PRODUCT INFORMATION

REFLUDAN® Lepirudin powder for injection or infusion

Name of the Drug

Lepirudin (INN) (CAS 138068-37-8)
Powder for solution for injection or infusion.

Lepirudin ([Leu\(^1\), Thr\(^2\)]-63-desulfohirudin) is a recombinant hirudin derived from yeast cells with the molecular formula \( C_{287}H_{440}N_{80}O_{111}S_6 \) and a molecular weight of 6979.5 Daltons. The chemical structure is shown below:

```
  1     5    10    15
Leu Thr Tyr Thr Asp Cys Thr Glu Ser Gly Gln Asn Leu Cys Leu
  16   20    25    30
Cys Glu Gly Ser Asn Val Cys Gly Gln Gly Asn Lys Cys Ile Leu
  31   35    40    45
Gly Ser Asp Gly Glu Lys Asn Gln Cys Val Thr Gly Glu Gly Thr
  46   50    55    60
Pro Lys Pro Gln Ser His Asn Asp Gly Asp Phe Glu Glu Ile Pro
  61   65
Glu Glu Tyr Leu Gln
```

Description

Lepirudin ([Leu\(^1\), Thr\(^2\)]-63-desulfohirudin) is composed of 65 amino acids and characterised by the two first N-terminal amino-acids: Leu 1, Thr 2. It contains 6 cysteine residues which form 3 disulfide bonds (6-14, 16-28 and 22-39). Lepirudin differs from a natural hirudin variant by having the N-terminal isoleucine substituted by leucine.

The isoelectric point is about pH 3.7.

REFLUDAN contains mannitol as bulking and tonicity agent and sodium hydroxide for adjustment to pH 7. REFLUDAN is a sterile lyophilised white powder to be reconstituted with isotonic saline or water for injections for intravenous injection or infusion. Upon reconstitution a clear, colourless solution is obtained.

Biochemically, lepirudin acts as a highly specific direct inhibitor of thrombin. Its activity is measured in a chromogenic assay. One anti-thrombin unit (ATU) is the amount of hirudin that neutralises one unit of WHO preparation 89/588 of thrombin. The specific activity of lepirudin is approximately 16,000 ATU/mg.

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Its mode of action is independent of antithrombin III. Platelet factor 4 does not inhibit lepirudin. One molecule of hirudin binds to one molecule of thrombin and thereby blocks the thrombogenic activity of thrombin.

**Pharmacology**

*Pharmacodynamics*

The pharmacodynamic effect of REFLUDAN on the proteolytic activity of thrombin was routinely assessed by monitoring the increase of activated partial thromboplastin time (aPTT) or thrombin time (TT) values. An increase in aPTT was observed for increasing plasma concentrations of lepirudin, with no saturable effect up to the highest dose (0.5 mg/kg IV bolus). Thrombin time however frequently exceeded the upper limit of the measurement range, even at low plasma concentrations of lepirudin, which renders this test unsuitable for routine monitoring of REFLUDAN therapy.

The pharmacodynamic response essentially depends on plasma drug levels, which, in turn depends on the individual patient’s renal function (see “Pharmacokinetics”). For patients undergoing additional thrombolysis, elevated aPTT-ratios were observed at low lepirudin plasma concentrations and further response to increasing plasma concentrations was relatively flat. In other populations, the response was steeper. At plasma concentrations of 1.5 μL/mL, expected aPTT ratios are nearly 3.0 for healthy volunteers and patients treated with thrombolytics (r-tPA, streptokinase), 2.3 for Heparin Induced Thrombocytopenia (HIT) type II patients and 2.1 for patients with deep venous thrombosis.

**Pharmacokinetics**

The metabolic pathways have not been satisfactorily defined in humans. No PK studies in patients with hepatic impairment have been conducted and there are no definitive protein binding studies in humans other than with thrombin. There are no PK interaction studies.

**Distribution, Metabolism, Elimination**

The pharmacokinetic properties of lepirudin following IV administration are well described by a two-compartment model. Distribution is essentially confined to extracellular fluids and is characterised by an initial half-life of approximately 10 minutes. Elimination follows a first order process and is characterised by a terminal half-life of about 1.3 hours in young healthy volunteers. Kinetics were linear from 0.1 to 0.4 mg/kg after single IV bolus doses.

Both excretion and metabolism take place in the kidney, and about 48% of the dose administered is detectable in the urine. About 35% of the dose is excreted as unchanged compound. The systemic clearance of lepirudin decreases in proportion to the existing glomerular filtration rate.
Females
In female patients, the systemic clearance is about 25% lower than in male patients. See Table 1 below.

Elderly (>65)
In elderly subjects, the systemic clearance of lepirudin is about 20% lower than in young adults. See Table 1 below.

Renal Impairment
In patients with terminal renal insufficiency (creatinine clearance below 15 mL/min) and on haemodialysis, prolonged elimination half-lives of about 2 days were observed. See Table 1 below.

Dose adjustment on the basis of creatinine clearance is recommended (see “Dosage and Administration”: Table 6 Reduction of maintenance dose in patients with renal impairment). There is no accumulation after repeat IV bolus administration.

Table 1 **Systemic clearance (Cl) and volume of distribution at steady state (Vss) of lepirudin**

<table>
<thead>
<tr>
<th></th>
<th>Cl (mL/min) Mean (% CV*)</th>
<th>Vss (L) Mean (% CV*)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Healthy young subjects</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(n = 18, age 18-60 years)</td>
<td>164 (19.3%)</td>
<td>12.2 (16.4%)</td>
</tr>
<tr>
<td>Healthy elderly subjects</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(n = 10, age 65-80 years)</td>
<td>139 (22.5%)</td>
<td>18.7 (20.6%)</td>
</tr>
<tr>
<td>Renally impaired patients</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(n = 16, creatinine clearance below 80 mL/min)</td>
<td>61 (89.4%)</td>
<td>18.0 (41.1%)</td>
</tr>
<tr>
<td>HIT† patients (n = 73)</td>
<td>114 (46.8%)</td>
<td>32.1 (98.9%)</td>
</tr>
</tbody>
</table>

* CV: Coefficient of variation
† HIT: Heparin induced thrombocytopenia

**Clinical Trials**

Heparin induced thrombocytopenia (HIT) is described as an allergy-like adverse reaction to heparin. It can be found in about 1% to 2% of patients treated with heparin for more than 4 days. The clinical picture of HIT is characterised by thrombocytopenia alone or in combination with thromboembolic complications (TECs). These complications comprise the entire spectrum of venous and arterial thromboembolism including deep venous thrombosis, pulmonary embolism, myocardial infarction, ischemic stroke, and occlusion of limb arteries, which may ultimately result in necroses requiring amputation. Furthermore, there is evidence to suggest that warfarin-induced venous limb gangrene may be associated with HIT. Without further treatment, the mortality in HIT patients with new TECs is about 20% to 30% (Fondu 1995; Greinacher 1995; Warkentin, Chong, et al., Warkentin, Elavathil, et al. 1997).

The conclusion that REFLUDAN is an effective treatment for HIT is based upon the data of two prospective, historically controlled clinical trials ("HAT-1" study and "HAT-2" study). It should
be noted that these trials were named on the basis of the prior terminology for the disease i.e. heparin associated thrombocytopenia or HAT. The trials were comparable with regard to study design, primary and secondary objectives, and dosing regimens, as well as general study outline and organisation. They both used the same historical control group for comparison. This historical control was mainly compiled from a recent retrospective registry of HIT patients.

Overall, 198 (HAT-1: 82, HAT-2: 116) patients were treated with REFLUDAN and 182 historical control patients were treated with other therapies. All except 5 (HAT-1: 1, HAT-2: 4) prospective patients and all historical control patients were diagnosed with HIT using the heparin-induced platelet activation assay (HIPAA) or equivalent assays for testing. In total, 113 (HAT-1: 54, HAT-2: 59) prospective patients ("REFLUDAN") and 91 historical control patients ("historical control") presented with TECs at baseline (day of positive test result) and qualified for direct comparison of clinical endpoints.

The gender distribution was found to be similar in REFLUDAN patients and historical control patients. Overall, REFLUDAN patients tended to be younger than historical control patients. Table 2 summarises the demographic baseline characteristics of patients presenting with TECs at baseline.

Table 2: Demographic baseline characteristics of patients presenting with TECs

<table>
<thead>
<tr>
<th></th>
<th>REFLUDAN</th>
<th>Historical Control</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HAT-1 (n = 54)</td>
<td>HAT-2 (n = 59)</td>
</tr>
<tr>
<td>Males</td>
<td>27.8%</td>
<td>44.1%</td>
</tr>
<tr>
<td>Females</td>
<td>72.2%</td>
<td>55.9%</td>
</tr>
<tr>
<td>Age &lt;65 years</td>
<td>63.0%</td>
<td>67.8%</td>
</tr>
<tr>
<td>Age &gt;65 years</td>
<td>37.0%</td>
<td>32.2%</td>
</tr>
<tr>
<td>Mean age ± SD (years)</td>
<td>57 ± 17</td>
<td>58 ± 12</td>
</tr>
</tbody>
</table>

The key criteria of efficacy from a laboratory standpoint (n = 115 evaluable patients) were platelet recovery (increase in platelet count by at least 30% of nadir to values >100,000) and effective anticoagulation (aPTT ratio >1.5 with a maximum total 40% increase in the initial infusion rate).

The proportions of REFLUDAN patients presenting with TECs at baseline who showed platelet recovery, effective anticoagulation, or both (laboratory responders) are shown in Table 3. Comparable rates for the historical control group cannot be given, because (1) platelet counts were not monitored as closely as in the REFLUDAN group, and (2) most historical control patients did not receive therapies affecting aPTT.
Table 3: Proportions of laboratory responders among REFLUDAN patients presenting with TECs

<table>
<thead>
<tr>
<th></th>
<th>HAT-1</th>
<th>HAT-2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of evaluable patients</td>
<td>55</td>
<td>60</td>
</tr>
<tr>
<td>Platelet recovery</td>
<td>90.9%</td>
<td>95.0%</td>
</tr>
<tr>
<td>Effective anticoagulation</td>
<td>81.8%</td>
<td>75.0%</td>
</tr>
<tr>
<td>Both</td>
<td>72.7%</td>
<td>71.7%</td>
</tr>
</tbody>
</table>

Comparisons of clinical efficacy were made between REFLUDAN patients and historical control patients with regard to the combined and individual incidences of death, limb amputation, or new TEC.

The original main analyses included all events that occurred after laboratory confirmation of HIT. This approach was revealed to be substantially confounded by the relative contribution of the pre-treatment period (time between laboratory confirmation of HIT and start of treatment). Although short in duration (mean length 1.5 days in HAT-1 and 2.0 days in HAT-2), the pre-treatment period accounted for 45% and 26% of events observed in the main analyses of HAT-1 REFLUDAN patients and HAT-2 REFLUDAN patients, respectively. Therefore, initiation of treatment was set as the starting point for the analyses. For the historical control group, the first treatment selected within 2 days of laboratory confirmation of HIT was used for reference.

Seven days after start of treatment, the cumulative risk of death, limb amputation, or new TEC was 3.7% in the HAT-1 REFLUDAN patients and 16.9% in the HAT-2 REFLUDAN patients, as compared to 24.9% in the historical control group. At 35 days, when approximately 10% of patients were still at risk, the cumulative risk was 13.0% in the HAT-1 REFLUDAN patients and 28.9% in the HAT-2 REFLUDAN patients, as compared to 47.8% in the historical control group.

In an additional meta-analysis, the pooled REFLUDAN patients of the HAT-1 and HAT-2 studies who presented with TECs at baseline were compared to the respective historical control patients. Seven and 35 days after start of treatment, the cumulative risks of death were 4.4% and 8.9% in the REFLUDAN group, as compared to 1.4% and 17.6% in the historical control group. The cumulative risks of limb amputation were 2.7% and 6.5% in the REFLUDAN group, as compared to 2.6% and 10.4% in the historical control group. Most importantly, the cumulative risks of new TEC were 6.3% and 10.1% in the REFLUDAN group, as compared to 22.2% and 27.2% in the historical control group. As shown in Fig 1, the differences in the cumulative risk of death, limb amputation, or new TEC between the groups were statistically significant in favour of REFLUDAN in the analysis of time to event ($P = 0.004$ according to log-rank test).
The immediate impact of treatment on the combined risk of death, limb amputation, or new TEC is demonstrated by comparing pre-treatment period and treatment period in regard to average combined event rates per patient day. In the pre-treatment period, these rates were found to be 0.075 in the HAT-1 REFLUDAN patients, 0.052 in the HAT-2 REFLUDAN patients, and 0.040 in the historical control group. In the treatment period, the rates showed a marked reduction in the REFLUDAN patients, where they dropped to 0.005 (HAT-1) and to 0.018 (HAT-2), while there was only a moderate decrease to 0.030 in the historical control group.

In conclusion, REFLUDAN substantially reduced the risk of serious sequelae of HIT in comparison to a historical control group.

**Indications:**

REFLUDAN is indicated for

Treatment of acute heparin induced thrombocytopenia (HIT) type II patients with thrombocytopenia or thromboembolic complications.

**Contraindications**

REFLUDAN should not be used in patients with known hypersensitivity to hirudins or other constituents of REFLUDAN.
Thrombolytics (e.g. r-tPA and streptokinase) should not be administered concomitantly with REFLUDAN.

**Intracranial bleeding**

Intracranial bleeding, sometimes fatal, has been reported in patients treated with REFLUDAN. The risk of intracranial bleeding is increased when REFLUDAN is coadministered with thrombolytic agents (see “Adverse Reactions”).

In the case of active bleeding or bleeding tendency, it is generally advisable not to administer REFLUDAN. A careful assessment weighing the risk of REFLUDAN administration versus its anticipated benefit has to be made by the treating physician, particularly in the following situations:

- Recent puncture of large vessels or organ biopsy
- Anomaly of vessels or organs
- Recent cerebrovascular accident, stroke, or intracerebral surgery
- Severe uncontrolled hypertension
- Bacterial endocarditis
- Advanced renal impairment (“Precautions”, “Renal Impairment”)
- Haemorrhagic diathesis
- Recent major surgery
- Recent major bleeding (intracranial, gastrointestinal, intraocular, pulmonary bleeding)
- Overt signs of bleeding
- Recent active peptic ulcer
- More than 65 years of age

Pregnancy or lactation

**Precautions:**

**Anaphylaxis**

REFLUDAN may cause allergic reactions including anaphylaxis and shock (see “Adverse Reactions”). Fatal anaphylactic reactions have been reported in patients re-exposed to REFLUDAN in a second or subsequent treatment course. Therefore, alternative treatment options must be considered before the decision to re-expose a patient to REFLUDAN. As these reactions are immune-mediated, patients with recent exposure to hirudin or hirudin analog may be at an increased risk. Treatment initiation with REFLUDAN should be undertaken only in a setting where medical assistance is readily available and where there is access to treatment for anaphylactic reactions.

Patients should be informed that they have received REFLUDAN.

**Renal Impairment**

In case of renal impairment relative overdose might occur even under the standard dosage regimen. Therefore, the rate of infusion must be reduced in case of known or suspected renal insufficiency (see “Recommendations for Use in Patients with Renal Impairment” in the “Dosage and Administration” section and “Pharmacokinetics” in the “Pharmacology” section).
A careful assessment weighing the risk of REFLUDAN administration versus its anticipated benefit has to be made by the treating physician. It may be necessary to exclude patients with renal impairment from treatment with REFLUDAN.

**Yeast Sensitivity**
Caution should be taken when administering REFLUDAN to patients with known sensitivity to yeast.

**Antibodies:**
Antibody formation was observed in about 40% of HIT type II patients. This may increase the anticoagulant effect of REFLUDAN possibly due to delayed renal elimination of active lepirudin-antihirudin complexes. Strict monitoring of aPTT is necessary during long term prolonged treatment (see “Monitoring” in the “Dosage and Administration” section). However, no evidence of a neutralisation of REFLUDAN or of an allergic reaction associated with the positive antibody test results was found.

**Liver Impairment**
There is no experience with lepirudin in patients with significant liver impairment. Liver cirrhosis may also affect the renal excretion of lepirudin. Serious liver injury (e.g., liver cirrhosis) may enhance the anticoagulant effect of REFLUDAN due to coagulation defects secondary to reduced generation of vitamin K-dependent coagulation factors.

**Laboratory Tests**
The dosage rate should be adjusted according to aPTT (see “Monitoring” and “Dose Modification” in the “Dosage and Administration” section). Other thrombin-dependent coagulation assays are also affected. The high sensitivity of thrombin time to clinical doses of REFLUDAN makes this parameter unsuitable for monitoring.

**Interactions with Other Drugs**
Concomitant treatment with thrombolytics (e.g. r-tPA or streptokinase) may:
♦ Increase the risk of bleeding complications
♦ Considerably enhance the effect of REFLUDAN on aPTT prolongation

Concomitant treatment with coumarin derivatives (vitamin K antagonists) may also increase the risk of bleeding episodes.

Concomitant use with
♦ Antiplatelet agents other than acetylsalicylic acid, such as ticlopidine or clopidogrel,
♦ GpIIb/IIIa receptor antagonists such as eptifibatide, tirofiban, or abciximab,
♦ Other thrombin inhibitors such as low molecular weight heparins
has not been assessed.

Data on interactions with other drugs is extremely limited and no formal interaction studies have been undertaken.

**Use in Pregnancy**
Category B3.

As the safety of REFLUDAN for use in human pregnancy has not been established, REFLUDAN should not be administered to pregnant women (see “Contraindications”).
In preclinical studies, lepirudin and/or its metabolites were shown to cross the placental barrier and distribute to the fetus. Lepirudin caused embryonic deaths (early resorptions) in rabbits treated during gestation with IV lepirudin at 30 mg/kg/day for 13 days (360 mg/m²/day; 2.4 times the maximum human daily dose of 148 mg/m²/day based on body surface area and 7.5 times the human standard dose), and renal dilatation in rats treated during early or late gestation with IV lepirudin at 30 mg/kg/day (180 mg/m²/day; 1.2 times the maximum human dose of 148 mg/m²/day). There was no evidence for teratogenic activity in either species and no adverse effects on offspring development were observed in the rat studies.

**Use in Lactation**
As the safety of REFLUDAN for use in nursing mothers has not been established, REFLUDAN should not be administered during lactation (see “Contraindications”).

**Use in Children**
The safety and effectiveness of REFLUDAN in children has not been established.

**Use in Elderly**
Patients of advanced age have an increased risk of bleeding complications with anti-coagulation. Factors such as potential renal impairment, weight and aPTT need to be taken into account when considering dose adjustment (see “Dosage and Administration” section)

**Carcinogenesis, Mutagenesis and Impairment of Fertility**
Long term animal studies to evaluate potential for carcinogenesis have not been performed with lepirudin. Lepirudin was not genotoxic in the Ames test, the Chinese hamster cell (V79/HGPRT) forward gene mutation test, the A549 human cell unscheduled DNA synthesis (UDS) test, the Chinese hamster V79 cell chromosomal aberration test or the mouse micronucleus test. An effect on fertility and reproductive performance of male and female rats was not seen with lepirudin at intravenous doses up to 30 mg/kg/day (180 mg/m²/day; 1.2 times the recommended maximum human total daily dose based on a body surface area of 1.45 m² for a 50 kg subject).

**Adverse Reactions**

**Adverse Events Reported in HIT Patients**
The following safety information is based on all 198 patients treated with REFLUDAN in the HAT-1 and HAT-2 studies. The safety profile of 113 REFLUDAN patients from these studies who presented with TECs at baseline is compared to 91 such patients in the historical control.

**Haemorrhagic Events**
Bleeding was the most frequent adverse event observed in patients treated with REFLUDAN. Table 4 gives an overview of all haemorrhagic events which occurred in at least two patients.
**Table 4: Haemorrhagic events***

<table>
<thead>
<tr>
<th>Bleeding event</th>
<th>HAT-1 (n = 198)</th>
<th>REFLUDAN (n = 113)</th>
<th>Historical control (n = 91)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bleeding from puncture sites and wounds</td>
<td>14.1%</td>
<td>10.6%</td>
<td>4.4%</td>
</tr>
<tr>
<td>Anaemia or isolated drop in haemoglobin</td>
<td>13.1%</td>
<td>12.4%</td>
<td>1.1%</td>
</tr>
<tr>
<td>Other haematoma and unclassified bleeding</td>
<td>11.1%</td>
<td>10.6%</td>
<td>4.4%</td>
</tr>
<tr>
<td>Haematuria</td>
<td>6.6%</td>
<td>4.4%</td>
<td>0</td>
</tr>
<tr>
<td>Gastrointestinal and rectal bleeding</td>
<td>5.1%</td>
<td>5.3%</td>
<td>6.6%</td>
</tr>
<tr>
<td>Epistaxis</td>
<td>3.0%</td>
<td>4.4%</td>
<td>1.1%</td>
</tr>
<tr>
<td>Haemothorax</td>
<td>3.0%</td>
<td>0</td>
<td>1.1%</td>
</tr>
<tr>
<td>Vaginal bleeding</td>
<td>1.5%</td>
<td>1.8%</td>
<td>0</td>
</tr>
<tr>
<td>Intracranial bleeding**</td>
<td>0</td>
<td>1.8%</td>
<td>2.2%</td>
</tr>
</tbody>
</table>

*Patients may have suffered more than one event.

** Intracranial bleeding has subsequently been reported in post-marketing use (see Post-Marketing Adverse Reactions)

Other haemorrhagic events seen in clinical trials and/or post-marketing experience include haemoperitoneum, haemoptysis, liver bleeding, lung bleeding, rectal bleeding, mouth bleeding, pulmonary haemorrhage, post-operative haemothorax, haemopericardium and retroperitoneal bleeding.
**Nonhaemorrhagic Events**
Table 5 gives an overview of the most frequently observed nonhaemorrhagic events.

<table>
<thead>
<tr>
<th></th>
<th>Patients with TECs</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HAT-1 (n = 198)</td>
</tr>
<tr>
<td></td>
<td>HAT-2 (All patients) (n = 198)</td>
</tr>
<tr>
<td></td>
<td>REFLUDAN (n = 113)</td>
</tr>
<tr>
<td></td>
<td>Historical control (n = 91)</td>
</tr>
<tr>
<td>Fever</td>
<td>6.1%</td>
</tr>
<tr>
<td>Abnormal liver function</td>
<td>6.1%</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>4.0%</td>
</tr>
<tr>
<td>Sepsis</td>
<td>4.0%</td>
</tr>
<tr>
<td>Allergic skin reactions</td>
<td>3.0%</td>
</tr>
<tr>
<td>Heart failure</td>
<td>3.0%</td>
</tr>
<tr>
<td>Abnormal kidney function</td>
<td>2.5%</td>
</tr>
<tr>
<td>Unspecified infections</td>
<td>2.5%</td>
</tr>
<tr>
<td>Multi-organ failure</td>
<td>2.0%</td>
</tr>
<tr>
<td>Pericardial effusion</td>
<td>1.0%</td>
</tr>
<tr>
<td>Ventricular fibrillation</td>
<td>1.0%</td>
</tr>
</tbody>
</table>

*Patients may have suffered more than one event.

**Adverse Events Reported in Other Populations**
The following safety information is based on a total of 2302 individuals who were treated with REFLUDAN in clinical pharmacology studies (n = 323) or for clinical indications other than HIT (n = 1979).

**Intracranial Bleeding**
Intracranial bleeding was the most serious adverse reaction found in populations other than HIT patients. It generally occurred in patients with acute myocardial infarction who were started on both REFLUDAN and thrombolytic therapy with r-tPA or streptokinase. However, fatal intracranial bleeding has been reported with REFLUDAN in the absence of concomitant thrombolytic therapy. The overall frequency of this potentially life-threatening complication among patients receiving both REFLUDAN and thrombolytic therapy was 0.6% (7 out of 1134 patients).

**Allergic Reactions**
Allergic reactions or suspected allergic reactions in populations other than HIT patients include (in descending order of frequency*):

- Airway reactions (cough, bronchospasm, stridor, dyspnea): common
- Unspecified allergic reactions: uncommon
- Skin reactions (pruritus, urticaria, rash, flushes, chills): uncommon
- General reactions (anaphylactoid or anaphylactic reactions): uncommon
- Shock, including fatal shock: rare
- Oedema (facial oedema, tongue oedema, larynx oedema, angio-oedema): rare
- Injection site reactions, including pain: rare

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*The CIOMS (Council for International Organisation of Medical Sciences) III standard categories are used for classification of frequencies:

<table>
<thead>
<tr>
<th>Category</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>very common</td>
<td>10% or more</td>
</tr>
<tr>
<td>common (frequent)</td>
<td>1 to &lt;10%</td>
</tr>
<tr>
<td>uncommon (infrequent)</td>
<td>0.1 to &lt;1%</td>
</tr>
<tr>
<td>rare</td>
<td>0.01 to &lt;0.1%</td>
</tr>
<tr>
<td>very rare</td>
<td>0.01% or less</td>
</tr>
</tbody>
</table>

About 53% (n = 46) of all allergic reactions or suspected allergic reactions occurred in patients who concomitantly received thrombolytic therapy (e.g., streptokinase) for acute myocardial infarction and/or contrast media for coronary angiography.

**Post-Marketing Adverse Reactions**
In intensified post-marketing surveillance in HIT type II, fatal bleeding was reported in 1% and intracranial bleeding in 0.2% of patients.

**Dosage and Administration**
Treatment with REFLUDAN should be initiated under the guidance of a physician with experience in coagulation disorders.

**Dosage**

Treatment of Acute HIT type II Patients and Thromboembolic Disease

Initial dosing should be preceded by a baseline aPTT and treatment should not be initiated in patients with an aPTT of 2.5 or more in order to avoid overdosing.

- 0.4 mg/kg body weight intravenously as an initial bolus dose given over 15 to 20 seconds.
- followed by 0.15 mg/kg body weight/hour as a continuous intravenous infusion for 2-10 days or longer if clinically needed.

The dosage depends on the patients body weight (see “Table 7: Initial IV bolus” and “Table 8: Continuous IV infusion”). This is valid up to a body weight of 110 kg. In patients with a body weight of greater than 110 kg the dose should not be increased beyond that for a body weight of 110 kg. The maximum injection volume or infusion rate as indicated in Tables 7 and 8 must not be exceeded, regardless of body weight.

**Standard Dosage Recommendations**

**Monitoring:**
- In general, the dosage (infusion rate) should be adjusted according to the aPTT ratio.
- The target range for the aPTT ratio during treatment (therapeutic window) should be 1.5 to 2.5. Data from clinical trials in HIT patients suggest that with aPTT ratios higher than this target range, the risk of bleeding increases, while there is no incremental increase in clinical efficacy.
- As stated in “Dosage and Administration: Initial Dosage”, REFLUDAN should not be started in patients presenting with a baseline aPTT ratio of 2.5 or more, in order to avoid initial overdosing.
• The first aPTT determination for monitoring treatment should be done 4 hours after start of the REFLUDAN infusion. Dosage adjustments should be made if indicated by the aPTT.

• Follow-up aPTT determinations for monitoring and treatment are recommended at least once daily, as long as treatment with REFLUDAN is ongoing. Dosage adjustments should be made if indicated by the aPTT.

• More frequent aPTT monitoring is highly recommended in patients with renal impairment or serious liver injury (see Dosage and Administration: “Monitoring”, “Dose Modifications” and “Recommendations for Use in Patients with Renal Impairment”) or with an increased risk of bleeding.

Dose Modifications:

• Any aPTT ratio out of the target range is to be confirmed at once before drawing conclusions with respect to dose modifications, unless there is a clinical need to react immediately.

• If the confirmed aPTT ratio is above the target range, the infusion should be stopped for two hours. At restart, the infusion rate should be decreased by 50% (no additional intravenous bolus should be administered). The aPTT ratio should be determined again 4 hours later.

• If the confirmed aPTT ratio is below the target range, the infusion rate should be increased in steps of 20%. The aPTT ratio should be determined again 4 hours later.

• In general, an infusion rate of 0.21 mg/kg/h should not be exceeded without checking for coagulation abnormalities which might be preventive of an appropriate aPTT response.

Recommendations for Use in Patients with Renal Impairment

As lepirudin is almost exclusively excreted and metabolised renally (see “Pharmacokinetics”), in case of renal impairment, relative overdose might occur even with the standard dosage regimen. Therefore, the rate of infusion and the bolus dose must be reduced in case of known or suspected renal insufficiency (creatinine clearance below 60 mL/min or creatinine value above 15 mg/L). Dose adjustments should preferably be based on creatinine clearance values as obtained from a reliable method (24 h urine sampling). If creatinine clearance is not available then dose adjustment should be made based on the serum creatinine.

In all patients with renal impairment, the bolus dose is to be reduced to 0.2 mg/kg body weight.

There is only limited information on the therapeutic use of REFLUDAN in HIT patients with significant renal impairment. The dosing recommendations for renal impairment are only tentative as they are based mainly on single dose studies in a small number of patients with renal impairment.

The maintenance dose given under section “Dosage and Administration”, Table 8 must be reduced according to Table 6. Additional aPTT monitoring is mandatory.
Table 6: reduction of maintenance dose in patients with renal impairment

<table>
<thead>
<tr>
<th>Creatinine clearance [mL/min]</th>
<th>Creatinine value [mg/L]</th>
<th>Adjusted maintenance dose [% of original dose]</th>
</tr>
</thead>
<tbody>
<tr>
<td>45-60</td>
<td>16-20</td>
<td>50%</td>
</tr>
<tr>
<td>30-44</td>
<td>21-30</td>
<td>30%</td>
</tr>
<tr>
<td>15-29</td>
<td>31-60</td>
<td>15%</td>
</tr>
<tr>
<td>below 15 *</td>
<td>above 60 *</td>
<td>avoid or STOP infusion! *</td>
</tr>
</tbody>
</table>

* In haemodialysis patients or in case of acute renal failure (creatinine clearance below 15 mL/min or creatinine value above 60 mg/L), infusion of REFLUDAN is to be avoided or stopped. Only if aPTT values have fallen below the lower therapeutic level (1.5 times the normal control value) may further IV bolus doses of 0.1 mg / kg body weight be considered every other day.

Switching to Oral Anticoagulants

If a patient is scheduled to receive coumarin derivatives (vitamin K antagonists) for oral anticoagulation after REFLUDAN therapy, the following should apply: Coumarin derivatives should be initiated only when platelet counts are normalising. The intended maintenance dose should be started with no loading dose. To avoid prothrombotic effects when initiating coumarin, continue parenteral anticoagulation for 4 to 5 days (oral anticoagulant package insert for information). The parenteral agent can be discontinued when the INR stabilises within the desired target range.

Method of Administration

General Remarks on Reconstitution and Dilution

- Reconstitution and further dilution are to be carried out under sterile conditions.
- For reconstitution, water for injections or isotonic saline are to be used.
- For further dilution, isotonic saline or glucose 5% is suitable.
- REFLUDAN should not be mixed with other substances except for water for injection, isotonic saline or glucose 5%.
- For rapid, complete reconstitution, inject 1 mL of diluent into the vial and shake it gently. On reconstitution a clear, colourless solution is obtained within 3 minutes.
- Parenteral drugs should be examined visually for particulate matter and discoloration prior to administration. Do not use solutions which are cloudy or contain particles.
- To reduce the microbiological hazard, use as soon as possible after reconstitution. If storage is necessary, hold at 2-8°C for no more than 24 hours. It remains stable for up to 24 hours at room temperature (e.g. during infusion).
- The preparation should be warmed to room temperature before administration.
- Any unused solution must be discarded appropriately.

IV Bolus

For the IV bolus injection, a solution with a concentration of 5 mg/mL is needed.

- Reconstitute one vial (50 mg of REFLUDAN) with 1 mL of either water for injections or isotonic saline.
- The final concentration of 5 mg/mL is obtained by transfer into a sterile, single-use syringe (of at least 10 mL capacity) and further dilution to a total volume of 10 mL using isotonic saline or glucose 5%.
- The final solution is to be applied in a body weight-dependent fashion and the maximum dose is not to be exceeded regardless of body weight (see “Table 7: Initial IV bolus” below).

The intravenous injection is to be carried out slowly.

**Table 7: Initial IV bolus**

REFLUDAN solution, concentration 5 mg/mL:
Examples for standard injection volume according to body weight

<table>
<thead>
<tr>
<th>Body weight [kg]</th>
<th>Injection volume [mL]</th>
<th>Dosage (0.4 mg/kg bw)</th>
<th>Dosage (0.2 mg/kg bw)</th>
</tr>
</thead>
<tbody>
<tr>
<td>50</td>
<td>4.0</td>
<td>2.0</td>
<td></td>
</tr>
<tr>
<td>60</td>
<td>4.8</td>
<td>2.4</td>
<td></td>
</tr>
<tr>
<td>70</td>
<td>5.6</td>
<td>2.8</td>
<td></td>
</tr>
<tr>
<td>80</td>
<td>6.4</td>
<td>3.2</td>
<td></td>
</tr>
<tr>
<td>90</td>
<td>7.2</td>
<td>3.6</td>
<td></td>
</tr>
<tr>
<td>100</td>
<td>8.0</td>
<td>4.0</td>
<td></td>
</tr>
<tr>
<td>≥110</td>
<td>8.8</td>
<td>4.4</td>
<td></td>
</tr>
</tbody>
</table>

**Intravenous Infusion**

For continuous IV infusion, a solution with a concentration of 2 mg/mL is needed.

- Reconstitute two vials (each containing 50 mg of REFLUDAN) with 1 mL each using either water for injections or isotonic saline.
- The final concentration of 2 mg/mL is obtained by transfer of both solutions into one sterile, single-use perfusor syringe (50 mL capacity) and further dilution to a total volume of 50 mL using isotonic saline or glucose 5%.
- The infusion speed of the perfusor automate (mL/hour) is to be set in a body weight-dependent fashion (see “Table 8: Continuous IV infusion”, below).
- The perfusor syringe has to be changed every 24 hours after the first start of infusion, at the latest.

**Table 8: Continuous IV infusion**

REFLUDAN solution, concentration 2 mg/mL
Examples for standard infusion speed (mL per hour) according to body weight

<table>
<thead>
<tr>
<th>Body weight [kg]</th>
<th>Infusion speed [mL/h]</th>
<th>Dosage (0.15 mg/kg bw/h)</th>
<th>Dosage (0.1 mg/kg bw/h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>50</td>
<td>3.8</td>
<td>2.5</td>
<td></td>
</tr>
<tr>
<td>60</td>
<td>4.5</td>
<td>3.0</td>
<td></td>
</tr>
<tr>
<td>70</td>
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<td>5.0</td>
<td></td>
</tr>
<tr>
<td>≥110</td>
<td>8.3</td>
<td>5.5</td>
<td></td>
</tr>
</tbody>
</table>
**Overdosage**

In case of overdose (indicated by excessively high aPTT values) the risk of bleeding may be increased. Currently, no specific antidote against lepirudin is available. If life-threatening bleeding occurs and excessive plasma levels of lepirudin are suspected, the following recommendations should be followed:

- Immediately stop REFLUDAN administration
- Determine aPTT and other coagulation parameters as appropriate
- Determine haemoglobin and prepare for blood transfusion
- Follow the current guidelines for treating patients with shock

Additionally, individual case reports and *in-vitro* data suggest that either haemofiltration or haemodialysis (using a high flux dialysis membrane with a cut off point of 50,000 Daltons) may be useful in REFLUDAN overdosage.

**Presentation:**

REFLUDAN is supplied as a sterile white powder (freeze dried material) in 2 mL injection vials. REFLUDAN is available in packs of 10 vials, each containing 50 mg lepirudin. Store below 25°C. Do not freeze. Protect from light.

**Sponsor:**

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Level 7, 607 St Kilda Road
Melbourne Vic 3004

AUST R No: 73442

Date of TGA approval: 1 March 2000
Date of safety-related notification: 9 December 2005