Thames Valley
Family Health Team

THE DOSE- Fall 2021

In this issue:

Dopamine agonist withdrawal syndrome (DAWS)

Bottom line: DAWS can occur during a taper or after a discontinuation of a dopamine agonist, symptoms can last from days to years. Treatment: reintroduction of a dopamine agonist at the lowest effective dose.

- Health Canada has found a causal association with pramipexole, quinagolide and ropinirole
- It is unclear if it is a class effect with the current evidence
- **Incidence:** can be as high as 19% in Parkinson's Disease. Incidence is unknown when treating RLS.
- **Risk factors:** impulse control disorder (gambling, eating, hypersexuality), higher doses and cumulative exposure.
- **Frequency** of DAWS **unrelated** to the speed of taper
  - **Onset:** during a taper or discontinuation of a dopamine agonist
- **Symptoms:** agitation (most frequent), anxiety, panic attacks, depression, irritability, drug craving, insomnia, daytime fatigue, diaphoresis, nausea, vomiting, flushing, orthostasis, pain
- **Duration:** patient specific- Symptoms can last from days to years
- **Treatment:** reintroduction of a dopamine agonist at lowest effective dose
  - **Note: Levodopa is not an effective treatment of DAWS**

NACI Updated Recommendations- Spacing of vaccinations

Bottom line: "COVID-19 vaccines may be given at the same time as, or any time before or after, other vaccines, including live, non-live, adjuvanted, and non-adjuvanted vaccines"

- At present, although limited data, there are no specific safety concerns besides an increase in temporary side effects with co-administration.
- Studies looking at simultaneous administration are currently underway.
- If possible, it is preferred to give vaccines on the same day at different injection sites compared to giving vaccines a few days apart.

For up-to-date information for COVID-19 vaccinations:
https://tools.cep.health/tool/covid-19-vaccines/
NACI Recommendations on the use of COVID-19 Vaccines click here

Tips for Managing Premarin Vaginal Cream Shortage - *"Opportunity to get a bit less messy?"*

Premarin vaginal cream has been backordered since the spring of 2021. Based on information current to September 19th, it is expected that the backorder will continue until approx. Jan 2022 but may be available periodically depending on supply.

In the meantime, consider the following alternatives for vaginal estrogen therapy(2):

Product	Dosing	ODB Coverage	Cost
Estring® Estradiol-17β ring	1 ring every 3 months (releases 7.5 mcg/day)	Yes – no LU	$123.20/ring (90d)
Vagifem 10® Estradiol-17β tablet	10 mcg tablet inserted vaginally every 3-4 days (twice weekly)	Yes – no LU	$109.40/18 tablets
Estragyn® Estrone 0.1% cream	0.5-4mg (0.5-4g of cream) once daily for used cyclically 3 weeks on, 1 week off	No	$25.99/ 20g tube $57.79/45g tube

Tips for using vaginal estrogens (3):

- use the lowest dose that is effective at controlling symptoms;
- these products appear safe to use even in patients with breast cancer history if first-line non-hormonal treatments have failed due to less systemic effect (4);
- usually women do not require concurrent progesterone therapy (though RCT data >1 yr is lacking).

Academic Detailing: A year in review

Falls Prevention and Management: Coming soon to an office near you...

- **Did you know**….85% of injury-related hospitalizations among those ≥65 years of age are caused by falls!
- Prevention can be as easy as asking these simple questions:
  1. Have you experienced a fall in the last year?
  2. Do you feel unsteady when walking, standing or climbing the stairs?
  3. Do you worry about falling?

Insulin Therapy in Type 2 Diabetes

Do you ever wonder if your patient's basal insulin dose is too high?

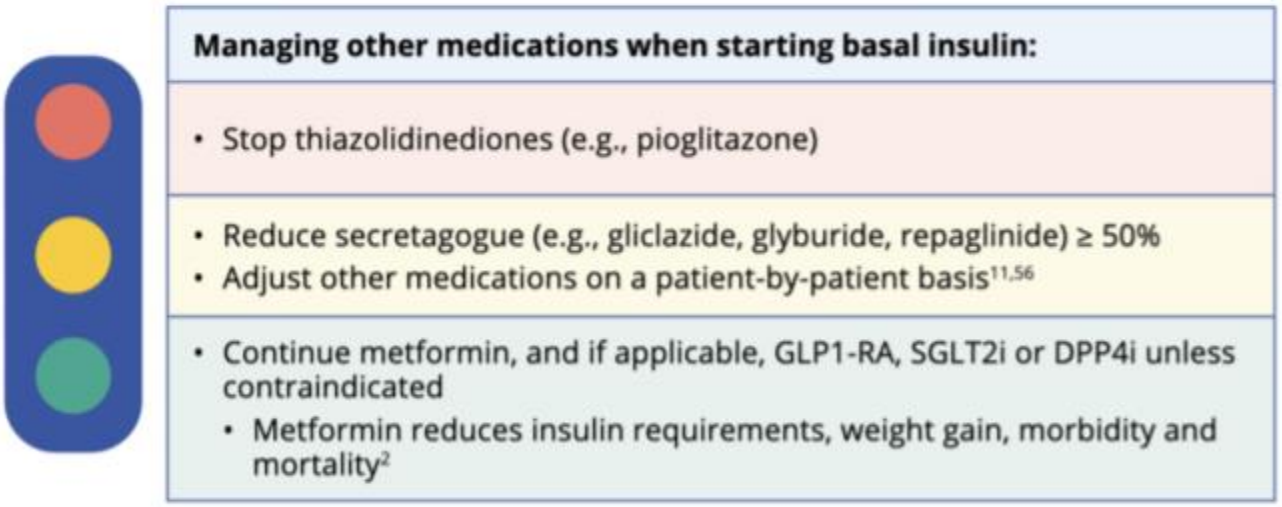
- A patient's diabetic regime should be reassessed if basal insulin dose is >0.5-1 unit/kg/day and not at target
- Your patient is having recurrent hypoglycemic events

How to determine if your patient is having nocturnal hypoglycemia:

Presentation	Management and Prevention
Nocturnal Hypoglycemia: • Occurs when blood glucose is <4 between 12-6 am • Patients are less sensitive to usual neurogenic symptoms of hypoglycemia during sleep and are most likely to experience severe hypoglycemia[22] Common Symptoms: headache, disturbed sleep, abnormal dreams, sweating (patients may notice wet sheets or pillows when they wake up)[21]	If on insulin, monitor blood glucose levels in the middle of the night 1-2 times per month.[2] If patient is experiencing nocturnal hypoglycemia, identify other reversible causes first THEN: • Consider increasing frequency of self-monitoring blood glucose during night hours or • initiate continuous or flash glucose monitors with overnight capability (DexCom® 6, FreeStyle Libre® 2 or FreeStyle Libre® with NightRider BluCon®)[21] • Consider reducing basal insulin dose by 5-10%[16,23] • Consider switching basal insulin to morning administration[23] • Consider switching to longer-acting basal insulin[23]

Provided by the Centre of Effective Practice

How should I adjust non-insulin antihyperglycemic agents when starting basal insulin?

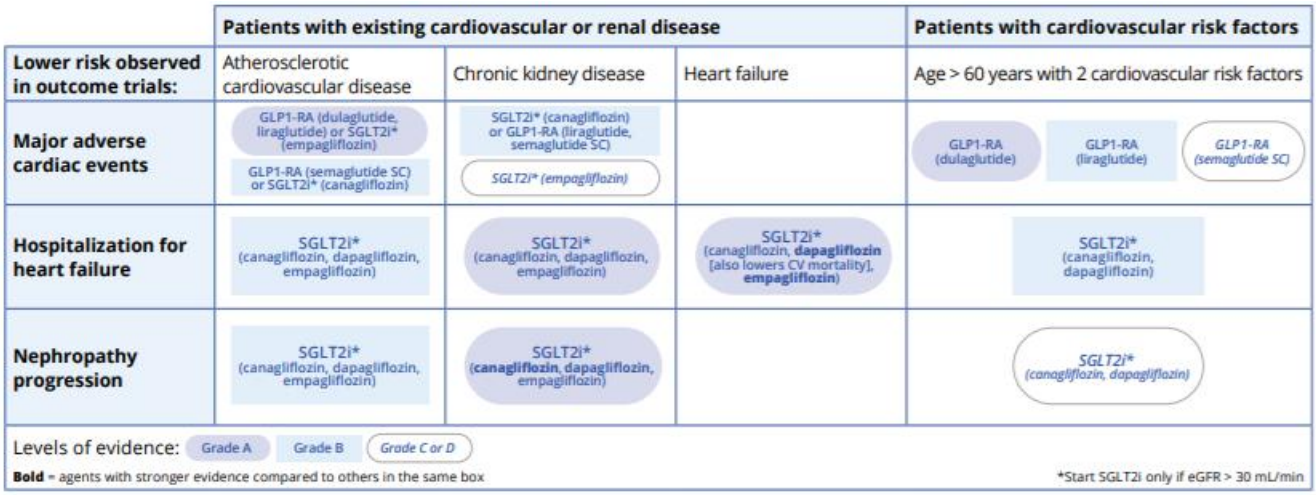


Provided by the Centre of Effective Practice

In an academic detailing visit, we could discuss antihyperglycemic dosage adjustments when initiating basal insulin, switching basal insulins and starting GLP-1s or SGLT2s.

Non-Insulin therapy for the management of Type 2 diabetes

- Do you have questions about which medications have additional benefits besides lowering blood sugar?



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- We can help review when to use each agent, the pros and cons, and help clarify your questions about the new and old agents.

For an academic detailing session please contact your clinic pharmacists. For non-FHT physicians please contact Nicole Seymour RPh (nicole.seymour@cep.health)

Pharmacist Practice Spotlight: How to improve your patient outcomes through collaboration

Opioid Rotation

77-year-old male referred to the FHT team pharmacist for a chronic pain. He was recently discharged from hospital for alcohol use disorder.

NKDA

Best Possible Medication History (Sources of information: EMR, Patient Interview, Community Pharmacy, Consult Notes)

Medication Management: Self, struggling to take medications regularly

Prescription Medications	Over-the-Counter Medications
Hydromorphone 30 mg per 24 hrs (low back &neck pain) Trazodone 100 mg PO HS (sleep and nerve pain) Atorvastatin 20 mg PO HS (secondary prevention –CABG, IHD) Ramipril 10 mg PO OD (secondary prevention – HTN) Lansoprazole 30 mg PO OD (heartburn) Zopiclone 5 mg PO HS (insomnia) Thiamine 100 mg PO OD (alcohol withdrawal) Folic acid 5 mg PO OD (alcohol withdrawal) Potassium 8 mEq PO OD (hypokalemia)	Sleep aid – diphenhydramine 50 mg PO HS PRN (~ 1 tab per week) Ibuprofen 200 mg PO PRN (~ one tab every few weeks)

Assessment & Suggestions:

Chronic Pain:

- "Mentally slow" on the phone, difficult time processing our conversation
- Stated he had a hard time focusing, as "pain blurs everything"
- Denied significant improvement with hydromorphone (pain scale baseline 7/10 reduced to 5/10 on hydromorphone)

Combination of opioid, sleep aid, and trazodone increase risk of depression, reduced mental sharpness, decreased energy, GI (nausea/vomiting), and falls/fractures/opioid harms.

Literature states when doses of opioids exceed 100 morphine equivalents (MEQ)/day, patients are at significantly higher risk of fatal overdose with no added benefit (most benefits, if any, are recognized between 30 to 50 MEQ/day)

Benefit of an opioid rotation

- may facilitate improvements in pain control with a reduction in overall opioid burden/side effects
- ~30% improvement in pain scores
- Significant improvement in physical function (16.7-point improvement on the SF-36 scale)

Pharmacist Suggestion:

When switching or rotating opioids there is only partial cross tolerance, so the equivalent new opioid dose should be reduced by 25-50% to accommodate.

Direct switch from hydromorphone to morphine (Morphine ER 70 mg PO Q 24 h) + morphine 5 mg IR PO Q 4 h breakthrough pain.

Depression:

- PHQ-9 = 13, he reacted poorly to multiple antidepressants in the past
- Patient reports that trazodone has been helpful for "nerve pain" in his right arm

Pharmacist suggestion:

- Trial increase trazodone to a therapeutic dose for depression 200-400mg qhs
- re-check PHQ-9 in 4-8 weeks to monitor for efficacy (ideally see improvements in sleep, etc)

- If there is no improvement, then reduce back his dose and trial an SNRI/SSRI (his high dose of opioids is likely also contributing to his low mood and energy).

Insomnia:

- His sleep aids, opioid, and trazodone all increase his risk of CNS adverse effects.
- Once his depression/ pain control improves (with both opioid reduction and increase in antidepressant dose) his sleep should improve.
- For every 6 older adults we treat with a sleep aid one will suffer from an increased risk of cognitive impairment, delirium, fall, fracture or MVA. Benefits of sleep aids are short lived, and generally do not extend beyond 4 weeks.

Future suggestion:

- Avoid use of diphenhydramine due to anticholinergic burden and lack of benefit for sleep
- Consider registration for CBT-I through TVFHT: Register for a Program – Thames Valley FHT
- Consider tapering of zopiclone by ~25% every 2 weeks as tolerated

Zopiclone 5 mg PO HS X 1 night, zopiclone 2.5 gm PO HS X 1 night (in conjunction with increase in trazodone dose) X 2 weeks Zopiclone 2.5 mg PO HS X 2 weeks Zopiclone 2.5 mg PO HS every other night X 2 weeks Zopiclone 2.5 mg PO HS every third night X 2 weeks discontinue

Summary of recommendations

1. Direct switch from hydromorphone to morphine (Morphine ER 70 mg PO Q 24 h) + morphine 5 mg IR PO Q 4 h breakthrough pain.
2. Trial of increasing Trazodone to 200mg qhs and reassess in 4-8 weeks to monitor improvement in mood
3. Avoid use of diphenhydramine due to anticholinergic burden and lack of benefit for sleep
4. Consider a taper of zopiclone and a referral to the Dream-ON CBTi program
5. Recommended blister packaging due to the complexity of medication and dose changes for taper

Future suggestions

1. Add ASA 81mg daily for 2nd prevention
2. Consider smoking cessation and a referral to TVFHT program Leave the Pack Behind

Follow-Up - 3 days post opioid rotation to morphine

- Patient tolerated opioid rotation well
- **Currently using morphine ER 70mg + Morphine IR 5mg daily at lunch. This equates to a change in 150 MEQ down to 75 MEQ!**
- Denied any signs or symptoms of opioid withdrawal
- Pain had improved to 3/10 on morphine ER 70mg daily compared to 5/10 on hydromorphone

The pharmacist and physician continue to monitor and support the patient together.

Helpful resource for an opioid rotation:

Opioid Manager: Switching Opioids tool

The tool can be found here and uploaded into the EMR or PDF version

Contraceptive Update:

Coverage options for patients who do not have drug plans:

Kyleena or Mirena IUS (levonorgestrel-releasing IUS) are available at a cost of $45.00 for select individuals.

To be eligible

- a patient must be prescribed an IUS per the Health Canada indication
- not have access to insurance to cover their IUS
- have a low household income.
- The program application can be accessed by Health Care Providers at https://bayer.health-loyalty.com (registration required)

Note: IUS are delivered to the patient typically within 5 days after the submission is approved and payment has been received (online via credit card or Interac online). **This program can end at any time without notification.**

Another alternative for affordable access to contraceptives is through the Southwest or Middlesex-London Public Health Unit Sexual Health Programs(1,2), which can provide the products – including oral, injectable, IUS and IUD – at lower cost than through the pharmacies for patients without coverage.

Depo Provera Shortage

Health Canada has temporarily approved the importing of Depo- Provera from the US. The US product is supplied in a glass prefilled syringe that includes a 22 gauge 1.5" syringe for administration. The product does not have DIN but has a NDC (see below)

Please note the expiry on the box and on the syringe DO NOT MATCH. According to Pfizer drug information, the expiry on the box is the expiry for Depo-Provera. The expiry listed on the syringe is for the syringe itself

Click here for additional information (https://www.pfizer.ca/sites/default/files/202106/Signed_Final_DHCPL_Depo-Provera_28June2021_EN.pdf)

A new birth control to the Canadian Market:

Nextstellis (drospirenone 3mg and estetrol 14.2mg)

Bottom line: A new monophasic CHC that has similar efficacy in preventing pregnancy to other CHCs. It has a novel estrogen that may have less effect on metabolic parameters compared to other CHCs. However, the long-term benefit and risks are not known as the longest study has been 13 cycles. The cost is twice the price of other CHC options.

The progesterone:

- Drospirenone is found in other birth controls Yaz and Yazmin. It has antimineralcorticoid activity comparable to 25mg of spironolactone.
- In theory, it could increase the risk of hyperkalemia. This was rarely seen in trials <0.1%. There could be increased risk of hyperkalemia in renal or hepatic disease or taking concomitant drugs that increase potassium levels (ACEI/ARB, spironolactone etc.)

The estrogen:

- Estetrol (E4) is a plant-based estrogen that is supposed to be more selective. It may have less effect on lipids (TG, LDL) and weight compared to ethinyl estradiol.

Dosing: Take 1 tablet once daily (**24 active pink pills and 4 white inert pills**)

Efficacy:

- Similar efficacy in preventing pregnancy ~98% (Pearl index 2.65) similar to other combined hormonal contraceptives (CHC).
- There is a decrease in efficacy with BMI >30kg/m^2 (Pearl Index of 2.94).
- It has not been evaluated in females >35kg/m^2.

Tolerability:

Side effects occurring greater than 2%: bleeding irregularities, mood disturbance, headache, breast symptoms, dysmenorrhea, acne, increased weight (~1lb), and decreased libido.

- Trial had a 50% discontinue rate over 12 months
- 7% discontinued the study due to side effects
- It has comparable unscheduled bleed events and duration of other CHCs.
  - Unscheduled spotting occurred in ~15%-20%
- Median schedule bleeding duration during the hormone free interval was 4-5 days

Unknowns:

- There is currently not enough data to conclusively evaluate the risk for VTEs. In the small trials, the risk was estimated at 3.66 per 10,000 women-years. This is similar to other CHCs. The company will be required to conduct a post marketing surveillance to define the risk.
- The long-term benefits and risks of Estetrol are not known (trial length was 13 cycles)

Cost: $18.75/ per pack plus pharmacy fee. This is approx. 2x the price of other CHCs.

Suvexx (Naproxen 500mg/sumatriptan 85mg)

Bottom line: In patients who suffer from migraines who have an inadequate response to triptan monotherapy, combination therapy of naproxen/sumatriptan could be a benefit. The combination product Sumatriptan/ naproxen would be less expensive than using the individual agents.

Indication: acute treatment of migraine
How it works: sumatriptan is an agonist of 5-HT1B/1D leading to vasoconstriction and inhibiting the release of inflammatory neuropeptides. Naproxen inhibits COX enzyme leading to an anti-inflammatory effect

Efficacy compared to placebo:
Migraine with mild pain: Pain free at 2hrs: 50% in Suma/naproxen vs 18% with placebo (NNT 3-4)
Migraine with mod-severe pain: Pain free at 2hrs: 28% Suma/naproxen vs 7.7% with placebo (NNT5-6)

Efficacy compared to sumatriptan
Pain free at 2hrs: 32% in Suma/naproxen vs 23% with sumatriptan (NNT 10)
Headache relief at 2hrs: 62% Suma/naproxen vs 52% with sumatriptan (NNT10)

Dosing: 1 tablet taken at the start of a migraine. A 2nd dose may be given after at least 2 hrs. Maximum is 2 doses in 24hrs

- Note: Triptans use should be limited to less than 10 days per month to reduce the risk of medication overuse headaches

Contraindications: Cardiovascular or cerebrovascular dx, cardiac conduction disorders, uncontrolled HTN, Peripheral vascular disease, hemiplegic or basilar migraine, IBD, active ulcer or GI bleeding,
hyperkalemic, CrCl <30ml/min pregnancy* or allergy to any component
Common ADR: dizziness, paresthesia, nausea, dyspepsia, dry mouth, abdominal pain, chest tightness/discomfort and throat tightness
Drug interactions: Avoid MAOI, Ergot containing medications, anti-platelet/coagulants, lithium, digoxin
Cost: ~$10.17 per tablet plus pharmacy fees (not currently covered by ODB) Note: Sumatriptan 50mg or 100mg $10/tablet

Did you know?

Almotriptan, naratriptan, rizatriptan and sumatriptan can be covered by ODB through the EAP program if the following criteria are met:

For the treatment of migraines with or without aura in patients who failed adequate trials of other medications for migraines (e.g. acetaminophen, NSAIDs) and where the following information is provided:

• Details of migraine prophylactic regimens (e.g. amitriptyline, beta-blockers) tried or rationale why they are inappropriate; and

• The number of attacks, duration, and severity of migraines. Headache diaries can be found here: https://migrainecanada.org/diaries/

Why is it important to screen for depression in patients with elevated blood glucose levels?

- The rates of depression are higher in patients with diabetes compared to the general public
  - 10-20% higher in patients with prediabetes
  - 2 times higher in patient with type 2 diabetes
  - 3 times higher in patients with type 1 diabetes
- On average 3 out of 10 patients with diabetes will have co-morbid depression[3]
- Patients with diabetes and depression increases the risk of micro and macro complications (including mortality), non-compliance to medical treatment and reduced self-care[3,4]

ODB formulary updates:

Actonel DR (risedronate) is now an interchangeable generic. The cost is now ~$4.75/ tablet plus pharmacy fees

Trurapi (insulin aspart) 100u/ml is available in a prefilled pen (solostar) and cartridges.

- **Biosimilar to Novorapid**. To learn more about biosimilars click here
- Trurapi and Novorapid have been shown to have similar pharmacokinetic/dynamics, effectiveness and safety.
- As with all biosimilars, it is not interchangeable. The brand name (Truapi or Novorapid) would need to be specified on a prescription.
- Trurapi is **30% less expensive** compared to Novorapid and does not require an LU code ($47 vs $67 per 5 pens)

Did you know…

Patients under 12 years old requiring a Metered Dose Inhalers (ie. Salbutamol etc.) and have ODB coverage can have a Valved holding chambers (aerochamber®, Optichamber ®) covered with a prescription.

Regulatory Update:

Controlled Drug and Substances Act (CDSA) Exemption Extended to Sept 30, 2026 This exemption allows:

- controlled drugs and substances to be prescribed verbally
- Prescriptions for controlled drugs to be transferred between pharmacies for improving patient care.
  - At this time this **does not include** an extension to the changes allowed during COVID to the provincial regulations under the Pharmacy Act, which enabled pharmacists to renew and adapt prescriptions for controlled substances for patient care including de-prescribing.

Drug recalls:

Certain lots of Glucagon (D239382A, expiry date May 10, 2022) have been recalled due to a manufacturing error. The affected lot has been shipped as a liquid instead of the usual powder that needs to be reconstituted. Glucagon lots from this recall **should not be used** as efficacy/safety is unknown. Patients should be encouraged to check their supply at home for the affected lots.

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Dopamine agonist withdrawal syndrome (DAWS)

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2. A Pilot Prospective, Multicenter Observational Study of Dopamine Agonist Withdrawal Syndrome in Parkinson's Disease. Mov Disord Clin Pract. 2015 Mar 16;2(2):170-174.

COVID- 19 vaccination recommendations

https://www.canada.ca/en/public-health/services/immunization/national-advisory-committee-on-immunization-naci/recommendations-use-covid-19-vaccines/summary-updates-september-28-2021.html

Tips for Managing Premarin Vaginal Cream Shortage

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4. ACOG: Committee Opinion No. 659: The Use of Vaginal Estrogen in Women With a History of Estrogen-Dependent Breast Cancer. Obstet Gynecol. 2016 Mar;127(3):e93-e96

ODB formulary updates

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Garg SK, et al. Efficacy and safety of insulin aspart biosimilar SAR341402 versus originator insulin aspart in people with diabetes treated for 26 weeks with multiple daily injections in combination with insulin glargine: a randomized open-label trial (GEMELLI 1) Diabetes Technol Ther. 2020;22(2):85–95.

Regulatory Update: Controlled Drug and Substances Act

https://www.canada.ca/en/health-canada/services/health-concerns/controlled-substances-precursor-chemicals/policy-regulations/policy-documents/section-56-1-class-exemption-patients-pharmacists-practitioners-controlled-substances-covid-19-pandemic.html

Drug recalls

https://healthycanadians.gc.ca/recall-alert-rappel-avis/hc-sc/2021/76507a-eng.php

Suvexx

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2. Law S, Derry S, Moore RA. Sumatriptan plus naproxen for the treatment of acute migraine attacks in adults. Cochrane Database of Systematic Reviews 2016, Issue 4. Art. No.: CD008541. DOI: 10.1002/14651858.CD008541.pub3.
3. Osman, N, Worthington, I, Lagman-Bartolome, A. Headache in Adults. In: Jovaisas, Barbara, editor. Therapeutics [Internet]. Ottawa (ON): Canadian Pharmacists Association; c2021 [updated Jul 2021; cited 2021 Sept 29]. Available from: http://www.e-therapeutics.ca. Also available in paper copy from the publisher.

Triptan coverage criteria
https://www.health.gov.on.ca/en/pro/programs/drugs/docs/frequently_requested_drugs.pdf

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