

PRODUCT MONOGRAPH

^{Pr}**REFLUDAN[®]**

lepirudin [rDNA] lyophilized powder (MFR) for intravenous injection

50 mg vial

Antithrombotic

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ACTION AND CLINICAL PHARMACOLOGY

REFLUDAN (lepirudin [rDNA] for injection) is a highly specific direct inhibitor of thrombin. Lepirudin (chemical designation: [Leu¹, Thr²]-63-desulfohirudin) is a recombinant hirudin produced in yeast cells. Natural hirudin is produced in trace amounts as a family of highly homologous isopolypeptides by the leech *Hirudo medicinalis*.

The activity of lepirudin is measured with a chromogenic assay. One anti-thrombin unit (ATU) is the amount of lepirudin that neutralizes one unit of World Health Organization preparation 89/588 of thrombin. The specific activity of lepirudin is approximately 16,000 ATU/mg. Its mode of action is independent of antithrombin III. Platelet factor 4 does not inhibit lepirudin. One molecule of lepirudin binds to one molecule of thrombin and thereby blocks the thrombogenic activity of thrombin. As a result, all thrombin dependent coagulation assays are affected, e.g., activated partial thromboplastin time (aPTT) and PT (INR) values increase in a dose-dependent fashion.

Pharmacodynamics

In clinical studies, the pharmacodynamic effect of lepirudin on the proteolytic activity of thrombin was routinely assessed as an increase in aPTT. This was observed with increasing plasma concentrations of lepirudin, with no saturable effect up to the highest tested dose (0.5 mg/kg body weight intravenous bolus). Thrombin time frequently exceeded 200 seconds, even at low plasma concentrations of lepirudin, which renders this test unsuitable for routine monitoring of REFLUDAN therapy.

The pharmacodynamic response defined by the aPTT increase depends on plasma drug levels, which in turn depend on the individual patient's renal function (see **ACTION AND CLINICAL PHARMACOLOGY: Pharmacokinetics**). For patients undergoing additional thrombolysis, elevated aPTT ratios (aPTT at a time after REFLUDAN administration over an aPTT reference value, usually median of the laboratory normal range for aPTT) were already 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 1500 ng/mL, aPTT ratios were nearly 3.0 for healthy volunteers, 2.3 for patients with heparin induced thrombocytopenia (HIT), and 2.1 for patients with deep venous thrombosis. In patients treated for acute coronary syndromes (ACS), a prolongation of the aPTT to 73-75 seconds (mean values during infusion period) was found at REFLUDAN plasma concentrations of 1,400 ng/mL .

Pharmacokinetics

The pharmacokinetic properties of lepirudin following intravenous administration are well described by a two-compartment model. Distribution is essentially confined to extracellular fluids and is characterized by an initial half-life of approximately 10 minutes. Elimination follows a first-order process and is characterized by a terminal half-life of about 1.3 hours in young healthy volunteers. As the intravenous dose is increased over the range of 0.1 to 0.4 mg/kg, the plasma concentration increases proportionally.

Lepirudin is probably partially hydrolysed into amino acids in the kidney. Half of the dose administered is detectable in the urine. About 35% of the dose is excreted as unchanged compound. The systemic clearance of lepirudin is proportional to the glomerular filtration rate or creatinine clearance. Dose adjustment based on creatinine clearance is recommended (see **DOSAGE AND ADMINISTRATION: II. Monitoring and Adjustment of Therapy, b. Use in Renal Impairment**). In patients with marked renal insufficiency (creatinine clearance below 15 mL/min), elimination half-lives are prolonged up to two days.

The systemic clearance of lepirudin in women is about 25% lower than in men. In elderly patients, the systemic clearance of lepirudin is 20% lower than in younger patients. This may be explained by the lower creatinine clearance in elderly patients compared to younger patients.

Table 1 summarizes the systemic clearance (Cl) and volume of distribution at steady state (V_{ss}) of lepirudin for various study populations.

Table 1: Systemic Clearance (Cl) and Volume of Distribution at Steady State (V_{ss}) of Lepirudin		
Population	Cl (mL/min) Mean (% CV*)	V_{ss} (L) Mean (% CV*)
healthy young subjects (n=18; 18-60 years)	164 (19.3%)	12.2 (16.4%)
healthy elderly subjects (n=10; 65-80 years)	139 (22.5%)	18.7 (20.6%)
renally impaired subjects (n=16; creatinine clearance < 80 mL/min)	61 (89.4%)	18.0 (41.1%)
heparin induced thrombocytopenia patients (n=73)	114 (46.8%)	32.1 (98.9%)

* CV: Coefficient of variation

INDICATIONS AND CLINICAL USE

Acute Coronary Syndromes

REFLUDAN (lepirudin [rDNA] for injection) is indicated for anticoagulation in adult patients with acute coronary syndromes (ACS); i.e. unstable angina/acute myocardial infarction without ST elevation. In patients with ACS, REFLUDAN is intended for use with ASA.

Heparin Induced Thrombocytopenia

REFLUDAN is indicated for anticoagulation in patients with heparin induced thrombocytopenia (HIT) and associated thromboembolic disease in order to prevent further thromboembolic complications (see **PHARMACOLOGY: Clinical Trial Data** for efficacy results).

CONTRAINDICATIONS

Acute Coronary Syndromes

REFLUDAN is contraindicated in patients with a generalized hemostatic abnormality such as hemophilia, Christmas disease, idiopathic thrombocytopenic purpura and in patients with active bleeding from a local lesion such as acute ulcer or ulcerating carcinoma; in patients who have had recent cranial, spinal, eye or ear surgery or trauma; hypersensitivity to hirudins; shock.

Heparin Induced Thrombocytopenia

REFLUDAN (lepirudin [rDNA] for injection) is contraindicated in patients with known hypersensitivity to hirudins.

WARNINGS

Hemorrhagic Events

Due to the increased risk of bleeding, which may be life-threatening, concomitant use of REFLUDAN (lepirudin [rDNA] for injection) with thrombolytic therapy is not recommended. There has been limited experience with concomitant thrombolytic therapy in patients with HIT; in the OASIS-1 and OASIS-2 clinical trials (in patients with ACS), concomitant treatment with thrombolytics was not studied (see **DOSAGE AND ADMINISTRATION: II. Monitoring and Adjustment of Therapy, c. Concomitant Use with Thrombolytic Therapy**). In postmarketing experience, there have been rare reports of intracranial bleeding with REFLUDAN in the absence of concomitant thrombolytic therapy (see **ADVERSE REACTIONS**).

In the setting of patients at risk for bleeding or bleeding risk, a careful assessment weighing the risk with REFLUDAN administration versus its anticipated benefit should be made by the treating physician. It may be necessary to exclude such patients from treatment with REFLUDAN. Situations with increased bleeding risk include:

- 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 (see **WARNINGS: Renal Impairment**)
- hemorrhagic diathesis
- recent major surgery
- overt signs of bleeding
- recent major bleeding (e.g., intracranial, gastrointestinal, intraocular or pulmonary bleeding).
- Recent active peptic ulcer
- Age >65 (see **PRECAUTIONS: Geriatric Use**)

Patients who weigh less than 50 kg are at an especially high risk of bleeding unless appropriate dosage reductions are made. In the OASIS-2 clinical trial, the observed rate of bleeding events was higher in the subgroup of REFLUDAN patients who weighed less than 50 kg, compared to those who weighed greater than 50 kg. This is most likely attributable to the fact that there was no dosage adjustment for body weight made for patients weighing less than 55 kg. The initial dosage of REFLUDAN should be adjusted for all body weights less than 100 kg (See **DOSAGE AND ADMINISTRATION, I. Initial Dosage, Acute Coronary Syndromes**).

Renal Impairment

With renal impairment, relative overdose might occur even with the standard dosage regimen. Therefore, the bolus dose and the rate of infusion must be reduced in patients with known or suspected renal insufficiency. In clinical trials, REFLUDAN was not evaluated in patients with ACS and a serum creatinine above 2.0 mg/dL (175 µmol/L) prior to initiation of treatment and dosage regimen was adjusted during treatment based on serum creatinine. With this regimen in the OASIS-2 clinical trial, an increased risk of hemorrhagic adverse events was observed in patients with serum creatinine above 1.5 mg/dL. Therefore, a careful assessment weighing the risk of REFLUDAN administration versus its anticipated benefit should be made by the treating physician. It may be necessary to exclude such patients from treatment with REFLUDAN (see **ACTION AND CLINICAL PHARMACOLOGY: Pharmacokinetics** and **DOSAGE AND ADMINISTRATION: II. Monitoring and Adjustment of Therapy, b. Use in Renal Impairment**).

PRECAUTIONS

General

Antibodies

Formation of anti-hirudin antibodies was observed in about 15% of ACS patients and 40% of HIT patients treated with REFLUDAN (lepirudin [rDNA] for injection) during clinical development. Very few patients in the clinical trials received the drug on more than one occasion. Therefore, the true frequency of antibody formation in patients who may be exposed to repeat courses of therapy may be higher. These antibodies may **increase** the anticoagulant effect of REFLUDAN, possibly due to delayed renal elimination of active lepirudin-antihirudin complexes (see **PHARMACOLOGY: Animal Pharmacology, Pharmacokinetics**). Therefore, strict ongoing monitoring of aPTT is necessary during prolonged therapy (see **DOSAGE AND ADMINISTRATION: II. Monitoring and Adjustment of Therapy, a. Standard Recommendations**). No evidence of neutralization of REFLUDAN was found with positive antibody test results.

Allergic Reactions

Allergic reactions occurred in some patients (see **ADVERSE REACTIONS**) but were not found to be correlated with the presence of antibodies to REFLUDAN. However, because a causal relationship of the allergic reactions to REFLUDAN therapy cannot be excluded with certainty, it is recommended to monitor patients receiving REFLUDAN with regard to signs and symptoms of allergic reactions. Anaphylactic reactions have been reported in post-marketing experience, including rare reports of serious anaphylactic reactions that have resulted in shock or death. These reactions have been reported during initial administration or upon second or subsequent re-exposure(s).

Re-exposure

During the HAT-1 and HAT-2 clinical studies, a total of 13 patients were re-exposed to REFLUDAN. One of these patients experienced a mild allergic skin reaction during the second treatment cycle. In post marketing experience, anaphylaxis after re-exposure has been reported (see **Allergic Reactions** and **ADVERSE REACTIONS**).

Liver Injury

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

Heparin Induced Thrombocytopenia

In general, the dosage (infusion rate) should be adjusted to the aPTT ratio (patient aPTT at a given time over an aPTT reference value, usually median of the laboratory normal range for aPTT (see **DOSAGE AND ADMINISTRATION: II. Monitoring and Adjustment of Therapy, a. Standard Recommendations**). Other thrombin-dependent coagulation assays are changed by REFLUDAN.

Drug Interactions

Concomitant use of REFLUDAN with the following agents has not been assessed and may increase the risk of bleeding complications:

- antiplatelet agents other than ASA such as ticlopidine or clopidogrel
- GpIIb/IIIa-receptor antagonists such as eptifibatide, tirofiban, or abciximab
- other thrombin inhibitors such as low-molecular-weight heparins

Concomitant treatment with thrombolytics (e.g. recombinant tissue plasminogen activator [rt-PA] or streptokinase) may increase the risk of bleeding complications, and considerably enhance the effect of REFLUDAN on aPTT prolongation (see **WARNINGS: Hemorrhagic Events; ADVERSE REACTIONS: Adverse Events Reported in Other Populations, Intracranial Severe Bleeding** and **DOSAGE AND ADMINISTRATION: II. Monitoring and Adjustment of Therapy, c. Concomitant Use With Thrombolytic Therapy**).

Concomitant treatment with coumarin derivatives (warfarin or other vitamin K antagonists) or drugs that affect platelet function may also increase the risk of bleeding (see **DOSAGE AND ADMINISTRATION: II. Monitoring and Adjustment of Therapy, d. Use in Patients Scheduled for a Switch to Oral Anticoagulation**).

Patients with a history of diabetes mellitus appeared to not respond to REFLUDAN as well as heparin in one clinical trial. The reason for this observation is unknown and may have been a chance finding.

Use in Pregnant Women

There are no adequate and well-controlled studies to evaluate the efficacy or safety of REFLUDAN in pregnancy. If the use of REFLUDAN is being considered, the treating physician must weigh the potential benefit of treatment versus any potential risks (including bleeding complications) that may occur during pregnancy.

Teratogenic effects have been studied in rats (see **TOXICOLOGY: Reproductive Toxicity**). Because animal reproductive studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed and potential benefits outweigh the risk. It is not known whether the drug crosses the placental barrier in humans (see **PHARMACOLOGY: Animal Pharmacology - Pharmacokinetics**).

Use in Nursing Mothers

It is not known whether lepirudin is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from REFLUDAN, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Use in Pediatrics

Safety and effectiveness in children have not been established. Two children, an 11 year old girl and a 12 year old boy, were treated with REFLUDAN in the HAT-2 study. Both children presented with thromboembolic complications at baseline. REFLUDAN doses given ranged from 0.15-0.22 mg/kg/h for the girl and from 0.1 mg/kg/h (in conjunction with urokinase) to 0.7 mg/kg/h for the boy. Treatment with REFLUDAN was completed after 8 and 58 days, respectively, without serious adverse events.

Geriatric Use

REFLUDAN is known to be substantially excreted by the kidney, and the risk of adverse reactions to this drug may be greater in patients with impaired renal function. In clinical trials, the percentage of hemorrhagic events increased in patients over 65 years of age (from 6.7% to 11%). Decreased renal function is more frequent in elderly patients, so care should be taken in dose selection, and in monitoring renal function.

The frequency of nonhemorrhagic events also increased in elderly patients. Dosage adjustments, in both elderly and younger patients, should be made based on renal functions, weight and aPTT (see **DOSAGE AND ADMINISTRATION: II. Monitoring and Adjustment of Therapy**).

ADVERSE REACTIONS

Severe Bleeding

In clinical trials, major bleeding events occurred in 1.2% of patients with acute coronary syndromes treated with REFLUDAN (lepirudin [rDNA] for injection), and in 0.7% of patients treated with unfractionated heparin. This difference was statistically significant ($p=0.0243$). In these trials, patients with aPTT values ≥ 100 seconds were at higher risk of major bleeding.

Severe bleeding may lead to hypovolemia, hypotension and shock and their clinical sequelae. Severe bleeding and, in particular, intracranial bleeding may be life threatening. Intracranial bleeding was the most serious adverse reaction found in populations other than HIT patients. Intracranial bleeding occurred in patients with acute myocardial infarction who received both REFLUDAN and thrombolytic therapy (rt-PA or streptokinase). 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). Although no intracranial bleeding was observed in 1168 subjects or patients who did not receive concomitant thrombolysis, in postmarketing experience there have been rare reports of intracranial bleeding with REFLUDAN in the absence of concomitant thrombolytic therapy (see **WARNINGS**). The most frequently reported major bleeding in acute coronary syndrome patients were GI bleeds, the majority of which required blood transfusion. The frequency of life-threatening bleeding events was substantially reduced in clinical studies in patients with acute coronary syndrome in which concomitant thrombolysis was not administered.

Hypersensitivity and Injection Site Reactions

Based on clinical study data and postmarketing experience, hypersensitivity reactions may be assumed to occur in <1% of patients. These include: airway reactions (cough, bronchospasm, stridor, dyspnea), skin reactions (pruritus, urticaria, rash, flushes, chills), general allergic reactions (including anaphylactoid or anaphylactic reactions), edema (facial edema, tongue edema, larynx edema, angioedema), injection site reactions and injection site pain. Cases of shock and death from anaphylactic reactions have rarely been reported. (See **PRECAUTIONS.**)

Adverse Events Reported in ACS Patients

The most frequently reported adverse events in the OASIS-1 and OASIS-2 clinical trials were bleeding events.

OASIS-2 Clinical Trial

The incidence rates in Table 2 and Table 3 reflect the scheduled 72-hour treatment period for REFLUDAN or heparin and a subsequent follow-up period until study Day 7. All patients were to receive concomitant ASA treatment.

Hemorrhagic Adverse Events

	OASIS-2 Clinical Trial	
	REFLUDAN (n = 5,047)	Heparin (n = 5,033)
Minor Bleeding	7.7%	4.5%
Major Bleeding †	1.2%	0.7%
Life-threatening ‡	0.4%	0.4%
Fatal	0.1%	0.1%

* Patients may have experienced more than one event

† Major bleeding was defined as fatal, life-threatening, permanently or significantly disabling bleeding events, or events that required surgical intervention or transfusion of 2 or more units of packed red cells or equivalent.

‡ Life-threatening bleeding was defined as major bleeding events that were fatal, intracranial, required surgical intervention or transfusion of 4 or more units of blood products or plasma expanders.

Table 3: Hemorrhagic adverse events with incidences $\geq 1\%$ in the OASIS-2 clinical trial from randomization to Day 7; irrespective of causal relationship to treatment*		
	OASIS-2 Clinical Trial	
	REFLUDAN (n = 5,047)	Heparin (n = 5,033)
Hematuria	2.1%	0.7%
Injection site hemorrhage	2.1%	1.9%
Epistaxis	1.4%	0.6%
GI hemorrhage	1.3%	0.7%

* Patients may have experienced more than one event

Table 4: Hemorrhagic adverse events in patients according to body weight in the OASIS-2 clinical trial (see footnote*)				
Weight	OASIS-2 Clinical Trial			
	REFLUDAN (n = 5,047)	Heparin (n = 5,033)	Total	p-value
< 50 kg	16/98 (16.33%)	4/77 (5.19%)	20/175 (11.43%)	0.0297
50 - 100 kg	408/4720 (8.64%)	244/4677 (5.22%)	652/9397 (6.94%)	0.0001
> 100 kg	22/228 (9.65%)	15/279 (5.38%)	37/507 (7.30%)	0.0853

* The REFLUDAN dosage was not adjusted in patients with body weight < 55 kg in the OASIS-2 clinical trial, which probably resulted in overdosage in this sub-group.

Other hemorrhagic adverse events reported in >0.2% of REFLUDAN patients in the OASIS-2 clinical trial included hemoptysis, gum hemorrhage, subcutaneous hematoma, and surgical bleeding.

Nonhemorrhagic Adverse Events

In the OASIS-2 clinical trial, nonhemorrhagic adverse events from randomization to Day 7 (irrespective of causal relationship to treatment) were reported with REFLUDAN and heparin at a similar frequency. Adverse events reported with REFLUDAN at an incidence from >0.2% to $\leq 0.5\%$ included heart arrest, shock, MI, rash, confusion, and hypotension. There were no nonhemorrhagic adverse events at a frequency >0.5%.

OASIS-1 Clinical Trial

The incidence rates in Table 5 and subsequent text reflect the scheduled 72-hour treatment period for REFLUDAN or heparin and a subsequent follow-up period until study Day 7.

Hemorrhagic Adverse Events

	OASIS-1 Clinical Trial		
	REFLUDAN 0.2 mg/kg bolus, 0.10 mg/kg/hour infusion (n = 270)	REFLUDAN 0.4 mg/kg bolus, 0.15 mg/kg/hour infusion (n = 265)	Heparin (n = 369)
Minor Bleeding	16.3%	21.5%	10.6%
Major Bleeding †	0.7%	1.1%	1.1%
Life-threatening ‡	0.7%	0.8%	0.8%
Fatal	0	0.4%	0

* Patients may have experienced more than one event

† Major bleeding was defined as fatal, life-threatening, permanently or significantly disabling bleeding events, or events that required surgical intervention or transfusion of 2 or more units of packed red cells or equivalent.

‡ Life-threatening bleeding was defined as major bleeding events that were fatal, intracranial, required surgical intervention or transfusion of 4 or more units of blood products or plasma expanders.

The types of hemorrhagic adverse events observed in REFLUDAN-treated patients in the OASIS-1 clinical trial were similar to those reported in the OASIS-2 clinical trial. From randomization to Day 7, the most frequent hemorrhagic adverse event (irrespective of causal relationship to treatment) was skin hemorrhage. Other hemorrhagic events that occurred in >1% of REFLUDAN-treated patients (either dose group; nor specifically listed in the OASIS-2 clinical trial data above) included hemoptysis, rectal bleeding, subcutaneous hematoma and hematemesis. More hemorrhagic adverse events occurred with REFLUDAN compared to heparin; this difference was primarily due to a higher incidence of epistaxis and hematuria in REFLUDAN-treated patients.

Nonhemorrhagic Adverse Events

In the OASIS-1 clinical trial, the nonhemorrhagic adverse events (possibly treatment related) that occurred in 1% to 3% of REFLUDAN patients (either dose group) included headache, nausea, diarrhea, bradycardia, hypotension, insomnia, dyspepsia, fever, pain, vasodilation, rash, increased serum creatinine, and ventricular tachycardia.

Adverse Reactions Reported in HIT Patients

The following safety information is based on 403 HIT patients treated in the two open, historically-controlled clinical studies (n=198) and in an additional uncontrolled study that was performed to increase the knowledge about the safety profile of patients with HIT (n=205).

Hemorrhagic Events

Bleeding was the most frequent adverse reaction observed in patients treated with REFLUDAN. Table 6 gives an overview of all hemorrhagic events which occurred in at least two patients receiving REFLUDAN in clinical studies HAT-1 and HAT-2.

Table 6: Hemorrhagic Events which occurred in at least two patients in clinical studies HAT-1 and HAT-2			
Hemorrhagic Event	Clinical Studies HAT-1, HAT-2 (n= 198)	Patients with TECs	
		REFLUDAN (n= 113)	Historical control (n= 91)
Bleeding from puncture sites and wounds	14.1%	10.6%	4.4%
Anemia or isolated drop in hemoglobin	13.1%	12.4%	1.1%
Other hematoma and bleeding	11.1%	10.6%	4.4%
Hematuria	6.6%	4.4%	0
Gastrointestinal and rectal bleeding	5.1%	5.3%	6.6%
Epistaxis	3.0%	4.4%	1.1%
Hemothorax	3.0%	0	1.1%
Vaginal bleeding	1.5%	1.8%	0
Intracranial bleeding	0	0	2.2%

Other possibly related hemorrhagic events, which were reported in one patient each, were gastrointestinal hemorrhage, hematemesis, hemoperitoneum, hemoptysis, hemorrhagic gastritis, intracerebral bleeding, lung hemorrhage, mouth hemorrhage, retroperitoneal bleeding and subcutaneous hematoma.

Nonhemorrhagic events

Table 7 gives an overview of the most frequently observed nonhemorrhagic events in clinical studies HAT-1 and HAT-2.

Table 7: Incidence of Most Frequent ($\geq 1\%$) Nonhemorrhagic Events* Considered At Least Possibly Related to REFLUDAN in Clinical Studies HAT-1 and HAT-2	
Event	All REFLUDAN Patients (n=198)
SGOT increased	3.0%
fever	2.5%
prothrombin increased	1.5%
allergic reaction	1.0%
eczema	1.0%
rash	1.0%

*Patients may have experienced more than one event.

The following other nonhemorrhagic events were assessed as at least possibly related, and occurred in one patient each among all 198 patients treated with REFLUDAN.

Body as a Whole: abscess, infection superimposed.

Cardiovascular System: coronary thrombosis, pericardial effusion, vasodilatation, ventricular fibrillation

Digestive System: diarrhea, gastritis, liver function test abnormal, vomiting

Hemic and Lymphatic System: antinuclear antibody present, thrombocytopenia

Nervous System: agitation, convulsion, sweating increased

Skin and Appendages: skin necrosis

Thromboembolism: arterial thrombosis, pulmonary embolus, thrombophlebitis of arm

In the open multicenter clinical trial HAT-3, a total of 54% (111/205) experienced adverse events. The following type of major bleedings were observed: Bleeding at invasive/instrumented sites gastrointestinal, urogenital, pericardial and intracerebral bleedings. One intracerebral bleeding occurred during the study. Four of the observed major bleeding events were fatal. The most frequent minor bleeding events were isolated drop in hemoglobin (6/205) hematuria, and hematomas (7/205). Of these, 53 patients (26%) had possibly related adverse events. The most frequently observed adverse events other than bleeding events previously described were the following: pneumonia (5%), new TEC-arterial peripheral (4%), multi organ failure (4%), fever (3%), sepsis (3%) and shock (2%). Eight patients (4%) experienced a total of 11 allergic reactions.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

In case of overdose, as suggested by excessively high aPTT values, the risk of bleeding is increased.

No specific antidote for REFLUDAN (lepirudin [rDNA] for injection) is available. If life-threatening bleeding occurs and excessive plasma levels of lepirudin are suspected, the following steps should be followed:

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

Individual clinical case reports and animal data suggest that either hemofiltration or hemodialysis (using high flux dialysis membranes with a molecular weight cut-off point of 50,000 Daltons) may be useful in this situation.

In studies in pigs the application of von Willebrand Factor (vWF, 66 IU/kg) markedly reduced the bleeding time prolongation by lepirudin. The clinical significance of this data is unknown.

Coagulant complex anti-inhibitor was effective in completely inhibiting lepirudin induced prolongation of whole blood coagulation time (WBCT) in rabbits at a dose of 50 U/kg (see **PHARMACOLOGY: Animal Pharmacology - Pharmacodynamics**). The clinical significance of these data is unknown. Due to its procoagulant effects, the use of coagulant complex anti-inhibitor should only be considered in cases of life-threatening bleeding. As there is no experience in humans in the presence of lepirudin, no dosing recommendations can be given. Careful dose titration is necessary in order to avoid the risk of further thromboembolic complications or disseminated intravascular coagulation (DIC) caused by overdose. The clinical usefulness of coagulation tests such as activated partial thromboplastin time, whole blood clotting time, activated clotting time, or bleeding time in this particular setting is not known.

DOSAGE AND ADMINISTRATION

I. Initial Dosage

Acute Coronary Syndromes

Anticoagulation in adult patients with acute coronary syndromes:

- 0.4 mg/kg body weight (**up to 100 kg**) slowly intravenously (eg. over 15 to 20 seconds) as a bolus dose,
- followed by 0.15 mg/kg body weight (**up to 100 kg**)/hour as a continuous intravenous infusion. REFLUDAN (lepirudin [rDNA] for injection) should be infused for 72 hours.
- A bolus must not be given if, for any reason (eg, previous heparin treatment) the baseline aPTT is higher than 60 seconds, and infusion is not to be started if the aPTT is higher than 100 seconds. Heparin treatment must be discontinued before REFLUDAN treatment is started.

Normally the initial dosage depends on the patient's body weight. This is valid up to a body weight of 100 kg in patients with ACS. In ACS patients with a body weight exceeding 100 kg, the initial dosage should not be increased beyond the 100 kg body weight dose (maximal initial bolus dose of 40 mg, maximal initial infusion dose of 15 mg/hour). (See also **III.**

Administration; Initial Intravenous Bolus, Table 10 and **III. Administration; Intravenous Infusion, Table 11**).

Heparin Induced Thrombocytopenia

Anticoagulation in Adult Patients with HIT and Associated Thromboembolic Disease:

The initial dose of REFLUDAN is 0.4 mg/kg body weight (up to 110 kg) given as a slow (e.g., over 15 to 20 seconds) intravenous bolus injection. This is followed by a continuous intravenous infusion of 0.15 mg/kg/hour (up to 110 kg) for 2 - 10 days, or longer if clinically needed (see **III. Administration** for directions on preparation and dilution).

Normally, the initial dosage depends on the patient's body weight. This is valid up to a body weight of 110 kg in patients with HIT. In HIT patients with a body weight exceeding 110 kg, the initial dosage should not be increased beyond the 110 kg body weight dose (maximum initial bolus dose of 44 mg; maximum initial infusion dose of 16.5 mg/h; see **Tables 10 and 11** under **III. Administration, b. Initial Intravenous Bolus** and **c. Intravenous Infusion**).

II. Monitoring and Adjustment of Therapy

a. **Standard Recommendations**

Monitoring: Acute Coronary Syndromes

Any aPTT value 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. Target range (therapeutic window) for the aPTT is between 60 and 100 seconds. It is recommended that aPTT measurements be done before REFLUDAN treatment, 6 to 8 hours after the start of treatment, and daily thereafter for the duration of treatment in all patients. Heparin treatment must be discontinued before REFLUDAN treatment is started. The bolus must not be given if the aPTT is higher than 60 seconds and the infusion must not be started if the aPTT is higher than 100 seconds. The same applies to patients with elevated aPTT for other reasons. More frequent measurements may be required in the course of the treatment if the aPTT is too high or too low. These measurements will be used to adjust the infusion of REFLUDAN according to Table 8.

The standard initial infusion rate given in **Table 11 : Standard Infusion Rates According to Body Weight** must be reduced according to the recommendations given in **Table 9** below. Additional aPTT monitoring is highly recommended.

Table 9: Reduction of Infusion Rate in Patients With Renal Impairment			
Creatinine Clearance (mL/min)	Serum Creatinine (mg/dL)	Adjusted Infusion Rate	
		% of Standard Initial Infusion Rate	mg/kg/h
45-60	1.6-2.0	50%	0.075
30-44	2.1-3.0	30%	0.045
15-29	3.1-6.0	15%	0.0225
below 15*	above 6.0*	Avoid or STOP infusion!*	

* In hemodialysis patients or in case of acute renal failure (creatinine clearance below 15 mL/min or serum creatinine above 6.0 mg/dL), infusion of REFLUDAN is to be avoided or stopped. Additional intravenous bolus doses of 0.1 mg/kg body weight should be considered every other day only if the aPTT ratio falls below the lower therapeutic limit of 1.5 (see **also II. Monitoring and Adjustment of Therapy, a. Standard Recommendations**).

c. Concomitant Use With Thrombolytic Therapy

Acute Coronary Syndromes

In patients with acute coronary syndrome, concomitant treatment with thrombolytics was not studied. Concomitant use of REFLUDAN and thrombolytics is not recommended in patients with ACS.

Heparin Induced Thrombocytopenia

Clinical trials in HIT patients have provided only limited information on the combined use of REFLUDAN and thrombolytic agents. The following dosage regimen of REFLUDAN was used in a total of nine HIT patients in clinical studies who presented with thromboembolic complications at baseline and received both REFLUDAN and thrombolytic therapy (rt-PA, urokinase or streptokinase): initial intravenous bolus of 0.2 mg/kg body weight, followed by continuous intravenous infusion of 0.1 mg/kg/hour.

The number of patients receiving combined therapy was too small to identify differences in clinical outcome of patients who received both REFLUDAN and thrombolytic therapy as compared to those who received REFLUDAN alone. The combined incidences of death, limb amputation, or new thromboembolic complication were 22.2% and 20.7%, respectively. While there was a 47% relative increase in the overall bleeding rate in patients who were started on both REFLUDAN and thrombolytic therapy versus REFLUDAN alone (55.6% vs. 37.9%), there were no differences in the rates of major bleeding events (fatal or life-threatening bleeds, bleeds that were permanently or significantly disabling, overt bleeds requiring transfusion of two or

more units of packed red blood cells, bleeds necessitating surgical intervention, intracranial bleeds) between the groups (11.1% vs. 11.2%). Although no intracranial bleeding has been observed in any of these patients, the risk of this potentially life-threatening complication may be increased in conjunction with thrombolytic agents (see **ADVERSE REACTIONS: Intracranial Bleeding**).

Special attention should be paid to the fact that thrombolytic agents *per se* may increase the aPTT ratio. Therefore, aPTT ratios with a given plasma level of lepirudin are usually higher in patients who receive concomitant thrombolysis than in those who do not (see also **ACTION AND CLINICAL PHARMACOLOGY: Pharmacodynamics**).

d. Use in Patients Scheduled for a Switch to Oral Anticoagulation

REFLUDAN monotherapy influences the INR/prothrombin time in a dose dependent, gradual and linear fashion (mean INR increase +0.14 with aPTT in the recommended therapeutic range in the absence of other anticoagulants).

In REFLUDAN-treated patients with aPTT values within the recommended target range receiving overlapping therapy with oral anticoagulants and who had stable therapeutic INR values, a cumulative analysis of two prospective trials did not find evidence of a relevant decrease in INR values upon cessation of REFLUDAN treatment.

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 normalizing. 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. The parenteral agent can be discontinued when INR stabilizes within the desired target range.

Acute Coronary Syndromes

In patients with acute coronary syndromes in the OASIS-2 clinical trial, warfarin treatment was initiated in a sub-group of patients 12 to 30 hours after starting REFLUDAN therapy. Warfarin was administered with a loading dose of 10 mg, followed by 3 mg/day for 3 days. Subsequent warfarin doses were adjusted by the treating physician to achieve an international normalized ratio (INR) of 2.5 (range 2 to 3).

Heparin Induced Thrombocytopenia

If a patient is scheduled to receive coumarin derivatives (vitamin K antagonists) for oral anticoagulation after REFLUDAN therapy, the dose of REFLUDAN should first be gradually reduced in order to reach an aPTT ratio just above 1.5 before initiating oral anticoagulation. As soon as an international normalized ratio (INR) of 2.0 is reached, REFLUDAN therapy should be stopped.

III. Administration

a. Directions on Preparation and Dilution

REFLUDAN should not be mixed with other drugs or diluents except for Water for Injection USP, 0.9% Sodium Chloride Injection USP or 5% Dextrose Injection.

Reconstitution and further dilution are to be carried out under sterile conditions. For reconstitution, Water for Injection USP or 0.9% Sodium Chloride Injection USP are to be used. For further dilution, 0.9% Sodium Chloride Injection USP or 5% Dextrose Injection are suitable.

For rapid, complete reconstitution, inject 1 mL of diluent into the vial and shake it gently. After reconstitution a clear, colourless solution is usually obtained in a few seconds, but definitely in less than 3 minutes.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit. Do not use solutions that are cloudy or contain particles.

It is recommended that the reconstituted solution be used immediately. The diluted solution for Intravenous administration remains stable for up to 24 hours at 2° to 25° C. The preparation should be allowed to reach room temperature before administration. Discard any unused solution appropriately.

b. Initial Intravenous Bolus

For intravenous bolus injection, use a solution with a concentration of 5 mg/mL.

Preparation of a REFLUDAN solution with a concentration of 5 mg/mL:

- Reconstitute one vial (50 mg of lepirudin) with 1 mL of Water for Injection USP or 0.9% Sodium Chloride Injection USP.
- The final concentration of 5 mg/mL is obtained by transferring the entire contents of the vial into a sterile, single-use syringe (of at least 10 mL capacity) and diluting the solution to a total volume of 10 mL, using Water for Injection USP, 0.9% Sodium Chloride Injection USP or 5% Dextrose Injection.

The final solution is to be administered according to body weight (see [Table 10](#) and **I. Initial Dosage**). Intravenous injection of the bolus is to be carried out slowly (over 15 to 20 seconds).

Table 10: Standard Bolus Injection Volumes According to Body Weight for a 5 mg/mL Concentration		
Body Weight (kg)	Injection Volume	
	Dosage 0.4 mg/kg	Dosage 0.2 mg/kg*
< 50	Adjust injection volume for body weight: $(0.4 \times \text{BW}) / 5 = \text{injection volume (mL)}$	Adjust injection volume for body weight: $(0.2 \times \text{BW}) / 5 = \text{injection volume (mL)}$
50	4.0 mL	2.0 mL
60	4.8 mL	2.4 mL
70	5.6 mL	2.8 mL
80	6.4 mL	3.2 mL
90	7.2 mL	3.6 mL
100†	8.0 mL †	4.0 mL †
≥ 110‡	8.8 mL ‡	4.4 mL ‡

* Dosage recommended for all patients with renal insufficiency (see [II. Monitoring and Adjustment of Therapy, b. Use in Renal Impairment](#))

† Highest recommended initial dose in ACS patients

‡ Highest recommended initial dose in HIT patients

c. Intravenous Infusion

For continuous intravenous infusion, solutions with concentrations of 0.2 mg/mL or 0.4 mg/mL may be used.

Preparation of a REFLUDAN solution with a concentration of 0.2 or 0.4 mg/mL:

- Reconstitute two vials (each containing 50 mg of lepirudin) with 1 mL each using either Water for Injection USP or 0.9% Sodium Chloride Injection USP.
- The final concentrations of 0.2 mg/mL or 0.4 mg/mL are obtained by transferring the entire contents of both vials into an infusion bag containing 500 mL or 250 mL, respectively, of 0.9% Sodium Chloride Injection USP or 5% Dextrose Injection.

The infusion rate (mL/h) is to be set according to body weight (see **Table 11** below and **I. Initial Dosage**).

Table 11: Standard Infusion Rates According to Body Weight*		
Body Weight (kg)	Infusion Rate at 0.15 mg/kg/h	
	500 mL Infusion Bag 0.2 mg/mL	250 mL Infusion Bag 0.4 mg/mL
< 50	Adjust infusion rate for body weight: $(0.15 \times \text{BW}) / 0.2 = \text{infusion rate (mL/h)}$	Adjust infusion rate for body weight: $(0.15 \times \text{BW}) / 0.4 = \text{infusion rate (mL/h)}$
50	38 mL/h	19 mL/h
60	45 mL/h	23 mL/h
70	53 mL/h	26 mL/h
80	60 mL/h	30 mL/h
90	68 mL/h	34 mL/h
100 †	75 mL/h †	38 mL/h †
≥ 110 ‡	83 mL/h ‡	41 mL/h ‡

* For dosage adjustment in patients with renal impairment, please refer to Table 9: Reduction of Infusion Rate in Patients with Renal Impairment.

† Highest recommended initial dose in ACS patients

‡ Highest recommended initial dose in HIT patients

The intravenous infusion solution remains stable for up to 24 hours at room temperature.

PHARMACEUTICAL INFORMATION

Drug Substance

Proper Name: lepirudin

Chemical Name: [Leu¹, Thr²]-63-desulfohirudin

Chemical Formula: C₂₈₇H₄₄₀N₈₀O₁₁₁S₆

Chemical Structure:



Molecular Weight: 6979.5

Description:

REFLUDAN (lepirudin [rDNA] for injection) is supplied as a sterile, white, freeze-dried powder for injection or infusion and is freely soluble in water for injection or isotonic saline. The isoelectric point of lepirudin is approximately 3.7. The pH of lepirudin dissolved in 1 mL of water (50 mg/mL) is in the range of 6 - 8.

Composition

Each vial of REFLUDAN for single-use only contains 50 mg lepirudin. Other ingredients are 40 mg mannitol and sodium hydroxide for adjustment of pH to approximately 7. Contains no preservative.

Stability and Storage Recommendations

Do not use past expiry date on labels. Unopened vials of REFLUDAN should be stored between 2°C and 25°C.

Reconstituted Solutions

REFLUDAN should not be mixed with other drugs or diluents except for Water for Injection USP, 0.9% Sodium Chloride Injection USP or 5% Dextrose Injection.

For reconstitution, Water for Injection or 0.9% Sodium Chloride Injection USP are to be used. For further dilution, 0.9% Sodium Chloride Injection USP or 5% Dextrose Injection are to be used.

To prepare REFLUDAN for intravenous bolus injection or intravenous infusion, refer to **DOSAGE AND ADMINISTRATION: III. Administration** for diluent volumes.

Once reconstituted, it is recommended that REFLUDAN be used immediately. The reconstituted solution remains stable for up to 24 hours between 2°C and 25°C.

Intravenous admixtures should be inspected visually for clarity, particulate matter, precipitate, discolouration and leakage prior to administration whenever solution and container permit.

AVAILABILITY OF DOSAGE FORMS

REFLUDAN (lepirudin [rDNA] for injection) is supplied as a sterile, white, freeze-dried powder for intravenous injection or infusion in 2 mL injection vials containing 50 mg lepirudin. Available in packages of 10 vials.

PHARMACOLOGY

Animal Pharmacology

Pharmacodynamics

In Vitro Studies

In vitro studies with human and dog blood revealed that lepirudin increased aPTT, thromboelastogram (TEG), and thrombin time and decreased Quick values and thrombus stability (concentrations ≥ 0.001 mg/mL), but did not alter hematologic parameters or platelet aggregation (concentrations ≤ 1 mg/mL). Lepirudin neutralized thrombin in solution as well as thrombin bound to fibrin. The antithrombotic effects of lepirudin and heparin were comparable in standard human plasma. Adverse effects on dog and human blood cells were not observed.

Lepirudin had no pharmacologic effects on isolated organs of the guinea pig (ileum, atria and trachea) or the rat (uterus and vas deferens).

In Vivo Studies

Dose dependent prolongations of thrombin time were observed following single i.v. doses of lepirudin (0.031-10 mg/kg) in rats, dogs, cats and monkeys. Intravenously administered lepirudin slightly increased aPTT in all species, increased thromboplastin time in monkeys and increased parameters of thromboelastography in cats, dogs and monkeys. With single s.c. doses of lepirudin (0.031-10 mg/kg), dose-dependent prolongations of thrombin time were observed in rats, dogs and monkeys. Partial thromboplastin time was only slightly affected. Oral and intraduodenal administration in monkeys yielded no effects on coagulation.

The antithrombotic efficacy of lepirudin was investigated in several models of induced thrombosis, including the laser induced thrombus model, and the wire coil model. Dose-dependent thromboinhibitory effects were observed following single i.v. doses of lepirudin in rats, rabbits, dogs and monkeys, and following single s.c. doses in rats and rabbits. Thromboinhibitory effects were also observed following a 10 hour infusion in rats (40 or 80 $\mu\text{g}/\text{kg}/\text{min}$) and a 4-hour infusion in dogs (0.1-10.0 mg/kg). Antithrombotic effects were time-dependent in rats treated with a single i.v. dose of 0.25 mg/kg lepirudin prior to thrombus induction. After a single dose of 0.1 mg/kg i.v. inhibition of thrombus formation was maintained during the observation period of 4 hours.

Coagulant complex anti-inhibitor was effective in inhibiting lepirudin (0.1 mg/kg) induced prolongation of coagulation time in rabbits, with complete inhibition following doses of 50-100 U/kg, and with some inhibition also seen at a dose of 25 U/kg. In pigs receiving a lepirudin infusion of 0.3 mg/kg/h for seven hours, normalization of bleeding time was achieved within one hour by administration of von Willebrand factor preparations (66 U/kg), without affecting the antithrombotic action of lepirudin, as demonstrated by aPTT and prothrombin time prolongation.

Lepirudin exerted no remarkable effects on physiological organ systems, except for its pharmacodynamic effect on coagulation. Intravenous doses of ≤ 100 mg/kg in mice had no effect on central nervous system function or on gastrointestinal transit time. In rats, water and electrolyte excretion were not affected at doses ≤ 100 mg/kg i.v. A single dose of 1 mg/kg i.v. had no appreciable effect on blood glucose values in rats or rabbits. No anti-inflammatory effect on carrageenan-induced paw edema was observed in rats at doses of 1 mg/kg (pretreatment) or 3 mg/kg (following carrageenan injection). No changes in arterial blood

pressure and/or heart rate were observed in cats or rats following a single i.v. injection of 1 or 10 mg/kg, respectively.

Pharmacokinetics

Disposition of single doses of lepirudin in plasma was rapid and essentially dose-independent in all animal species studied, and could be described by a two-compartmental model, with $t_{1/2\alpha}$ ranging from 0.1 to 0.35 h and $t_{1/2\beta}$ ranging from 0.66 to 1.86 h (3.2 h in one monkey study). Dose normalized AUCs after intravenous administration were found to be approximately 1100, 1700, 4500, 4600 and 6300 ng•h/mL for rats, rabbits, rhesus monkeys, cynomolgus monkeys and man, respectively. These data indicate that clearance values were similar between monkeys and man, but were moderately higher in rabbits, and markedly higher in rats. In all species, the volume of distribution was only moderately greater than the extracellular fluid volume, indicating no extensive distribution of lepirudin.

Species	Rat	Rabbit	Monkey (Rhesus)	Monkey (Cynomolgus)	Monkey (Cynomolgus)	Man
Dose	1 mg/kg	1 mg/kg	1 mg/kg	1 mg/kg	10 mg/kg	0.4 mg/kg
No. / Sex	3/M	3/M+F	3/M	4/M+F	4/M+F	9/M+F
C_{max} (ng/mL)	3200	4500	2900	9690	78740	2924
t_{max} (h)	0.08	0.08	0.25	0.08	0.08	0.17
AUC _{0-∞} (ng•h/mL)	1140	1740	4460	4620	33100	2500
AUC/Dosage (mL/min/kg)	1140	1740	4460	4620	3310	6250
CL/f (mL/min/kg)	14.7	9.8	4.3	3.7	5.2	2.7
V _{ss} (L/kg)	0.68	0.45	-	0.52	0.40	0.24
$t_{1/2\alpha}$ (h)	0.1	0.13	0.35	0.17	0.13	0.24
$t_{1/2\beta}$ (h)	0.66	0.80	1.08	3.22	1.86	1.33

Distribution in the rat after i.v. administration of (3-tyrosinyl-¹²⁵I)-labelled lepirudin was rapid, with highest levels of radioactivity in the kidneys and urinary bladder, and moderate levels in plasma, lung and thyroid gland. Except for plasma, kidneys and urinary bladder, all other organs showed lower radioactivity concentrations (µg-equiv./g) than blood. Concentrations in the brain were low, indicating that lepirudin did not readily cross the blood brain barrier. Following administration of 1 mg/kg radiolabelled lepirudin in 14th and 18th day pregnant rats, tissue distribution in dams was comparable to that seen in non-pregnant rats, with placenta levels close to blood levels. However, radioactivity in the fetus was at background levels, indicating little or no passage across the placental barrier.

Plasma protein binding of lepirudin (2 µg/mL) was approximately 3% in human plasma and 4% in monkey plasma using equilibrium dialysis at 37°C.

It is thought that lepirudin is metabolized by sequential cleavage of terminal amino acids by kidney exoproteases having carboxypeptidase and dipeptidase-like activity. Metabolism of lepirudin yielded similar patterns for monkeys and man, with the three primary urinary metabolites (in addition to lepirudin) retaining biological activity.

The main route of elimination was urinary excretion. Following a 1 mg/kg dose in rats, dogs and cynomolgus monkeys, approximately 70%, 78-86% and 75-90%, respectively, of radioactivity was excreted in 24 hours. Unchanged drug accounted for 0% of urinary excretion in rats and 67% in cynomolgus monkeys.

Neither autoradiography nor tissue-level analyses revealed any signs of long-term accumulation. No accumulation was observed after multiple dosing in rats (1-100 mg/kg for 28 days), rabbits (1-100 mg/kg for 28 days) or monkeys (1-30 mg/kg for 90 days), except in monkeys that formed antibodies against lepirudin following 90 daily doses. In monkeys with antibody formation, there was a pronounced decrease in lepirudin clearance associated with an increase in AUC (median ratio of Day 90/Day 1 values = 1.8) and an increase in terminal half-life (median ratio of Day 90/Day 1 values = 1.8) relative to single dosing. These changes were not observed in animals without antibody formation. aPPT trough levels appeared to increase for animals with positive antibody levels.

Clinical Trials

I. Acute Coronary Syndromes

Two large-scale clinical trials were conducted to study the efficacy and safety of REFLUDAN in the management of patients with acute coronary syndromes (unstable angina/acute myocardial infarction without ST elevation). In both trials, REFLUDAN was compared to unfractionated heparin in the presence of ASA.

OASIS-2 (Organization to Assess Strategies for Ischemic Syndromes)

The OASIS-2 trial was a double-blind, randomized trial of REFLUDAN versus heparin in 10,141 patients in 15 countries. The patients were randomized to receive a 72-hour treatment with REFLUDAN (bolus: 0.4 mg/kg, infusion: 0.15 mg/kg/hour) or standard unfractionated heparin (bolus: 5,000 U, infusion: 15 U/kg/hour). Patients were to take ASA (325 mg/day while in hospital and 80-325 mg/day after discharge from hospital). The dosage of study medication was adjusted starting 6 to 8 hours after the start of infusion in order to keep the aPTT within the target range of 60 to 100 seconds. Additionally, infusion rates were adjusted for renal function where necessary. Approximately 24 hours into the infusion, eligible patients were randomized to a warfarin substudy.

Patients with typical chest pain suspected to represent unstable angina or acute myocardial infarction (MI) without ST elevation were eligible for the study if they presented within 12 hours from the onset of the most recent episode of chest pain. Admission ECG changes consistent with ischemia were required for all patients under the age of 60. Patients >60 years could be included without ECG changes if they had other objective evidence of coronary artery disease (CAD) such as history of prior MI, chronic unstable angina, revascularization procedure, cardiac catheterization showing significant CAD, or positive exercise stress test. Major exclusion criteria included active bleeding or high risk of bleeding, recent stroke (<1 year), known renal impairment (serum creatinine >2.0 mg/dL), recent percutaneous transluminal coronary angioplasty (PTCA) (<6 months), suspected MI with ST elevation, planned thrombolysis or direct PTCA, cardiogenic shock requiring inotropic agents, history of heparin-induced thrombocytopenia, and age <21 and >85 years.

Mean patient age was 64 years (range 22 to 86 years); 50% of the patients were older than 65 years; and 61% were male; 81% were Caucasian, 13% Latin American, and 6% black,

south/other Asian, or other. The recruitment pattern was Western Europe 27%, US and Canada 20%, Eastern Europe 20%, Latin America 17%, and Australia/Israel/South Africa 16%.

Efficacy results of OASIS-2 included the combined incidence of cardiovascular (CV) death or new MI up to Day 7 (primary endpoint) and the combined incidence of CV death, new MI, or refractory angina up to Day 7 (secondary endpoint). Additional analyses for these composite endpoints included the incidences at 72 hours, Day 35, and Day 180 as well as times to first event. Furthermore, the incidences of cardiac interventions and radiological evidence of heart failure that was not associated with the event leading to admission to the trial were assessed. All deaths, MIs, and refractory angina events were centrally adjudicated by a blinded adjudication committee.

The findings for the double composite endpoint of CV death or new MI and the triple composite endpoint of CV death, new MI, or refractory angina were as follows (Table 13):

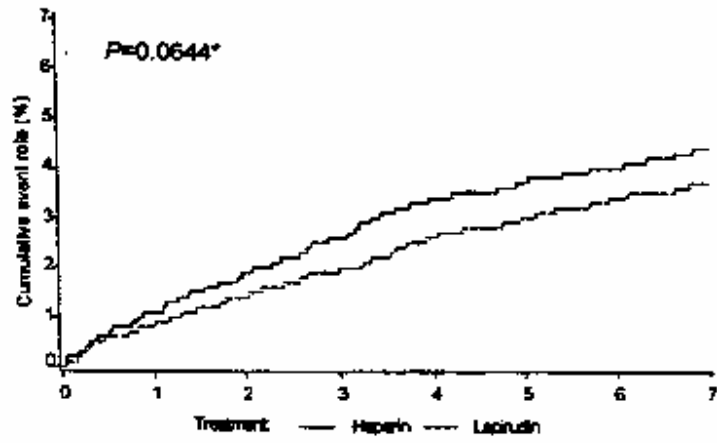
Table 13: OASIS-2 efficacy results for double and triple endpoints						
Composite endpoint	n (%) of patients with events				Relative risk (95% CI)	p-value
Time period	REFLUDAN n=5,045		Heparin n=5,033			
CV death or new MI						
Up to 72 hours	99	(2.0%)	132	(2.6%)	0.74 (0.57 - 0.97)	0.0229
Up to 7 day	178	(3.5%)	211	(4.2%)	0.83 (0.68 - 1.02)	0.0714
Up to 35 days	337	(6.7%)	377	(7.5%)	0.88 (0.76 - 1.03)	0.0896
Up to 180 days	517	(10.2%)	541	(10.7%)	0.95 (0.83 - 1.08)	0.3377
CV death, new MI, refractory angina						
Up to 72 hours	154	(3.1%)	199	(4.0%)	0.76 (0.62 - 0.95)	0.0108
Up to 7 days	279	(5.5%)	336	(6.7%)	0.82 (0.69 - 0.96)	0.0138
Up to 35 days	633	(12.5%)	675	(13.4%)	0.92 (0.82 - 1.04)	0.16
Up to 180 days	1,026	(20.3%)	1,055	(21.0%)	0.96 (0.87 - 1.06)	0.3559

In OASIS-2, 17% fewer REFLUDAN than heparin patients experienced the primary endpoint of CV death or new MI at Day 7 (double composite endpoint: 3.5% vs 4.2%; $p = 0.0714$). The incidence of the secondary endpoint of CV death, new MI or refractory angina at Day 7 was significantly reduced by 18% (triple composite endpoint: 5.5% vs 6.7%; $p = 0.0138$). The effects were predominantly achieved during the 72-hour treatment period. At the end of treatment, the relative risk reductions were 26% for the double composite endpoint (2.0% vs 2.6%; $p = 0.0229$) and 24% for the triple composite endpoint (3.1% vs 4.0%; $p = 0.0108$). The

early absolute benefit of REFLUDAN was well preserved over time up to Day 180. When all-cause mortality rather than CV death was considered in the composite endpoints, the findings for both composite endpoints were further improved for REFLUDAN at Day 35 and Day 180.

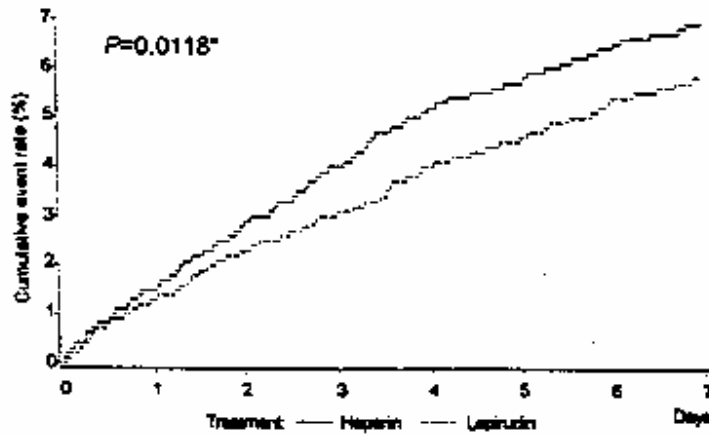
Time to event analyses for the double and triple composite endpoints support the early absolute reduction of events with REFLUDAN compared to heparin. The Kaplan-Meier analysis shows early separation; this effect was maintained to Day 180.

Fig 1: CV death or new MI to Day 7



*Log-rank test

Fig 2: CV death, new MI, or refractory angina to Day 7



*Log-rank test

The incidence of all individual components (CV death, new MI, and refractory angina) of the composite endpoints was lower in the REFLUDAN group than in the heparin group at all time points. In the double composite endpoint, the relative contribution of new MI to the overall beneficial effect of REFLUDAN was stronger than that of CV death (absolute difference between treatment groups: 25 MIs and 8 CV deaths). In the triple composite endpoint, the incidence of refractory angina contributed to the beneficial effect of REFLUDAN compared to heparin at Day 7 to the same extent as new MI (absolute difference between treatment groups: 24 episodes of refractory angina).

Fewer REFLUDAN patients (6.7%) than heparin patients (8.1%) required early therapeutic cardiac interventions (other than cardiac catheterization) up to Day 7 after randomization ($p = 0.0109$). From Day 2 through Day 7, the incidence of radiological evidence of heart failure that was not associated with the event leading to admission to the trial was significantly lower in REFLUDAN patients than in heparin patients (1.8% vs 2.7%; $p = 0.0064$).

Treatment with warfarin did not significantly affect the efficacy and safety outcomes of this trial.

OASIS-1 (Organization to Assess Strategies for Ischemic Syndromes)

The dose-finding OASIS-1 trial enrolling 909 patients had a very similar design to OASIS-2. Patients were randomized to receive a 72-hour treatment with standard unfractionated heparin (bolus: 5,000 U, infusion: 1,000-1,200 U/hour) or two different doses of REFLUDAN (lower dose: bolus 0.2 mg/kg, infusion 0.10 mg/kg/hour; higher dose: bolus 0.4 mg/kg, infusion 0.15 mg/kg/hour) in addition to ASA.

In OASIS-1, a primary analysis of efficacy was the quadruple endpoint of CV death, new MI, refractory angina, or severe angina at Day 7. This endpoint was significantly reduced in the REFLUDAN group by 44% (9.4% vs 15.6%; $p = 0.0176$). The relative risk reduction for the double and triple endpoints at Day 7 were of similar magnitude compared to the quadruple endpoint. At all other time points up to the end of study, the number of double, triple and quadruple endpoints was also lower with REFLUDAN (0.15 mg/kg/hour) compared to heparin.

In the combined analyses of OASIS-1 (all doses) and OASIS-2, REFLUDAN was significantly more effective than heparin in the treatment of unstable angina or acute MI without ST elevation (Table 14).

Table 14: Clinical Trials OASIS-1 and OASIS-2: combined efficacy results for double and triple endpoints						
Composite endpoint	n (%) of patients with events				Relative risk (95% CI)	p-value
Time period	REFLUDAN n=5,583		Heparin n=5,404			
CV death or new MI						
Up to 72 hours	108	(1.9%)	142	(2.6%)	0.73 (0.56 - 0.94)	0.0132
Up to Day 7	192	(3.4%)	229	(4.2%)	0.8 (0.66 - 0.98)	0.0268
Up to Day 35	369	(6.6%)	408	(7.5%)	0.86 (0.74 - 1.00)	0.0434
CV death, new MI, refractory angina						
Up to 72 hours	166	(3.0%)	214	(4.0%)	0.74 (0.60 - 0.91)	0.0039
Up to Day 7	299	(5.4%)	360	(6.7%)	0.79 (0.68 - 0.93)	0.0043
Up to Day 35	672	(12.0%)	714	(13.2%)	0.9 (0.81 - 1.01)	0.0769

In these analyses, REFLUDAN significantly reduced the incidence of CV death or new MI at all time points up to Day 35. The absolute difference in event rates (expressed as the percentage of patients in each treatment group) observed up to 72 hours, Day 7, Day 35, and end of study was 0.7%, 0.8%, 0.9%, and 0.7%, respectively, for the double composite endpoint and 1.0%, 1.3%, 1.2%, and 1.2%, respectively, for the triple composite endpoint, indicating stability of the results over time.

II. Heparin Induced Thrombocytopenia

Heparin induced thrombocytopenia (HIT) (also referred to as heparin-associated thrombocytopenia type II or HAT type II) is described as an immune mediated adverse reaction to heparin. It occurs in about 1-2% of patients treated with heparin for more than four days. The clinical picture of HIT is characterized by thrombocytopenia alone or in combination with thromboembolic complications (TECs), comprising 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 necrosis 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%.

The efficacy of REFLUDAN in reducing the risk of the serious sequelae of HIT was demonstrated in two prospective, historically controlled clinical trials (“HAT-1” and “HAT-2”), which were comparable in study design and dosing, and used the same historical control group

for comparison. This historical control group was mainly compiled from a recent retrospective European registry of HIT patients.

Overall, 198 patients (HAT-1: 82; HAT-2: 116) were treated with REFLUDAN and 182 historical control patients were treated with other therapies. All except 5 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 REFLUDAN patients (HAT-1: 54; HAT-2: 59) and 91 historical control patients both 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 15 summarizes the demographic baseline characteristics of patients presenting with TECs at baseline.

Table 15: Demographic Baseline Characteristics of Patients Presenting With TECs			
	REFLUDAN		Historical
	Study HAT-1 (n=54)	Study HAT-2 (n=59)	
males	27.8%	44.1%	35.2%
females	72.2%	55.9%	64.8%
age < 65 years	63.0%	67.8%	44.0%
age ≥ 65 years	37.0%	32.2%	56.0%
mean age ± SD (years)	57 ± 17	58 ± 12	64 ± 14

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 16. 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 16: Proportions of Laboratory Responders Among REFLUDAN Patients Presenting with TECs		
	Study HAT-1	Study HAT-2
number of evaluable patients	55	60
platelet recovery	90.9%	95.0%
effective anticoagulation	81.8%	75.0%
both	72.7%	71.7%

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

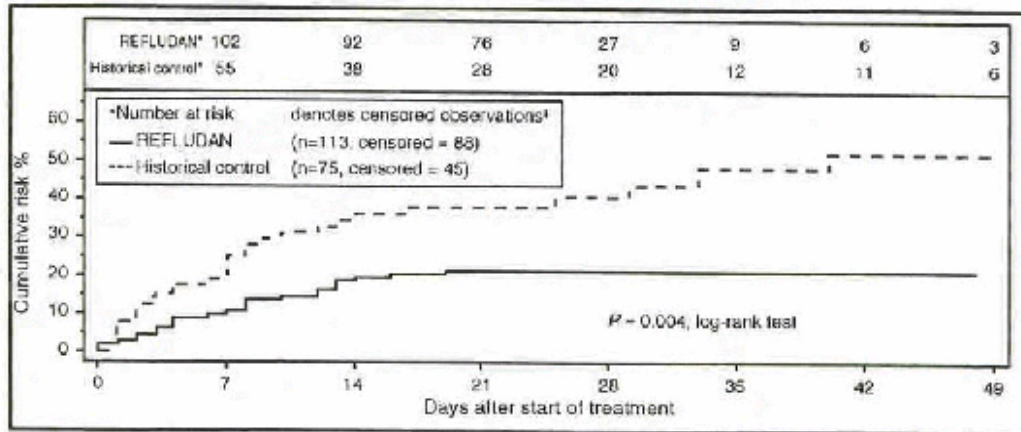
The original main analyses included all events that occurred after laboratory confirmation of HIT. This approach revealed to be substantially confounded by the relative contribution of the pretreatment period (time between laboratory confirmation of HIT and start of treatment). Although short in duration (mean length 1.5 days in HAT-1 and 2.0 days in HAT-2), the pretreatment period accounted for 45% and 26% of events observed in the main analyses of HAT-1 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 ($p=0.851$). 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 ($p=0.792$). 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 ($p=0.005$). As shown in Figure 3, differences in the cumulative risk of death, limb amputation, or new TECs 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 statistically significant reduction in the cumulative risk

of death, limb amputation, or new TECs was mainly due to a statistically significant reduction in the new TECs. The incidences of death and limb amputations showed numerical but not statistically significant differences compared to the historical control in favour of REFLUDAN.

Figure 3: Cumulative Risk of Death, Limb Amputation, or New Thromboembolic Complication After Start of Treatment



(Kaplan-Meier curves)

† Censored observations: Patients who did not reach a disease endpoint during their period of follow-up

The immediate impact of treatment on the combined risk of death, limb amputation or new TEC is demonstrated by comparing pretreatment period and treatment period with regard to average combined event rates per patient day. In the pretreatment 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 REFLUDAN treated patients, where they dropped by 93% to 0.005 (HAT-1) and by 65% to 0.018 (HAT-2), while there was only a moderate decrease by 25% to 0.030 in the historical control group.

TOXICOLOGY

Acute Toxicity

The acute toxicity of intravenous doses of lepirudin was investigated in mice (0.1-1000 mg/kg), rats (1-1000 mg/kg) and monkeys (1-100 mg/kg). No toxicity was observed up to the highest doses administered in each species.

The acute toxicity of subcutaneously administered lepirudin was also investigated in mice (1-1250 mg/kg) and rats (1-500 mg/kg). No toxicity was observed up to the highest dose administered in each species. One rat in the 100 mg/kg group died due to rapid blood loss in the subcutaneous tissue. Local injection site reactions, consisting of hemorrhages, hematomas

and/or nodules, were seen in mice at doses of 500 mg/kg s.c. and higher, and in rats at doses of 10 mg/kg s.c. and higher. These were attributed to the pharmacologic action of lepirudin.

Chronic Toxicity

Chronic toxicity studies were conducted in rats and monkeys and revealed no specific toxic effects of lepirudin. Findings were generally a consequence of the antithrombotic action of lepirudin.

Table 17: Chronic Toxicity Studies in the Rat			
Duration	Route	Dose (mg/kg/day)	Key Findings
72 h	i.v. bolus and infusion	0.2 or 0.4 mg/kg bolus + 0.10 or 0.15 mg/kg/h infusion for 72 h	Well tolerated with no treatment related toxic manifestations or mortality.
1 month	s.c.	1, 10, 100	1 and 10 mg/kg doses well tolerated. Hematoma and swelling/nodule formation at injection site of all treatment groups. Death in 6 animals in the 100 mg/kg group due to excessive bleeding. Histopathological changes in these animals consistent with antithrombotic effects of lepirudin.
	i.v. bolus	10, 100	Both doses well tolerated. Local bleeding and necrosis, increased spleen weights, decreased erythrocyte, hemoglobin and hematocrit values, and reddened/enlarged iliac lymph nodes seen at 100 mg/kg dose. Dose-dependent sinus catarrh in regional lymph nodes observed. Increased erythropoiesis in bone marrow and extramedullary hematopoiesis in liver and spleen seen in one 100 mg/kg animal.
3 months	s.c.	0.4, 2, 10	0.4 and 2 mg/kg doses well tolerated. 10 mg/kg dose resulted in mortality in 4/30 animals, increased thrombin times, decreased RBC parameters, increased reticulocyte counts, increased inorganic phosphorus, increased erythropoiesis and severe hemorrhage/ hematoma at injection sites.
	i.v. bolus	1, 10, 100	1 mg/kg dose well tolerated. Deaths of 2/24 and 9/36 animals in 10 and 100 mg/kg groups due to anemia, hemoperitoneum and/or hemorrhages. Histopathological findings were dose-dependent increase of hemosiderin deposits in spleen, increased erythropoiesis in spleen and bone marrow, and hemorrhage and inflammatory reaction at injection site accompanied by moderate sinus histiocytosis in regional lymph node.

Table 18: Chronic Toxicity Studies in the Monkey			
Duration	Route	Dose (mg/kg/day)	Key Findings
72 h	i.v. bolus and infusion	0.2 or 0.4 mg/kg bolus + 0.10 or 0.15 mg/kg/h infusion for 72 h	Well tolerated, with no treatment related toxic manifestations or mortality.
7 days (2 days in 50 mg/kg group)	i.v. bolus	0.1, 1, 10, 50	All doses well tolerated, with no treatment related toxic manifestations or mortality. Hematomas at blood collection sites in 50 mg/kg animals.
14 days	i.v. bolus and infusion	0.4 mg/kg bolus + 14 day infusion of 0.15 mg/kg/h	Well tolerated, with no treatment related toxic manifestations or mortality.
1 month	i.v. bolus	0.1, 1, 10	All doses well tolerated. Transient focal retinopathy and focal pinpoint retinal hemorrhages observed at 10 mg/kg. Transient unilateral or bilateral focal pinpoint retinal hemorrhages also noted at 1 mg/kg.
3 months	i.v.	1, 10, 30	1 mg/kg well tolerated. 1/8 and 3/12 monkeys in 10 and 30 mg/kg groups died due to internal bleeding and anemia. Moderate to marked anemia seen at 10 and 30 mg/kg. Injection site hematomas dose-related in severity.
	s.c.	0.3, 3, 30 (given in two divided doses at 8 h intervals)	0.3 and 3 mg/kg doses generally well tolerated. At 30 mg/kg, signs of anemia, loss of appetite, extensive bleeding at injection sites, external/internal hemorrhages and hematomas, and death/sacrifice of 2/8 animals.

Local Tolerance

Lepirudin was well tolerated by rabbits after single intravenous (25 mg in 0.5 mL), subcutaneous (5-50 mg in 0.5 mL), intra-arterial (25 mg in 0.5 mL) and paravenous (5 mg in 0.1 mL) injections, as well as after multiple (8 mg in 0.5 mL once daily for seven days) intravenous injections. Perivascular redness and/or slight bleeding was observed in some treated animals, but similar findings were also often found in controls. These observations were attributed to the pharmacologic effects of lepirudin.

Antigenicity

Guinea pigs were tested for sensitizing properties by using dermal challenge with lepirudin after two intradermal and one dermal inductions. Intradermal induction was performed both with and without complete Freund's adjuvant (CFA). CFA and lepirudin/CFA caused severe dermal reactions, while lepirudin without CFA produced no evidence of allergic reactions, indicating no evidence of sensitization potential.

In a series of immunization experiments in guinea pigs, anaphylactic reactions and death were observed in nearly all animals following challenge with an intravenous dose of 1.0 mg/kg lepirudin in animals that were immunized with subcutaneous doses of lepirudin (0.1 or 1.0 mg) in CFA. Improved tolerance to lepirudin was observed in challenged animals immunized with

0.1, 1 or 5 mg lepirudin s.c. without CFA, indicating that lepirudin has a weak sensitizing potential, but that the severe anaphylactic reactions were due to the CFA.

In Guinea pigs immunized with lepirudin (0.1, 1.0 or 5.0 mg, s.c. on Day 0, 7 and 14) without the presence of CFA and rechallenged for a second time on Day 42 following the first challenge on Day 28 with Lepirudin (1.0 mg/kg, i.v.), anaphylactic reactions (death, reversible shock-like symptoms and redness in the ears) were observed in the high dose (5.0 mg) group.

Guinea pigs were injected with three s.c. doses of 1 or 5 mg lepirudin at weekly intervals and challenged two weeks after the last dose with 1 mg lepirudin; anti-hirudin antibodies were detected in nearly all animals and titers increased after the challenge. With the exception of a respiratory reaction in one animal in the 5 mg group, the lepirudin challenge was well tolerated.

Anti-hirudin antibodies were detected in rabbits that had been immunized with 5 mg lepirudin and CFA on Days 1, 8, 22 and 29. Initial onset of antibody formation was on Days 11-15 with peak levels on Day 22. No clear evidence of antibody formation was achieved in rabbits receiving i.v. injections of 5 mg lepirudin in Aerosil® on Days 1-5 and again on Days 22-26. Similar findings were observed in monkeys that had been immunized with lepirudin and CFA: anti-hirudin antibodies were produced and serious toxicity was observed. No such effects were detected in monkeys that had not received adjuvant. Nevertheless, it should be noted that in the 13-week i.v. toxicity study in monkeys, formation of anti-hirudin antibodies in several monkeys resulted in a prolongation of terminal half-life and an increase of AUC plasma values of lepirudin (see **PHARMACOLOGY: Animal Pharmacology - Pharmacokinetics**).

Reproductive Toxicity

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 body surface area).

Teratology studies with lepirudin performed in pregnant rats 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 body surface area) and in pregnant rabbits at intravenous doses up to 30 mg/kg/day (360 mg/m²/day, 2.4 times the recommended maximum human total daily dose based on body surface area) have revealed no teratogenic effects at any dose level. In the rabbits receiving 30 mg/kg/day, the post-implantation loss was higher than that of the control group (34.5% vs. 8.3%; p<0.001) and the mean number of live fetuses was consequently lower than that of the control group (6.3 vs. 8.9). The No Observable Effect Level for embryofetal development was thus 30 mg/kg/day for rats and 10 mg/kg/day for rabbits.

Following intravenous administration of lepirudin at 30 mg/kg/day (180 mg/m²/day, 1.2 times the recommended maximum human total daily dose based on body surface area) during organogenesis and perinatal-postnatal periods, pregnant rats showed an increased maternal mortality generally associated with dystocia and bleeding at delivery. An increased incidence of dilation of the renal pelvis (10.4%) and a reversible developmental delay occurred in surviving pups from the dams in the 30 mg/kg/day group; postweaning parameters were normal in this dose group. The No Observable Effect Level for pre- and postnatal development was 10 mg/kg/day.

Mutagenicity and Carcinogenicity

Lepirudin was not genotoxic in the Ames test, the Chinese hamster cell (V79/HGPRT) forward mutation assay, the A549 human cell line unscheduled DNA synthesis (UDS) assay, the Chinese hamster V79 cell chromosome aberration test, or the mouse micronucleus test. Long-term animal studies to evaluate the potential for carcinogenesis have not been performed with lepirudin.

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