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.
Each ml of the solution contains 10000 anti-Xa IU equivalent to 100 mg enoxaparin sodium.
One mg (0.01 ml) of enoxaparin sodium corresponds approximately to 100 anti-Xa IU. LOVENOX 6000 anti-Xa IU is equivalent to 60 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.

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

In a large multicenter study, 20479 patients with acute ST-segment elevation myocardial infarction having received fibrinolytic, treatment were randomized to receive either:

Based on Enoxaparin-CCDSv09; CCDSv10; CCDSv11; CCDSv12
enoxaparin as an IV bolus injection of 3 000 anti-Xa IU immediately followed by a dose of 100 anti-Xa IU/kg SC, then by an SC injection of 100 anti-Xa IU/kg every 12 hours, or unfractionated heparin by the IV route as a bolus injection of 60 IU/kg (maximum 4 000 IU) followed by a continuous infusion at a dose adjusted to the activated partial thromboplastin time. The SC injections of enoxaparin were administered until discharge from hospital or for a maximum period of 8 days (in 75% of cases for at least 6 days). Half the patients receiving heparin were administered the drug for less than 48 hours (in 89.5% of cases ≥ 36 hours). All the patients were also treated with aspirin for at least 30 days. The enoxaparin dosage was adjusted for patients aged 75 years or more: 75 IU/kg as an SC injection every 12 hours, without an initial IV bolus injection.

During the study, 4716 (23%) patients underwent coronary angioplasty under antithrombotic treatment using blinded study drugs. Patients did not receive an additional dose if the last SC injection of enoxaparin had been given less than 8 hours balloon inflation, or, received an IV bolus injection of 30 anti-Xa IU/kg if the last SC injection of enoxaparin had been given more than 8 hours before balloon inflation.

Enoxaparin significantly reduced the incidence of primary end point events (composite end point consisting of myocardial infarction relapse and all-cause mortality within 30 days after inclusion : 9.9% in the enoxaparin group versus 12.0% in the unfractionated heparin group (relative risk reduction of 17% (p<0.01)). The incidence of myocardial infarction relapse was significantly lower in the enoxaparin group (3.4% versus 5%, p<0.001, relative risk reduction 31%). The incidence of deaths was lower in the enoxaparin group, with no statistically significant difference between the groups (6.9% versus 7.5%, p=0.11).

The benefit of enoxaparin in terms of the primary endpoint was consistent, irrespective of subgroup: age, sex, location of myocardial infarction, history of diabetes of myocardial infarction, type of thrombolytic administered and interval between the first clinical signs and treatment initiation.

Enoxaparin demonstrated a significant benefit versus unfractionated heparin in terms of the primary efficacy criterion, both in patients who had undergone coronary angioplasty within 30 days after inclusion (10.8% versus 13.9%, 23% reduction in relative risk) and in patients who did not have coronary angioplasty (9.7% versus 11.4%, 15% reduction in relative risk).

The incidence of major bleeding at 30 days was significantly higher (p<0.0001) in the enoxaparin group (2.1%) versus the heparin group (1.4%). There was a higher incidence of gastrointestinal bleeding in the enoxaparin group ( 0.5%) versus the heparin group (0.1%), while the incidence of intracranial bleeding was similar in both groups (0.8% with enoxaparin versus 0.7% with heparin).

The analysis of the composite criteria measuring overall clinical benefit showed statistically significant superiority (p<0.0001) for enoxaparin versus unfractionated heparin : a relative risk reduction of 14% in favor of enoxaparin (11.0% versus 12.85) for the composite criteria consisting of death, myocardial infarction relapse, or major bleeding (TIMI criteria) at 30 days.

Based on Enoxaparin-CCDSv09; CCDSv10; CCDSv11; CCDSv12
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 sub-cutaneous administration and single intravenous injection.

**Bioavailability**
Subcutaneously administered enoxaparin is rapidly and completely absorbed (approximately 100%). Peak plasma activity is observed between 3 and 4 hours after administration. This peak activity (expressed as anti-Xa IU) is $0.18 \pm 0.04$ anti-Xa IU (after 2000 IU), $0.43 \pm 0.11$ anti-Xa IU (after 4000 IU) in prophylactic therapy, and $1.01 \pm 0.14$ anti-Xa IU (after 10000 IU) in curative treatment.

An IV bolus injection of 3000 anti-XaIU followed by 100 anti-Xa IU/kg by the SC route every 12 hours leads to a first peak in anti-Factor Xa levels of 1.16 IU/ml (n=16) and a mean exposure corresponding to 88% of the steady state level. Steady state is reached as of the second day of treatment.

Enoxaparin pharmacokinetics appear to be linear over the recommended dose ranges. Intrapatient and inter-patient variability is low. After repeated subcutaneous administration of 4000 anti-Xa IU once daily in healthy volunteers, the steady state is reached on day 2 with mean enoxaparin activity of approximately 15% higher than that obtained after a single dose. Steady-state enoxaparin activity levels are well predicted by single dose pharmacokinetics. After repeated subcutaneous administration of 100 anti-Xa IU/kg b.i.d., the steady state is reached between day 3 and 4 with mean exposure about 65% higher than after a single dose, and with maximum and minimum anti-Xa activity of about 1.2 and 0.52 anti-Xa IU/ml respectively. Based on enoxaparin sodium pharmacokinetics, this difference in steady state is expected and is within the therapeutic range. Plasma anti-IIa activity after subcutaneous administration is about 10-fold lower than anti-Xa activity. The mean maximum anti-IIa activity is observed approximately 3 to 4 hours following subcutaneous injection and reaches 0.13 anti-IIa IU/ml following repeated administration of a 100 anti-Xa IU/kg dose b.i.d.

No pharmacokinetic interaction has been observed between enoxaparin and the thrombolytic agent when co-administered.

**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**

Based on Enoxaparin-CCDSv09; CCDSv10; CCDSv11; CCDSv12
Following subcutaneous injection, the apparent anti-Xa activity elimination half-life is higher for low molecular weight heparins than for unfractionated heparins. Enoxaparin exhibits a monophasic elimination pattern with a half-life of about 4 hours after a single subcutaneous dose to about 7 hours after repeated dosing. With low molecular weight heparin, plasma anti-IIa activity decay occurs more quickly than that of plasma 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 change does not affect dosages or the administration schedule in prophylactic therapy 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 over 75 years of age using the Cockcroft formula before initiating treatment with LMWH.

**Patients with mild to moderate renal failure** (i.e. creatinine clearance >30 ml/min):

In certain cases, it may be useful to monitor the circulating anti-factor Xa activity to prevent overdose when enoxaparin is used as curative treatment.

**INDICATIONS**

This heparin is a low molecular weight heparin (LMWH)

This heparin is a low-molecular-weight heparin (LMWH). It is indicated for:

- Treatment of acute ST-segment Elevation Myocardial Infarction (STEMI) as an adjunctive to thrombolytic treatment and in combination with anti aggregation treatment, including patients to be managed medically or with subsequent Percutaneous Coronary Intervention (PCI).

**DOSAGE AND ADMINISTRATION**

**SUBCUTANEOUS ROUTE** (except for patient with acute ST-segment elevation myocardial infarction, in whom IV bolus administration is required).

This presentation is suitable for adults.

This drug is not to be injected via the intramuscular route.

One milliliter of solution for injection is equivalent to approximately 10 000 anti-Xa IU of enoxaparin.

*Based on Enoxaparin-CCDSv09; CCDSv10; CCDSv11; CCDSv12*
**Subcutaneous injection technique:**
The dose of enoxaparine to be injected should be adjusted according to patient bodyweight and any excess volume discarded before administering the injection. When there is no excess volume, the air should not be expelled from the syringe before the injection.

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 forefinger. This skin fold should be held throughout the injection.

**Intravenous (bolus) injection technique / Using the multidose vial of Lovenox 30 000 anti-Xa IU/3 ml for the treatment of acute ST-segment elevation myocardial infarction:**

Treatment is initiated with an IV bolus injection, immediately followed by an SC injection. The multidose vial should be used to allow the initial dose of 3 000 IU, i.e. 0.3 ml to be withdrawn using a graduated 1 ml syringe (insulin-type syringe).
This dose of enoxaparin should be injected into a venous line, and must not be mixed or administered with other medicinal products. To avoid any traces of other medicinal products and therefore to prevent them from mixing with enoxaparin, the injection line must be rinsed with a sufficient quantity of normal saline or glucose solution before and after IV bolus injection of enoxaparin. Enoxaparin can be safely administered with 0.9% normal saline solution or 5% glucose solution.
In the hospital setting, the multidose vial can be used to:
- obtain the required 100 IU/kg dose for the first SC injection, to be given along with the IV bolus, and then the required 100 IU/kg doses for SC injection, repeated every 12 hours,
- obtain the 30 IU/kg dose for IV bolus injection for patients undergoing subsequent coronary angioplasty.

**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).

**Curative treatment of deep vein thrombosis (DVT), with or without pulmonary embolism, without signs of clinical severity**

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

**Administration schedule:**
Two injections daily at 12-hour intervals.

*Based on Enoxaparin-CCDSv09; CCDSv10; CCDSv11; CCDSv12*
Dose:
The dose per injection is 100 anti-Xa IU/kg.
LMWH dosage has not been evaluated in terms of bodyweight in patients weighing more than 100 kg or less than 40 kg. The efficacy of LMWH treatment may be slightly lower in patients weighing more than 100 kg, and the risk of hemorrhage may be higher in patients weighing less than 40 kg. Specific clinical monitoring must be carried out in these patients.

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

Curative treatment of unstable angina/non-Q-wave myocardial infarction
A dose of 100 anti-Xa IU/kg of enoxaparin is administered by subcutaneous injection twice daily at 12-hour intervals, in combination with aspirin (recommended doses: 75 to 325 mg orally, following a minimum loading dose of 160 mg).
The recommended duration of treatment is about 2 to 8 days, until the patient is clinically stable.

Treatment of acute ST-segment elevation myocardial infarction in combination with a thrombolytic agent in patients eligible or not for subsequent coronary angioplasty.
An initial IV bolus injection of 3 000 anti-Xa IU followed by an SC injection of 100 anti-Xa IU/kg within 15 minutes, then every 12 hours (a maximum of 10 000 anti-Xa IU for the first two SC doses). The first dose of enoxaparin should be administered at any time between 15 minutes before and 30 minutes after the start of thrombolytic treatment (whether fibrin-specific or not). The recommended duration of treatment is 8 days, or until the patient is discharged from hospital if the hospitalization period is less than 8 days.

Concomitant treatment:
administration of aspirin must be instituted as soon as possible after symptoms appear, and maintained at a dosage of between 75 mg and 325 mg daily for at least 30 days, unless otherwise indicated.
Patient treated by coronary angioplasty:
- if the last SC injection of enoxaparin was performed less than 8 hours before balloon inflation, no additional administration is necessary.
- if the last SC injection was performed more than 8 hours before balloon inflation, an IV bolus of 30 anti-Xa IU/kg of enoxaparin must be administered. In order to improve the accuracy of the volumes to be injected, it is recommended to dilute the drug to 300 IU/ml (i.e. 0.3 ml of enoxaparin diluted in 10 ml) (see table below).
Volumes to inject when dilution is performed for coronary angioplasty patients:

<table>
<thead>
<tr>
<th>Weight</th>
<th>Required dose</th>
<th>Volume to inject when diluted to 300 IU/ml (i.e. 0.3 ml of enoxaparin diluted in 10ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kg</td>
<td>IU</td>
<td>MI</td>
</tr>
<tr>
<td>45</td>
<td>1350</td>
<td>4.5</td>
</tr>
<tr>
<td>50</td>
<td>1500</td>
<td>5</td>
</tr>
<tr>
<td>55</td>
<td>1650</td>
<td>5.5</td>
</tr>
<tr>
<td>60</td>
<td>1800</td>
<td>6</td>
</tr>
<tr>
<td>65</td>
<td>1950</td>
<td>6.5</td>
</tr>
<tr>
<td>70</td>
<td>2100</td>
<td>7</td>
</tr>
<tr>
<td>75</td>
<td>2250</td>
<td>7.5</td>
</tr>
<tr>
<td>80</td>
<td>2400</td>
<td>8</td>
</tr>
<tr>
<td>85</td>
<td>2550</td>
<td>8.5</td>
</tr>
<tr>
<td>90</td>
<td>2750</td>
<td>9</td>
</tr>
<tr>
<td>95</td>
<td>2850</td>
<td>9.5</td>
</tr>
<tr>
<td>100</td>
<td>3000</td>
<td>10</td>
</tr>
</tbody>
</table>

In patients aged 75 and over, treated for acute ST-segment elevation myocardial infarction, the initial IV bolus injection should not be administered. An SC dose of 75 anti-Xa IU/kg every 12 hours should be administered (maximum of 7 500 anti-Xa IU for the first two injections only).

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.

- **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.

Based on Enoxaparin-CCDSv09; CCDSv10; CCDSv11; CCDSv12
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.

PRECAUTIONS FOR USE

Hemorrhage
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 mmol/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.

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.

Based on Enoxaparin-CCDSv09; CCDSv10; CCDSv11; CCDSv12
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 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 $1.20 \pm 0.17$ 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.

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

Based on Enoxaparin-CCDSv09; CCDSv10; CCDSv11; CCDSv12
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).

Clinical 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:

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

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

Based on Enoxaparin-CCDSv09; CCDSv10; CCDSv11; CCDSv12
Bleeding complications were considered major in the following cases:
- If the hemorrhage caused a significant clinical event
- If accompanied by a hemoglobin decrease of \( \geq 2 \) g/dl or transfusion of 2 or more units of blood products,
- Retroperitoneal and intracranial hemorrhages were always considered major.

As with other anticoagulants, hemorrhage 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

<table>
<thead>
<tr>
<th>MedDRA system organ class</th>
<th>DVT prophylaxis in surgical patients</th>
<th>DVT prophylaxis in medical patients</th>
<th>Curative treatment of DVT with or without PE</th>
<th>Unstable angina/non-ST-segment elevation myocardial infarction</th>
<th>ST-segment elevation myocardial infarction (STEMI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Rare: Retroperitoneal hemorrhage</td>
<td></td>
<td>Uncommon: Intracranial hemorrhage, retroperitoneal hemorrhage</td>
<td>Rare: Retroperitoneal hemorrhage</td>
<td>Uncommon: Intracranial hemorrhage, retroperitoneal hemorrhage</td>
</tr>
</tbody>
</table>

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

**Thrombocytopenia and thrombocytosis.**

<table>
<thead>
<tr>
<th>MedDRA system organ class</th>
<th>DVT prophylaxis in surgical patients</th>
<th>DVT prophylaxis in medical patients</th>
<th>Curative treatment of DVT with or without PE</th>
<th>Unstable angina/non-ST-segment elevation myocardial infarction</th>
<th>ST-segment elevation myocardial infarction (STEMI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Common: Thrombocytopenia</td>
<td></td>
<td>Common: Thrombocytopenia</td>
<td>Common: Thrombocytopenia</td>
<td>Very rare: Immuno-allergic thrombocytopenia</td>
</tr>
</tbody>
</table>

*: 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.

<table>
<thead>
<tr>
<th>MedDRA system organ class</th>
<th>Undesirable effects (all indications combined)</th>
</tr>
</thead>
</table>

Based on Enoxaparin-CCDSv09; CCDSv10; CCDSv11; CCDSv12
| Immune system disorders | Common: Allergic reaction which may lead to treatment discontinuation in some cases)  
Rare: Anaphylactic or anaphylactoid reaction |
|-------------------------|----------------------------------------------------------------------------------|
| Hepatobiliary disorders | Very common: Hepatic enzymes increase (mainly transaminases**)  
Uncommon: Bullous dermatitis |
| 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, hemorrhage, 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: Hyperkalemia |

* 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 immunoonallergic thrombocytopenia (HIT). The incidence remains poorly evaluated.

Based on Enoxaparin-CCDSv09; CCDSv10; CCDSv11; CCDSv12
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

**Hepatobiliary 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 hemorrhage, certain patients can be treated with protamine sulfate, taking the following factors into account:

- its efficacy is far lower than that reported in overdoses with unfractionated heparin,
- due to its 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-Xa IU 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.
  - if the injection of enoxaparin sodium was given more than 12 hours previously, it is not necessary to administer protamine

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

Nevertheless, the anti-Xa activity cannot be completely neutralized.

**Based on Enoxaparin-CCDSv09; CCDSv10; CCDSv11; CCDSv12**
Furthermore, the neutralization may be transient due to the absorption pharmacokinetics of low molecular-weight heparin, which may require dividing the total calculated dose of protamine into several injections (2 to 4) given over 24 hours. 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.

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

**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 serious type II heparin induced thrombocytopenia (HIT), whether caused by unfractionated or low-molecular-weight heparin (see Section Precautions for use).
- Bleeding or tendency to bleed related to impaired hemostasis (a possible exception to this contraindication may be disseminated intravascular coagulation, when not related to heparin treatment (see Section Precautions for use).
- Organic lesion likely to bleed
- Clinically significant active bleeding
- Intracerebral hemorrhage
- As there are no relevant data, severe renal failure (creatinine clearance of approximately 30 ml/min as per the Cockcroft formula), except in the particular case of dialysis patients. In patients with severe renal failure, unfractionated heparin should be used.
  For the calculation using the Cockcroft formula, a recent bodyweight measurement is necessary (see Section Precautions for use).
- Spinal or epidural anesthesia must never be performed in patients under curative LMWH treatment.

**This medicinal product is generally not advisable in the following cases:**
- Acute extensive ischemic stroke, with or without impaired consciousness.
  If the stroke is caused by embolism, enoxaparin must not be administered for 72 hours following the event.
  The efficacy of curative doses of LMWH has however not yet been established, regardless of the cause, extent or clinical severity of cerebral infarction.
- Acute infectious endocarditis (except for some embolicogenic cardiac conditions).
- Mild to moderate kidney failure (creatinine clearance between 30 and 60 ml/min).

In addition, this drug is generally not advisable when combined with the following (see section Interactions with other medicines and other forms of interaction):
1. Acetylsalicylic acid at analgesic, antipyretic and anti-inflammatory doses,
2. NSAIDs (systemic use)
3. Dextran 40 (parenteral use)

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 hemorrhage (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.

Combinations requiring precautions for use
+ Oral anticoagulants
  Potentiation of the anticoagulant effect.
  When heparin is replaced by an oral anticoagulant, clinical monitoring must be intensified.

Combinations to take into aPTT. As no clinical relevance has 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 bleeding.

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.

Based on Enoxaparin-CCDSv09; CCDSv10; CCDSv11; CCDSv12
Current clinical data are insufficiently relevant to determine a possible malformative or fetotoxic effect of enoxaparin administered at curative doses throughout pregnancy.

The use of curative doses of enoxaparin is therefore not recommended throughout pregnancy as a precaution.
Spinal or epidural anesthesia must never be performed during curative treatment with LMWH.

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

Presentations
Prefilled syringes 6000 anti-Xa IU/0.6 ml; Box of 2
Reg.No.DKI0185600143A1

Store below 25° C. Do not freeze.

ON MEDICAL PRESCRIPTION ONLY
HARUS DENGAN RESEP DOKTER

Manufactured by:
Sanofi Winthrop Industrie,
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Imported by:
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