D&T Decisions

... from the Drugs and Therapeutics Committee

Central Zone

Issue # 63: Dec. 16, 2016

Inside this Issue…..

Additions to Formulary
- Idarucizumab, *Praxbind*™
- Ranibizumab, *Lucentis*®
- Aflibercept, *Eylea*®
- Fidaxomicin, *Dificid*®

Expanded Restrictions
- Bevacizumab, *Avastin*®

Pre-Printed Orders

Other - Idarucizumab Audit Tool

The following policies were approved by the Medical Advisory Committee (Oct16, Nov16) on the recommendation of the Drugs and Therapeutics Committee (Jun16, Sep 16).

I. Additions to Formulary

Idarucizumab, *Praxbind*™

Idarucizumab is a specific reversal agent for dabigatran. There are currently three direct oral anticoagulants (DOACs) on the Canadian market: dabigatran, rivaroxaban and apixaban. Dabigatran is an oral thrombin inhibitor that reversibly binds to the active site of thrombin which inactivates thrombin and prevents the conversion of fibrinogen to fibrin. Rivaroxaban and apixaban are factor Xa inhibitors; therefore, the mechanism of action differs from that of dabigatran. All anticoagulants have the potential to cause serious life-threatening bleeding; however, idarucizumab only reverses the action of dabigatran.

Idarucizumab is a humanized, mouse, monoclonal antibody fragment that binds to dabigatran and its metabolites. Its reversal of the anticoagulant effects of dabigatran is within 5 minutes of administration. The 12 to 17 hour half-life of dabigatran is adequate for planned interruptions to therapy before elective surgery; therefore, the indications for idarucizumab are for emergency surgery/ urgent procedures or life threatening/ uncontrolled bleeding.

Idarucizumab was issued Canadian marketing authorization with conditions based on interim results of the RE-VERSE AD case series study (n = 90). This ongoing trial intends to recruit 300 patients from more than 400 hospitals and includes adult patients taking dabigatran divided into two groups: group A includes patients with overt, uncontrollable, or life-threatening bleeding who are felt to require reversal, and group B includes patients who require surgery or other invasive procedures that cannot wait for at least 8 hours for the effect of dabigatran to wear off. Patients receive 5 g of IV idarucizumab administered as 2.5 g in 2 infusions no more than 15 minutes apart. The Canadian Monograph states that there is limited data to support the administration of an additional 5 g.

In the interim analysis of REVERSE-AD, there were 18 deaths overall (9 in each group) with 5 of the deaths due to bleeding. Five patients had a thrombotic event, including deep vein thrombosis, pulmonary embolism, left atrial thrombosis, ischemic stroke, and myocardial infarction.

Since idarucizumab is costly and clinical data is limited, an audit tool has been developed to help determine criteria for use, clinical benefits and safety. Prescribers are required to complete the audit tool and return the completed form to Pharmacy. The site Pharmacy Department will summarize all Audit Tool information and send to the NSHA Drugs and Therapeutics Committee every six months. The Idarucizumab Audit Tool is attached.

Approved Restriction:
For rapid reversal of the anticoagulant effects of dabigatran in patients:
- with overt, uncontrolled, or life-threatening bleeding
- who require surgery or other invasive procedures that cannot wait for at least 8 hours for the effect of dabigatran to wear off

Ranibizumab, *Lucentis*®
Aflibercept, *Eylea*®

Ranibizumab and aflibercept are vascular endothelial growth factor (VEGF) antagonists that are currently administered by an ophthalmologist as an intravitreal injection in the Ophthalmology Clinic at the Central Zone VG site of the NS Health Authority. This therapy is currently funded by the NS Department of Health and Wellness (DHW) through the Provincial High Cost Drug Program via Pharmacare. There is no cost impact of this therapy to NSHA; however, there was a request to add these medications to the Central Zone Formulary to align the Formulary with existing practices in the Ophthalmology Clinic. Ranibizumab and aflibercept have Health Canada approved indications for the treatment of retinal conditions.

Retinal conditions affect a large number of people and there has been widespread adoption of effective, although costly, VEGF antagonist therapy to treat these conditions. Elevated intraocular levels of the protein VEGF can be associated with intraocular neovascularization (i.e., formation of new blood vessels in the eye). Intraocular neovascularization is common to many retinal conditions [e.g., wet age-related macular degeneration (AMD), diabetic macular edema (DME) and retinal vascular occlusion (RVO)]. When injected into the eye, VEGF antagonists inhibit the abnormal angiogenesis that underlies many diseases that affect the retina and cause vision loss.

Approved Restriction:
For intravitreal administration by Ophthalmology as per NS Pharmacare criteria.

Fidaxomicin, *Dificid*®

Fidaxomicin is a narrow spectrum macrolide antibiotic approved for the treatment of *Clostridium difficile* (*C. difficile*) infection. Fidaxomicin works by inhibiting RNA polymerase to inhibit RNA synthesis and exerts a bactericidal effect on bacteria. *C. difficile* infection is transmitted via the fecal-oral route and is a frequently occurring nosocomial and community infection associated with antibiotic use.

Mild to moderate *C. difficile* infections are treated with metronidazole. Severe presentations are treated with oral vancomycin as it has been shown to be more efficacious than metronidazole in serious infections. Following the treatment of acute *C. difficile* infection, recurrence rates vary from 20 to 60%. For a first recurrence, retreatment with metronidazole or vancomycin may be appropriate depending on the severity. Oral vancomycin is currently on the CDHA Formulary, with the following restrictions: treatment of severe or life-threatening pseudomembranous colitis (PMC); an alternative for the treatment of PMC because of treatment failure with, or contraindication to, metronidazole; recommendation of the Division of Infectious Diseases.

Fidaxomicin has been shown to be non-inferior to vancomycin for the cure of first episode and first recurrence of *C. difficile* infections. Compared to vancomycin, fidaxomicin has the advantage of less frequent dosing and a shorter time to resolution of symptoms (3 days versus 5 days). Fidaxomicin is generally well tolerated and rates of adverse events and serious adverse events were similar to vancomycin. Side effects of fidaxomicin include hypersensitivity, gastrointestinal intolerance [nausea, vomiting, abdominal pain, gastrointestinal hemorrhage (4%)], anemia (2%) and neutropenia (2%).

Approved Restriction:
On the recommendation of the Division of Infectious Diseases for:

- *Clostridium difficile* infections that have failed therapy with metronidazole and vancomycin
- Patients with a documented allergy to vancomycin
- Patients with a documented severe adverse drug reaction to vancomycin

II. Expanded Restrictions

Bevacizumab, *Avastin*®

Bevacizumab is a recombinant humanised monoclonal antibody that selectively binds to and neutralises the biologic activity of human vascular endothelial growth factor (VEGF). Bevacizumab is formulary restricted for use in metastatic colorectal cancer, advanced ovarian cancer and carcinoma of the cervix (according to approved guidelines). Although bevacizumab is only approved by Health Canada to treat certain types of metastatic cancer, it is compounded for intraocular injection and used "off-label" to treat retinal conditions. The small dose of bevacizumab required for intravitreal injection is associated with a significantly lower cost compared to the VEGF antagonists that are indicated for retinal conditions (i.e., ranibizumab and aflibercept).

Bevacizumab is currently funded by the NS Department of Health and Wellness (DHW) through the Provincial High Cost Drug Program via Pharmacare to be administered by an ophthalmologist as an intravitreal injection. There is no cost impact of this therapy to NSHA; however, there was a request to add a new restriction criterion for bevacizumab to align the Central Zone Formulary with existing practices in the VG Ophthalmology Clinic.

Approved Restriction:
For intravitreal administration by Ophthalmology as per NS Pharmacare criteria.

III. Pre-Printed Orders

The following pre-printed orders have been approved by the Medical Advisory Committee on the recommendation of the Drugs and Therapeutics Committee.

PPO 0226	PACLitaxel/CARBOplatin – Gyne Regimen
PPO 0302	Post-Cardiac Catheterization/PCI/EP Order
PPO 0540	Intravenous Antiplatelet/Antithrombin for Acute Coronary Syndromes
PPO 0541	Coleman Protocol for Low Risk Lymphoblastic Lymphoma Induction Phase - Weeks 1-3
PPO 0542	Coleman Protocol for Low Risk Lymphoblastic Lymphoma CNS Prophylaxis Phase - Weeks 4-8
PPO 0543	Coleman Protocol for Low Risk Lymphoblastic Lymphoma Consolidation Phase – Weeks 9-21
PPO 0544	Coleman Protocol for Low Risk Lymphoblastic Lymphoma Maintenance Phase - Weeks 22-52
PPO 0545	Brentuximab vedotin: Relapsed/Refractory Hodgkin Lymphoma or Relapsed/ Refractory Systemic Anaplastic Large Cell Lymphoma
PPO 0546	Nanoparticle Albumin Bound PACLItaxel with Gemcitabine Metastatic Pancreatic Cancer
PPO 0536	Subcutaneous Infusions – Palliative Care
PPO 0539	High Dose Insulin for Calcium Channel Blocker or Beta-Blocker Overdose – Adult

PPO 0551	CARBOplatin and Weekly PACLItaxel – Gyne Regimen
PPO 0490	Oral Sucrose for Procedural Pain Management (In neonates and infants less than or equal to 12 months)
PO 0554	Romidepsin – Relapsed/Refractory Peripheral and/or Cutaneous T Cell Lymphoma
PPO 0555	NIH-Like CycloPHOSPHAMIDE Lupus Nephritis Protocol
PPO 0556	Medical Assisted Dying – Physician Administered IV Protocol

The information contained in this newsletter may also be accessed online:
http://cdhaintra/departmentservices/pharmacy/Formulary/index.cfm

Published by the Pharmacy Department, Central Zone
Editor: Deborah MacIntyre, B.Sc. (Pharm.), ACPR
Drug Information Pharmacist

Tel: (902) 473-4248
Email: debbie.macintyre@nshealth.ca

Patient Label

Idarucizumab Audit Tool*

Date of administration (DD/MM/YY): _____ Location: _____

Prescribers must complete this Audit Tool after idarucizumab administration.

Idarucizumab is restricted for use in NSHA for the rapid reversal of the anticoagulant effects of **dabigatran** for ONE of the following indications (check one):

□ **Overt, uncontrolled, or life-threatening bleeding** Specify the source/location of bleed:
□ **Surgery or other invasive procedure required that cannot wait for at least 8 hours for the effect of dabigatran to wear off** Surgery or invasive procedure required: _____ Date and time of last dabigatran dose:

Patient Outcome Assessment

Did the patient experience **benefit** (e.g., bleeding stopped or controlled, hemodynamically stable, surgery or invasive procedure performed)? Yes □ No □ Unsure □ Provide details: _____
Did the patient experience **hypersensitivity or other serious adverse reaction**(s)? Yes □ If yes, please describe: _____ No □ Unsure □

Prescriber (Signature): _____ Name (Printed):_____

***The prescriber will complete the Audit Tool and return to the site Pharmacy Department.**

Patient Follow-up

Did the patient experience any **thrombotic event(s)** within 72 hours of receiving idarucizumab? Yes □ If yes, describe: _____ No □ Unsure □