT-related thromboembolic complications. If continued anticoagulant therapy appears to be essential, heparin must be replaced by an antithrombotic agent of a different chemical group of such as sodium danaparoid or hirudine, 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 (one stage prothrombin time expressed as the INR) must be intensified to monitor the effect of oral anticoagulants.
As there is an interval before the oral anticoagulant has reached its maximum effect, heparin therapy should be maintained at an equivalent dose so that the INR remains 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 utility of laboratory tests for assessing the efficacy of LMWH treatment has not been established. However, 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 concern the curative indications of LMWH, due to the doses administered, in patients with:
- mild to moderate renal insufficiency (creatinine clearance of approximately

Lembar Kemasan : Informasi bagi pengguna
LOVENOX 4000 Anti-Xa IU/0.4 mL
Enoxaparin sodium
Larutan untuk injeksi dalam jarum suntik yang sudah terisi (pre-filled syringe)

sanofi

Baca lembaran ini dengan seksama sebelum Anda mulai menggunakan obat ini:
- Simpanlah lembaran ini. Anda mungkin perlu untuk membacanya lagi.
- Jika Anda memiliki pertanyaan lebih lanjut atau tidak yakin akan hal apa pun, tanyakan kepada dokter atau apoteker Anda untuk informasi lebih lanjut.
- Obat ini diresepkan hanya untuk Anda saja. Jangan berikan kepada orang lain. Itu dapat membahayakan mereka, meskipun tanda-tanda penyakit mereka sama dengan Anda.
- Jika ada efek samping yang serius, atau jika Anda melihat ada efek samping yang tidak tercantum dalam lembaran ini, bicaralah dengan dokter atau apoteker Anda.

Apa yang tercantum dalam lembaran ini:

1. APA ITU LOVENOX 4 000 Anti-Xa IU / 0,4 ml, larutan untuk injeksi pada jarum suntik yang sudah diisi DAN APA KEGUNAANNYA.
Kelompok farmakoterapi
AGEN ANTI-THROMBOTIC

Indikasi terapeutik
Obat ini adalah antikoagulan (pengencer darah) yang termasuk dalam kelompok obat yang disebut heparin berat molekul rendah. Ini mencegah pembekuan darah dari pembentukan di pembuluh darah vena atau arteri (trombosis) dan juga mencegah mereka kembali membeku.
Obat ini digunakan dalam kasus-kasus tertentu yaitu pencegahan terjadinya thromboemboli vena (sumbatan pembuluh darah balik) pada operasi risiko sedang atau tinggi
Pencegahan terjadinya thrombosis vena dalam pada pasien: gagal jantung kelas III dan IV menurut klasifikasi NYHA, gagal pernafasan akut, infeksi akut atau rematik akut dengan risiko terjadinya sumbatan pembuluh darah balik.
Pencegahan sumbatan pada hemodialisa (pada umumnya berlangusng 4 jam atau kurang)

2. APA YANG PERLU ANDA KETAHUI SEBELUM ANDA MENGGUNAKAN LOVENOX 4 000 Anti-Xa IU / 0,4 ml, larutan untuk injeksi pada jarum suntik yang sudah terisi) (pre-filled syringe)

Daftar informasi yang diperlukan sebelum menggunakan produk obat
Tak dapat diterapkan

Kontraindikasi
Jangan gunakan larutan Lovenox 4 000 Anti-Xa IU / 0,4 ml untuk injeksi pada jarum suntik yang sudah terisi jika salah satu dari hal berikut ini terjadi:

PENGGUNAAN OBAT INI	KONTRAINDIKASI	TIDAK DIREKOMENDASIKAN
	• jika Anda alergi terhadap obat ini, untuk heparin atau turunannya, termasuk heparin berat molekul rendah lainnya, • jika Anda pernah mengalami penurunan trombosit yang serius yang disebabkan oleh heparin (trombosit memainkan peran penting dalam pembekuan darah), • jika Anda memiliki gangguan pembekuan darah, • jika Anda terluka (internal atau eksternal) yang cenderung mengeluarkan darah, • jika Anda mengalami pendarahan otak, • jika Anda mengalami gagal ginjal yang parah (kecuali Anda menerima dialisis), • jika Anda perlu memiliki anestesi epidural atau spinal, karena jenis anestesi ini dikontraindikasikan selama pengobatan kuratif dengan Lovenox, • jika Anda mengalami pendarahan yang berlebihan	• jika Anda juga mengonsumsi aspirin (pada dosis yang digunakan untuk mengobati rasa sakit dan demam), obat anti-inflamasi non-steroid (NSAID) atau dekstran (obat yang digunakan dalam resusitasi), • selama beberapa hari pertama setelah stroke tanpa perdarahan, • dalam banyak kasus endokarditis (infeksi jantung), • jika Anda mengalami gagal ginjal ringan hingga sedang.

Tindakan pencegahan; Peringatan khusus

Berhati-hatilah dengan larutan Lovenox 4 000 Anti-Xa IU / 0,4 ml untuk injeksi pada jarum suntik yang sudah terisi (pre-filled syringe)

Peringatan
Resiko terjadinya perdarahan pada setiap pengobatan dengan heparin. Untuk menghindari pendarahan, penting agar Anda tidak melebihi dosis yang ditentukan dan bahwa Anda hanya perlu melakukan perawatan selama dokter Anda memberi tahu Anda (lihat Bagian "Tindakan Pencegahan").
Sebelum pengobatan dengan obat ini, anda perlu melakukan evaluasi fungsi ginjal.
Sebelum dan selama diobati dengan Lovenox, Anda harus menjalani tes darah berulang untuk memeriksa jumlah trombosit secara rutin (biasanya dua kali seminggu).
Risiko kekurangan trombosit dapat terjadi selama pengobatan heparin. Jika ini terjadi, pengobatan heparin harus dihentikan dan peningkatan pemantauan diberlakukan, karena mungkin ada komplikasi serius, termasuk trombosis, meskipun ini mungkin terlihat paradoks.
Jika Lovenox digunakan untuk mencegah pembekuan darah dari pembentukan vena (trombosis vena) pada pasien yang terkulai di tempat tidur karena kondisi medis yang akut
Jika Anda memiliki infeksi akut atau penyakit rematik akut (penyakit yang mempengaruhi sendi), Anda tidak dapat diberikan Lovenox kecuali Anda memenuhi salah satu kriteria berikut: usia di atas 75 tahun, tumor, riwayat penyakit vena, obesitas, pengobatan hormon, jantung kegagalan pernafasan gagal atau kronis.
Tidak direkomendasikan penggunannya pada anak-anak.
Penggunaan obat ini untuk mencegah peristiwa thromboembolic (pembekuan darah yang pecah dan memblokir pembuluh darah lain) tidak dianjurkan pada pasien yang memiliki katup jantung prostetik mekanik, terutama wanita hamil.
Diperlukan pemeriksaan laboratorium terkait pembekuan darah sebelum dan selama pengobatan.

JANGAN SUNTIKKAN OBAT INI KE OTOT. Instruksi untuk injeksi harus benar-benar diperhatikan.

Tindakan pencegahan
Seperti halnya semua antikoagulan, perdarahan bisa terjadi. Jika pendarahan terjadi, penyebabnya harus diidentifikasi dan perawatan yang tepat dapat dimulai.

Dalam beberapa kasus, terutama dalam pengobatan kuratif, mungkin ada risiko perdarahan jika:
- Anda sudah tua
- berat badan Anda kurang dari 40kg
- Anda memiliki gagal ginjal
- pengobatan dilanjutkan setelah 10 hari,
- Anda meminum obat-obatan tertentu pada saat yang bersamaan dengan Lovenox (lihat "Obat-obatan lainnya dan Lovenox"),
- Anda meminum obat-obatan yang meningkatkan risiko pendarahan pada saat yang bersamaan dengan Lovenox (lihat "Obat-obatan lainnya dan Lovenox").

Jika salah satu hal di atas berlaku untuk Anda, Anda mungkin memerlukan pemantauan khusus, yaitu pemeriksaan medis dan mungkin tes darah.
Anestesi epidural atau spinal dan kebocoran lumbal tidak dikontraindikasikan ketika Lovenox digunakan sebagai pengobatan pencegahan. Namun, tindakan pencegahan tertentu harus dilakukan. Interval antara injeksi Lovenox dan anestesi harus diperhatikan dan pasien harus dipantau secara ketat. Meskipun ini adalah tindakan pencegahan, memar di tulang belakang mungkin masih terjadi.
Jika Anda sedang atau pernah memiliki penyakit hati atau ginjal, maag atau luka lain yang mungkin berdarah, beri tahu dokter Anda.

Interaksi dengan produk obat lainnya
Obat-obatan lainnya dan Lovenox
Karena memungkinkan terjadinya pendarahan, selalu beritahukan kepada dokter Anda jika Anda mengkonsumsi salah satu obat berikut:
- Aspirin,
- Obat anti-inflamasi non-steroid (OAINS)
- Penghambat agregasi platelet (obat-obatan yang digunakan untuk mencegah pembekuan seperti abciximab, eptifibatide, iloprost, ticlopidine, dan tirofiban),
- dekstran (obat yang digunakan dalam resusitasi),
- antikoagulan oral (obat-obatan yang mengurangi pembekuan darah dengan menghambat vitamin K).

Katakan kepada dokter atau apoteker Anda jika Anda baru saja mengkonsumsi obat lain, termasuk obat-obatan yang diperoleh tanpa resep.
Dokter akan menyesuaikan tindakan yang diberikan kepada Anda.

Interaksi dengan makanan dan minuman
Tak dapat diterapkan.

Penggunaan oleh wanita hamil atau menyusui
Kehamilan dan Menyusui
Kehamilan
Obat ini sebaiknya tidak digunakan selama trimester pertama kehamilan. Selama trimester kedua dan ketiga kehamilan, obat ini dapat digunakan hanya jika dokter menganggap perlu.
Jika Anda mengetahui bahwa Anda hamil selama perawatan, bicarakan dengan dokter Anda. Hanya dokter Anda yang dapat memutuskan apakah perlu melanjutkan perawatan.
Mintalah saran dokter atau apoteker Anda sebelum mengkonsumsi obat apapun.

Menyusui
Obat ini tidak kontraindikasi pada wanita menyusui.

Material Name	: PI-PIL LOVENOX 4000-1	Plant code : KSF/XXXXXX	
Country	: Indonesia	Min. point size of text	: 6 pt
Version number	: 1	Type of text	: OceanSans Pro SAN Family
Date	: 13.09.2023	Dimensions	: 380 mm X 300 mm
Material	: HVS 60 g/m²	Type of prefold	: 3 x Horizontal & 2 x Vertical
Pharmacode	: XXXXX	Dimension after folded	: 95 mm x 37.5 mm (± 2 mm)
Prepared by	: Rahmat Hafid		

Printing Colour
Pantone Black CVC

Technical Information
outline

DISETUJUI OLEH BPOM: 31/10/2023

ID EREG100022VR12300552

Mintalah saran dokter atau apoteker Anda sebelum mengkonsumsi obat apapun.

Atlit
Tak dapat diterapkan.

Efek pada kemampuan mengemudi atau menggunakan mesin
Tak dapat diterapkan.

Daftar zat tambahan dengan efek tidak diketahui
Tak dapat diterapkan.

3. BAGAIMANA CARA MENGGUNAKAN LOVENOX 4 000 Anti-Xa IU / 0,4 mL, larutan untuk injeksi dalam jarum suntik yang sudah terisi
Instruksi untuk penggunaan yang tepat
Tak dapat diterapkan.

Dosis, Metode, dan/atau jalur administrasi, Frekuensi pemberian dan Lama pengobatan
Dosis
Dokter Anda akan memutuskan berapa banyak Lovenox yang harus Anda gunakan dan untuk berapa lama, tergantung pada berat badan Anda dan alasan obat tersebut digunakan.
Sebagai pencegahan:
•Dalam pembedahan beresiko sedang: dosisnya adalah satu suntikan harian 2 000 Anti-Xa IU / 0,2 ml (20 mg / 0,2 ml).
•Dalam operasi berisiko tinggi (operasi pinggul dan lutut). Dosis adalah satu suntikan harian 4 000 Anti-Xa IU / 0,4 ml (40 mg / 0,4 ml).
Sebagai pencegahan pada pasien yang mengalami kondisi medis akut
Dosisnya adalah satu suntikan harian 4 000 anti-Xa IU / 0,4 ml (40 mg / 0,4 ml).

Hemodialisis
Dosis yang akan diberikan adalah 100 Anti-Xa IU / kg.
1 ml larutan untuk injeksi setara dengan sekitar 10.000 Anti-Xa IU enoxaparin.
Jika obat ini harus diganti dengan antikoagulan yang diminum, suntikan tidak akan segera dihentikan; Anda akan menerima kedua perawatan selama beberapa hari. Ini untuk memberi cukup waktu agar obat kedua menjadi aktif dan untuk tes pembekuan darah Anda mencapai tingkat yang ditentukan oleh dokter Anda.

Metode administrasi
• Sebagai pencegahan : 1 suntikan perhari
• Hemodialisis: obat disuntikkan langsung ke jalur arteri sirkuit hemodialisis, pada awal sesi dialisis.

Lama pengobatan
• Ketika Lovenox digunakan untuk mengobati gumpalan darah di vena (trombosis vena), pengobatan biasanya tidak berlangsung lebih dari 10 hari.
• Ketika Lovenox digunakan untuk mengobati jenis angina tertentu, perawatan biasanya berlangsung antara 2 dan 8 hari, sampai kondisi pasien stabil.
• Ketika Lovenox digunakan untuk mengobati serangan jantung (serangan jantung), durasi perawatan yang dianjurkan adalah 8 hari, atau sampai pasien meninggalkan rumah sakit, jika periode rawat inap kurang dari 8 hari.
Jika anda mempunyai pertanyaan lain mengenai penggunaan obat ini, tanyakan kepada dokter atau apoteker Anda untuk informasi lebih lanjut.

Gejala dalam kasus overdosis dan tindakan yang harus diambil
Jika Anda menggunakan lebih banyak Lovenox 4 000 Anti-Xa IU / 0,4 ml larutan untuk injeksi pada jarum suntik yang sudah terisi sebelumnya dari yang seharusnya:
Hubungi dokter dengan cepat karena risiko pendarahan.

Tindakan yang harus diambil ketika satu atau lebih dosis terlewat
Tak dapat diterapkan.

Risiko efek penarikan
Tak dapat diterapkan.

4. KEMUNGKINAN EFEK SAMPING
Deskripsi tentang efek samping
Seperti semua obat-obatan, Lovenox dapat menimbulkan efek samping meskipun tidak semua orang mengalaminya.

Efek samping berikut ini dapat terjadi:
- Perdarahan yang bisa serius, dan/atau mungkin tidak terlihat dengan mata telanjang (misalnya darah di urin, mimisan, perdarahan di perut atau usus, pendarahan di otak, perdarahan di belakang peritoneum (membran pelapis dinding lambung dan yang menutupi hati, lambung, limpa, kantung empedu dan usus). Jika ini terjadi, segera hubungi dokter atau perawat Anda.
- Jarang, memar di tulang belakang (hematoma intraspinal) yang dapat menyebabkan cedera neurologis seperti kelumpuhan permanen, ketika Lovenox diberikan kepada pasien yang menerima anestesi spinal.
- Menurunkan jumLah trombosit dalam darah Anda, yang mungkin serius dalam beberapa kasus dan yang harus segera dilaporkan kepada dokter Anda (lihat Bagian 2). Inilah sebabnya mengapa jumLah trombosit perlu diperiksa secara teratur.
- Peningkatan reversibel dalam jumLah trombosit
- Jarang, reaksi kulit yang serius, umumnya di tempat suntikan (nekrosis kulit).
- Memar, kurang lebih nodul menyakitkan di bawah kulit di tempat suntikan. Nodul menghilang secara alami dan bukan alasan untuk menghentikan pengobatan.
- Reaksi kulit alergi atau reaksi alergi yang mempengaruhi seluruh tubuh Anda, yang harus segera dilaporkan ke dokter Anda. Reaksi kulit termasuk bercak merah gatal (gatal-gatal) gatal (pruritus), kemerahan (eritema) atau lebih jarang gangguan kulit yang menyebabkan lepuh (dermatitis bullous).
- Osteoporosis (demineralisasi skeletal yang membuat tulang Anda lebih mudah patah) jika Anda menggunakan Lovenox untuk waktu yang lama.
- Sakit kepala
- Rambut rontok
- Kerusakan hati
- Nilai-nilai laboratorium abnormal dari tes darah
  - Peningkatan jumLah enzim hati tertentu dalam darah,
  - Peningkatan kadar potasium,
  - Peningkatan jumLah sel darah putih tertentu yang disebut eosinofil, baik sendiri atau dengan gangguan kulit.
  - Turunnya jumLah sel darah merah dalam darah setelah mengalami perdarahan.
- Sangat jarang, radang pembuluh darah kecil, dipicu oleh reaksi alergi.

Pelaporan efek samping
Jika Anda mendapat efek samping, bicarakan dengan dokter, apoteker, atau perawat Anda. Termasuk kemungkinan efek samping yang tidak tercantum dalam leaflet ini. Dengan melaporkan efek samping, Anda dapat membantu memberikan informasi lebih lanjut tentang keamanan obat ini.

5. CARA MENYIMPAN LOVENOX 4 000 Anti-Xa IU / 0,4 mL, larutan untuk injeksi pada jarum suntik yang sudah terisi
Jauhkan dari penglihatan dan jangkauan anak-anak.

Tanggal Kadaluarsa
Jangan gunakan obat ini setelah tanggal kadaluarsa yang tercantum pada kotak dan label setelah {EXP}. Tanggal kadaluarsa mengacu pada hari terakhir bulan tersebut.
Batas kadaluarsa 24 bulan sejak tanggal produksi. Lihat pada kemasan.

Kondisi penyimpanan
Jangan simpan pada suhu di atas 25ºC.
Simpan dalam kemasan aslinya.

Apabila diperlukan, peringatan pada tanda-tanda kerusakan tertentu yang terlihat
Jangan membuang obat apa pun melalui air limbah atau limbah rumah tangga. Tanyakan apoteker Anda bagaimana membuang obat-obatan yang tidak lagi Anda gunakan. Langkah-langkah ini akan membantu melindungi lingkungan.

6. INFORMASI LEBIH LANJUT
Daftar lengkap zat aktif dan zat tambahan
Isi dari Lovenox 4 000 Anti-Xa IU / 0,4 ml larutan untuk injeksi pada jarum suntik yang sudah terisi (pre-filled syringe)

Zat aktifnya adalah:
Enoxaparin sodium.
Jarum suntik yang diisi penuh 0,4 ml mengandung 4 000 Anti-Xa IU, setara dengan 40 mg enoxaparin sodium.

Bahan lainnya adalah:
Air untuk suntikan

Pemerian :
Jernih, larutan tidak berwarna sampai kuning pucat

Bentuk dan isi dari obat
Bentuk dan isi dari paket Lovenox 4 000 Anti-Xa IU / 0,4 ml larutan untuk injeksi pada jarum suntik yang sudah terisi
Lovenox 4 000 Anti-Xa IU / 0,2 ml adalah larutan untuk injeksi dalam jarum suntik yang sudah terisi 0,4 ml, dan dikemas dalam kotak dengan 2 jarum suntik.

Reg.No.DKI0185600143A1

HARUS DENGAN RESEP DOKTER

Mengandung Babi

DNA babi tidak terdeteksi pada produk akhir.
Uji dilakukan oleh laboratorium independen menggunakan metode RT-PCR.

Diproduksi oleh:
Sanofi Winthrop Industrie,
Maison-Alfort - France

Didaftarkan oleh:
PT Kalventis Sinergi Farma,
Jakarta - Indonesia

30 mL/min to 60 mL/min calculated using the Cockcroft formula). As LMWH is primarily eliminated by the renal route, unlike standard unfractionated heparin, any renal insufficiency can result in relative overdose. Severe renal insufficiency is a contraindication to the use of LMWH at curative treatment;
- extreme bodyweight (thinness or even cachexia, obesity);
- Unexplained bleeding.

In contrast, laboratory monitoring is not recommended at prophylactic doses if the LMWH treatment is consistent with the therapeutic recommendations (particularly treatment duration), nor 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 assays 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 preceding assay, and a possible LMWH dose adjustment should be considered.
The anti-Xa activity observed varies for each LMWH and each dosage regimen.
For information, based on available data, the mean value (± standard deviation) observed 4 hours after 7th injection of enoxaparin given at a dose of 100 anti-Xa IU/kg/injection b.i.d. was 1.20 ± 0.17 anti-Xa IU/mL.
This mean value was observed during clinical trials for anti-Xa activity assays carried out by a chromogenic method (amidolytic).

*** Activated partial thromboplastin time (aPTT)**
Some LMWHs moderately increase aPTT. As no clinical relevance has been established, there is no need to monitor treatment using this tests.

Spinal/epidural anesthesia in patients given preventive treatment with LMWH
- Epidural or spinal anesthesia must never be performed in patients under curative LMWH treatment.
- As with other anticoagulants, there have been rare reports of spinal hematomas following administration of LMWH during spinal/epidural anesthesia, resulting in long-term or permanent paralysis.
  The risk of intra-spinal hematoma appears to be higher in epidural anesthesia with a catheter than in spinal anesthesia.
  The risk of these rare events may be increased by prolonged post-operative use of indwelling epidural catheters and in patients who have undergone spinal surgery or have spinal deformities (e.g. ankylosing spondylitis).
- Placement or removal of the catheter is best performed when the anticoagulant effect of enoxaparin is low. However, the exact timing to reach a sufficiently low anticoagulant effect in each patient is not known.
- If pre-operative LMWH treatment is required (long term bedridden patients, trauma) and if the benefit of local/regional spinal anesthesia has been carefully weighed, patients who received a pre-operative injection of LMWH can be anesthetized provided that an interval of at least 12 hours is respected between the heparin injection and the spinal anesthesia. Since anti-Xa levels are, however, still detectable after this 12-hour interval, a neuraxial hematoma can still occur. Close neurological monitoring is recommended due to the risk of intraspinal hematoma.

In almost all patients, prophylactic treatment with LMWH can be initiated within 6 to 8 hours after the anesthesia or removal of the catheter, under neurogical monitoring.
Extra caution should be exercised during co-administration with other drugs which affect hemostasis (specifically non-steroidal anti-inflammatory drugs, aspirin).

Situations involving particular risk
Monitoring of treatment should be intensified in the following cases:
- hepatic insufficiency,
- history of gastro-intestinal ulcers or any other organic lesion likely to bleed,
- vascular chorioretinal disease,
- post-operatively, following cerebral or spinal cord surgery,
- lumbar puncture: this should only be considered taking into account the risk of intraspinal bleeding. It should be postponed whenever possible
- combined use with drug which have an effect on hemostasis

Coronary angioplasty revascularization procedure
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 perform hemostasis at the vascular puncture site following coronary angioplasty. If an occlusion device is used, the introducer can be removed immediately. If manual compression is performed, the introducer must be removed 6 hours after the last SC/IV 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.

ADVERSE EFFECTS
The adverse reactions observed in clinical studies and reported in post-marketing experience are detailed below.
Frequencies are defined using the following convention: very common (≥1/10), common (≥1/100, <1/10), uncommon (≥1/1 000, <1/100), rare (≥1/10 000, <1/1,000), very rare (<1/10,000), frequency not known (cannot be estimated from the available data). Frequency for undesirable effects reported during the post-marketing period is defined as "not known" (cannot be estimated from the available data).

Cinical trials experience
Enoxaparin was evaluated in more than 15,000 patients in clinical trials.
The number of patients, indication and dosage regimen are presented in detail in the following table:

	VTE prophylaxis in surgical patients	DVT prophylaxis in medical patients during acute illness	Treatment of DVT with or without PE	Treatment of unstable angina or non-Q-wave myocardial Infarction	Treatment of ST-segment elevation myocardial infarction (STEMI)
Number of patients exposed to enoxaparin	1776	1169	559	578	10176
Dosage Regimen	40 mg SC o.d.	40 mg SC o.d.	1 mg/kg SC q 12h or 1.5 mg/kg SC o.d.	1 mg/kg SC q 12 h	30 mg IV bolus followed by 1 mg/kg SC Q 12 h.

Haemorrhage
In clinical studies, haemorrhages were the most commonly reported reaction. These included major haemorrhages, reported in 4.2 % of patients (surgical patients). Some of these cases were fatal.

Bleeding complications were considered major in the following cases:
• If the haemorrhage caused a significant clinical event
• If accompanied by a hemoglobin decrease of ≥ 2 g/dl or transfusion of 2 or more units of blood products,
• Retroperitoneal and intracranial haemorrhages were always considered major.

As with other anticoagulants, haemorrhage may occur in the presence of associated risk factors such as:
• organic lesions liable to bleed,
• invasive procedures or concomitant use of medications affecting hemostasis

MedDRA system organ class	DVT prophylaxis in surgical patients	DVT prophylaxis in medical patients	Curative treatment of DVT with or without PE	Unstable angina/non-ST-segment elevation myocardial Infarction	ST-segment elevation myocardial infarction (STEMI)
Vascular disorders	Very common: Haemorrhage * Rare: Retroperitoneal haemorrhage	Common: Haemorrhage *	Very common: Haemorrhage * Uncommon: Intracranial haemorrhage, retroperitoneal haemorrhage	Common: Haemorrhage * Rare: Retroperitoneal haemorrhage	Common: Haemorrhage * Uncommon: Intracranial haemorrhage, retroperitoneal hemorrhage

* for example: hematoma, ecchymosis (other than at the injection site), wound hematoma, hematuria, epistaxis and gastrointestinal haemorrhage.

Thrombocytopenia and thrombocytosis.

MedDRA system organ class	DVT prophylaxis in surgical patients	DVT prophylaxis in medical patients	Curative treatment of DVT with or without PE	Unstable angina/non-ST-segment elevation myocardial Infarction	ST-segment elevation myocardial infarction (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: Immunoallergic thrombocytopenia

*: Platelet count > 400 g/l

Other adverse reactions observed in clinical studies
These reactions are presented below, irrespective of the indication, by system organ class, frequency grouping and decreasing order of seriousness.

MedDRA system organ class	Undesirable effects (all indications combined)
Immune system disorders	Common: Allergic reaction which may lead to treatment discontinuation in some cases) Rare: Anaphylactic or anaphylactoid reaction
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 hematoma*, injection site pain, other injection site reaction (e.g. edema, haemorrhage, allergic reaction, inflammation, nodules, other reactions) Uncommon: Skin necrosis at injection site which may occur after symptoms of purpura or infiltrated, painful erythematous plaques, requiring immediate treatment discontinuation. Local irritation.
Investigations	Rare: Hyperkaliemia

* The risk is increased in the event of failure to comply with the recommended injection technique or use of inappropriate injection material

Post marketing experience
The following adverse reactions have been identified during postapproval use of Lovenox. Because these reactions are reported voluntarily, the frequency is "not known" (cannot be estimated from the available data).

Immune System Disorders
Cutaneous or systemic allergic effects (anaphylactic or anaphylactoid reactions, including shock), which, in certain cases, may lead to treatment discontinuation.

Nervous System Disorders
Headache

Vascular Disorders
Hemorrhagic episodes that mainly occur in the following context:
• associated risk factors: organic lesions likely to bleed and certain drug combinations (see Interaction with other medicinal products and other forms of interactions), age, renal failure, low body weight.
• failure to comply with therapeutic recommendations, particularly duration of treatment and dose adjustment based on body weight.

Rare cases of spinal hematoma have been reported with low molecular weight heparins (LWMWH) in patients receiving spinal anesthesia, analgesia or epidural anesthesia. These hematomas have resulted in more or less serious neurologic injury, including long-term or permanent paralysis.

Blood and lymphatic system disorders:
Thrombocytopenia has been reported.
There are two types:
• Type I, i.e. the most common cases, usually moderate (more than 100 000/mm³), of early onset (before the fifth day) which do not require treatment discontinuation;
• Type II, i.e. rare, serious immunoallergic thrombocytopenia (HIT). The incidence remains poorly evaluated.

Asymptomatic and reversible elevation of the platelet count.

Hemorrhagic anemia

Hypereosinophilia, occurring in isolated cases or along with skin reactions, resolving on treatment discontinuation.

Skin and subcutaneous disorders
Vasculitis due to skin hypersensitivity.

Skin necrosis observed in most cases at the injection site. These reactions may be preceded by purpura or by infiltrated and painful erythematous plaques. Treatment must be discontinued immediately in these cases.

Alopecia

Hepatobilary disorders
Hepatocellular or cholestatic liver injury.

Musculoskeletal and connective tissue disorders
Osteoporosis following long-term therapy.

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

In case of haemorrhage, 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 unwanted 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 the 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 can be administered if the enoxaparin sodium was given more than 8 hours earlier, or if a second dose of protamine appears necessary.
  - administration of protamine is not necessary if the enoxaparin injection was given more than 12 hours earlier.

The above recommendations are intended for patients with normal renal function receiving repeated doses.
Nevertheless, the anti-Xa activity of enoxaparin cannot be completely neutralized.
Furthermore, the neutralization may only be transient due to the absorption pharmacokinetics of low molecular weight heparin.
This may require dividing the total calculated dose of protamine into several injections (2 to 4) given over 24 hours.
- Serious consequences are likely after ingestion of low molecular weight heparin, even in massive quantities (no cases reported), due to the low gastric and intestinal absorption of the drug.

CONTRA INDICATIONS
This medical product must not be used in the following situations:
- Hypersensitivity to enoxaparin, heparin or heparin derivatives, including other LMWHs,
- History of thrombocytopenia with enoxaparin or any other heparin, whether caused by unfractionated or low molecular weight heparin (see Section Precautions for use).
- History of immune mediated heparin-induced thrombocytopenia (HIT) within the past 100 days or in the presence of circulating antibodies
- Hemorrhagic manisfestations or tendency to bleed related to impaired hemostasis (a possible exception to this contraindication may be disseminated intravascular coagulation, when it is not related to heparin therapy (see Precaution for use).
- Organic lesion likely to bleed
- Clinically significant active bleeding
- Acute infectious endocarditis (except when occurring on a mechanical prosthesis).
- In the absence of data, severe renal failure (i.e. creatinine clearance < 30 ml/min), except in dialysis which is a special case. In these cases, use unfractionated heparin.

This medicinal product is generally not advisable in the following cases:
- mild to moderate renal failure (creatinine clearance > 30 and < 60 ml/min).
- haemorrhagic stroke
- uncontrolled arterial hypertension,

or in combination with (see Interactions with other medicinal products):
- acetylsalicylic acid (for analgesia and antipyretic therapy)
- NSAIDs
- dextran
- ticlopidine

INTERACTIONS WITH OTHER MEDICINES 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 and unfractionated heparin), ciclosporin and tacrolimus, trimethoprim.
Occurrence of hyperkalemia may depend on possible related risk factors.
This risk is potentiated when the above-mentioned drugs are co-administered.

Inadvisable combinations
+ **Acetylsalicylic acid at analgesic, antipyretic and anti-inflammatory doses** (and,by extrapolation, other salicylates):
  Increased risk of hemorrhage (salicylate-induced platelet function inhibition and gastroduodenal mucosal damage).
  Use a non-salicylate antipyretic analgesic (such as paracetamol).
+ **NSAIDs** (systemic use):
  Increased risk of haemorrhage (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 hemorrhage (inhibition of platelet function by dextran 40). Adjust heparin dosage so that the coagulation test performed as a measure of hypocoagulability does not exceed 1.5 times the control value during co administration and after discontinuation of dextran 40.
+ **Ticlodipine:**
  Increased risk of haemorrhage (inhibition of platelet function by ticlodipine)

Combinations requiring precautions for use
+ **Corticoids (glucocorticoids)** (except for hydrocortisone used as replacement therapy in Addison's disease) (systemic use and, in certain cases local uses, i.e. intramuscular, intraarticular or cutaneous use of rectal washout).
  Heparin-related increase in the risk of haemorrhage specific to corticoid therapy (gastric mucosa, vascular fragility), at high doses or during prolonged treatment lasting more than ten days. If the combination cannot be avoided clinical monitoring must be intensified.
+ **Oral anticoagulants**
  Potentiation of the anticoagulant effect.
  When heparin is replaced by an oral anticoagulant, clinical monitoring must be intensified.

Combinations to take into consideration
+ **Platelet aggregation inhibitors** (other than acetylsalicylic acid at analgesic, antipyretic and anti-inflammatory doses; NSAIDs): abciximab, acetylsalicylic acid at antiaggregant doses in cardiological and neurological indications, baraprost, clopidogrel, eptifibatide, iloprost, ticlopidine, tirofiban.
  Increased risk of hemorrhage.

Patients under 65 years of age
Combinations to take into consideration
Combined use of drugs which variably affect hemostasis potentiate 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 means of continued clinical monitoring and possible laboratory tests: oral anticoagulants, platelet aggregation inhibitors (abciximab, NSAIDs, acetylsalicylic acid at any dose, clopidogrel, eptifibatide, iloprost, ticloprost, ticlopidine, tirofiban) and thrombolytic agents.

PREGNANCY AND LACTATION
Pregnancy
There is no evidence from animal studies that enoxaparin has teratogenic potential.
In the absence of any teratogenic effect in animals, no such effect is expected in man. To date, substances responsible for malformation in humans have proved to be teratogenic in animals during well-conducted studies into two species.

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, prevented heparin treatment should be interrupted whenever possible within 12 hours before anesthesia at the latest.

Prophylactic 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 anesthesia at the latest.

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

Shelf Life
24 months

Presentations
Prefilled syringes 4000 anti-Xa IU/0.4 ml; Box of 2
Reg.No.DKI0185600143A1

Do not store above 25º C.

ON MEDICAL PRESCRIPTION ONLY
HARUS DENGAN RESEP DOKTER

Mengandung Babi

DNA babi tidak terdeteksi pada produk akhir.
Uji dilakukan oleh laboratorium independen menggunakan metode RT-PCR.

Manufactured by:
Sanofi Winthrop Industrie,
Maison-Alfort, France

Registered by:
PT Kalventis Sinergi Farma,
Jakarta - Indonesia

Based on Enoxaparin Sodium-CCDSv13

DISETUJUI OLEH BPOM: 31/10/2023

Material Name	: PI-PIL LOVENOX 4000-1	Plant code : KSF/XXXXXX	
Country	: Indonesia	Min. point size of text	: 6 pt
Version number	: 1	Type of text	: OceanSans Pro SAN Family
Date	: 13.09.2023	Dimensions	: 380 mm X 300 mm
Material	: HVS 60 g/m²	Type of prefold	: 3 x Horizontal & 2 x Vertical
Pharmacode	: XXXXX	Dimension after folded	: 95 mm x 37.5 mm (± 2 mm)
Prepared by	: Rahmat Hafid		

Printing Colour
Pantone Black CVC

Technical Information
outline

ID EREG100022VR12300552