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

Vaccine-induced Immune Thrombotic Thrombocytopenia (VITT) VITT (ref 1)

- Follow guidelines as per Heparin induced thrombocytopenia below

Heparin induced thrombocytopenia (HIT)

- **All patients with HIT must be managed in conjunction with haematology**
- Prior to commencement **stop heparin** and take baseline aPTT, PT and fibrinogen (CLAUSS) (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

- It is expected that the APTT will rise and fall in a linear fashion with dosage adjustment [(ref 1)]
- If baseline aPTT elevated- discuss target aPTT with Haematology. **Argatroban levels may be required**
- All other parenteral anticoagulants should be discontinued and time allowed for their effect to decline before commencing argatroban

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

- See Tables 1 and 2 above for doses
- In moderate liver impairment, there is an approximate **4-fold decrease in clearance** relative to those with normal hepatic function [(ref 3)]
- 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

PCI in patients with, or at risk of HIT/HITT S- see under Further Information

If starting warfarin therapy for patient on argatroban

1. Warfarin should only be commenced when there is resolution of thrombocytopenia (to avoid coumarin-associated microvascular thrombosis and venous limb gangrene)
2. To avoid prothrombotic effects and to ensure continuous anticoagulation, argatroban must be continued during the initiation of warfarin therapy
3. **A minimum overlap of argatroban and warfarin of at least 5 days is advised**
4. **Argatroban has a significant effect on the INR**
5. **NO loading doses of warfarin to be given**
6. Start with the intended maintenance dose of warfarin (no greater than 5mg daily)
7. 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]
8. Repeat INR 4 to 6 hours after stopping argatroban, to ensure INR is therapeutic prior to permanent discontinuation of argatroban[ref 3]
9. If INR is below the desired therapeutic range recommence argatroban and repeat the procedure above (steps 2 to 6)
10. **Take INR at least daily**

Monitoring

- See above

Further information

- In trials for patients with HIT-II undergoing PCI investigations, ACT measurements were carried out using Haemotec and Haemochrom equipment
- APTTr; the patient's activated partial thromboplastin time divided by either the laboratory's normal value or the patient's own baseline value
- Argatroban interferes with CLAUSS fibrinogen measurement. Derived fibrinogen results will also be reduced on argatroban treatment [ref 1]

Percutaneous coronary interventions (PCI) in patients with, or at risk of HIT/HITTS

1. A slow intravenous injection of 350 micrograms/kg should be given via a large bore IV line over 3 to 5 minutes. This is followed by a continuous infusion of 25micrograms/kg/min
2. Activated clotting time (ACT) should be checked 5 to 10 minutes after the bolus dose is completed
3. The procedure may proceed if the ACT is greater than 300 seconds
4. If the ACT **is less than 300 seconds**, an additional IV bolus dose of 150 micrograms/kg should be administered, and the continuous infusion rate should be increased to 30 micrograms/kg/minute
5. The ACT should be checked 5 to 10 minutes later. If the ACT is **greater than 450 seconds,** the infusion rate should be decreased to 15 microgram/kg/minute, and the ACT checked again 5 to 10 minutes later
6. Once the ACT is between 300 and 450 seconds, the infusion dose should be continued for the duration of the procedure. Additional ACTs should be drawn about every 20 to 30 minutes during a prolonged procedure [ref 3]
7. In the case of dissection, impending abrupt closure, thrombus formation during the procedure, or inability to achieve or maintain an ACT over 300 seconds, additional bolus doses of 150micrograms/kg may be administered and the infusion rate increased to 40micrograms/kg/minute. Recheck ACT after each additional bolus or change in infusion rate[ref 3]
8. If a patient requires anticoagulation after the procedure, argatroban may be continued at a reduced dose of 2 micrograms/kg/minute with close monitoring of **APTT.** Adjust rate of infusion as needed (ref 3)
9. Use of high doses of Argatroban in patients who have undergone **percutaneous coronary intervention (PCI)** with **clinically significant hepatic disease** or AST/ALT levels greater than or equal to three times the upper limit of normal should be avoided [ref 3]

Storage

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

direct sunlight)

References

UK SPC (Exembol) 13th Sept 2017

1. Dr Ruth Gilmore, Consultant Haematologist, 20th April 2021

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

3. Uptodate accessed online13th Feb 2019

Therapeutic classification

Parenteral anticoagulants

BNF
Blood clots