

Refludan® (Lepirudin recombinant-DNA for injection)

Indication

Indicated for anticoagulation therapy in patients with HIT and associated thromboembolic disease in order to prevent further thromboembolic complications.

Description

Lepirudin is a recombinant hirudin derived from yeast cells that has a similar structure as natural hirudin produced by the leech *Hirudo medicinalis*.

Pharmacology

Lepirudin is a specific direct inhibitor of thrombin, the first step in common pathway of both the intrinsic and extrinsic coagulation cascade, leading to anticoagulation effects. The thrombin-dependent assays such as activated partial prothomboplastin time (aPTT) are affected and the dose-response is linear.

Pharmacokinetics

Elimination: Renal (dosage based on renal function)

Half life: 1.3 hours

Calculating Ideal Body Weight (IBW)

Male IBW = 50 kg + (2.3 kg x Inches above 5 feet)

Female IBW = 45.5 + (2.3 kg x Inches above 5 feet)

Calculating Creatinine Clearance (CrCl)

$$\text{Male CrCl} = \frac{(140 - \text{Age}) \times \text{IBW}}{72 \times \text{Scr}}$$

$$\text{Female CrCl} = \frac{(140 - \text{Age}) \times \text{IBW}}{72 \times \text{Scr}} \times 0.85$$

*Use Adjusted Body Weight for obese patients (>1.3 x IBW)

$$\text{Adjusted Body Weight} = \text{IBW} + 0.4 (\text{ABW} - \text{IBW})$$

ABW = Actual Body Weight
Scr = Serum Creatinine

*Use the Scr value of 1 mg/dL for the calculation of CrCl in the elderly (age > 65 years old) if the observed Scr value is < 1 mg/dL.

Initial Bolus Dose for HIT

*Maximum dose: Should exceed the dose for a 110 kg patient

- **Solution preparation of initial bolus dose:** Reconstitute contents of 1 vial (50 mg of lepirudin) with 1 mL of sterile water or normal saline. Draw contents into a sterile 10 mL syringe and add normal saline or D5W to obtain a total volume of 10 mL with a final concentration of 5 mg/mL.
- **Initial bolus dose based on CrCl or Scr:** (given slowly over 15-20 seconds)

Body Weight (kg)	Pt with CrCl \geq 60 mL/min - dosage 0.4 mg/kg	Pt with CrCl < 60 mL/min or Scr > 1.5 mg/dL - dosage 0.2 mg/kg
50	20 mg (or 4 mL)	10 mg (or 2 mL)
60	24 mg (or 4.8 mL)	12 mg (or 2.4 mL)
70	28 mg (or 5.6 mL)	14 mg (or 2.8 mL)
80	32 mg (or 6.4 mL)	16 mg (or 3.2 mL)
90	36 mg (or 7.2 mL)	18 mg (or 3.6 mL)
100	40 mg (or 8 mL)	20 mg (or 4 mL)
110 or more	44 mg (or 8.8 mL)	22 mg (or 4.4 mL)

Initial Maintenance Dose for HIT

- **Solution preparation of maintenance dose:** Reconstitute two 50 mg lepirudin vials each with 1 mL of sterile water or normal saline. The contents of both vials (100 mg total) are then transferred to 250 mL bag of normal saline to make a final concentration of 0.4 mg/mL.
- **Initial maintenance dose based on CrCl or Scr:**

Body Weight (kg)	CrCl	>60 mL/min	45-60 mL/min	30-44 mL/min	15-29 mL/min
	Scr	<1.5 mg/dL	1.6-2 mg/dL	2.1-3 mg/dL	3.1-6 mg/dL
	Dosage	0.15 mg/kg/hr	0.075 mg/kg/hr	0.045 mg/kg/hr	0.0225 mg/kg/hr
50	Infusion Rate	19 mL/hr	9.5 mL/hr	5.7 mL/hr	3 mL/hr
60	Infusion Rate	23 mL/hr	11.5 mL/hr	7 mL/hr	3.5 mL/hr
70	Infusion Rate	26 mL/hr	13 mL/hr	7.8 mL/hr	4 mL/hr
80	Infusion Rate	30 mL/hr	15 mL/hr	9 mL/hr	4.5 mL/hr
90	Infusion Rate	34 mL/hr	17 mL/hr	10.2 mL/hr	5.1 mL/hr
110	Infusion Rate	38 mL/hr	19 mL/hr	11.4 mL/hr	5.7 mL/hr
>110	Infusion Rate	41 mL/hr	20.5 mL/hr	12.3 mL/hr	6.2 mL/hr

Maintenance Dose for Acute Renal Failure or Hemodialysis (CrCl > 15 mL/min or Scr > 6 mg/dL)

- Bolus injection of 0.1 mg/kg every other day may be given if the aPTT falls below therapeutic limits

Monitoring Parameters and Dosage Adjustments

Monitoring

- Obtain baseline aPTT and then q4h thereafter
- Target aPTT: 1.5-2 times baseline value
- Once therapeutic aPTT is obtained, then aPTT should be obtained at least once a day

Dosage Adjustments

aPTT Value	Dosage Adjustment
Above therapeutic value	Stop infusion for 2 hours and restart infusion at 50% of previous rate
1.5 – 2 x baseline (therapeutic)	No change
Below therapeutic value	Increase rate by 20% and determine new aPTT in 4 hours

- An infusion rate of 0.21 mg/kg/hr should not be exceeded without checking for coagulation abnormalities.

Adverse Effects

- Hemorrhagic Events including hematomas and bleeding at puncture sites and intracranial hemorrhage (when used with fibrinolytics).
- Allergic reactions including airway reactions such as cough, bronchospasm, and dyspnea.

Contraindication

Hypersensitivity to hirudins

Drug Interactions

Concomitant use of fibrinolytics and warfarin can significantly increase the risk of bleed.