Argatroban Intravenous for Adults

Who can administer

May be administered by registered competent doctor or nurse/midwife

Important information

- Ordered on advice of consultant haematologist only
- **Unlicensed** preparation **in Ireland**
- **IMPORTANT: The ACT is NOT the same as the aPTT. Results are not interchangeable.**
- See under Dose for adjustments required in **renal or hepatic impairment**

Available preparations

Exembol 250mg per 2.5ml vial (contains **ethanol** 1g / 2.5ml vial)

Reconstitution

- Already in solution
- **Dilute further prior to administration**

Infusion fluids

- Sodium chloride 0.9% or Glucose 5%
- **Mix by repeated inversion of the infusion bag for 1 minute**

Methods of intravenous administration

Continuous intravenous infusion (administer using an electronically controlled infusion device)

- Add 250mg (2.5ml) vial to 250ml infusion fluid (no need to remove 2.5ml from bag)
- Using a 1mg per ml solution (250mg in 250ml) - set up the continuous infusion
- Adjust dose as per 'Dose'

Slow intravenous injection (Percutaneous intervention only, see dose under Further Information)

- Given over 3 to 5 minutes

Dose in adults

Heparin induced thrombocytopenia (HIT)

- **All patients with HIT must be managed in conjunction with haematology**
- If baseline aPTT elevated- discuss target aPTT with Haematology
- **APTTr;** the patient's activated partial thromboplastin time divided by either the laboratory's normal value or the patient's own baseline value
- Prior to commencement **stop heparin** and take baseline aPTT, PT and fibrinogen (CLAUSS) [ref 1]
- Argatroban is a direct thrombin inhibitor. Its anticoagulant effect is measured by the APTTr and INR, which increase in a dose dependent manner. Dose adjustments are based on the APTTr as shown in the

table below.

- **Daily monitoring is sufficient after 2 consecutive aPTT within target range if no dose adjustments were made** [(ref 1)]
- Argatroban interferes with the **Clauss Fibrinogen** assay resulting in falsely low results. The **derived fibrinogen** assay may be more reliable but both will be abnormal at higher argatroban concentrations[(ref 1)]
- The lab MUST be informed that patient is receiving argatroban[(ref 1)]

Table 1: Recommended starting doses and monitoring intervals (see table 3 below for flow rates)

	Argatroban dose (mcg/kg/minute)	**Interval to check aPTT after initial dose and each dose change thereafter**
Standard dose	2	2 hours
Critically ill patients*	0.5	4 hours
Moderate hepatic impairment**	0.5	4 hours
*** Multi-system organ failure, ICU patients, heart failure, post cardiac surgery, anasarca**		
**** Moderate hepatic impairment (Child Pugh B)**		

Table 2: Dose modifications and monitoring intervals (see Table 3 below for flow rates)

Standard dosing schedule			**Critically ill/Hepatically impaired patients**	
Initial infusion rate 2mcg/kg/minute			**Initial infusion rate 0.5mcg/kg/min**	
aPTT	**Infusion rate change**	**Next aPTT**	**Infusion rate change**	**Next aPTT**
<1.5 patient's baseline	Increase by **0.5**mcg/kg/min	2 hours	Increase by **0.1**mcg/kg/min	4 hours
1.5 to 3 times patient's baseline *(and less than 100 seconds)*	No change **Ideal range:** 1.5 to 2.5 patient's baseline aPTT as per Dr Gilmore	2 hours After 2 consecutive aPTT within target range, check at least 24 hours	No change	4 hours After 2 consecutive aPTT within target range, check at least every 24 hours
> 3 times patient's baseline or if over 100 seconds	Discontinue infusion until APTT is within desired range (typically within 2 hours of discontinuation) - restart at 50% of the previous rate	2 hours	Discontinue infusion until APTT is within desired range (typically within 2 hours of discontinuation) - restart at 50% of the previous rate	4 hours

- The maximum recommended dose is 10 microgram/kg/minute
- The maximum recommended duration of treatment is 14 days, although there is limited experience with administration for longer periods

Table 3: Infusion rate in ml/HOUR of a 1mg/1ml infusion				
Dose/Weight (kg)	0.1micrograms/kg/min	0.5micrograms/kg/**min**	1micrograms/kg/**min**	2micrograms/kg/**min**
50	0.3	1.5	3	6
60	0.36	1.8	3.6	7.2
70	0.42	2.1	4.2	8.4
80	0.48	2.4	4.8	9.6
90	0.54	2.7	5.4	10.8
100	0.6	3	6	12
110	0.66	3.3	6.6	13.2
120	0.72	3.6	7.2	14.4
130	0.78	3.9	7.8	15.6
140	0.84	4.2	8.4	16.8
150	0.9	4.5	9	18

Patients with HIT Type II undergoing percutaneous coronary intervention (PCI)

- Limited data is available from the use of argatroban in patients with HIT Type II undergoing percutaneous coronary intervention
- Based on the data, when there is no alternative, therapy could be initiated with a bolus dose of 350 microgram/kg over 3 to 5 minutes
- This is followed by an infusion dose of 25 microgram/kg/min
- ACT should be checked 5 to 10 minutes after the bolus dose is completed
- The procedure may proceed if the ACT is greater than 300 seconds
- If the ACT is below 300 seconds, an additional bolus dose of 150 microgram/kg should be administered, the infusion rate be increased to 30 microgram/kg/min, and the ACT should be checked 5 to 10 minutes later
- If the ACT is higher than 450 seconds the infusion rate should be decreased to 15 microgram/kg/min and ACT values be checked 5 to 10 minutes later
- Once a therapeutic ACT between 300 to 450 seconds has been achieved, the infusion dose should be continued for the duration of the procedure
- ACT measurements were recorded using both Haemotec and Haemochrom devices
- The efficacy and safety of argatroban use in combination with GPIIb/IIIa inhibitors has not been established.

Renal impairment

- No **initial** dosage adjustment necessary in mild to severe renal impairment. Monitor aPTT closely.
- **Haemodialysis: limited data. Consult haematologist and see specialist texts**

Liver impairment

- Use with extreme caution in hepatic impairment
- See Tables 1 and 2 above for doses
- Reversal of the anticoagulant effects of argatroban may take longer in this setting (more than four hours)
- Argatroban is **contraindicated** in patients with severe hepatic impairment

Changing to oral anticoagulation [ref 1]

- A Haematology Consultant (ideally with Special Interest in Coagulation) will decide on the timing, duration and choice of oral anticoagulant
- Patients with HIT require a minimum of three months of oral anticoagulation
- **If starting DOAC**
  - stop argatroban and start DOAC
  - Rivaroxaban, apixaban and dabigatran have all been used in this situation
- **If starting warfarin therapy for patient on argatroban**
  - Warfarin should only be commenced when there is resolution of thrombocytopenia (to avoid coumarin-associated microvascular thrombosis and venous limb gangrene)
  - To avoid prothrombotic effects and to ensure continuous anticoagulation, argatroban must be continued during the initiation of warfarin therapy
  - **A minimum overlap of argatroban and warfarin of at least 5 days is advised**
  - **Argatroban has a significant effect on the INR**
  - **NO loading doses of warfarin to be given**
  - Start with the intended maintenance dose of warfarin (no greater than 5mg daily)
  - Discontinue argatroban when INR reaches up to 4 **for at least two days,** on COMBINED therapy (INR should be 2 greater than desired target range- eg in patients with target INR of 2 to 3, INR on combined argatroban and warfarin should be 4 to 5) [ref 3]
  - Repeat INR 4 to 6 hours after stopping argatroban, to ensure INR is therapeutic prior to permanent discontinuation of argatroban[ref 3]
  - If INR is below the desired therapeutic range recommence argatroban and repeat the procedure above (steps 2 to 6)
  - **Take INR at least daily**

Monitoring

- See above

Storage

- Store below 25^{0}C
- Do not refrigerate or freeze
- The diluted solution is stable for 24 hours if kept at 25^{0}C or less (do not expose the diluted solution to direct sunlight)

References

UK SPC (Exembol) 31/10/2024

1. Dr Ruth Gilmore, Consultant Haematologist, 26/03/2025

2. Heparin induced thrombocytopenia - a comprehensive clinical review, Salter et al. JACC Vol 67, No 21, 2016

Therapeutic classification

Parenteral anticoagulants

BNF
Blood clots