

ENOXA Médís® 2000 anti-Xa UI/0,2 ml - ENOXa Médís® 4000 anti-Xa UI/0,4 ml

ENOXA Médís® 6000 anti-Xa UI/0,6 ml - ENOXa Médís® 8000 anti-Xa UI/0,8 ml

### Enoxaparin sodium

#### FORMS AND PRESENTATIONS:

ENOXA Médís 2000 UI anti-Xa 0,2 ml: Enoxaparin sodium 20 mg/0,2 ml, injectable solution, box of 02 pre-filled syringes.  
ENOXA Médís 4000 UI anti-Xa 0,4 ml: Enoxaparin sodium 40 mg/0,4 ml, injectable solution, box of 02 pre-filled syringes.  
ENOXA Médís 6000 UI anti-Xa 0,6 ml: Enoxaparin sodium 60 mg/0,6 ml, injectable solution, box of 02 pre-filled syringes.  
ENOXA Médís 8000 UI anti-Xa 0,8 ml: Enoxaparin sodium 80 mg/0,8 ml, injectable solution, box of 02 pre-filled syringes.

#### COMPOSITION PER PRE-FILLED SYRINGE:

	Quantity per syringe			
	ENOXA Médís 2000 UI anti-Xa 0,2 ml	ENOXA Médís 4000 UI anti-Xa 0,4 ml	ENOXA Médís 6000 UI anti-Xa 0,6 ml	ENOXA Médís 8000 UI anti-Xa 0,8 ml
Active compound : Enoxaparin sodium	20 mg	40 mg	60 mg	80 mg
Excipients :	.....s.q.f.			
WFI	s.q.f. 0,2 ml	s.q.f. 0,4 ml	s.q.f. 0,6 ml	s.q.f. 0,8 ml

#### PHARMACOLOGICAL PROPERTIES:

Pharmaco-therapeutic class: Antithrombotic agent/heparin group.

Enoxaparin sodium is a low molecular weight heparin with a high anti-Xa activity (100 IU/mg), and low anti-IIa or anti-IIIa activity (28 times required for the various indications). Enoxaparin sodium does not increase bleeding time. At preventive doses, Enoxaparin sodium causes no notable modification of activated Partial Thromboplastin Time (aPTT). It neither influences platelet aggregation nor binding of fibrinogen to platelets.

The pharmacokinetic parameters have been determined in terms of course of plasma anti-Xa activity and also by anti-IIa activity at the recommended dosage ranges. The absolute bioavailability of Enoxaparin sodium after subcutaneous administration is close to 100%. The mean maximum plasma anti-Xa activity is observed 3 to 4 hours after subcutaneous injection. Enoxaparin sodium pharmacokinetics appear to be linear over the recommended dosage range. Even at a 4-fold increase in steady-state blood levels, no change has been reported in terms of bleeding time. The difference is expected and within the therapeutic ranges. The mean maximum plasma anti-IIa activity is observed approximately 3 to 4 hours following subcutaneous injection. Enoxaparin sodium is primarily metabolized in the liver. The elimination half-life of anti-Xa activity is approximately 4 hours after a single administration to about 7 hours after repeated administration. Renal clearance of active fragments represents about 10% of the administered dose and total renal excretion 40% of the dose. In the elderly, since renal function is known to decline with age, the elimination may be reduced. In patients with severe renal impairment (creatinine clearance < 30 ml/min), the AUC is significantly increased after repeated subcutaneous administration of 4000 anti-Xa UI once daily. In a single study, elimination rate appeared similar in patients undergoing dialysis.

#### THERAPEUTIC INDICATIONS:

##### ENOXA Médís 2000 UI anti-Xa:

- Prophylactic Treatment of the venous thrombo-embolic disease in surgery, at the risk moderate or high.
- Prevention of the coagulation of the circuit of extracorporeal circulation during the hemodialysis.
- ENOXA Médís 4000 anti-Xa UI:
- Enoxaparin sodium is indicated for:
  - Prophylaxis of venous thrombo-embolic disease in surgery, at the risk moderate or high.
  - Prophylaxis of venous thrombo-embolic disease in medical patients bedridden due to acute illness.
  - Care insufficiency of stage III or IV of classification NYHA.
  - Acute respiratory insufficiency.
  - Episode of acute infection or rheumatologic affection associated at least another factor of venous risk thrombo-embolism.
- Prevention of the coagulation of the circuit of extracorporeal circulation during the hemodialysis.

##### ENOXA Médís 6000 anti-Xa UI and ENOXa Médís 8000 anti-Xa UI:

- Enoxaparin sodium is indicated for:
  - The active treatment of deep vein thrombosis formed, with or without pulmonary embolism without evidence of clinical severity excluding pulmonary embolism may thrombotic or surgical treatment.
  - Treatment of unstable angina and myocardial infarction without Q wave in the acute phase, in combination with aspirin.
  - Treatment of acute myocardial infarction with ST segment elevation in combination with thrombolytic therapy in eligible or not a secondary coronary angioplasty patients.

#### CONTRAINDICATIONS:

- Enoxaparin sodium must not be used in the following situations:
  - In patients with known hypersensitivity (allergy) to either Enoxaparin sodium, heparin or other low molecular weight heparins.
  - In patients with active major bleeding and conditions with a high risk of uncontrolled hemorrhage including recent hemorrhagic stroke.

#### DOSE AND MODE OF ADMINISTRATION:

Strictly follow the recommended dosage unless directed otherwise by the doctor  
**Prophylaxis of venous thromboembolic disease in surgical patients:**  
In patients with a moderate thromboembolism risk (e.g. abdominal surgery) the recommended dose of Enoxaparin sodium is 2000 anti-Xa UI (0,2 ml) or 4000 anti-Xa UI (0,4 ml) once daily by subcutaneous injection. In general surgery, the first injection should be given 2 hours before the surgical procedure.  
In patients with a high thromboembolism risk (e.g. orthopedic surgery) the recommended dose of Enoxaparin sodium given by subcutaneous injection is 4000 anti-Xa UI (0,4 ml) once daily initiated 12 hours preoperatively. Enoxaparin sodium treatment is usually prescribed for an average period of 7 to 10 days. Longer treatment duration may be appropriate in some patients and the treatment should be continued for as long as there is a risk of venous thromboembolism.  
In patients with moderate thromboembolism risk, Enoxaparin sodium treatment with 4000 anti-Xa UI once daily for 3 weeks following the initial therapy has been proven to be beneficial in orthopedic surgery.

#### Prophylaxis of venous thromboembolic disease in medical patients:

The recommended dose of Enoxaparin sodium is 4000 anti-Xa UI (0,4 ml) once daily by subcutaneous injection. Treatment with Enoxaparin sodium is prescribed for a minimum of 6 days and continued until the return to full ambulation, for a maximum of 14 days.  
**Treatment of deep vein thrombotic with or without pulmonary embolism :**

Enoxaparin sodium can be administered subcutaneously either as a single daily injection of 150 anti-Xa UI/kg or as twice daily injections of 100 anti-Xa UI/kg. In patients with complicated thromboembolic disorders, a dose of 100 anti-Xa UI/kg twice daily is recommended. Enoxaparin sodium treatment is usually prescribed for an average period of 10 days.

Oral anticoagulant therapy should be initiated when appropriate and Enoxaparin sodium treatment should be continued until a therapeutic anticoagulant effect has been achieved (International Normalisation Ratio 2 to 3).

#### Treatment of unstable angina and non-Q-wave myocardial infarction:

The recommended dose of Enoxaparin sodium is 100 anti-Xa UI/kg every 12 hours by subcutaneous injection, administered concurrently with oral aspirin (100 to 325 mg once daily). Treatment with Enoxaparin sodium in these patients should be prescribed for a minimum of 2 days and continued until clinical stabilization. The usual duration of treatment is 2 to 8 days.

#### Prevention of thrombus formation in extra corporeal circulation during hemodialysis:

The recommended dose of Enoxaparin sodium is 100 anti-Xa UI/kg. For patients with a high risk of hemorrhage, the dose should be reduced to 80 anti-Xa UI/kg for double vascular access or 75 anti-Xa UI/kg for single vascular access. During hemodialysis Enoxaparin sodium should be introduced into the arterial line of the circuit at the beginning of the dialysis session. The effect of this dose is usually sufficient for a 4-hour session. However, if fibrin rings are found, a further dose of 50 to 100 anti-Xa UI/kg may be given.

#### Special population :

- Elderly: No dosage adjustment is necessary, unless kidney function is impaired.
- Children: Enoxaparin sodium is not recommended in children.
- Renal impairment:
  - Severe renal impairment: A dosage adjustment is required for patients with severe renal impairment (creatinine clearance < 30 ml/min), since Enoxaparin sodium exposure is significantly increased in this patient population. The following dosage adjustments are recommended: Prophylactic dose ranges: 2000 anti-Xa UI once daily; Therapeutic dose ranges: 100 anti-Xa UI/kg once daily.
  - Moderate and mild renal impairment: Careful clinical monitoring is recommended.
  - Hepatic impairment: Caution should be used in hepatically impaired patients.

#### Mode of administration:

Enoxaparin sodium should be injected by deep subcutaneous route in prophylactic and curative treatment and by intravascular route during hemodialysis.

#### DO NOT ADMINISTER BY THE INTRAMUSCULAR ROUTE.

Aspiration of the contents of the syringe should not be expelled before the injection. The subcutaneous injection should preferably be made when the patient is lying down. Enoxaparin sodium is administered in the subcutaneous tissue of the anterolateral or posterolateral abdominal wall, alternately on the left and the right side. The injection itself consists in introducing the needle perpendicularly and not tangentially, through the skin into a fold of skin between the thumb and index finger. The skin fold should be held throughout the injection.

#### WARNING AND PRECAUTIONS OF USE:

- Spinal/Epidural anesthesia:

- Low Molecular Weight Heparins should not be used interchangeably since they differ in their manufacturing process, molecular weights, specific anti-Xa activities, units and dosage. Very careful attention and compliance with the specific instructions on use of each product are absolutely essential.

As with other anticoagulants, there have been cases of neuraxial hematomas reported with the concurrent use of Enoxaparin sodium and spinal/epidural anesthesia resulting in long-term or permanent paralysis. These events are rare with Enoxaparin sodium. In dosage regimens of 4000 anti-Xa UI once daily or lower, to reduce the potential risk of bleeding during epidural or spinal anesthesia, the placement and removal of the catheter is best performed when the anticoagulant effect of Enoxaparin sodium is low: 10 to 12 hours after administration of 4000 anti-Xa UI or less daily doses of Enoxaparin sodium or 24 hours following the administration of higher doses (1000 anti-Xa UI/kg twice daily or 150 anti-Xa UI/kg once daily). The subsequent administration should be given no sooner than 2 hours after catheter removal.

#### Heparin-induced thrombocytopenia:

Enoxaparin sodium is to be used with extreme caution in patients with a history of heparin-induced thrombocytopenia (decrease in blood platelets count) with or without thrombosis.  
- Percutaneous coronary revascularisation procedures:  
To minimize the risk of bleeding following the vascular instrumentation during the treatment of unstable angina, the vascular access should be closed 6 to 8 hours before the procedure.  
The next scheduled dose should be given no sooner than 6 to 8 hours after sheath removal. The site of the procedure should be observed for signs of bleeding or hematoma formation.

- Pregnant women with mechanical prosthetic heart valves:  
The use of Enoxaparin sodium in pregnant women with mechanical prosthetic heart valves has not been adequately studied. Pregnant women with mechanical prosthetic heart valves may be at a higher risk for thromboembolism.

- Laboratory tests:  
At doses used for prophylaxis of venous thromboembolism, Enoxaparin sodium does not influence bleeding time and global blood coagulation tests significantly, nor does it affect platelet aggregation or binding of fibrinogen to platelets. At higher doses, increases in aPTT (activated Partial Thromboplastin Time) and ACT (Activated Clotting Time) may occur. Increases in aPTT and ACT are not linearly correlated with increasing Enoxaparin sodium anti-thrombotic activity and therefore these tests are unsuitable and unreliable for monitoring Enoxaparin sodium therapy.

#### Precautions of use:

- Bleeding :  
As with other anticoagulants, bleeding may occur at any site. Enoxaparin sodium should be used with caution in conditions with increased potential for bleeding, such as impaired hemostasis, history of peptic ulcer, recent ischemic stroke, uncontrolled severe arterial hypertension, diabetic retinopathy and recent neuro- or ophthalmologic surgery, concomitant use of medications affecting hemostasis.

- Mechanical prosthetic heart valves:  
The use of Enoxaparin sodium for thromboprophylaxis in patients with mechanical prosthetic heart valves has not been adequately studied.

- Elderly:  
No increase in bleeding is observed in the elderly at prophylactic doses while at therapeutic doses bleeding complications may be observed particularly in patients 80 years of age and older. Careful monitoring is recommended.

- Renal impairment:  
In patients with renal impairment, there is an increase in exposure of Enoxaparin sodium which increases the risk of bleeding. Therefore, in patients with severe renal impairment, a dosage adjustment is recommended for prophylactic and therapeutic dose ranges. Although no dosage adjustment is recommended in patients with moderate and mild renal impairment, careful monitoring is advised.

- Low weight patients:  
In low weight patients (women < 45 kg and men < 57 kg), an increase in exposure of Enoxaparin sodium with prophylactic doses has been observed which may lead to a higher risk of bleeding. Therefore, careful monitoring is recommended.

#### - Monitoring of platelet count:

The risk of antibody-mediated heparin-induced thrombocytopenia also exists with Low Molecular Weight Heparins. Such thrombocytopenia is usually observed between the 5th and the 21st day following the beginning of Enoxaparin sodium treatment. Therefore, monitoring of platelet count level is necessary regardless of the therapeutic indication and the dosage administered. It is recommended that the platelet counts be measured before the initiation of the treatment and regularly thereafter during treatment. If a significant decrease of the platelet count (30 to 50% of the initial count) is observed, the treatment must be discontinued and the patient switched to another therapy.

#### • Overdose :

Accidental overdose after intravenous, extra corporeal or subcutaneous administration of massive doses of Enoxaparin sodium may lead to bleeding complications. Neutralization may be obtained by slow intravenous injection of protamine; however the anti-Xa activity of Enoxaparin sodium is never completely neutralized (maximum about 60%). 1 mg protamine can be used to neutralize the anticoagulant effect of about 1 mg Enoxaparin sodium. If Enoxaparin sodium was administered in the previous 8 hours. An infusion of 0.5 mg protamine per 1 mg of Enoxaparin sodium may be administered if Enoxaparin sodium was administered greater than 8 hours previous to the protamine administration, or if it has been determined that a second dose of protamine is required. After 12 hours of the Enoxaparin sodium injection, protamine administration may not be required.

#### PRECANCY AND LACTATION:

In humans, there is no evidence that Enoxaparin sodium crosses the placental barrier during the second trimester. There is no information available concerning the first and the third trimesters. As there are no adequate and well-controlled studies in pregnant women, Enoxaparin sodium should be used during pregnancy only if the doctor has established a clear need. Pregnant women with mechanical prosthetic heart valves may be at a higher risk for thromboembolism.

As a precaution, lactating mothers receiving Enoxaparin sodium should be advised to avoid breast-feeding.

#### DRUG INTERACTIONS:

In order to avoid possible interactions with other medicines, inform your doctor or pharmacist about any other current treatment.

It is recommended that agents which affect hemostasis should be discontinued prior to Enoxaparin sodium therapy (unless strictly indicated) such as acetylsalicylic acid (and derivatives), NSAIDs (general route) including ketorolac, ticlopidine, clopidogrel, dextran 40 (parenteral use), glucocorticoids (general route), thrombolytics and anticoagulants, other anti platelet aggregation agents including glycoprotein IIb/IIIa antagonists. As with other low molecular weight Heparins, if the combination is indicated, Enoxaparin sodium should be used with careful clinical and laboratory monitoring when appropriate.

#### ADVERSE EFFECTS:

- Hemorrhage (bleeding): This may occur during treatment with any anticoagulants in the presence of associated risk factors such as: Organic lesions liable to bleed; invasive procedures or the use of medications affecting hemostasis (e.g. aspirin).

Major hemorrhage including retroperitoneal and intracranial bleeding has been reported. Some of these cases have been lethal. Cases of neuraxial hematomas with the concurrent use of Enoxaparin sodium and spinal/epidural anesthesia or spinal puncture (with or without anesthesia) have resulted in varying degrees of neurologic injuries including long or permanent paralysis have been reported.

- Thrombocytopenia: mild and transient thrombocytopenia (abnormally low platelet count level). In rare cases, immuno-allergic thrombocytopenia with thrombosis (formation of clot in the veins). In some cases thrombosis was complicated by organ infarction (tissue death by lack of oxygen) or limb ischemia (deficiency of blood supply).

- Local reactions: Pain, hematoma (bluish marks) and mild local irritation may follow the subcutaneous injection of Enoxaparin sodium. Rarely, hard inflammatory nodules, which are not cystic enclosures of Enoxaparin sodium, have been observed at the injection site. They resolve after a few days and should not cause treatment discontinuation. Exceptional cases of skin necrosis (skin lesion including irreversible damages) at the injection site have been reported with heparins and Low Molecular Weight Heparins. These phenomena are usually preceded by purpura (small hemorrhage in the skin) or erythematous plaques (red inflammatory rash), infiltrated and painful. Treatment must be discontinued.

- Others: Although rare, cutaneous (blisters eruptions) or systemic allergic reactions including anaphylactoid reactions may occur. Very rare cases of hypersensitivity cutaneous vasculitis (blood vessel inflammation) have been reported. Asymptomatic and reversible increases in platelet counts and liver enzyme levels (transaminases) have been reported.

#### DELIVERY CONDITIONS:

List I - Only on medical prescription.

#### SPECIAL PRECAUTIONS OF STORAGE:

Do not store above 25°C.

#### PRESENTATIONS AND M.A. NUMBERS:

Specialities	M.A.	Presentations
ENOXA Médís® 2000 anti-Xa UI/0,2 ml	923 349 1	Box of 02 pre-filled syringes
ENOXA Médís® 4000 anti-Xa UI/0,4 ml	923 349 2	Box of 02 pre-filled syringes
ENOXA Médís® 6000 anti-Xa UI/0,6 ml	923 349 3	Box of 02 pre-filled syringes
ENOXA Médís® 8000 anti-Xa UI/0,8 ml	923 349 4	Box of 02 pre-filled syringes

#### Marketing Authorisation Holder and Manufacturer:

LES LABORATOIRES MEDIS

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#### This is a drug

- A drug is a specific product.
- A drug is a product acting on your health and its use, therefore, must be controlled and supervised for you.
- Strictly respect the doctor's prescription and the instructions.
- Follow your pharmacist's advice by this drug : its indication, use, contraindications, precautions, etc.
- Do not disseminate your drug, know yourself during the prescription period.
- Do not stop the prescription or increase the dosage without consulting your doctor.

KEEP ANY DRUG OUT OF THE REACH OF CHILDREN.

#### هذا دواء

- الدواء منتج محدد.
- الدواء منتج يؤثر على صحتك واستخدامه، لذلك يجب مراقبته وتوجيهه لك.
- يجب احترام وصفة الطبيب والارشادات.
- اتبع نصيحة الصيدلي بهذا الدواء : ابعاده، استخدامه، التحذيرات، الاحتياطات، الخ.
- لا تشارك دواءك، اعرف نفسك جيداً أثناء فترة الوصفة.
- لا تتوقف عن الوصفة أو تزيد الجرعة دون استشارة الطبيب.

لا تترك أي دواء في متناول أيدي الأطفال

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