Prescribing Protocol SESLHDPR/719

Argatroban for Heparin induced Thrombocytopenia (HIT)

Areas where Protocol/Guideline applicable	Medical Officers, Nurses/Midwives, Pharmacists
Authorised Prescribers:	Haematologists or Medical Officers under the direct supervision of a Haematologist
Indication for use	Heparin induced thrombocytopenia (HIT)
Clinical condition Patient selection: Inclusion criteria	Patients with HITT as diagnosed in consultation with a treating haematologist, based initially on clinical scoring (e.g. 4T score), which may be complemented via laboratory testing as time permits. This drug is most likely to benefit patients with HITT fulfilling the following criteria, and would be considered a first line therapy in these indications: 1. Patients with significant renal impairment (CrCl < 30 mL/min) where other agents are contraindicated OR 2. Situations where rapid reversal of anticoagulation may be required (unstable/critically ill patients or unplanned surgery or other invasive procedure) OR 3. Deemed at high risk of bleeding. 4. Suspected COVID-19 Vaccine Induced Thrombocytopenia with Thrombosis
Contra-indications	• Uncontrolled bleeding • Hypersensitivity to argatroban or to any of the excipients • Severe hepatic dysfunction
Precautions	Major and fatal bleeding has been reported as with all anticoagulants for treating patient with HIT Hematologic: Risk of hemorrhage may be increased in severe hypertension, after lumbar puncture, spinal anesthesia, major surgery (especially involving the brain, spinal cord, or eye), in conditions associated with increased bleeding (eg, congenital or acquired bleeding disorders), gastrointestinal lesions (eg, ulcerations), or with concomitant use of antiplatelet agents, thrombolytics, and other anticoagulants Hepatic impairment or congestion (e.g., heart failure, multiple organ system failure or severe anasarca) delays the clearance of argatroban and leads to a slower time to achieve steady state, over-shooting of the target aPTT and a longer reversal time. Dose reduction is recommended in these circumstances. Note: Argatroban is contraindicated in severe hepatic dysfunction. Airway, skin, and generalised hypersensitivity reactions have been reported.
Proposed Place in Therapy	For patients not fulfilling one of these criteria, Argatroban would be a second line therapy only to be used if there is clear treatment failure with an alternative agent such as Fondaparinux, Danaparoid or a NOAC. Once a patient stabilises there is an expectation they would be transitioned to an alternative anticoagulant.

Argatroban for Heparin induced Thrombocytopenia (HIT)

Dosage

CHECK BASELINE APPT PRIOR TO STARTING THERAPY
IF BASELINE aPTT > 37 SEC, CONSULT HAEMATOLOGIST FOR INDIVIDUALIZED DOSE ADJUSTMENT PROTOCOL.

Patients without hepatic impairment:
Initial dosing: Commence infusion at ≤ 2 microgram/kg/min.

In patients who have bleeding risks or concerns about argatroban clearance (cardiac failure, mild liver impairment, multiple organ system failure, severe anasarca or who are post cardiac surgery) discuss dosing with Haematologist and consider commencing at infusion at 0.5 to 1.2 microgram/kg/min.

2 microgram/kg/min Dose		1 microgram/kg/min Dose	
Body Weight (kg)	**Infusion rate (mL/hr)**	**Body Weight (kg)**	**Infusion rate (mL/hr)**
50	6	50	3
60	7	60	4
70	8	70	4
80	10	80	5
90	11	90	5
100	12	100	6
110	13	110	6
120	14	120	7
130	16	130	8
140	17	140	8

Dose adjustment in patients without hepatic impairment:

aPTT (sec)	Dose adjustment	Repeat aPTT in
< 40	Increase (↑) by 1 microgram/kg/min	2 hours
41 - 45	Increase (↑) by 0.5 microgram/kg/min	2 hours
45 – 90 **AND aPTT 1.5 – 3 times baseline**	No change. *Continue at current rate.*	2 hours. Once TWO consecutive results are in range, measure ONCE daily.
91 – 100	Decrease (↓) by 0.5 microgram/kg/min	2 hours
> 100	**Stop infusion for 60 minutes.** Decrease (↓) by 1 microgram/kg/min	2 hours

Argatroban for Heparin induced Thrombocytopenia (HIT)

Dosage (continued)

Critically ill or moderate hepatically impaired patients:

Initial dosing: Commence infusion at 0.5 microgram/kg/min.

Body Weight (kg)	Infusion rate (mL/hr)
50	1.5
60	1.8
70	2.1
80	2.4
90	2.7
100	3
110	3.3
120	3.6
130	3.9
140	4.2

Dose adjustment in critically ill / hepatically impaired patients:

aPTT (sec)	Dose adjustment	Repeat aPTT in
< 40	Increase (↑) by 0.2 microgram/kg/min	Within 4 hours
41 – 45	Increase (↑) by 0.1 microgram/kg/min	Within 4 hours
45 - 90	No change. *Continue at current rate.*	After 4 hours. Once TWO consecutive results are in range, measure ONCE daily.
91 – 100	Decrease (↓) by 0.1 microgram/kg/min	Within 4 hours
> 100	**Stop infusion for 60 minutes.** Decrease (↓) by 0.2 microgram/kg/min	Within 4 hours
> 150	**Stop infusion for 60 minutes.** Decrease (↓) by 0.4 microgram/kg/min	Within 4 hours

Patients on Haemodialysis:

On alternate days: 250 microgram/kg single administration or 250 microgram/kg intravenous bolus followed by 2.0 microgram/kg/min infusion, starting 4 hours before haemodialysis. Target aPTT ratio is 1.5 – 3.0

Patients on Haemofiltration:

0.5 – 2.0 microgram/kg/min dependent on liver function. Target aPTT ratio is 1.5 – 3.0

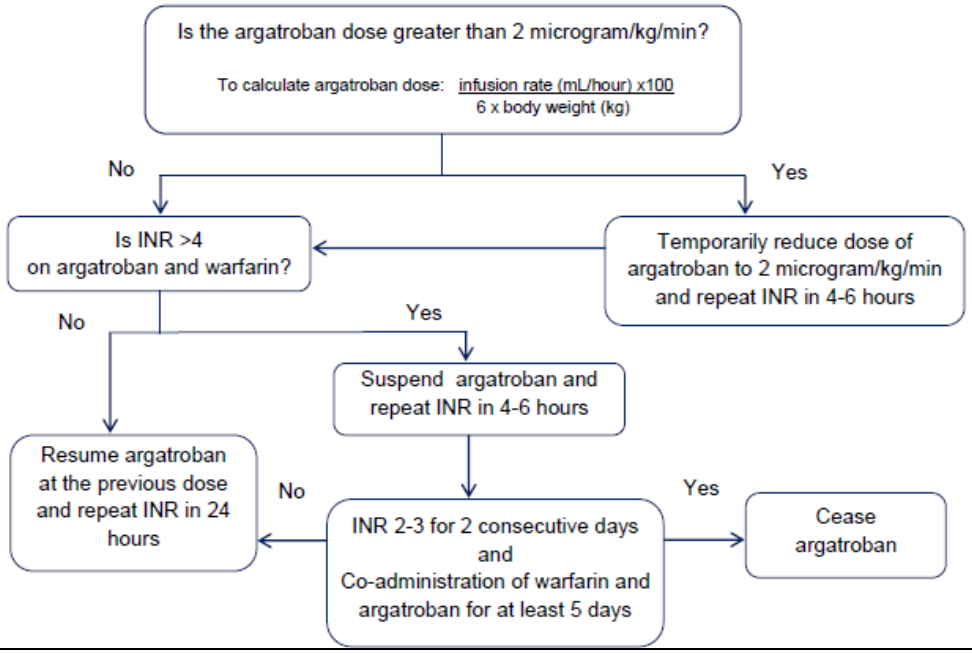
Obesity (BMI up to 51 kg/m2):

No dosing adjustment required when actual body weight-based dosing to target coagulation response is utilised.

Geriatric:

No dose adjustment necessary in geriatric patients.

Argatroban for Heparin induced Thrombocytopenia (HIT)

Duration of therapy	Patient dependent, until platelet recovery and / or able to be safely transitioned to warfarin or a separate non intravenous non heparin anticoagulant
Important Drug Interactions	Other anticoagulants. **Conversion to warfarin** • Warfarin should not commence until the platelet count is in the therapeutic range. • To avoid prothrombotic effects and ensure continuous anticoagulation argatroban and warfarin should overlap for at least 5 days. • Co-administration of warfarin and argatroban results in increased PT and INR beyond that produced by warfarin alone without additional effect on vitamin K-dependent factor Xa activity. • Prescribe 5mg warfarin and continue the argatroban infusion, check INR daily and review result using the algorithm below. Seek advice from haematology if required. 
Prescribing Instructions	Prescribe infusion orders in eFluids. Refer to Rate Change – Prescriber Initiated QRG. Document the patient's target aPTT in patient's eMR progress notes. **Medications** | **14/11/2022 13:31** **Heparin induced thrombocytopenia - 1** **argatroban additive 250 mg [1 microg/kg/min]** **Sodium Chloride 0.9% intravenous solution 250 mL** 250 mL, IV Continuous Infusion, 3.6 mL/hr, 1 bag(s) | **Pending** Not given within 5 days. **Administration Information** argatroban Sodium Chloride 0.9% intravenous solution

Argatroban for Heparin induced Thrombocytopenia (HIT)

	Each order in eFluids corresponds to **one bag** only. Prescribers must ensure that new infusion orders are available in a timely manner, enabling nursing staff to continuously administer the drug infusion, where required. **Note:** An argatroban infusion must be recharted and replaced at least every 24 hours.
Administration Instructions	Dilute one vial (250 mg) in 250 mL of compatible solution to give a final concentration of 1 mg/mL
Monitoring requirements	**Check baseline aPTT prior to STARTING therapy.** **If baseline aPTT > 37 secs, consult a Haematologist for an Individualised dose adjustment protocol.** Other monitoring: anticoagulation (routinely), FBC (daily), PT (daily). Observe for signs and symptoms of bleeding. If patient actively bleeding, notify medical or haematology registrar or consultant immediately. **Argatroban infusions must be closely monitored to achieve an aPTT 1.5 to 3 times baseline** see dose adjustment tables in Dosage section. Medical officers are responsible for monitoring aPTT. Nursing staff may request a medical officer review when aPTT results become available. Medical officers are responsible for prescribing any rate changes in eFluids. Any future infusion orders, already prescribed, must also be updated each time a rate change is required. See Quick Reference Guide: Modifying the Rate of an Infusion. Nursing staff MUST document the administration of rate changes in MAR and note when the next aPTT is next due in the Comment box. If no adjustments are required, document this and other details relevant for the infusion in the progress notes. If the infusion has been paused (i.e., rate is 0 mL/hr) for longer than 60 minutes, nursing staff to contact the doctor for clarification unless clearly documented. See Quick Reference Guide: Documenting a Rate Change (Prescriber Initiated). **Ensure that the patient has ongoing infusions charted unless Haematology or the treating team has specifically documented or advised to cease the argatroban infusion.**
Management of Complications	• There is no specific reversal agent for Argatroban. • Elimination half-life: 40-50 mins, prolonged in hepatic impairment. • Dosing in renal impairment: no dose adjustment required, with or without renal replacement therapy. • Argatroban has a marked effect on INR.

Prescribing Protocol SESLHDPR/719

Argatroban for Heparin induced Thrombocytopenia (HIT)

Basis of Protocol/Guideline: (including sources of evidence, references)	Based on St Vincent's Hospital ICU Argatroban protocol. 1. St Vincent's Hospital Intensive Care Service Medication Administration Guidelines: Argatroban. September 2021 2. St Vincent's Hospital: Argatroban for Heparin-Induced Thrombocytopenia (HIT). March 2015. 3. RPAH Haematology Manual, Heparin Induced Thrombocytopenia (HIT) Guidelines, Version 3. June 2019 4. Product Information, Argatroban. Sandoz Canada. Revised 01/2011 5. Crit Care Med. 2007; 35(4):1165 – 1176. 6. Argatroban in Extracorporeal Membrane Oxygenation. Martin Beiderlinden, et al., Artificial Organs 31(6):461–465, Blackwell Publishing 7. Burstein B et al. Anticoagulation with direct thrombin inhibitors during extracorporeal membrane oxygenation. World J Crit Care Med 2019; 8(6): 87-98. 8. Geli J et al. Argatroban anticoagulation for adult extracorporeal membrane oxygenation: A systematic review. J of Intensive Care Med 2021; 1-13 9. Fisser C et al. Argatroban versus heparin in patients without heparin-induced thrombocytopenia during venovenous extracorporeal membrane oxygenation: a propensity-score matched study. Crit Care 2021; 25: 160 10. Up to Date – Argatroban Drug Information (accessed 13/07/2021)
Groups consulted in development of this guideline	Intradepartmental discussion amongst all haematologists.

AUTHORISATION	
Author (Name)	Charles Shuttleworth
Position	Staff Specialist Haematology
Department	Haematology Department
Department Contact	Charles Shuttleworth charles.shuttleworth@health.nsw.gov.au

GOVERNANCE	
Enactment date *Reviewed* (Version 2) *Reviewed* (Version 3)	October 2021 February 2023
Expiry date:	February 2025
Ratification date by SESLHD DTC	2nd March 2023
Chairperson, DTC	Dr John Shephard
Version Number	2