CORE SAFETY PROFILE

REVIPARIN SODIUM

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 artertial hypertension, bacterial endocarditis and endocarditis lenta, active gastrointestinal ulceration or haemorrhage, haemorrhagic stroke, spinal, ear or ophthalmological surgery, intraocular bleeding, or injuries thereof. 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).

Clivarin 5726 IU anti-Xa /mL, solution for injection (vial)
Neonates, in particular premature newborns (the solution contains benzyl alcohol which is associated with the risk of the “gasping baby syndrome”) (see section 4.6).

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 reviparin.

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.

Clivarin 17178 IU anti-Xa /ml, solution for injection, in prefilled syringe
Clivarin 5726 IU anti-Xa /ml, solution for injection, in prefilled syringe
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.

Clivarin 5726 IU anti-Xa /mL, solution for injection (vial)
Clivarin multidose vial contains benzyl alcohol. As benzyl alcohol may pass to foetus and as the foetus has an increased sensitivity to benzyl alcohol, products containing benzyl alcohol

should not be given to pregnant women. (Clivarin prefilled syringes do not contain benzyl alcohol).

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 which occurred in more than 1% of 1273 patients receiving reviparin injection in the two phase III studies (COLUMBUS and CORTES) are shown in the following table. The events considered at least possibly related to reviparin or with no causality opinion are ranked by organ class and under headings of frequency, using the following convention: common (>1/100, <1/10).

Body system	**Frequency**	**Adverse reactions**
Nervous system disorders	Common	Headache
Vascular disorders	Common	Haematoma (subcutaneous) Thrombosis
Respiratory, thoracic and mediastinal disorders	Common	Epistaxis
Gastrointestinal disorders	Common	Constipation
Musculoskeletal, connective tissue and bone tissue disorders	Common	Aching limbs
General disorders and administration site conditions	Common	Fever Injection site haemorrhage
Investigations	Common	Liver function test abnormal

The following are adverse reactions from Postmarketing Surveillance or other Clinical Trials with this or other formulations of reviparin. 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 medicinal products 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 of reviparin. The bolus dose of protamine should not exceed 50 mg (refer to the manufacture’s instructions for protamine).