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

Capital Health

Issue #57: Dec. 19, 2013

Inside this Issue…..

The following policies were approved by the District Medical Advisory Committee (Oct13, Nov13, Dec13) on the recommendation of the District Drugs and Therapeutics Committee (Sep13, Oct13, Nov13).

I. Additions to Formulary

Lurasidone, *Latuda*®

Lurasidone is an atypical antipsychotic that functions as an antagonist with high affinity at dopamine D2 receptors and serotonin 5-HT2A and 5-HT7 receptors. It is antagonist with moderate affinity at alpha 2C and alpha 2A adrenergic receptors as well as a partial agonist at serotonin 5-HT 1A receptors. It exhibits little or no affinity for histamine H1 and muscarinic M1 receptors.

A review of nine randomized, controlled trials (RCTs) evaluated the efficacy and safety of lurasidone for the treatment of schizophrenia. Seven of the trials were placebo-controlled, acute treatment trials of six weeks duration. A three week trial compared lurasidone with ziprasidone and a 52 week trial compared lurasidone with risperidone. Psychiatric signs and symptoms were assessed using various instruments. In the 52 week trial comparing lurasidone and risperidone in stable patients, there were no statistically significant differences between symptom scores; however, lurasidone failed to demonstrate non-inferiority to risperidone for time to relapse which was assessed as a secondary outcome.

Although there is a lack of long term efficacy trials, lurasidone has the advantage of once daily dosing, and it may be useful for treating the cognitive and memory deficits seen in schizophrenia. Also, lurasidone has a low propensity to cause weight gain, metabolic abnormalities and QTc interval changes. Lurasidone must be taken with food or at least 350 calories.

Lurasidone has been approved for addition to Formulary with the following restriction:

Approved Restriction:
For the treatment of schizophrenia.

Tinzaparin, *Innohep*®

Tinzaparin is a low molecular weight heparin (LMWH) that was considered for addition to Formulary for the treatment of deep vein thrombosis (DVT) and pulmonary embolism in patients with renal impairment. At CDHA, the current Formulary LMWHs are dalteparin and enoxaparin (enoxaparin is restricted to the management of Acute Coronary Syndromes). LMWHs are often preferred over unfractionated heparin (UFH) since they are administered subcutaneously once to twice daily, are less likely to cause Heparin Induced Thrombocytopenia (HIT) and exhibit a more predictable dose-response relationship, generally requiring less monitoring. However, since LMWHs have primarily renal excretion, patients with reduced renal function may be at an increased bleeding risk due to LMWH accumulation. Therefore, many patients with a Cr_{CL} < 30 mL/minute will continue to receive UFH.

Tinzaparin has a relatively large molecular weight compared to other LMWHs and is likely eliminated via the reticulo-endothelial system thereby preventing accumulation in reduced renal function. A multicenter, randomized, controlled trial sought to determine the safety profile of tinzaparin versus UFH in elderly patients with moderate to severe renal impairment treated for acute DVT. The study was stopped early as an interim analysis revealed excess mortality in the tinzaparin treatment arm when compared to the UFH arm. This prompted Health Canada to issue a warning not to use tinzaparin in patients over 70 years of age with poor renal function. A follow-up analysis of the study revealed that rates of bleeding and recurrent venous thromboembolism (VTE) were actually similar in the two treatment arms since some baseline characteristics were over-represented in the tinzaparin arm confounding the observed

increase in mortality. A substudy evaluated the accumulation of tinzaparin in patients with moderate to severe renal impairment. There was no accumulation of tinzaparin (a surrogate endpoint) among the subset of patients. There was also no correlation found between accumulation ratio and Cr_{Cl}; however, the substudy lacked the power to define differences in clinical endpoints such as major bleeding.

Rabeprazole

Rabeprazole has been added to the Formulary. For further details, refer to Section II - Removal of Therapeutic Interchange.

Omeprazole

Omeprazole has been added to the Formulary. For further details, refer to Section II - Removal of Therapeutic Interchange.

II. Removal of Therapeutic Interchange

Proton Pump Inhibitors (PPIs)

Studies indicate that there are no clinically important differences among standard doses of proton pump inhibitors (PPIs). CDHA has had a formulary therapeutic interchange (TI) for PPIs for over ten years; however, our preferred formulary PPI has changed frequently due to changes in the acquisition cost for medications within this class. A challenge with implementing TIs around contract pricing is that the TI may lose its cost benefit when the contract prices change.

Pantoprazole magnesium (Tecta) became our formulary oral PPI in June 2012 because it was the most cost effective PPI at Capital Health and it was a full benefit on the Provincial Formulary. However, in September 2013, the Provincial Formulary moved pantoprazole magnesium from a regular benefit to an exception status benefit requiring special authorization. Patients with Provincial coverage who are currently using pantoprazole magnesium will be grandfathered pending additional Provincial analysis of PPI prescribing, utilization and cost. Currently, rabeprazole and standard dose omeprazole are open benefit on the Provincial Formulary.

The oral proton pump inhibitor therapeutic interchange has been removed from the Formulary. Pantoprazole magnesium will remain formulary (cost effective at CDHA). Rabeprazole and omeprazole have been added to the Formulary (open benefit on the Provincial Formulary).

Note - since lansoprazole fastabs remain the most convenient PPI for administration via enteral tubes, the therapeutic interchange for PPIs via enteral tube will remain unchanged.

III. Removal of Restrictions

Iron dextran

As a result of increased reporting of serious adverse events to iron dextran by Nephrology, the District Drugs and Therapeutics Committee recommended a suspension on iron dextran use. Since November 2012, iron sucrose has been the only IV iron formulation to be used across the District, unless a physician obtained informed consent to continue iron dextran in current users.

There has been further investigation into the adverse events through the manufacturer and Health Canada's Vigilance Program. Also, major Renal Programs across the country were contacted and a literature review of all adverse drug reactions (ADRs) associated with IV irons was conducted. Limitations to the review include its limit to Renal Programs (many areas outside of nephrology use IV iron), ADR reporting is voluntary, absence of standardized definitions of ADRs and reporting biases.

The suspension of iron dextran use has been lifted. Both iron dextran and iron sucrose will remain on the Formulary with no restrictions and the Formulary status of IV irons will be revisited following a complete formulary evaluation.

IV. Other – New Drug Formulation

Epoprostenol, *Caripul*®

Epoprostenol is Health Canada approved for the long term intravenous treatment of primary pulmonary hypertension and secondary pulmonary hypertension due to the scleroderma spectrum of diseases in NYHA functional Class III and Class IV patients who did not respond to conventional therapy. Originally added to the Formulary in 1999, epoprostenol has been available as Flolan®. The use of Flolan (epoprostenol with glycine and mannitol excipients – epoprostenol GM) is complicated by a lack of stability in aqueous solution. Flolan is only stable for 8 hours at room temperature; however, the solution is stable for 24 hours if the temperature is maintained at 2 to 8ºC with frozen gel packs.

Caripul is a new formulation of epoprostenol (epoprostenol with l-arginine and sucrose excipients – epoprostenol AS) with improved stability. Health Canada approved Caripul as a new entity as its formulation differed from Flolan; however, its approval was based on the Flolan pivotal trials. Diluted Caripul has a room temperature stability of 48 hours if administration is immediate. Diluted Caripul solutions may also be stored at 2 to 8ºC for up to 8 days followed by either 24 or 48 hours of administration at room temperature (stability is concentration dependent). Compared to Flolan which requires a drug-specific proprietary diluent, Caripul has the advantage of reconstitution with either sterile water for injection or sodium chloride 0.9% injection. Caripul is also less expensive than Flolan.

Since there is currently limited data regarding using Caripul by the inhalation route, Flolan will remain Formulary for this route of administration.

Caripul has been approved for addition to Formulary with the following restriction:

Approved Restriction:
For intravenous use. Health Care Professionals should use both the brand name Caripul and generic name epoprostenol when prescribing.

V. New Guidelines

Cabazitaxel, *Jevtana™*

A new Guideline for the role of cabazitaxel in castration resistant metastatic prostate cancer (CRPC) has been approved by the District Drugs and Therapeutics Committee.

Approved Use:
In combination with prednisone for the treatment of CRPC in patients who have received previous treatment with a docetaxel containing regimen, disease progression and an ECOG performance status (PS) 0-2.

Bendamustine, *Treanda®*

1. New Guidelines have been approved for the role of Bendamustine in Low Grade Non-Hodgkin's Lymphoma (NHL).

Approved Use:
In combination with rituximab in patients who have documented evidence of CD20 positive low grade NHL with an ECOG performance status (PS) 0-2. (Monotherapy with bendamustine will not be funded.)

This includes:
Initial Therapy **–** In combination with rituximab as a first line option.

Relapsed/Refractory Therapy **–** In combination with rituximab in the relapsed/refractory setting in bendamustine naïve patients who previously received rituximab based therapy, achieved a response of at least one year's duration since the last rituximab administration and chooses a bendamustine combination as a therapeutic option.

Retreatment **–** In combination with rituximab as a retreatment option in patients who previously received rituximab – bendamustine based therapy and achieved a response of at least one year's duration since the last rituximab administration and/or two years from the last bendamustine dose.

2. New Guidelines have been approved for the role of bendamustine in Chronic Lymphocytic Leukemia (CLL)

Approved Use:
As a single first line agent in patients with Binet Stage B or C CLL and SLL with WHO performance status (PS) ≤ 2 not medically fit to tolerate fludarabine based regimens.

VI. Medication Policies

The following policies have been approved by the District 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.

MM 20-001	Potassium Chloride for Intravenous Infusion
MM 50-003	Medication Reconciliation
MM 05-030	Patients Own Medication
MM 50-020	Medication Safe Handling and Storage
MM 35-001	Narcotics and Controlled Drugs
MM xx-xxx	Short Term Patient Specific Medication Supplies during Episodic Care, Transfers, Passes and Discharges

VII. IV Manual

New Monographs
acetaZOLAMIDE
Busulfan

Revised Monographs
Abciximab
Abciximab Dosing Chart
Ampicillin
Anti-thymocyte globulin (rabbit)
Epoprostenol
Fat Emulsion
Gentamicin
Haloperidol
Hydroxyethyl Starch
Iron DEXTRAN
Iron SUCROSE
Meropenem
Methylene Blue
Multivitamins
Pamidronate
Penicillin G Sodium
ROCuronium
ROCuronium Infusion Table
Succinylcholine
Tobramycin

Removed Monographs
Digoxin Immune Globulin (Digibind)
Etomidate
Thiotepa

VIII. Pre-Printed Orders

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

PPO 0451	Inpatient Management of Alcohol Withdrawal Syndrome – Acute Psychiatric Patients
PPO 0454	Pharmacist Order Clarification – Renal Dose Adjustment
PPO 0353	Multiple Myeloma – VMP for Transplant Ineligible Patients (Bortezomib, Melphalan, Prednisone)
PPO 0459	Cardiac Catheterization/ Percutaneous Coronary Intervention (PCI) - 24 Hour Transfer Patient
PPO 0460	STEMI Admission to CCU STEMI bed

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 Pharmacist

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