Title BIVALIRUDIN INFUSION FOR HEPARIN INDUCED THROMBOCYTOPENIA (HIT)

This drug guideline has been prepared to standardise the prescribing, administration and dispensing of this specific medication. Additional information relating to this drug can be found in the references listed and by contacting the Alfred Medicines Information Service on 62002.

Areas Applicable: Alfred Hospital – ICU ONLY

Areas NOT Applicable: Caulfield, Sandringham

Description	
Drug Presentation	• 250mg vial for reconstitution
Prescribing Requirements /Restrictions	• **Use of bivalirudin, along with the diagnosis of heparin-induced thrombocytopenia (HIT), should be done only in consultation with the Haemostasis Thrombosis (HTH) Service** Prescribing and administration of bivalirudin is restricted to: 1. The Intensive Care Unit for the *indications* listed below. 2. For patients with HIT undergoing cardiac bypass surgery • The prescribing and administration of bivalirudin for indications **not** listed below requires individual patient use (IPU) approval in addition to HTH consultation prior to initiation
Drug Storage/ Availability	• Store below 25 degrees. Do not freeze.
Action[1,2,3] (Pharmacology & Pharmacokinetics)	• Bivalirudin is a reversible direct thrombin inhibitor • Elimination is predominantly by proteolytic enzyme inactivation (80%) whilst renal clearance accounts for approximately 20% of its elimination • The initial clearance half-life of bivalirudin is 25 minutes. Clearance is not dose dependent but is reduced to 80% of normal in patients with moderate (eGFR 30-59 mL/min) and severe (eGFR 10-29 mL/min) renal impairment to 80% of normal. Clearance in dialysis patients is reduced to 20% of normal. • Approximately 25% of bivalirudin is removed by haemodialysis.
Indications[1,2]	• Anticoagulation in patients with HIT and who are critically ill (in ICU, with impaired renal function and who may need urgent reversal of anticoagulation), including: ○ Treatment of HIT with/without thrombosis ○ Alternative to heparin in patients with previously diagnosed HIT, in whom the risk of heparin use is deemed to be too high. This includes the maintenance of extra-corporeal circuits (e.g., continuous renal replacement therapy, extra-corporeal membranous oxygenation, ventricular assist devices). • In discussion with HTH consultant, circuit anticoagulation for extra-corporeal membrane oxygenation (ECMO) where there is recurrent circuit or patient **thrombosis** despite heparinisation ○ Patients refractory to high-dose heparinisation **without thrombosis** is not an indication for bivalirudin *Note*: if patient is planned for cardiac surgery requiring bypass then the hospital guideline 'Management of Heparin-Induced Thrombocytopenia (HIT) Patients

	for Cardiac Surgery' should be followed. • HIT is a clinicopathologic syndrome caused by platelet activating antibodies that recognise complexes of platelet factor 4-heparin and result in thrombocytopenia +/- arterial or venous thrombosis.
Contraindications	• Hypersensitivity or allergy to bivalirudin • Active major bleeding (relative depending on indication) • Concomitant thrombolytics • Severe acute hypertension and subacute bacterial endocarditis
Precautions[1,3]	• Patients at increased risk of bleeding. This will include patients with an INR > 1.5, systolic blood pressure > 170 mmHg and those with low haematocrit. • Bivalirudin is not directly reversible and no direct antidote is available. If bleeding occurs and reversal is clinically warranted, cease infusion. Consult Haemostasis Thrombosis Service. Haemodialysis or haemo-filtration can help to reduce plasma levels. • Caution should be also be exercised in patients previously treated with lepirudin who developed lepirudin antibodies • Management around surgery requires close liaison with Haemostasis Thrombosis service, in particular for any patient planned for cardiothoracic surgery. Discussion between the Anaesthetic Transplant Coordinator, Cardiac Surgeon, Intensivist and Haemostasis Thrombosis consultant should occur.
Administration	
Loading Dose	• Loading doses (boluses) are generally not required. Contact Haemostasis Thrombosis Unit for further information.
Dose Range[1,3,7,8]	• Initial dosing is dependent on actual bodyweight and renal function (see Table 1). Dose reduction required if creatinine clearance <60mL/min. • Weight-based dosing capped at maximum 150 kg **Table 1:** Recommended starting dose (mg/kg/hr) **Renal Function (Estimated creatinine clearance mL/min)** / **Starting dose (mg/kg/hour)** >60 mL/min — 0.1 30-60 mL/min — 0.05 – 0.08 ≤29 mL/min — 0.02 – 0.05 Continuous renal replacement therapy (CRRT) — 0.03 – 0.05 *Note*: Dosing for HIT in this guideline is lower than dosing used for HIT patients undergoing cardiac surgery – see separate guideline
Intravenous Infusion	**Prepare a 1mg/mL infusion:** Drug Dose: 250 mg* Make up infusion in 250 mL bag Compatible Solutions 5% glucose, 0.9% sodium chloride Final concentration 1 mg/mL 1 mL/hour = 1 mg/hour Usual Dose Range 0.02-0.1 mg/kg/hour Infusion Pump Carefusion Alaris * Each vial should be reconstituted with 5mL of water for injection

Duration of Therapy[2]	• Therapy is generally continued until the drug is no longer required (i.e. in extracorporeal circuits) or until an alternative anticoagulant is established.
	• Crossover with other anticoagulants:
	  ○ For patients who are being considered for transfer to general wards, consult Haemostasis Thrombosis Unit for use of danaparoid or fondaparinux
	  ○ For patients being transferred onto warfarin
	  ○ Do not start warfarin until the platelet count has returned to normal (>150). Lower initial doses should be used (maximum 5 mg daily).
	  ○ Bivalirudin should be continued together with warfarin therapy for a minimum of five days and until two consecutive therapeutic INRs have been reached before bivalirudin is ceased
	
	Note: bivalirudin may falsely elevate INR (lab effect, ~0.4-0.5 only)

Monitoring[3,4,5]	The manufacturer recommends use of the activated clotting time (ACT) to monitor bivalirudin (majority of experience is intra-operative). The Alfred preferentially uses APTT to monitor. Always state that the patient is on bivalirudin on APTT request form. Measure APTT:- (see Table 2* below for target APTT) • At baseline prior to initiation of bivalirudin. ○ If raised due to preceding anticoagulant therapy, consideration should be given to withholding the bivalirudin infusion until the APTT normalises. Consult the Haemostasis Thrombosis Service. • Every 3 hours – dose adjustments should be made as necessary until the target APTT range has been achieved on 3 consecutive measurements (i.e. steady state reached) • Subsequent APTT levels should be taken every 24 hours as long as APTT remains in therapeutic range unless otherwise clinically indicated • More frequent monitoring is recommended in patients with renal impairment, severe hepatic impairment, extracorporeal circuits or unstable patients. Please note: - The APTT is not suited for quantitative bivalirudin measurement and high plasma levels of bivalirudin cannot reliably be estimated by this assay.

Titration Parameters[3,4,5]

Table 2 describes the target APTT depending on indication and/or risk and recommended dose adjustments based on APTT These parameters may need to be altered to reflect lower or higher APTT target range. Consult Haemostasis Thrombosis Service if further guidance is required.

Table 2. Dose adjustments based on target APTT.

Target aPTT (sec)	Patient group	**Measured** aPTT(sec)	Dose recommendations
Target aPTT **60-80**	1. Patients with suspected or confirmed HIT or 2. patients with indications for full anticoagulation (e.g. DVT, PE, AF, mechanical heart valve)	<45	↑ by 0.01mg/kg/hr
		45-59	↑ by 0.005mg/kg/hr
		60-80	No change
		81-95	↓ 0.005mg/kg/hr
		96-100	Hold for 2 hour, then restart at a dose 0.01mg/kg/hr less than the previous dose.
		>110	Hold and recheck aPTT every 3 hour until aPTT is in goal range, then restart at a dose 0.01mg/kg/hr less than the previous dose
Target aPTT **40-60**	1. Patients with a high risk of bleeding or 2. patients requiring DVT prophylaxis with a remote history of DVT	<40	↑ by 0.005 mg/kg/hr
		40-60	No change
		61-75	↓ by 0.005 mg/kg/hr
		76-90	Hold for 2 hour, then ↓by 0.01mg/kg/hr
		>90	Hold and recheck aPTT every 3 hour until aPTT in goal range, then restart at a dose 0.01mg/kg/hr less than the previous dose

Continuous Renal Replacement Therapy and Thrombosis Prophylaxis

- Circuits should **not** be primed with heparin for patients receiving bivalirudin. Both priming runs should be with sodium chloride 0.9% (normal saline) only.
- If circuit restarted within 3 hours, resume bivalirudin at previous rate and measure APTT at 3 hours and titrate according to Table 2.
- If circuit not restarted and anti-coagulation is still required – APTT should be taken at 3 hours and adjust infusion as per Table 3 once APTT result available.
- Vascaths (and other access devices) should not be flushed or locked with heparin or bivalirudin. Contact clinical pharmacist or ICU clinical educator for advice

Stopping for surgery or other procedures	• Bivalirudin may need to be stopped for up to several hours before invasive procedures and surgery. • Haemostasis Thrombosis Service should be consulted preferably at least 24 hours before invasive procedures or surgery to guide stopping bivalirudin or use of alternative therapies peri-operatively.
How to Wean Infusion/Dose	• No weaning necessary. • The infusion may be stopped abruptly.
Y-site Incompatibilities	• Alteplase, amiodarone, amphotericin, caspofungin, chlorpromazine, dantrolene, diazepam, pentamidine, prochlorperazine, phenytoin, reteplase, streptokinase and vancomycin
Y-Site Compatibility	• Bivalirudin should be administered alone.
Stability	• Once reconstituted, the solution is stable for 24 hours under refrigeration • The diluted solution (0.5mg-5mg/mL) is stable at room temperature for 24 hours.
pH	• 5 – 6 when reconstituted
Practice Points	
Side Effects	• Bleeding – major, life-threatening and fatal • Bivailrudin is a relatively small polypeptide and therefore should have minimal antigenicity. Rare allergic reactions including anaphylaxis, shock, skin and injection site reactions, angioedema, respiratory symptoms have been reported • Gastrointestinal: nausea and vomiting • Musculoskeletal: Back pain and chest pain • General: headache, pyrexia
Use in Pregnancy/Lactation	For the most up to date information, refer to The Women's Pregnancy and Breastfeeding Medicines Guide https://thewomenspbmg.org.au.acs.hcn.com.au/search • *Pregnancy* –Consult a haematologist with obstetric experience for further guidance. • *Breastfeeding* – Published reports describing the use of bivalirudin during breastfeeding have not been located. The transfer of bivalirudin into breast milk is limited by the short half-life of the medicine. Breastfed infants are therefore unlikely to be exposed to significant amounts of bivalirudin following maternal therapy. However, due to potential adverse effects in the breastfed infant, consider an alternative therapy if possible. • Contact medicines information on ext 62002 for advice.

KEY RELATED DOCUMENTS

Alfred Health Drug Formulary Guideline

Key Legislation, Acts & Standards

Charter of Human Rights and Responsibilities Act 2006 (Vic)[1]

[1] REMINDER: Charter of Human Rights and Responsibilities Act 2006 – All those involved in decisions based on this guideline have an obligation to ensure that all decisions and actions are compatible with relevant human rights.

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General resources also used in the preparation of this monograph include: *MIMS* [On-Line] (accessed 1/9/2013); Burridge N (ed) *Australian Injectable Drugs Handbook*. 5th Edition. Melbourne: The Society of Hospital Pharmacists of Australia, 2011; Ashley C, Currie A (Eds) The Renal Drug Handbook. 3rd Edition, 2009

KEYWORDS

Angiomax®

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