Direct Thrombin Inhibitor (DTI) Dosing Guidelines

For Prevention & Treatment of Thrombosis in Heparin-Induced Thrombocytopenia (HIT)

1. Before starting a DTI
   - Stop all heparin (including catheter flushes), enoxaparin or dalteparin, and warfarin
   - Obtain baselines labs (if none in the past 24 hours)- CBC, PTT, PT/INR, Basic Metabolic Profile, LFTs
   - If aPTT is > 65 seconds, do not start DTI
     - Recheck aPTT every 2 hours until < 65 seconds, then start DTI
   - Monitor a CBC and aPTT at least daily during treatment
   - Consider consulting Hematology

2. If the patient has a baseline aPTT of **22 – 37 seconds** (**UHS reference interval, updated June 2009**):
   - The **target aPTT is 45 - 70 seconds**
   - This is lower than heparin anticoagulation goals and approximately 2 X UHS normal range
   - If the baseline aPTT is > 40 seconds, Hematology consult is recommended

3. **Lepirudin** dosing recommendations:
   - Initiate dose at **0.075 mg/kg/hour**, bolus dosing not recommended
     (Note: lower than FDA-approved initial dosing)
   - Check aPTT every 4 hours until consecutive values are in range, and at least daily thereafter

   - **In patients with renal dysfunction**, CrCl≤ 60 mL/min or SCr >1.5 mg/dL
     - **Use argatroban**
     - Half-life of lepirudin can be extended up to 2 days (normal half-life 1.3 hours)

   - **Adjusting lepirudin dose based on the aPTT: Revised June 2009**

aPTT	Directions
< 40 seconds	Increase infusion rate in increments of 20% Recheck aPTT 4 hours after dosage change
45 – 70 seconds	No change
> 75 seconds	Stop infusion for 2 hour and restart at 50% reduced infusion rate Recheck aPTT 4 hours after restart

   - **Conversion to Warfarin**

     If decision is made to continue anticoagulation with oral therapy (warfarin) after lepirudin infusion, several steps should be taken to avoid the pro-thrombotic effects of warfarin:
     - Do not use warfarin as monotherapy in acute HIT
     - Do not initiate warfarin until the platelet count has rebounded to >100 K/µL
     - Before initiating warfarin, gradually reduce the rate of lepirudin until the aPTT ratio is ~45 seconds).
     - Do not use a loading dose of warfarin; initiate therapy with expected maintenance dose
     - **Overlap** warfarin and lepirudin therapy for at least 5 days – to allow for the 1/2–lives of all the clotting factors
     - Measure INR daily; INR will be affected by lepirudin as well as by warfarin
     - Stop lepirudin when INR stabilizes (at least 2 daily readings) within the desired target range (2 to 3) – but not before 5 days of total overlap.
     - Check INR 4 to 6 hours after stopping lepirudin to assure that therapeutic goal is maintained

Argatroban dosing recommendations:

- Initiate dose at **1 mcg/kg/min** (Note: this is lower than FDA-approved initial dosing)
- Check aPTT every 2 hours until consecutive values are in range, and at least daily thereafter
  - **In patients with hepatic impairment**
    - Initiate dose at 0.5 mcg/kg/min
    - Half-life can be extended up to 180 minutes (3 x normal half-life of 39-51 minutes)
    - **Use lepirudin**
  - **In patients with renal impairment**
    - Argatroban is not renally eliminated, and does not require initial dosage adjustments

**Clinical conditions which may warrant dosing as low as 0.1 or 0.2 mcg/kg/min:
High risk of bleeding
Coagulopathy
Severe liver disease
Severe kidney disease

- **Adjusting argatroban dose based on aPTT: Revised June 2009**

aPTT	Directions
< 40 seconds	Increase infusion rate in increments of 20% Recheck aPTT 2 hours after dosage change**
45 – 70 seconds	No change
> 75 seconds	Stop infusion for 1 hour and restart at 50% reduced infusion rate Recheck aPTT 2 hours after restart

**For clinical condition listed above, consider more intense monitoring to assure the patient has reached steady-state before doses are increased (ex. aPTT every 2 hrs X 4, then increase dose if aPTT < 30 sec)

- **Conversion to Warfarin**

  If the decision is made to continue anticoagulation with oral therapy (warfarin) after argatroban infusion, several steps should be taken to avoid the pro-thrombotic effects of warfarin:
  - Do not use warfarin as monotherapy in acute HIT
  - Do not initiate warfarin until the platelet count has rebounded to >100 K/µL
  - Do not use a loading dose of warfarin; initiate therapy with expected maintenance dose
  - **Overlap** warfarin and argatroban therapy for at least 5 days – to allow for the half–lives of all the clotting factors
  - Measure INR daily; INR will be significantly affected by argatroban as well as by warfarin; however increased INR may not correspond to an increased risk of bleeding
  - To stop argatroban infusion, see table below:

For doses ≤ 2 mcg/kg/min	For doses > 2 mcg/kg/min
• Discontinue argatroban when the INR is > 4 on combined therapy (& and least 5 days of overlap) • Check INR 4 to 6 hours after stopping argatroban to assure therapeutic goal (INR 2 - 3) is maintained • If repeat INR is below desired therapeutic range (2 - 3) resume argatroban & repeat procedure daily until desired therapeutic range on warfarin alone is reached	• INR cannot be reliably predicted at argatroban doses > 2 mcg/kg/min • Temporarily reduce dose of argatroban to 2 mcg/kg/min (in order to predict INR on warfarin alone) • Repeat INR 4 to 6 hours after reduction and follow the process outlined for doses up to 2 mcg/kg/min

This is to be used as a guide and should not supersede clinical judgment. For questions call pharmacy or consider consulting Hematology.