D&T Decisions

… from the Drugs and Therapeutics Committee

nova scotia health authority

Issue #68: Feb. 12, 2020

Inside this Issue…

The following policies were approved by the Medical Advisory Committee (Oct 19, Jan 20) on the recommendation of the Drugs and Therapeutics Committee (Sep19, Oct 19, Nov 19, Dec 19).

I. Additions to Hospital Formulary

Vortioxetine/ *Trintellix*®

Vortioxetine is an antidepressant with a novel receptor binding profile (i.e., an inhibitor of SERT, 5-HT3, 5-HT7, and 5-HT1D receptors, a partial agonist of the 5-HT1B receptor, and an agonist at the 5-HT1A receptor) that may have a positive impact on overall patient functioning and cognitive function in patients with major depressive disorder. Several systematic reviews have demonstrated lower dropout rates with vortioxetine compared to other antidepressants; however, meta-analyses have shown inconsistent benefit or inferiority of vortioxetine compared to other agents for both major depressive disorder and generalized anxiety disorder.

A study in healthy male adults showed that vortioxetine caused only a small elevation in QTc and a case report indicates that it may be safer in overdose than some other antidepressant medications. Vortioxetine is more expensive than other approved Hospital Formulary antidepressants.

Approved Restriction:
Restricted to psychiatry for patients who have had
- treatment failure with at least two other antidepressants OR
- Antidepressant intolerance due to weight gain, cardiac or sexual adverse effects.

Paliperidone palmitate/ *Invega Trinza*®

Invega Trinza is a paliperidone palmitate prolonged-release injection that is formulated and indicated for every 3 month injection for the treatment of schizophrenia in adult patients. The 3 month injection is to be used only after at least four months of adequate treatment with the 1 month Invega Sustenna injection formulation (i.e., the tolerability, efficacy and consistent maintenance dose of paliperidone palmitate prolonged-release injection should be established). The Invega Sustenna formulation was reviewed and added to the former Capital Health Formulary in Nov., 2011.

A double blind, phase 3 study found that the paliperidone palmitate 3 month formulation was non-inferior to the 1 month formulation and that relapse rates were similar in both groups. Another study assessed the injection site reactions and/ or pain associated with both the 3 and 1 month long acting formulations and found that there was no more injection site pain associated with the larger injection volume of the higher doses administered with the 3 month formulation.

Approved Restriction:
For the maintenance treatment of schizophrenia and related psychotic disorders (not dementia related) in patients who have been stabilized on therapy with injectable paliperidone for at least four months.

Ivermectin/ *Stromectol*™

Approved by Health Canada in Nov. 2018, ivermectin is a broad spectrum oral antiparasitic agent belonging to the avermectin class known for efficacy in treating most intestinal worms (e.g., *Onchocerca volvulus, Strongyloides stercoralis)* and not having cross-resistance with other antiparasitic treatments.

Onchocerciasis, also known as river blindness, is prevalent in Africa and other tropical regions. *Onchocerca volvulus* is a filarial threadworm parasite transmitted by blackflies carrying infective

larvae. In humans, larvae remain in the subcutaneous tissue where they form nodules and develop into mature worms (macrofilariae). Worms can live for 15 years in these nodules; however, the microfilaria typically live 1 to 2 years and often remain in the subcutaneous tissue and lymphatic system, but may migrate to the eyes. When they die, a local inflammatory response is triggered, leading to severe pruritus, skin lesions, rashes and depigmentation. In the case of ocular deposition, opaque corneal patches and cataracts form, leading to visual impairment and blindness.

Strongyloidiasis is an infection caused by *Strongyloides stercoralis,* an intestinal worm transmitted to humans via contact with larvae containing soil. It is also endemic to tropical climates, including Africa, South America and South East Asia. While it can present with cutaneous and gastrointestinal symptoms, it is asymptomatic in approximately 60% of cases. Once filarial larvae penetrate the skin, they migrate to the lungs via venous circulation, where they are then expectorated and swallowed. Once in the gastrointestinal tract, larvae develop into adult females and release eggs. These eggs hatch into non-infectious larvae, which are then excreted in the stool and, outside of the human host, transform into infectious larvae. Autoinfection is problematic in strongyloidiasis, due to the ability of the non-infectious larvae to transform to the infectious form while still in host's gastrointestinal tract. These infectious larvae can penetrate the gut wall and enter the blood stream to begin the cycle again. *Strongyloides* hyperinfection is a complication of chronic *Strongyloides* infection. If the host becomes immunosuppressed or if an immunosuppressed patient contracts *Strongyloides*, the larvae reproduce uncontrollably, leading to dissemination to vital organs, such as the lungs, liver and brain.

The efficacy and safety of ivermectin has been demonstrated in onchocerciasis and strongyloidiasis. It is considered the drug of choice due to its side effect profile and relative lack of resistance, despite long-term use.

Approved Restriction:
For the treatment of intestinal strongyloidiasis, onchocerciasis, or cutaneous larva migrans.

Amino Acid 10%/ *Primene*®

Primene is an amino acid 10% solution for injection providing a mixture of essential and nonessential amino acids as well as taurine and cysteine. Evidence supports that high protein supplementation is required in specific patient populations (e.g., critical care, renal, hepatic, cancer, surgical, obese, wound healing and elderly patients) and that there are extensive patient consequences of inadequate protein provision.

NSHA regional sites without a Parenteral Nutrition (PN) compounder cannot provide PN that meets the protein requirements of many patients; therefore, supplemental amino acid infusions may need to be administered concurrently with PN. *Primene* has been added to the NSHA Hospital Formulary as a cost effective supplemental amino acid 10% solution.

Acetaminophen injection

Acetaminophen is a centrally acting non-opioid, non-salicylate analgesic with antipyretic effects. Although enteral acetaminophen is a common household medication that has been used for decades, the IV formulation has only recently been approved by Health Canada making it one of the few non-opioid analgesics available for the oral, rectal and IV route. Previously, access to acetaminophen IV required approval through Health Canada's Special Access Program (SAP).

Acetaminophen is a recognized part of the multimodal analgesia approach that is preferred for treating peri- and post-operative pain. This approach to analgesia utilizes different classes of medications (e.g., acetaminophen, NSAIDs, antidepressants, alpha2 receptor agonists, local anesthetics, opioids) that act on different receptors and sensory pathways resulting in synergistic analgesic therapy, lower medication doses, fewer side effects, improved recovery and lower overall costs. Recent Clinical Practice Guidelines for the prevention and management of pain in adult critical care patients suggest acetaminophen as an adjunct to opioids to decrease pain intensity and opioid consumption especially in patients at higher risk of opioid related safety concerns. Acetaminophen has a well-established safety profile (although there are overdose and liver toxicity concerns).

Acetaminophen injection is a more expensive option for analgesia; however, the IV route may be appropriate for certain clinical situations including when the enteral route is not suitable or available. The acetaminophen 4 g maximum daily adult dose includes all routes of administration.

Approved Restriction:
Restricted to Critical Care for patient analgesia in clinical situations when the enteral route is not possible.

Iron isomaltoside/ *Monoferric™*

Iron isomaltoside is a parenteral iron consisting of a stable iron core with an isomaltoside carbohydrate shell. The tight iron-carbohydrate matrix of iron isomaltoside may reduce the risk of infusion reactions that are caused when large amounts of "free" (labile) iron are released into the blood; therefore, compared to other available parenteral irons, higher doses may be administered at a faster rate (i.e., iron isomaltoside 1000 mg infused over 20 minutes).

The results of three prospective, randomized, comparative, open-label, multi-centre trials have demonstrated comparative efficacy of iron isomaltoside and iron sucrose. Two of the trials showed an increase in hemoglobin with iron isomaltoside comparable to iron sucrose in patients with iron deficiency anemia (IDA) of different etiologies and the third trial showed maintenance of hemoglobin levels in non-IDA hemodialysis patients. Although the iron isomaltoside loading dose is comparatively more costly, administration of iron isomaltoside may provide an opportunity for fewer patient visits, reduced chair-time and reduced utilization of healthcare resources.

Approved Restriction:
- Nephrology patients with non-dialysis dependent chronic kidney disease, patients receiving peritoneal or home dialysis.
- Clinical situations when rapid parenteral iron administration is necessary (e.g., perioperative and hematology patients).

Brivaracetam/ *Brivlera*®

Brivaracetam is an antiepileptic drug indicated as adjunctive therapy in the management of partial-onset seizures in adult patients with epilepsy who are not satisfactorily controlled with conventional therapy. The IV formulation is marketed as an alternative for partial-onset seizures when oral administration is temporarily not feasible. Similar to most new generation antiepileptic drugs, brivaracetam IV may be used off label for status epilepticus (SE). According to SE treatment guidelines, rapid administration of benzodiazepines is first line management, followed by IV antiepileptic drugs. Since SE is a medical emergency, it is crucial to have medications readily available.

Brivaracetam is a selective, high affinity ligand for SV2A and the modulation of SV2A's effect on neurotransmitter release is its proposed mechanism of action. This mechanism of action is unique compared to that of other available treatment options; therefore, use of brivaracetam may be valuable when a patient continues to have seizures despite the use of voltage gated sodium channel blockers (e.g., lacosamide) or in situations when cardiovascular risk factors exist.

There are a small number of observational retrospective studies and case reports of the use of brivaracetam IV for SE. Brivaracetam IV was generally well tolerated and has a favorable drug interaction profile compared to other antiepileptic drugs. The oral formulation, an exception status benefit with NS Pharmacare, has also been added to the NSHA Hospital Formulary.

Approved Restriction:

Brivaracetam IV:

- Second line for management of seizures after consultation with a neurologist;
  OR
- Partial-onset seizures in patients maintained on oral brivaracetam when oral administration is temporarily not feasible.

Brivaracetam oral:

- Patients maintained on established therapy.
  OR
- For the adjunctive treatment of refractory partial-onset seizures (POS) in patients who are currently receiving two or more antiepileptic drugs, and who have had an inadequate response or intolerance to at least three other antiepileptic drugs.
- The patient must be under the care of a physician experienced in the treatment of epilepsy.

Dolutegravir & rilpivirine/ *Juluca*

Juluca is a new combination formulation of the integrase inhibitor dolutegravir and the non-nucleoside reverse transcriptase inhibitor (NNRTI) rilpivirine that is indicated as a complete regime to replace a current antiretroviral regimen for the treatment of HIV-1 infection in adults who are virologically stable and suppressed. The cost of the combination formulation is similar to each component separately and the NS Department of Health and Wellness has added *Juluca* to the Exception Drug Fund Formulary. *Juluca* has been added to the NSHA Hospital Formulary for continuation of home therapy.

II. Removal from Hospital Formulary

Ticlopidine

The antiplatelet drug ticlopidine is no longer available in Canada; therefore, it has been removed from the NSHA Hospital Formulary.

III. Revised Restrictions

Paliperidone palmitate/ *Invega Sustenna*®

The NSHA Hospital Formulary restrictions for the paliperidone palmitate prolonged-release injection that is formulated and indicated for every 1 month injection (Invega Sustenna) have been revised to align with the NS Pharmacare exception status criteria.

Approved Restriction:

For the maintenance treatment of schizophrenia and related psychotic disorders (not dementia related) in patients who are not adherent to an oral antipsychotic;
OR
Who are currently receiving a long-acting injectable antipsychotic and require an alternative long acting injectable antipsychotic.

IV. Removal of Restrictions

Clopidogrel

NS Pharmacare has removed the exception status criteria for clopidogrel making it a full benefit. Since the NSHA Hospital Formulary restrictions for clopidogrel reflect the former NS Pharmacare criteria, these restrictions have been removed.

V. Therapeutic Interchange

Micafungin

The therapeutic interchange for micafungin has been revised:

Preparation:	Dispensed as:
Micafungin	Caspofungin 70 mg IV on day 1 , followed by 50 mg IV q24h (Exception: micafungin is to be interchanged to caspofungin 150 mg IV q24h for infective endocarditis)

Removal of Interchanges for Discontinued Medications

The NSHA Therapeutic Interchange (TI) Project is creating a single TI list as part of the NSHA Hospital Formulary. Evaluation of the NSHA hospitals' legacy TI lists has identified seven TI for products that are no longer available on the Canadian market (the most recent product discontinuation was 2011). The following TIs are removed from the NSHA Hospital Formulary:

Preparation (Year Discontinued)	Dispensed as:
Flurbiprofen 0.03% ophthalmic solution (Ocufen) (2011)	Diclofenac sodium 0.1% ophthalmic solution (CDHA)
Piroxicam Suppositories (2004)	Naproxen 500mg suppository (CDHA)
Fenoterol MDI (Berotec) (2007)	Salbutamol MDI same dose (Colchester)
Fenoterol 0.5 mL/neb Solution (2005)	Salbutamol 2.5 mg nebule (Colchester)
Sulfacetamide Sodium Solution (no strength) (2011)	Sulfacetamide Sodium 10% Solution (CDHA)

VI. New Guidelines

Nivolumab/ *Opdivo*® plus Ipilimumab/ *Yervoy*®

Two new guidelines have been approved for nivolumab plus ipilimumab.

A new guideline has been approved for the role of nivolumab plus ipilimumab for the treatment of patients with IMDC intermediate or poor-risk advanced or metastatic renal cell carcinoma.

Approved Restriction:

As combination use of nivolumab plus ipilimumab for the treatment of patients with IMDC intermediate or poor-risk advanced or metastatic renal cell carcinoma based on the International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) criteria. Eligible patients should be previously untreated in the metastatic setting and have a good performance status (KPS ≥ 70). Treatment should continue until disease progression or unacceptable toxicity.

A new guideline has been approved for the role of nivolumab plus ipilimumab for the treatment of patients with unresectable or metastatic melanoma.

Approved Restriction:

As combination use of nivolumab plus ipilimumab for the treatment of patients with unresectable or metastatic melanoma regardless of BRAF status who are treatment naïve, or may have received prior treatment with BRAF-targeted therapy, with an ECOG performance status of 0-1 and with stable brain metastases, if present. Treatment should continue until unacceptable toxicity or disease progression.

Bevacizumab/ *Mvasi*® *brand*

NSHA Cancer Care Program will use the biosimilar Mvasi brand bevacizumab in all New Cancer Drug Fund (NCDF) protocols prescribing bevacizumab (according to approved guidelines).

Approved Restrictions:

Metastatic Colorectal Cancer (MCRC):

In combination with first or second line (combination) chemotherapy such as irinotecan/fluoropyrimidine or oxaliplatin/ fluoropyrimidine-based chemotherapy in patients who have documented evidence of locally advanced or MCRC, with an ECOG performance status 0-2.

In any one patient, only one option as first or second line combination therapy is allowed until disease progression on that therapy.

Mvasi brand bevacizumab may be considered in combination with single agent fluoropyrimidine therapy such as 5FU/LV or capecitabine.

Cervical Cancer:

In combination with chemotherapy for patients with metastatic (stage IVB), persistent or recurrent carcinoma of the cervix of all histologic subtypes (except small cell) and good performance status.

Retreatment with bevacizumab plus chemotherapy may be offered to patients who have achieved a complete response (with previous bevacizumab and chemotherapy) and off treatment for at least 6 months.

Ovarian Cancer:

As a first line treatment of patients with advanced stage ovarian cancer at a high risk of progression (stage III with > 1cm residual disease, stage III unresectable or stage IV) epithelial ovarian, primary peritoneal or fallopian tube cancer and good performance status.

This would include initial treatment in combination with chemotherapy (cycles 2-6) and maintenance therapy for up to 12 additional cycles or until disease progression whichever occurs first.

Platinum-Resistant Ovarian Cancer:

In combination with paclitaxel, topotecan, or pegylated liposomal doxorubicin for the treatment of patients with platinum-resistant recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who have received no more than two prior anticancer regimens, good performance status, no contraindications to bevacizumab, and whose disease is not primary platinum refractory. Treatment should continue until disease progression or unacceptable toxicity.

Avelumab/ *Bavencio*®

A new guideline has been approved for the role of avelumab for metastatic Merkel Cell Carcinoma.

Approved Restriction:

For the treatment of adult patients with metastatic Merkel Cell Carcinoma who have received prior cytotoxic chemotherapy or, who are ineligible to receive first-line cytotoxic chemotherapy, (e.g. contraindications for treatment with cytotoxic chemotherapy). Patients must have a good performance status. Treatment should be discontinued upon confirmed disease progression or unacceptable toxicity. For patients who achieve a complete response (CR), treatment should continue for a maximum of 12 months after confirmation of CR.

Midostaurin/ *Rydapt*™

A new guideline has been approved for the role of midostaurin in FLT-3 mutated acute myeloid leukemia

Approved Restriction:

For the treatment of adult patients with newly diagnosed FMS-like tyrosine kinase 3 (FLT-3) mutated acute myeloid leukemia when used in combination with standard cytarabine and daunorubicin

(7+3) induction and cytarabine consolidation chemotherapy. Patients should be deemed fit to receive standard induction and consolidation chemotherapy.

VII. Expanded Guidelines

Brentuximab vedotin/ *Adcetris*®

A new guideline has been approved for the role of brentuximab vedotin for the post-autologous stem cell transplant (ASCT) consolidation treatment of patients with Hodgkin's Lymphoma (HL) who are at increased risk of relapse or progression.

Approved Use:

For the post-autologous stem cell transplant (ASCT) consolidation treatment of patients with Hodgkin lymphoma (HL) at increased risk of relapse or progression as outlined in the AETHERA trial:

- Refractory to frontline therapy **or**
- Relapsed less than 12 months from frontline therapy **or**
- Relapse 12 months or greater after frontline therapy with extranodal disease.

Consolidation treatment should be initiated within four to six weeks post-ASCT or upon recovery from ASCT and continued until a maximum of 16 cycles, disease progression or unacceptable toxicity, whichever comes first.

VIII. Medication Policies

The following hospital policies have been approved by the Medical Advisory Committee on the recommendation of the Drugs and Therapeutics Committee.

BEL-MM-001	Dalteparin for Anticoagulation in the Extracorporeal Circuit during Hemodialysis
NSHA MM-MA-005	Medication Independent Double Check
NSHA CAN-GA-001	Development and Revision of Orders Sets for Cancer Systemic Therapy Policy
CAN-ST-005	Biosimilars in Oncology

IX. Order Sets

The following order sets have been approved by the Medical Advisory Committee on the recommendation of the Drugs and Therapeutics Committee.

NS_OSAMCC NS	AVELumab – Merkel Cell Carcinoma
NS_OSCTPC NS	Component Transfusion – Plasma and Cryoprecipitate
NS_OSDCG NS	DOCEtaxel/CARBOplatin – Gyne Regimen
NS_OSGG NS	Gemcitabine Single Agent – Gynecology Regimen
NS_OSCE NS	Squamous Cell Carcinoma
NS_OSCTRBC NS	Component Transfusion – Red Blood Cells and Platelets
NS_OSGDSTS NS	Gemcitabine/DOCEtaxel – Soft Tissue Sarcoma
NS_OSGSAB NS	Gemcitabine/CISplatin – Advanced Bladder Regimen
NS_OSGSPO NZ	General Surgery Post-Operative Orders
NS_OSGSPOS NZ	General Surgery Preoperative Orders – Same Day Admission
NS_OSMH NS	Management of Hypophosphatemia
NS_OSZA NS	Zoledronic Acid
PPO0291MR CZ	Intensive Care Unit Admission Orders
NS_OSECMO NS	Extracorporeal Membrane Oxygenation (ECMO)
NS_OSCVSP NS	Cardiovascular Surgery Postoperative Orders
NS_OSHCREM NS	Hemodialysis Catheter Related Blood Steam Infection – Empiric Management
NS_OSHCRCP NS	Hemodialysis Catheter Related Blood Steam Infection – Confirmed Pathogen
NS_PPOEMPAPD NS	Empiric Management of Peritonitis Associated with Peritoneal Dialysis
NS_PPOPDLP NS	Peritoneal Dialysis Leak Protocol
NS_OSCRPO NS	Cardiac Rehabilitation Program Orders
NS_OSPRPO NS	Pulmonary Rehabilitation Program Orders
CB_POSPANUTHLIFR EZ	Parenteral Nutrition Lipid Free
CB_POSPANUTHLI EZ	Parenteral Nutrition with Lipids
NS_OSPCEAW WZ	Patient Controlled Epidural Analgesia
NS_OSPCAW WZ	Patient Controlled Analgesia
NS_OSDRL NS	DHAP with/without Rituximab (IV/Subcut) – Lymphoma
PPO 0603 CZ	Inpatient Psychiatry Admission Acute Care and Short Stay

X. IV Manual

The NSHA IV Drug Therapy Manual has been moved to the NSHA Intranet:
http://intra.nshealth.ca/clinical-resources/infusiontherapy/IV%20Drug%20THerapy%20Manual/SitePages/Home.aspx.

In conjunction with the Smart Pump Drug Library Working Group and Clinical Care Area Working Groups, a large number of monographs have undergone revisions to achieve standardization and support upcoming smart pump implementation. Further details regarding the launch of the NSHA IV Drug Therapy Manual Website and the IV monograph updates may be found in the NSHA memo:
http://intra.nshealth.ca/clinical-resources/infusiontherapy/IV%20Drug%20THerapy%20Manual/Update%20Memos/IV%20Manual%20Update%20190930.pdf

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

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

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