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MHEC Circular No 119/2007

Attention all Consultants
Medical Officers
Pharmacists
Nurses

Re: Temporary replacement of Heparin Calcium.

Kindly note that Heparin Calcium 5,000 IU/0.2ml pre-filled syringes will be temporary out of stock.

Until it is once again available Heparin Sodium 5,000 IU/1ml in 5ml multidose vials will replace Heparin Calcium in all cases **except** in pregnancy where Enoxaparin Sodium pre-filled syringes will be used.

Please note that since Heparin Sodium varies in concentration from Heparin Calcium (pre-filled syringe) there will be a change in the volume of injection that is administered. Heparin Sodium is available as a multidose preparation containing a total of 25,000 IU/vial which can be given by intravenous or subcutaneous administration. Hence a 1ml volume administered using a 1ml insulin syringe of Heparin Sodium contains 5,000 IU which is equivalent to the previously available 0.2ml volume (pre-filled syringe) of Heparin Calcium 5,000 IU.

Once first punctured, Heparin Sodium multidose vials must be stored in the refrigerator at 2 to 8 degrees for a maximum of 14 days from the date of first puncture.

The package information leaflet of Heparin Sodium and the Summary of Product Characteristics of Enoxaparin are annexed for your reference and information.

For your attention please,

Dr. R. Busuttil
Director General (Health)

Annex 1

Dosage in the elderly
Treatment dosage: Lower treatment dosages may be required, however, standard treatment dosages should be given initially and then subsequent dosages and/or dosage intervals should be individually adjusted according to changes in thrombin clotting time, whole blood clotting time and/or activated partial thromboplastin time.
Prophylactic dosage: Dosage alterations are unnecessary for prophylaxis in the elderly.

Pregnancy
Treatment dosage: Standard treatment dosages should be given initially by continuous intravenous infusion or every 12 hours by subcutaneous injection. Intermittent intravenous injections are not advised. Subsequent dosages and/or dosage intervals should be individually adjusted according to changes in thrombin clotting time, whole blood clotting time and/or activated partial thromboplastin time.
Prophylactic dosage: It is recommended that plasma heparin levels be maintained below 0.4 units/ml, as determined by specific anti-Xa assay. A suggested dosage is 5,000 units every 12 hours in the early pregnancy, increasing to 10,000 units every 12 hours in the last trimester. The dosage should be reduced during labour and the standard prophylactic dosage is suitable in the puerperium.

Contra-indications, warnings, etc.

Contra-indications: Haemorrhagic disorders and patients with an actual or potential bleeding site e.g. peptic ulcer.
Heparin Injection BP contains Benzyl Alcohol and is therefore contra-indicated in newborn infants, especially in immature neonates.
Precautions: Heparin therapy should be given with caution to patients with impaired renal or hepatic function.
Oral anticoagulants or drugs which interfere with platelet function, eg aspirin and dextran solutions should be administered with caution.
Pregnancy and lactation: Although animal studies have not been performed, epidemiological studies indicate that if drug therapy is needed in pregnancy, the use of heparin in the recommended dosage is acceptable. Heparin does not cross the placenta or appear in breast milk.
Adverse reactions: Hypersensitivity and acute reversible thrombocytopenia may occur rarely. Osteoporosis and alopecia have been reported after prolonged therapy.
Overdosage: The effect of heparin can be reversed immediately by intravenous administration of a 1 % protamine sulphate solution. The dose of protamine sulphate required for neutralisation should be determined accurately by titrating the patient's plasma. It is important to avoid overdosage of protamine sulphate because protamine itself has anticoagulant properties. A single dose of protamine sulphate should never exceed 50 mg. Intravenous injection of protamine may cause a sudden fall in blood pressure, bradycardia, dyspnoea and transitory flushing, but these may be avoided or diminished by slow and careful administration.

Pharmaceutical precautions

Store below 25 °C.
Heparin has been reported to be incompatible in aqueous solutions with certain substances, eg some antibiotics, hydrocortisone and phenothiazines, narcotic analgesics and some antihistamines.

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PAC3E600-10

HEPARIN INJECTION BP

Presentation

Heparin Injection BP 1,000 units per ml: each ml contains 1,000 units Heparin Sodium (mucous) with 1 % Benzyl Alcohol as preservative. Other ingredients: Sodium Chloride, Water for Injections.
Heparin Injection BP 5,000 units per ml: each ml contains 5,000 units Heparin Sodium (mucous) with 1 % Benzyl Alcohol as preservative. Other ingredients: Sodium Chloride, Water for Injections.
Heparin Injection BP 25,000 units per ml: each ml contains 25,000 units Heparin Sodium (mucous) with 1 % Benzyl Alcohol as preservative. Other ingredients: Water for Injections.

Uses

Mode of Action: Heparin is a naturally occurring anti-coagulant which prevents the coagulation of blood in-vivo and in-vitro. It potentiates the inhibition of several activated coagulation factors, including thrombin and factor X.
Indications: Treatment of thrombo-embolic disorders such as deep vein thrombosis, acute arterial embolism or thrombosis, thrombophlebitis, pulmonary embolism, fat embolism.
Prophylaxis against deep vein thrombosis and thromboembolic events in susceptible patients.

Dosage and administration

Treatment dosage
Intravenous administration: 5,000 – 10,000 units every 4 hours or 500 units/kg bodyweight daily as a continuous infusion in sodium chloride injection or dextrose injection. The dose should be individually adjusted according to coagulation tests.
Subcutaneous administration: The initial dose is 250 units/kg bodyweight. Further doses should be given every 12 hours and individually adjusted according to coagulation tests.
Dosage adjustment: It is recommended that dosages be adjusted to maintain a thrombin clotting time, whole blood clotting time or activated partial thromboplastin time 1.5 – 2 times that of control on blood withdrawn 4 – 6 hours after the first injection or commencement of infusion and at similar intervals until the patient is stabilised.
Prophylactic dosage
Administration is by subcutaneous injection.
Patients undergoing major elective surgery: 5,000 units should be given 2 hours preoperatively and then every 8 – 12 hours post-operatively for 10 – 14 days or until the patient is ambulant whichever is the longer.
Following myocardial infarction: 5,000 units should be given twice daily for 10 days or until the patients is mobile.
Other patients: 5,000 units should be given every 8 – 12 hours.
Dosage in children
Treatment dosage: Standard treatment dosages should be given initially. Subsequent dosages and/or dosage intervals should be individually adjusted according to changes in thrombin clotting time, whole blood clotting time and/or activated partial thromboplastin time.

PAC3E600-10

Annex 2

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Clexane

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Concentration of 10.000 anti-Xa IU/ml (100 mg/ml)

Clexane INJ. SOL. 2000 anti-Xa IU/0.2 ml (20 mg/0.2 ml)	: Enoxaparin sodium 2000 anti-Xa IU/0.2 ml (20 mg/0.2 ml)
Clexane INJ. SOL. 4000 anti-Xa IU/0.4 ml (40 mg/0.4 ml)	: Enoxaparin sodium 4000 anti-Xa IU/0.4 ml (40 mg/0.4 ml)
Clexane INJ. SOL. 6000 anti-Xa IU/0.6 ml (60 mg/0.6 ml)	: Enoxaparin sodium 6000 anti-Xa IU/0.6 ml (60 mg/0.6 ml)
Clexane INJ. SOL. 8000 anti-Xa IU/0.8 ml (80 mg/0.8 ml)	: Enoxaparin sodium 8000 anti-Xa IU/0.8 ml (80 mg/0.8 ml)
Clexane INJ. SOL.10.000 anti-Xa IU/1.0 ml (100 mg/01.0 ml)	: Enoxaparin sodium 10.000 anti-Xa IU/1.0 ml (100 mg/1.0 ml)

3. PHARMACEUTICAL FORM

Solution for injection

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

- Clexane (enoxaparin sodium) is indicated for the prophylaxis of deep vein thrombophlebitis in particular when associated with orthopaedic or general surgery, major colorectal or cancer surgery.
- It is indicated for the treatment of deep vein thrombosis with or without pulmonary embolism.

- It is indicated for prophylaxis of venous thromboembolism in medical patients (non surgical patients) bedridden due to acute illnesses including cardiac insufficiency, respiratory failure, severe infections or rheumatic diseases.
- It is also indicated for the treatment of unstable angina and non-Q-wave myocardial infarction, administered concurrently with aspirin.
- Clexane (enoxaparin sodium), being a Low Molecular Weight Heparin, is also indicated as an anticoagulant in extra corporeal circulation during haemodialysis.

IN NEED OF PROPHYLAXIS AGAINST VENOUS THROMBOSIS ARE:

Moderate risk patients:
Those who will undergo a surgical operation with a duration that will exceed 30 minutes and are over 40 years old.

High risk patients:

- Patients, who undergo any surgical operation, are over 40 years old and have history of previous venous thrombosis or pulmonary embolism or extensive malignant disease.
- Patients who will undergo an orthopaedic operation.
- Also, as high thromboembolism risk patients, are considered the patients who undergo major colorectal or cancer surgery.

Pathology patients:

- Patients with hemiplegia.
- Patients over 65 years old, which are to be confined to bed for more than 72 hours and show at least one additional risk factor for deep vein thrombophlebitis (e.g. heart fatigue, chronic lung failure, severe infection, obesity, etc.).
- Patients undergoing in extra-corporeal circulation during a haemodialysis session.

4.2 Posology and method of administration

Prophylaxis of deep vein thrombosis

- In patients with a moderate risk of thromboembolism (e.g. abdominal surgery), the recommended dose of enoxaparin sodium is 2000 anti-Xa IU (20 mg) or 4000 anti-Xa IU (40 mg) 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 risk of thromboembolism (e.g. orthopedic surgery), the recommended dose of enoxaparin sodium given by subcutaneous injection, is 4000 anti-Xa IU (40 mg) once daily, initiated 12 hours prior to surgery or 3000 anti-Xa IU (30 mg) twice daily, initiated 12 to 24 hours after surgery.

Enoxaparin sodium treatment should be prescribed for as long as there is a risk of

thromboembolism, usually until the patient is discharged from the clinic or hospital (an average period of 7 to 10 days after the surgery). Continued therapy with 4000 anti-XA IU (40 mg) once daily for 3 weeks following the initial therapy has been proven to be beneficial in orthopaedic surgery. Under normal conditions of use, enoxaparin sodium does not alter the general blood coagulation tests and therefore, it is pointless to monitor the progress of the treatment with these tests.

For special recommendations concerning dosing intervals for *"spinal/epidural anesthesia"* and *"percutaneous coronary revascularisation procedures"*, see section 4.4 "Special warnings and precautions for use".

Prophylaxis of venous thromboembolism in medical (non surgical) patients

The recommended dose of enoxaparin sodium is 4000 anti-Xa IU (40 mg) 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 thrombosis with or without pulmonary embolism

For the treatment of deep vein thrombosis with or without pulmonary embolism, 100 anti-Xa IU/kg (1 mg/kg) of body weight of enoxaparin sodium are administered twice daily (every 12 hours), subcutaneously.

In patients with no thromboembolic risk followed also by no symptoms of pulmonary embolism 150 anti-Xa IU/kg (1.5 mg/kg) Clexane should be given once daily.

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 IU/kg (1 mg/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 extra corporeal thrombus during haemodialysis

In patients who undergo repeated sessions of haemodialysis, the prevention of thrombosis is the extra corporeal circulation during haemodialysis is achieved by the administration of one dose of 100 anti-Xa IU/kg (1 mg/kg) into the arterial line of the circuit of the haemodialysis at the beginning of the session.

The effect of this dose is usually sufficient for a 4-hour session of haemodialysis; however, if fibrin rings are found, for example after a longer than normal session, a further dose of 50 to 100 anti-Xa IU/kg (0.5 to 1 mg/kg) may be given.

For patients with a high risk of haemorrhage, the recommended dose should be reduced to 50 anti-Xa IU/kg (0.5 mg/kg) (for double vascular access) or 75 anti-Xa IU/kg (0.75 mg/kg) (for single vascular access).

Elderly:

No dosage reduction is necessary in the elderly, unless kidney function is impaired (see sections 4.4 "Special warnings and special precautions for use" - *Haemorrhage in the elderly*, 5.2 "Pharmacokinetic properties" - *Elderly* and 4.2 "Dosage and administration" - *Renal impairment*).

Renal insufficiency:

See sections 4.4 "Special warnings and special precautions for use" - *Renal impairment* and 5.2 "Pharmacokinetic properties" - *Renal impairment*.

- ***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 therapeutic dosage ranges:

Standard dosing	***Severe renal impairment***
100 anti-Xa IU/kg (1 mg/kg) twice daily	100 anti-Xa IU/kg (1 mg/kg) once daily
150 anti-Xa IU/kg (1.5 mg/kg) once daily	100 anti-Xa IU/kg (1 mg/kg) once daily

The following dosage adjustments are recommended for prophylactic dosage ranges:

Standard dosing	***Severe renal impairment***
4000 anti-Xa IU (40 mg) once daily	2000 anti-Xa IU (20 mg) once daily
2000 anti-Xa IU (20 mg) once daily	2000 anti-Xa IU (20 mg) once daily

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

- ***Moderate and mild renal impairment***

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

Low weight:

See section 4.4 “Special warnings and special precautions for use”.

Hepatic impairment:

In the absence of clinical studies, caution should be used in hepatically impaired patients.

Children:

The safety and efficacy of enoxaparin sodium in children has not been established.

Method of administration

The intravascular route is used during hemodialysis. Do not administer by the intramuscular route.

The pre-filled disposable syringe is ready for immediate use.

Injection should be made preferably when the patient is lying down. Enoxaparin sodium is administered by deep subcutaneous injection. Do not expel the air bubble from the syringe before the injection to avoid the loss of drug when using the 2000 anti-Xa IU (20 mg) and 4000 anti-Xa IU (40 mg) pre-filled syringes. The administration should be alternated between the left and right anterolateral or posterolateral abdominal wall.

The whole length of the needle should be introduced vertically into a skin fold gently held between the thumb and index finger. The skin fold should not be released until the injection is complete. Do not rub the injection site after administration.

When using ampoules or vials of enoxaparin sodium, the volume to be injected should be measured precisely with a graduated syringe fitted with an appropriate needle for subcutaneous injection.

4.3 Contraindications

The use of Clexane should be avoided in the following cases:

- Hypersensitivity to either enoxaparin sodium, heparin or its derivatives including other Low Molecular Weight Heparins;

- Active bleeding or serious blood coagulation disorder;

- History or presence of thrombocytopenia following administration of enoxaparin or other heparin through a type II immunologic mechanism (with positive "*in vitro*" aggregation, in the presence of enoxaparin sodium). See section 4.4 "Special warnings and special precautions for use";

- Active gastroduodenal ulcer;

- Cerebrovascular episodes (unless there are systemic embolisms).

- Acute bacterial endocarditis.

4.4 Special warnings and special precautions for use

4.4.1 Warnings

- ***General:***

Low molecular weight heparins present differences in their manufacturing process, molecular weights, specific anti-Xa activity, units and dosage. Therefore, it is noted that in order to avoid errors during treatment, there should not be a change from a product of a certain pharmaceutical company to a product of another company. Special caution and compliance to the package insert leaflet of each pharmaceutical product should be paid. Furthermore, caution should be exercised as several pharmaceutical strengths exist.

- ***Spinal/epidural anaesthesia:***

As with other anticoagulants, there have been cases of neuraxial haematomas reported with the concurrent use of enoxaparin sodium and spinal/epidural anaesthesia. These may result in long-term or permanent paralysis. The risk of these events is higher with the use of post-operative indwelling epidural catheters or with the concomitant use of additional drugs affecting haemostasis such as NSAIDs (see section 4.5 "Interactions with other medicinal products and other forms of interaction"). The risk also appears to be increased by traumatic or repeated neuraxial puncture.

The pharmacokinetic profile of enoxaparin sodium should be considered when scheduling or using epidural or spinal anaesthesia/analgesia in conjunction to enoxaparin sodium administration to reduce the risk of bleeding in the spinal canal. Placement and removal of the catheter is best performed prior to enoxaparin sodium administration. Otherwise, it is important that this occurs when the anticoagulant effect of enoxaparin sodium is low.

Placement or removal of a catheter should be delayed for 12 hours after administration of deep vein thrombosis prophylactic doses of enoxaparin sodium, whereas patients receiving higher doses of enoxaparin sodium, e.g. 100 anti-Xa IU/kg (1 mg/kg), twice daily or 150 anti-Xa IU/kg (1.5 mg/kg) once daily, will require longer delays, i.e. at least 24 hours after the most recent dose of enoxaparin sodium in order to allow for normalization of the patient's coagulation status. The subsequent enoxaparin sodium dose should be given no sooner than 2 hours after catheter removal.

If the physician decides to administer anticoagulation while the catheter remains in place, extreme vigilance and frequent monitoring of the neurological status is required.

Patients anticoagulated or scheduled to be anticoagulated for thromboprophylaxis should be frequently monitored for signs and symptoms of neurological impairment. Although the clinical manifestations of neuraxial haematomas may be influenced by the anaesthetic procedures, signs and symptoms of neuraxial haematomas including midline back pain, sensory and motor deficits (numbness or weakness in lower limbs), bowel and/or bladder dysfunction should be monitored. Patients should be instructed to inform their health practitioner immediately if they experience any of the above signs or symptoms. If signs or symptoms of neuraxial haematomas are suspected, urgent diagnosis and treatment including spinal cord decompression are necessary.

- ***Heparin-induced thrombocytopenia (HIT):***

Enoxaparin sodium should not be used in patients with a history of antibody-mediated heparin-induced thrombocytopenia, (type II), with or without thrombosis. The risk for re-occurrence of type II thrombocytopenia may remain for some years.

- ***Percutaneous coronary revascularisation procedures***

To minimize the risk of bleeding following the vascular instrumentation during the treatment of unstable angina, the vascular access sheath should remain in place for 6 to 8 hours following a subcutaneous dose of enoxaparin sodium. 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***

There have been isolated post marketing reports of valve thrombosis in pregnant women with mechanical prosthetic heart valves while receiving enoxaparin sodium for thromboprophylaxis. Pregnant women with mechanical prosthetic heart valves may be at a higher risk for thromboembolism.

- ***Mechanical prosthetic heart valve***

Isolated cases of prosthetic heart valve thrombosis have been reported in patients with mechanical prosthetic heart valves who have received enoxaparin sodium for thromboprophylaxis. Confounding factors, including underlying disease and insufficient clinical data, limit the evaluation in whom thrombosis led to maternal and foetal death.

- ***Laboratory tests***

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 antithrombotic activity and therefore these tests are unsuitable and unreliable for monitoring enoxaparin sodium activity.

4.4.2 Precautions

Intramuscular use is prohibited.

Enoxaparin sodium, as with any other anticoagulant therapy, should be used with caution in conditions with increased potential for bleeding, such as: impaired hemostasis, recent ischemic stroke, uncontrolled severe arterial hypertension or in patients with a history of peptic ulcer, diabetic retinopathy, recent neuro- or ophthalmologic surgery. (See section 4.5 “Interactions with other medicinal products and other forms of interaction”.)

Hemorrhage in the elderly:
No increased bleeding tendency is observed in the elderly with the prophylactic dosage ranges. Elderly patients (especially patients eighty years of age and older) may be at an increased risk for bleeding complications with the therapeutic dosage ranges. Careful clinical monitoring is advised (see section 4.2 “Dosage and method of administration” - *Elderly* and 5.2 “Pharmacokinetic properties” - *Elderly*).

Renal impairment:
In patients with renal impairment, there is an increase in exposure of enoxaparin sodium which increases the risk of bleeding. Since exposure of enoxaparin sodium is significantly increased in patients with severe renal impairment (creatinine clearance < 30 ml/min), a dosage adjustment is recommended for therapeutic and prophylactic dosage ranges. Although no dose adjustment is recommended in patients with moderate (creatinine clearance 30-50 ml/min) and mild (creatinine clearance 50-80 ml/min) renal impairment, careful clinical monitoring is advised (see section 4.2 “Dosage and method of administration” - *Renal impairment* and 5.2 “Pharmacokinetic properties” - *Renal impairment*).

Liver impairment:
See section 4.2 “Dosage and method of administration”.

- ***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 (see section 5.2 “Pharmacokinetic properties” - *Weight*).

- ***Monitoring of platelet counts:***

The risk of antibody-mediated (type II) heparin-induced thrombocytopenia exists both with fractionated as well with Low Molecular Weight Heparins. Should thrombocytopenia (type II) occurs, it usually appears between the 5th and the 21st day following the beginning of enoxaparin sodium treatment. Therefore, it is recommended that the platelet counts be measured before the initiation of therapy with enoxaparin sodium and then regularly thereafter during the treatment. In practice, if a confirmed significant decrease of the platelet count is observed (30

to 50% of the initial value), enoxaparin sodium treatment must be immediately discontinued and the patient switched to another therapy.

4.5 Interactions with other medicinal products and other forms of interaction

Clinical studies revealed no adverse effects which could be caused by drug interactions. Enoxaparin sodium should be administered with extreme caution when in combination with the following drugs, due to the possibility of interaction with the mechanisms of blood coagulation: oral anticoagulants, inhibitors of platelet aggregation, systemic steroid agents and non-steroid anti-inflammatory drugs, salicylates, acetyl salicylic acid, dextran, ticlopidine, clopidogrel, other anti-platelet agents including glycoprotein Iib/IIIa antagonists.

4.6 Pregnancy and lactation

Use during pregnancy:
Animal studies have not shown any evidence of foetotoxicity or teratogenicity.

In the pregnant rat, the transfer of ^{35}S-enoxaparin sodium across the maternal placenta to the foetus is minimal.

In humans, there is no evidence that enoxaparin sodium crosses the placental barrier during the second trimester of pregnancy. There is no information available concerning the first and the third trimester.

As there are no adequate and well-controlled studies in pregnant women and because animal studies are not always predictive of human response, this drug should be used during pregnancy only if the physician has established a clear need.

In a clinical study of pregnant women with prosthetic heart valves given enoxaparin sodium (1 mg/kg b.i.d.) to prevent thromboembolism, two women developed clots resulting in blockage of the valve and leading to death. In the absence of additional dosing, efficacy and safety information in this circumstance, enoxaparin sodium is not recommended for use in pregnant women with prosthetic heart valves.

Use during lactation:
In lactating rats, the concentration of ^{35}S-enoxaparin sodium or its labelled metabolites in milk is very low.

It is not known whether unchanged enoxaparin sodium is excreted in human breast milk. The oral absorption of enoxaparin sodium is unlikely.

However, as a precaution, lactating mothers receiving enoxaparin sodium should be advised to avoid breast-feeding.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Haemorrhage:
During enoxaparin sodium therapy, bleeding may occur in the presence of associated risk factors such as: organic lesions liable to bleed, invasive procedures or the use of medications affecting haemostasis (see section 4.5 “Interactions with other medicinal products and other forms of interaction”). The origin of the bleeding should be investigated and appropriate treatment instituted. Major haemorrhage including retroperitoneal and intracranial bleeding has been reported. Some of these cases have been lethal.

There have been reports of neuraxial haematomas with the concurrent use of enoxaparin sodium and spinal/epidural anaesthesia or spinal puncture. These events have resulted in varying degrees of neurologic injuries including long-term or permanent paralysis (see section 4.4 “Special warnings and special precautions for use”).

Thrombocytopenia:
Mild, transient, asymptomatic thrombocytopenia (type I) has been reported during the first days of therapy. Rare cases of immuno-allergic thrombocytopenia with or without thrombosis have been reported (see section 4.4 “Special warnings and special precautions for use”).

Local reactions:
Pain, hematoma, 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 at the injection site have been reported with heparins and Low Molecular Weight Heparins. These phenomena are usually preceded by purpura or erythematous plaques, infiltrated and painful. Treatment must be discontinued.

Others:
Very rare cases of hypersensitivity cutaneous vasculitis have been reported.

4.9 Overdosage

Usually, the intake of large quantities of enoxaparin sodium, is not expected to have serious consequences, due to the low absorption of the drug by the stomach and the intestine.

Accidental overdosage with enoxaparin sodium after intravenous, extra corporeal or subcutaneous administration may lead to haemorrhagic complications due to its anticoagulant effects.

The anticoagulant effects can be largely neutralized by the slow intravenous injection of protamine (sulphuric or hydrochloric). The dose of protamine depends on the dose of enoxaparin sodium injected: 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.

However, even with high doses of protamine, the anti-Xa activity of enoxaparin sodium is never completely neutralised (maximum about 60%). In this way, the anti-thrombotic effect is maintained.

5. PHARMACOLOGICAL PROPERTIES

Pharmacotherapeutic group: Heparin group; ATC code: B01AB05

5.1 Pharmacodynamic properties

Enoxaparin sodium is a Low Molecular Weight Heparin (LMWH) with a mean molecular weight of approximately 4,500 daltons. In the *in vitro* purified system, enoxaparin sodium has a high anti-Xa activity (approximately 100 IU/mg) and low anti-IIa or anti-thrombin activity (approximately 28 IU/mg).

The pharmacodynamic parameters were studied in healthy volunteers to whom enoxaparin sodium in concentrations ranged between 10.000 and 20.000 anti-Xa IU/ml (100 to 200 mg/ml) were administered and found comparative levels.

At doses used for prophylaxis of venous thrombosis, 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.

Clinical data in the treatment of unstable angina and non-Q-wave myocardial infarction

In a large multicenter study, 3,171 patients enrolled at the acute phase of unstable angina or non-Q-wave myocardial infarction were randomised to receive in association with aspirin (100 to 325 mg once daily), either subcutaneous enoxaparin sodium 100 anti-Xa IU/kg (1 mg/kg) every 12 hours or intravenous unfractionated heparin adjusted based on activated partial thromboplastin time (aPPT). Patients had to be treated in hospital for a minimum of 2 days and a maximum of 8 days, until clinical stabilisation, revascularisation procedures or hospital discharge. The patients had to be followed up to 30 days. Enoxaparin sodium compared to heparin significantly decreased the incidence of recurrent

angina, myocardial infarction and death, with a relative risk reduction of 16.2% at day 14, sustained over the 30-day period. Furthermore, fewer patients in the enoxaparin sodium group underwent revascularisation with either percutaneous transluminal coronary angioplasty (PTCA) or coronary artery bypass grafting (CABG) (15.8% relative risk reduction at day 30).

5.2 Pharmacokinetic properties

a) General characteristics

The pharmacokinetic parameters of enoxaparin sodium have been studied primarily in terms of the time course of plasma anti-Xa activity, and also by anti-IIa activity, at the recommended dosage ranges after single and repeated subcutaneous administration and after single intravenous administration.

The quantitative determination of anti-Xa and anti-IIa pharmacokinetic activities was conducted by the validated amidolytic methods with specific substrates and an enoxaparin standard calibrated against the international standard for LMWHs (NIBSC).

- *Bioavailability and absorption:*

The absolute bioavailability of enoxaparin sodium after subcutaneous injection, based on anti-Xa activity, is close to 100%. Injection volume and dose concentration over the range of 10.000 to 20.000 anti-Xa IU/ml (100-200 mg/ml) does not affect pharmacokinetic parameters in healthy volunteers.

The mean maximum plasma anti-Xa activity is observed 3 to 5 hours after subcutaneous injection and achieves approximately 0.2, 0.4, 1.0 and 1.3 anti-Xa IU/ml following subcutaneous administration of 2000, 4000 anti-Xa IU, 100 anti-Xa IU/kg (1 mg/kg) and 150 anti-Xa IU/kg (1.5 mg/kg) doses, respectively.

Enoxaparin pharmacokinetics appear to be linear over the recommended dosage ranges. Intra-patient and inter-patient variability is low. After repeated subcutaneous administration of 4000 anti-Xa IU (40 mg) once daily and 150 anti-Xa IU/kg (1.5 mg/kg) once daily regimens in healthy volunteers, the steady-state is reached on day 2 with an average exposure ratio about 15% higher than after a single dose. Steady-state enoxaparin activity levels are well predicted by singly dose pharmacokinetics. After repeated subcutaneous administration of the 100 anti-Xa IU/kg (1 mg/kg) twice daily regimen, the steady-state is reached from day 3 to 4 with mean exposure about 65% higher than after a single dose and mean peak and trough levels of about 1.2 and o0.52 IU/ml, respectively.
Based on enoxaparin sodium pharmacokinetics, this difference in steady state is expected and within the therapeutic range.

Plasma anti-IIa activity after subcutaneous administration is approximately ten-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 IU/ml and 0.19 IU/ml following repeated administration of 100 anti-Xa IU/kg (1 mg/kg) twice daily and 150 anti-Xa IU/kg (1.5 mg/kg) once daily, respectively.

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

Metabolism and elimination:
Enoxaparin sodium is a low clearance drug with a mean anti-Xa plasma clearance of 0.74 l/h after a 150 anti-Xa IU/kg (1.5 mg/kg) 6-hour intravenous infusion.

Elimination appears monophasic with a half-life of about 4 hours after a single-subcutaneous dose to about 7 hours after repeated dosing.

Enoxaparin sodium is primarily metabolized in the liver by desulfation and/or depolymerisation to lower molecular weight species with much reduced biological potency. Renal clearance of active fragments represents about 10% of the administered dose and total renal excretion of active and non-active fragments 40% of the dose.

b) *Characteristics in special populations*

Elderly:
Based on the results of a population pharmacokinetic analysis, the enoxaparin sodium kinetic profile is not different in elderly subjects compared to younger subjects when renal function is normal. However, since renal function is known to decline with age, elderly patients may show reduced elimination of enoxaparin sodium (see 4.4 “Special warnings and special precautions for use” - *Hemorrhage in the elderly*, 4.2 “Dosage and method of administration” - *Elderly* and 5.2 “Pharmacokinetic properties” - *Renal impairment*).

Renal impairment:
A linear relationship between anti-Xa plasma clearance and creatinine clearance at steady state has been observed, which indicates decreased clearance of enoxaparin sodium in patients with reduced renal function. Anti-Xa exposure represented by AUC, at steady-state, is marginally increased in mild (creatinine clearance 50-80 ml/min) and moderate (creatinine clearance 30-50 ml/min) renal impairment after repeated subcutaneous of 4000 anti-Xa IU (40 mg) once daily doses. In patients with severe renal impairment (creatinine clearance <30 ml/min), the AUC at steady state is significantly increased on average by 65% after repeated subcutaneous 4000 anti-Xa IU (40 mg) once daily doses (see sections 4.4 “Special warnings and special precautions for use” - *Renal impairment* and 4.2 “Dosage and method of administration” - *Renal impairment*).

Weight:
After repeated subcutaneous 150 anti-Xa IU/kg (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/m^2) compared to non-obese control subjects, while A_{max} 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 4000 anti-Xa IU (40 mg) dose, that anti-Xa exposure is 50% 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" - *Low weight*).

Haemodialysis:
In a single study, elimination rate appeared similar but AUC was two-fold higher than control population, after a single 25 to 50 anti-Xa IU/kg (0.25 or 0.50 mg/kg) intravenous dose.

5.3 Preclinical safety data

Not applicable.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Water for injections
Nitrogen (as protector).

6.2 Incompatibilities

Do not admix with other products.

6.3 Shelf-life

Clexane INJ. SOL. 2000 anti-XA IU/0.2 ml (20 mg/0.2 ml)	: 36 months
Clexane INJ. SOL. 4000 anti-XA IU/0.4 ml (40 mg/0.4 ml)	: 36 months
Clexane INJ. SOL. 6000 anti-XA IU/0.6 ml (60 mg/0.6 ml)	: 36 months
Clexane INJ. SOL. 8000 anti-XA IU/0.8 ml (80 mg/0.8 ml)	: 36 months
Clexane INJ. SOL. 10.000 anti-XA IU/1.0 ml (100 mg/1.0 ml)	: 36 months

6.4 Special precautions for storage

Store at room temperature, not exceeding 25 ^{o}C.
Pre-filled syringes should not be frozen.

6.5 Nature and contents of container

Clexane 2000 anti-Xa IU/0.2 ml

(20 mg/0.2 ml):	Box that contains 2 pre-filled syringes of 0.2 ml in blister packaging.
Clexane 4000 anti-Xa IU/0.4 ml (40 mg/0.4 ml):	Box that contains 2 pre-filled syringes of 0.4 ml in blisters packaging.
Clexane 6000 anti-Xa IU/0.6 ml (60 mg/0.6 ml):	Box that contains 2 pre-filled syringes of 0.6 ml in blister packaging.
Clexane 8000 anti-Xa IU/0.8 ml (80 mg/0.8 ml):	Box that contains 2 pre-filled syringes of 0.8 ml in blister packaging.
Clexane 10000 anti-Xa IU/1.0 ml (100 mg/1.0 ml):	Box that contains 2 pre-filled syringes of 1.0 ml in blister packaging.

6.6 Instructions for use/handling

See section 4.2 "Posology and method of administration".

7. MARKETING AUTHORISATION HOLDER

Aventis Pharma AEBE
2, Aftocratoros Nicolaou street
GR-176 71 Athens
Greece
Tel.: 0030 210 90 01 600
Tel. Malta: 00356 21 493 022

8. MARKETING AUTHORISATION NUMBER

MA082/00701 – Clexane [100mg/ml] solution for injection
MA082/00702 - Clexane [20mg/0.2ml] solution for injection
MA082/00703 – Clexane [40mg/0.4ml] solution for injection
MA082/00704 - Clexane [60mg/0.6 ml] solution for injection
MA082/00705 – Clexane [80mg/0.8 ml] solution for injection

9. DATE OF FIRST AUTHORIZATION / RENEWAL OF MA

24th February 2006

10. DATE OF REVISION OF THE TEXT

30th April 2007