# SUMMARY OF THE PRODUCT CHARACTERISTICS

## 1 NAME OF THE MEDICINAL PRODUCT

Clivarin 5726 IU anti-Xa /ml, solution for injection, in prefilled syringe
Clivarin 1432 IU anti-Xa /0.25ml, solution for injection, in prefilled syringe

## 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

1 ml solution contains: reviparin sodium 5726 IU anti-Xa
0.25 ml contains: reviparin-sodium 1432 IU anti-Xa
0.6 ml contains: reviparin-sodium 3436 IU anti-Xa
0.9 ml contains: reviparin-sodium 5153 IU anti-Xa

This medicinal product contains 80 mg of sodium per ml solution.

For a full list of excipients, see section 6.1.

## 3 PHARMACEUTICAL FORM

Solution for injection in prefilled syringe.
Clear, colourless to slightly yellowish, solution.

## 4 CLINICAL PARTICULARS

### 4.1 Therapeutic indications

Prevention of venous thromboembolism in general surgery and in orthopaedic surgery
Treatment of venous thrombosis

### 4.2 Posology and method of administration

For subcutaneous use only.

The prefilled syringe is intended for single use of Clivarin only. It is ready for use once the needle shield has been removed. The residual volume of the prefilled syringe has been taken into account during the filling process. The injection is to be given into a pinched-up fold of the skin of the abdominal wall (between umbilicus and iliac crest) or on the front of the thigh. The needle should be inserted and removed perpendicularly and pulled straight out in the same manner. It has been designed so that aspiration prior to injection is not necessary.

*Prophylaxis of venous thromboembolism in surgery:*
Surgery and immobilised trauma patients with normal risk for thromboembolic complications. The usual daily dose is 1432IU **(**0.25 ml**)** given subcutaneously once daily. The first injection should be given 2 hours before surgery or immediately when the patient is immobilised. The duration of therapy depends on the nature of the underlying disease and length of time the patient is at risk (immobilisation), and as such should be decided individually. Generally treatment until the patient is fully mobile is recommended. In general surgery, 7-14 days is the norm. Trauma patients with increased risk of thrombosis should receive prophylaxis as long as they are immobilised (experience is available regarding prophylaxis for 40-45 days until

removal of circular plaster of the lower part of the legs). In clinical studies involving approximately 2600 patients, 877 (33.5%) received prophylaxis for four weeks or longer.

*Surgery patients with increased risk for thromboembolic complications (i.e. orthopaedic surgery for total hip or knee replacement):*
The usual daily dose is 3436IU (0.60ml) given subcutaneously once daily. The first injection should be given 12 hours before surgery. The prophylaxis should be administered until the patient is fully mobile, but it is recommended for at least for 14 days.

*Treatment of venous thrombosis:*
A daily dose of 143 IU anti-Xa/kg body weight divided in two subcutaneous injections is recommended for the initial treatment of deep vein thrombosis ). The maximum daily dose is 10,307 IU.

Oral anticoagulation can be started at the same time with the goal of achieving a PK-INR (International Normalised Ratio) in the therapeutic target range of 2.0 – 3.0. Clivarin treatment should be given for at least 5-7 days.

In clinical studies the following dose scheme has proven to be effective:

| Bodyweight | Reviparin dose | Volume |
|---|---|---|
| 35 - 45 kg | 2863 IU anti-Xa twice daily | 0.50 ml |
| 46 - 60 kg | 3436 IU anti-Xa twice daily | 0.60 ml |
| > 60 kg | 5153 IU anti-Xa twice daily | 0.90 ml |

For patients over 60 kg experience is available with the administration of 10,307 IU once daily (refer to the summary of product characteristics for Clivarin 17178 IU anti-Xa/ml, solution for injection).

*Children*
Reviparin is not indicated for use in children.

*Renal impairment*
Clivarin should be used with caution in patients with mild to moderate renal impairment (see section 4.4 and 5.2). The use of reviparin is contraindicated in patients with severe renal impairment (creatinine clearance less than 30ml/minute) (see section 4.3).

*Hepatic impairment*
Use of reviparin in patients with hepatic impairment has not been studied.

## 4.3 Contraindications

Hypersensitivity to reviparin or to any of the excipients of Clivarin (see section 6.1), or other low molecular heparin preparations and/or heparin, e.g., history of known or suspected immunological mediated heparin induced thrombocytopenia (type II).

Severe renal impairment (creatinine clearance less than 30ml/minute).

Haemorrhage: Reviparin like other anticoagulants should not be used in conditions associated with an elevated bleeding risk, such as active haemorrhage, haemorrhagic diathesis,

deficiency of coagulation factors, severe thrombocytopenia, uncontrolled arterial hypertension, bacterial endocarditis and endocarditis lenta, active gastrointestinal ulceration or haemorrhage, haemorrhagic stroke, spinal, ear or ophthalmological surgery, intraocular bleeding, or injuries there of. Severe impairment of liver and pancreas function.
Treatment with Clivarin in therapeutic doses is contraindicated while/during lumbar puncture, spinal or epidural anaesthesia is performed (see also section 4.4).

## 4.4 Special warnings and special precautions for use

*Warnings*
Haemorrhage: Reviparin, like other anticoagulants should be used with extreme caution in patients treated concomitantly with other anticoagulants or platelet inhibitors.

Reviparin should be used in caution in patients with cerebral stroke, cerebral aneurysm or cerebral neoplasma.

In patients undergoing epidural or spinal anaesthesia or lumbar puncture, the prophylactic use of heparin may very rarely be associated with epidural or spinal haematomas, resulting in prolonged or permanent paralysis (see section 4.8). The risk is increased by the use of an epidural or spinal catheter for anaesthesia, by the concomitant use of medicinal products affecting haemostasis such as nonsteroidal anti-inflammatory medicinal products (NSAIDs), platelet inhibitors or anticoagulants (see section 4.5), and by traumatic or repeated puncture. Reviparin should be administered in an appropriate time interval of 12 hours (minimum 6-8 hours) before and after insertion or removal of the epidural catheter.

When reaching a decision as to the interval between the last heparin administration at prophylactic doses and the placement or removal of an epidural or spinal catheter, the product characteristics and the patient profile should be taken into account. The subsequent dose of reviparin should not take place until at least four hours after removal of the catheter. The subsequent dose should be delayed until the surgical procedure is completed.

Should a physician decide to administer anticoagulation treatment in the context of epidural or spinal anaesthesia, extreme vigilance and frequent monitoring must be exercised to detect any signs and symptoms of neurological impairment, such as back pain, sensory and motor deficits (numbness and weakness in lower limbs) and bowel or bladder dysfunction. Nurses should be trained to detect such signs and symptoms. Patients should be instructed to inform a nurse or a clinician immediately if they experience any of the above symptoms.

If signs or symptoms of epidural or spinal haematoma are suspected, urgent diagnosis and treatment including spinal cord decompression should be initiated.

Reviparin like other LMWHs, can suppress adrenal secretion of aldosterone leading to hyperkalaemia, particularly in patients such as those with diabetes mellitus, chronic renal failure, pre-existing metabolic acidosis, a raised plasma potassium or taking potassium sparing medicinal products. The risk of hyperkalaemia appears to increase with the duration of therapy but it is usually reversible. Serum electrolytes should be measured in patients at risk before starting reviparin therapy and monitored regularly thereafter particularly if treatment is prolonged beyond about 7 days.

Occasionally a mild transient thrombocytopenia (type I) at the beginning of therapy with heparin with platelet counts between 100,000/mm³ and 150,000/mm³ due to temporary platelet

activation has been observed (see section 4.8). As a rule, no complications occur, therefore treatment can be continued.

In rare cases antibody-mediated severe thrombocytopenia (type II) with platelet counts clearly below 100,000/mm³ has been observed with LMWHs (see section 4.8). This effect usually occurs within 5 to 21 days after the beginning of treatment; in patients with a history of heparin-induced thrombocytopenia this may occur sooner.

Platelet counts are recommended before administration of reviparin, on the first day of therapy and then regularly 3 to 4 days and at the end of therapy with reviparin in practice, treatment must be discontinued immediately and an alternative therapy initiated if a significantly reduced platelet count is observed (30 to 50 %), associated with positive or unknown results of in-vitro tests for anti-platelet antibody in the presence of reviparin or other LMWHs and/or heparins.

Reviparin cannot be used interchangeably (unit for unit) with unfractionated heparin or other low molecular weight heparins as they differ in their manufacturing process, molecular weight distribution, anti Xa- and anti IIa-activities, units, and dosage. Special attention and compliance with the instructions for specific use of each product is therefore required.

When given in therapeutic doses in patients with moderate renal impairment (creatinine clearance 30 to 50ml/minute), monitoring of anti Xa levels should be considered (desired levels approximately 0.5-1 U/ml at 3-4 h after dose).

Reviparin must not be administered intramuscularly.

Intramuscular injections of other medications should be avoided during reviparin treatment due to the higher risk of haematomas.

*Precautions*
Reviparin should be used only under strict medical observation.

General: Clivarin may not be mixed with other injections or infusions.

Elderly patients often demonstrate impaired renal function which would reduce the elimination of reviparin. Reviparin should be used with care in these patients.

Diabetic retinopathy

Laboratory tests: periodic platelet counts are recommended during the course of treatment with Clivarin.

Caution is recommended at concomitant treatment with medicinal products that raise serum potassium levels, oral anticoagulants and aspirin.

Only limited data on the safety and efficacy of Clivarin in children are available.

This medicine contains 144 mg sodium in 1.8ml (equivalent to 10,307 IU, the maximum daily dose of Clivarin). This should be taken into account when prescribing for patients on a controlled sodium diet.

The injection needle's inner needle-cover contains natural rubber (latex). This may cause severe allergic reactions in patients sensitive to latex.

## 4.5 Interaction with other medicinal products and other forms of interaction

Caution must be used when reviparin is administered concomitantly with oral anticoagulants, cephalosporin-type antibiotics or medicinal products that raise serum potassium levels. Caution must be used when reviparin is administered concomitantly with non-steroidal anti-inflammatory agents, salicylates, medicinal products affecting platelet function or plasma expanders (dextran) because of the potentiation of the risk of haemorrhage.

The effects of heparin may be reduced by nitroglycerin infusions.

No pharmacokinetic interaction studies have been performed.

## 4.6 Pregnancy and lactation

Controlled clinical studies on the use of low molecular weight heparin in pregnancy have not been performed. In studies during the second and third trimesters, passage of low molecular weight heparin over the placental barrier could not be identified. In *ex vivo* experiments performed on an unknown number of perfused human placentas, passage of reviparin through the placenta could not be demonstrated even if the doses administered were much higher than those in therapeutic use.

In a clinical study in more than 50 pregnant women with repeated miscarriages, reviparin in prophylactic dosages during the entire pregnancy appeared to be safe.

Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/foetal development, partutition or postnatal development.

Caution should be exercised when prescribing to pregnant women.

*Lactation*
Information on passage of reviparin into breast milk is not available. Oral absorption of reviparin is unlikely. However, the use of reviparin during breast-feeding is not advised.

## 4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed.

## 4.8 Undesirable effects

Adverse reactions with this or other formulations of reviparin which occurred in more than 1% of 1273 patients receiving reviparin injection in the two phase III studies (COLUMBUS and/or CORTES), other clinical trials or from Postmarketing Surveillance are shown in the following table. The events considered at least possibly related to reviparinare ranked by organ class and under headings of frequency, using the following convention: very common (≥ 1/10), common (≥1/100, <1/10), uncommon (≥ 1/1,000, < 1/100), rare (≥ 1/10,000, < 1/1,000), very rare (< 1/10,000) and not known (cannot be estimated from the available data).

| Body system | Frequency | Adverse reactions |
|---|---|---|
| | | |
| Blood and lymphatic system disorders | Not Known | Thrombocytopenia |
| Immune System Disorders | Not Known | Hypersensitivity |
| Nervous system disorders | Common | Headache |
| Vascular disorders | Common | Haematoma (subcutaneous)<br>Thrombosis |
| Respiratory, thoracic and mediastinal disorders | Common | Epistaxis |
| Gastrointestinal disorders | Common | Constipation |
| Musculoskeletal and connective bone tissue disorders | Common | Pain in extremity |
| | Not Known | Osteoporosis |
| General disorders and administration site conditions | Common | Fever<br>Injection site haemorrhage |
| | Not Known | Local tissue reactions |
| Investigations | Common | Liver function test abnormal |

The following are adverse reactions from Postmarketing Surveillance or other Clinical Trials with this or other formulations ofreviparin. Estimates of frequency cannot be made since such events are reported voluntarily from a population of unknown size.

*Blood and lymphatic system disorders*
Mild thrombocytopenia may occur.

Severe thrombocytopenia conditioned by an immunologic response may infrequently occur accompanied by paradoxical tendency for thrombosis (heparin induced thrombocytopenia type II). Skin necrosis may occur at the subcutaneous injection site.

*Immune system disorders*
Allergic reactions may occur with symptoms such as nausea, aching limbs, urticaria, vomiting, pruritus, dyspnoea and hypotension. Hypersensitivity and anaphylactic reactions to reviparin are rare.

*Vascular disorders*
Dose-dependent side effects include an increased incidence of bleeding, particularly from the skin, mucosa, wounds, gastrointestinal tract and urogenital tract. Slight bleeding at the injection site may occur with normal doses.

*Muscular and connective tissue disorders*
After fairly long term use of standard heparin (months) osteoporosis may develop, particularly in predisposed patients. This adverse drug reaction cannot be ruled out in the case of reviparin. Clinical trials with other low molecular weight heparins and also with reviparin have shown that the risk of osteoporosis probably is lower as compared to standard heparin.

*General disorders and administration site conditions*
Local tissue reactions (induration, reddening, discoloration and small haematomas) have been seen at the injection site.

*Investigations*
Elevated serum transferases (ALT, AST and gamma-GT) are observed.

### 4.9 Overdose

Overdosage of low molecular weight heparin results in hypocoagulability and thus in an increased risk of bleeding.

Slight bleeding or haematoma at the injection site may occur with normal doses but should not generally entail stopping treatment. Slow intravenous injection of the antidote protamine immediately and completely neutralises reviparin's anti IIa activity while partly neutralising anti Xa activity. The protamine dose must be adjusted to the reviparin dose.

*Treatment:*
About 17.5 mg protamine is required to neutralise a dose of reviparin (1432 IU). The half-life of low molecular weight heparin must be taken into account. 1mg of protamine netralises 81.8 IU anti-Xa ofreviparin. The bolus dose of protamine should not exceed 50 mg (refer to the manufacture's instructions for protamine).

## 5 PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Anticoagulantia, heparin group.
ATC code B01AB08

Clivarin (reviparin) Solution for Injection is composed of fragmented heparin sodium extracted from porcine intestinal mucosa in an aqueous solution and has a mean molecular weight of 3150 – 5150. Of the numerous biological effects of low molecular weight heparin, in clinical terms its action on blood coagulation is the most important.

Reviparin is involved in different phases of blood coagulation. Because of its marked inhibitory action on factor Xa and comparatively low level of anti IIa activity, low molecular weight heparin is at its most active during the preliminary stages of coagulation. Reviparin's ratio of anti Xa activity to anti IIa activity is 3.6 – 6.1 *in vitro* (the ratio for unfractionated heparin is 1).

### 5.2 Pharmacokinetic properties

With subcutaneous injection of reviparin the plasma levels peak after 3 hours then plateau and start to decline at 4 - 6 h after administration. Pharmacokinetic studies in 24 healthy subjects performed with reviparin demonstrated that a single subcutaneous dose of reviparin 1432 IU anti-Xa/0.25ml led to a mean $C_{max}$ (measured as anti-Xa-activity) of 0.14±0.03 IU/ml. Similar studies performed with higher doses of reviparin, indicate that the mean $C_{max}$ of reviparin increases with increase in dose.

The elimination half-life of subcutaneous reviparin is about 3 h, total clearance about 18 ml/min and the volume of distribution about 5 litres and are independent of dose. The compound is excreted mainly in the urine. The pharmacokinetic parameters with respect to anti-Xa activity and anti-IIa activity are virtually identical.

After subcutaneous administration the bioavailability of reviparin is about 95 %. Studies in healthy subjects have not shown any major inter-individual variation of the bioavailability.

*Renal impairment:* No studies have been performed to establish an appropriate dose of reviparin in patients with renal impairment. However, as the mechanism of clearance is predominantly renal, elimination may be delayed depending on the severity of renal dysfunction. Patients with renal impairment are expected to have increased exposure (AUC) and longer half-life compared to patients with normal renal function (see section 4.4).

### 5.3 Preclinical safety data

Toxicity, especially bleeding, occurs at dose levels considerably higher than the recommended dose and is related to the exaggerated pharmacodynamic effects of overdosing.

Studies with heparin and other low molecular weight heparins have shown osteoporotic effects, development of cataract and delayed healing of fractures and recalcification of the skeleton. It is not known if reviparin shows similar effects.

Studies of toxicity to reproduction and genotoxicity reveal no special hazard for humans. No carcinogenicity studies have been performed.

## 6 PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

Sodium chloride
Sodium hydroxide
Water for injection

### 6.2 Incompatibilities

Clivarin must not be mixed with other medicinal products.

### 6.3 Shelf-life

3 years

### 6.4 Special precautions for storage

No special precautions for storage.

### 6.5 Nature and content of container

Available in the following pack sizes:

*Clivarin 1432 IU anti-Xa/0.25 ml, solution for injection in prefilled syringe*
2 x 0.25 ml (0.25 ml = 1432 IU anti-Xa) – ungraduated syringe
5 x 0.25 ml (0.25 ml = 1432 IU anti-Xa) – ungraduated syringe
10 x 0.25 ml (0.25 ml = 1432 IU anti-Xa) – ungraduated syringe
20 x 0.25 ml (0.25 ml = 1432 IU anti-Xa) – ungraduated syringe
100 x 0.25 ml (0.25 ml = 1432 IU anti-Xa) – ungraduated syringe

*Clivarin 5726 IU anti-Xa/ml solution for injection in prefilled syringe*
2 x 0.6 ml (0.6 ml = 3436 IU anti-Xa) – graduated syringe*
5 x 0.6 ml (0.6 ml = 3436 IU anti-Xa) – graduated syringe*
10 x 0.6 ml (0.6 ml = 3436 IU anti-Xa) – graduated syringe*
20 x 0.6 ml (0.6 ml = 3436 IU anti-Xa) – graduated syringe*
100 x 0.6 ml (0.6 ml = 3436 IU anti-Xa) – graduated syringe*

2 x 0.9 ml (0.9 ml= 5153 IU anti-Xa) - graduated syringe*
5 x 0.9 ml (0.9 ml = 5153 IU anti-Xa) - graduated syringe*
10 x 0.9 ml (0.9 ml = 5153 IU anti-Xa) - graduated syringe*
20 x 0.9 ml (0.9 ml = 5153 IU anti-Xa) - graduated syringe*
100 x 0.9 ml (0.9 ml = 5153 IU anti-Xa) - graduated syringe*

Prefilled syringe (ungraduated and graduated) type I glass with a stainless steel needle. Inner needle shield of natural rubber (latex) or polyisoprene based rubber (latex free). Outer needle shield of polypropylene and a plunger of polypropylene or polycarbonate. Optional ultrasafe passive delivery system.

Not all pack sizes may be marketed.

### 6.6 Instructions for use and handling, and disposal (if appropriate)

For single use only any unused solution should be discarded.

## 7 MARKETING AUTHORISATION HOLDER

## 8 MARKETING AUTHORISATION NUMBER(S)

Clivarin 5726 IU anti-Xa /ml (0.6ml/0.9ml): DE/H/2865/002
Clivarin 1432 IU anti-Xa /0.25ml: DE/H/2865/001

## 9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Clivarin 5726 IU anti-Xa /ml: 2005-02-17/2010-02-17
Clivarin 1432 IU anti-Xa /0.25ml: 1995-03-15//2010/03-15

## 10 DATE OF REVISION OF THE TEXT

* Syringe is marked with 0.05 ml graduations