D&T Decisions
...from the District Drugs and Therapeutics Committee
Capital Health
Nova Scotia

Capital Health

Issue #55: May 29, 2013

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The following policies were approved by the District Medical Advisory Committee (Mar13, Apr13, May13) on the recommendation of the District Drugs and Therapeutics Committee (Nov13, Feb13, Mar 13, Apr 13).

I. Additions to Formulary

Ticagrelor, *Brilinta*®

Ticagrelor, an oral platelet aggregation inhibitor, is the first member of the new cyclopentyltriazolopyrimidines (CPTP) antiplatelet class. Ticagrelor acts on platelet $P2Y_{12}$ receptors and reversibly inhibits ADP-mediated platelet activation and aggregation. This differs from the irreversible binding of the thienopyridine agents (e.g., ticlopidine, clopidogrel and prasugrel).

A large trial (PLATO) evaluated the effect of ticagrelor compared to clopidogrel in patients admitted to hospital with an acute coronary syndrome. The primary endpoint (a composite of death from vascular causes, myocardial infarction, or stroke) occurred less in patients receiving ticagrelor than clopidogrel. The percentage of patients having a major bleed was similar between the two treatment arms; however, more patients on ticagrelor experienced non CABG related major bleeding. The percentage of patients with both dyspnea and dyspnea requiring discontinuation of study treatment was statistically higher for ticagrelor compared with clopidogrel.

The Atlantic Cardiovascular Society has developed the Atlantic Anti-platelet Initiative (AAPI) Atlantic Canadian Guidelines for the Acute Use of Oral Anti-Platelet Therapy. Generally, these AAPI Guidelines recommend that ticagrelor should be used in patients with high risk features, while clopidogrel is still first line in most clinical situations. The District Drugs and Therapeutics Committee has approved the addition of ticagrelor to Formulary with restrictions as per the exception status criteria in the Nova Scotia Pharmacare Formulary:

Approved Restriction:
To be taken in combination with ASA 75 mg to 150 mg daily for patients with acute coronary syndrome [i.e., ST elevation myocardial infarction (STEMI), non-ST elevation myocardial infarction (NSTEMI), or unstable angina (UA)], as follows:
STEMI
- STEMI patients undergoing primary percutaneous coronary intervention (PCI)

NSTEMI or UA
- Presence of high risk features irrespective of intent to perform revascularization:
  - High GRACE risk score (>140)
  - High TIMI risk score (5-7)
  - Second ACS within 12 months
  - Complex or extensive coronary artery disease e.g., diffuse three vessel disease
  - Definite documented cerebrovascular or peripheral vascular disease
  - Previous CABG

  OR
- Undergoing PCI + high risk angiographic anatomy

- Coverage duration 12 months

Insulin Glargine, *Lantus*®
Insulin Detemir, *Levemir*®

Insulin glargine and detemir are long-acting recombinant human insulin analogues with a relatively long duration of action and a relatively peakless pharmacokinetic profile. Since insulin glargine and detemir may reduce the risk of hypoglycemia, patients may be able to reach glucose targets more effectively.

Although some studies have shown a reduced risk of overall and severe hypoglycemia with the long acting insulin analogues as compared to insulin NPH, meta-analyses have not consistently shown this benefit. However, meta-analyses have generally found that in most populations there are benefits of the long acting insulin analogues for the reduction of nocturnal

hypoglycemia, particularly in adults with type 2 diabetes. Comparisons of the two long acting insulins have not established any clinically relevant difference between the two in terms of overall, nocturnal or severe hypoglycemia.

The most commonly reported serious adverse reaction with both insulin glargine and insulin detemir is hypoglycemia. Other commonly reported adverse events include injections site reaction, and pain, as well as headache and GI problems. The District Drugs and Therapeutics Committee has approved the addition of insulin glargine and insulin detemir to Formulary with restrictions as per the exception status criteria in the Nova Scotia Pharmacare Formulary:

Approved Restriction:
For the treatment of patients who have been diagnosed with Type 1 or Type 2 diabetes requiring insulin and have taken NPH and/or premix insulin daily at optimal dosing

AND

Have experienced unexplained nocturnal hypoglycemia at least once a month despite optimal management

OR

Have documented severe or continuing systemic or local allergic reactions to existing insulin(s).

Meropenem

Meropenem and imipenem are carbapenem antibiotics with similar spectrums of activity. In 2011, meropenem was removed from Formulary and imipenem became the carbapenem of choice at Capital Health (with approved restrictions). Susceptibilities indicate that imipenem has better activity against Pseudomonas and a switch to imipenem results in cost savings. There is a therapeutic interchange for meropenem to imipenem and a therapeutic dosage interchange for imipenem.

Since meropenem penetrates the CNS more readily, it is reasonable to use meropenem over imipenem for CNS infections. Imipenem remains the cabepenem of choice for other indications and the therapeutic interchange will be maintained. Meropenem has been approved for addition to Formulary with the following restriction:

Approved Restriction:
Restricted to Infectious Disease for CNS infections.

II. Revised Restrictions

Rivaroxaban, Xarelto®

Rivaroxaban, an anticoagulant that directly inhibits Factor Xa, is an oral once daily medication that does not require routine blood monitoring and has fewer drug/food interactions compared to warfarin. Rivaroxaban is currently on the Capital Health Formulary, restricted to the prophylaxis of venous thromboembolism in patients who have undergone total hip or total knee replacement surgery. In 2011, Health Canada approved rivaroxaban for the prevention of stroke and systemic embolism in patients with atrial fibrillation.

A large non-inferiority trial (ROCKET-AF) evaluated the effect of rivaroxaban compared to warfarin in patients with non-valvular atrial fibrillation. The proportion of patients who experienced a primary outcome [composite of stroke (ischemic or hemorrhagic) or systemic embolism] was lower for rivaroxaban than for warfarin.

There was no statistically significant difference in the proportion of patients experiencing a serious adverse event or a major bleed between rivaroxaban and warfarin; however, the proportion of patients experiencing an intracranial hemorrhage was statistically significantly lower for rivaroxaban than for warfarin. The most common serious adverse event in both groups was cardiac failure. The District Drugs and Therapeutics Committee has approved the addition of rivaroxaban to Formulary with restrictions as per the exception status criteria in the Nova Scotia Pharmacare Formulary:

Approved Restriction:
At risk patients with non-valvular atrial fibrillation (AF) who require rivaroxaban for the prevention of stroke and systemic embolism AND in whom:

- Anticoagulation is inadequate following a reasonable trial on warfarin;

OR

- Anticoagulation with warfarin is contraindicated or not possible due to inability to regularly monitor via International Normalized Ration (INR) testing (i.e. no access to INR testing services at a laboratory, clinic, pharmacy, and at home).

Dabigatran, *Pradaxa™*

Dabigatran is a direct thrombin (Factor IIa) inhibitor currently on the Capital Health Formulary restricted to the prevention of venous thromboembolic events in patients who have undergone elective total hip or total knee replacement surgery. Health Canada has also approved dabigatran for the prevention of stroke and systemic embolism in patients with atrial fibrillation. The major advantage of dabigatran compared to warfarin is that it does not require routine blood monitoring (i.e., INR) and dabigatran has less drug/food interactions.

A large non-inferiority trial (RE-LY) compared dabigatran to warfarin in patients with non-valvular atrial fibrillation. The primary outcome was the incidence of a composite endpoint comprised of stroke or systemic embolism. The annual incidence of the primary composite endpoint was lower for dabigatran compared with warfarin.

The incidence of major bleeding was similar between warfarin and dabigatran 150 mg; however, it was statistically significantly greater for warfarin compared to dabigatran 110 mg. Both doses of dabigatran had a significantly lower incidence of intracranial hemorrhage as compared to warfarin. Treatment discontinuation due to gastrointestinal disorders (dyspepsia) occurred more frequently with dabigatran and there was a significantly higher rate of major gastrointestinal bleeding with dabigatran 150 mg compared to warfarin. The District Drugs and Therapeutics

Committee has approved the addition of dabigatran to Formulary with restrictions as per the exception status criteria in the Nova Scotia Pharmacare Formulary:

Approved Restriction:
At risk patients with non-valvular atrial fibrillation (AF) who require dabigatran for the prevention of stroke and systemic embolism AND in whom:

- Anticoagulation is inadequate following a reasonable trial on warfarin;

OR

- Anticoagulation with warfarin is contraindicated or not possible due to inability to regularly monitor via International Normalized Ration (INR) testing (i.e. no access to INR testing services at a laboratory, clinic, pharmacy, and at home).

III. New Guidelines

Ipilimumab, *Yervoy*

A new Guideline for the role of ipilimumab for metastatic melanoma has been approved by the District Drugs and Therapeutics Committee.

Approved Use:
Initial Treatment: As a single agent for the treatment of unresectable Stage III or IV melanoma in patients who have received at least one prior systemic treatment for advanced melanoma and ECOG performance status (PS) ≤ 1.

Retreatment: At the time of disease progression, re-induction may be considered if patients have had stable disease for at least three months or have previously experienced a complete or partial response to ipilimumab and ECOG PS ≤ 1.

IV. Other

Inhaled Corticosteroids

The Capital Health Formulary currently has four approved inhaled corticosteroids: ciclesonide, beclomethasone, budesonide and fluticasone. When ciclesonide (Alvesco®) was added to Formulary in 2011, the D&T Committee requested that a Formulary Evaluation be conducted to review this class of medications.

A meta-analysis evaluating the effectiveness and safety of inhaled corticosteroids concluded that it is not possible to conduct pair-wise comparisons of all four inhaled corticosteroids due to the lack of head-to-head randomized controlled trials.

The evidence to date does not indicate significant differences in the efficacy or side effect profiles of the four inhaled corticosteroids; therefore, ciclesonide, beclomethasone, budesonide and fluticasone will remain Formulary.

V. Medication Policies

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

CC xx-xxx	Administration of Cancer Chemotherapy
CC 07-xxx	Emergency Department Pain Protocol

VI. Pre-Printed Orders

The following pre-printed orders have been approved by the Medical Advisory Committee on the recommendation of the District Drugs and Therapeutics Committee.

PPO 0044	Allogeneic Bu (12.8) Cy (120) Transplant Orders (Bone Marrow) Related
PPO 0050	Allogeneic Bu (12.8) Cy (120) Transplant Orders (Peripheral Blood) Related
PPO 0436	Geriatric Assessment Unit/ Progressive Care Unit
PPO 0437	Hip Fracture Admission/ Pre-operative Orders
PPO 0438	Hip Fracture Post-operative Orders
PPO 0446	Intravenous Insulin Infusion
PPO 0447	Pain Management Protocol

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

Published by the Pharmacy Department, Capital Health
Editor: Deborah MacIntyre, B.Sc. (Pharm.), ACPR
Drug Information

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