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PHARMACY AND THERAPEUTICS NEWSLETTER

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In This Issue...

Changes to Formulary

Additions

Clinicians should review medication information prior to administering any unfamiliar medication. Resources include: VCH PDTM, Lexicomp®, or UpToDate®.

1. **Tiotropium soft mist inhaler 2.5 mcg/ actuation (Spiriva® Respimat®)**
   - Anticholinergic inhaler
   - Tiotropium delivered via the Handihaler® device remains on formulary.

2. **Idarucizumab 2.5 g injection (Praxbind®)**
   - Reversal agent for dabigatran (Pradaxa®)
   - Restricted to patients on dabigatran with severe life-threatening bleeding or who require emergent procedures within 8 hours where normal hemostasis is required.
   - See page 2 for drug review

3. **Posaconazole 100 mg delayed release tablets (Posanol®)**
   - Antifungal agent
   - Restricted to Infectious Disease and L/BMT services for prophylaxis or treatment of invasive fungal infections.

4. **Moxifloxacin 0.5% ophthalmic drops (Vigamox®)**
   - Quinolone antibacterial eye drop
   - Quinolone eye drops other than ciprofloxacin 0.3% will be interchanged to moxifloxacin per Table 1.

Table 1. Quinolone Ophthalmic Interchange

Eye Drop Ordered	Eye Drop Dispensed
Gatifloxacin 0.3% (Zymar®)	Moxifloxacin 0.5% (same number of drops and frequency)
Ofloxacin 0.3% (Ocuflox®)	

5. **Filgrastim (G-CSF) 300 mcg, 480 mcg pre-filled syringes (Grastofil®)**
   - Hematopoietic agent
   - Grastofil® is a lower cost biosimilar brand of G-CSF(Neupogen®)
   - The two brands are considered "switchable" at any point during therapy for BCCA and HIV/AIDS approved indications, as response to therapy can be readily monitored.
   - The following formulary restrictions will be applied when G-CSF is ordered:

Table 2. Filgrastim (G-CSF) Restrictions

Formulary Restriction	Filgrastim Brand Dispensed
Indications outlined in BCCA Benefit Drug List & patients registered with BCCA	Grastofil®
Approval of Centre for Excellence in HIV/AIDS	Grastofil®
Hematology Apheresis Unit donors	Neupogen®
Pediatrics	Neupogen®

Deletions

1. Droperidol injection (Inapsine®)
2. Ferumoxytol injection (Feraheme®)
3. Vitalux® AREDS multivitamin tabs with lutein
   - Replacement: Vitalux® Advanced caplets (contains lutein 5 mg)
4. Ofloxacin 0.3% eye drops (Ocuflox®)

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New Drug/Drug Products

Idarucizumab (Praxbind®)

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Idarucizumab is a specific reversal agent for the novel oral anticoagulant dabigatran (Pradaxa®). It has been added to BCHA formulary for use in patients on dabigatran with severe life-threatening bleeding or who require emergent procedures within 8 hours where normal hemostasis is required.

Mechanism of Action

Idarucizumab is a monoclonal antibody that binds specifically to dabigatran, preventing dabigatran from binding to thrombin. Idarucizumab is structurally similar to thrombin but has ~350 times greater affinity for dabigatran than does native thrombin, thereby forming a stable complex and reversing the anticoagulant effect of dabigatran.[1]

Pharmacokinetics/Pharmcodynamics

Normalization of abnormal bleeding tests occurs within minutes; hemostasis in patients with bleeding is restored at a median of 11.4 hours.[2] Duration of activity is at least 24 hours. Idarucizumab is metabolized to small peptides and a portion is renally cleared (32% within 6 hrs); the terminal half-life is 10.3 hours.[1]

Literature Evaluation

There is one uncontrolled prospective cohort study, RE-VERSE AD, supporting the use of idarucizumab as a reversal agent for dabigatran.[2] This was a single arm, prospective study of 2 groups of patients on dabigatran primarily for atrial fibrillation:

- Group A (n=51): overt, uncontrollable or life threatening bleeding requiring a reversal agent
- Group B (n=39): patients requiring urgent surgery or other invasive procedure that could not be delayed for at least 8 hours.

All patients were given idarucizumab 2.5 g IV bolus x 2 doses no more than 15 minutes apart. The primary endpoint was maximum reversal of anticoagulant effect of dabigatran based on dilute thrombin time (dTT) or ecarin clotting time (ECT), within 4 hours after idarucizumab administration.

This interim analysis showed that the median maximal percentage reversal in both groups was 100% (95%CI 100 to 100). Idarucizumab normalized laboratory values in 88-98% of patients within minutes (dTT normalized in 93-98% patients, ECT normalized in 88-89% patients). Median time to restoration of hemostasis in patients who presented with bleeding (Group A) was 11.4 hours, and median time to surgery (Group B) was 1.5 hours (range 1.2-26.5 hours). Normal intraoperative hemostasis was reported in 92% of patients.

There were 21 serious adverse events reported (some patients experienced more than 1 event): 18 deaths (9 in each group), 5 thrombotic events, 2 GI hemorrhages, 1 wound infection, 1 delirium, 1 right ventricular failure, and 1 pulmonary edema.

Dosage

Idarucizumab 5 g (administered as two separate 2.5 g/50 mL bolus doses, given no more than 15 minutes apart.

The elimination half-life of dabigatran is expected to be longer in patients with renal impairment. Thus, renal function should be considered when deciding whether the use of idarucizumab is indicated.

Renal Function (eGFR)	Appropriate Window for Idarucizumab Administration after Last Dose of Dabigatran
Above 50 mL/min	Up to 2 days
30-50 mL/min	Up to 4 days
Less than 30 mL/min	Up to 6 days

Adverse Effects

- Hypersensitivity reactions (fever, rash, pruritus, bronchospasm)
- Others: hypokalemia (7%), constipation (7%), pneumonia (6%), delirium (7%)
- Note, patients are at risk for a thromboembolic event as reversing anticoagulation with idarucizubmab will expose patients to the thrombotic risk of the underlying disease.

Monitoring

- Signs and symptoms of bleeding
- Baseline CBC, INR/PTT, TT, fibrinogen, eGFR
- Repeat PTT and TT at 4, 12, and 24 hours after idarucizumab administration

When to Restart Anticoagulation

Anticoagulation with dabigatran or other therapies may be considered 24 hours after idarucizumab is administered if the patient is stable and there are no signs of bleeding.

Conclusion

Idarucizumab reverses the anticoagulant effect of dabigratran within minutes, with cessation of bleeding at a median of 11.4 hours. The regional Pre-Printed Order for idarucizumab (PPO #988) is posted on the VCH intranet.

References

[1] Finks SW, Rogers KC. Amer J Med 2016;130(5):e196-e197.
[2] Pollack CV et al. NEJM 2015;373(6):511-520.