D&T Decisions

... from the Drugs and Therapeutics Committee

nova scotia health authority

Central Zone (formerly CDHA)

Issue #59: April 30, 2015

Inside this Issue…

The following policies were approved by the Medical Advisory Committee (Sep14, Oct14, Nov14, Dec14, Feb15, Mar15) on the recommendation of the Drugs and Therapeutics Committee (Jun14, Sep14, Oct14, Nov 14, Jan15, Feb15, Mar15).

I. Additions to Formulary

Fat Emulsion 20%, *SMOFlipid™*

Prior to 2013, the only IV fat emulsion approved for use in Canada (Intralipid®) was composed entirely of soybean oil (SO). Alternative oil-based fat emulsions [e.g., medium chain triglyceride (MCTs), olive oils (OOs), and fish oils (FOs)], have been used extensively in Europe for many years and have recently been approved for use in Canada. SMOFlipid® is a unique blend of four oils (SO/ MCT/ OO/ FO) and provides a balanced profile of polyunsaturated (PUFA), monounsaturated (MUFA), and saturated fatty acids (SA) as well as omega 3 fatty acids (from the FO component).

The American Society of Parenteral and Enteral Nutrition (ASPEN) is recommending that alternative IV fat emulsions should be made available for the following reasons: less pro-inflammatory effects; less immune suppression; more antioxidant effects; a better alternative energy source than standard SO for many critically ill patients; lowers the risk of parenteral nutrition-associated liver disease; and minimizes the impact of future shortages of IV fat emulsion by having more than one product available. Although the cost of SMOFlipid is marginally higher than Intralipid, its use may be associated with a decrease in infection rate and length of hospital stay. However, there is a potential for more intolerance to SMOFlipid (i.e., intolerance to SO and FO).

Buprenorphine/ naloxone, *Suboxone®*

Suboxone sublingual (sl) tablets are a fixed dose combination of buprenorphine (a partial agonist at the mu-opioid receptor) and naloxone (an opioid antagonist) indicated for substitution treatment in opioid adult drug dependence. Naloxone administered orally or sl has no detectable pharmacological activity but when injected, it can rapidly precipitate opioid withdrawal; therefore, the naloxone component is intended to deter IV abuse.

Since buprenorphine is a partial mu receptor agonist with lower intrinsic activity at the receptor site compared to full mu opioid agonists (e.g., heroin, oxycodone or methadone), the risk of overdose is reduced. Also, because of its high receptor affinity, buprenorphine acts as an opioid antagonist by displacing other opioids from opioid receptors. This pharmacological property has two clinical implications: first, the reinforcing effects of other opioids are blocked and second, patients who are physically dependent on opioids may experience precipitated withdrawal if they ingest buprenorphine while they still have opioids in their system. Results from randomized controlled trials indicate that when compared to methadone, treatment with *Suboxone* may have similar effects on retention in treatment and the use of heroin or other opioids. Advantages of *Suboxone* include that it appears to be safer in overdose due to ceiling effect, administration requires less nursing time, it is the only alternative

currently available for patients in whom methadone is contraindicated and it is more accessible than methadone for some patients.

Approved Restriction:
- for treatment of opioid dependence for patients in whom methadone is contraindicated (e.g., patients at high risk of, or with, QT prolongation, or hypersensitivity to methadone)
- for the treatment of opioid dependence for appropriate patients ages 18 to 24 years
- recommended to be prescribed by a physician licensed to prescribe methadone for opioid dependence

Methylphenidate extended release, *Concerta*®

Although there are several methylphenidate formulations available in Canada, the only Formulary methylphenidate has been the immediate release tablets. Stimulant medications are first-line agents for the treatment of ADHD in children and adults and are widely used in correctional facilities. Extended release tablets provide a more gradual onset of action without the euphoric qualities sometimes observed with immediate-release agents and the longer duration of action may also reduce the likelihood of rebound symptoms.

Concerta is a unique long acting oral formulation that allows for once daily dosing. The tablets resemble conventional tablets and use osmotic pressure to deliver methylphenidate hydrochloride at a controlled rate. Stimulant medications are associated with a high potential for diversion and abuse; therefore, the Central Nova Correctional facility would like to restrict methylphenidate treatment to brand name *Concerta* because these tablets are difficult to manipulate into a formulation that can be abused. Although *Concerta* usage is associated with an increase in incremental cost, the potential staffing and safety benefits include less risk of medication errors due to the avoidance of multiple methylphenidate products, decreased nursing administration time with once daily dosing and less risk of diversion and abuse. Methylphenidate extended release tablets have been added to the Formulary and brand name *Concerta* will be stocked.

Ferumoxytol, *Feraheme*®

There are currently four parenteral iron products available in Canada: iron dextran complex, iron sucrose, sodium ferric gluconate and ferumoxytol. These parenteral iron agents vary in indication, dosing regimens and monitoring recommendations. Iron dextran is indicated for treatment of iron deficiency with general dosing guidelines while the other available parenteral iron products are indicated and dosed specifically for nephrology indications. Iron deficiency anemia (IDA) is common in patients with chronic kidney disease (CKD); however, other patient populations may also require parenteral iron therapy (e.g., oncology patients, surgery patients, patients with inflammatory bowel disease, critical care patients and heart failure patients). The Formulary status of IV irons has been evaluated and iron dextran and iron sucrose will remain Formulary. Sodium ferric gluconate will remain non-formulary while ferumoxytol has been added to Formulary with restrictions.

Health Canada's approval of ferumoxytol was based on three randomized, open-label, controlled clinical trials comparing IV ferumoxytol to oral iron in anemic patients with chronic kidney disease. Subsequently, two randomized, open-label, multicenter five week trials were published comparing ferumoxytol (two IV injections of 510 mg within 5 ± 3 days for a cumulative dose of 1.02 g) with iron sucrose (cumulative 1 g dose). The FIRST trial compared these two IV irons in adult patients with CKD (n = 162) while the other trial involved patients with IDA of any cause (n = 605). Ferumoxytol demonstrated noninferiority to iron sucrose in both trials.

All IV iron preparations can cause serious and sometimes life threatening hypersensitivity reactions. It is difficult to establish the relative incidence of hypersensitivity reactions to the various IV iron preparations because the absolute rates of occurrence are low and prospective studies often lack predictive power because of the small sample size. Due to information on serious allergic reactions, there have been two Health Canada endorsed important safety information communications for ferumoxytol (July and Nov., 2014). Although ferumoxytol was originally indicated for IV injection administered undiluted over at least 17 seconds, Health Canada has recommended that ferumoxytol should only be administered as an IV infusion. The ferumoxytol contraindications have also been expanded to include patients with any known history of drug allergy.

The recommended ferumoxytol 510 mg single dose is higher than the recommended single doses for other IV irons; therefore, ferumoxytol may be dosed less frequently compared to other IV iron formulations resulting in a decrease in the frequency of outpatient visits to achieve and/or maintain IDA correction.

Approved Restriction:
- For the treatment of iron deficiency anemia in patients with chronic kidney disease. Ferumoxytol is not approved for in-centre or satellite hemodialysis patients.
- Patients who have been identified by the Perioperative Blood Management Program (Anesthesia) who require parenteral iron replacement prior to surgery.
- Contraindicated in patients with documented true drug allergy.

Duloxetine, *Cymbalta*®

Duloxetine is indicated for major depressive disorder, generalized anxiety disorder, neuropathic pain associated with diabetic peripheral neuropathy, chronic low back pain, and the management of pain associated with fibromyalgia and osteoarthritis of the knee. It acts as a serotonin (5HT) and norepinephrine (NE) reuptake inhibitor (SNRI). The resultant increase in 5HT and NE explains its antidepressant activity. Duloxetine has equal affinity for both 5HT and NE reuptake inhibition. This differs from venlafaxine which inhibits NE reuptake at doses above 150 mg. Inhibition of dopamine reuptake occurs at high doses for both agents. The action against pain is proposed to be due to potentiation of descending inhibitory pain pathways in the CNS.

In major depressive disorder, duloxetine has been compared to placebo and other antidepressants. Guidelines consider

duloxetine as one of the first line agents for the treatment of major depressive disorder; however, duloxetine is more expensive than other first line agents. Duloxetine does not require the gradual dose increases with initiation or dose decreases with discontinuation that are necessary with venlafaxine. Duloxetine is associated with less risk of hypertension than venlafaxine and less risk of sexual dysfunction than some SSRIs; however, duloxetine has more potential for drug interactions than venlafaxine and is associated with a high incidence of nausea.

Approved Restriction:
For patients with treatment resistant depression or who have had intolerable side effects leading to the discontinuation of other antidepressants.

Mupirocin ointment, *Bactroban*®

Various techniques are commonly employed in an attempt to reduce the frequency of peritonitis in patients undergoing peritoneal dialysis (PD). PD exit site colonization with pathogenic organisms can lead to exit site infections and peritonitis. Current clinical guidelines suggest the use of a topical agent at the PD catheter site and either mupirocin or gentamicin is recommended. Historically, gentamicin 0.1% cream was the Formulary topical antibiotic product applied at the PD exit site; however, it is no longer available on the Canadian market.

The MP^3 Study was a multicenter, double-blind, randomized, controlled trial that compared mupirocin 2% ointment to Polysporin Triple Ointment (P^3) in PD patients. Application of P^3 to the PD catheter exit site was not shown to be superior to exit site mupirocin in the prevention of PD-related infections. The only statistically significant difference between the two groups was that patients in the P^3 group were at an increased risk of fungal infection.

Budesonide/ Formoterol, *Symbicort*®

Symbicort is a combination turbohaler of budesonide (a corticosteroid) and formoterol (a bronchodilator) for inhalation. Inhaled budesonide (*Pulmicort*® turbuhaler) and formoterol (*Oxeze*® turbuhaler) are Formulary medications at Central Zone. Combination therapy is recommended in current guidelines and dispensing a *Symbicort* turbuhaler is cost effective compared to dispensing two turbuhalers (i.e., *Pulmicort* plus *Oxeze*).

II. Non-Formulary

Morphine SR suppositories, *MS Contin® supp*

Gentamicin topical cream, ophthalmic ointment, ophthalmic solution and beads

Morphine SR suppositories (*MS Contin® supp)*, gentamicin topical cream, gentamicin ophthalmic ointment, gentamicin ophthalmic solution and gentamicin beads (*Septopal*) are no longer available in Canada; therefore, these medications are removed from the Formulary.

Saquinavir, *Invirase*®

The HIV protease inhibitor / antiretroviral agent saquinavir is no longer used at Central Zone and has been removed from the Formulary.

III. Expanded Restrictions

Rivaroxaban, *Xarelto*®

Rivaroxaban is an oral anticoagulant that directly inhibits Factor Xa. The Formulary restrictions for rivaroxaban include the prevention of stroke and systemic embolism in patients with atrial fibrillation, and the prevention of venous thromboembolism (VTE) in patients following total knee replacement or total hip replacement.

Standard treatment of VTE [deep vein thrombosis (DVT) and pulmonary embolism (PE)] has consisted primarily of anticoagulation using heparin and vitamin K antagonists. Advantages of rivaroxaban over standard therapy include fixed dosing (as opposed to weight-adjusted dosing of heparins and INR-adjusted dosing of warfarin) and ease of administration (oral dose). In the EINSTEIN studies, treatment with rivaroxaban was noninferior to standard therapy with enoxaparin and a vitamin K antagonist, recurrent VTE occurred at similar rates in both groups, and there was less major bleeding in the rivaroxaban group. In addition, in the hospital setting, the cost of rivaroxaban is favorable compared to standard therapy.

Approved Restriction:
For the treatment of DVT or PE, for a duration of up to six months.

IV. Therapeutic Interchange

Dalteparin Prefilled Syringe, *Fragmin*®

Dalteparin (*Fragmin*®) is an unrestricted Formulary low molecular weight heparin typically used for the prophylaxis of venous thromboembolism (VTE) in surgical and medical patients, and for the treatment of acute VTE (deep venous thrombosis and pulmonary embolus). Treatment doses are given subcutaneously and are weight based: 200 units/kg once daily (and 150 units/kg for extended treatment in cancer) in patients with normal renal function. For patients at risk of bleeding, dosing should be modified to 100 units/kg twice daily. Doses are calculated based on the patient's actual body weight.

At Central Zone, it is currently common practice to administer dalteparin subcutaneously to patients for the treatment of VTE using 1 mL ampoules (10,000 units/mL). However, dalteparin is also available as prefilled syringes with safety needle devices in the following doses: 7,500 units/ 0.3 mL, 10,000 units/ 0.4 mL, 12,500 units/ 0.5 mL, 15,000 units/ 0.6 mL, and 18,000 units/ 0.72 mL. Using the 1 mL ampule requires dose calculations and drawing up doses in syringes which can lead to errors and needle stick injuries. Patients are also administered a higher volume from the ampule which can be less comfortable on injection. If patients go home on dalteparin therapy, they can

receive education on self-injection of syringes before discharge. The manufacturer's product monograph and experience from other institutions indicate that weight-based doses can be rounded (dose banded) to available prefilled syringe sizes. Using the syringes instead of the 1 mL ampules is estimated to be slightly cost saving to cost neutral.

A therapeutic interchange has been approved for dalteparin weight-based treatment doses. Doses will be rounded and dispensed as the nearest syringe size according to the following table:

Ordered as: Dalteparin Dose (units)	Will be dispensed as: Dalteparin Prefilled Syringe Dose (units)
6,400 – 8,600*	7,500
8,800 – 11,200	10,000
11,400 – 13,600	12,500
13,800 – 16,400	15,000
16,600 – 19,000	18,000
19,200 – 21,200	20,000
21,400 – 23,600	22,500
23,800 – 26,200	25,000
26,400 – 27,600	27,500
27,800 – 30,200	30,000
30,400 – 32,600	32,500
32,800 – 35,400	35,000
35,600 – 38,000*	38,000

*Contact the prescriber for treatment doses < 6,400 units or > 38,000 units

V. Revised Therapeutic Interchange

Topical Preparations

The Formulary has a therapeutic interchange for topical preparations: when an order does not specify cream or ointment, a cream is dispensed. Polysporin topical is an exception to this interchange and the ointment is dispensed. Mupirocin ointment will also be included as an exception to this therapeutic interchange.

VI. Removal of Therapeutic Interchange

Vancomycin oral

The Formulary has had a therapeutic interchange for oral vancomycin capsules. When the relatively expensive vancomycin capsules were ordered, injectable vancomycin (to be reconstituted and administered orally at the prescribed dosage) was dispensed. The Pharmacy Medication Safety Committee considers injectable vancomycin for oral administration a potential source of error. Also, oral formulations of vancomycin are now less expensive.

The vancomycin capsule therapeutic interchange has been removed from the Formulary and the Pharmacy Department will now supply vancomycin capsules or suspension for oral or nasogastric administration respectively.

VII. New Guidelines

Pertuzumab, *Perjeta*®

A new Guideline for the role of pertuzumab in metastatic breast cancer (MBC) has been approved by the District Drugs and Therapeutics Committee.

Approved Use:
In combination with trastuzumab and a taxane for patients with HER2 positive + advanced/ incurable MBC (ECOG PS 0-1) who have not received prior anti-HER2 therapy or chemotherapy for metastatic disease. Patients may be eligible for combination therapy with a >/= 6 month disease-free interval following completion of adjuvant trastuzumab.

Arsenic trioxide, *Trisenox*®

A new Guideline for the role of arsenic trioxide in acute promyelocytic leukemia (APL) has been approved by the District Drugs and Therapeutics Committee.

Approved Use:
Initial Therapy - In combination with all trans-retinoic acid (ATRA) in the first line setting as a treatment for the induction of remission and /or consolidation of low to intermediate risk APL and as a consolidation treatment for high risk APL after induction with ATRA plus chemotherapy for patients with the t(15;17) translocation and PMURAR-alpha gene expression.

Relapsed/ Refractory/ Retreatment Therapy - As a treatment for the induction of remission and consolidation in patients with APL who have relapsed after completion of first line therapy including ATO based regimens or who have disease refractory to non-ATO based regimens for patients with the t(15; 17) translocation and PMURAR-alpha gene expression.

Pediatric Patient Population - As a treatment for the pediatric APL population as described above in the initial and relapsed/refractory/retreatment therapy criteria.

Trastuzumab emtansine, *Kadcyla*®

A new Guideline for the role of trastuzumab emtansine in metastatic breast cancer has been approved by the District Drugs and Therapeutics Committee.

Approved Use:
As second line treatment for patients with HER2 positive + unresectable locally advanced or MSC (ECOG PS 0-1) who have received prior treatment with trastuzumab (+/- pertuzumab) plus chemotherapy in the metastatic setting or have disease recurrence during or within 6 months of completing adjuvant therapy with trastuzumab plus chemotherapy.

For current patients (on an interim basis only) who are receiving

a second or later line of anti-HER2 therapy trastuzumab emtansine is approved at time of disease progression (ECOG PS 0-1).

In future, once the current patient population has had this treatment option trastuzumab emtansine will be funded as second line therapy only.

VIII. Revised Guidelines

Pemetrexed, *Alimta*®

Approved Use:

1. First Line and Continued Maintenance

A) In combination with platinum as a first line treatment option in patients with advanced or metastatic NSCLC with non-squamous histology who have an ECOG PS of 0-2.

B) In those patients who achieved stable disease or better post 4 cycles of first line pemetrexed/ platinum based induction therapy and have ECOG PS of 0-1 an option to continue maintenance pemetrexed as a single agent is available (continued maintenance therapy).

2. Switch Maintenance

As a single agent maintenance treatment option (switch maintenance) in patients with advanced or metastatic or with non-squamous histology immediately following a non-pemetrexed containing first line platinum doublet who have an ECOG PS of 0-2 and have achieved clinical benefit (tumor response or stable disease) from first line therapy.

3. Second Line

As a single agent second line treatment option in patients with advanced or metastatic NSCLC with non-squamous histology who have an ECOG PS of 0-2 after failure of only one prior line of therapy.

In any one patient, only one of these options may be used during the course of therapy for the treatment of advanced or metastatic NSCLC.

IX. Expanded Guidelines

Gemcitabine, *Gemzar*®

A randomized phase III trial for patients with relapsed or refractory aggressive lymphoma demonstrated that gemcitabine in combination with CISplatin and dexamethasone (GDP) is associated with a noninferior response rate, similar transplantation rate, event free survival and overall survival compared to CYTarabine, dexamethasone and CISplatin (DHAP) with less toxicity, hospitalization and superior quality of life.

Approved Use:

In combination with CISplatin and dexamethasone (GDP) as an alternate to the CYTarabine, dexamethasone and CISplatin (DHAP) regimen for patients with relapsed/refractory aggressive histology lymphoma.

Rituximab may be added to either regimen according to established criteria.

PACLItaxel, *Taxol*

CISplatin and fluorouracil (5-FU) in combination with radiotherapy is the standard neoadjuvant chemotherapy for the potentially curable population of esophageal patients eligible for resection. A randomized phase III trial studied a regimen of chemotherapy (paclitaxel/carboplatin) that demonstrated an overall survival benefit as part of a preoperative regimen with radiotherapy compared to surgery alone. Currently, there is no head to head comparison of these chemotherapy regimens. The PACLItaxel/CARBOplatin regimen provides patients with an effective combination with a very different side effect profile and acceptable toxicity. It offers an alternative option for patients who would be intolerant or ineligible for CISplatin based chemotherapy which is common in this patient population. It represents an outpatient regimen that is less toxic in terms of hydration issues, acute and prolonged nausea and vomiting (which can lead to hospital admissions) and offers an alternative to the existing regimen with a very different toxicity profile (e.g., less ototoxicity, less nephrotoxicity).

Approved Use:

In combination with CARBOplatin as an alternate to the CISplatin/fluorouracil (5-FU) regimen with radiotherapy as neoadjuvant therapy for esophageal cancer.

X. Medication Policies

The following policies have been approved by the Medical Advisory Committee on the recommendation of the Drugs and Therapeutics Committee. These policies will be added to the Medication Policy and Procedure Manual.

MM 20-030	Oral Contraceptives
MM 20-031	Emergency Contraceptive Pill
MM 20-021	Medicinal Marihuana
MM 15-xxx	Administration of Medications, Vaccines and Ordering of Diagnostic Tests to Staff by Employee Health
MM 15-013	Administration of Influenza Immunizations to CH Staff by Flu Champions
MM 05-040	Clinical Pharmacist Prescribing
MM 20-010	Immunization Administration
MM 50-003	Medication Reconciliation
MM 15-003	Medication Orders

XI. 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 0492	OXALIplatin (with Capecitabine)
PPO 0493	Folfirinox – Advanced Pancreatic Adenocarcinoma
PPO 0494	Capecitabine (Xeloda) with Radiation – Neo-adjuvant Rectal
PPO 0155	Neuraxial Analgesia- DGH

PPO 0387	Parenteral Nutrition (PN) Order
PPO 0087	Acute Lymphocytic Leukemia, Dana Farber Protocol Phase 1 – Induction
PPO 0088	Acute Lymphocytic Leukemia, Dana Farber Protocol Phase 2 – CNS
PPO 0089	Acute Lymphocytic Leukemia, Dana Farber Protocol Phase 3 - Intensification
PPO 0091	Acute Lymphocytic Leukemia, Dana Farber Protocol Phase 4 – Continuation
PPO 0264	Nebulized Epoprostenol Initiation Orders
PPO 0500	Alteplase (tPA) for Thrombolysis in ST Elevation Acute Coronary Syndrome
PPO 0059	Internal Medicine Admission Orders
PPO 0259	Venous Thromboembolism (VTE) Prophylaxis – Surgery
PPO 0503	Ipilimumab – Metastatic Melanoma
PPO 0496	Request for Subcutaneous Immunoglobulin (Hizentra)
PPO 0502	Cabazitaxel – Metastatic Prostate Cancer
PPO 0504	Pertuzumab/ Trastuzumab (with Taxane) – Metastatic Breast Cancer
PPO 0507	Rituximab Desensitization – Rheumatology
PPO 0342	Post-op Gynecological High Dose Rate Brachytherapy (Inpatients)
PPO 0343	Pre-op Gynecological High Dose Rate Brachytherapy
PPO 0344	Prophylaxis of Contrast Nephropathy
PPO 0511	Post-op Gynecological High Dose Rate Brachytherapy (Outpatients)
PPO 0303	Methadone Order Form – VG Site – Palliative Care
PPO 0424	Hemochromatosis Phlebotomy Standing Orders
PPO 0501	Acute Hemodialysis Start on Immunosuppression

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

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