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 (Jun25, Sep25) on the recommendation of the Drugs and Therapeutics Committee (Apr 25, May 25, Jun 25).

I. Additions to Hospital Formulary

Cenobamate/ *Xcopri™*

Cenobamate is an oral antiepileptic agent approved by Health Canada in June 2023 as adjunct therapy for patients with partial-onset seizures not controlled using conventional therapy. The mechanism of cenobamate in partial-onset seizures is not fully established; however, pre-clinical studies demonstrate fast and slow inactivation of voltage-gated sodium channels that results in reduced neuronal hyperexcitability, as well as $GABA_A$ positive allosteric modulation that increases neuronal inhibition. More than 30% of patients do not have epilepsy control and with each additional antiepileptic drug failure, the likelihood of seizure control declines; therefore, it is largely recognized that effective, novel antiepileptic medications are important to improve seizure control in individuals with treatment-resistant epilepsy.

A 2024 Cochrane review concludes that when cenobamate is used alongside one or more antiepileptic medication(s) it is "probably better than placebo" for reducing seizures by at least 50% and for seizure freedom in adults with drug-resistant focal epilepsy. The moderate certainty of this conclusion is influenced by the unclear risk of bias for two randomized controlled trials funded by the drug company. Cenobamate had statistically significant benefits for seizure reduction per month during the maintenance period. This review also indicates that the long-term impact of cenobamate currently remains unclear and that its use as monotherapy or for generalized seizures is not established.

A 2024 network meta-analysis indicates that cenobamate had increased efficacy compared to other antiepileptic drugs for adjunctive treatment of focal-onset seizures. Cenobamate was significantly better than placebo and five other antiepileptic drugs (brivaracetam, lacosamide, eslicarbazepine, perampanel and zonisamide) for a 50% or greater reduction in seizures from baseline and seizure freedom. In terms of treatment-emergent adverse events (TEAEs) or TEAES leading to discontinuation, cenobamate is not significantly different from each of the five studied antiepileptic drugs.

A slow dosage titration schedule is recommended for cenobamate to prevent DRESS (Drug Rash with Eosinophilia and Systemic Symptoms). Cenobamate is contraindicated in patients with Familial Short QT syndrome (or with a family history), or a history of a short QT interval. Other possible adverse effects include ataxia, dizziness, vertigo, nystagmus, hyperkalemia, hepatotoxicity, somnolence, fatigue, headache and diplopia.

Approved Restriction:
Patients with medically refractory focal epilepsy who have failed at least two other antiseizure medications. Initiation of new therapy must be under the supervision of a neurologist.

Clevidipine/ *Cleviprex™*

Clevidipine is a selective dihydropyridine calcium channel blocker that causes arterial vasodilation in the peripheral vasculature. This medication's uniqueness is its rapid onset and titratability that allows for rapid blood pressure control. Injectable clevidipine was approved by Health Canada in 2023 indicated for the management of acute blood pressure elevation in perioperative settings.

A hypertensive emergency is a potentially lethal hypertensive crisis where acute and sudden elevation of blood pressure is associated with target end-organ damage. Hypertensive crisis generally presents as headache, faintness, neurological deficit, vision changes, chest pain and dyspnea but can also be asymptomatic. Patients in the acute state are at risk of severe fatal complications such as but not limited to hypertensive encephalopathy, intracerebral hemorrhage, acute papilledema,

aortic dissection, pulmonary edema, acute renal failure and microangiopathic hemolytic anemia (MAHA). The commonly affected end-organ is the myocardium, resulting in a myocardial infarction (MI). Patients with hypertension and end-organ damage present to the hospital requiring rapid and aggressive blood pressure lowering to prevent hypoxic end-organ injury; therefore, rapid-acting intravenous (IV) antihypertensives are used. Treatment choice is generally based on the end-organ damage type, generating the need for a more diverse and efficacious rapid IV antihypertensive such as clevidipine.

Clevidipine has been approved in the US since 2008, indicated for the reduction of blood pressure when oral therapy is not feasible. Although Health Canada's indication is specific to perioperative settings, clevidipine has been used off-label to lower blood pressure in acute settings for patients experiencing a hypertensive crisis. Although smaller trials provide significant insight into the use of clevidipine in such emergencies, more robust evidence is required. Clevidipine is a therapeutic choice for patients who present to acute care with life-threatening hypertensive crises when short-acting beta-blocker therapy is not suitable, or in combination when beta-blocker alone is not effective.

Approved Restriction:
Treatment of acute life-threatening hypertensive crisis when short-acting beta-blocker therapy is not suitable, or in combination with a beta blocker when beta-blocker alone is not effective in the event of:

- Hypertensive emergency with new or worsening end-organ damage
  OR
- Aortic dissection

Isoflurane

Despite decades of safe and effective use of inhaled anesthetics in NS operating rooms, the Formulary status of these agents has been inconsistent within the province and as a result, isoflurane is not currently listed in the NS Health Hospital Formulary. The QEII and IWK ICUs are preparing for the use of isoflurane and seroflurane (currently listed as Formulary) as treatment options for indications in critically ill patients (e.g., status epilepticus, status asthmaticus and sedation).

The One Person One Record (OPOR) Oracle Health Clinical Information System (CIS) Computerized Provider Order Entry (CPOE) catalog only includes Formulary medications; therefore, adding inhaled anesthetics to the NS Health Hospital Formulary facilitates inclusion in the CIS CPOE. The automation of the NS Health order entry process with the CPOE catalogue will provide numerous clinical and safety benefits for patients and the healthcare system including reduced medication errors and increased efficiency.

Isoflurane has been added to the NS Health Hospital Formulary for consistency, to align with the IWK Health Centre Formulary and to facilitate safe ordering and administration in the ICU setting.

Methoxyflurane/ *Penthrox*®

Methoxyflurane (Penthrox®) is a halogenated hydrocarbon anesthetic volatile liquid for inhalation indicated for the short-term relief of moderate to severe acute pain, associated with trauma or interventional medical procedures, in conscious adult patients. Penthrox® is a hand-held inhaler intended for self-administration under the supervision of a healthcare practitioner. The mechanism of action for methoxyflurane in analgesia is not clearly understood.

Methoxyflurane (Penthrox®) has been added to the NS Health Hospital Formulary based on the IWK Health Reserved/ Restricted Formulary status (Women's Health, Gynecology).

Approved Restriction:
For procedural pain during gynecological procedures:

- IUD insertion
  OR
- Endometrial biopsy.

Isavuconazole/ *Cresemba*®

Isavuconazole is a second-generation triazole antifungal that has a broad-spectrum of activity against yeasts, molds, and dimorphic fungi including *Candida, Cryptococcus, Trichosporon, Aspergillus, and Mecorales* species. Available as both oral and injectable, isavuconazole was Health Canada approved in 2019 for the treatment of invasive aspergillosis and invasive Mucormycosis. Isavuconazole works by blocking synthesis of ergosterol, an essential component of the fungal cell membrane. Subsequently, this inhibition leads to the weakening of the structure and function of the fungal cell membrane.

Isovuconazole exhibits predictable and linear pharmacokinetics limiting the need for therapeutic drug monitoring. The bioavailability of oral isavuconazole (98%) is similar to IV administration. Isavuconazole has a relatively tolerable side effect profile compared to other azole antifungals, a reduced risk of hepatotoxicity compared to voriconazole and eliminates the concern for QTc prolongation. A moderate CYP3A4 inhibitor, isavuconazole has minimal effect on CYP2C9/19 and is considered to have fewer drug interactions compared to voriconazole and posaconazole. A literature review of the evidence for efficacy and safety demonstrates the utility of isavuconazole in the treatment of invasive aspergillosis and mucormycosis.

Invasive aspergillosis is a serious infection affecting mostly immunocompromised patients. Risk factors include neutropenia, glucocorticoid use, and hematopoietic/solid organ transplants. *Aspergillus fumigatus* is the most common cause. In the 2016 Infectious Diseases Society of America (IDSA) guidelines on the diagnosis and management of aspergillosis, voriconazole is recommended as the preferred agent for treatment and prevention of invasive aspergillosis (IA); however, voriconazole is limited by its need for therapeutic drug monitoring, side effect profile, and drug interactions. Alternative therapies include liposomal amphotericin B, posaconazole, and isavuconazole. Use of amphotericin B is often undesirable given the concern of renal toxicity and lack of oral dosage form. Additionally, primary therapy

with an echinocandin (e.g., caspofungin) is not recommended unless azole (e.g., voriconazole and posaconazole) or polyene antifungals (e.g., amphotericin B) are contraindicated. More recent guidelines from Australia and Europe recommend isavuconazole as a first-line treatment alternative to voriconazole for invasive aspergillosis.

Mucormycosis is a serious fungal infection associated with a high all-cause mortality caused by Mucorales (e.g., *Rhizopus* spp, *Mucor* spp, and *Lichtheimia* spp, *Rhizomucor* spp, *Cunninghamella* spp, *Apophysomyces* spp, and *Saksenaea* spp). Risk factors for mucormycosis include hematological malignancy, solid organ or haemopoietic stem-cell transplants, prolonged neutropenia, diabetics with uncontrolled hyperglycemia, and dialysis. The main route of infection in an immunocompromised patient is through inhalation of sporangiospores, while immunocompetent host infections often involve cutaneous/ soft tissue. Along with surgical debridement, amphotericin B, posaconazole, and isavuconazole are first line treatments. Other commonly used antifungals, fluconazole and voriconazole, do not have reliable antifungal coverage for mucormycosis and are considered ineffective. Of the guideline recommended agents, amphotericin B is limited by nephrotoxicity and posaconazole has more evidence in the setting of salvage therapy. Isavuconazole is an attractive option given its oral and IV availability and safety profile.

Isavuconazole should be used as an alternative antifungal agent when first line options are unavailable, ineffective or intolerable.

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

Landiolol/ *Sibboran*

Landiolol is an ultra-short-acting injectable beta blocker that was Health Canada approved in 2023 for the short-term reduction of ventricular rate in patients over 18 years of age with supraventricular tachycardia including atrial fibrillation and atrial flutter in perioperative, postoperative, or other acute circumstances where short-term control of the ventricular rate with a short acting agent is desirable. Landiolol has higher ratio of beta 1 to beta 2 receptor affinity when compared other IV beta blockers and has a half-life of 4 minutes, which allows for a rapid onset and offset of effect.

Patients can experience new onset atrial fibrillation (NOAF) during surgery and/ or critical care that is associated with an increased risk of post operative complications and an increased length of hospital stay. The current Canadian Cardiovascular Society/ Canadian Heart Rhythm Society Comprehensive Guidelines for the Management of Atrial Fibrillation state that management of post operative atrial fibrillation involves IV rate control agents such as beta blockers, non-dihydropyridine calcium channel blockers, or amiodarone. In patients with ventricular dysfunction, digoxin or amiodarone are the preferred treatments for NOAF.

Although landiolol has been in use for over 20 years in Japan, the evidence for its efficacy and safety is still emerging. Presently, there is little evidence for landiolol on mortality or morbidity and insufficient safety data apart from the effects on heart rate (HR) and blood pressure. A systematic review established that administration of landiolol to patients with left ventricular dysfunction resulted in a higher likelihood of achieving their target HR when compared to other antiarrhythmic medications; however, since this systematic review excluded postoperative patients as well as patients experiencing sepsis, more research is required to determine the applicability of these findings to critically ill patients. Another randomized control trial published in 2023 evaluated the role of landiolol in treating NOAF secondary to septic shock. This trial was stopped early due to a safety signal that landiolol may increase mortality when compared to the standard of care.

Landiolol was not added to the NS Health Hospital Formulary.

III. Removal of Restrictions

DexmedeTOMidine/ *Precedex*®

DexmedeTOMidine is a potent, selective αlpha$_2$ adrenergic agonist with sedative, anxiolytic, analgesic and opioid sparing properties that was added to the Capital Health Formulary in 2010 with restrictions specific to the intensive care unit (ICU) and the operating room (OR). In 2015, the ICU restriction criteria were revised, and an additional acute pain service indication was added to the Formulary restrictions for patients identified as highly opioid tolerant (HOT). Based on Clinical Practice Guidelines, another revision to the dexmedeTOMidine ICU restrictions was made in 2021. Unlike other sedatives, dexmedeTOMidine may induce a sedative state similar to physiologic sleep without respiratory depression by acting on αlpha$_2$ receptors in the locus caeruleus. (D&T Decisions #46: 2011; D&T Decisions #60: 2015; D&T Decisions #71: 2021).

In May 2025, D&T approved a request from QEII Palliative Medicine to expand the Formulary dexmedeTOMidine restrictions to include end of life sedation (in the hospital setting) for palliative patients who desire a lighter, more rousable sedation (i.e., alternative to midazolam or methotrimeprazine) who may also experience delirium or have difficult to control pain.

Terminal delirium is a common, distressing end of life symptom that may require management with sedation; however, palliative sedation can limit a patient's rousability and meaningful end of life interactions. Use of dexmedeTOMidine in palliative patients is supported by the comparative patient safety evidence of increased rousability and decreased delirium in the critical care, perioperative and pain setting. A 2024 systematic review of dexmedeTOMidine identified 14 palliative care efficacy studies (i.e., experimental, cohort, cross-sectional, nested case-control, case series/ reports; n = 120) for the control of pain and delirium. Rousable sedation was described in most patients and dexmedeTOMidine was often reported as better for delirium than other palliative options. Many studies found that the use of dexmedeTOMidine resulted in reduced opioid dosage and a reduction in the need for rescue medications.

Following the approval of the Hospital Formulary restriction for Palliative Care (D&T approved May 2025), Critical Care requested the removal of all dexmedeTOMidine Formulary restrictions based on the Society of Critical Care Medicine Pain, Agitation, Delerium, Immobility and Sleep (PADIS) 2025 focused update that recommends "Using dexmedeTOMidine over propofol for sedation in mechanically ventilated adult patients admitted to the ICU where light sedation and/ or a reduction in delirium are of highest priorities."

The Hospital Formulary restrictions for dexmedeTOMidine are removed (D&T approved June 2025). Hospital units meeting the NS Health IV Drug Therapy Manual monitoring parameters may administer dexmedeTOMidine intravenously and the Palliative Care subcutaneous administration is guided by criteria for continuous palliative sedation initiation as per NS Health Policy Guidelines.

IV. Medication Policies

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

MM-SR-040	Medication Orders
MM-MA-001	Medication Administration
CL-PT-060	Peripheral Nutrition via Peripheral or Central Lines

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