Danaparoid IS A HIGH RISK MEDICINE

USE WITH CAUTION AND ENSURE THE DIRECTIONS WITHIN THIS PROTOCOL ARE FOLLOWED CAREFULLY

Areas where applicable	SESLHD Hospitals
Authorised Prescribers:	Medical Officers. Danaparoid may only be commenced on the advice of a Senior Medical Officer and in consultation with haematology
Indications for Use	**SESLHD formulary approved indication(s):** **Treatment of heparin-induced thrombocytopenia (HIT) (intravenous infusion)**: Danaparoid is not registered in Australia for the treatment of heparin-induced thrombocytopenia but is commonly used for this indication. Patient consent should be obtained. Also in suspected COVID-19 Vaccine Induced Thrombocytopenia with Thrombosis (treatment as per local therapeutic practice for HIT) **Non-formulary indication(s) (requiring IPU – individual patient approval):** Prevention of VTE (subcutaneous use only) in patients with a history of heparin-induced thrombocytopenia. Prevention of VTE (subcutaneous use only) in patients undergoing general or orthopaedic surgery.
Important Safety Considerations for Use in HIT	**Danaparoid should only be used in consultation with Haematology.** • HIT is a complication of heparin therapy with a high rate of thrombotic complications. If the diagnosis is confirmed by a haematologist (or suspected based on assessment using the 4T score) then all forms of heparin (unfractionated and low molecular weight heparins) including heparin flushes, must be discontinued and an alternative anticoagulant started. • Thrombocytopenia is not a contraindication to anticoagulation in patients with HIT and platelet transfusions should be avoided unless critical bleeding. • If the patient is on warfarin, this should be reversed using vitamin K 5mg IV or oral, and not restarted until the platelet count is normal for 2 days. • Patients should be screened for asymptomatic proximal DVT which may influence the duration of anticoagulant therapy • Danaparoid does not cross the placenta. Danaparoid has been used in a small number of pregnant patients, the information is still considered to be insufficient to access safety in pregnancy, (category C). There is not data available on danaparoid secretion into breast milk. Seek further advice if considering danaparoid in pregnancy and lactation. • Danaparoid is mainly eliminated by renal excretion.

Contraindications	• Haemorrhagic stroke in acute phase • Uncontrolled active bleeding • Severe haemorrhagic diathesis e.g. haemophilia and idiopathic thrombocytopenic purpure • Hypersensitivity to danaparoid. • Hypersensitivity to sulfite. • A positive *in vitro* aggregation test in the presence of danaparoid in patients with a history of thrombocytopenia induced by heparin-like anticoagulants. • Severe renal and/or hepatic insufficiency. • Severe hypertension. • Severe gastric or duodenal ulcer, unless it is the reason for operating. • Acute bacterial endocarditis. • Diabetic retinopathy.
Precautions	• Moderate renal and/or hepatic insufficiency - dosing modification is required (see Dosage - Renal Impairment). An alternative anticoagulant which is not renally cleared is argatroban • Danaparoid contains sodium sulphite. In asthmatic patients hypersensitive to sulphite it can result in bronchospasm and/or anaphylactic shock. Avoid in patients with sulphur allergy. • Do not inject IM – risk of haematoma
Important Drug Interactions	• In confirmed or suspected HIT all forms of heparin must be discontinued (unfractionated and low molecular weight) including heparin flushes • Antiplatelet agents e.g. aspirin / clopidogrel / NSAIDs may increase the risk of haemorrhage
Place in Therapy	Danaparoid is a non-heparin anticoagulant used to treat HIT. Alternative anticoagulants used to treat HIT include bivalirudin, fondaparinux, argatroban, and lepirudin. Consult haematology regarding choice of therapy for the individual patient. Argatroban and lepirudin are not currently registered in Australia, but are available via the TGA Special Access Scheme.
Presentation	**Danaparoid Sodium** Each ampoule contains 750 anti-factor Xa units (approximately 55mg) of danaparoid sodium in 0.6 mL water for injection
Administration Instructions	The administration of danaparoid involves an IV bolus followed by a maintenance infusion. It must be administered by an infusion pump. <u>Bolus</u> - Draw up required loading dose according to patient's weight and give as intravenous bolus <u>Maintenance IV infusion</u> – draw up 3 ampoules of 750 units/0.6mL (2250 units) and add to 250mLs of 5% Glucose (final concentration 9 units/mL)

Dosage

(Include dosage adjustment for specific patient groups)

Treatment of HIT

Loading dose IV bolus

- Bolus dose is according to weight:
  < 60 kg 1500 units
  60 – 75 kg 2250 units
  75 – 90 kg 3000 units
  > 90 kg 3750 units.

(Haematology may advise omission of bolus if high risk of bleeding or HIT without thrombosis)

Initial IV Infusion (9 units/mL infusion- see administration instructions)

- 400 units/hour (= 44.4mL/hour) for 4 hours**; then
- 300units/hour (= 33.3mL/hour) for 4 hours; then
- 200 units/hour (=22.2mL/hour) **or** 150 units/hour (=16.6mL/hour) for patients with GFR<30mL/min

*** 2 hourly infusion rate change (instead of 4 hourly) may be more appropriate and safer in the following patients:*

- *patients who do not have severe or life-threatening HIT-associated thrombosis*
- *patients who are at high risk of bleeding*
- *patients who have severe renal impairment (GFR<30mL/min)*

Maintenance IV infusion

- The infusion has to be adjusted achieve target anti-Xa level 0.5 – 0.8 units/mL)
- Danaparoid has a plasma elimination half-life for anti-Xa of ~ 25 hours.
- First anti-Xa assay should be taken after 24 hours from commencement of initial infusion
- Infusion adjusted according to algorithm below
- Repeat anti-Xa at least once daily whilst on danaparoid.

Suggested algorithm for adjustment of IV infusion

Anti-Xa level (units/mL)	Dose adjustment	Calculation	Action
<0.5	Increase infusion rate by 20%	New rate x 1.2	Monitor anti-Xa every 24 hours
0.5 – 0.8	GOAL RATE = NO CHANGE	No Change	Monitor anti-Xa every 24 hours
0.8 – 1.0	Decrease infusion rate by 20%	New rate x 0.8	Monitor anti-Xa every 24 hours
>0.1	Decrease infusion rate by 50%	New rate x 0.5	Monitor anti-Xa every 24 hours

In some treatment settings, it may be advisable to aim for a lower anti-Xa level (e.g. 0.3 units/mL) for a patient with a high risk of bleeding. A higher anti-Xa level may be sought (e.g. 0.8-1.0 units/mL) for a patient with life or limb threatening venous or arterial thrombosis, or extra corporeal circulation clotting during continuous renal replacement therapy (CRRT), provided that bleeding is not a problem.

Anti-Xa levels should be rechecked every 24 hours

Renal Impairment	Use with caution and consultation with Haematology. • Consider alternative anticoagulant if CrCl<30mL/min especially if there is an increased bleeding risk. • The elimination half-life is significantly prolonged and the drug will accumulate. Monitoring of Anti Xa levels and suitable dose reduction is required (consider reduction of the loading dose and maintenance dose by approximately one third in a patient with CrCl < 30mL/min if there is a risk of bleeding and the patient does not have acute thrombosis). Dialysis Patients with **acute HIT** on CRRT (continuous renal replacement therapy - ICU) or Intermittent HD (Haemodialysis) should initially receive the therapeutic intravenous regimen (as described in Dosage section). If the patient does not have a confirmed acute thrombosis then consider going straight to the maintenance infusion dose of 150-200 units/hour after the IV bolus dose. Intermittent haemodialysis with a past history of HIT (but **not acute HIT**) First and second dialysis – • >55kg give 3750 units IV bolus prior to dialysis • <55kg give 2500 units IV bolus prior to dialysis Subsequent dialysis sessions are guided by anti-Xa levels and the presence of circuit clotting. • >55kg and NO significant circuit clotting give 3000 units IV bolus prior to dialysis • >55kg and significant clotting of circuit give 3750 units IV bolus prior to dialysis • <55kg and NO significant circuit clotting give 2000 units IV bolus prior to dialysis • <55kg and significant clotting of circuit give 2500 units IV bolus prior to dialysis Danaparoid will accumulate and subsequent dosing must be guided by Anti-Xa levels pre and during each dialysis. Aim for a plasma Anti-Xa level <0.3units/mL pre-dialysis and 0.5-0.8units/mL during dialysis Patients on dialysis must have their dialysis prescription clearly annotated to avoid inadvertent use of heparin for circuit anticoagulation

Additional considerations	Invasive procedures Danaparoid has a long half-life and should be stopped at least 24 hours prior to any invasive procedures. It is therefore not the preferred anticoagulant in patients at high bleeding risk or likely to require urgent invasive procedures. Consult haematology for advice in these circumstances. Prophylactic administration Consider prophylactic dosing only in the following groups: • patients with a past history of HIT that require DVT prophylaxis (not active HIT) • consider in patients with a moderate pre-test probability of HIT in the absence of recent thrombosis, prior to confirmation by laboratory testing, particularly if risk factors for bleeding are present • Administer via subcutaneous injection at a dose of 750 units BD. Transition to warfarin Danaparoid does not interfere with the INR Warfarin should not be started until platelet count is normal (>150 x 10^9/L) for 2 days. Warfarin should be initially given in low doses (maximum 5 mg). Warfarin and danaparoid should be overlapped for at least 5 days and at least 2 consecutive INR measurements are within the therapeutic range (2.0-3.0) Transition to DOAC DOAC should not be started until platelet count is normal (>150 x 10^9/L) for 2 days. Start immediately after ceasing danaparoid, if continuous danaparoid infusion Start in place of the next danaparoid dose, if subcutaneous danaparoid dose
Duration of therapy	**HIT with thrombosis** Oral anticoagulation should be continued for a minimum of 3 months in patients with confirmed thrombosis. **HIT without thrombosis** Therapeutic danaparoid is continued until platelets have normalised for at least 2 days. Because the risk of thrombosis remains high for 2-4 weeks after treatment is initiated, consideration should be given to continuing anticoagulant therapy with an alternative agent or warfarin for 2-4 weeks unless the patient is judged to be at a high risk of bleeding complications.
Prescribing Requirements	All medication orders for danaparoid must include: - Drug, dose, route and indication the intended duration of therapy and the word "ANTICOAGULANT" printed clearly. Treatment of HIT is an off-label indication in Australia and therefore patient consent for use must be obtained using Form S0199 Consent for Exceptional Use of Medicine

Monitoring Requirements	**Anti Xa target plasma levels are 0.5 – 0.8 units/mL** • Factor Xa levels should be checked every 24 hours • Request forms should clearly indicate patient is on danaparoid. • The anti-factor Xa activity half-life is 25 hours but biologic half-life due to thrombin generation inhibition activity is approximately 7 hours. • For dosage adjustments, see dosage section above
Management of complications	• There is no antidote to danaparoid and it is not removed by dialysis. In the case of haemorrhage cease danaparoid administration immediately. • In cases of severe bleeding, plasmapheresis may reduce danaparoid levels • Blood transfusion may be required
Documentation	• Adverse drug reaction (ADR) history and new ADRs during an episode of care must be documented as specified in SESLHDPR/267 Medicine: Continuity of Management and Documentation • Danaparoid prescription and administration should be documented on the IV fluid chart • A medication label must be added to bag and labelling as per SGSHHS_CLIN191 - Labelling injectable medications. After checking danaparoid ampoules with a second RN, complete an additive label including patient identification and the strength of danaparoid infusion being used, which must also be co-signed by the second RN. Attach additive label to the loaded bag.
Storage requirements	Do not store above 30°C. Do not freeze. Keep the ampoules in the outer carton to protect from light.
Basis of Protocol/ Guideline (1): (including sources of evidence, references)	1. Linkins L A, Dans A L,. Moores Lisa K, Bona R,. Davidson B L, Schulman S,Crowther M. Treatment and Prevention of Heparin-Induced Thrombocytopenia: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest 2012:141(2 Supplement) e495S-e530S. doi:10.1378/chest.11-2303 2. Shenk J F, Pindur G, Stephan B, Morsdrop S, Mertzlufft F, Kroll H, On the prophylactic and therapeutic use of danaproid sodium (Orgaron) in patients with heparin Induced Thrombocytopenia. Clin Appl Thrombosis/haemostasis. 2003: 9 (1): 25 -32. 3. Gallus A, Clinical protocol/guideline. Government of South Australia. Southern Adelaide Local Health Network. 4. Fanchini M. Heparin –induced thrombocytopenia: an update. Thromb Journal.2005:3;14 doi:10.1186/1477-9560-3-14 5. Kelly L, Morgan B, Danaparoid, Critical Care Trauma Centre, London Health care Sciences Centre Canada. Protocol. 2006. 6. Magnani H, Wester JP. Is Danaparoid Anticoagulation Suitable for Patients with HIT and ARF Requiring CVVRT? An Analysis of Case Reports. Netherland Journal of Critical Care. 2004: 8(4):293 – 301.https://www.omicsonline.org/scientific-reports/2155-9864-SR-423.pdf 7. Warkentin, T., & Greinacher, A. (2012) (5th ed., pp.466-488). *Heparin-induced thrombocytopenia*. Boca Raton: CRC Press.

Basis of Protocol/ Guideline (2): (including sources of evidence, references)	Online resources Mimsonline.com.au.acs.hcn.com.au. (2017). Available at: https://www.mimsonline.com.au.acs.hcn.com.au/Search/Search.aspx [Accessed 17 May 2017]. Amhonline.amh.net.au.acs.hcn.com.au. (2017). Available at: https://amhonline.amh.net.au.acs.hcn.com.au/chapters/chap-07/anticoagulants/heparins/danaparoid [Accessed 17 May 2017]. Aidh.hcn.com.au. (2017). *Australian Injectable Drugs Handbook, 6th Edition*. [online] Available at: http://aidh.hcn.com.au/browse/d/danaparoid [Accessed 17 May 2017]. Ebs.tga.gov.au. (2017). *TGA eBS - Product and Consumer Medicine Information Licence*. [online] Available at: https://www.ebs.tga.gov.au/ebs/picmi/picmirepository.nsf/pdf?OpenAgent&id=CP-2014-PI-02467-1 [Accessed 5 Apr 2017]. Uptodate.com.acs.hcn.com.au. (2017). [online] Available at: https://www.uptodate.com.acs.hcn.com.au/contents/danaparoid-drug-information?source=search_result&search=danaparoid&selectedTitle=1~26 [Accessed 5 Apr. 2017]. Lhsc.on.ca. (2017). *DANAPAROID (OrgaranR)*. [online] Available at: http://www.lhsc.on.ca/Health_Professionals/CCTC/monograph/danaparoid.htm [Accessed 16 May 2017]. **https://www.mplsheart.com/wp-content/uploads/2017/07/Switching%20To-From%20Anticoagulants.pdf**
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