Thames Valley Family Health Team

THE DOSE- Winter 2023

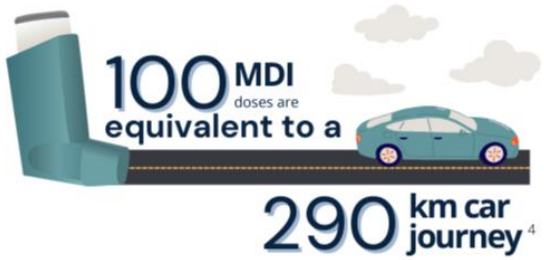
Happy New Year!

In this issue:

Later in this issue… More information on the newly approved drug, **Ubrelvy® (ubrogepant)** - an oral, small-molecule, calcitonin gene–related peptide receptor antagonist. It is indicated for acute treatment of moderate to severe migraines, with or without aura. It may be considered if triptans are contraindicated, ineffective, or poorly tolerated, with caution as it has several drug interactions. Click here to jump to the full-length drug information summary.

Saving the world, one canister at a time: climate conscious inhaler prescribing

CASCADES is a Canadian initiative to address healthcare's contributions to the climate crisis, led by the Centre for Sustainable Health Systems. Hydrofluorocarbons (HFCs) used as propellants in traditional metered dose inhalers (MDIs) act as greenhouse gases when released from the canister and are known to have significant global warming potential. Other inhaler types, such as dry powder inhalers (DPIs, such as Turbuhaler®, Diskus®, Ellipta®), and soft mist inhalers (SMIs, such as Respimat®), which do not use propellants, are associated with less carbon emissions and environmental impact.



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The CASCADES website has a suite of tools including considerations for prescribing, infographics to help with shared decision making, and other tools and templates to help make your inhaler prescribing practice more sustainable.

Three tips to jumpstart your "greener" practice:

1. ***In all patients, using any type of inhaler, educate and review proper inhaler technique***.
   X 12-71% of the time patients use their inhalers incorrectly.
   ✓ Improved technique leads to better clinical outcomes, less waste, and with MDIs, less propellant emissions. FHT team members such as the Respiratory Therapists and Pharmacists can help with this education.
2. ***Engaging in shared decision making with the patient about the switch is more likely to lead to a successful switch***
   X Forced switches may cause harm.
   ✓ CASCADES has a patient letter that may help with communication with patients.
3. ***Minimize the carbon footprint of MDIs for patients who need to remain on them*** (e.g. young or elderly patients, patients with strong preference or financial constraints, those with severe COPD)
   ✓ Encourage use of a spacer, and bringing inhalers to the pharmacy to be recycled and incinerated

To treat or not to treat? Risk and benefits of treatments for acute cough

When assessing patients with acute cough this season, consider the following pearls:

Consider the potential benefits of treatment options	**Weigh the benefits against the known harms of treatment options**
• Non-prescription options for cough have been reviewed in several meta-analyses and have been found to have no strong evidence for or against benefit (Cochrane, 2014) • Data is limited for use of inhalers for post-infectious cough (only 2 RCTs for Inhaled corticosteroids (ICS) and 1 RCT for bronchodilators). In a meta-analysis of the 2 ICS trials, placebo improved cough scores by ~50% over 2 weeks, and the ICS treatment about 5-10% more. Ipratropium/salbutamol was found to slightly improve cough when compared to placebo after 10 days (69% vs 37%), however notably in all arms >80% of patients' cough was resolved after 20 days. • Honey has not been studied in adults but has been shown to be effective in children (see below) • Combination cold products containing a decongestant and an antihistamine have been found to be effective at reducing overall symptoms of the common cold (though this includes other symptoms such as fever, chills, runny nose etc) (Cochrane, 2022)	• While the magnitude (if any) of benefit of cough treatments is questionable, the potential harms are well known • Dextromethorphan: metabolized by CYP 2D6 (potential for increased toxicity when taken with 2D6 inhibitors e.g. fluoxetine), adds to serotonergic burden of medications, possible drowsiness, dizziness • Codeine/hydrocodone: drowsiness, nausea, constipation, risk of opioid misuse, dependence and addiction, risk of overdose and likely little added benefit when added to other opioids (e.g. in patients taking opioids for chronic pain); metabolized by CYP 2D6 and 3A4, concurrent use with inhibitors would decrease effectiveness as would genetic variability of 2D6 activity • First-generation antihistamines: have strong anticholinergic properties which may cause drowsiness, dry mouth, constipation, confusion • Combination products: can cause dizziness, drowsiness; decongestants can cause elevated blood pressure in patients with uncontrolled hypertension • Some therapeutic options (e.g. increased fluid intake, humidifiers, nasal saline, honey) are very low-risk; adverse effects with guaifenesin and menthol lozenges are uncommon at usual doses
Address underlying conditions and exacerbating triggers • Treat underlying conditions such as GERD and asthma which may be causing the cough • Advise about trigger avoidance (e.g. tobacco smoke, occupational inhaled irritants)	**Think of the children!** • Codeine and other opioid containing products are not recommended by Health Canada for children under the age of 18 due to the potential for increased risk of problematic use later in life • Health Canada has also advised against the use of OTC cough and cold agents in children under the age of 6, due the lack of established benefit and risk of misuse, overdose, and rare side effects • Honey has been found to possibly be effective in children – with greater symptom relief than placebo, no treatment or diphenhydramine, and no difference in symptom impact compared to dextromethorphan (Cochrane, 2018) – though it should be avoided in children <1 year old or those who are immunocompromised. Doses in the studies included in the Cochrane review ranged from 1-2 tsp (5-10mL) one to three times daily

Should you *try* out the new *tri*-ple therapy inhaler, Breztri?

Breztri® Aerosphere pMDI* (182 mcg budesonide / 8.2 mcg glycopyrronium (as bromide) / 5.8 mcg formoterol fumarate dihydrate) is the second "triple therapy" LAMA/LABA/ICS* combination inhaler to be released to the Canadian market for the treatment of COPD (the other being Trelegy® Ellipta - fluticasone furoate/umeclidinium/vilanterol).

Place in therapy: for patients with severe COPD who have failed "dual therapy" with LAMA/LABA, or who have severe symptoms and/or exacerbations

Dose: 2 inhalations twice daily

A few practical notes on triple therapy…

- Triple therapy is associated with higher incidences of adverse effects related to the ICS (thrush 5%, hoarseness 5%, pneumonia 2%/year).
- There is limited evidence to suggest triple therapy reduces mortality; its evidence for use is related to reduction of COPD exacerbation
    - 1.07 moderate-severe exacerbations/year with Breztri® compared to 1.25/year with glycopyrrolate/formoterol (rate ratio, 0.76; 95% CI, 0.69 to 0.83; P<0.001) and 1.42/year with budesonide/formoterol (rate ratio, 0.87; 95% CI, 0.79 to 0.95; P=0.003)
- If a triple therapy is indicated, a combination product reduces the risk of accidental ICS monotherapy, which is associated with increased mortality (NNH 87/year) (such as, in the case where a patient continues using ICS product and mistakenly self-discontinues their LAMA/LABA product)

Choosing between triple products: For patients who do not have the inspiratory force to inhale the dry powder inhalation of Trelegy®, Breztri® would be a preferred option. Recommend a spacer to help with timing the pMDI inhalations, and reduce environmental impact. Both Trelegy® and Breztri® are covered by ODB using LU code **638** (for reduction of exacerbations in patients with COPD). Out of pocket cost is ~$150 plus pharmacy markup and fees.

…but I thought you just said not to prescribe pMDIs?: As mentioned above, dry power inhalers are not appropriate for everyone, and some patients may still require a pMDI. AstraZeneca, the manufacturer of Breztri® is working with Honeywell to innovate new propellants with a lower carbon footprint, and Breztri® is expected to be the first product they use this technology in when it is available.

* pMDI = pressurized metered dose inhaler LAMA = Long Acting Muscarinic Agent; LABA = Long Acting Beta-Agonist; ICS: Inhaled Corticosteroid

Community pharmacist update: Minor Ailments Prescribing – happening now!

This section was contributed by University of Toronto class of 2023 PharmD student, Sabih Jamil

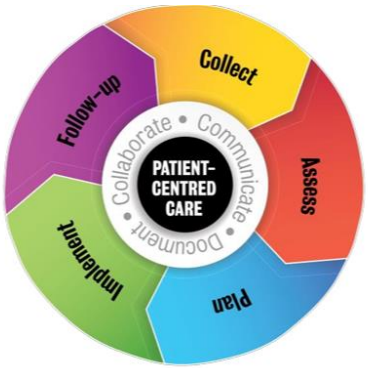
Starting January 1, 2023, all Part A pharmacists, interns, and students will be authorized to prescribe for 13 minor ailments as defined under the regulations. Minor ailments are health conditions that can be managed by self-care strategies or minimal treatment. These conditions are: 1) usually short-term, 2) do not require lab results, 3) can be reliably differentiated from serious conditions, 4) their treatment is unlikely to mask other conditions, and 5) require minimal or short-term follow-up. The approved minor ailments include:

- Allergic rhinitis
- Candidal stomatitis (oral thrush)
- Conjunctivitis (bacterial, allergic, and viral)
- Dermatitis (atopic, eczema, allergic and contact)
- Dysmenorrhea
- Gastroesophageal reflux disease (GERD)
- Hemorrhoids
- Herpes labialis (cold sores)
- Impetigo
- Insect bites and urticaria (hives)
- Tick bites, post-exposure prophylaxis
- Musculoskeletal sprains and strains
- Urinary tract infections (uncomplicated)

These conditions will be **self-diagnosed by the patient**. Pharmacists will be able to prescribe based on their assessment of the patient. The purpose of pharmacist's assessment is not to diagnose but to choose the most appropriate treatment option. The assessment also includes **referring to other health care providers when appropriate**. Pharmacists will not be ordering diagnostic tests or blood work, performing urine dips or point-of-care testing as part of this service – cases warranting this type of assessment would be referred to the patient's primary care provider.

Speaking of urine dips… did you know that most major guidelines recommend against urine culture for uncomplicated UTI, and <2% of cultures result in meaningful impact on choice of treatment for acute cystitis?
Click here for an evidence summary about empiric treatment

Each time the pharmacist interacts with a patient regarding a condition, they can use the Minor Ailment Service Framework to guide the interaction. The steps in this framework include: 1) collect, 2) assess, 3) plan, 4) implement, and 5) follow-up. Treatment algorithms have been developed by the Ontario College of Pharmacists for conditions where anti-infectives may be prescribed, in consultation with Public Health Ontario (see links - uncomplicated UTI and post-exposure tick prophylaxis).



Step 1: **collecting** subjective and objective information about the patient;
Step 2: **assessing** the collected data to identify problems and set priorities;
Step 3: creating an individualized care **plan** that is evidence-based and cost-effective;
Step 4: **implementing** the care plan; and
Step 5: monitoring the patient over time during **follow-up** encounters to evaluate the effectiveness and safety of the plan & modify it as needed.

Image Source: OPA Prescribing for Minor Ailments Course N.Nakhla

After the patient interaction, pharmacists must **document and notify the primary care provider**, where applicable. The documentation will include: 1) rationale for prescribing, 2) monitoring/follow-up plan, and 3) copy of the prescription. The document needs to be clear, concise, timely, legible, and retrievable. The documentation is intended to inform the physician of the interaction. ***The liability of prescribing is assumed by the prescribing pharmacist.***

Odds and Ends: new generics, ODB formulary updates

- Januvia® and Janumet® now have approved generic equivalents (covered by ODB), priced at half the cost of the trade products ($0.89-1.77/tablet + markup/fees, down from $1.63-3.55/tablet)
- Arazlo® (tazarotene 0.045% lotion) is the newest product covered by ODB for acne vulgaris (requires LU 636 for acne vulgaris). For a list of the other acne options covered by ODB see the Spring 2021 Issue of The Dose
- In December 2022, the Ministry of Health released a statement indicating that they would require patients using certain biologics - Copaxone®, Enbrel®, Humalog®, Humira®, Lantus®, NovoRapid®, Remicade®, and Rituxan® to transition to biosimilar products
    - The transition period will begin March 31, 2023, and patients are expected to be transitioned by December 29, 2023 – ODB suggests the patient meets with their care team to select a biosimilar product, have it prescribed (not directly interchangeable), and develop a transition plan for monitoring
    - Exemptions will be considered on a case-by-case basis, likely through EAP application
    - Similar policies are already in place in 8 other Canadian jurisdictions - British Columbia, Alberta, New Brunswick, Quebec, Northwest Territories, Nova Scotia, and Saskatchewan.

A 5-point Refresher on Biosimilars

A comparison of trials using SGLT2 inhibitors for chronic kidney disease

This section was contributed by University of Toronto class of 2023 PharmD student, Sabih Jamil

Sodium-glucose cotransporter 2 inhibitors (SGLT2i) are a unique class of antihyperglycemic agents that have demonstrated reduction of albuminuria and preservation of kidney function in clinical trials involving patients with type 2 diabetes. The CREDENCE (Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation) trial demonstrated the reno-protective effects of canagliflozin 100mg daily in patients with type 2 diabetes with chronic kidney disease. This highlighted the need to evaluate the effects of other SGLT2 inhibitors to preserve kidney function in diabetic and non-diabetic chronic kidney disease patients. The EMPA-KIDNEY (Study of Heart and Kidney Protection with Empagliflozin) trial was done to assess the efficacy and safety of empagliflozin on the progression of kidney disease and cardiovascular disease in a wide range of patients with CKD. The DAPA-CKD (Dapagliflozin and Prevention of Adverse Outcomes in Chronic Kidney Disease) trial was performed to assess the efficacy and safety of dapagliflozin in patients with chronic kidney disease, with or without type 2 diabetes. Both trials are summarized in the Table on the following page.

Trial	EMPA-KIDNEY	DAPA-CKD
Study Design	Randomized, double-blind, placebo controlled	Randomized, double-blind, placebo controlled
Intervention	Empagliflozin 10 mg once daily vs. placebo	Dapagliflozin 10 mg once daily vs. placebo
Patient Characteristics	8,184 patients Mean age: 63.8±13.9 years 33.2% female 54% without diabetes eGFR: 37.3±14.5 ml/min/1.73 m^2 Median urinary albumin(mg)-to-creatinine (g) ratio: 329	4,304 patients Mean age: 61.8±12.1 years 33.1% female 32.5% without diabetes eGFR: 43.1±12.4 ml/min/1.73 m^2 Median urinary albumin(mg)-to-creatinine(g) ratio: 949
Patient Meds: ACEi/ARB	85.7%	98.4%
Diuretic	41.2%	43.1%
Statin	66.3%	64.8%
Follow-up	2 years	2.4 years
End Points	Primary outcome: - First occurrence of progression of kidney disease or death from cardiovascular causes Secondary outcomes: - Hospitalization for heart failure or death from cardiovascular causes - Hospitalization for any cause - Death from any cause	Primary outcome: - Composite of first occurrence of decline of at least 50% in eGFR, onset of end-stage kidney disease, or death from renal or cardiovascular causes Secondary outcomes: - Composite kidney outcome defined as decline in the eGFR of at least 50%, end-stage kidney disease, or death from renal causes - Composite cardiovascular outcome defined as hospitalization for heart failure or death from cardiovascular causes - Death from any cause
Results: Primary Outcome	Empagliflozin 13.1% (432/3304) Placebo 16.9% (558/3305) (hazard ratio, 0.72; 95% CI, 0.64 to 0.82; P<0.001) **NNT = 24 patients/2 years**	Dapagliflozin 9.2% (197/2152) Placebo 14.5% (312/2152) (hazard ratio, 0.61; 95% CI, 0.51 to 0.72; P<0.001) **NNT = 19 patients / 2.4 years**
Secondary Outcome	- Hospitalization for heart failure or death from cardiovascular causes occurred in 4.0% of patients in the empagliflozin group and 4.6% of patients in the placebo group (hazard ratio, 0.84; 95% CI, 0.67 to 1.07; P=0.15) - Death from any cause occurred in 4.5% of patients in the empagliflozin group and 5.1% of patients in the placebo group (hazard ratio, 0.87; 95% CI, 0.70 to 1.08; P=0.21)	- Composite kidney outcome occurred in 6.6% of patients in dapagliflozin group and 11.3% of patients in placebo group (hazard ratio, 0.56; 95% CI, 0.45 to 0.68, p<0.001) - Composite cardiovascular outcome occurred in 4.6% of patients in dapagliflozin group and 6.4% of patients in placebo group (hazard ratio, 0.71; 95% CI, 0.55 to 0.92, p<0.009) - Death from any cause occurred in 4.7% of patients in dapagliflozin group and 6.8% of patients in placebo group (hazard ratio, 0.69; 95% CI, 0.53 to 0.88, p<0.004)

Bottom Line: Among a broad range of patients with CKD, with or without diabetes, empagliflozin 10mg led to a lower risk of progression of kidney disease or death from cardiovascular causes than placebo. (NNT = 24/2yrs)
For patients with CKD, with or without diabetes, dapagliflozin led to a lower risk of a composite of decline in the eGFR of at least 50%, end-stage kidney disease, or death from renal or cardiovascular causes than placebo. (NNT =19/2.4yrs)

SGLT2i Common Questions and Practical Tips

Are SGLT2i approved by Health Canada for use in patients with CKD without diabetes?

At this time, dapagliflozin is the only SGLT2 indicated for use in adults with CKD without diabetes. However, empagliflozin has also been studied more recently in this population as outlined above.

Is the reno-protective benefit of SGLT2i a class effect?

All three SGLT2i agents have shown reno-protective effects for patients with diabetes. However, only empagliflozin and dapagliflozin have been studied and shown benefits in patients with CKD without diabetes.

What is the mechanism of kidney protection for SGLT2i?

By reducing the reabsorption of sodium in the proximal tubule of the kidney, SGLT2i restore the tubular glomerular feedback, which leads to a reduction in the kidney blood flow, decrease in glomerular hyperfiltration, and decrease in intraglomerular pressure. This relieves the strain and stress on kidneys and helps prevent damage.

What are the target doses of empagliflozin and dapagliflozin for patients with CKD?

The target dose for both empagliflozin and dapagliflozin is 10 mg once daily. Using doses higher than the standard dose of 10 mg has not been studied.

What were the safety outcomes for empagliflozin and dapagliflozin?

Empagliflozin: The incidence of urinary tract infection, hyperkalemia, acute kidney injury, serious or symptomatic dehydration, liver injury, and bone fracture were broadly similar in the empagliflozin and the placebo group.

Dapagliflozin: The incidence of amputation, diabetic ketoacidosis, fracture, renal-related adverse event, major hypoglycemia, and volume depletion were similar overall in the dapagliflozin and placebo groups.

Is there a risk of hypoglycemia with SGLT2i for patients without diabetes?

Severe hypoglycemic episodes were not observed in patients without diabetes for both empagliflozin and dapagliflozin.

Does patient's furosemide have to be adjusted before starting SGLT2i?

Adjusting patient's existing medications depends on patient's symptoms. If patient has volume depletion, it should be corrected before starting an SGLT2i. If patient is euvolemic, furosemide dose reduction is not required but can be considered. If patient has volume depletion after starting SGLT2i, furosemide dose should be decreased by 30-50%. Monitoring of blood pressure and volume status is recommended.

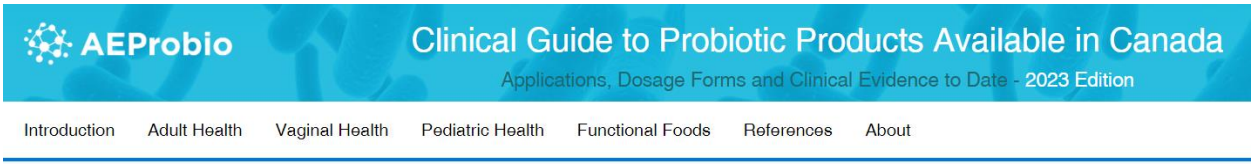
When should SGLT2i be discontinued?

Empagliflozin is contraindicated and should be stopped in patients with eGFR less than 20 ml/min/1.73 m^2, end stage renal disease, and patients with dialysis.
Dapagliflozin has insufficient data to support its use in patients with eGFR less than 25 ml/min/1.73 m^2. It should be discontinued when dialysis is started.

Are SGLT2i covered by ODB for use in CKD patients without diabetes?

SGLT2i are paid for by ODB for anyone with ODB coverage. They do not require an LU code or special authorization.

Drug Information Tool Spotlight:
Support probiotic recommendations with evidence using probioticchart.ca



You know you want to recommend a probiotic for a patient, but how to you respond when the patient asks which specific product they should purchase?

The Clinical Guide to Probiotic Products Available in Canada (www.probioticchart.ca) is a Canadian clinical guide which is designed to help health care providers make evidence-based recommendations for probiotic use.

In the broader categories of adult health, vaginal health, pediatric health, and functional foods, the charts list individual trade products, and the indications for which evidence exists for use (e.g. for antibiotic associated diarrhea, or irritable bowel syndrome). The chart also includes references to specific studies, an assessment of the quality of the evidence (Level I-III), and the recommended dosing for each product.

Limitations: This tool does not include an exhaustive list – there is quite rigorous exclusion criteria. It does not include generic products which have not had funding for individual studies, or products which have had a change in strain of probiotic. It is funded through a grant by the industry-sponsored Alliance for Education on Probiotics.

Potential: The information in this chart can be used as a complement to clinical knowledge and other evidence and references, such as the Natural Medicines Database. It is a quick way to view the evidence that exists for use of some probiotic products in Canada.

Ubrelvy® (ubrogepant)

This section was contributed by University of Toronto class of 2023 PharmD student, Sabih Jamil

Drug name	ubrogepant – 50 mg, 100 mg
Drug class	Calcitonin gene-related peptide receptor antagonist
Indication	Acute treatment of moderate to severe migraine, with and without aura
Dosing	50 to 100 mg as a single dose; if symptoms persist or return, may repeat dose after 2 hours. Maximum: 200 mg per 24 hours.
Dose adjustment	Renal Impairment: CrCl ≥30 mL/min: No dosage adjustment necessary. CrCl 15 to 29 mL/min: 50 mg as a single dose; if symptoms persist or return, may repeat dose after 2 hours. Maximum dose: 100 mg per 24 hours. CrCl <15 mL/min: Avoid (has not been studied). Hepatic Impairment: Mild to moderate (Child-Pugh class A, B): No dosage adjustment necessary. Severe (Child-Pugh class C): 50 mg as a single dose; if symptoms persist or return, may repeat dose after 2 hours. Maximum dose: 100 mg per 24 hours.
Contraindications/ Precautions	Contraindications: Concomitant use of strong CYP3A4 inhibitors (e.g. clarithromycin, ketoconazole, nirmaltrelvir-ritonavir (Paxlovid)) Precautions: Renal or hepatic impairment
Pregnancy/ Breastfeeding/ Special populations	Based on data from animal reproduction studies, **ubrogepant may cause fetal harm**. It is not known if ubrogepant is present in breast milk. Effects on breast-fed infant and milk production are also unknown. Safety and efficacy are not established in pediatric patients. Insufficient data for patients ≥65 years old.

ADRs	The most common adverse events are nausea (4%), somnolence (2-3%), and dry mouth (2%). Serious adverse events include appendicitis, spontaneous abortion, pericardial effusion, and seizure.
Drug interactions	BCRP Inhibitors (e.g. clopidogrel, leflunomide): May increase the serum concentration of ubrogepant. Use an initial ubrogepant dose of 50 mg and second dose (at least 2 hours later if needed) of 50 mg when used with a BCRP inhibitor (LexiComp). Ciprofloxacin: May increase the serum concentration of ubrogepant. Use an initial ubrogepant dose of 50mg and avoid a second dose within 24 hours when used concurrently with ciprofloxacin (LexiComp). CYP3A4 Inducers: May decrease the serum concentration of ubrogepant. Examples of inducers include carbamazepine, phenytoin, primidone, St. John's wort Nirmaltrelvir-ritonavir (Paxlovid): Paxlovid should not be started until 12 hours after the last dose of ubrogepant, and ubrogepant should not be administered again until 3 days after Paxlovid treatment is completed (Liverpool COVID-19 Drug Interactions Resource) CYP3A4 Inhibitors: May increase the serum concentration of ubrogepant. Examples of strong inhibitors listed in Contraindications section above; examples of moderate inhibitors include erythromycin, fluconazole, diltiazem, verapamil. P-glycoprotein Inhibitors: May increase the serum concentration of ubrogepant. Use an initial ubrogepant dose of 50 mg and second dose (at least 2 hours later if needed) of 50 mg when used with a P-gp inhibitor (LexiComp).
Efficacy	1672 participants with migraine, with or without aura, were assigned in a 1:1:1 ratio to receive placebo, ubrogepant 50 mg, or ubrogepant 100 mg. The percentage of participants who had freedom from migraine pain at 2 hours was 11.8% in the placebo group, 19.2% in the 50 mg ubrogepant group (P=0.002), and 21.2% in the 100 mg ubrogepant group (P<0.001). No head-to-head trials have been performed to compare ubrogepant with other drugs for migraine.
Place in therapy	Ubrogepant should be considered for patients who have contraindications for triptans or when triptans are ineffective and poorly tolerated.
Cost/coverage	Is not yet established for the Canadian market Cost in the United States is approximately $85 per dose

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