

## *In This Issue...*

<i>Changes to Formulary</i>	1
<i>PDTM Inclusion of Oncology Drugs</i>	1
<i>Expiry Dates of Sterile Pharmaceuticals</i>	2
<i>Ranitidine Recall</i>	2
<i>Tacrolimus Switch to Sandoz Brand</i>	2
<i>Allergy Documentation Form Revision</i>	2
<i>Pharmacy Awards</i>	2
<i>Empagliflozin Review</i>	3

## *Additions*

1. **Empagliflozin 10, 25 mg tabs (Jardiance®)**
  - Anti-diabetic agent
  - SGLT2 inhibitor used as monotherapy, or as an add-on to conventional therapy such as metformin
  - Restricted to treatment of type 2 diabetes after inadequate glycemic control on maximum tolerated doses of dual therapy with metformin and sulfonylureas, or patients intolerant to a sulfonylurea
  - See Page 3 for drug review
2. **Rifaximin 550 mg tabs (Zaxine®)**
  - Antibiotic used to treat patients with resistant hepatic encephalopathy
  - Rifaximin is poorly absorbed and reduces ammonia production by eliminating ammonia-producing colonic bacteria
  - Restricted to management of overt hepatic encephalopathy in combination with the maximum tolerated dose of lactulose
3. **Insulin glargine 100 units/mL (Basaglar KwikPen®)**
  - Long-acting insulin preparation currently covered by PharmaCare
  - Lantus® brand of insulin will also remain on formulary
4. **Ethyl Alcohol 40% (Vodka)**
  - For use in patients enrolled in the Managed Alcohol Program

## *Deletions*

The following items are no longer available from the manufacturer:

1. **Fluphenazine decanoate injection (Modecate®)**
2. **Clodronate injection (Bonefos®)**
  - Alternatives: Pamidronate, Zoledronic acid
3. **Cefaclor tabs (Ceclor®)**
4. **Calcium 500 mg, 1000 mg effervescent tabs (Calcium Sandoz®, Gramcal®)**
  - Alternative: calcium liquid 100 mg Ca<sup>++</sup>/5 mL

## *Updated Policies*

### 1. PDTM INCLUSION OF ONCOLOGY DRUGS

Since August 2019, the most commonly used oncology drugs at VCH-PHC have been gradually reintroduced into the Parenteral Drug Therapy Manual (PDTM). Current PDTM monographs for drugs used for both non-oncology and oncology indications have been updated to include the oncology-related information (e.g. methotrexate).

As this will be a gradual process, if the oncology drug monograph is not found within the PDTM, please continue to use the link found on the right-hand margin of the on-line PDTM to access the BC Cancer Drug Monographs.

### EDITORIAL STAFF:

Karen Shalansky, Pharm.D., FCSHP  
 Tim Lau, Pharm.D., FCSHP  
 Ruby Sangha, B.Sc.(Pharm.), ACPR  
 Nilu Partovi, Pharm.D., FCSHP

Any comments, questions, or concerns with the content of the newsletter should be directed to the editors. Write to VA Pharmaceutical Sciences Vancouver General Hospital, 855 W12th Ave, Vancouver BC V5Z 1M9, send a FAX to 604-875-5267 or email karen.shalansky@vch.ca

## 2. EXPIRY DATES OF STERILE PHARMACEUTICALS

Sterile pharmaceuticals must be discarded as per Table 1 unless otherwise indicated on the label. Revisions to this table are bolded and include:

- Vials for parenteral use with preservative: 28 days, **for one patient only (except for influenza vaccine)**
- **Syringes containing medications drawn from a vial or ampoule: 12 hours or at the end of each shift change, whichever is sooner**

This table can be found in the formulary at: [www.vhpharmsci.com/VHFormulary](http://www.vhpharmsci.com/VHFormulary)

Product	Once opened, discard after:
Eye drops with preservative	30 days
Eye drops without preservative (commercial - single dose)	single use only
Eye drops without preservative (manufactured in pharmacy)	expiry date labelled by pharmacy
Vials for parenteral use with preservative	28 days, <b>for one patient only (except for influenza vaccine)<sup>1</sup></b>
Vials for parenteral use without preservative	<b>single use only</b>
Ampoules	single use only
<b>Syringes containing medications drawn from a vial or ampoule</b>	<b>12 hours or at the end of each shift change, whichever is sooner<sup>2,3</sup></b>
Bags for I.V. use (with or without added drugs)	24 hours <sup>2,4</sup>
Bags for epidural use (prepared in pharmacy)	48 hours
Bags for epidural use (prepared in nursing unit)	24 hours
Bags/bottles for irrigation use (e.g. NS, BSS) (with or without added drugs)	24 hours <sup>2</sup> (provided only 1 entry puncture)

<sup>1</sup> Label vial with patient name (other than flu vaccine); store under appropriate temperature conditions.

<sup>2</sup> Stability data may indicate that the solutions must be discarded earlier. Check the PDTM or contact pharmacy.

<sup>3</sup> Refer to "Preparation of Parenteral Medications for Administration by Syringe" Policy (D-00-11-30070|CA\_3900) for further details regarding pre-drawing of medications.

<sup>4</sup> If a nurse adds medication to an IV bag on the nursing unit (ie. not in pharmacy), the infusion should be started within 1 hr of preparation.

## 3. RANITIDINE RECALL

Due to contamination of oral ranitidine with a suspected carcinogen, N-nitrosodimethylamine (NDMA), all oral ranitidine products have been recalled in Canada. Suggested formulary alternatives include:

- ⇒ Oral antacids (e.g. Diovol<sup>®</sup> Plus, Calcium (e.g. Tums<sup>®</sup>))
- ⇒ Pantoprazole tablets or injection
- ⇒ Esomeprazole tablets for tube feeds

## 4. TACROLIMUS SWITCH TO SANDOZ BRAND

There are now two different brands of tacrolimus available on formulary (Prograf<sup>®</sup> and Sandoz<sup>®</sup>)

As of Nov 4, 2019, for SOT and L/BMT patients:

- For **new patients**: tacrolimus (Sandoz<sup>®</sup>) will be dispensed
- For **current patients** already on tacrolimus: the brand specified on the order will be dispensed. If no brand name is specified, the brand the patient was on prior to admission will be dispensed (per PharmaNet records)
- For tacrolimus **liquid** orders: The Sandoz<sup>®</sup> brand will be provided

## 5. ALLERGY DOCUMENTATION FORM REVISION

The Allergy/Intolerance Status Form has been revised as part of the alignment with Cerner/CST implementation. The most significant changes are:

- The form must be completed by a designated health care professional (DHCP)
  - ⇒ Physicians, pharmacists and authorized nurses in designated areas can complete the form. Dietitians can complete the food allergy section.
- Documentation of FOUR allergy types is now added:
  - ⇒ Allergy, Intolerance, Side effect, Contraindication (see back of form for examples)
- Environment section has been added, which includes documentation of latex allergy

## *Pharmacy Awards*

**Dr Charles Au** was honoured with the "New Preceptor of the Year" award by the Lower Mainland Pharmacy Services (LMPS) Residency program for the 2018-2019 year.

**Dr Charles Au** also received the "Preceptor of the Year" award by the UBC Office of Experiential Education (OEE) for the second year practicum course.

## New Drugs/Drug Products

### Empagliflozin

Ming Chang, B.Sc.(Pharm.), Lily Lin, Pharm.D., Charles Au, Pharm.D.

Empagliflozin (Jardiance<sup>®</sup>) is a sodium-glucose cotransporter-2 (SGLT2) inhibitor approved by Health Canada in 2015 for use in type 2 diabetes mellitus (T2DM), as monotherapy or as an add-on to conventional therapy such as metformin.

#### Pharmacology and pharmacokinetics

SGLT2 is a transporter protein found in the proximal tubule of renal nephrons and is responsible for reabsorbing 90% of glucose that is filtered by the kidney.<sup>1</sup> By inhibiting SGLT2, empagliflozin substantially increases urinary glucose excretion. Empagliflozin has a half-life of ~12 hours; it is metabolized primarily through glucuronidation and is excreted predominantly in the urine (50% as unchanged drugs) and feces.

#### Place in therapy

Empagliflozin improves glycemic control and decreases hemoglobin A1C by 0.5-0.7%.<sup>2</sup> Advantages of SGLT2 inhibitors include their cardiovascular (CVS) benefits, their low risk of hypoglycemia, and modest decreases in weight and blood pressure.<sup>3,4</sup>

The CVS safety of empagliflozin was established by EMPA-REG OUTCOME, an international, double-blinded, randomized controlled trial evaluating CVS outcomes of empagliflozin 10 or 25 mg/day compared to placebo in patients with T2DM receiving standard of care.<sup>3</sup> The majority of subjects (99%) had an established history of CVS disease (coronary or peripheral artery disease, or history of myocardial infarction (MI) or stroke). For the primary composite outcome of CVS death, nonfatal MI and stroke, empagliflozin met both non-inferiority and superiority criteria compared to placebo over 3.1 years of follow-up (Table 2). Empagliflozin also

achieved statistically significant reductions in all-cause mortality (HR 0.68, 95% CI 0.57-0.82), CVS death (HR 0.62, 95% CI 0.49-0.77) and hospitalization for heart failure (HR 0.65, 95% CI 0.50-0.85) in exploratory analyses.

In a sub-group analysis of the EMPA-REG OUTCOME trial, pre-specified renal effects of empagliflozin were examined.<sup>5</sup> Empagliflozin (N=4124) was shown to significantly lower the risk of incident or worsening nephropathy when compared to placebo (N=2061) (12.7% vs 18.8%, HR 0.61; 95% CI 0.53-0.70). Patients in the empagliflozin arm also had a significantly lower risk of the renal composite outcome of doubling of serum creatinine, initiation of renal-replacement therapy, or death from renal disease (HR 0.54; 95% CI 0.40-0.75).

The 2018 Diabetes Canada guidelines<sup>6</sup> recommend that empagliflozin be considered as a preferred adjunct to metformin in T2DM patients with established CVS disease to reduce the risk of CVS events (Grade A, Level 1A), heart failure hospitalization (Grade B, Level 2), or progression of nephropathy (Grade B, Level 2). Other therapies in this recommendation include liraglutide for the reduction of CVS events, (Grade A, Level 1A) and canagliflozin for the reduction of CVS events (Grade C, Level 2), heart failure hospitalization (Grade C, Level 2) or nephropathy progression (Grade C, Level 3). If there is no clinical evidence of CVS disease, second-line therapy after metformin should be based on patient specific factors such as renal function, degree of hyperglycemia and other comorbidities (e.g. congestive heart failure, hepatic disease).

Upcoming studies (EMPEROR-Reduced and EMPEROR-Preserved) should give better insight into the utility of empagliflozin in heart failure with both reduced and preserved ejection fraction. The upcoming EMPEROR-Kidney trial will help

**Table 2. Outcomes from EMPA-REG OUTCOME Trial**

	Placebo (N=2333)	Empagliflozin (N=4687)	Hazard Ratio (95% CI)	P-value
<b>Primary Outcome, number (%)</b> Death from cardiovascular causes, non-fatal MI, or nonfatal stroke Non-inferiority Superiority	282 (12.1)	490 (10.5)	0.86 (0.74-0.99)	<0.001 0.04
<b>Secondary Outcome, number (%)</b> Death from cardiovascular causes, non-fatal MI, nonfatal stroke, or hospitalization for unstable angina Non-inferiority Superiority	333 (14.3)	599 (12.8)	0.89 (0.78-1.01)	<0.001 0.08

determine the safety and efficacy of empagliflozin in patients with end stage kidney disease.

### Dosage

Empagliflozin is dosed initially at 10 mg once daily with or without food, and can be increased to 25 mg daily as necessary for improved blood sugar control. Empagliflozin should be avoided with eGFR < 30 mL/min (Table 3). Close monitoring of renal function and glucose levels is recommended in patients with eGFR < 60 mL/min.<sup>1</sup>

**Table 3. Empagliflozin Renal Dose Adjustment<sup>1</sup>**

eGFR	Dose Recommendation
> 44 mL/min	No dosage adjustment
30-44 mL/min	Recommended not to initiate therapy, but do not discontinue in patients already taking it
< 30 mL/min or on dialysis	Contraindicated

### Monitoring

Due to its mechanism of action, empagliflozin causes glycosuria, which may increase the risk of genital and urinary tract infections. In the EMPA-REG OUTCOME trial<sup>3</sup>, empagliflozin increased the risk of genital mycotic infections three-fold. Although the risk of urinary tract infections was not increased in clinical trials, patients with a history of recurrent or complicated urinary tract infections were excluded from studies. Empagliflozin is also associated with Fournier's gangrene, a rare but severe, necrotizing infection of the external genitalia and perianal region.<sup>1</sup>

Empagliflozin has diuretic and natriuretic effects as it promotes both sodium and glucose urinary excretion. It should not be started in patients who are hypovolemic, and patients on concomitant diuretics may require diuretic dosage adjustment.<sup>1</sup>

Euglycemic diabetic ketoacidosis (euDKA) is a rare but serious adverse effect of SGLT2 inhibitors.<sup>7</sup> Precipitants to ketoacidosis include intercurrent illness, surgery, decreased carbohydrate intake, dehydration, and excessive alcohol intake.<sup>7</sup> Symptoms of euDKA are similar to conventional DKA (nausea, vomiting, abdominal pain, confusion, hyperventilation, fatigue). However, in the presence of SGLT2 inhibitor-induced glycosuria, serum glucose levels may be only mildly elevated or normal, which can lead to a missed diagnosis. The incidence of ketoacidosis in the EMPA-REG OUTCOME trial was < 1%.<sup>3</sup> If a patient on an SGLT2 inhibitor presents with potential signs and

symptoms of DKA, evaluation for the presence of ketones in the serum and urine are recommended even in the presence of a normal blood glucose.<sup>6</sup> Patients on SGLT2 inhibitors should be instructed to hold this medication during acute illness and to avoid ketogenic diets.

### Formulary and coverage considerations

Empagliflozin has been added to formulary with the same restrictions as per PharmaCare Special Authority requirements:

- Restricted to treatment of type 2 diabetes after inadequate glycemic control on maximum tolerated doses of dual therapy with metformin and sulfonylureas, or patients who are intolerant to a sulfonylurea.

Other SGLT2 inhibitors on the Canadian market are dapagliflozin, canagliflozin and ertugliflozin; however, only empagliflozin is currently covered by PharmaCare.

### References

1. Empagliflozin. In: Lexicomp. Hudson (OH): Lexicomp Inc.: [updated 28 Aug 2019].
2. Regier L, Jenson B, Rutherford L, Crawley A. Antihyperglycemic agents. Rx Files March 2017.
3. Zinman B, Wanner C, Lachin JM *et al.* Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes (EMPA-REG OUTCOME). *NEJM* 2015;373(22):2117-28.
4. Häring H-U, Merker L, Seewaldt-Becker E *et al.* Empagliflozin as add-on to metformin in patients with type 2 diabetes: a 24-week, randomized, double-blind, placebo-controlled trial. *Diabetes Care* 2014;37(6):1650-1659.
5. Wanner C, Inzucchi SE, Lachin JM *et al.* Empagliflozin and progression of kidney disease in Type 2 diabetes. *NEJM* 2016;375:323-334.
6. Diabetes Canada Clinical Practice Guidelines Expert Committee. Diabetes Canada 2018 Clinical Practice Guidelines for the Prevention and Management of Diabetes in Canada. *Can J Diabetes* 2018;42(Suppl 1):S1-S325.
7. Zhang L, Tamilia M. Euglycemic diabetic ketoacidosis associated with the use of a sodium-glucose cotransporter-2 inhibitor. *Can Med Assoc J* 2018;190(25):E766-8.