ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Refludan 20 mg powder for solution for injection or infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains 20 mg lepirudin.

(Lepirudin is a recombinant DNA product derived from yeast cells)

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder for solution for injection or infusion.

White to almost white lyophilised powder.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Anticoagulation in adult patients with heparin-induced thrombocytopenia (HIT) type II and thromboembolic disease mandating parenteral antithrombotic therapy.

The diagnosis should be confirmed by the HIPAA (heparin induced platelet activation assay) or an equivalent test.

4.2 Posology and method of administration

Treatment with Refludan should be initiated under the guidance of a physician with experience in coagulation disorders.

Initial dosage

Anticoagulation in adult patients with HIT type II and thromboembolic disease:

– 0.4 mg / kg body weight intravenously as a bolus dose
– followed by 0.15 mg / kg body weight / hour as a continuous intravenous infusion for 2 - 10 days or longer if clinically needed.

Normally, the dosage depends on the patient's body weight. This is valid up to a body weight of 110 kg. In patients with a body weight exceeding 110 kg the dosage should not be increased beyond the 110 kg body weight dose (see also tables 2 and 3, below).

Monitoring and modification of the Refludan dosage regimen

Standard recommendations

Monitoring:
– In general, the dosage (infusion rate) should be adjusted to the activated partial thromboplastin time, aPTT.
– The first aPTT determination should be done 4 hours after start of Refludan therapy.

– The aPTT should be monitored at least once daily. More frequent determinations may be necessary, for example, in patients with renal impairment or with an increased risk of bleeding.
– Target range (therapeutic window) for the aPTT:
  - Using "Actin FS" or "Neothromtin" on automated coagulometers the target range for the aPTT is 1.5 fold to 3 fold prolongation of the normal control value.
  - With other reagents, the upper limit of the therapeutic aPTT window should be reduced to 2.5 fold prolongation of the normal control value.
  - To obtain specific and exact aPTT limits, the laboratory equipment / test reagent used may be calibrated by spiking standardised human plasma with 0.15 µg/ml lepirudin (lower limit) and 1.5 µg/ml lepirudin (upper limit).

Dose modifications:
– 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.
– If the confirmed aPTT value is above the target range, the infusion should be stopped for two hours. At restart, the infusion speed should be decreased by 50 % (no additional intravenous bolus should be administered). The aPTT should be determined again 4 hours later.
– If the confirmed aPTT value is below the target range, the infusion speed should be increased by 20 %. The aPTT should be determined again 4 hours later.
– In general, an infusion rate of 0.21 mg/kg/hour should not be exceeded without checking for coagulation abnormalities which might be preventing an appropriate aPTT response.

Recommendations for use in patients scheduled for a switch to oral anticoagulation

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 (see oral anticoagulant package insert for information). The parenteral agent can be discontinued when the International Normalised Ratio (INR) stabilises within the desired target range.

Recommendations for use in patients with renal impairment

As lepirudin is almost exclusively excreted and metabolised renally (see also section 5.2), the patient's renal function should be considered prior to administration. In case of renal impairment relative overdose might occur even under standard dosage regimen. Therefore, the bolus dose and infusion rate must be reduced in case of known or suspected renal insufficiency (creatinine clearance below 60 ml/min or creatinine value above 15 mg/l [133 µmol/l]).

In clinical trials, Refludan was not therapeutically administered to HIT type II patients with significant renal impairment. The following dosage recommendations are based on single-dose studies in a small number of patients with renal impairment. Therefore, these recommendations are only tentative.

Whenever available, dose adjustments should be based on creatinine clearance values as obtained from a reliable method (24 h urine sampling). In all other cases the dose adjustment is based on the creatinine value.

In any case, the bolus dose must be reduced to 0.2 mg / kg body weight.

The infusion rate must be reduced according to table 1. Additional aPTT monitoring is mandatory.

Table 1: Reduction of infusion rate in patients with renal impairment

Creatinine clearance [ml/min]	**Creatinine value** [mg/l (µmol/l)]	**Adjusted infusion rate** [% of original dose]
45 – 60	16 – 20 (141 - 177)	50 %
30 – 44	21 – 30 (178 - 265)	30 %
15 – 29	31 - 60 (266 - 530)	15 %
below 15*	above 60 (530)*	avoid or STOP infusion !*

* In haemodialysis patients or in case of acute renal failure (creatinine clearance below 15 ml/min or creatinine value above 60 mg/l [530 µmol/l]), infusion of Refludan is to be avoided or stopped. Only if aPTT values have fallen below the lower therapeutic limit (see Monitoring: target range), further intravenous bolus doses of 0.1 mg / kg body weight may be considered every other day.

Method of administration

Reconstitute the lyophilisate as described in section 6.6.

Initial intravenous bolus:

For intravenous bolus injection, a solution with a concentration of 5 mg/ml is needed.
Intravenous injection is to be carried out slowly.

Table 2: Examples for standard injection volume according to body weight

Body weight [kg]	**Injection volume** [ml]	
	Dosage 0.4 mg / kg body weight	**Dosage 0.2** mg / kg body weight
50	4.0	2.0
60	4.8	2.4
70	5.6	2.8
80	6.4	3.2
90	7.2	3.6
100	8.0	4.0
≥ 110	8.8	4.4

Intravenous infusion:

For continuous intravenous infusion, a solution with a concentration of 2 mg/ml is needed.
The speed of the perfusor automate [ml per hour] is to be set in a body weight dependent fashion.

Table 3: Examples for standard infusion speed according to body weight

Body weight [kg]	**Infusion speed** [ml/h]	
	Dosage 0.15 mg / kg body weight / h	**Dosage 0.1** mg / kg body weight / h
50	3.8	2.5
60	4.5	3.0
70	5.3	3.5
80	6.0	4.0
90	6.8	4.5
100	7.5	5.0
≥ 110	8.3	5.5

4.3 Contraindications

- Known hypersensitivity to lepirudin, to hirudins or to any of the excipients
- Pregnancy and lactation (see section 4.6)

Where there is active bleeding or bleeding tendency it is generally not advisable to administer Refludan. The physician should carefully weigh the risk of Refludan administration versus its anticipated benefit, taking into account possible measures to control bleeding.

This particularly includes the following situations with increased bleeding risk:

- 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
- Haemorrhagic diathesis
- Recent major surgery
- Recent bleeding (e.g. intracranial, gastrointestinal, intraocular, pulmonary)
- Overt signs of bleeding
- Recent active peptic ulcer
- Age > 65 years.

4.4 Special warnings and precautions for use

- Anaphylaxis: Refludan may cause allergic reactions including anaphylaxis and shock (see section 4.8). 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.
- In case of renal impairment relative overdose may occur even under a standard dosage regimen. Therefore, the treating physician should carefully weigh the risk of administration versus its anticipated benefit. It may be necessary to exclude patients with renal impairment from treatment with lepirudin regimen. The rate of infusion must be reduced in case of known or suspected renal insufficiency (see sections 4.2, and 5.2).
- 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 lepirudin due to coagulation defects secondary to reduced generation of vitamin K-dependent coagulation factors.
- Formation of anti-hirudin antibodies was observed in about 40 % of HIT type II patients and have been reported especially with a treatment period exceeding five days. This may result in an enhanced anticoagulant effect of lepirudin, possibly due to delayed renal elimination of active lepirudin-antihirudin complexes. Therefore, strict monitoring of aPTT is necessary also during prolonged therapy. No evidence of a neutralisation of lepirudin or of an allergic reaction associated with the positive antibody test results was found.
- Experience of combined therapy with thrombolytic agents in patients with HIT type II is very limited. Since the risk of serious bleeding is considerable in this situation, the dosage of Refludan should be substantially reduced. The optimal dose regimen of Refludan in these circumstances is not known.
- Paediatric Use: Safety and effectiveness in paediatric patients have not been established.
- Elderly: Patients of advanced age have an increased risk of bleeding complications with anticoagulation. With respect to lepirudin dosage the potential of renal impairment in elderly

patients is to be taken into account. No specific dosage adjustment is made for elderly patients. Dosing adjustments are based on renal function, weight, and aPTT (see section 4.2).

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed.

Concomitant treatment with thrombolytics (e.g. rt-PA 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) and drugs that affect platelet function may also increase the risk of bleeding.

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.

4.6 Pregnancy and lactation

The safety of Refludan for use in human pregnancy or lactation has not been established.
In a standard embryo-foetal toxicity trial, decreased pup and maternal survival was observed.

There is currently no information available on the use of Refludan during lactation.

Refludan should therefore not be administered to pregnant women or nursing mothers.

4.7 Effects on ability to drive and use machines

Not relevant.

4.8 Undesirable effects

The majority of undesirable effects experienced by patients treated with Refludan were generally related to bleeding (>1/10). Life-threatening bleeding events (including intracranial bleeding) were uncommonly reported (≥1/1,000 to <1/100) in patients with acute coronary syndrome included in clinical studies. In intensified post-marketing surveillance in HIT type II, fatal bleeding was reported in 1 % and intracranial bleeding in 0.2 % of patients

Adverse events reported on Refludan are shown in the table below:

Very common (>1/10); Common (>1/100, <1/10); Uncommon (>1/1,000 <1/100); Rare (>1/10,000 <1/1,000); Very Rare (<1/10,000)		
System Organ Class	Very common	Rare
Immune System Disorders		Anaphylactic/oid reactions
Vascular Disorders	Anemia or drop in the haemoglobin value without obvious source of bleeding Haematoma Bleeding from puncture sites Epistaxis Haematuria Gastrointestinal bleeding Vaginal bleeding Rectal bleeding Pulmonary haemorrhage Postoperative haemothorax Haemopericardium Intracranial bleeding	Hot flushes Shock including fatal shock
Respiratory, thoracic and mediastinal disorders		Cough Stridor Dyspnea
Skin and Subcutaneous Tissue Disorders		Allergic Skin Reactions (including rash) Pruritus Urticaria Angio-oedema (including: face oedema, tongue oedema, larynx oedema)
General Disorders and Administration Site Conditions		Fever Chills Injection site reactions including pain.

4.9 Overdose

In case of overdose 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 shock-therapy.

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

Results from studies in pigs showed that the application of von Willebrand Factor (vWF, 66 I.U./kg body weight) markedly reduced the bleeding time.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antithrombotic agent - direct thrombin inhibitor, ATC Code: B01AE02

Lepirudin ([Leu1, Thr2]-63-desulfohirudin) is a recombinant hirudin derived from yeast cells. The polypeptide composed of 65 amino acids has a molecular weight of 6979.5 Dalton. Natural hirudin is produced in trace amounts as a family of highly homologous iso-polypeptides by the leech *Hirudo medicinalis*.

Lepirudin is 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.

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.
As a result all thrombin dependent coagulation assays are affected, e.g. the aPTT values increase in a dose-dependent fashion.

The clinical information on HIT type II in this SPC is based upon the data of two prospective trials comprising a total of 198 HIT type II patients treated with Refludan. In the indication HIT type II with thromboembolic disease (125 patients) the overall mortality during the study period was approximately 9 % while amputations and new thromboembolic complications were recorded in 6 % and 10 %, respectively.

5.2 Pharmacokinetic properties

The pharmacokinetic properties of lepirudin following intravenous administration are well described by a two-compartment model. Distribution is essentially confined to extra-cellular 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.

Both, excretion and metabolism take place in the kidney, and about 45 % 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. In female patients the systemic clearance is about 25 % lower as compared to male patients.

In elderly patients the systemic clearance of lepirudin is about 25 % lower as compared to younger patients. Age alone causes a 7 % reduction in clearance from the age of 30 to 70 years. The majority of the difference in clearance between young and elderly patients is due to the differences in renal function. In patients with terminal renal insufficiency prolonged elimination half-lives of about 2 days were observed.

5.3 Preclinical safety data

General toxicity
Single and repeat-dose toxicity studies in mice, rats and monkeys showed the adverse responses that could be expected from an exaggerated pharmacodynamic impact of lepirudin. In monkeys retinal haemorrhages occurred. Moreover, in rats slight to moderate sinushistiocytosis of the regional lymph nodes and decreased haemosiderin deposits in the spleen were observed. Antibodies against hirudin

which appeared in several of the treated monkeys resulted in prolongation of the terminal half-life and an increase in systemic exposure to lepirudin.

Mutagenicity
Lepirudin was not mutagenic or clastogenic in standard assays for such effects.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

– Mannitol
– Sodium hydroxide for adjustment to pH 7

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

3 years.
After reconstitution: use immediately.

6.4 Special precautions for storage

Do not store above 25°C.
Do not freeze.
Keep the vial in the outer carton.

6.5 Nature and contents of container

Injection vial:
Colourless glass vial (glass type I) sealed with bromobutyl rubber infusion stopper, plastic flip-off cap and aluminium cap.

Presentations:
– Pack with 1 vial
– Pack with 10 vials

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

General recommendations
– Reconstitution and further dilution must be carried out under sterile conditions.
– For reconstitution water for injections or sodium chloride 9 mg/ml (0.9 %) solution are to be used.
– For further dilution, sodium chloride 9 mg/ml (0.9 %) or glucose 5 % solutions are suitable.
– For rapid, complete reconstitution, inject 0.4 ml of diluent into the vacuum vial and shake it gently. On reconstitution a clear, colourless solution is usually obtained within less than 3 minutes.
– Do not use solutions which are cloudy or contain particles.
– The reconstituted solution is to be used immediately.
– The preparation should be warmed to room temperature before administration.
– Any unused solution must be discarded appropriately.

– For injection only polypropylene syringes may be used.

Preparation of a Refludan solution with a concentration of **5** mg/ml
For intravenous bolus injection a solution with a concentration of 5 mg/ml is needed:
– Reconstitute one vial (20 mg of lepirudin) with 0.4 ml of either water for injections or sodium chloride 9 mg/ml (0.9 %) solution.
– The final concentration of 5 mg/ml is obtained by transfer into a sterile, single-use syringe (of at least 5 ml capacity) and further dilution to a total volume of 4 ml using sodium chloride 9 mg/ml (0.9 %) or glucose 5 % solution.
– The final solution is to be administered in a body weight-dependent fashion (see section 4.2).

Preparation of a Refludan solution with a concentration of **2** mg/ml
For continuous intravenous infusion, a solution with a concentration of 2 mg/ml is needed:
– Reconstitute two vials (each containing 20 mg of lepirudin) with 0.4 ml each using either water for injections or sodium chloride 9 mg/ml (0.9 %) solution.
– 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 20 ml using sodium chloride 9 mg/ml (0.9 %) or glucose 5 % solution.
– The infusion speed of the perfusor automate is to be set in a body weight-dependent fashion (see section 4.2).
– The perfusor syringe must be changed at least every 12 hours after the start of the infusion.

7. MARKETING AUTHORISATION HOLDER

Celgene Europe Ltd., 1 Longwalk Road, Stockley Park, Uxbridge, UB11 1DB, United Kingdom

8. MARKETING AUTHORISATION NUMBERS

EU/1/97/035/003 REFLUDAN - 20 mg - Powder for solution for injection or infusion - 1 vial
EU/1/97/035/004 REFLUDAN - 20 mg - Powder for solution for injection or infusion - 10 vials

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 13-03-1997
Date of last renewal: 05-03-2007

10. DATE OF REVISION OF THE TEXT

Detailed information on this product is available on the website of the European Medicines Agency (EMEA) http://www.emea.europa.eu

1. NAME OF THE MEDICINAL PRODUCT

Refludan 50 mg powder for solution for injection or infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains 50 mg lepirudin.

(Lepirudin is a recombinant DNA product derived from yeast cells)

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder for solution for injection or infusion.

White to almost white lyophilised powder.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Anticoagulation in adult patients with heparin-induced thrombocytopenia (HIT) type II and thromboembolic disease mandating parenteral antithrombotic therapy.

The diagnosis should be confirmed by the HIPAA (heparin induced platelet activation assay) or an equivalent test.

4.2 Posology and method of administration

Treatment with Refludan should be initiated under the guidance of a physician with experience in coagulation disorders.

Initial dosage

Anticoagulation in adult patients with HIT type II and thromboembolic disease:

– 0.4 mg / kg body weight intravenously as a bolus dose
– followed by 0.15 mg / kg body weight / hour as a continuous intravenous infusion for 2 - 10 days or longer if clinically needed.

Normally, the dosage depends on the patient's body weight. This is valid up to a body weight of 110 kg. In patients with a body weight exceeding 110 kg the dosage should not be increased beyond the 110 kg body weight dose (see also tables 2 and 3, below).

Monitoring and modification of the Refludan dosage regimen

Standard recommendations

Monitoring:
– In general, the dosage (infusion rate) should be adjusted to the activated partial thromboplastin time, aPTT.
– The first aPTT determination should be done 4 hours after start of Refludan therapy.

– The aPTT should be monitored at least once daily. More frequent determinations may be necessary, for example, in patients with renal impairment or with an increased risk of bleeding.
– Target range (therapeutic window) for the aPTT:
  - Using "Actin FS" or "Neothromtin" on automated coagulometers the target range for the aPTT is 1.5 fold to 3 fold prolongation of the normal control value.
  - With other reagents, the upper limit of the therapeutic aPTT window should be reduced to 2.5 fold prolongation of the normal control value.
  - To obtain specific and exact aPTT limits, the laboratory equipment / test reagent used may be calibrated by spiking standardised human plasma with 0.15 µg/ml lepirudin (lower limit) and 1.5 µg/ml lepirudin (upper limit).

Dose modifications:
– 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.
– If the confirmed aPTT value is above the target range, the infusion should be stopped for two hours. At restart, the infusion speed should be decreased by 50 % (no additional intravenous bolus should be administered). The aPTT should be determined again 4 hours later.
– If the confirmed aPTT value is below the target range, the infusion speed should be increased by 20 %. The aPTT should be determined again 4 hours later.
– In general, an infusion rate of 0.21 mg/kg/hour should not be exceeded without checking for coagulation abnormalities which might be preventing an appropriate aPTT response.

<u>Recommendations for use in patients scheduled for a switch to oral anticoagulation</u>

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 (see oral anticoagulant package insert for information). The parenteral agent can be discontinued when the International Normalised Ratio (INR) stabilises within the desired target range.

<u>Recommendations for use in patients with renal impairment</u>

As lepirudin is almost exclusively excreted and metabolised renally (see also section 5.2), the patient's renal function should be considered prior to administration. In case of renal impairment relative overdose might occur even under standard dosage regimen. Therefore, the bolus dose and infusion rate must be reduced in case of known or suspected renal insufficiency (creatinine clearance below 60 ml/min or creatinine value above 15 mg/l [133 µmol/l]).

In clinical trials, Refludan was not therapeutically administered to HIT type II patients with significant renal impairment. The following dosage recommendations are based on single-dose studies in a small number of patients with renal impairment. Therefore, these recommendations are only tentative.

Whenever available, dose adjustments should be based on creatinine clearance values as obtained from a reliable method (24 h urine sampling). In all other cases the dose adjustment is based on the creatinine value.

In any case, the bolus dose must be reduced to 0.2 mg / kg body weight.

The infusion rate must be reduced according to table 1. Additional aPTT monitoring is mandatory.

Table 1: Reduction of infusion rate in patients with renal impairment

Creatinine clearance [ml/min]	**Creatinine value** [mg/l (µmol/l)]	**Adjusted infusion rate** [% of original dose]
45 – 60	16 – 20 (141 - 177)	50 %
30 – 44	21 – 30 (178 - 265)	30 %
15 – 29	31 - 60 (266 - 530)	15 %
below 15*	above 60 (530)*	avoid or STOP infusion !*

* In haemodialysis patients or in case of acute renal failure (creatinine clearance below 15 ml/min or creatinine value above 60 mg/l [530 µmol/l]), infusion of Refludan is to be avoided or stopped. Only if aPTT values have fallen below the lower therapeutic limit (see Monitoring: target range), further intravenous bolus doses of 0.1 mg / kg body weight may be considered every other day.

Method of administration

Reconstitute the lyophilisate as described in section 6.6.

Initial intravenous bolus:

For intravenous bolus injection, a solution with a concentration of 5 mg/ml is needed.
Intravenous injection is to be carried out slowly.

Table 2: Examples for standard injection volume according to body weight

Body weight [kg]	**Injection volume** [ml]	
	Dosage 0.4 mg / kg body weight	**Dosage 0.2** mg / kg body weight
50	4.0	2.0
60	4.8	2.4
70	5.6	2.8
80	6.4	3.2
90	7.2	3.6
100	8.0	4.0
≥ 110	8.8	4.4

Intravenous infusion:

For continuous intravenous infusion, a solution with a concentration of 2 mg/ml is needed.
The speed of the perfusor automate [ml per hour] is to be set in a body weight dependent fashion.

Table 3: Examples for standard infusion speed according to body weight

Body weight [kg]	**Infusion speed** [ml/h]	
	Dosage 0.15 mg / kg body weight / h	**Dosage 0.1** mg / kg body weight / h
50	3.8	2.5
60	4.5	3.0
70	5.3	3.5
80	6.0	4.0
90	6.8	4.5
100	7.5	5.0
≥ 110	8.3	5.5

4.3 Contraindications

– Known hypersensitivity to lepirudin, to hirudins or to any of the excipients
– Pregnancy and lactation (see section 4.6)

Where there is active bleeding or bleeding tendency it is generally not advisable to administer Refludan. The physician should carefully weigh the risk of Refludan administration versus its anticipated benefit, taking into account possible measures to control bleeding.

This particularly includes the following situations with increased bleeding risk:
– 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
– Haemorrhagic diathesis
– Recent major surgery
– Recent bleeding (e.g. intracranial, gastrointestinal, intraocular, pulmonary)
– Overt signs of bleeding
– Recent active peptic ulcer
– Age > 65 years.

4.4 Special warnings and precautions for use

– Anaphylaxis: Refludan may cause allergic reactions including anaphylaxis and shock (see section 4.8). 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.
– In case of renal impairment relative overdose may occur even under a standard dosage regimen. Therefore, the treating physician should carefully weigh the risk of administration versus its anticipated benefit. It may be necessary to exclude patients with renal impairment from treatment with lepirudin regimen. The rate of infusion must be reduced in case of known or suspected renal insufficiency (see sections 4.2, and 5.2).
– 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 lepirudin due to coagulation defects secondary to reduced generation of vitamin K-dependent coagulation factors.
– Formation of anti-hirudin antibodies was observed in about 40 % of HIT type II patients and have been reported especially with a treatment period exceeding five days. This may result in an enhanced anticoagulant effect of lepirudin, possibly due to delayed renal elimination of active lepirudin-antihirudin complexes. Therefore, strict monitoring of aPTT is necessary also during prolonged therapy. No evidence of a neutralisation of lepirudin or of an allergic reaction associated with the positive antibody test results was found.
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– Paediatric Use: Safety and effectiveness in paediatric patients have not been established.
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patients is to be taken into account. No specific dosage adjustment is made for elderly patients. Dosing adjustments are based on renal function, weight, and aPTT (see section 4.2).

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No interaction studies have been performed.

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Concomitant treatment with coumarin derivatives (vitamin K antagonists) and drugs that affect platelet function may also increase the risk of bleeding.

Concomitant use with
– antiplatelet agents other than acetylsalicylic acid, such as ticlopidine or clopidogrel,
– GpIIb/IIIa receptor antagonists such as eptifibatide, tirofiban, or abciximab,
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has not been assessed.

4.6 Pregnancy and lactation

The safety of Refludan for use in human pregnancy or lactation has not been established.
In a standard embryo-foetal toxicity trial, decreased pup and maternal survival was observed.

There is currently no information available on the use of Refludan during lactation.

Refludan should therefore not be administered to pregnant women or nursing mothers.

4.7 Effects on ability to drive and use machines

Not relevant.

4.8 Undesirable effects

The majority of undesirable effects experienced by patients treated with Refludan were generally related to bleeding (>1/10). Life-threatening bleeding events (including intracranial bleeding) were uncommonly reported (≥1/1,000 to <1/100) in patients with acute coronary syndrome included in clinical studies. In intensified post-marketing surveillance in HIT type II, fatal bleeding was reported in 1 % and intracranial bleeding in 0.2 % of patients

Adverse events reported on Refludan are shown in the table below:

Very common (>1/10); Common (>1/100, <1/10); Uncommon (>1/1,000 <1/100); Rare (>1/10,000 <1/1,000); Very Rare (<1/10,000)		
System Organ Class	Very common	Rare
Immune System Disorders		Anaphylactic/oid reactions
Vascular Disorders	Anemia or drop in the haemoglobin value without obvious source of bleeding Haematoma Bleeding from puncture sites Epistaxis Haematuria Gastrointestinal bleeding Vaginal bleeding Rectal bleeding Pulmonary haemorrhage Postoperative haemothorax Haemopericardium Intracranial bleeding	Hot flushes Shock including fatal shock
Respiratory, thoracic and mediastinal disorders		Cough Stridor Dyspnea
Skin and Subcutaneous Tissue Disorders		Allergic Skin Reactions (including rash) Pruritus Urticaria Angio-oedema (including: face oedema, tongue oedema, larynx oedema)
General Disorders and Administration Site Conditions		Fever Chills Injection site reactions including pain.

4.9 Overdose

In case of overdose 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 shock-therapy.

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

Results from studies in pigs showed that the application of von Willebrand Factor (vWF, 66 I.U./kg body weight) markedly reduced the bleeding time.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antithrombotic agent – direct thrombin inhibitor, ATC Code: B01AE02

Lepirudin ([Leu1, Thr2]-63-desulfohirudin) is a recombinant hirudin derived from yeast cells. The polypeptide composed of 65 amino acids has a molecular weight of 6979.5 Dalton. Natural hirudin is produced in trace amounts as a family of highly homologous iso-polypeptides by the leech *Hirudo medicinalis*.

Lepirudin is 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.

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.
As a result all thrombin dependent coagulation assays are affected, e.g. the aPTT values increase in a dose-dependent fashion.

The clinical information on HIT type II in this SPC is based upon the data of two prospective trials comprising a total of 198 HIT type II patients treated with Refludan. In the indication HIT type II with thromboembolic disease (125 patients) the overall mortality during the study period was approximately 9 % while amputations and new thromboembolic complications were recorded in 6 % and 10 %, respectively.

5.2 Pharmacokinetic properties

The pharmacokinetic properties of lepirudin following intravenous administration are well described by a two-compartment model. Distribution is essentially confined to extra-cellular 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.

Both, excretion and metabolism take place in the kidney, and about 45 % 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. In female patients the systemic clearance is about 25 % lower as compared to male patients.

In elderly patients the systemic clearance of lepirudin is about 25 % lower as compared to younger patients. Age alone causes a 7 % reduction in clearance from the age of 30 to 70 years. The majority of the difference in clearance between young and elderly patients is due to the differences in renal function. In patients with terminal renal insufficiency prolonged elimination half-lives of about 2 days were observed.

5.3 Preclinical safety data

General toxicity
Single and repeat-dose toxicity studies in mice, rats and monkeys showed the adverse responses that could be expected from an exaggerated pharmacodynamic impact of lepirudin. In monkeys retinal haemorrhages occurred. Moreover, in rats slight to moderate sinushistiocytosis of the regional lymph nodes and decreased haemosiderin deposits in the spleen were observed. Antibodies against hirudin

which appeared in several of the treated monkeys resulted in prolongation of the terminal half-life and an increase in systemic exposure to lepirudin.

Mutagenicity
Lepirudin was not mutagenic or clastogenic in standard assays for such effects.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

– Mannitol
– Sodium hydroxide for adjustment to pH 7

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

3 years.
After reconstitution: use immediately.

6.4 Special precautions for storage

Do not store above 25°C.
Do not freeze.
Keep the vial in the outer carton.

6.5 Nature and contents of container

Injection vial:
Colourless glass vial (glass type I) sealed with bromobutyl rubber infusion stopper, plastic flip-off cap and aluminium cap.

Presentations:
– Pack with 1 vial
– Pack with 10 vials

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

General recommendations
– Reconstitution and further dilution must be carried out under sterile conditions.
– For reconstitution water for injections or sodium chloride 9 mg/ml (0.9 %) solution are to be used.
– For further dilution, sodium chloride 9 mg/ml (0.9 %) or glucose 5 % solutions are suitable.
– For rapid, complete reconstitution, inject 1 ml of diluent into the vacuum vial and shake it gently. On reconstitution a clear, colourless solution is usually obtained within less than 3 minutes.
– Do not use solutions which are cloudy or contain particles.
– The reconstituted solution is to be used immediately.
– The preparation should be warmed to room temperature before administration.
– Any unused solution must be discarded appropriately.

– For injection only polypropylene syringes may be used.

Preparation of a Refludan solution with a concentration of **5** mg/ml
For intravenous bolus injection a solution with a concentration of 5 mg/ml is needed:
– Reconstitute one vial (50 mg of lepirudin) with 1 ml of either water for injections or sodium chloride 9 mg/ml (0.9 %) solution.
– 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 sodium chloride 9 mg/ml (0.9 %) or glucose 5 % solution.
– The final solution is to be administered in a body weight-dependent fashion (see section 4.2).

Preparation of a Refludan solution with a concentration of **2** mg/ml
For continuous intravenous infusion, a solution with a concentration of 2 mg/ml is needed:
– Reconstitute two vials (each containing 50 mg of lepirudin) with 1 ml each using either water for injections or sodium chloride 9 mg/ml (0.9 %) solution.
– 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 sodium chloride 9 mg/ml (0.9 %) or glucose 5 % solution.
– The infusion speed of the perfusor automate is to be set in a body weight-dependent fashion (see section 4.2).
– The perfusor syringe must be changed at least every 12 hours after the start of the infusion.

7. MARKETING AUTHORISATION HOLDER

Celgene Europe Ltd., 1 Longwalk Road, Stockley Park, Uxbridge, UB11 1DB, United Kingdom

8. MARKETING AUTHORISATION NUMBERS

EU/1/97/035/001 REFLUDAN - 50 mg - Powder for solution for injection or infusion - 1 vial
EU/1/97/035/002 REFLUDAN - 50 mg - Powder for solution for injection or infusion - 10 vials

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 13-03-1997
Date of last renewal: 05-03-2007

10. DATE OF REVISION OF THE TEXT

Detailed information on this product is available on the website of the European Medicines Agency (EMEA) http://www.emea.europa.eu

ANNEX II

A. MANUFACTURER OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURING AUTHORISATION HOLDER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OF THE MARKETING AUTHORISATION

A. MANUFACTURER OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURING AUTHORISATION HOLDER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer of the biological active substance

CSL Behring GmbH
Emil-von-Behring-Straße 76
35041 Marburg
Germany

Name and address of the manufacturer responsible for batch release

CSL Behring GmbH
Emil-von-Behring-Straße 76
35041 Marburg
Germany

B. CONDITIONS OF THE MARKETING AUTHORISATION

- **CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE IMPOSED ON THE MARKETING AUTHORISATION HOLDER**

Medicinal product subject to restricted medical prescription (See Annex I: Summary of Product Characteristics, section 4.2)

- **CONDITIONS OR RESTRICTIONS WITH REGARD TO SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT**

Not applicable.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING AND THE IMMEDIATE PACKAGING

OUTER CARTON: 20 mg x 1 VIAL

1. NAME OF THE MEDICINAL PRODUCT

Refludan 20 mg powder for solution for injection or infusion

lepirudin

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 vial contains 20 mg lepirudin.

3. LIST OF EXCIPIENTS

Also contains: mannitol, sodium hydroxide.

4. PHARMACEUTICAL FORM AND CONTENTS

1 vial of powder for solution for injection or infusion.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Intravenous use.
Reconstitute one vial (20 mg of lepirudin) with 0.4 ml of either water for injections or sodium chloride 9 mg/ml (0.9 %) solution. Further dilution is necessary prior to use. Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

The reconstituted solution is to be used immediately.
Do not use solutions which are cloudy or contain particles.

8. EXPIRY DATE

EXP {MM/YYYY}

9. SPECIAL STORAGE CONDITIONS

Do not store above 25°C. Do not freeze.
Keep the vial in the outer carton.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Discard unused solution appropriately.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Celgene Europe Ltd., 1 Longwalk Road, Stockley Park, Uxbridge, UB11 1DB, United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/97/035/003

13. BATCH NUMBER

Lot {number}

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted

PARTICULARS TO APPEAR ON THE OUTER PACKAGING AND THE IMMEDIATE PACKAGING

OUTER CARTON: 20 mg x 10 vials

1. NAME OF THE MEDICINAL PRODUCT

Refludan 20 mg powder for solution for injection or infusion

lepirudin

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 vial contains 20 mg lepirudin.

3. LIST OF EXCIPIENTS

Also contains: mannitol, sodium hydroxide.

4. PHARMACEUTICAL FORM AND CONTENTS

10 x 1 vial of powder for solution for injection or infusion.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Intravenous use.
Reconstitute one vial (20 mg of lepirudin) with 0.4 ml of either water for injections or sodium chloride 9 mg/ml (0.9 %) solution. Further dilution is necessary prior to use. Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

The reconstituted solution is to be used immediately.
Do not use solutions which are cloudy or contain particles.

8. EXPIRY DATE

EXP {MM/YYYY}

9. SPECIAL STORAGE CONDITIONS

Do not store above 25°C. Do not freeze.
Keep the vial in the outer carton.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Discard unused solution appropriately.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Celgene Europe Ltd., 1 Longwalk Road, Stockley Park, Uxbridge, UB11 1DB, United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/97/035/004

13. BATCH NUMBER

Lot {number}

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL LABEL: 20 mg

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Refludan 20 mg powder for solution for injection or infusion
Lepirudin
Intravenous use

2. METHOD OF ADMINISTRATION

Read the package leaflet before use

3. EXPIRY DATE

<EXP {MM/YYYY}>

4. BATCH NUMBER

Lot {number}

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

PARTICULARS TO APPEAR ON THE OUTER PACKAGING AND THE IMMEDIATE PACKAGING

OUTER CARTON: 50 mg x 1 VIAL

1. NAME OF THE MEDICINAL PRODUCT

Refludan 50 mg powder for solution for injection or infusion
lepirudin

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 vial contains 50 mg lepirudin.

3. LIST OF EXCIPIENTS

Also contains: mannitol, sodium hydroxide.

4. PHARMACEUTICAL FORM AND CONTENTS

1 vial of powder for solution for injection or infusion.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Intravenous use.
Reconstitute one vial (50 mg of lepirudin) with 1 ml of either water for injections or sodium chloride 9 mg/ml (0.9 %) solution. Further dilution is necessary prior to use. Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

The reconstituted solution is to be used immediately.
Do not use solutions which are cloudy or contain particles.

8. EXPIRY DATE

EXP {MM/YYYY}

9. SPECIAL STORAGE CONDITIONS

Do not store above 25°C. Do not freeze.
Keep the vial in the outer carton.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Discard unused solution appropriately.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Celgene Europe Ltd., 1 Longwalk Road, Stockley Park, Uxbridge, UB11 1DB, United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/97/035/001

13. BATCH NUMBER

Lot {number}

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted

PARTICULARS TO APPEAR ON THE OUTER PACKAGING AND THE IMMEDIATE PACKAGING

OUTER CARTON: 50 mg x 10 vials

1. NAME OF THE MEDICINAL PRODUCT

Refludan 50 mg powder for solution for injection or infusion
lepirudin

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 vial contains 50 mg lepirudin.

3. LIST OF EXCIPIENTS

Also contains: mannitol, sodium hydroxide.

4. PHARMACEUTICAL FORM AND CONTENTS

10 x 1 vial of powder for solution for injection or infusion.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Intravenous use.
Reconstitute one vial (50 mg of lepirudin) with 1 ml of either water for injections or sodium chloride 9 mg/ml (0.9 %) solution. Further dilution is necessary prior to use. Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

The reconstituted solution is to be used immediately.
Do not use solutions which are cloudy or contain particles.

8. EXPIRY DATE

EXP {MM/YYYY}

9. SPECIAL STORAGE CONDITIONS

Do not store above 25°C. Do not freeze.
Keep the vial in the outer carton.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Discard unused solution appropriately.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Celgene Europe Ltd., 1 Longwalk Road, Stockley Park, Uxbridge, UB11 1DB, United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/97/035/002

13. BATCH NUMBER

Lot {number}

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL LABEL: 50 mg

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Refludan 50 mg powder for solution for injection or infusion
Lepirudin
Intravenous use.

2. METHOD OF ADMINISTRATION

Read the package leaflet before use

3. EXPIRY DATE

<EXP {MM/YYYY}>

4. BATCH NUMBER

Lot {number}

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

B. PACKAGE LEAFLET

PACKAGE LEAFLET: INFORMATION FOR THE USER

Refludan 20 mg powder for solution for injection or infusion
Lepirudin

Read all of this leaflet carefully before you start using this medicine.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:

1. WHAT REFLUDAN IS AND WHAT IT IS USED FOR

Refludan is an antithrombotic medicine.

Antithrombotics are medicines to prevent formation of blood clots (thrombosis).

Refludan is used for anticoagulation in adult patients with heparin-induced thrombocytopenia (HIT) type II and thromboembolic disease requiring injected antithrombotic medicines. HIT type II is an illness which can occur after you have received heparin containing medicines. It constitutes a certain kind of allergy towards heparin. It may result in a too low number of blood platelets and/or clots in your blood vessels (thrombosis).

This may additionally lead to deposition of clots in organs.

2. BEFORE YOU USE REFLUDAN

Do not use Refludan
- if you are allergic (hypersensitive) to lepirudin, to hirudins or any of the other ingredients of Refludan.
- if you are pregnant or breast-feeding.

Take special care with Refludan
If you have a bleeding tendency, your doctor will weigh the risk of Refludan administration against its benefit. Thus, please tell your doctor if you have or have had:
– Recent puncture of large vessels or organs
– Anomaly of vessels or organs
– Recent stroke, accident or surgery involving the brain
– High blood pressure
– Inflammation of the inner membrane of the heart
– **Advanced kidney disease**
– **Advanced bleeding tendency**
– Recent major surgery

– Recent bleeding (e.g. in brain, stomach/intestine, eye, lung)
– Obvious signs of bleeding
– Recent active peptic ulcer
– Age > 65 years

Please inform your doctor if you suffer from reduced kidney function or liver cirrhosis (advanced disease of the liver) for he will then reduce the dosage.

You should also inform your doctor if you have ever received Refludan, hirudin or a hirudin analogue.

Taking other medicines
Please inform your doctor or pharmacist if you are taking or have recently taken any other medicines, even those not prescribed.

Medicines given to break up clots or tablets to prevent clot formation (coumarins) may increase the risk of bleeding when given at the same time.

Pregnancy and breast-feeding
Ask your doctor or pharmacist for advice before taking any medicine.

Refludan should not be administered to pregnant women or nursing mothers.

3. HOW TO USE REFLUDAN

Your doctor will determine and control the dosage and duration of your treatment with Refludan according to your clinical condition, your body weight, and certain laboratory values.

If you have the impression that the effect of Refludan is too strong or too weak, talk to your doctor or pharmacist.

Refludan, once reconstituted with an appropriate solvent, will be administered into a vein, by injection and then by infusion.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Refludan can have side effects, although not everybody gets them.

Very common (at least 1 in 10 people)
– Bleeding

Reported bleeding events include: anaemia or drop in the haemoglobin value without obvious source of bleeding, bruising, bleeding from puncture sites, nose bleeding, blood in urine, gastrointestinal bleeding, vaginal bleeding, rectal bleeding, pulmonary haemorrhage, bleeding into chest space and around the heart following surgery, bleeding into the brain.

Severe bleeding and, in particular, intracranial bleeding may be fatal. In intensified post-marketing surveillance in HIT type II, fatal bleeding was reported in 1 % and intracranial bleeding in 0.2 % of patients. Severe bleeding may lead to decreased volume of circulating blood, low blood pressure, shock, and their clinical sequelae.

Rare (less than 1 in 1,000 people affected)
– Allergic skin reactions (including rash), itching, hot flushes, fever, chills.
– Anaphylactic/oid reactions including urticaria, difficulty in breathing (e.g. consisting of spasms), cough, sharp sound when breathing, build-up of water in the body and in the inner

wall of a vessel (including: face oedema, tongue oedema, throat oedema). In severe cases these may lead to shock and death.
– Injection site reactions, including pain.

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

5. HOW TO STORE REFLUDAN

Keep out of the reach and sight of children.

Do not use Refludan after the expiry date which is stated on the carton and the vial after EXP.

Do not store above 25°C. Do not freeze.

Keep the -vial in the outer carton.

Do not use Refludan if the reconstituted solution is cloudy or contains particles.

Once reconstituted Refludan is to be used immediately.

Any unused solution must be discarded appropriately.

6. FURTHER INFORMATION

What Refludan contains
The active substance is lepirudin, a recombinant DNA product derived from yeast cells.

The other ingredients are mannitol (E421) and sodium hydroxide for PH adjustment.

What Refludan looks like and contents of the pack
Refludan is a white powder for solution for injection or infusion supplied in a vial containing 20 mg lepirudin. Refludan is available in packs of 1 or 10 vials. Not all pack sizes may be marketed.

Marketing Authorisation Holder
Celgene Europe Ltd., 1 Longwalk Road, Stockley Park, Uxbridge, UB11 1DB, United Kingdom.

Manufacturer
CSL Behring GmbH, Emil-von-Behring-Straße 76, 35041 Marburg, Germany.

This leaflet was last approved on {date}

Detailed information on this medicine is available on the European Medicines Agency (EMEA) web site: http://www.emea.europa.eu

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The following information is intended for medical or healthcare professionals only:

Instructions for use and handling:

General recommendations

- Reconstitution and further dilution must be carried out under sterile conditions.
- For reconstitution water for injections or sodium chloride 9 mg/ml (0.9 %) solution are to be used.
- For further dilution sodium chloride 9 mg/ml (0.9 %) or glucose 5 % solutions are suitable.
- For rapid, complete reconstitution, inject 0.4 ml of diluent into the vacuum vial and shake it gently. On reconstitution a clear, colourless solution is usually obtained within less than 3 minutes.
- Do not use solutions which are cloudy or contain particles.
- The reconstituted solution is to be used immediately.
- The preparation should be warmed to room temperature before administration.
- Any unused solution must be discarded appropriately.
- For injection only polypropylene syringes may be used.

Preparation of a Refludan solution with a concentration of **5** mg/ml

For intravenous. bolus injection a solution with a concentration of 5 mg/ml is needed:

- Reconstitute one vial (20 mg of lepirudin) with 0.4 ml of either water for injections or sodium chloride 9 mg/ml (0.9 %) solution.
- The final concentration of 5 mg/ml is obtained by transfer into a sterile, single-use syringe (of at least 5 ml capacity) and further dilution to a total volume of 4 ml using sodium chloride 9 mg/ml (0.9 %) or glucose 5 % solution.
- The final solution is to be administered in a body weight-dependent fashion.

Preparation of a Refludan solution with a concentration of **2** mg/ml

For continuous intravenous infusion, a solution with a concentration of 2 mg/ml is needed:

- Reconstitute two vials (each containing 20 mg of lepirudin) with 0.4 ml each using either water for injections or sodium chloride 9 mg/ml (0.9 %) solution.
- 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 20 ml using sodium chloride 9 mg/ml (0.9 %) or glucose 5 % solution.
- The infusion speed of the perfusor automate is to be set in a body weight-dependent fashion.
- The perfusor syringe must be changed at least every 12 hours after the start of the infusion.

PACKAGE LEAFLET: INFORMATION FOR THE USER

Refludan 50 mg powder for solution for injection or infusion
Lepirudin

Read all of this leaflet carefully before you start using this medicine.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:

1. WHAT REFLUDAN IS AND WHAT IT IS USED FOR

Refludan is an antithrombotic medicine.

Antithrombotics are medicines to prevent formation of blood clots (thrombosis).

Refludan is used for anticoagulation in adult patients with heparin-induced thrombocytopenia (HIT) type II and thromboembolic disease requiring injected antithrombotic medicines. HIT type II is an illness which can occur after you have received heparin containing medicines. It constitutes a certain kind of allergy towards heparin. It may result in a too low number of blood platelets and/or clots in your blood vessels (thrombosis).

This may additionally lead to deposition of clots in organs.

2. BEFORE YOU USE REFLUDAN

Do not use Refludan
- if you are allergic (hypersensitive) to lepirudin, to hirudins or any of the other ingredients of Refludan.
- if you are pregnant or breast-feeding.

Take special care with Refludan:
If you have a bleeding tendency, your doctor will weigh the risk of Refludan administration against its benefit. Thus, please tell your doctor if you have or have had:
– Recent puncture of large vessels or organs
– Anomaly of vessels or organs
– Recent stroke, accident or surgery involving the brain
– High blood pressure
– Inflammation of the inner membrane of the heart
– **Advanced kidney disease**
– **Advanced bleeding tendency**
– Recent major surgery

– Recent bleeding (e.g. in brain, stomach/intestine, eye, lung)
– Obvious signs of bleeding
– Recent active peptic ulcer
– Age > 65 years

Please inform your doctor if you suffer from reduced kidney function or liver cirrhosis (advanced disease of the liver) for he will then reduce the dosage.

You should also inform your doctor if you have ever received Refludan, hirudin or a hirudin analogue.

Taking other medicines
Please inform your doctor or pharmacist if you are taking or have recently taken any other medicines, even those not prescribed.

Medicines given to break up clots or tablets to prevent clot formation (coumarins) may increase the risk of bleeding when given at the same time.

Pregnancy and breast-feeding
Ask your doctor or pharmacist for advice before taking any medicine.

Refludan should not be administered to pregnant women or nursing mothers.

3. HOW TO USE REFLUDAN

Your doctor will determine and control the dosage and duration of your treatment with Refludan according to your clinical condition, your body weight, and certain laboratory values.

If you have the impression that the effect of Refludan is too strong or too weak, talk to your doctor or pharmacist.

Refludan, once reconstituted with an appropriate solvent, will be administered into a vein, by injection and then by infusion.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Refludan can have side effects although not everybody gets them.

Very common (at least 1 in 10 people)
– Bleeding

Reported bleeding events include: anaemia or drop in the haemoglobin value without obvious source of bleeding, bruising, bleeding from puncture sites, nose bleeding, blood in urine, gastrointestinal bleeding, vaginal bleeding, rectal bleeding, pulmonary haemorrhage, bleeding into chest space and around the heart following surgery, bleeding into the brain.

Severe bleeding and, in particular, intracranial bleeding may be fatal. In intensified post-marketing surveillance in HIT type II, fatal bleeding was reported in 1 % and intracranial bleeding in 0.2 % of patients. Severe bleeding may lead to decreased volume of circulating blood, low blood pressure, shock, and their clinical sequelae.

Rare (less than 1 in 1,000 people affected)
– Allergic skin reactions (including rash), itching, hot flushes, fever, chills.
– Anaphylactic/oid reactions including urticaria, difficulty in breathing (e.g. consisting of spasms), cough, sharp sound when breathing, build-up of water in the body and in the inner

wall of a vessel (including: face oedema, tongue oedema, throat oedema). In severe cases these may lead to shock and death.
– Injection site reactions, including pain.

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

5. HOW TO STORE REFLUDAN

Keep out of the reach and sight of children.

Do not use Refludan after the expiry date which is stated on the carton and the vial after EXP.

Do not store above 25°C. Do not freeze.

Keep the vial in the outer carton.

Do not use Refludan if the reconstituted solution is cloudy or contains particles.

Once reconstituted Refludan is to be used immediately.

Any unused solution must be discarded appropriately.

6. FURTHER INFORMATION

What Refludan contains
The active substance is lepirudin, a recombinant DNA product derived from yeast cells.

The other ingredients are mannitol (E421) and sodium hydroxide for pH adjustment.

What Refludan looks like and contents of the pack
Refludan is a white powder for solution for injection or infusion supplied in a vial containing 50 mg lepirudin. Refludan is available in packs of 1 or 10 vials. Not all pack sizes may be marketed.

Marketing Authorisation Holder
Celgene Europe Ltd., 1 Longwalk Road, Stockley Park, Uxbridge, UB11 1DB, United Kingdom.

Manufacturer
CSL Behring GmbH, Emil-von-Behring-Straße 76, 35041 Marburg, Germany.

This leaflet was last approved on {date}

Detailed information on this medicine is available on the European Medicines Agency (EMEA) web site: http://www.emea.europa.eu

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The following information is intended for medical or healthcare professionals only:

Instructions for use and handling:

General recommendations

- Reconstitution and further dilution must be carried out under sterile conditions.
- For reconstitution water for injections or sodium chloride 9 mg/ml (0.9 %) solution are to be used.
- For further dilution sodium chloride 9 mg/ml (0.9 %) or glucose 5 % solutions are suitable.
- For rapid, complete reconstitution, inject 1 ml of diluent into the vacuum vial and shake it gently. On reconstitution a clear, colourless solution is usually obtained within less than 3 minutes.
- Do not use solutions which are cloudy or contain particles.
- The reconstituted solution is to be used immediately.
- The preparation should be warmed to room temperature before administration.
- Any unused solution must be discarded appropriately.
- For injection only polypropylene syringes may be used.

Preparation of a Refludan solution with a concentration of **5** mg/ml

For intravenous. bolus injection a solution with a concentration of 5 mg/ml is needed:

- Reconstitute one vial (50 mg of lepirudin) with 1 ml of either water for injections or sodium chloride 9 mg/ml (0.9 %) solution.
- 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 sodium chloride 9 mg/ml (0.9 %) or glucose 5 % solution.
- The final solution is to be administered in a body weight-dependent fashion.

Preparation of a Refludan solution with a concentration of **2** mg/ml

For continuous intravenous infusion, a solution with a concentration of 2 mg/ml is needed:

- Reconstitute two vials (each containing 50 mg of lepirudin) with 1 ml each using either water for injections or sodium chloride 9 mg/ml (0.9 %) solution.
- 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 sodium chloride 9 mg/ml (0.9 %) or glucose 5 % solution.
- The infusion speed of the perfusor automate is to be set in a body weight-dependent fashion.
- The perfusor syringe must be changed at least every 12 hours after the start of the infusion.