

Area for pharmacode

**Lovenox**<sup>®</sup>

# Enoxaparine sodium 2000anti-Xa IU/0.2 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.**

**Compositon**

Active ingredient: enoxaparin sodium.

Solvent - water for injections.

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 2000 anti-Xa IU is equivalent to 20 mg.

**PHARMACOLOGICAL PROPERTIES**

**Pharmacodynamics properties**

ANTI-THROMBOTIC 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.

**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 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 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 sodium anti-Xa activity is about 5 liters and is close to the blood volume.

*Metabolism*

Enoxaparin sodium is primarily metabolized 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 subjects*

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.
- Prevention of clotting in the extracorporeal circulating during hemodialysis (generally a session of 4 hours or less).

**DOUSAGE AND ADMINISTRATION**

KSF/XXXXXX

**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 method:**

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).

**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.

*Administration schedule:*

One injection per day.

*Dosage:*

The dose must be determined based on the 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 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.
- 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.

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

**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 haemorrhage (particularly pre- and post-operative dialysis) or with active haemorrhage, 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 haemorrhage:**

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

Serious haemorrhage 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 haemorrhage.

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 LWHW 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 device 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.

**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 Contraindications). 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 reinstating 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.

- an immediate platelet count for verification
- 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.
- 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 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 neuronal 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 neurological monitoring.

Extra caution should be exercised during

## Lembar Kemasan : Informasi bagi pengguna LOVENOX 2000 Anti-Xa IU/0.2 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:**

- Apa itu Lovenox 2 000 Anti-Xa IU / 0,2 mL larutan untuk injeksi pada jarum suntik yang sudah terisi (pre-filled syringe) dan apa kegunaannya
- Apa yang perlu Anda ketahui sebelum menggunakan larutan Lovenox 2 000 Anti-Xa IU / 0,2 mL untuk injeksi pada jarum suntik yang sudah terisi (pre-filled syringe).
- Cara menggunakan larutan Lovenox 2 000 Anti-Xa IU / 0,2 mL untuk injeksi pada jarum suntik yang sudah terisi (pre-filled syringe)
- Kemungkinan efek samping
- Cara menyimpan larutan Lovenox 2 000 Anti-Xa IU / 0,2 mL untuk injeksi dalam jarum suntik yang sudah terisi (pre-filled syringe)
- Informasi lainnya

**1. APA ITU LOVENOX 2000 Anti-Xa IU / 0,2 mL, larutan untuk injeksi pada jarum suntik yang sudah diisi DAN APA KEGUNAANNYA.**

*Kelompok farmakoterapi*

AGEN ANTI-THROMBOTIC

*Indikasi terapeutik*

Obat ini adalah antiokoagulan (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.

- sebagai pengobatan pencegahan, untuk mencegah pembentukan gumpalan darah,
- sebagai pengobatan kuratif, ketika gumpalan darah sudah terbentuk.

Obat ini digunakan dalam kasus-kasus tertentu dalam operasi di mana ada risiko bekuan darah berkembang di pembuluh darah vena (flebitis). Ini juga digunakan untuk mencegah pembentukan penggumpalan darah dari dalam tabung mesin dialisis (digunakan pada pasien dengan gagal ginjal).

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

*Daftar informasi yang diperlukan sebelum menggunakan produk obat*

Tak dapat diterangkan

*Kontraindikasi*

**Jangan gunakan larutan Lovenox 2 000 Anti-Xa IU / 0,2 mL untuk injeksi pada jarum suntik yang sudah terisi jika salah satu dari hal berikut ini terjadi:**

PENGUNAAN OBAT INI	KONTRAIKASIKASI	TIDAK DIREKOMENDASIKAN
	<ul style="list-style-type: none"><li>jika Anda alergi terhadap obat ini, untuk heparin atau turunannya, termasuk heparin berat molekul rendah lainnya,</li> <li>jika Anda pernah mengalami penurunan trombosit yang serius yang disebabkan oleh heparin (trombosit memainkan peran penting dalam pembekuan darah),</li> <li>jika Anda memiliki gangguan pembekuan darah,</li> <li>jika Anda terluksa (internal atau eksternal) yang cenderung mengeluarkan darah,</li> <li>jika Anda mengalami pendarahan yang berlebihan.</li> <li>jika anda mengalami infeksi pada jantung dan gagal ginjal berat</li></ul>	<ul style="list-style-type: none"><li>jika Anda mengalami gagal ginjal yang ringan-sedang,</li> <li>selama 24 jam pertama setelah pendarahan otak,</li> <li>jika Anda berusia di atas 65 tahun dan juga mengonsumsi aspirin (pada dosis yang digunakan untuk mengobati rasa sakit dan demam) obat anti-inflamasi nonsteroid atau dekstran.</li> <li>Hipertensi tidak terkontrol</li> <li>Dalam kombinasi dengan obat lain yaitu aspirin, AINS, dextran, ticlopidine</li></ul>

*Tindakan pencegahan: Peringatan khusus*

**Berhati-hatilah dengan larutan Lovenox 2 000 Anti-Xa IU / 0,2 mL untuk injeksi pada jarum suntik yang sudah terisi (pre-filled syringe)**

**Peringatan**

Untuk menghindari adanya risiko 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.

*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 2 000 Anti-Xa IU / 0,2 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).
- Jika ada peningkatan risiko terjadinya thromboemboli vena (sumbatan pada pembuluh darah balik) pada pasien operasi, maka dosis obat seperti operasi berisiko tinggi.

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 anticoagulan yang diminun, 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.
Jika terdapat fibrin rings (sumbatan) pada alat hemodialisis, dosis tambahan 50-100 IU/kg dapat diberikan bergantung pada waktu hemodialisa tersebut.
Jika pasien hemodialisis merupakan pasien risiko tinggi pendarahan, maka dosis yang digunakan yaitu 50 IU/kg (jika menggunakan akses vaskular ganda) atau 75 IU/kg (jika menggunakan akses vascular tunggal).

**Metode administrasi**

Obat ini diberikan sebagai suntikan dibawah kulit Anda (injeksi subkutan)(kecuali bila digunakan selama dialysis)
jangan menyuntikkan obat ini ke otot.

**Frekuensi administrasi**

•Sebagai perawatan pencegahan dalam pembedahan: 1 suntikan setiap hari.
•Hemodialisis: obat disuntukkan langsung ke jalur arteri sirkuit hemodialysis, pada awal sesi dialysis.

**Lama pengobatan**

Perawatan biasanya tidak lebih dari 10 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 2 000 Anti-Xa IU / 0,2 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*

Seperi 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, kantong 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.

**Jelaporan 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 2 000 Anti-Xa IU / 0,2 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 25°C.

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 2 000 Anti-Xa IU / 0,2 mL larutan untuk injeksi pada jarum suntik yang sudah terisi (pre-filled syringe)**

**Zat aktifnya adalah:**

Enoxaparin sodium.
Jarum suntik yang diisi penuh 0,2 mL mengandung 2 000 Anti-Xa IU, setara dengan 20 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 2 000 Anti-Xa IU / 0,2 mL larutan untuk injeksi pada jarum suntik yang sudah terisi**
Lovenox 2 000 Anti-Xa IU / 0,2 mL adalah larutan untuk injeksi dalam jarum suntik yang sudah terisi 0,2 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

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,
- lumbur 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

**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 more than 15,000 patients in clinical trials.

The number of patients, indication and dosage regimen are presented in detail in the following table:

	<b>VTE prophylaxis in surgical patients</b>	<b>DVT prophylaxis in medical patients during acute illness</b>	<b>Treatment of DVT with or without PE</b>	<b>Treatment of unstable angina or non-Q-wave myocardial Infarction</b>	<b>Treatment of ST-segment elevation myocardial infarction (STEMI)</b>
<b>Number of patients exposed to enoxaparin</b>	1776	1169	559	578	10176
<b>Dosage Regimen</b>	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

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

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

*Thrombocytopenia and thrombocytosis.*

<b>MedDRA system organ class</b>	<b>DVT prophylaxis in surgical patients</b>	<b>DVT prophylaxis in medical patients</b>	<b>Curative treatment of DVT with or without PE</b>	<b>Unstable angina/non-ST-segment elevation myocardial Infarction</b>	<b>ST-segment elevation myocardial infarction (STEMI)</b>
<b>Blood and lymphatic system disorders</b>	Very common: Thrombocytosis* <p>Common: Thrombocytopenia</p>	Uncommon: Thrombocytopenia	Very common: Thrombocytosis * <p>Common: Thrombocytopenia</p>	Uncommon: Thrombocytopenia	Common: Thrombocytosis* <p>Thrombocytopenia</p> <p>Very rare: Immuno-allergic thrombocytopenia</p>

\*: 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.

<b>MedDRA system organ class</b>	<b>Undesirable effects (all indications combined)</b>
<b>Immune system disorders</b>	Common: Allergic reaction which may lead to treatment discontinuation in some cases) <p>Rare: Anaphylactic or anaphylactoid reaction</p>
<b>Hepatobiliary disorders</b>	Very common: Hepatic enzymes increase (mainly transaminases**)
<b>Skin and subcutaneous tissue disorders</b>	Common: urticaria, pruritus, erythema, <p>Uncommon: Bullous dermatitis</p>
<b>General disorders and administration site conditions</b>	Common: Injection site hematoma*, injection site pain, other injection site reaction (e.g. edema, haemorrhage, allergic reaction, inflammation, nodules, other reactions) <p>Uncommon: Skin necrosis at injection site which may occur after symptoms of purpura or infiltrated, painful erythematous plaques, requiring immediate treatment discontinuation. Local irritation.</p>
<b>Investigations</b>	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*

Haemorrhagic 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.

Haemorrhagic anemia

Hyperosinophilia, 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

*Hepatobiliary disorders*

Hepatocellular or cholestatic liver injury.

*Muskuloskeletal 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 manifestations 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 recommended in cases of:**

- 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 haemorrhage (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.

+ **Ticlopidine:**
Increased risk of haemorrhage (inhibition of platelet function by ticlopidine)

*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 mucoasa, 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**

Potential 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, baprost, clopidogrel, eptifibatide, iloprost, ticlopidine, tirofiban.

Increased risk of haemorrhage.

**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, ticlofiban) 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, preventive 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 in principle gastro-intestinal absorption by neonates is unlikely in principle, treatment with enoxaparin, is not contraindicated in breast-feeding.

**Presentations**

Prefilled syringes 2000 anti-Xa IU/0.2 mL; Box of 2 Reg.No.DKI0185600143A1

**Do not store above 25° 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