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All formulary changes and policy/procedure updates have been approved by the Drugs and Therapeutics (D&T) Committee and Medical Advisory Council (MAC).

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## *Changes to Formulary*

### **Additions**

- Sumatriptan 50mg, 100mg tablets, 6mg/0.5mL injection (Imitrex®)**
  - Serotonin agonist indicated for acute treatment of migraine attacks
  - See page 2 for review
- Argatroban injection**
  - Alternative to danaparoid for use in patients with heparin-induced thrombocytopenia and renal failure
  - Restricted to Hematology Service
  - See page 3 for review
- Activated Protein C injection (drotrecogin alfa, Xigris®)**
  - Anti-sepsis therapy for reduction of mortality in adults with severe sepsis who

have a high risk of death

- Patients must meet all criteria on the "Activated Protein C for Severe Sepsis" pre-printed order (PPO) form
- See page 5 for review

### **Deletions**

- Lepirudin injection (Refludan®)**
  - Alternative: Argatroban injection

## *Updated Policies/Procedures*

### **1. Drug Formulary Update 2003**

All VGH, UBCH and GF Strong nursing units have been updated with the 2003 formulary. The sections in the formulary are colour coded and have been expanded to include:

- Green section: contains a more extensive section on Pharmacy Policy and Procedures related to drug prescribing, dispensing and administration
- Yellow section: contains several comparison charts of different classes of drugs as well as dosing guidelines for select drugs, serum drug level monitoring and antimicrobial dosing

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- c White section: contains all formulary drugs at VGH, UBCH and GF Strong classified according to their pharmacological action
- d Pink section: contains the index which is used to locate specific page numbers for each drug located in the white section of the formulary. The index lists both generic and trade names.

If there are any questions regarding the formulary, please contact Dr. Karen Shalansky at 604-875-4839.

## 2. Amphotericin B Lipid Complex (Abelcet®)

Amphotericin B lipid complex (Abelcet®) is the formulation of choice for patients with decreased renal function who require amphotericin therapy. Amphotericin liposomal (AmBisome®) is reserved for those patients who experience serious infusion-related reactions from Abelcet® (e.g. hypotension, arrhythmias). Both products require Pharmacy and/or Infectious Diseases approval.

## 3. Verbal/Telephone Orders Amendment

The verbal/telephone order policy has been amended to allow pharmacists to take telephone orders to initiate the compounding of a chemotherapy preparation. The receipt of a written chemotherapy order is still required prior to its actual dispensing.

## 4. Revised Drug Administration Policies

**Sonographers are authorized to administer alprostadil (Prostin VR®) into the corpus cavernosa** (for determination whether a patient's impotence is vasculogenic in origin).

The **standard insulin infusion concentration** for intensive control of glucose in the critical care areas is **100U/100mL**.

## *New Drug/Drug Products*

### 1. Sumatriptan (Imitrex®)

Ruby Sangha, B.Sc. (Pharm), Karen Shalansky, Pharm.D.,  
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Sumatriptan is indicated for the acute treatment of migraine attacks, with or without aura.<sup>1</sup> It is structurally related to serotonin and is an agonist at 5-HT<sub>1D</sub> and 5-HT<sub>1B</sub> receptors. As such,

sumatriptan vasoconstricts dilated cerebral blood vessels, inhibits the release of vasoactive neuropeptides by trigeminal nerves and inhibits nociceptive neurotransmission.<sup>2</sup>

### *Comparison to Other Agents*

Sumatriptan has been shown to be superior to placebo for acute migraine treatment.<sup>3</sup> Efficacy rates compared to placebo are significantly higher after 2 hours (60% vs. 38%, p<0.001) and 4 hours (79% vs. 47%, p<0.001).<sup>4</sup> Sumatriptan is also effective in relieving other symptoms such as nausea, vomiting, photophobia, and phonophobia and in reducing clinical disability.<sup>5</sup>

There are currently no "triptans" on formulary at VHHSC. Table 1 compares the current serotonin agonists for migraine treatment available in Canada. Differences amongst the oral triptans are considered to be relatively small.<sup>6</sup> Sumatriptan 100mg orally has been shown to be superior to oral ergotamine 2mg and single doses of aspirin 900mg plus metoclopramide 10mg.<sup>4</sup> Similarly, subcutaneous (SC) use has also shown higher response rates compared to dihydroergotamine and other acute migraine treatments (e.g. oral analgesics, non-steroidal anti-inflammatory drugs).<sup>4</sup>

**Table 1. Comparison of Triptans for Migraine Therapy**

Drug	T <sub>max</sub>	Half-Life (hrs)	Typical Dose	VHHSC Cost
Nara-triptan (Amerge®)	3.8 hrs (range 2-5 hrs)	5-8	1-2.5mg	\$13.16-13.86
Riza-triptan (Maxalt®)	1-1.5 hrs (tablets)	2-3	5-10mg (tablet/wafer)	\$13.85 (5 and 10mg)
Suma-triptan (Imitrex®)	PO: 2 hrs (range 0.5-5 hrs) SC: 15 minutes	2	PO: 50-100mg SC: 6mg	PO: \$13.86-15.27 SC: \$37.08
Zolmi-triptan (Zomig®)	2-4 hrs	2.5-3 (parent)	2.5-5mg	\$13.86-27.71

T<sub>max</sub> = time to maximum concentration in blood

### *Adverse Events*

The most frequently reported adverse events from oral sumatriptan compared to placebo are nausea/vomiting (14% vs 7%), taste disturbances (11% vs 3%), malaise/fatigue (9% vs 3%) and dizziness/vertigo (6% vs 2%).<sup>4</sup> Some of these symptoms are

also typical of migraines. In patients receiving SC sumatriptan, the most common adverse effects are minor injection site reactions and nausea.<sup>5</sup>

Both oral and SC sumatriptan have been reported to cause angina-like symptoms such as chest pressure, tightness and pain in 2-3% of patients, possibly resulting from coronary artery constriction.<sup>5,7</sup> The majority of serious cardiovascular effects, including coronary vasospasm with ischemia, unstable angina, myocardial infarction and cardiac arrhythmias, occur within a few hours of administration of the drug in patients with a history of cardiovascular disease or those with cardiovascular risk factors.<sup>5</sup> As such, sumatriptan is contraindicated in patients with a history of cardiac, cerebrovascular or peripheral vascular disease, and in patients with uncontrolled hypertension.<sup>1,6</sup>

#### Dosage

Oral: 50-100mg; may repeat in 2 hours if migraine returns or partial response; maximum 200mg per 24 hour period.<sup>1</sup>

Injection: 6mg SC; may repeat in 1 hour if migraine returns or partial response; maximum 12mg per 24 hour period.<sup>1</sup>

#### Conclusion

Sumatriptan provides good efficacy and tolerability and has the longest clinical experience amongst the triptans. Unlike the other triptans, sumatriptan offers a parenteral formulation, which may offer an advantage if the oral route is not feasible. The SC route offers the fastest relief of symptoms compared to oral administration. Sumatriptan is contraindicated in patients with a history of cardiovascular disease and cautious use is advised in those with cardiovascular risk factors.

#### References

1. Imitrex<sup>®</sup> Product Monograph. CPS 2001.
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## 2. Argatroban Injection

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Argatroban is an anticoagulant for use in patients with heparin-induced thrombocytopenia (HIT).

#### Pharmacology

Argatroban is a small synthetic molecule that reversibly inhibits thrombin. It is highly selective for thrombin and is capable of inhibiting the action of free and clot-bound thrombin.<sup>1,2</sup> Argatroban is eliminated primarily by hepatic metabolism and biliary secretion. Its elimination half-life is 0.8 hours.<sup>1,3</sup> Renal dysfunction does not affect the clearance of argatroban whereas moderate hepatic impairment is associated with an increased half-life of 2.5 hours.<sup>1</sup>

Argatroban increases, in a dose-dependent fashion, the aPTT, INR and thrombin time.<sup>1</sup> Steady-state levels of anticoagulation are reached within 2.5 hours after initiation of argatroban infusion or after dosage adjustments.<sup>1</sup>

**Table 1. Comparison of Anticoagulants for HIT**

Drug	Argatroban	Lepirudin <sup>a</sup> (Refludan <sup>®</sup> )	Danaparoid (Orgaran <sup>®</sup> )
<b>Mechanism of Action</b>	Direct thrombin inhibitor	Direct thrombin inhibitor	Inactivates factors Xa and IIa
<b>Monitoring</b>	aPTT 1.5-3x baseline	aPTT 1.5-2.5x baseline	Anti-Xa level (if severe renal failure)
<b>Plasma Half-Life</b>	0.8 hrs	1.3 hrs	25 hrs (anti-Xa activity)
<b>Peak Onset</b>	1-3 hrs	2-3 hrs	4-5 hrs
<b>Cross-reactivity with HIT antibodies</b>	0%	0%	< 10%
<b>Dose</b>	2mcg/kg/minute	0.4mg/kg, then 0.15mg/kg/hr	1500-3750 U, then gradual decrease to 200U/hr
<b>Dosage in Renal Impairment</b>	No Dose Adjustment	Avoid if CrCl < 15mL/min	Dose guided by anti-Xa levels
<b>Cost/day (Maintenance)</b>	\$510.00	\$504.00	\$108-126.00

<sup>a</sup>Non-formulary drug at VHHSC

### *Comparable Formulary Agents*

Lepirudin was initially approved for formulary addition in June 2002. Although more costly than danaparoid, its advantages include lack of cross-reactivity with HIT antibodies, ease of monitoring via aPTT, and shorter elimination half-life enabling rapid dose titration as well as discontinuation of anticoagulation in patients with planned invasive procedures. Argatroban has only recently been approved for use in Canada.

Like lepirudin, argatroban is also a direct thrombin inhibitor and is monitored via aPTT. Approximately 50% of lepirudin-treated patients develop drug-specific antibodies that can alter its anticoagulant effects, hence complicating monitoring and dosing.<sup>2</sup> Because argatroban is a small and synthetic molecule, it does not induce formation of antibodies that can alter its clearance. As well, both lepirudin and danaparoid require special attention to dosing in patients with renal failure, whereas argatroban can be safely used without dosage adjustments. Compared with lepirudin, argatroban has an even shorter half-life enabling rapid dose titration and reversal of its anticoagulant effects.<sup>2,6</sup>

There are no published studies comparing argatroban with lepirudin or danaparoid. In a nonrandomized multicenter study, 160 patients with isolated HIT and 144 patients with HIT thrombosis syndrome (HITTS) received argatroban 2mcg/kg/min for 6 days.<sup>2</sup> Clinical outcomes over 37 days were compared with 193 historical-controlled subjects (147 HIT and 46 HITTS). The incidence of the primary composite outcome of all-cause death, all-cause amputation or new thrombosis favoured argatroban (25.6% vs 38.8% in HIT group,  $p=0.014$ , and 43.8% vs. 56.5% in HITTS group,  $p=0.13$ ). Bleeding events were similar between the groups.

### *Adverse Events*

The major side effect associated with argatroban is bleeding. In a nonrandomized study, bleeding events were similar with a trend to more major bleeding with argatroban in patients with HITTS (argatroban 11.1% vs. historical control 2.2%,  $p=0.077$ ).<sup>2</sup> There is no specific antidote to argatroban. Gastrointestinal symptoms such as vomiting and diarrhea appeared to occur more commonly in the argatroban than control group (vomiting 5% vs 0%; diarrhea 11% vs 2%).<sup>1,2</sup>

### *Dosage*

The recommended initial dose for treatment of HIT in adult patients without hepatic impairment is 2mcg/kg/min (maximum 10mcg/kg/min), administered as a continuous infusion. Argatroban therapy is monitored using aPTT which should be maintained between 1.5 to 3 times the baseline value.<sup>1,4</sup> Therapeutic aPTT is generally achieved within 2.5 hours of commencing an infusion.<sup>4</sup> No dosage adjustments are required in patients with renal impairment but dosage should be reduced to 0.5mcg/kg/min with hepatic impairment.<sup>1</sup>

Argatroban has a synergistic effect on INR in patients receiving warfarin which affects interpretation of the INR during conversion to anticoagulation with warfarin. The INR should be interpreted differently for patients receiving argatroban up to 2mcg/kg/min than those receiving > 2mcg/kg/min. An INR of 4.0 in patients receiving warfarin in combination with argatroban 2mcg/kg/min may be interpreted as an INR between 2-3 attributed to warfarin alone.<sup>4,5</sup> Argatroban infusion should be stopped when the INR is > 4.0 and a repeat INR obtained after 4-6 hours. If the repeat INR is subtherapeutic, argatroban infusion should be resumed and this procedure repeated daily until INR is in the therapeutic range. The interpretation of INR on combined therapy in patients receiving argatroban > 2mcg/kg/min is less well established. For such patients, it is recommended that the argatroban dose be decreased to 2mcg/kg/min and an INR obtained 4-6 hours later.<sup>5</sup> Thereafter, the process outlined above should be followed.

### *Place in Therapy*

Argatroban offers several theoretical advantages over danaparoid for HIT patients. It is easily monitored via aPTT and its anticoagulant effect is rapidly reversible. While argatroban is more costly than danaparoid, it is probably more cost-effective in special populations who require anti-Xa level monitoring to guide therapy with danaparoid (e.g. severe renal impairment, unusually low or high body weight). Argatroban is currently restricted to Hematology for use as an alternate to danaparoid.

### *References*

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### 3. Activated Protein C (drotrecogin - Xigris®)

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Recombinant human activated protein C (rhAPC) (generic name: drotrecogin alfa) is indicated for the reduction of mortality in adult patients with severe sepsis (sepsis associated with acute organ dysfunction) who have a high risk of death (e.g. as determined by APACHE II, or multiple acute organ dysfunctions).<sup>1</sup>

#### Pharmacology

RhAPC is a biological agent that has activity in severe sepsis and septic shock via anti-inflammatory, anticoagulant, and fibrinolytic properties.<sup>2</sup> It is thought to inhibit production and release of proinflammatory cytokines (e.g. TNF, IL-1, IL-6), and limit neutrophil activation and ongoing endothelial damage due to tissue factor expression and activation.<sup>2-4</sup> RhAPC acts as an anticoagulant by cleaving activated clotting factors V and VIII, leading to a reduction in thrombin generation.<sup>2-4</sup> It also acts to restore fibrinolytic activity by inactivating fibrinolytic inhibitors (platelet activator inhibitor-1 and thrombin activatable fibrinolysis inhibitor). Ultimately, these actions reduce inflammation and propensity for clotting. Both are factors that may contribute to multiple organ dysfunction syndrome in patients with severe sepsis and septic shock.<sup>2-5</sup>

Although protein C is produced endogenously, it cannot always be activated properly to perform its physiological functions due to physiological disruptions in the endothelium of septic patients.<sup>6</sup> This endogenous activated protein C deficiency has been associated with increased mortality in patients with severe sepsis or septic shock.<sup>7</sup>

#### PROWESS Trial

There has been only one large phase III clinical trial for rhAPC: Protein C Worldwide Evaluation in Severe Sepsis Study (PROWESS).<sup>8</sup> This was a prospective, randomized, placebo-controlled multicentre 2 year trial of 1690 patients. Patients were included if they had at least 3 or 4 criteria for systemic inflammatory response syndrome

(SIRS), known or suspected infection, and at least one organ/system dysfunction lasting less than 24 hours. To reduce confounding variables and improve safety, patients were excluded if they were not expected to survive 28 days due to an underlying medical condition (e.g. neoplasm), or if they were at increased risk of bleeding.

Patients were administered rhAPC 24mcg/kg/hr or placebo infusion for 96 hours. The primary outcome was 28-day all-cause mortality. Secondary outcomes included changes in baseline levels of IL-6 and D-dimer, and serious adverse events.

Overall, the 28-day all-cause mortality was 24.7% in the rhAPC group compared to 30.8% in the placebo group ( $p=0.005$ , absolute risk reduction 6.1%, number needed to treat (NNT) 16). Subsequent analysis showed that mortality benefit was restricted to patients with an APACHE II score of 25 or greater.<sup>9-11</sup> This group of patients demonstrated a 13% absolute risk reduction in mortality, with an NNT of 8.<sup>9-11</sup> RhAPC showed significant reductions in the surrogate markers of inflammation and coagulation. IL-6 levels were significantly lower in the treatment group on days 1 and 4-7 ( $p<0.05$ ). As well, d-dimer levels were also significantly lower on days 1-7 ( $p<0.05$ ).

The overall incidence of adverse events was 12.5% in the rhAPC group and 12.1% in the placebo group ( $p=0.084$ ). There was a trend toward increased serious bleeding during the 28-day study period (3.5% rhAPC vs 2.0% placebo,  $p=0.06$ ). The incidence of bleeding during the 96-hour infusion was significantly higher with rhAPC (2.4% vs 1%,  $p=0.024$ ).<sup>9</sup>

In conclusion, rhAPC at a dosage of 24mcg/kg/hr via continuous infusion over 96 hours produced a significant reduction in all-cause mortality in a highly selected group of patients with severe sepsis and/or septic shock. There was a significantly higher risk of serious bleeding with rhAPC during the 96-hour infusion period.

#### Potential Risks/Contraindications

Given its known mechanism of action as an anticoagulant and fibrinolytic, the most predictable and significant adverse effect from rhAPC is bleeding. In the PROWESS trial<sup>8</sup>, the rate of serious bleeding was 3.5% and the intracranial hemorrhage rate was 0.2% over the 28-day study

period. Most of the serious bleeding complications were related to invasive or surgical procedures, or in patients with meningitis or thrombocytopenia (platelet counts  $< 30,000/\text{mm}^3$ ).<sup>8-10</sup> Patients with the greatest risk for serious bleeding were those with APACHE II scores  $< 19$ ; these patients also had the least mortality benefit from rhAPC.<sup>10</sup>

Since the publication of PROWESS, many patients have been given rhAPC in other open-label and compassionate use protocols. The Food and Drug Administration has reported that despite similar usage criteria, 13 of 520 patients (2.5%) had suffered intracranial hemorrhages, with 8 (1.5%) occurring during the infusion period.<sup>9,10</sup>

#### Absolute contraindications to rhAPC at VGH are:

- time from first sepsis-induced organ dysfunction/failure to protein C anticipated to be  $> 48$  hrs
- suspected or proven active internal bleeding; trauma with an increased risk of life-threatening bleeding
- intracranial neoplasm, mass lesion or raised intracranial pressure, cerebral herniation;
- history of intracerebral A-V malformation, cerebral aneurysm
- history of congenital bleeding diatheses; presence of epidural catheter
- recent (within 3 months) hemorrhagic stroke; recent (within 2 months) intracranial or intraspinal surgery, or severe head trauma requiring hospitalisation
- known hypersensitivity to protein C
- acute pancreatitis with no established source of infection
- platelets  $< 30,000/\text{mm}^3$
- INR  $> 3.0$  or aPTT  $> 120$  seconds

#### Any of the following drugs:

- warfarin (within 7 days) if the INR exceeds 1.2
- glycoprotein IIb/IIIa antagonists (within 7 days)
- ASA  $> 650\text{mg}/\text{day}$  (within 3 days)
- thrombolytic therapy (within 3 days) (treatment of thromboses within a catheter permitted)
- protein C (within 24 hours)
- low molecular weight heparin (within 12 hours) at higher than prophylactic doses
- antithrombin III (within 12 hours) at a dose  $> 10,000\text{U}$
- unfractionated heparin (within 8 hours) to treat an active thromboembolic event (prophylactic treatment with doses  $\leq 15,000\text{U}/\text{day}$  permitted)

#### Dosage/Pharmacokinetics

The dose of RhAPC is 24mcg/kg/hour as a continuous infusion for 96 hours. RhAPC is inactivated by endogenous plasma protease inhibitors and has an elimination half-life of 1.6 hours.<sup>1,4</sup> The clearance of rhAPC is not affected

by acute renal or hepatic dysfunction, and no dosage adjustments are necessary in these settings.<sup>1</sup>

#### Pharmacoeconomics

There have been two pharmacoeconomic evaluations of rhAPC based on the results of the PROWESS study.<sup>12,13</sup> Both studies confirm a relatively favourable cost per life-year gained when rhAPC is limited to patients with APACHE II scores  $\geq 25$ . The incremental cost per life-year gained is \$28,993Cdn or \$40,000-48,000Cdn per QALY (quality-adjusted life-year gained). The drug acquisition cost of rhAPC for a 96-hour treatment course is  $\sim \$10,000$ .

#### Conclusions

RhAPC represents a novel therapy for adult patients with severe sepsis (sepsis associated with acute organ dysfunction lasting  $< 48$  hours) who have a high risk of death. Based on results from the phase III clinical trial (PROWESS), rhAPC reduces 28-day mortality in the entire cohort by 6.1%. The mortality benefit, however, was restricted to patients with an APACHE II score  $\geq 25$ , with an absolute reduction in mortality of 13% in this group. In order to obtain rhAPC at VHHSC, patients must meet all criteria on the "activated protein C for severe sepsis" PPO.

#### References

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