D&T Decisions

… from the Drugs and Therapeutics Committee

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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 (Oct 24, Mar 25) on the recommendation of the Drugs and Therapeutics Committee (Sep 24, Nov 24, Feb 25).

I. Additions to Hospital Formulary

Cariprazine/ *Vraylar*®

Cariprazine, an oral atypical antipsychotic, is a partial agonist of serotonin 5-HT-1A and dopamine D2 receptors as well as an antagonist of serotonin 5-HT-2A activity. Approved by Health Canada in 2022, cariprazine is indicated for the treatment of schizophrenia, bipolar mania and bipolar depression in adults. The two active cariprazine metabolites have long half-lives and steady state is usually reached within 8 weeks. Cariprazine is primarily metabolized by CYP 3A4 with approximately 21% excreted renally.

Evidence for cariprazine in schizophrenia includes three 6-week double-blind studies (MD-16, MD-04, and MD-05) demonstrating that cariprazine significantly improved symptoms of psychosis compared to placebo. Study 188-05 was a 26-week trial that demonstrated that cariprazine resulted in a greater improvement in negative symptoms of schizophrenia compared with risperidone.

The efficacy of cariprazine in the acute management of bipolar mania was established in three 3-week placebo-controlled trials (MD 31, MD 32, MD 33) in patients who met criteria for bipolar I disorder with manic or mixed episodes with or without psychotic features. Superiority to placebo was demonstrated for both the primary and secondary efficacy measures.

The efficacy of cariprazine in the management of bipolar depression was established in one 8-week trial (MD 56) and two 6-week placebo-controlled trials (MD- 53 and MD- 54) in patients who met criteria for depressive episodes associated with bipolar I disorder; however, there were mixed efficacy results from the 3 trials and superiority versus placebo was dose dependent.

Most patients in the trials reported one or more adverse events (AEs). Insomnia, akathisia, and headache were the most reported AEs in the cariprazine groups. There was a low frequency of discontinuation due to extrapyramidal symptoms.

Cariprazine is listed as a benefit on the NS Provincial Drug Plan Formulary (i.e., Pharmacare) with exception criteria for the treatment of schizophrenia in adults.

II. Non-Formulary

Andexanet alfa/ *Ondexxya*®

Andexanet alfa is a reversal agent for Factor Xa (FXa) inhibitors that is Health Canada approved (April 2023) for adult patients treated with rivaroxaban or apixaban when rapid reversal of anticoagulation is needed due to life-threatening or uncontrolled bleeding. There are four direct oral anticoagulants (DOACs) available on the Canadian market of which three are FXa inhibitors: rivaroxaban, apixaban, edoxaban. The reversal of edoxaban with andexanet alfa is considered off label. Since the DOAC dabigatran has a different mechanism of action, its approved reversal agent is idarucizumab/ *Praxbind*® (addition to NS Health Hospital Formulary in 2016; D&T Decisions #63: Dec. 16, 2016).

DOACs are frequently used for indications such as atrial fibrillation and the prevention and treatment of venous thrombus embolisms. The major concern with these agents is the risk of major bleeding due to their ability to reduce blood clotting. Management of bleeding for patients on DOACs has been mostly conservative in nature. In the case of minor bleeding, the DOAC is typically continued, and the patient is monitored. In the case of severe/ life-threatening bleeding, the DOAC is held, supportive transfusions (e.g., red blood cells and platelets) may be used, and reversal or pro-hemostatic agents [e.g., 4-factor prothrombin complex (PCC)] are considered. PCC is not a specific antidote and is thought to lessen the significance of bleeding by delivering massive amounts of factors II and X; however, PCC's place in therapy is debated due to a lack of evidence for its effect on disability and mortality.

Andexanet alfa is a recombinant modified human FXa protein that binds to FXa inhibitors in the plasma, subsequently restoring endogenous FXa levels and its role in normal hemostasis. Andexanet alfa has a quick onset and has been shown to decrease anti-FXa activity within 2 minutes of the initial bolus dose. The CADTH Canadian Plasma Protein Product Expert Committee (CPEC) recommendation of "do not reimburse" was based on three main trials: ANNEXA-A and ANNEXA-R are randomized control trials (RCTs) that investigate the effects of andexanet alfa versus placebo in healthy adults on apixaban and rivaroxaban, respectively; ANNEXA-4 is a multicenter, open-label, single arm study that investigated the effects of andexanet alfa in patients with acute bleeding. Major limitations of this evidence are the high reliance on surrogate outcomes and the lack of comparison to the standard of care for managing major bleeds in patients on FXa inhibitors.

The NS Health Hospital Formulary status of andexanet alfa was initially considered in February 2024 with a reconsideration in Nov. 2024 following the publication of the ANNEXA-I trial (May 2024).

ANNEXA-I is a multicenter, randomized, prospective, open label, phase 4 trial investigating the use andexanet alfa versus usual care (any treatments other than andexanet alfa, including no treatment) in adult patients (n = 530) presenting with an acute intracranial hemorrhage (ICH) within 15 hours of taking an oral factor Xa inhibitor (apixaban, rivaroxaban, or edoxaban). This trial was stopped early because of superior efficacy in the andexanet group for the primary endpoint (i.e., rate of effective hemostasis at 12 hours): 67% versus 53%; adjusted difference 13.4% (95% CI: 4.6 to 22.2; P = 0.003).

The main safety concern involving the use andexanet alfa is thrombotic events. Patients being treated with FXa inhibitors have an underlying medical condition that predisposes them to thrombotic events. Andexanet alfa also has anti-tissue factor pathway inhibitor (TFPI) effects by binding to TFPI which is a naturally occurring anticoagulant found in the plasma. Therefore, when andexanet alfa is administered the risk of thrombotic events is increased.

The safety outcome analysis of the ANNEXA-I trial included (andexanet alfa versus usual care): ≥ 1 thrombotic event 10.3% versus 5.6% (adjusted difference, 4.6%; 95% CI: 0.1 to 9.2; P=0.048); ischemic stroke 6.5% versus 1.5% (adjusted difference, 5.0%; 95% CI: 1.5 to 8.8); death 27.8% versus 25.5% (adjusted difference, 2.5%; 95% CI: -5.0 to 10.0; P=0.51).

Andexanet alfa is not currently Health Canada approved for the reversal of factor Xa inhibitors when immediate surgery is necessary. Another potential safety concern is the unintended reversal of unfractionated and low molecular weight heparin in patients receiving andexanet alfa before urgent vascular or cardiac surgery requiring cardiopulmonary bypass.

The current andexanet alfa evidence is limited to reversal in the setting of ICH and it remains uncertain whether the observed reduction in hematoma expansion improves patient outcomes despite the increase in thrombotic events, particularly ischemic stroke. Further studies are needed to define the risk/ benefit of andexanet alfa in optimal patient populations; therefore, andexanet alfa was not added to the NS Health Hospital Formulary.

III. Removal of 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). These Hospital Formulary restrictions were expanded to include patients receiving hematopoietic stem cell transplant or CAR T-cell therapy for the treatment of pain and fever when the oral route is not an option (D&T Decisions #75: July 5, 2023). Requests to expand the NS Health Hospital Formulary acetaminophen injection restrictions to include anesthesia were denied due to the cost of the product per dose and concerns regarding the ability to limit the use to a proposed restriction criteria (D&T Decisions #69: July 28, 2020).

There have been two recent NS Health Drug Utilization Evaluations (DUEs) for acetaminophen injection. A WZ DUE was designed to assess the appropriateness of acetaminophen injection usage based on proposed criteria for the perioperative setting. A CZ initiative by the Cardiac Surgical Service launched new protocols to support Enhanced Recovery After Surgery (ERAS) including the reduction of opioid dosing intraoperatively to support early extubation in the OR prior to transfer to CVICU. Both these projects identified lower than anticipated acetaminophen injection usage and cost as well as anecdotal appreciation for improved multimodal pain options to support patient care.

Given the results of the recent NS Health DUEs assessing acetaminophen injection, the decreased cost of acetaminophen injection and the support of Opioid Stewardship (i.e., Opioid Wisely – Choosing Wisely Canada) the NS Health Hospital Formulary restrictions for acetaminophen injection have been removed.

IV. New Guidelines

Pegfilgrastim/ *Lapelga®, others*

Pegfilgrastim is a granulocyte-colony stimulating factor (G-CSF) indicated to decrease the incidence of infection, as manifested by febrile neutropenia, in patients with non-myeloid malignancies receiving myelosuppressive cancer agents. Febrile neutropenia is a major dose-limiting toxicity of many regimens used to treat oncology patients and is considered an oncologic emergency. Patients with febrile neutropenia require significant healthcare resources as it can often lead to prolonged hospitalizations and treatment with broad-spectrum antibiotics. Prevention of febrile neutropenia with G-CSFs is an integral part of supportive care protocols for many patients undergoing myelosuppressive treatments. Considered a standard of care for this patient population, pegfilgrastim is used as either primary or secondary prophylaxis in patients who are at an elevated risk of developing febrile neutropenia and is given as a single dose at least 24 hours after myelosuppressive treatment.

Filgrastim is currently on the NS Health Hospital Formulary for primary and secondary prophylaxis of febrile neutropenia in patients receiving myelosuppressive chemotherapy. Filgrastim is usually given subcutaneously once daily for five to seven days (starting one to three days after receiving treatment). A concern raised with starting filgrastim in hospital is trying to coordinate a discharge plan for patients if the course of filgrastim is not completed before discharge. With the life-threatening risks associated with febrile neutropenia, it is crucial that patients receive all prescribed doses in a timely manner.

Although there are no significant issues accessing pegfilgrastim in the outpatient setting, there is an access gap while patients are admitted to hospital. Since pegfilgrastim is a time sensitive drug, some patients cannot wait until coverage is arranged and/ or discharge to receive a dose. Also, inpatients and/ or their family members who are comfortable with administering injections can be taught during their hospital admission how to administer the pegfilgrastim prefilled autoinjector for future outpatient cycles.

Approved Restriction:

For the primary and secondary prophylaxis of febrile neutropenia in patients receiving myelosuppressive systemic therapies for cancer.

Mogamulizumab/ *Poteligeo®*

A new guideline has been approved for the role of mogamulizumab in relapsed or refractory mycosis fungoides or Sézary syndrome.

Approved Restriction:

For the treatment of adult patients with relapsed or refractory histologically confirmed mycosis fungoides (MF) or Sézary syndrome (SS) who have failed at least 1 prior course of systemic therapy.

Epcoritamab/ *Epkinly™*

A new guideline has been approved for the role of epcoritamab in relapsed or refractory large B-cell lymphoma.

Approved Restriction:

For the treatment of adults with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) not otherwise specified, DLBCL transformed from indolent lymphoma, high-grade B-cell lymphoma, primary mediastinal B-cell lymphoma, or follicular lymphoma grade 3B who have:

- Received 2 or more lines of systemic therapy; **and**
- Received or are ineligible to receive chimeric antigen receptor (CAR) T-cell therapy.

Glofitamab/ *Columvi®*

A new guideline has been approved for the role of glofitamab in relapsed or refractory diffuse large B-cell lymphoma.

Approved Restriction:

For the treatment of adults with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) not otherwise specified, DLBCL transformed from indolent lymphoma, high-grade B-cell lymphoma, primary mediastinal B-cell lymphoma, or follicular lymphoma grade 3B who have:

- Received 2 or more lines of systemic therapy; **and**
- Received or are ineligible to receive chimeric antigen receptor (CAR) T-cell therapy.

Dostarlimab/ *Jemperli*

A new guideline has been approved for the role of dostarlimab in advanced endometrial cancer.

Approved Restriction:

For the treatment of adult patients with primary advanced or recurrent mismatch repair deficient (dMMR) or microsatellite instability-high (MSI-H) endometrial cancer not amenable to curative therapy in combination with carboplatin and paclitaxel.
Patients must meet at least one of the following:

- Primary stage III or IV endometrial cancer,
- Experiencing first recurrence and have not previously received systemic therapy in the advanced setting,
- Received prior neoadjuvant or adjuvant systemic therapy and a first recurrence at a minimum of 6 months after completion of treatment.

Calaspargase pegol/ *Asparlas®*

A new guideline has been approved for the role of calaspargase pegol in acute lymphoblastic leukemia.

Approved Restriction:

For the treatment of acute lymphoblastic leukemia (ALL) as a component of a multi-agent chemotherapeutic regimen.

Nivolumab & relatlimab/ *Opdualag™*

A new guideline has been approved for the role of nivolumab and relatlimab in unresectable or metastatic melanoma.

Approved Restriction:

For the treatment of adult and pediatric patients 12 years of age or older with unresectable or metastatic melanoma (regardless of BRAF mutation status) who have not received prior systemic therapy for unresectable or metastatic melanoma.

V. Expanded Guidelines

Bevacizumab/ *Mvasi®, biosimilars*

A new guideline has been approved for the role of bevacizumab in unresectable or metastatic colorectal cancer.

Approved Restriction:

In combination with trifluridine-tipiracil for the treatment of adult patients with unresectable or metastatic colorectal cancer who:

- Have previously been treated with, or are not candidates for, available therapies including fluoropyrimidine-, oxaliplatin, and irinotecan-based chemotherapies, anti-VEGF biological agents, and, if RAS wild-type, anti-EGFR agents; and
- Have disease progression or demonstrated intolerance to a maximum of 2 prior chemotherapy regimens for the treatment of unresectable or metastatic colorectal cancer.

Obinutuzumab/ *Gazyva®*

A new guideline has been approved for the role of obinutuzumab in relapsed or refractory diffuse large B-cell lymphoma.

Approved Restriction:

To be used for lymphodepletion as part of a glofitamab treatment regimen for large B-cell lymphoma.

Pembrolizumab/ *Keytruda®*

Three new Guidelines have been approved for pembrolizumab.

A new guideline has been approved for the role of pembrolizumab in unresectable or metastatic HER2-positive gastric or gastroesophageal junction adenocarcinoma.

Approved Restriction:

In combination with trastuzumab, fluoropyrimidine- and platinum-containing chemotherapy for the first-line treatment of adult patients with locally advanced unresectable or metastatic human epidermal growth factor receptor 2 (HER2)-positive gastric or gastroesophageal junction (GEJ) adenocarcinoma, whose tumours express PD-L1 (CPS ≥ 1 as determined by a validated test).

A new guideline has been approved for the role of pembrolizumab in locally advanced unresectable or metastatic biliary tract cancer.

Approved Restriction:

For the first-line treatment of patients with locally advanced unresectable or metastatic biliary tract cancer (BTC) in combination with gemcitabine plus platinum-based chemotherapy.

A new guideline has been approved for the role of pembrolizumab in (neo)adjuvant melanoma.

Approved Restriction:

For the adjuvant treatment of patients with cutaneous melanoma with completely resected Stage IIB, IIC, and IIIA (limited to lymph node metastases of ≥ 1 mm) to Stage IV (8th edition of the American Joint Committee on Cancer [AJCC] melanoma staging system), regardless of BRAF status. Disease must be completely resected including in-transit metastases; however, presence of regional lymph nodes with micrometastases after sentinel lymph node biopsy alone is allowed. Patients should have a good performance status and brain metastases, if present, must be completely resected (or definitively treated with stereotactic radiation)**.** Eligible patients should continue treatment until disease progression or a maximum of 1 year, whichever comes first.

Trastuzumab/ *Trazimera®, biosimilars*

A new guideline has been approved for the role of trastuzumab in in unresectable or metastatic HER2-positive gastric or gastroesophageal junction adenocarcinoma.

Approved Restriction:

In combination with pembrolizumab, fluoropyrimidine- and platinum-containing chemotherapy for the first-line treatment of adult patients with locally advanced unresectable or metastatic human epidermal growth factor receptor 2 (HER2)-positive gastric or gastroesophageal junction (GEJ) adenocarcinoma, whose tumours express PD-L1 (CPS ≥ 1 as determined by a validated test).

Nivolumab/ *Opdivo®*

Two new Guidelines have been approved for nivolumab.

A new guideline has been approved for the role of nivolumab in advanced or metastatic renal cell carcinoma.

Approved Restriction:

In combination with cabozantinib for the treatment of adult patients with advanced (not amenable to curative surgery or radiation therapy) or metastatic renal cell carcinoma (RCC) who have not received prior systemic therapy for advanced RCC.

A new guideline has been approved for the role of nivolumab in adjuvant melanoma.

Approved Restriction:

For the adjuvant treatment of patients with completely resected Stage IIB, IIC, and IIIA (limited to lymph node metastases of ≥ 1 mm) to Stage IV (8th edition of the American Joint Committee on Cancer [AJCC] melanoma staging system) cutaneous or mucosal melanoma, regardless of BRAF status. Disease must be completely resected including in-transit metastases; however, presence of regional lymph nodes with micrometastases after sentinel lymph node biopsy alone is allowed.

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