D&T Decisions

… from the Drugs and Therapeutics Committee

The information in this newsletter may also be accessed online.
To request a change to the NS Health Hospital Formulary, select & complete the online "Formulary Request Form":
NSH Pharmacy Formulary (nshealth.ca)

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The following policies were approved by the Medical Advisory Committee (Jan 23, Apr 23, May 23, Jun 23) on the recommendation of the Drugs and Therapeutics Committee (Oct 22, Nov 22, Feb 23, Mar 23, Apr 23).

I. Additions to Hospital Formulary

Agalsidase alfa/ *Replagal*®
Agalsidase beta/ *Fabrazyme*®

Note: Patient provides own medication

Agalsidase alfa (Replagal®) and agalsidase beta (Fabrazyme®) are injectable medications indicated for long-term enzyme replacement therapy in patients with a confirmed diagnosis of Fabry Disease (α-galactosidase A deficiency).

Fabry Disease is a rare X-linked inherited lysosomal storage disorder that is due to a wide range of mutations in the galactosidase alpha gene causing a defect of α-galactosidase A enzyme activity. Fabry Disease is a multi-systemic progressive disorder that initiates at a cellular level with disruption of basic metabolic processes and a cascade of events. The age of onset, clinical manifestations and disease progression is variable. Approved by Health Canada in 2004, enzyme replacement is life-long therapy and remains the standard of care.

Replagal® and Fabrazyme® are administered as home infusion therapy (usually every 1 to 2 weeks) funded by the NS Department of Health and Wellness. Medication is delivered directly to the patient's home and administration is supported by a private agency. The Nova Scotia Fabry Disease Program advises patients that if they are admitted to hospital, they should provide their own medications. It was also requested that the QEII Hospital Pharmacy stock a limited supply for the rare occasion that a hospitalized patient is not able to access their own supply. Both agalsidase alfa and agalsidase beta have been added to the NS Health Hospital Formulary with the note that patients provide their own medication when possible.

Buprenorphine & naloxone/ *Suboxone*® film

Suboxone is a fixed dose combination of buprenorphine (a partial agonist at the mu-opioid receptor) and naloxone (an opioid antagonist) that is indicated for substitution treatment in opioid drug dependence in adults. Naloxone has no detectable pharmacological activity when administered by the oral, sublingual, or buccal route; however, when injected, it can rapidly precipitate opioid withdrawal. Therefore, the naloxone component of Suboxone is intended to deter IV abuse.

When Suboxone was added to the NSHA Hospital Formulary in Sept. 2014 (D&T Decisions #59; April 30, 2015), the only available dosage form in Canada was a sublingual tablet. In 2021, Health Canada approved a new Suboxone soluble film dosage form. The

Suboxone soluble film may be administered sublingually (for both induction and maintenance therapy) or buccally (for maintenance therapy).

The two Suboxone dosage forms are not considered bioequivalent. Switching between the sublingual tablets and soluble film dosage forms or routes of administration may result in variations in blood plasma concentrations, which could lead to inadvertent overdosing or under dosing, including opioid withdrawal.

Buprenorphine extended-release inj/ *Sublocade*®

Sublocade® is a buprenorphine extended-release subcutaneous injection that is indicated for the management of moderate to severe opioid use disorder in adult patients who have been inducted and clinically stabilized on a transmucosal buprenorphine-containing product. Buprenorphine extended-release injection should be used as part of a complete treatment plan that includes counselling and psychosocial support. Available through a controlled distribution process, buprenorphine extended-release injection should only be prescribed and administered subcutaneously in the abdominal region by a healthcare provider who has completed the Sublocade® Certification Program.

Buprenorphine extended-release injection has a long half-life and should only be administered monthly with a minimum of 26 days required between consecutive doses. Patients who have been initiated and stabilized for a minimum of 7 days on the equivalent of 8 to 24 mg per day of a transmucosal buprenorphine-containing product may be transitioned to buprenorphine extended-release injection. Buprenorphine extended-release subcutaneous injection is initiated at 300 mg per month for two months, followed by a maintenance dose of 100 mg per month. The maintenance dose may be increased to 300 mg per month only if the patient does not demonstrate satisfactory clinical response to and can tolerate the 100 mg dose.

Brexpiprazole/ *Rexulti*®

Brexpiprazole is an atypical antipsychotic indicated for the treatment of schizophrenia and as an adjunct in the treatment of major depressive disorder. The efficacy of brexpiprazole is thought to be mediated through a combination of partial agonist activity at serotonergic 5-HT1A and dopaminergic D2 receptors and antagonist activity at serotonergic 5-HT2A receptors.

Brexpiprazole efficacy versus placebo was demonstrated in the Beacon, Vector, Lighthouse and Equator trials. The most common adverse events associated with brexpiprazole treatment include headache, insomnia, agitation, akathisia and moderate weight gain.

Semaglutide/ *Ozempic*®

Semaglutide, a glucagon-like peptide-1 receptor agonist (GLP-1RA), has multiple brands available in Canada that differ in approved indications and dosage forms. Ozempic® is an injectable semaglutide indicated as combination therapy for the once weekly treatment of adult patients with type 2 diabetes mellitus to improve glycemic control.

Semaglutide acts as an agonist on the GLP-1 receptor to promote glucose-dependent insulin secretion from the beta cells of the pancreas and cause a glucose-dependent decrease in glucagon secretion. When blood glucose is high, semaglutide stimulates insulin secretion (glucagon secretion is impaired) and, in contrast, when blood glucose levels are low, insulin secretion is decreased (glucagon secretion is not hindered). Semaglutide also decreases blood glucose by slowing gastric emptying.

There is evidence that GLP-1RAs have cardio-renal benefits in high-risk patient populations. Drugs in this class lower the risk of major adverse cardiovascular events (MACE) in patients with atherosclerotic cardiovascular disease (ASCVD) and/or chronic kidney disease. They are also preferred to lower the risk of MACE in patients who do not have established ASCVD, but have cardiovascular risk factors (e.g., tobacco use, hypertension, dyslipidemia, central obesity, and age ≥ 60 years). Independent of cardio-renal benefits, GLP-1 agonists decrease A1C between 0.6 to 1.4%, and lead to 1.1 to 4.4 kg weight loss. There is also less risk of hypoglycemia associated with GLP-1 agonists compared to other agents when used as add-on antihyperglycemic therapy.

Semaglutide subcutaneous injection has a long half-life and can be dosed once weekly. Multiple randomized controlled trials have assessed the safety and efficacy of subcutaneous semaglutide including the SUSTAIN trials 1 through 8 and the Sineo Study. These trials are placebo-controlled and/or semaglutide has been compared to interventions including sitagliptin, exenatide, insulin glargine, dulaglutide and canagliflozin. Most of these trials were designed to assess efficacy outcomes whereas the cardiovascular outcomes trial SUSTAIN-6 and the Sineo Study assessed semaglutide safety.

Colchicine extended-release/ *Myinfla™*

Myinfla™ is a colchicine 0.5 mg extended-release tablet that was approved by Health Canada in 2021 for the reduction of atherothrombotic events in adult patients with existing coronary artery disease (CAD), in addition to standard therapies, including LDL-C lowering and antithrombotic drug treatment. Patients who have experienced an acute coronary syndrome (ACS) and are managed with optimal medical therapy, have a substantial risk of recurrent events. The increased risk may be due to residual inflammation, as both adaptive and innate immunity play a pivotal role in the atherogenic process.

An anti-inflammatory and anti-mitotic medication, colchicine is known for its use in pericarditis, familial Mediterranean fever and gout. Colchicine has been available in Canada for many years as a 0.6 mg immediate release tablet (listed on both the NS Health Hospital and Pharmacare Formularies). Myinfla™ is not listed as a benefit on the NS Provincial Drug Plan Formulary (i.e., Pharmacare).

Pre-clinical data suggests that colchicine exhibits its cardioprotective effects by suppressing smooth muscle cell proliferation, lymphocyte migration activity and the pro-thrombotic activity of oxidative low-density lipoproteins in atherosclerotic plaques. LoDoCo was one of the first trials that investigated colchicine's utility in ACS (2013); however, due to trial limitations

including a small sample size and lack of placebo control, it was thought as hypothesis generating rather than practice changing. In 2019/20, the results of three trials (LoDoCo2, COLCOT, Australian COPS) reported further investigations regarding the efficacy and safety of colchicine for the prevention of cardiovascular events in patients with CAD.

Dalbavancin/ *Xydalba*®

Dalbavancin is a lipoglycopeptide antibiotic approved for the treatment of gram-positive acute skin and structure infections. Dalbavancin offers bactericidal activity against many gram-positive organisms including methicillin-resistant staphylococcus aureus (MRSA) and *Enterococcus faecalis* (vancomycin susceptible). Compared to vancomycin and linezolid, dalbavancin has an infrequent dosing schedule based on its long elimination half-life (8.5 - 10.75 days).

Dalbavancin has demonstrated non-inferiority to traditional treatments for acute skin and soft tissue infections. A phase II, randomized, open-label study suggested that dalbavancin (1.5 g IV on day 1 and 8) was effective compared to investigator-chosen standard of care for the treatment of gram-positive osteomyelitis (n = 80). Dalbavancin (1 g IV on day 1 and 500 mg on day 8) showed statistical superiority over vancomycin for gram-positive catheter-associated blood stream infections. Observational retrospective studies support dalbavancin therapy for gram-positive infective endocarditis.

Due to cost and the lack of extensive safety data, dalbavancin may be appropriate for patients who are pending discharge and require treatment of gram-positive infections in which vancomycin, linezolid, daptomycin or beta-lactams cannot be used and/ or are deemed impractical for use due to the patient's housing instability or inability to access/maintain appropriate care of a central venous catheter.

Approved Restriction:

Addition to the systemic antimicrobial formulary as a red category agent (i.e., requiring Antimicrobial Stewardship review within 72 hours). Guidelines for use are available on the NS Health Antimicrobial Stewardship website and app.

II. Non-Formulary

Ranolazine/ *Corzyna™*

Approved by Health Canada in 2020, ranolazine is indicated as add-on therapy for the symptomatic treatment of patients with stable angina pectoris who are inadequately controlled or intolerant to first-line antianginal therapies, including beta-blockers and calcium channel blockers. Ranolazine is a selective inhibitor of the late sodium current (INaL) in cardiomyocytes, which is thought to contribute to the macrovascular pathogenesis of angina (e.g., oxygen consumption in cardiomyocytes via calcium overload). Some findings also suggest that ranolazine has a role in microvascular angina (e.g., anti-inflammatory effects).

Three core multi-centered, randomized, double-blind, placebo-controlled trials [i.e., ERICA (2006), TERISA (2013), CARISA (2004)] assessed ranolazine in patients with coronary artery disease and stable angina pectoris. The ERICA and TERISA trials both showed a statistically significant reduction in angina episodes per week (the primary efficacy measure); however, both studies found no difference in Quality-of-Life or all-case-mortality. The primary efficacy outcome assessed in the CARISA trial was exercise duration on a treadmill at trough ranolazine levels (i.e., 12-h post-dose) and there was a statistically significant increase with ranolazine compared to placebo. Like the ERICA and TERISA trials, the ranolazine groups in the CARISA trial showed a reduced incidence of angina attacks and nitroglycerin use; however, there was also no difference found for all-cause mortality.

In 2021, the CADTH Canadian Drug Expert Committee (CDEC) recommended that ranolazine not be reimbursed and ranolazine is not not listed as a benefit on the NS Provincial Drug Plan Formulary (i.e., Pharmacare). The CADTH review concluded that there were several limitations in the core studies including a lack of reporting study methodology and lack of generalizability that led to uncertainty when interpreting the results; therefore, the clinical significance of the outcomes remains unclear. Ranolazine remains non-formulary at NS Health Hospitals.

III. Expanded Restrictions

Acetaminophen injection

Acetaminophen injection was added to the NS Health Hospital Formulary in 2020 with restrictions to Critical Care for patient analgesia in clinical situations when the enteral route is not possible (D&T Decisions #68: Feb. 12, 2020).

Patients admitted to the Hematology Service for cellular therapy or transplant, including CAR T-cell therapy, experience fever and pain that has a variety of causes. Fever is commonly caused by infection with most patients developing febrile neutropenia after high-dose chemotherapy. Patients receiving CAR T-cell therapy experience fever due to cytokine release syndrome. Options to treat pain and fever are limited in hematology oncology patients. Although opioids have no antipyretic effect, they may be used to treat pain. Since non-steroidal anti-inflammatories are generally avoided due to effects on platelets, acetaminophen is the first (and usually only) choice to treat fever.

Due to the severity of mucositis, hematology oncology patients are often unable to tolerate oral medications. Patients receiving CAR T-cell therapy commonly experience neurotoxicity that may also prevent them from being able to swallow oral medications. Since most or all patients also develop fever due to cytokine release syndrome, they require antipyretic therapy with acetaminophen. Importantly, these patients do not have feeding tubes that would allow for the administration of crushed oral medications and given their profound neutropenia, suppositories are contraindicated. When a patient is no longer able to swallow, nursing will notify pharmacy to transition their medications to IV where possible.

Approved Restriction:

To Hematology for patients who have received hematopoietic stem cell transplant or CAR T-cell therapy to treat pain and fever when the oral route is not an option.

IV. Restrictions

Glecaprevir & pibrentasvir/ *Maviret*®
Sofosbuvir & velpatasvir/ *Epclusa*®
Ledipasvir & sofosbuvir/ *Harvoni*®
Elbasavir & grazoprevir/ *Zepatier*®

Four hepatitis C virus (HCV) direct acting antivirals were added to the NS Health Hospital Formulary in 2020 without Formulary restrictions (D&T Decisions #69: July 28, 2020).

Despite the unrestricted Formulary status, the NS Health approval of HCV therapy was intended for incarcerated patients. HCV infection rates have been high among inmates of Canadian correctional facilities and guidelines recommend treatment for chronically infected individuals whose jail sentence is sufficiently long to complete a recommended course of antiviral therapy.

For most NS Health inpatients, treatment of HCV infection is not urgent and may be best handled via outpatient program funding models (a treatment course costs more than $20 000). During a patient's hospital stay, healthcare professionals may explore/ arrange outpatient access to these medications (e.g., private payers +/- Pharmacare +/- patient assistance programs).

Approved Restriction:
Adult patients with hepatitis C viral (HCV) infections who are admitted to NS Health on established HCV therapy or initiation of new therapy for incarcerated patients.

V. New Guidelines

DAUNOrubicin and cytarabine liposome/ *Vyxeos*®

A new guideline has been approved for the role of DAUNOrubicin and cytarabine liposome (Vyxeos®) for the of treatment of patients with newly diagnosed therapy-related acute myeloid leukemia (t-AML) or AML with myelodysplasia-related changes (AML-MRC).

Approved Restriction:
For the treatment of adult patients with newly diagnosed therapy-related acute myeloid leukemia (t-AML) or AML with myelodysplasia-related changes (AML-MRC). Patients must be deemed fit to receive intensive induction chemotherapy.

Treatment with liposomal DAUNOrubicin and cytarabine is for a maximum of 2 cycles of induction therapy. Patients with complete remission (CR) or complete remission with incomplete count recovery (CRi) following induction therapy may receive up to 2 additional cycles of liposomal DAUNOrubicin and cytarabine as consolidation therapy.

VI. Revised Guidelines

Pembrolizumab/ *Keytruda*®

A new guideline has been approved for the role of pembrolizumab for the of treatment of patients with relapsed or refractory classical Hodgkin Lymphoma (cHL).

Approved Restriction:
For the treatment of adult and pediatric patients with refractory or relapsed classical Hodgkin Lymphoma (cHL) who have failed autologous stem cell transplant (ASCT), or who are not candidates for multi-agent salvage chemotherapy and ASCT.

Treatment should continue for a maximum duration of 2 years or until confirmed disease progression or unacceptable toxicity, whichever occurs first.

VII. Expanded Guidelines

Avelumab/ *Bavencio*®

A new guideline has been approved for the role of avelumab for the treatment of patients with unresectable, locally advanced or metastatic urothelial carcinoma.

Approved Restriction:
For the first-line maintenance treatment of patients with histologically confirmed, unresectable, locally advanced, or metastatic urothelial carcinoma whose disease has not progressed with first-line platinum-based induction chemotherapy.

Eligible patients should have a good performance status with documented locally advanced unresectable or stage IV disease before having received first-line chemotherapy. First-line chemotherapy should be platinum-based, and patients must have received 4 to 6 cycles of treatment with chemotherapy. Patients must not have experienced disease progression (i.e., they must have had an ongoing complete response, partial response, or stable disease). Patients may continue to receive avelumab until confirmed disease progression or unacceptable toxicity, whichever occurs first.

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 adult patients with metastatic or recurrent squamous or non-squamous, non–small cell lung cancer (NSCLC).

Approved Restriction:
As combination use of nivolumab plus ipilimumab and two cycles of platinum doublet chemotherapy, for the first-line treatment of adult patients with locally advanced (not amenable to curative intent therapy), metastatic or recurrent, squamous or non-squamous, non–small cell lung cancer (NSCLC) with no known epidermal growth factor receptor (EGFR) or anaplastic lymphoma kinase (ALK) genomic tumour aberrations. Patients should have a good performance status. Treatment may continue until confirmed disease progression or unacceptable toxicity to a maximum of two years, whichever occurs first.

A new guideline has been approved for the role of nivolumab plus ipilimumab for the treatment of adult patients with unresectable malignant pleural mesothelioma (MPM).

Approved Restriction:
As combination use of nivolumab plus ipilimumab for the treatment of adult patients with unresectable malignant pleural mesothelioma (MPM) who have not received prior systemic therapy. Patients should have a good performance status. Treatment with nivolumab in combination with ipilimumab should continue until confirmed disease progression or unacceptable toxicity to a maximum of two years, whichever occurs first.

Pembrolizumab/ *Keytruda*®

A new guideline has been approved for the role of pembrolizumab for the of treatment of patients with advanced or metastatic esophageal or gastroesophageal junction (GEJ) cancer.

Approved Restriction:

In combination with platinum and fluoropyrimidine-based chemotherapy for the first line treatment of patients with locally advanced unresectable or metastatic squamous cell carcinoma or HER-2 negative adenocarcinoma of the esophagus or HER2 negative adenocarcinoma of the gastroesophageal junction (GEJ).

Treatment should continue until confirmed disease progression or unacceptable toxicity to a maximum of 2 years, whichever occurs first.

Durvalumab/ *Imfinzi*®

A new guideline has been approved for the role durvalumab for the treatment of adult patients with extensive stage small cell lung cancer.

Approved Restriction:

In combination with etoposide and platinum chemotherapy for the first line treatment of adult patients with extensive-stage small cell lung cancer. Patients should have a good performance status. Treatment should continue until unacceptable toxicity or disease progression.

VIII. Medication Policies

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

M-MS-025	Administration of Ketamine via CADD®-Solis Pump for Pain Management in Burn Patients
CAN-ST-003	Administration of Subcutaneous Systemic Therapy for Cancer

IX. Other

Ketorolac oral

Historically, the Formulary status of ketorolac oral varied within legacy Hospital Formularies in Nova Scotia; therefore, ketorolac oral remains on legacy order sets at hospitals where it was approved as a Formulary medication. Since the on-line NS Health Formulary only includes ketorolac injectable and its restrictions, there was a request for a Formulary evaluation of the oral formulation.

Ketorolac is a non-steroidal anti-inflammatory drug (NSAID) that provides analgesic activity through inhibition of cyclooxygenase enzyme inhibition (COX 1 and COX 2 inhibition), which results in reduced production of prostaglandins such as thromboxanes and prostacycline. Unlike other NSAIDs that are only available in Canada as oral formulations, ketorolac has a parenteral formulation that is approved for intramuscular administration. Although not an approved Health Canada indication, ketorolac IV usage is substantiated in the literature and used frequently in the healthcare setting.

Ketorolac's indication for use in acute pain includes a warning that duration of parenteral ketorolac should not exceed 2 days and combined duration of intramuscular and oral treatment should not exceed 5 days to avoid potential GI and cardiovascular adverse effects.

Oral ketorolac is non-formulary at IWK Health and not listed as a benefit on the NS Provincial Drug Plan Formulary (i.e., Pharmacare) and will be considered non-formulary at NS Health Hospitals. However, a temporary Formulary restriction is approved to permit non-formulary usage of ketorolac oral tablets at NS Health Hospitals while there is withdrawal of legacy Formulary use.

Approved Restriction:

Ketorolac Oral Tablet (non-formulary) – restricted to use at NS Health Hospitals where ketorolac oral had legacy Formulary status. NS Health intends to withdraw legacy Formulary use of ketorolac oral by Sept. 1, 2023 (Exception: the withdrawal date for the use of ketorolac oral on approved NS Health legacy order sets is March 1, 2024).

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