LMPS PHARMACY AND THERAPEUTICS NEWSLETTER

Lower Mainland Pharmacy Services

SPRING 2015

Health Canada Update: Ibuprofen

Courtesy: Keiran Shah and France Carriere, Pharmacy Residents.

On April 23rd, 2015 Health Canada issued a safety update relating to prescription-strength ibuprofen and the risk of heart attack and stroke at high doses.

- Ibuprofen is a non-steroidal anti-inflammatory (NSAID) used as an analgesic, antipyretic, and anti-inflammatory. Currently, the maximum recommended prescription daily dose is 2400 mg in Canada.
- Health Canada conducted a safety review analyzing epidemiological data to investigate the association between higher doses of ibuprofen and the risk of heart and stroke adverse events.
- The review concluded that there was evidence of an association between ibuprofen at a daily dose of 2400 mg or more and an increased risk of heart attack and stroke related adverse events, especially in those having a history of, or other risk factors for, these events. The risk increases with dose and duration of use.
- The review also concluded that there was no evidence to show an increased risk in cardiovascular events in patients using a maximum daily dose of 1200 mg or less when taken for a short duration of time (7 days or less).
- Health Canada advises that ibuprofen at a daily dose of 2400 mg or more should be avoided in patients with ischemic heart disease, cerebrovascular disease, congestive heart failure, or risk factors for cardiovascular disease.

Inside this issue:

Health Canada Update: Zopiclone

On November 19th, 2014 Health Canada issued a safety update relating to zopiclone dosage guidelines to minimize the risk of next-day impairment.

- The recommended starting dose has been reduced to 3.75 mg. Zopiclone should be taken once per night at bedtime. The lowest effective dose for each patient should be used.
- The prescribed dose should not exceed 5 mg in elderly patients, in patients with hepatic or renal impairment or those currently treated with potent CYP3A4 inhibitors. Dose adjustment may be required with concomitant use with other CNS-depressant drugs.
- Patients should be instructed to wait at least 12 hours after dosing before driving or engaging in other activities requiring full mental alertness, especially for elderly patients and for patients who take the 7.5 mg dose.

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BCHA Formulary Updates

BCHA Pharmacy and Therapeutics Committee decisions for November 2014, and February 2015. Implementation dates for these decisions may vary at different sites.

Formulary Additions

apixaban tablets (ELIQUIS®)
Health Canada Indication: prevention of venous thromboembolic events (VTE) in adult patients who have undergone elective knee or hip replacement surgery; the prevention of stroke and systemic embolism in patients with atrial fibrillation; the treatment of venous thromboembolic events (deep vein thrombosis [DVT], pulmonary embolism [PE]) and prevention of recurrent DVT and PE.
BCHA Restriction: at risk patients with non-valvular atrial fibrillation, for the prevention of stroke and systemic embolism in whom

- anticoagulation is inadequate following at least a 2 month trial of warfarin OR
- anticoagulation using warfarin is contraindicated or not possible due to inability to regularly monitor the patient via International Normalized Ratio (INR) testing in the community (i.e. no access to INR testing services at a laboratory, clinic, pharmacy and at home)

(See page 5 for warfarin and novel oral anticoagulants comparison chart.)

linagliptin tablets (TRAJENTA®)
Health Canada Indication: adult patients with type 2 diabetes mellitus to improve glycemic control
BCHA Restriction: combination treatment for type 2 diabetes mellitus when insulin NPH is not an option AND after inadequate glycemic control on maximum tolerated doses of metformin AND a sulfonylurea

cetirizine tablets, syrup (REACTINE ®)
Health Canada Indication: relief of the symptoms associated with seasonal allergic rhinitis; fast and long-lasting relief of itching due to allergic skin reactions such as hives
BCHA Restriction: pediatric patients

isopropyl myristate 50% - cyclomethicone 50% rinse (RESULTZ®)
Health Canada Indication: head lice treatment

The following drugs are added with the BCHA Restriction: to indications outlined in the BCCA Benefit List AND patients who are registered with BCCA
afatinib oral solid **(GIOTRIF®)**
vismodegib oral solid (**ERIVEDGE®)**
dabrafenib oral solid **(TAFINLAR®)**

pyrimethamine powder—added for compounding

Formulary Deletions

DELETED: The following agents have been removed from the BCHA formulary since they have been discontinued by the only manufacturer:

- methoxsalen topical and enteral
- phenol 6% injection
- bismuth subgallate tablets
- pyrimethamine tablets
- triamcinolone hexacetonide injection

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BCHA Formulary Updates

Therapeutic Interchange Program Update

Courtesy: Keiran Shah and France Carriere, Pharmacy Residents.

DPP-4 INHIBITOR (GLIPTIN) – NEW THERAPEUTIC INTERCHANGE POLICY

Linagliptin (TRAJENTA®) has been added to the BCHA formulary and is part of a new therapeutic interchange. Sitagliptin and saxagliptin are excluded from formulary.

Mechanism of Action: Linagliptin, saxagliptin and sitagliptin are dipeptidyl peptidase 4 (DPP-4) inhibitors. They increase incretin hormone concentrations by inhibiting DPP-4, the enzyme that hydrolyzes these hormones. Increased levels of incretin hormones improve beta cell responsiveness to glucose, enhancing the synthesis and release of insulin. Incretin hormones also decrease glucagon synthesis, reducing the production of glucose by hepatic cells.

Why linagliptin? There is one trial that suggests this agent may reduce the risk of complications related to diabetes. This evidence is not definitive but appears stronger compared to sitagliptin and saxagliptin. Linagliptin dosing does not need to be adjusted for patients with renal dysfunction. The acquisition cost is slightly lower than the other agents.

Pharmacare: Pharmacare currently provides limited coverage for both linagliptin and linagliptin-metformin via the Special Authority program.
Special Authority Criteria and the BCHA Formulary Restrictions are:

- as part of a combination treatment for type 2 diabetes mellitus when insulin NPH is not an option AND after inadequate glycemic control on maximum tolerated doses of metformin AND a sulfonylurea

Therapeutic Interchange Protocol: Orders for sitagliptin and saxagliptin will be automatically substituted to linagliptin 5 mg PO daily. If a combination sitagliptin-metformin or saxagliptin-metformin product is ordered, this will be substituted to linagliptin 5 mg PO daily with metformin at the same dose.

DRUG ORDERED (GLIPTIN OR COMBINATION)	DRUG DISPENSED
sitaGLIPtin (any dose)	linagliptin 5 mg PO daily
saxagliptin (any dose)	linagliptin 5 mg PO daily
sitaGLIPtin – metFORMIN 50 – 500 mg 50 – 850 mg 50 – 1000 mg	linagliptin 5 mg PO daily AND metFORMIN same dose and frequency
sitaGLIPtin – metFORMIN XR 50 – 1000 mg	linagliptin 5 mg PO daily AND metFORMIN 500 mg PO twice daily
saxagliptin – metFORMIN 2.5 – 500 mg 2.5 – 850 mg 2.5 – 1000 mg	linagliptin 5 mg PO daily AND metFORMIN same dose and frequency

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BCHA Formulary Updates

Excluded Drugs

Excluded drugs are defined as medications or medication classifications that have been assessed by the B.C. Health Authorities Pharmacy and Therapeutics Committee and have been intentionally excluded from the formulary.

Medications in this category offer little advantage over what is currently available. These drugs are not stocked in hospitals. There may be exceptional cases where a patient will require an Excluded Drug. Each Health Authority has a process for reviewing and monitoring requests for the exceptional use of Excluded drugs. Patients may be instructed to provide their own medication in these cases.

Drug name	Rationale and Possible Formulary Alternatives
dual dimethicone spray (NYDA®)	Alternate formulary agents available: isopropyl myristate 50%-cyclomethicone 50% (RESULTZ®) and permethrin (NIX®, KWELLADA®)
incobotulinumtoxinA powder for reconstitution (XEOMIN®)	Formulary alternative: botulinum toxin type A (BOTOX®)
indacaterol capsule for inhalation (ONBREZ BREEZHALER®)	No evidence that indacaterol is more beneficial than current formulary long-acting beta agonists, and is more expensive. Formulary alternative: formoterol, salmeterol
moxifloxacin eye drops (VIGAMOX®)	Moxifloxacin has not been shown to be superior to formulary ophthalmic fluoroquinolones. Formulary alternative: ofloxacin, ciprofloxacin
saxagliptin and saxagliptin-metformin tablets (ONGLYZA®, KOMBOGLYZE®)	Linagliptin may have clinical benefit, has dosing simplicity and fewer drug interactions. Automatic Therapeutic Interchange to: linagliptin
sitagliptin and sitagliptin-metformin tablets (JANUVIA®, JANUMET XR®)	Linagliptin may have clinical benefit, has dosing simplicity and fewer drug interactions. Automatic Therapeutic Interchange to: linagliptin
tadalafil tablets (ADCIRCA®)	In placebo-controlled trials, the benefits of tadalafil for pulmonary arterial hypertension (PAH) appear similar to that of sildenafil. Tadalafil is more costly than sildenafil. Formulary alternative: sildenafil

Pre-operative Management of Low Molecular Weight Heparins

The Parenteral Drug Therapy Manual has been updated with revised recommendations for pre-operative management of low molecular weight heparins. This change was approved at VCH-PHC Regional Pharmacy and Therapeutics Committee in February 2015.

Drug	Dosing	Timing before surgery
dalteparin or enoxaprin	Treatment dosing – Q24H	Do not give dose within 36 hours of surgery May give 50% of dose 24 hours pre-op in patients at high risk of thrombosis
	Treatment dosing – Q12H	Do not give dose within 24 hours of surgery
	Prophylactic dosing	Do not give dose within 12 hours of surgery
fondaparinux	Treatment dosing	Do not give dose within 48 hours of surgery
	Prophylactic dosing	Do not give dose within 24 hours of surgery

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Warfarin and Novel Oral Anticoagulants Comparison Chart

Courtesy: VGH Pharmacy and Therapeutics Newsletter, Apr 2015

Drug	warfarin (COUMADIN®)	apixaban [1] (ELIQUIS®)	rivaroxaban [2] (XARELTO®)	dabigatran [3] (PRADAX®)
Indications/Dose [4] Orthopedic Prophylaxis	Dosing based on target INR 1.5 to 2.3	2.5 mg PO BID TKR x 10 to 14 days THR x 32 to 38 days	10 mg PO daily TKR x 14 days THR x 35 days	220 mg PO daily or 150 mg PO daily [5] TKR x 10 days THR x 28 to 35 days
Stroke Prevention in Atrial Fibrillation	Dosing based on target INR 2 to 3	5 mg PO BID [9]	20 mg PO daily with food or 15 mg PO daily with food [7,8]	150 mg PO BID or 110 mg PO BID [6]
Acute VTE Treatment	Dosing based on target INR 2 to 3	10 mg PO BID x 7 days, then 5 mg BID for up to 6 months	15 mg PO BID x 3 weeks, then 20 mg PO daily with food [8]	150 mg PO BID after 5 to 10 days of parenteral antico-agulation
Target Inhibition	Vitamin K epoxide reduc-tase complex	Factor Xa	Factor Xa	Factor IIa (Thrombin)
Monitoring	INR	Not needed	Not needed	Not needed
Oral Bioavailability	99%	50%	66 to 100%	6 to 7%
Time to Peak	36 to 72 hours [10]	3 to 4 hours	2 to 4 hours	2 hours
Half-Life	20 to 60 hours	8 to 15 hours	9 to 13 hours	14 to 17 hours
Elimination	Hepatic (Cytochrome P450)	27% renal 73% biliary	66% renal (36% unchanged) 33% biliary	80% renal 20% biliary
Adjust Dose for Renal Failure	No	Yes (Contraindicated if CrCl less than 15 to30 mL/min)	Yes (Contraindicated if CrCl less than 30 mL/min)	Yes (Contraindicated if CrCl less than 30 mL/min)
CYP Metabolism	Yes— CYP 2C9, 1A2, 3A4, 2C19	Yes— 15% CYP3A4	Yes— 30% CYP3A4	No
P-Glycoprotein Sub-strate	No	Yes	Yes	Yes

1 Apixaban is formulary restricted to stroke prevention in patients with atrial fibrillation if warfarin cannot be used
2 Rivaroxaban is formulary restricted to orthopedic prophylaxis, and for stroke prevention in patients with atrial fibrillation if warfarin cannot be used
3 Dabigatran is formulary restricted to patients on this medication prior to admission
4 Approved indications in Canada
5 eGFR 30-50 mL/min, dabigatran dose for orthopedic prophylaxis = 150 mg daily
6 eGFR 30-50 mL/min and patient 75 years or greater + risk factors for bleeding, consider dabigatran 110 mg BID for stroke prevention in atrial fibrillation
7 eGFR 30-50 mL/min, rivaroxaban dose for stroke prevention = 15 mg daily
8 Rivaroxaban doses greater than 10 mg/day should be taken with food
9 If patient has 2 or the following: age 80 years or greater, weight 60 kg or less, serum creatinine 133 µmol/L or above, consider apixaban 2.5 mg BID; avoid use if CrCl less than 30 mL/min (per BC Pharmacare)
10 Full antithrombotic effect delayed for 72 to 96 hours after initiation

TKR = Total Knee Replacement; THR = Total Hip Replacement; VTE = Venous Thromboembolism;
CrCl = Creatinine Clearance; CYP = Cytochrome P450 enzyme system

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Antimicrobial Stewardship: ASPIRES Tidbits

Courtesy: VCH ASPIRES Team — Dr Titus Wong, Dr Tim Lau

Indications for Ertapenem Use

Provincial Formulary Criteria (as per BC Health Authorities P&T Committee):

- Restricted to documented or suspected infections that:
  - ◊ Involve multi-drug resistant organisms in an **OUTPATIENT or AMBULATORY SETTING** where other agents (e.g. piperacillin-tazobactam, ticarcillin-clavulanate, ceftazidime, meropenem, imipenem) cannot be used due to intolerance, resistance or inconvenience in the ambulatory setting.
- Guidance for appropriate use:
  - ◊ Indicated for directed therapy of polymicrobial infections based on culture and susceptibility results for treatment of:
    - Infections with extended-spectrum β-lactamase (ESBL)-producing Gram negative bacilli (where piperacillin-tazobactam or alternate formulary agents cannot be used);
    - Select polymicrobial infections (only when *Enterococcus* spp., *Pseudomonas* spp., and *Acinetobacter* spp. are **NOT** deemed key pathogens).

Inappropriate use:

- Inpatient use
- *Enterococcus* spp., *Pseudomonas* spp., and *Acinetobacter* spp. (ertapenem is ineffective)
- First-line for community-acquired urinary tract infections (with no risk factors for multi-drug resistant organisms)
- Empiric therapy for nosocomial pneumonia
- Empiric therapy for intraabdominal infections (community- or nosocomially-acquired)
- Non-purulent cellulitis (usually *Streptococcus pyogenes*)

Alternate agents:

- Limit use of carbapenems except when coverage of highly resistant pathogens is absolutely necessary
- Some alternative agents are listed in the following table:

Broad-spectrum coverage	Gram-negative rods (<u>including</u> ESBLs) when tested sensitive	Gram-negative rods (<u>excluding</u> ESBLs) when tested sensitive
ceftriaxone + metronidazole PO/IV clindamycin PO/IV + ciprofloxacin PO/IV piperacillin-tazobactam vancomycin + ciprofloxacin PO/IV + metronidazole PO/IV	ciprofloxacin PO/IV co-trimoxazole PO/IV gentamicin piperacillin-tazobactam	ampicillin, or amoxicillin ± clavulanate PO cephalexin PO or cefazolin or cefixime PO or ceftriaxone ciprofloxacin PO/IV co-trimoxazole PO/IV gentamicin

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QUESTIONS? COMMENTS?
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