Prescribing Information

Clexane/ Clexane Forte Pre-filled Syringes

1. NAME OF THE MEDICINAL PRODUCT
Clexane Syringes
Clexane Forte Syringes

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Clexane pre-filled syringes (100mg/ ml)

<table>
<thead>
<tr>
<th>Injection</th>
<th>Enoxaparin sodium concentrate (equivalent IU anti-Xa activity)</th>
</tr>
</thead>
<tbody>
<tr>
<td>20mg</td>
<td>20mg (equivalent to 2,000 IU anti-Xa activity) in 0.2ml water</td>
</tr>
<tr>
<td>40mg</td>
<td>40mg (equivalent to 4,000 IU anti-Xa activity) in 0.4ml water</td>
</tr>
<tr>
<td>60mg</td>
<td>60mg (equivalent to 6,000 IU anti-Xa activity) in 0.6ml water</td>
</tr>
<tr>
<td>80mg</td>
<td>80mg (equivalent to 8,000 IU anti-Xa activity) in 0.8ml water</td>
</tr>
<tr>
<td>100mg</td>
<td>100mg (equivalent to 10,000 IU anti-Xa activity) in 1.0ml water</td>
</tr>
</tbody>
</table>

Clexane Forte pre-filled Syringes (150mg/ ml)

<table>
<thead>
<tr>
<th>Injection</th>
<th>Enoxaparin sodium concentrate (equivalent IU anti-Xa activity)</th>
</tr>
</thead>
<tbody>
<tr>
<td>120mg</td>
<td>120mg (equivalent to 12,000 IU anti-Xa activity) in 0.8ml water</td>
</tr>
<tr>
<td>150mg</td>
<td>150mg (equivalent to 15,000 IU anti-Xa activity) in 1.0ml water</td>
</tr>
</tbody>
</table>

For a full list of the excipients see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection in prefilled syringes.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Enoxaparin is a low molecular weight heparin (LMWH)

Enoxaparin sodium is an anti-coagulant.

CLEXANE Solution for injection at 20mg and 40mg:

- Prophylactic treatment of thrombo-embolic disorders of venous origin and in particular in orthopedic surgery or in general surgery.
- Prevention of thrombus formation in the extra-corporeal circulation during hemodialysis.

CLEXANE Solution for injection at 40mg:

- Prophylactic treatment of deep vein thrombosis (DVT) in patients who are bedridden due to an acute medical disorder:
  - Heart failure (NYHA class III or IV)
- Acute respiratory failure
- Episode of acute infection or acute rheumatic disorder combined with at least one other venous thromboembolic risk factor.

**CLEXANE Solution for injection at 60mg, 80mg and 100mg:**

- Treatment of deep vein thrombosis (DVT).
- Treatment of unstable angina and non-Q-wave myocardial infarction, administered concurrently with aspirin.
- Treatment of pulmonary embolism.
- Treatment of acute ST-segment elevation myocardial infarction, in combination with a thrombolytic agent in patients eligible or not for subsequent coronary angioplasty.

**CLEXANE FORTE Solution for injection at 120mg and 150mg:**

- Treatment of deep vein thrombosis (DVT) once daily.
- Treatment of pulmonary embolism once daily.

### 4.2 Posology and method of administration

**SUBCUTANEOUS ROUTE** (except for patients undergoing hemodialysis and in patients 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.

- Clexane 100mg/ml - One milliliter of solution for injection is equivalent to approximately 10000 anti-Xa IU of enoxaparin.
- Clexane Forte 150mg/ml - One milliliter of solution for injection is equivalent to approximately 15000 anti-Xa IU of enoxaparin.

**Subcutaneous injection technique:**

The prefilled syringe is ready for immediate use; no air should be expelled before administering 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.

**General recommendation**

Regular monitoring of the platelet count is essential throughout the treatment due to the risk of heparin-induced thrombocytopenia (HIT) (see Section 4.4).

**Dosage per indication**

*Prophylactic treatment of venous thromboembolic disease in surgery*

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

For spinal and epidural anesthesia techniques, the benefit of a pre-operative injection of enoxaparin should be weighed against the theoretically increased risk of spinal hematoma (see Section 4.4).
• **Administration schedule**
  One injection daily.

• **Dose**
  The dose must be determined based on the individual risk related to the patient and the type of surgery.

  o **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 20mg (2000 anti-Xa IU, 0.2 ml).
    
    The studied dosage regimen involves administration of the first injection 2 hours before surgery.

  o **Surgery involving high thrombogenic risk:**
    
    - **Hip and knee surgery:**
      
      The dosage is 40mg (4000 anti-Xa IU, 0.4 ml) injected once daily.
      
      The studied dosage regimen involves either administration of the first injection of 40mg (4000 anti-Xa IU) (total dose) twelve hours before surgery, or a first injection of 20mg (2000 anti-Xa IU) (half dose) 2 hours before surgery.

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

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

  o in general surgery, the duration of LMWH treatment must be less than 10 days unless there is a patient-specific risk of venous thromboembolism (see Section 4.4);

  o the therapeutic benefit of prophylactic treatment consisting of an injection of 40mg (4000 anti-Xa IU)/day of enoxaparin for 4 to 5 weeks after hip surgery has been established;

  o if the patient is still at risk of venous thromboembolism after the recommended treatment duration, continuing prophylactic therapy must be considered, particularly by administration of oral anticoagulants;

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

*Prevention of clotting in the extracorporeal circulation/hemodialysis*

**INJECTION BY THE INTRAVASCULAR ROUTE** (in the arterial line of the dialysis circuit).

In patients undergoing repeated hemodialysis sessions, prevention of clotting in the extrarenal purification system is obtained by injecting an initial dose of 1mg (100 anti-Xa IU)/kg in the arterial line of the dialysis circuit at the beginning of the session.

This dose, administered as a single intravascular bolus injection, is only suitable for hemodialysis sessions of 4 hours or less. It may be adjusted subsequently given high inter- and intra-individual variability.
The maximum recommended dose is 1mg (100 anti-Xa IU)/kg.

In hemodialysis patients at high risk of hemorrhage (particularly pre- and post-operative dialysis) or with active hemorrhage, dialysis sessions may be carried out using a dose of 0.5mg (50 anti-Xa IU)/kg (double vascular access) or 0.75mg (75 anti-Xa IU)/kg (single vascular access).

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
  Enoxaparin sodium can be administered subcutaneously either as a single injection of 1.5mg/kg or as twice daily injections of 1 mg/kg.

• Dose
  The dose per injection is 1mg (100 anti-Xa IU)/kg twice daily or 1.5mg (150 anti-Xa IU)/kg as a single injection.

• 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 4.4). Oral anticoagulant treatment should therefore be initiated as soon as possible.

Curative treatment of unstable angina/non-Q-wave myocardial infarction

A dose of 1mg (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 30mg (3000 anti-Xa IU) followed by an SC injection of 1mg (100 anti-Xa IU)/kg within 15 minutes, then every 12 hours (a maximum of 100mg (10000 anti-Xa IU) for each of the first two SC doses only, followed by 1 mg/kg SC dosing for the remaining doses). For dosage in patients ≥75 years of age, see Dosage and Administration: Renal Impairment and Elderly.

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.

Patients 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 0.3mg (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 3mg (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 (Kg)</th>
<th>Required dose</th>
<th>Volume to inject when diluted to 3mg (300 IU/ml) (i.e. 0.3 ml of enoxaparin diluted in 10 ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mg (IU)</td>
<td>ml</td>
</tr>
<tr>
<td>45</td>
<td>13.5mg (1350 IU)</td>
<td>4.5</td>
</tr>
<tr>
<td>50</td>
<td>15mg (1500 IU)</td>
<td>5</td>
</tr>
<tr>
<td>55</td>
<td>16.5mg (1650 IU)</td>
<td>5.5</td>
</tr>
<tr>
<td>60</td>
<td>18mg (1800 IU)</td>
<td>6</td>
</tr>
<tr>
<td>65</td>
<td>19.5mg (1950 IU)</td>
<td>6.5</td>
</tr>
<tr>
<td>70</td>
<td>21mg (2100 IU)</td>
<td>7</td>
</tr>
<tr>
<td>75</td>
<td>22.5mg (2250 IU)</td>
<td>7.5</td>
</tr>
<tr>
<td>80</td>
<td>24mg (2400 IU)</td>
<td>8</td>
</tr>
<tr>
<td>85</td>
<td>25.5mg (2550 IU)</td>
<td>8.5</td>
</tr>
<tr>
<td>90</td>
<td>27mg (2700 IU)</td>
<td>9</td>
</tr>
<tr>
<td>95</td>
<td>28.5mg (2850 IU)</td>
<td>9.5</td>
</tr>
<tr>
<td>100</td>
<td>30mg (3000 IU)</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 0.75mg (75 anti-Xa IU)/kg every 12 hours should be administered (maximum of 75mg (7500 anti-Xa IU) for the first two injections only).

**Special populations**

**Elderly**

For treatment of acute ST-segment Elevation Myocardial Infarction in elderly patients ≥75 years of age, do not use an initial IV bolus. Initiate dosing with 0.75 mg/kg SC every 12 hours (maximum 75 mg for each of the first two SC doses only, followed by 0.75 mg/kg SC dosing for the remaining doses; see Clinical Trials: Acute ST-segment Elevation Myocardial Infarction).

No dose reduction is necessary in the elderly for other indications, unless renal function is impaired, however careful clinical observation is advised (see section 4.4).

**Children:** Not recommended, as dosage not established.

**Renal impairment:** (See also section 4.4 and 5.2)

- **Severe renal impairment:**

  A dosage adjustment is required for patients with severe renal impairment (creatinine clearance < 30 ml/min), according to the following tables, since enoxaparin sodium exposure is significantly increased in this patient population:

  The following dosage adjustments are recommended for the prophylactic dosage ranges.

<table>
<thead>
<tr>
<th>Normal Dosing</th>
<th>Severe renal impairment</th>
</tr>
</thead>
<tbody>
<tr>
<td>40 mg SC once daily</td>
<td>20 mg SC once daily</td>
</tr>
<tr>
<td>20 mg SC once daily</td>
<td>20 mg SC once daily</td>
</tr>
</tbody>
</table>
The following dosage adjustments are recommended for the treatment dosage ranges.

<table>
<thead>
<tr>
<th>Normal Dosing</th>
<th>Severe renal impairment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 mg/kg SC twice daily</td>
<td>1 mg/kg SC once daily</td>
</tr>
<tr>
<td>1.5 mg/kg SC once daily</td>
<td>1 mg/kg SC once daily</td>
</tr>
</tbody>
</table>

For treatment of acute STEMI patients < 75 years of age

30 mg-single IV bolus plus a 1 mg/kg SC dose followed by 1 mg/kg SC twice daily (Max 100mg for each of the first two SC doses)

For treatment of acute STEMI in elderly patients ≥ 75 years of age

0.75 mg/kg SC twice daily without initial bolus (Max 75mg for each of the first two SC doses)

The recommended dosage adjustments do not apply to the hemodialysis indication.

- **Moderate and Mild Renal impairment:**

Although no dosage adjustment are recommended in patients with moderate renal impairment (creatinine clearance 30-50 ml/min) or mild renal impairment (creatinine clearance 50-80 ml/min), careful clinical monitoring is advised.

**Hepatic impairment:** In the absence of clinical studies, caution should be exercised.

**Spinal/epidural anesthesia:**
For patients receiving spinal/epidural anesthesia see section 4.4, Spinal/epidural anesthesia.

**Body weight:**

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

**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.

(see also section 4.4 Special warnings and precautions for use and section 5.2 Pharmacokinetic properties).

**4.3 CONTRAINDICATIONS**

**Regardless of the dose (curative or preventive), this medicinal product MUST NOT BE USED in the following situations:**
- Hypersensitivity to enoxaparin, heparin or its derivatives, including the other LMWHs
- History of serious type II heparin-induced thrombocytopenia (HIT), whether caused by unfractionated or low-molecular-weight heparin (see Section 4.4)
- 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 4.4)
- Organic lesion likely to bleed
- Clinically significant active bleeding
At curative doses, this medicinal product MUST NOT BE USED in the following situations:
- Intracerebral hemorrhage
- Spinal or epidural anesthesia must never be performed in patients under curative LMWH treatment.

At curative doses, this medicinal product is GENERALLY NOT RECOMMENDED in the following cases:
- Acute extensive ischemic stroke, with or without impaired consciousness.
  If the stroke is caused by embolism, enoxaparin must not be administered for 72 hours following the event.
  The efficacy of curative doses of LMWH has however not yet been established, regardless of the cause, extent or clinical severity of cerebral infarction.
- Acute infectious endocarditis (except for some emboligenic cardiac conditions)

In addition, at curative doses, this drug should preferably not be used in all subjects, regardless of age, when combined with the following (see Section 4.5):
1. Acetylsalicylic acid at analgesic, antipyretic and anti-inflammatory doses,
2. NSAIDs (systemic use),
3. Dextran 40 (parenteral use).

At prophylactic doses, this medicinal product is GENERALLY NOT RECOMMENDED in the following situations:
- during the first 24 hours following intracerebral hemorrhage.

In addition, at prophylactic doses, this drug should preferably not be used in subjects over 65 years of age when used in combination with (see Section 4.5):
1. Acetylsalicylic acid at analgesic, antipyretic and anti-inflammatory doses,
2. NSAIDs (systemic use),
3. Dextran 40 (parenteral use).

4.4 Special warnings and special precautions for use

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

Special warnings

Risk of hemorrhage

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

Serious hemorrhagic 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 treatment recommendations (particularly treatment duration and dose adjustment based on bodyweight in curative treatment),
- co-administration with drugs increasing the risk of hemorrhage (see Section 4.5).

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

**Risk of heparin-induced thrombocytopenia (HIT)**

Should a patient treated with LMWH (at curative or preventive doses) develop thrombotic 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 LMWH is not recommended in children.

**Mechanical prosthetic heart valves**

Use of enoxaparin in the prevention of thromboembolic complications in patients with mechanical prosthetic heart valves has not specifically been studied.

Nevertheless, some isolated cases of thrombosis have been reported in patients with mechanical prosthetic heart valves receiving enoxaparin for the prevention of thromboembolic complications.

**Pregnant women**

In a clinical study in pregnant women with mechanical prosthetic heart valves who received 1mg (100 anti-Xa IU)/kg enoxaparin b.i.d. to reduce the risk of thromboembolic complications, 2 of 8 women developed thrombosis causing valve obstruction leading to maternal and fetal death. Moreover, isolated cases of thrombosis in pregnant women with mechanical prosthetic heart valves receiving enoxaparin for the prevention of thromboembolic complications have been reported as part of post-marketing surveillance of the drug. Therefore, the risk of thromboembolic complications in these patients could be higher.

**Hyperkalemia**

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

**Precautions for use**

**Hemorrhage**

As with all anticoagulants, bleeding can occur at any site (see Section 4.8). If bleeding occurs, and sometimes anemia, the origin of the hemorrhage must be investigated and appropriate treatment instituted.

**Renal function**

Before low-molecular-weight heparin treatment is initiated, it is essential to evaluate renal function, particularly in subjects 75 years or older, by determining creatinine clearance (Clcr), using the Cockcroft formula and based on a recent bodyweight measurement:
In male patients: 
\[ \text{Clcr} = \frac{(140 - \text{age}) \times \text{weight}}{0.814 \times \text{serum creatinine}} \]
where age is expressed in years, weight in kg and serum creatinine in μmol/l.

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

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

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

**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.

See Section 4.2 Posology and method of administration and section 5.2 Pharmacokinetic properties- Weight.

**Laboratory tests**

- **Platelet monitoring**

*Heparin-induced thrombocytopenia (HIT)*

There is a risk of serious, occasionally thrombogenic, heparin-induced thrombocytopenia (reported with unfractionated heparin and less often with LMWH) of immunologic origin, called type II HIT (see also Section 4.8).

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 (see Section 4.6)), the platelet counts should be performed 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 100000/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 isolated 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 several years or even indefinitely (see Section 4.3).

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

3) - prevention or treatment of HIT-related thrombotic complications.

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

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

*Replacement of heparin by oral anticoagulants*

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

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

*Monitoring of anti-factor Xa activity*

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

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

- severe and mild to moderate renal failure (creatinine clearance of approximately 30 ml/min to 60 ml/min calculated using the Cockroft formula). As LMWH is primarily eliminated by the renal route, unlike standard unfractionated heparin, any renal failure can result in relative overdose.

- extreme high or low bodyweight (thinness or even cachexia, obesity);

- unexplained bleeding.

In contrast, laboratory monitoring is not recommended at prophylactic doses if the LMWH treatment complies with the therapeutic recommendations (particularly treatment duration), 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
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 the 7th injection of enoxaparin given at a dose of 1 mg (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, monitoring of treatment using this test is of no use.

**Spinal/ epidural anesthesia**

There have been cases of intra-spinal haematomas reported with the concurrent use of enoxaparin sodium and spinal/epidural anaesthesia or spinal puncture resulting in long-term or permanent paralysis. These events are rare with enoxaparin sodium dosage regimens 40 mg once daily or lower. The risk is greater with higher enoxaparin sodium dosage regimens, use of post-operative indwelling catheters or the concomitant use of additional drugs affecting haemostasis such as non-steroidal anti-inflammatory drugs (NSAIDs) (see section 4.5 Interactions with Other Medicines). The risk also appears to be increased by traumatic or repeated neuraxial puncture or in patients with a history of spinal surgery or spinal deformity.

To reduce the potential risk of bleeding associated with the concurrent use of enoxaparin sodium and epidural or spinal anaesthesia/analgesia, the pharmacokinetic profile of the drug should be considered (see section 5.2 Pharmacokinetics). Placement and removal of the needle/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.

Placement or removal of an epidural or spinal needle or catheter should be delayed for at least 12 hours after administration of lower doses (20 mg once daily, 30 mg once or twice daily or 40 mg once daily) of enoxaparin, and at least 24 hours after the administration of higher doses (0.75 mg/kg twice daily, 1 mg/kg twice daily, or 1.5 mg/kg once daily) of enoxaparin. Anti-Xa levels are still detectable at these time points, and these delays are not a guarantee that neuraxial hematoma will be avoided. Patients receiving the 0.75 mg/kg twice-daily dose or the 1 mg/kg twice-daily dose should not receive the second enoxaparin dose in the twice-daily regimen to allow a longer delay before catheter placement or removal. Likewise, although a specific recommendation for timing of a subsequent enoxaparin dose after catheter removal cannot be made, consider delaying this next dose for at least four hours, based on a benefit-risk assessment considering both the risk for thrombosis and the risk for bleeding in the context of the procedure and patient risk factors. For patients with creatinine clearance < 30ml/minute, additional considerations are necessary because elimination of enoxaparin is more prolonged; consider doubling the timing of removal of a catheter, at least 24 hours for the lower prescribed dose of enoxaparin (30 mg once daily) and at least 48 hours for the higher dose (1 mg/kg/day).

Should the physician decide to administer anticoagulation in the context of epidural/spinal anaesthesia or lumbar puncture, frequent monitoring must be exercised to detect any signs and symptoms of neurological impairment such as midline back pain, sensory and motor deficits (numbness or weakness in lower limbs), bowel and/or bladder dysfunction. Patients should be instructed to inform their nurse or physician immediately if they experience any of
the above signs or symptoms. If signs or symptoms of spinal haematoma are suspected, urgent diagnosis and treatment including spinal cord decompression should be initiated.

- **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,
- chorioretinal vascular disease,
- post-operatively, following cerebral or spinal cord surgery,
- lumbar puncture: this should only be considered taking into account the risk of intra-spinal bleeding and should be postponed whenever possible,
- concomitant use of medicinal products affecting hemostasis (see Section 4.5).

**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.

**4.5 Interactions with other medicinal products and other forms of interaction**

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

- **Patients under 65 years of age receiving curative LMWH doses and elderly patients (more than 65 years) regardless of the LMWH dose**

**Inadvisable combinations**

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

+ **NSAIDs** (systemic use):
  Increased risk of bleeding (NSAID-induced platelet function inhibition and gastroduodenal mucosal damage).
  If co-administration cannot be avoided, close clinical monitoring is required.

+ **Dextran 40** (parenteral use):
  Increased risk of bleeding (inhibition of platelet function by 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 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, beraprost, clopidogrel, eptifibatide, iloprost, ticloidine, tirofiban.

Increased risk of bleeding.

• Patients under 65 years of age receiving prophylactic LMWH doses

Combinations to be taken into consideration

Combined use of drugs affecting various stages of hemostasis potentiates the risk of bleeding. Therefore, regardless of patient age, continued clinical monitoring and, if necessary, laboratory tests must be performed when co-administering LMWHs at prophylactic doses with oral anti-coagulants, platelet aggregation inhibitors (abciximab, NSAIDs, acetylsalicylic acid at any dose, clopidogrel, eptifibatide, iloprost, ticloidine, tirofiban) and thrombolytic agents.

4.6 PREGNANCY AND LACTATION

Pregnancy

There is no evidence from animal studies that enoxaparin has teratogenic effects. 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 in two species.

Prophylactic treatment during the first trimester and curative treatment

There are currently not enough relevant clinical data to evaluate possible teratogenic or fetotoxic effects of enoxaparin when the drug is administered prophylactically during the first trimester or at curative doses throughout pregnancy.

Consequently, as a precautionary measure, enoxaparin should preferentially not be administered prophylactically during the first trimester, nor at curative doses throughout pregnancy.

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

Epidural or spinal anesthesia should never be performed during curative treatment with LMWH.

Prophylactic treatment during the second and third trimesters

To date, there seems to be no evidence from clinical use of enoxaparin in a limited number of pregnancies during the second and third trimesters, that the drug administered at prophylactic doses has any particular teratogenic or fetotoxic effects. However, additional studies are needed to evaluate the effects of exposure under these conditions.

Therefore, prophylactic enoxaparin treatment during the second and third trimesters should only be considered if necessary.

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

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

4.7 EFFECTS ON ABILITY TO DRIVE AND OPERATE MACHINES

Enoxaparin has no effect on the ability to drive and operate machines.

4.8 UNDESIRABLE EFFECTS

The adverse reactions observed in clinical studies and reported in post-marketing experience are detailed below. Frequencies are defined as follows: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1000 to < 1/100); rare (≥ 1/10,000 to <1/1,000); very rare (< 1/10,000) or not known (cannot be estimated from available data). Post-marketing adverse reactions are designated with a frequency “Not known”.

Haemorrhages

In clinical studies, haemorrhages were the most commonly reported reaction. These included major haemorrhages, reported at most in 4.2 % of the patients (surgical patients¹). Some of these cases have been fatal.

As with other anticoagulants, haemorrhage may occur during enoxaparin therapy in the presence of associated risk factors such as: organic lesions liable to bleed, invasive procedures or the concomitant use of medications affecting haemostasis (see section 4.5 Interaction with other medicinal products and other forms of interaction). The origin of the bleeding should be investigated and appropriate treatment instituted.

<table>
<thead>
<tr>
<th>MedDRA system organ class</th>
<th>Prophylaxis in surgical patients</th>
<th>Prophylaxis in medical patients</th>
<th>Treatment in patients with DVT with or without PE</th>
<th>Treatment in patients with unstable angina and non-Q-wave MI</th>
<th>Treatment in patients with acute STEMI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vascular disorders</td>
<td>Common:*</td>
<td>Common:*</td>
<td>Common:*</td>
<td>Common:*</td>
<td>Common:*</td>
</tr>
<tr>
<td></td>
<td>Haemorrhage *</td>
<td>Haemorrhage *</td>
<td>Haemorrhage *</td>
<td>Haemorrhage *</td>
<td>Haemorrhage *</td>
</tr>
<tr>
<td></td>
<td>Rare:</td>
<td>Uncommon:</td>
<td>Rare:</td>
<td>Uncommon:</td>
<td>Intraplacental haemorrhage,</td>
</tr>
<tr>
<td></td>
<td>Retroperitoneal haemorrhage</td>
<td>Intracranial haemorrhage,</td>
<td>Retroperitoneal haemorrhage</td>
<td>Retroperitoneal haemorrhage</td>
<td>Retroperitoneal haemorrhage</td>
</tr>
</tbody>
</table>

*: such as haematoma, ecchymosis other than at injection site, wound haematoma, haematuria, epistaxis and gastro-intestinal haemorrhage.

¹ In surgical patients, haemorrhage complications were considered major: (1) if the haemorrhage caused a significant clinical event, or (2) if accompanied by an haemoglobin decrease ≥ 2 g/dL or transfusion of 2 or more units of blood products. Retroperitoneal and intracranial haemorrhages were always considered major.
## Thrombocytopenia and thrombocytosis

<table>
<thead>
<tr>
<th>MedDRA system organ class</th>
<th>Prophylaxis in surgical patients</th>
<th>Prophylaxis in medical patients</th>
<th>Treatment in patients with DVT with or without PE</th>
<th>Treatment in patients with unstable angina and non-Q-wave MI</th>
<th>Treatment in patients with acute STEMI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood and lymphatic system disorders</td>
<td>Very common: Thrombocytosis*</td>
<td>Uncommon: Thrombocytopenia</td>
<td>Very common: Thrombocytosis*</td>
<td>Uncommon: Thrombocytopenia</td>
<td>Common: Thrombocytosis*</td>
</tr>
<tr>
<td>Common: Thrombocytopenia</td>
<td></td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

*: Platelet increased > 400 G/L

## Other clinically relevant adverse reactions

These reactions are presented below, whatever the indications, by system organ class, frequency grouping and decreasing order of seriousness.

<table>
<thead>
<tr>
<th>MedDRA system organ class</th>
<th>All indications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immune system disorders</td>
<td>Common: Allergic reaction</td>
</tr>
<tr>
<td></td>
<td>Rare: Anaphylactic / anaphylactoid reaction (see also Postmarketing experience)</td>
</tr>
<tr>
<td>Hepatobiliary disorders</td>
<td>Very common: Hepatic enzymes increase (mainly transaminases **)</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>Common: Urticaria, pruritus, erythema,</td>
</tr>
<tr>
<td></td>
<td>Uncommon: Bullous dermatitis</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td>Common: Injection site haematoma, injection site pain, other injection site reaction*</td>
</tr>
<tr>
<td></td>
<td>Uncommon: Local irritation; skin necrosis at injection site</td>
</tr>
<tr>
<td>Investigations</td>
<td>Rare: Hyperkaliemia</td>
</tr>
</tbody>
</table>

*: such as injection site oedema, haemorrhage, hypersensitivity, inflammation, mass, pain, or reaction (NOS)

**: transaminases levels > 3 times the upper limit of normality

## Post marketing experience

The following adverse reactions have been identified during post-approval use. The adverse reactions are derived from spontaneous reports and therefore, the frequency is “not known” (cannot be estimated from the available data).

- **Immune System Disorders**
  - Anaphylactic / anaphylactoid reaction including shock

- **Nervous System Disorders**
  - Headache
- **Vascular Disorders**
  - Cases of spinal haematoma (or neuraxial haematoma) have been reported with the concurrent use of enoxaparin sodium as well as spinal/epidural anaesthesia or spinal puncture and post operative indwelling catheters. These reactions have resulted in varying degrees of neurologic injuries including long-term or permanent paralysis (see Section 4.4: Spinal/epidural anaesthesia).

- **Blood and Lymphatic System Disorders:**
  - Haemorrhagic anemia
  - Cases of immuno-allergic thrombocytopenia with thrombosis; in some of them thrombosis was complicated by organ infarction or limb ischaemia (see Section 6: Monitoring of platelet counts).
  - Eosinophilia

- **Skin and subcutaneous disorders**
  - Cutaneous vasculitis, skin necrosis usually occurring at the injection site (these phenomena have been usually preceded by purpura or erythematous plaques, infiltrated and painful). Treatment with enoxaparin sodium must be discontinued.
  - Injection site nodules (inflammatory nodules, which were not cystic enclosure of enoxaparin). They resolve after a few days and should not cause treatment discontinuation.
  - Alopecia

- **Hepatobiliary disorders**
  - Hepatocellular liver injury
  - Cholestatic liver injury

- **Musculoskeletal and connective tissue disorders**
  - Osteoporosis following long-term therapy (greater than 3 months)

- Valve thrombosis in patients with prosthetic heart valves have been reported rarely, usually associated with inadequate dosing (see section 4.4 Special warnings and precautions for use).

- Heparin products can cause hypoaldosteronism which may result in an increase in plasma potassium. Rarely, clinically significant hyperkalaemia may occur particularly in patients with chronic renal failure and diabetes mellitus (see section 4.4 Special warnings and precautions for use).

### 4.9 OVERDOSE

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

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

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

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

The protamine dose required depends on:

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

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

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

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

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.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties
Pharmacotherapeutic group: **ANTITHROMBOTIC AGENT**, ATC code: **B01 AB 05**

Enoxaparin is a low-molecular-weight heparin in which the antithrombotic and anticoagulant activities of standard heparin have been dissociated.

It is characterized by higher anti-Xa activity than anti-IIa or antithrombin activity. For enoxaparin, the ratio between these two activities is 3.6.

At prophylactic doses, it does not significantly affect the aPTT.

At curative doses, aPTT can be prolonged by 1.5 to 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 patients 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: enoxaparin as an IV bolus injection of 30mg (3000 anti-Xa IU) immediately followed by a dose of 1mg (100 anti-Xa IU)/kg SC, then by an SC injection of 1mg(100 anti-Xa IU)/kg every 12 hours, or unfractionated heparin by the IV route as a bolus injection of 60 IU/kg (maximum 4000 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: 0.75mg (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 before balloon inflation, or, received an IV bolus injection of 0.3mg (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<0.001)). The incidence of myocardial infarction relapse was significantly lower in the enoxaparin group (3.4% versus 5%, p<0.001, relative risk reduction 31%). The incidence of deaths was lower in the enoxaparin group, with no statistically significant difference between the groups (6.9% versus 7.5%, p=0.11).

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

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

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

The analysis of the composite criteria measuring overall clinical benefit showed statistically significant superiority (p<0.0001) for enoxaparin versus unfractionated heparin: a relative risk reduction of 14% in favor of enoxaparin (11.0% versus 12.8%) for the composite criteria consisting of death, myocardial infarction relapse, or major bleeding (TIMI criteria) at 30 days, and of 17% (10.1% versus 12.2%) for the composite criteria consisting of death, myocardial infarction relapse or intracranial bleeding at 30 days.

5.2 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 subcutaneous administration, and following single intravenous 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 2000 anti-Xa IU), 0.43 ± 0.11 (after 4000 anti-Xa IU) in prophylactic treatment, and 1.01 ± 0.14 (after 10000 anti-Xa IU) in curative treatment.

An IV bolus injection of 3000 anti-Xa IU 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. Intra-patient 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**

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

Enoxaparin exhibits a monophasic elimination pattern with a half-life of about 4 hours after a single subcutaneous dose to about 7 hours after repeated dosing.

With low-molecular-weight heparin, plasma decay occurs more quickly for anti-IIa activity than for anti-Xa activity.

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

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

**Weight**

After repeated subcutaneous 1.5 mg/kg once daily dosing, mean AUC of anti-Xa activity is marginally higher at steady state in obese healthy volunteers (BMI 30-48 kg/m²) compared to non-obese control subjects, while Amax is not increased. There is a lower weight-adjusted clearance in obese subjects with subcutaneous dosing.

When non-weight adjusted dosing was administered, it was found after a single-subcutaneous 40 mg dose, that anti-Xa exposure is 52% higher in low-weight women (<45 kg) and 27% higher in low-weight men (<57 kg) when compared to normal weight control subjects (see Section 4.4- Special warnings and special precautions for use).

**5.3 Preclinical safety data**

No long-term studies in animals have been performed to evaluate the carcinogenic potential of enoxaparin.

Enoxaparin was not mutagenic in *in vitro* tests, including the Ames test, the forward mutation test at the thymidine kinase (TK) locus of L5178Y mouse lymphoma cells, and human
lymphocyte chromosomal aberration test, and the _in vivo_ rat bone marrow chromosomal aberration test.

Enoxaparin was found to have no effect on fertility or reproductive performance of male and female rats at SC doses less than 20 mg/kg/day.

Teratogenicity studies have been conducted in gravid rats and rabbits at SC doses of enoxaparin less than 30 mg/kg/day.

There was no evidence of teratogenic effects or fetotoxicity due to enoxaparin.

Besides the anticoagulant effects of enoxaparin, there was no evidence of adverse effects during the following toxicity studies:

- 15 mg/kg/day in 13-week subcutaneous toxicity studies in rats and dogs
- 10 mg/kg/day in 26-week subcutaneous and intravenous toxicity studies in rats and monkeys.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Prefilled syringes: Water for injection.

6.2 Special precautions for storage

Do not store above 25°C. Do not refrigerate or freeze.
To be stored in the original packaging.

6.3 Nature and contents of outer packaging

**Clexane pre-filled syringes (100mg/ml)**

- 0.2 ml solution for injection in prefilled (glass) syringes with safety system
- 0.4 ml solution for injection in prefilled (glass) syringes with safety system
- 0.6 ml solution for injection in prefilled (glass) syringes with safety system
- 0.8 ml solution for injection in prefilled (glass) syringes with safety system
- 1.0 ml solution for injection in prefilled (glass) syringes with safety system

**Clexane Forte pre-filled Syringes (150mg/ml)**

- 0.8 ml solution for injection in prefilled (glass) syringes with safety system
- 1.0 ml solution for injection in prefilled (glass) syringes with safety system

6.4 Special precautions for disposal and handling

Dispose of the product safely as instructed by your healthcare professional.

For prefilled syringes with a safety system:
Clexane/ Clexane Forte is a solution for injection in prefilled syringes with an automatic safety system intended to prevent accidental needle sticks after injection. Instructions on how to use the device are provided in the Package Leaflet.

7. Manufacturer

Clexane pre-filled syringes (100mg/ml) - Sanofi Winthrop Industrie France
Clexane Forte pre-filled syringes (150mg/ml) - Sanofi Winthrop Industrie France

8. MARKETING AUTHORIZATION HOLDER

sanofi-aventis Israel ltd. P.O.B. 8090 Netanya 4250499