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Another study compared fesoterodine to placebo in patients who had suboptimal response to tolterodine. Both placebo and fesoterodine significantly reduced urgency urinary incontinence (UUI) when compared to baseline but fesoterodine significantly reduced UUI episodes compared to placebo in patients who did not have a satisfactory response to tolterodine. Fesoterodine also significantly reduced the number of urgency episodes per 24 hours and had significantly more patients report larger improvements in symptom scale measurements.

Approved Restriction:

For the treatment of overactive bladder with symptoms of urgency, urgency incontinence and urinary frequency in patients who have an intolerance or insufficient response to an adequate trial of immediate-release oxybutynin, solifenacin or tolterodine.

Tolterodine, *Detrol*^{*}

Tolterodine is approved for the symptomatic management of patients with overactive bladder with symptoms of urinary frequency, urgency, or urge incontinence, or any combination of these symptoms.

Tolterodine is a treatment option for patients who are unable to tolerate oxybutynin immediate release (IR) formulations due to side effects. Although evidence indicates that tolterodine is not better than oxybutynin or fesoterodine in improving quality of life, cure, improvement, leakage episodes or voids in 24 hours, it may be preferable for tolerability. Many patients are unable to tolerate anticholinergic drugs; therefore, tolterodine IR may be preferred over oxybutynin IR as study results show fewer medication withdrawals due to side effects and less dry mouth reported with tolterodine. Tolterodine is now a full benefit with NS Pharmacare.

The following policies were approved by the Medical Advisory Committee (Jan18, Mar18, May18, Jun18, Aug18) on the recommendation of the Drugs and Therapeutics Committee (Nov17, Dec17, Feb18, Mar18, Apr18, May18, Jun18).

I. Additions to Formulary

Fesoterodine, *Tovias*[®]

Fesoterodine is an antimuscarinic, antispasmodic drug approved by Health Canada for the treatment of patients with overactive bladder (OAB) with symptoms of urinary frequency, urgency, or urge incontinence, or any combination of these symptoms.

Although there were no trials directly comparing fesoterodine to the formulary medication oxybutynin, fesoterodine has been compared to tolterodine. A Cochrane review in 2012 reviewed anticholinergic medications in OAB and found three trials comparing extended release tolterodine and fesoterodine directly. The meta-analysis showed that in 24 hours there were statistically significant differences (favoring fesoterodine) for quality of life, patient reported cure or improvement, leakage episodes, frequency and urgency episodes; however, those taking fesoterodine had a higher risk of withdrawal due to adverse events at 12 weeks.

Raltegravir, *Isentress*^{® HD}

Isentress^{® HD} is a new once daily formulation of the integrase inhibitor raltegravir. Isentress^{® HD} is recommended in combination with other antiretroviral agents as a first-line option for the treatment of HIV infection.

Approved Restriction:

To be used in combination with other antiretroviral agents for patients being treated for HIV infection.

Elvitegravir/ cobicistat/ emtricitabine/ tenofovir alafenamide, *Genvoya*[®]

Genvoya[®], a new co-formulation of elvitegravir, cobicistat emtricitabine and tenofovir alafenamide, is recommended as a first-line option for the treatment of patients with HIV infection.

Empagliflozin, Jardiance®

Empagliflozin is indicated in adult patients with type 2 diabetes mellitus for use as an adjunct to diet and exercise to improve glycemic control when metformin is inappropriate (i.e., metformin contraindication or intolerance) or as add-on combination therapy when metformin used alone does not provide adequate glycemic control. Treatment of diabetes mellitus aims to control glycemic levels, minimize cardiovascular risk factors, avoid medications that can cause insulin abnormalities and decrease microvascular and macrovascular complications. Empagliflozin acts by inhibiting the sodium glucose co-transporter 2 (SGLT2) in the proximal renal tubules resulting in reduced reabsorption of filtered glucose from the tubular lumen and also lowering the renal threshold for glucose.

The Empagliflozin Cardiovascular Outcomes and Mortality in Type 2 Diabetes (EMPA-REG Outcome trial) was a randomized controlled trial that examined the effects of empagliflozin compared to placebo on cardiovascular morbidity and mortality in patients with type 2 diabetes at high risk for cardiovascular events who were receiving standard care. The primary composite outcome of death from cardiovascular disease, nonfatal myocardial infarction, or nonfatal stroke occurred in 10.5% of patients in the pooled empagliflozin group versus 12.1% of patients in the placebo group.

SGLT2 inhibitors may lower the threshold for developing diabetic ketoacidosis and patients taking an SGLT2 inhibitor who present with acidosis may have a lower blood sugar than expected. There is also an increased risk of genital infections and uro-sepsis with empagliflozin.

Sacubitril/ valsartan, Entresto®

Entresto is a combination dosage formulation of sacubitril (a neprilysin inhibitor) and valsartan [an angiotensin receptor blocker (ARB)] that is indicated for the treatment of heart failure with reduced ejection fraction (HFrEF) in patients with New York Heart Association (NYHA) Class II or III, to reduce the incidence of cardiovascular (CV) death and heart failure (HF) hospitalization.

Naturetic peptides and neprilysin are new molecular targets for the treatment of HF. Naturetic peptides cause vasodilation, diuresis, naturesis and lead to reduced cardiac filling pressures and reduced systemic blood pressure. Neprilysin is an enzyme that breaks down naturetic peptides; therefore, neprilysin inhibition results in increased vasodilation.

Activation of the renin angiotensin aldosterone system also contributes to HF progression. In recent years, neprilysin inhibitors were trialed alone and in combination with an angiotensin converting enzyme (ACE) inhibitor; however, there was a lack of benefit with neprilysin inhibition alone and despite some benefit with a neprilysin inhibition/ACE inhibitor combination, there was an increased risk of angioedema.

PARADIGM HF was a randomized controlled trial that compared a neprilysin inhibitor combined with an ARB (sacubitril/ valsartan) to enalapril alone in patients with class II-IV heart failure symptoms and reduced EF ($\leq 35\%$). Patients enrolled in PARADIGM-HF were receiving stable doses of an ACE inhibitor or an ARB in

combination with a beta blocker and often an aldosterone antagonist. Sacubitril/ valsartan reduced the risk of cardiovascular mortality or hospitalization for heart failure compared to enalapril.

Approved Restriction:

Treatment of heart failure with reduced ejection fraction (HFrEF) in patients with NYHA class II or III HF to reduce the incidence of CV death and HF hospitalization, if all of the following clinical criteria are met:

- Reduced LVEF ($< 40\%$).
- Patient has NYHA class II to III symptoms despite at least four weeks of treatment with a stable dose of an ACEI or an ARB in combination with a beta blocker and other recommended therapies, including an aldosterone antagonist (if tolerable).

II. Non-Formulary

InFLIXimab, Inflectra® brand

Inflectra® is a biosimilar (or subsequent entry biologic) based on the reference product Remicade®. It was approved by Health Canada and recommended by the Common Drug Review for rheumatologic indications that were extrapolated to support dermatologic and gastrointestinal indications. Biosimilars are not the generic version of the original biologic drug but are less expensive and have strict criteria for approval among regulatory bodies. These products are studied in comparison to the originator to determine effectiveness, safety, immunochemical properties and pharmacokinetic similarity.

Evidence of Inflectra® efficacy is described in the PLANETAS and PLANETRA studies for ankylosing spondylitis and rheumatoid arthritis, respectively. These 54 week randomized, double-blind, multi-centre trials were designed to compare the pharmacokinetics, safety and efficacy of Inflectra® (CT-P13) versus the reference product (Remicade®). The results of the PLANETAS study (ankylosing spondylitis) were similar for all the specified endpoints; however, this trial was only powered for pharmacokinetic endpoints rather than efficacy. Therapeutic equivalence was demonstrated in the PLANETRA study (rheumatoid arthritis) and secondary outcomes of efficacy and safety, as well as immunogenicity, were not dissimilar. Both trials had an open-label 102 week extension study when patients either remained on Inflectra® or were switched to Inflectra® from Remicade®. The response rates proved comparable for efficacy and safety in the maintenance and switch groups.

A 30 week post-marketing, open-label study included patients with active, moderate-severe Crohn's disease (CD), fistulizing CD and ulcerative colitis (UC) treated with Inflectra®. Patients were either switched from Remicade® or were treatment naïve. Clinical response and remission rates for all indications suggested there were no efficacy or safety concerns; however, it was not randomized or powered to assess efficacy. Comparison of adverse effects showed no differences to note between the two, whether treatment naïve or switched.

A randomized, double-blind, non-inferiority 52 week phase 4 trial (NOR-SWITCH) involved patients maintained on Remicade® for various indications who either continued treatment or switched to

Inflectra® at an equivalent dose. The primary outcome was disease worsening and results showed that Inflectra® was not inferior to the reference product; however, it was underpowered to show non-inferiority for individual diseases. Other outcomes of changes in disease activity, adverse events, immunogenicity and pharmacokinetic parameters were similar between the two.

Although Inflectra® has been introduced to the market at a lower price than Remicade®, at NSHA the current formulary brand Remicade® remains less costly. Therefore, Remicade® will remain formulary at NSHA and Inflectra® has not be added to the formulary at this time.

III. Revised Restrictions

InFLIXimab, Remicade® brand

The inFLIXimab formulary restrictions have been updated to include ulcerated colitis:

Approved Restriction:

Treatment of patients with a diagnosis of rheumatoid arthritis, ankylosing spondylitis, psoriasis, psoriatic arthritis, Crohn's disease, and ulcerative colitis as per the Pharmacare exception status criteria for inFLIXimab. At NSHA, Remicade® is the approved product since it is less costly than Inflectra®.

IV. New Guidelines

RiTUXimab subcut, Rituxan® SC

Approved Restriction:

As a therapeutic option in combination with chemotherapy or as maintenance therapy for patients who have documented evidence of CD20 positive low-grade Non-Hodgkin's Lymphoma (NHL) with an ECOG performance status of 0-2.

- Subcutaneous use will follow the eligibility criteria for the riTUXimab intravenous (IV) formulation for all low-grade NHL use including induction and maintenance treatment (single agent weekly riTUXimab is excluded).
- The first dose of riTUXimab must be administered IV with the IV formulation. Once the patient is seen to be able to complete the IV dose, the subcutaneous (Rituxan® SC) formulation may be started from the second cycle unless directed by the prescriber. (As per Administration of Subcutaneous RiTUXimab Protocol for Cancer Systemic Therapy 2017).

Ramucirumab, Cyramza®

Approved Restriction:

In combination with paclitaxel for patients with advanced or metastatic gastric cancer or gastro-esophageal junction (GEJ) adenocarcinoma with an ECOG performance status 0-1 and with disease progression following first line chemotherapy.

Blinatumomab, Blincyto®

Approved Restriction:

As a single agent treatment option in adult patients with

Philadelphia chromosome (Ph) negative relapsed or refractory B precursor acute lymphoblastic leukemia (ALL) and who have had at least two prior lines of therapy. Treatment should be in patients with a good performance status and continued until unacceptable toxicity or disease progression.

PANitumumab, Vectibix®

Two new Guidelines have been approved for PANitumumab.

A new Guideline for the use of PANitumumab in patients with progressive metastatic colorectal cancer following standard fluoropyrimidine, irinotecan and oxaliplatin based chemotherapy has been approved by the Drugs and Therapeutics Committee.

Approved Restriction:

As an optional single agent for patients with documented evidence of progressive metastatic colorectal cancer following standard fluoropyrimidine, irinotecan and oxaliplatin based chemotherapy with or without bevacizumab, confirmed KRAS gene wild type only, and ECOG performance status 0-2.

A new Guideline for the role of PANitumumab for first line treatment of patients with metastatic colorectal cancer has been approved by the Drugs and Therapeutics Committee.

Approved Restriction:

In addition to combination chemotherapy for the treatment of patients with wild-type KRAS metastatic colorectal cancer in the first line treatment setting who have a contraindication or intolerance to bevacizumab and who would otherwise be treated only with combination chemotherapy. Patients should have a good performance status. Treatment should continue until unacceptable toxicity or disease progression.

Filgrastim, Grastofil®

Grastofil® is a biosimilar (or subsequent entry biologic) based on the reference product Neupogen®. Biosimilars are not the generic version of the original biologic drug but are less expensive and have strict criteria for approval among regulatory bodies. These products are studied in comparison to the originator to determine effectiveness, safety, immunochemical properties and pharmacokinetic similarity.

The Guidelines for filgrastim have been revised. Neupogen® brand filgrastim will be reserved for patients aged less than 18 years, documented latex allergy, or for stem cell mobilization (see also Section V Revised Guidelines for filgrastim, Neupogen®). For all other patients, Grastofil® brand filgrastim will be prescribed. The use of Grastofil® is intended for the treatment of patients new to "therapy" irrespective of filgrastim therapy administered for a previous course of treatment (e.g., a patient who was treated with Neupogen® during previous chemotherapy cycles are considered new to therapy for the next cycle).

Approved Restrictions for filgrastim (Grastofil® brand prescribed unless Neupogen® brand specified below, age less than 18, or documented latex allergy):

Bone Marrow Transplantation (BMT)

- Stem cell mobilization (use Neupogen®)
- Post BMT engraftment (autologous)

Drug Induced or Chronic Neutropenia

- Drug induced neutropenia
- Chronic neutropenia (ANC less than $0.5 \times 10^9/L$) with recurrent infections

Primary Prophylaxis – Myelosuppressive Chemotherapy

- Febrile neutropenia when risk greater than or equal to 20% in approved myelosuppressive regimens
- Diffuse large B-cell lymphoma (DLBCL) patients greater than or equal to 65 years of age treated with CHOP-like regimens

Secondary Prophylaxis – Myelosuppressive Chemotherapy

- Febrile neutropenia (to decrease subsequent episodes)
- Neutropenic sepsis
- Profound neutropenia (ANC less than $0.5 \times 10^9/L$)
- As a result of dose reduction or delay
- To prevent dose reduction or delay

V. Revised Guidelines

Bevacizumab, *Avastin*®

Approved Restriction:

In **combination** with paclitaxel, topotecan or pegylated liposomal doxorubicin for the treatment of patients with platinum resistant recurrent epithelial ovarian, fallopian tube or primary peritoneal cancer who have received no more than two prior anticancer regimens, good performance status and whose disease is not primary platinum refractory. Treatment should continue until disease progression or unacceptable toxicity.

Filgrastim, *Neupogen*®

Neupogen® is the originator brand product of filgrastim. Grastofil® is a recently available biosimilar brand of filgrastim that is less expensive than Neupogen®; therefore, Neupogen® use has been further restricted (refer to Section IV New Guidelines for filgrastim, Grastofil® for the complete list of filgrastim restrictions).

Approved Restrictions (Neupogen®):

For pediatric patients (less than 18 years of age) as supportive care [according to the established recommendations for the use of white blood cell growth factors (filgrastim)].

For stem cell mobilization in patients with malignant diseases and in normal donors.

For patients who are unable to use available formats of Grastofil® due to documented latex allergy.

VI. Expanded Guidelines

Nivolumab, *Opdivo*®

Approved Restriction:

As a single agent treatment option for patients with squamous cell cancer of the head and neck (SCCHN) who either have a recurrence within six months of potentially curative platinum-based therapy, or recurrence after receiving platinum-based

therapy in a non-curative setting. Patients should have a good performance status. Treatment duration should continue until unacceptable toxicity or disease progression.

Clinical notes:

- For patients who have documented contraindications or severe intolerance to platinum-based chemotherapy, either nivolumab or non-platinum based therapies may be considered for first line use. This would be followed by a single agent chemotherapy after progression on nivolumab.

VII. Medication Policies

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

MM-CP-001 Administration of Subcutaneous Cancer Systemic Therapy

MM-CP-005 Administration of Subcutaneous RiTUXimab Protocol for Cancer Systemic Therapy

VIII. Pre-Printed Orders

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

PPO 0459 Admission Orders – 24h Transfer Patient and Cardiac Day Unit

PPO 0567 PACU Sympathomimetic Orders – Anesthesiology

PPO 0573 Allogeneic Cy (120) /TMI (1200) /Anti-thymocyte Globulin (Rabbit ATG) (4.5) Transplant Orders – Unrelated Myeloablative

PPO 0574 Allogeneic Flu / Cy / Anti-thymocyte Globulin (Rabbit ATG) Transplant Orders – Unrelated Non-Myeloablative

PPO 0589 Extracorporeal Membrane Oxygenation (ECMO)

PPO 0595 Rituximab and Idelalisib – Relapsed Chronic Lymphocytic Leukemia (CLL) / Small Lymphocytic Lymphoma (SLL)

PPO 0597 PACLItaxel/ CARBOplatin – Neoadjuvant Esophageal Cancer

PPO 0394 Management of Confirmed Pathogen Peritonitis Associated With Peritoneal Dialysis

PPO 0395 Empiric Management of Peritonitis Associated with Peritoneal Dialysis

PPO 0451 Inpatient Management of Alcohol Withdrawal Syndrome Acute Psychiatric Patients (IMAW Protocol)

PPO 0555 NIH-Like cyclophosphamide Lupus Nephritis Protocol

PPO 0592 Zoledronic Acid

- PPO 0597 Paclitaxel/Carboplatin – Neoadjuvant Esophageal Cancer
- PPO 0601 Desmopressin/Tranexamic Acid – Bleeding Prophylaxis and Treatment in Mild Von Willebrand Disease, Hemo A or Platelet Dysfunction.
- PPO 0602 Tenckhoff Catheter Insertion
- PPO 0603 Psychiatry Inpatient Admission – Acute Care and Short Stay
- PPO 0605 Post-operative Parathyroidectomy – Calcium Management in A Dialysis Patient
- PPO 0606 Desmopressin – Trial Dose Protocol
- PPO 0356 Acute Myelogenous Leukemia Consolidation HiDAC (6 dose)
- PPO 0357 Acute Myelogenous Leukemia Re-induction HiDAC (8 dose)
- PPO 0373 Acute Myeloid Leukemia Induction (“3+7”) Inpatient
- PPO 0575 Thoracic Surgery Admission Orders
- PPO 0581 Lung Surgery – Post-operative Orders
- PPO 0607 Sepsis Management in Children Greater than 28 Day of Age
- PPO 0608 Patient Controlled Analgesia (PCA), Colchester, East Hants HC
- PPO 0039 DHAP with/without RiTUXimab (IV/Subcut) – Relapsed/Refractory Diffuse Large B-Cell Lymphoma (DLBCL)/ Transformed Lymphoma and Low Grade Lymphoma
- PPO 0065 Acute Respiratory Distress Syndrome (ARDS) for Low Tidal Volume Mechanical Ventilation
- PPO 0084 CHOP/CVP with/ without Rituximab (IV/Subcut) – Low Grade and High Grade Non-Hodgkin Lymphoma (NHL)
- PPO 0127 RiTUXimab (Subcut/ IV) Maintenance – Low Grade Non-Hodgkin Lymphoma
- PPO 0417 Routine Hemodialysis Orders
- PPO 0436 Geriatric Assessment Unit/ Progressive Care Unit
- PPO 0464 Bendamustine/RiTUXimab (IV/Subcut) – Indolent Non-Hodgkin Lymphoma (NHL)
- PPO 0615 RiTUXimab IV - Non-malignant Hematologic Indications
- PPO 0616 Intensive Care Unit (ICU) Subcut Insulin Protocol for Patients Receiving 24 Hour Continuous Enteral Feed/ Parenteral Nutrition
- PPO 0618 Nivolumab (Single Agent: 14 Day Cycle)
- PPO 0619 Pembrolizumab
- PPO 0024 Outpatient High Dose CycloPHOSPHAMIDE Chemotherapy with G-CSF for Stem Cell Mobilization
- PPO 0213 Prismaflex CRRT Orders – Citrate/Calcium Chloride Regional Anticoagulation
- PPO 0214 Prismaflex Continuous Renal Replacement Therapy (CRRT) No Anticoagulation – Patients with Contraindication to Citrate Anticoagulation
- PPO 0238 Calcium Chloride Infusion
- PPO 0239 4% Sodium Citrate Anticoagulation
- PPO 0299 Pre-Cardiac Catheterization/Percutaneous Coronary Intervention (PCI)/Electrophysiology (EP) Orders
- PPO 0363 Citrate Toxicity Orders
- PPO 0385 Peritoneal Dialysis Catheter Repositioning Interventional Radiology Protocol
- PPO 0386 Home Peritoneal Dialysis
- PPO 0389 Peritoneal Dialysis CT Imaging Protocol
- PPO 0404 Peritoneal Dialysis Hernia Protocol
- PPO 0416 Continuous Ambulatory Peritoneal Dialysis Training Order
- PPO 0441 Cannabis Withdrawal
- PPO 0442 Stimulant (Cocaine or Amphetamines) Withdrawal
- PPO 0443 Benzodiazepine Withdrawal
- PPO 0510 Acute Promyelocytic Leukemia Induction
- PPO 0525 Acute Promyelocytic Leukemia – Consolidation (W1-8)
- PPO 0526 Acute Promyelocytic Leukemia – Consolidation (W9-16)
- PPO 0527 Acute Promyelocytic Leukemia – Consolidation (W17-24)
- PPO 0528 Acute Promyelocytic Leukemia – Consolidation (W25-28)
- PPO 0620 Nivolumab (Single Agent: 28 Day Cycle)
- PPO 0275 Pre/Post-Operative Peritoneal Dialysis Catheter Insertion
- PPO 0276 Peritoneal Dialysis and Bowel Protocol
- PPO 0320 Cardiovascular Surgery Standard Transfer Order
- PPO 0336 Filgrastim
- PPO 0385 Peritoneal Dialysis Catheter Repositioning Interventional Radiology Protocol
- PPO 0386 Home Peritoneal Dialysis
- PPO 0387 Parenteral Nutrition
- PPO 0563 Bevacizumab – Gynaecology Regimen
- PPO 0607 Sepsis Management in Children Greater than 28 Day of Age
- PPO 0609 Liver Transplant – Pre-operative/Intra-operative
- PPO 0610 Liver Transplant – Post-operative
- PPO 0621 Continuous Renal Replacement Therapy – Citrate Anticoagulation
- PPO 0622 Continuous Renal Replacement Therapy – No Anticoagulation
- PPO 0384 Peritoneal Dialysis Leak Protocol

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

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