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Argatroban Infusion Protocol for adult use

Royal Sussex County Hospital and Princess Royal Hospital

Patient's weight (kg)	Ward	Consultant

Prescribing

- **** Please discuss with haematologist before initiating argatroban****
- "Argatroban IV as per protocol" must be prescribed on anticoagulants section of drug chart
- Allergy status to heparin (if HIT) must be recorded on drug chart and "other charts in use" box on front of drug chart ticked and specified as argatroban protocol
- The half-life of argatroban is 45 minutes, this may be prolonged in hepatic dysfunction
- If thrombotic event is limb or life-threatening, please consider using initial infusion rate of 2mcg/kg/min while managing bleeding risks. This dose should be considered in symptomatic pulmonary emboli.

Contra-indications and cautions

CONTRAINDICATIONS	**CAUTIONS**
Uncontrolled bleeding	Severe hypertension
Hypersensitivity to argatroban	Diabetic retinopathy
Fructose intolerance (rare hereditary)	Immediately post lumbar puncture
Severe hepatic impairment	Spinal anaesthesia
	Major surgery (esp. involving brain, spinal cord or eye)
	Congenital or acquired bleeding disorders
	GI lesions (e.g. ulceration)

Administration

- Dilute argatroban 250mg in 2.5ml amp in either 250mL sodium chloride 0.9% or 250mL glucose 5% to give final concentration of 1mg/ml (1000mcg/ml)
- Preferably administer via central venous access to avoid potential venous irritation due to low ph. If given peripherally, monitor site closely for phlebitis
- Prior to administration perform baseline clotting screen and platelet count. Monitor FBC daily

Monitoring

- Obtain baseline APTT (secs) prior to initiating infusion **(DO NOT USE APTT ratio reported on ICE, see below)**
  - If baseline APTT is over 60 seconds – please discuss with haematology
  - See table 1 for initial infusion rates based on weight
  - APTT should be checked 2 h after commencing infusion and adjusted according to table 2 (divide patient's APTT by their baseline APTT for column one)
  - Therapeutic APTT target range according to the SPC is **1.5-3 times the baseline** value (e.g. if baseline APTT = 30 seconds, therapeutic range is 45-90 seconds). This target APTT range is not the same as a requested APTT ratio as it is relative to the patient's baseline. Adjusting the dose within the upper part of this range using an adapted dosing table is intended to avoid the APTT going too high.
  - Target APTT should not exceed 100 seconds
  - Check APTT every 2 hours until steady state is achieved (and 2 h after every dose change)
  - Once two consecutive readings are obtained within target range, APTT should be checked every 8-12 hours for the first 24 hours, then at least once daily

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- For critically ill patients or patients with hepatic impairment check APTT ratio 4 hours after starting infusion and 4 hours after a dose change.
- After 2 consecutive APTT ratios are within target range, check DAILY
- Maximum dose 10mcg/kg/min

Switching to warfarin :

- **Argatroban interferes with the INR assay**; stopping this drug too early could result in a lapse in therapeutic anticoagulation. Please seek haematology advice if necessary.
- Argatroban should be continued as bridging therapy with oral anticoagulation (of the coumarin type) for a minimum of 5 days and until the **INR is 4 or above** for 2 days (this INR value takes into account the effect of argatroban on INR assay to give false high reading)
- Warfarin and other coumarins should not be started until platelets are above 100 x 10^9d/l to avoid coumarin associated microvascular thrombosis and venous limb gangrene.
- **Do not use loading dose of warfarin – please start on predicted maintenance dose**
- Measure INR 4-6 hrs after stopping argatroban and restart infusion if INR is below target range

Switching to DOAC:

- DOACs will not be suitable for critical care patients, high bleeding risk patients, those that require invasive procedures or those with CrC <15ml/min or on dialysis. However, they may be considered for selected patients after discussion with a consultant haematologist
- STOP argatroban on initiation of a DOAC (DO NOT overlap)
- Use of DOACs in HIT is off-license but experience is increasing and the most studied DOAC for this indication is rivaroxaban. If a DOAC is being considered, dosing will depend on whether there is HIT with thrombosis and timing of diagnosis. Please discuss with haematology

This protocol is not for HIT patients undergoing PCI – please see SPC for specific information

Doctor's Signature……. **Print Name…….....**
Bleep Number……. **Date ……**

Treatment Discontinued: ☐	Date:	Doctor's Signature:

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To calculate standard **initial infusion rate** (ml/hr): $\frac{1\text{mcg/kg/min} \times \text{weight (kg)} \times 60\text{mins}}{1000\text{mcg/ml}}$

Table 1 Initial Rate of Argatroban Infusion (concentration 1mg/ml)

Body weight (kg)	Infusion Rate (ml/hr)		
	Standard dosing* **1 microgram/kg/min**	Critically ill or hepatically impaired patients (Child-Pugh class B) and post cardiac surgery **0.5 microgram/kg/min**	Patients with life or limb-threatening thrombotic events [4] **2 microgram/kg/min**
50	3.0	1.5	6.0
60	3.6	1.8	7.2
70	4.2	2.1	8.4
80	4.8	2.4	9.6
90	5.4	2.7	10.8
100	6.0	3.0	12.0
110	6.6	3.3	13.2
120	7.2	3.6	14.4
130	7.8	3.9	15.6
140	8.4	4.2	16.8

*Standard initial infusion rate differs from SPC which states 2mcg/kg/min and is based on specialist centre UK data, specific recommendation from the manufacturer[2,3] and King's College Hospital protocol.

Record of infusion preparation

Date	Time (24 hour clock)	Batch number of argatroban	Signature of nurse making infusion	Signature of second check	Line primed with new syringe?	
					Yes	No

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Baseline APTT (seconds) ……

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Table 2 Infusion rate adjustment of argatroban according to APTT ratio

	Initial Infusion Rate 1 mcg/kg/min and 2mcg/kg/min		Critically Ill/ Hepatically impaired patients (Child-Pugh Class B) /post cardiac surgery **Initial infusion rate 0.5 mcg/kg/min**	
APTT (s)	Infusion Rate change	Next APTT	Infusion Rate change	Next APTT
< 1.5 times baseline	Increase by 0.5 mcg/kg/min.	2 hours	Increase by 0.1 mcg/kg/min.	4 hours
1.5-2.5 times baseline (not exceeding 100s)	No change	2 hours After 2 consecutive APTTs within target range check at least once per day	No Change	4 hours After 2 consecutive APTTs within target range check at least once per day
2.5-3.0 times baseline (not exceeding 100s)	Reduce by 0.2mcg/kg/min	2 hours	Reduce by 0.1mcg/kg/min	4 hours
>3 times baseline (or APTT>100s)	Stop infusion until APTT is 1.5-3.0 times baseline Resume at 50% of the previous infusion rate	2 hours	Stop infusion until the APTT is 1.5-3.0 times the baseline Resume at 50% of the previous infusion rate	4 hours

Maximum dose: 10mcg/kg/min table adapted from King's College Hospital protocol

To calculate adjusted infusion rate (ml/hr):

$$A = \frac{\text{mcg/kg/min} \times \text{weight (kg)} \times 60\text{mins}}{1000\text{mcg/ml}} + \text{Current Infusion Rate (ml/hr)}$$ (where A is infusion rate change)

For Example:
A 60kg person with a current infusion rate of 3.6ml/hr has an APTT of 1.2 times baseline.
The infusion rate needs to be increased by **0.5mcg/kg/min.**

To calculate the rate increase:

$$\frac{\textbf{0.5}\text{mcg/kg/min} \times \textbf{60}\text{kg} \times \textbf{60}\text{min}}{\textbf{1000}\text{ mcg/ml}} = 1.8\text{ml/hr}$$

The new infusion rate (ml/hr) is 1.8ml/hr + 3.6ml/hr = 5.4ml/hr

See Medusa the injectable medicines guide for dosing calculator. Please contact ward pharmacist, medicines information or the on-call pharmacist via switchboard for further advice on this calculation if necessary

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ADMINISTRATION DETAILS

Date	Time (24 hr clock)	APTT/baseline APTT*	Infusion Rate (ml/hr)	Volume remaining in syringe	IV-trained nurse signature	Doctor signature**

* example: if baseline APTT is 35 seconds and after 2 hours of argatroban infusion it increases to 70 seconds, this is 2 times the baseline i.e. APTT/baseline APTT = 70/35=2
**signature only required if doctor is contacted in cases of clinical need (e.g: APPT >5 times baseline, patient bleeding)

References:

1. Summary of Product Characteristics Argatroban , Electronic Medicines Compendium UK, accessed 1/4/21
2. Hursting MJ, Soffer J Reducing harm associated with anticoagulation. Practical considerations of argatroban therapy in heparin-induced thrombocytopenia. Drug Safety 2009; 32(3):203-218.
3. Guidelines on the diagnosis and management of heparin induced thrombocytopenia: 2nd edition, British Haematological society guidelines 2012
4. Alatri A et al, Thrombosis Research 129 (2012) 426-433
   Consensus meeting on the use of argatroban in patients with HIT requiring antithrombotic therapy – A European Perspective

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