Package leaflet: Information for the user

Bivalirudin Cipla 250 mg powder for concentrate for solution for injection/ infusion

bivalirudin

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor.
- If you get any side effects talk to your doctor. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Bivalirudin Cipla is and what it is used for

Bivalirudin Cipla contains a substance called bivalirudin which is an antithrombotic medicine. Antithrombotics are medicines which prevent the formation of blood clots (thrombosis).

Bivalirudin Cipla is used to treat patients**:**
- with chest pain due to heart disease (acute coronary syndromes - ACS);
- who are having surgery to treat blockages in their blood vessels (angioplasty and/or percutaneous coronary intervention - PCI).

2. What you need to know before you use Bivalirudin Cipla

Do not use Bivalirudin Cipla
- if you are allergic to bivalirudin or any of the other ingredients of this medicine (listed in section 6) or hirudins (other blood thinning medicines);
- if you have, or have recently had, any bleeding from your stomach, intestines, bladder or other organs, for example, if you have noticed abnormal blood in your stools or urine (except from menstrual bleeding);
- if you have, or have had, difficulty with your blood clotting (a low platelet count);
- if you have severe high blood pressure;
- if you have an infection of the heart tissue;
- if you have severe kidney problems or if you need kidney dialysis.

Check with the doctor if you are not sure.

Warnings and precautions
Talk to your doctor before using Bivalirudin Cipla
- if bleeding occurs (if this happens, treatment with Bivalirudin Cipla will be stopped). Throughout your treatment, the doctor will check you for any signs of bleeding;
- if you have been treated before with medicines similar to Bivalirudin Cipla (e.g. lepirudin);

- before the start of the injection or infusion, the doctor will tell you about the signs of allergic reaction. Such a reaction is uncommon (may affect up to 1 in 100 people);
- if you are having radiation treatment in the vessels that supply blood to the heart (treatment called beta or gamma brachytherapy).

After being treated with Bivalirudin Cipla for a cardiac event, you should stay in the hospital for at least 24 hours and you should be monitored for any symptoms or signs similar to the ones that remind you of your cardiac event and resulted in your hospitalisation.

Children and adolescents
- if you are a child (less than 18 years of age), this medicine is not appropriate for you.

Other medicines and Bivalirudin Cipla
Tell your doctor
- if you are taking, or have recently taken or might take any other medicines;
- If you are taking blood thinners or medicines to prevent blood clots (anticoagulants or antithrombotics e.g. warfarin, dabigatran, apixaban, rivaroxaban, acetylsalicylic acid, clopidogrel, prasugrel, ticagrelor).

These medicines may increase the risk of side effects such as bleeding when given at the same time as Bivalirudin Cipla. Your warfarin blood test result (INR test) may be affected by Bivalirudin Cipla.

Pregnancy and breast-feeding
If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor for advice before taking this medicine.

Bivalirudin Cipla should not be used during pregnancy, unless clearly necessary. Your doctor will decide whether or not this treatment is appropriate for you. If you are breast-feeding, the doctor will decide whether Bivalirudin Cipla should be used.

Driving and using machines
The effects of this medicine are known to be short-term. Bivalirudin Cipla is only given when a patient is in hospital. It is, therefore, unlikely to affect your ability to drive or to use machines.

Bivalirudin Cipla contains sodium
This medicine contains less than 23 mg of sodium per vial, which means that it is essentially "sodium-free".

3. How to use Bivalirudin Cipla

Your treatment with Bivalirudin Cipla will be supervised by a doctor. The doctor will decide how much Bivalirudin Cipla you receive, and will prepare the medicine.

The dose given depends on your weight and on the kind of treatment you are being given.

Dosage

For patients with acute coronary syndromes (ACS) who are treated medically the recommended **starting dose** is:
- 0.1 mg/kg body weight as an intravenous injection, followed by an infusion (drip) into vein of 0.25 mg/kg body weight per hour for up to 72 hours.

If, after this, **you** then need percutaneous coronary intervention (PCI) treatment, the dosage will be increased to:

- 0.5 mg/kg body weight for the intravenous injection, followed by an infusion into vein of 1.75 mg/kg body weight, per hour for the duration of the PCI.
- When this treatment is finished, the infusion may go back to **0.25 mg/kg** body weight per hour for an additional 4 to 12 hours.

If you need to have a coronary artery bypass graft operation, treatment with bivalirudin will either be stopped one hour before the operation or an additional dose of 0.5 mg/kg body weight will be given by injection followed by an infusion of 1.75 mg/kg body weight per hour for the duration of surgery.

For patients starting with percutaneous coronary intervention (PCI) the recommended **dose** is:

- **0.75 mg/kg** body weight as an intravenous injection, followed immediately by an infusion (drip) into vein of **1.75 mg/kg** body weight, per hour for at least the duration of the PCI. The intravenous infusion may continue at this dose for up to 4 hours after the PCI and for STEMI patients (those with a severe type of heart attack) it should continue at this dose for up to 4 hours. The infusion may be followed by an infusion at a lower dose of 0.25 mg/kg body weight for an additional 4 to 12 hours.

If you have kidney problems, the dose of Bivalirudin Cipla may need to be reduced.

In the elderly, if their kidney function is decreased, the dose may need to be reduced.

The doctor will decide for how long you should be treated.

Bivalirudin Cipla is for injection, followed by infusion (drip), into a vein (never into a muscle). This is administered and supervised by a doctor experienced in caring for patients with heart disease.

If you receive more Bivalirudin Cipla than you should
Your doctor will decide how to treat you, including stopping the drug and monitoring for signs of ill effects.

If you have any further questions on the use of this medicine, ask your doctor.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

If you get any of the following, potentially serious, side effects:

- **while you are in hospital: tell the doctor or nurse immediately;**
- **after you've left hospital: contact your doctor directly or go immediately to the Emergency Department of your nearest hospital.**

The most common, (may affect up to 1 in 10 people) serious side effect of treatment with Bivalirudin, is major bleeding which could occur anywhere inside the body (e.g. stomach, digestive system (including vomiting blood or passing blood with the stools), abdomen, lungs, groin, bladder, heart, eye, ear, nose or brain). This may, **rarely**, result in a stroke or be fatal. Swelling or pain in the groin or the arm, back pain, bruising, headache, coughing blood, pink or red urine, sweating, feeling faint or sick or dizzy due to low blood pressure may be signs of internal bleeding. Bleeding is more likely to occur when Bivalirudin is used in combination with

other anticoagulant or antithrombotic medicines (see section 2 ‘Other medicines and Bivalirudin Cipla).

- Bleeding and bruising at the puncture site (after PCI treatment) may be painful. Rarely this may require surgery to repair the blood vessel in the groin (fistula, pseudoaneurysm) (may affect up to 1 in 1,000 people). Uncommonly (may affect up to 1 in 100 people) the number of blood platelets may be low which can worsen any bleeding. Gum bleeding (uncommon, may affect up to 1 in 100 people) is usually not serious.

- Allergic reactions,- are uncommon (may affect up to 1 in 100 people) and usually not serious but can become severe under some circumstances, and in rare cases may be fatal due to low blood pressure (shock). They may begin with limited symptoms such as itching, redness of the skin, rash or small bumps on the skin. Occasionally, reactions can be more severe with throat itching, throat tightening, swelling of the eyes, face, tongue or lips, high pitched whistling during inhaling (stridor), difficulty breathing or exhaling (wheezes).

- Thrombosis (blood clot) is an uncommon side effect (may affect up to 1 in 100 people) which may result in serious or fatal complications such as heart attack. Thrombosis includes coronary artery thrombosis (blood clot in the heart arteries or within a stent being felt as a heart attack which can also be fatal) and/or thrombosis in the catheter, both of which are rare (may affect up to 1 in 1,000 people).

If you get any of the following, (potentially less serious), side effects:
- **while you are in hospital: tell the doctor or nurse;**
- **after you’ve left hospital: first seek advice from your doctor. If you cannot get access to your doctor go immediately to the Emergency Department of your nearest hospital.**

Very common side effects (may affect more than 1 in 10 people):
- minor bleeding.

Common side effects (may affect up to 1 in 10 people):
- anaemia (a low blood cell count);
- haematoma (bruising).

Uncommon side effects (may affect up to 1 in 100 people):
- nausea (feeling sick) and/or vomiting (being sick).

Rare side effects (may affect up to 1 in 1000 people)
- INR test (warfarin blood test result) increased (see Section 2, Other medicines and Bivalirudin);
- angina or chest pain;
- slow heartbeat;
- rapid heartbeat;
- shortness of breath;
- reperfusion injury (no or slow reflow): impaired flow in the heart arteries after they have been reopened.

Reporting of side effects
If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via national reporting system listed in Appendix V*. By reporting side effects you can help provide more information on the safety of this medicine

5. How to store Bivalirudin Cipla

As Bivalirudin Cipla is a hospital only medicine, storage of Bivalirudin Cipla is the responsibility of healthcare professionals.

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the label and carton after 'EXP'. The expiry date refers to the last day of that month.

This medicinal product does not require any specific storage condition.

Reconstituted solution**:** Chemical and physical in-use stability has been demonstrated for 24 hours at 2–8°C. Store in a refrigerator (2–8°C). Do not freeze.

Diluted solution: Chemical and physical in-use stability has been demonstrated for 24 hours at 25°C and at 2–8°C. Do not store above 25°C. Do not freeze.

From a microbiological point of view, the product should be used immediately. If not used immediately, in use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2–8°C unless reconstitution/dilution has taken place in controlled and validated aseptic conditions.

The solution should be a clear colourless solution, without any visible extraneous matter.

The doctor will check the solution and will discard it, if it contains particles or is discoloured.

Do not throw away any medicines via wastewater. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Bivalirudin Cipla contains

- The active substance is bivalirudin. Each vial contains 250 mg bivalirudin. After reconstitution 1 ml contains 50 mg bivalirudin. After dilution 1 ml contains 5 mg bivalirudin.
- The other ingredients are mannitol and sodium hydroxide.

What Bivalirudin Cipla looks like and contents of the pack

Bivalirudin Cipla is a white to off-white lyophilised powder supplied in 10 ml vials (Type 1 glass) with stopper (butyl rubber) with seal (aluminum), containing 250 mg bivalirudin.

Pack sizes: 1 and 10 vials.

Not all pack sizes may be marketed

This medicinal product is authorised in the Member States of the EEA under the following names:

<To be completed nationally>

Marketing Authorisation Holder and Manufacturer

Marketing Authorisation Holder

< To be completed nationally>

Manufacturer

< To be completed nationally>

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The following information is intended for healthcare professionals only:

Healthcare professionals should refer to the Summary of Product Characteristics for full prescribing information.

Bivalirudin Cipla is indicated as an anticoagulant in adult patients undergoing percutaneous coronary intervention (PCI), including patients with ST-segment elevation myocardial infarction (STEMI) undergoing primary PCI.

Bivalirudin Cipla is also indicated for the treatment of adult patients with unstable angina/non-ST segment elevation myocardial infarction (UA/NSTEMI) planned for urgent or early intervention.

Bivalirudin should be administered with acetylsalicylic acid and clopidogrel.

Instructions for preparation

Aseptic procedures should be used for the preparation and administration of Bivalirudin.

Add 5 ml sterile water for injections to one vial of bivalirudin and swirl gently until completely dissolved and the solution is clear. 1 ml reconstituted solution contains 50 mg bivalirudin.

Withdraw 5 ml from the vial, and further dilute in a total volume of 50 ml of glucose 5% solution for injection, or sodium chloride 9 mg/ml (0.9%) solution for injection to give a final bivalirudin concentration of 5 mg/ml.

The reconstituted/diluted solution should be inspected visually for particulate matter and discolouration. Solutions containing particulate matter should not be used.

The reconstituted/diluted solution will be a clear colourless solution, without any visible extraneous matter.

Disposal

Any unused product or waste material should be disposed of in accordance with local requirements.

Incompatibilities

The following medicinal products should not be administered in the same intravenous line as bivalirudin since they result in haze formation, micro-particulate formation or gross precipitation; alteplase, amiodarone HCl, amphotericin B, chlorpromazine hydrochloride (HCl), diazepam, prochlorperazine edisylate, reteplase, streptokinase and vancomycin HCl.

The following six medicinal products show dose-concentration incompatibilities with bivalirudin. See section 6.2 from SmPC for the summary of compatible and incompatible concentrations of these compounds. The medicinal products incompatible with bivalirudin at higher concentrations are: dobutamine hydrochloride, famotidine, haloperidol lactate, labetalol hydrochloride, lorazepam and promethazine HCl.

Contraindications

Bivalirudin is contraindicated in patients with:

- a known hypersensitivity to the active substance or to any of the excipients listed in section 6.1of SmPC, or to hirudins
- active bleeding or increased risk of bleeding because of haemostasis disorders and/or irreversible coagulation disorders
- severe uncontrolled hypertension
- subacute bacterial endocarditis
- severe renal impairment (GFR<30 ml/min) and in dialysis-dependent patients

(see section 4.3 of SmPC*).*

Posology

Patients undergoing PCI, including patients with ST-segment elevation myocardial infarction (STEMI) undergoing primary PCI

The recommended dose of bivalirudin for patients undergoing PCI is an intravenous bolus of 0.75 mg/kg body weight followed immediately by an intravenous infusion at a rate of 1.75 mg/kg body weight/hour for at least the duration of the procedure. The infusion of 1.75 mg/kg body weight/hour may be continued for up to 4 hours post-PCI and at a reduced dose of 0.25 mg/kg body weight/hour for an additional 4-12 hours as clinical necessary. In STEMI patients the infusion of 1.75 mg/kg body weight/hour should be continued for up to 4 hours post-PCI and continued at a reduced dose of 0.25 mg/kg body weight/hour for 4 – 12 hours as clinically necessary (see section 4.4).

Patients should be carefully monitored following primary PCI for signs and symptoms consistent with myocardial ischaemia.

Patients with unstable angina/non-ST segment elevated myocardial infarction (UA/NSTEMI)

The recommended starting dose of bivalirudin for medically managed patients with acute coronary syndrome (ACS) is an intravenous bolus of 0.1 mg/kg followed by an infusion of 0.25 mg/kg/h. Patients who are to be medically managed may continue the infusion of 0.25 mg/kg/h for up to 72 hours.

If the medically managed patient proceeds to PCI, an additional bolus of 0.5 mg/kg of bivalirudin should be administered before the procedure and the infusion increased to 1.75 mg/kg/h for the duration of the procedure.

Following PCI, the reduced infusion dose of 0.25 mg/kg/h may be resumed for 4 to 12 hours as clinically necessary.

For patients who proceed to coronary artery bypass graft (CABG) surgery off pump, the intravenous infusion of bivalirudin should be continued until the time of surgery. Just prior to surgery, a 0.5 mg/kg bolus dose should be administered followed by a 1.75 mg/kg/h intravenous infusion for the duration of the surgery.

For patients who proceed to CABG surgery on pump, the intravenous infusion of bivalirudin should be continued until 1 hour prior to surgery after which the infusion should be discontinued and the patient treated with unfractionated heparin (UFH).

To ensure appropriate administration of bivalirudin, the completely dissolved, reconstituted and diluted product should be thoroughly mixed prior to administration (see section 6.6 of SmPC). The bolus dose should be administered by a rapid intravenous push to ensure that the entire bolus reaches the patient before the start of the procedure.

Intravenous infusion lines should be primed with bivalirudin to ensure continuity of drug infusion after delivery of the bolus.

The infusion dose should be initiated immediately after the bolus dose is administered, ensuring delivery to the patient prior to the procedure, and continued uninterrupted for the duration of the procedure. The safety and efficacy of a bolus dose of bivalirudin without the subsequent infusion has not been evaluated and is not recommended even if a short PCI procedure is planned.

An increase in the activated clotting time (ACT) may be used as an indication that a patient has received bivalirudin.

Renal impairment

Bivalirudin is contraindicated in patients with severe renal insufficiency (GFR<30 ml/min) and also in dialysis-dependent patients (see section 4.3 of SmPC).

In patients with mild or moderate renal insufficiency, the ACS dose (0.1 mg/kg bolus/0.25 mg/kg/h infusion) should not be adjusted.

Patients with moderate renal impairment (GFR 30-59 ml/min) undergoing PCI (whether being treated with bivalirudin for ACS or not) should receive a lower infusion rate of 1.4 mg/kg/h. The bolus dose should not be changed from the posology described under ACS or PCI above.

Hepatic impairment

No dose adjustment is needed.

(For full information on posology see section 4.2 of SmPC)

Shelf life

2 years

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From a microbiological point of view, the product should be used immediately. If not used immediately, in use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2–8°C unless reconstitution/dilution has taken place in controlled and validated aseptic conditions.