WINTER 2025

THE DOSE

Thames Valley Family Health Team's Quarterly Drug Information Newsletter

Thames Valley Family Health Team

Are you a healthcare provider outside of Thames Valley FHT? You can now sign up to receive emailed newsletters and Drug Info Blast updates here.
Have feedback or a topic suggestion? Email us at druginfo@thamesvalleyfht.ca

In this issue:

Lp(a) and ApoB: how do they affect CV outcomes?

What do Lp(a) and ApoB add to primary prevention of ASCVD?

- Traditional CV risk factors are accurate in predicting ASVCD risk, particularly when a validated risk calculator is used.
- Adding either Lp(a) or ApoB to usual risk factor screening **does not** significantly improve accuracy to predict CV risk.[1]

Lp(a) and ApoB: what are they, when to order? See page 6!

What do Lp(a) and ApoB add to secondary prevention of ASCVD?

- Established ASCVD = automatically high-risk; therefore, lipid panels (incl. Lp(a) or ApoB) for CV risk screening and rescreening are unnecessary.[1]
- ApoB is suggested as an alternative to LDL-C (see pg. 6), but there is no added benefit in monitoring either. Trials of fixed-dose, moderate-intensity statins show CV risk reduction benefits regardless of LDL-C levels achieved.[1]
- 2023 RCT in 4400 patients with CAD: treating to target LDL-C is noninferior to prescribing a high-intensity statin regardless of repeat LDL-C.[2]

Bottom line

- No evidence that treating to target Lp(a) or ApoB ↓ mortality or MACE.[1,2]
- **Primary prevention:** Adding Lp(a) or ApoB does not improve screening accuracy beyond usual CV risk factors +/- CV risk calculator.
- **Secondary prevention:** No outcomes difference between "treat to target" LDL-C or ApoB lipid levels strategy vs. fixed-dose statin approach.
- Canadian guidelines differ on whether to order Lp(a) and ApoB – **see page 6**

NACI updates HPV vaccination schedules

Unchanged: HPV vaccination is recommended for everyone 9-26 years of age.

New: NACI recommendations on what constitutes a full series of HPV vaccine[4]

Individuals 9 to 20 years of age	→ Should receive **one** dose of HPV vaccine
Individuals 21 to 26 years of age	→ Should receive two doses of HPV vaccine
Individuals ≥27 years of age	→ May receive two doses of HPV vaccine
Immunocompromised and/or living with HIV	→ Should receive three doses of HPV vaccine

Use Gardasil 9 (nonavalent 9vHPV) as it provides the most protection.

What is the evidence? In 9 to 20 year old females, data up to 11 years shows that one dose is highly effective for prevention of HPV infection.[5] WHO guidelines also recommend a 1 dose series.[6]

Ontario guidelines: Unchanged. A two-dose series continues to be funded from Grades 7 through 12. A two- to three-dose series continued to be funded for MSM ages 9-26 (high-risk population).[7,8]

Bottom line: **Single dose** of Gardasil-9 is **considered a full series** of HPV vaccinations for those aged 9-20. Ontario continues to fund a 2-dose series for school-aged individuals.

Metformin can be continued in stage 3 and 4 CKD (eGFR 15-45 mL/min/1.73m²)

Metformin is first-line in most adults with type 2 diabetes, including those with mild renal impairment (eGFR 45-60). Less is known about the role of metformin in moderate to severe CKD (eGFR 15-45) and clinicians may not feel as comfortable dose-adjusting or continuing it.

To date there are no blinded, placebo-controlled RCTs of metformin in advanced CKD.[9] Smaller trials demonstrated that **dose-reduced metformin is still safe** when CKD has progressed to stage 3 or 4.[10]

Lambourg et al. 2024[9]	
Cohort study of Scottish adults with T2DM. Compared outcomes of patients who **continued vs. stopped metformin when chronic kidney disease (CKD) progressed** (eGFR <30 mL/min/17.3m²).	
Outcomes	Primary outcome: All-cause mortality. Secondary: Major adverse cardiovascular events (MACE)
Patients	4278 adults. Mean age 77 (75% were 70+ years old), 14 years since diabetes diagnosis, mean eGFR 27 mL/min/1.72m², mean A1C 7.2%. 38% had CAD, and >80% were on an ACEI/ARB and statin.
Results	**Stopping metformin** was: ▪ Associated with significantly **increased risk of all-cause mortality** (HR 1.23; 95% CI 1.08-1.41). ▪ Not associated with increased risk of MACE. ▪ Associated with increased risk of mortality due to respiratory causes (secondary outcome).
Bottom line	Outcomes-based evidence supports the practice of **continuing metformin when eGFR <30,** which is associated with **lower all-cause mortality** compared to stopping metformin when CKD progresses to stage 3 or 4.

Why is metformin first-line?[11]

- Long-term safety data
- Effective in lowering A1C
- Reduces CV and all-cause mortality
- Low risk of weight gain
- No hypoglycemia risk
- Well-tolerated (with a slow initial dose titration)

Standard of care

To maximize CV and renal benefit of SGLT2 or GLP1-RA, ensure patients are also on:

- metformin AND
- statin AND
- ACEI or ARB

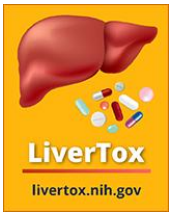
In the SGLT2 and GLP-1 CV and renal trials, most patients were on metformin, a statin, and ACEI or ARB at baseline.

Diabetes Canada renal dosing[12]

Continue metformin down to eGFR 15. Renal dosing:

- eGFR 45-60: No renal dose adjustment
- eGFR 30-45: 1000 mg/day maximum dose
- **eGFR 15-30: 500 mg/day maximum dose**

Practice tool spotlight: LiverTox



Inspired by a recent case: 65M with tinea corporis who failed topical therapy. Oral treatment is needed but the patient has cirrhosis from viral hepatitis. What oral antifungal is safest?

What is it? LiverTox is an American resource maintained by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK). It is evidence-based and regularly updated, with information on common medications and select natural health products.

What does it provide? The searchable drug database uses a 5-point "Likelihood score" from A (well-known cause) to E (unlikely cause) to categorize risk of hepatotoxicity. Includes guidance on potential outcomes, management, and less hepatotoxic therapeutic alternatives.

When is it most helpful? Assessing for medication-related causes/contributors to liver injury and comparing treatment options to determine what is safest for patients with liver dysfunction.

Bottom line: Like Briggs' Drugs in Pregnancy and Lactation, LiverTox uses categories (A through E) and evidence summaries to assess medications and natural health products for hepatotoxicity risk.

Link to LiverTox - freely available online!

Rapid fire: quick updates for busy primary care providers

Tirzepatide (Mounjaro®) prefilled pens now available

Tirzepatide (Mounjaro) is a dual glucose-dependent insulinotropic polypeptide (GIP) and GLP-1 receptor agonist indicated for type 2 diabetes, dosed once weekly.

It was previously only available in single-dose vials and patients used syringes to extract the dose.

Prefilled pens containing four doses each are available in the following strengths: 2.5 mg, 5 mg, 7.5 mg, 10 mg, 12.5 mg, and 15 mg.

Like insulin pens, the Mounjaro Kwikpen should be **primed with each use**.[13]

Cost per pen (1 month supply): $400-800. Not covered by public plans. Patients can apply to the Mounjaro patient support program for some support with copay cost.

GLP-1 RAs and risk of suicide and self-harm

Health Canada conducted a safety review of case reports of suicidal thoughts and self-harm in patients treated with glucagon-like peptide-1 receptor agonists (GLP-1 RAs).

Two observational studies examined this link and no clear association could be derived due to limitations in data quality. 15 case reports were identified with and found limited evidence for a causal link.[14]

Key messages:[15]

- Current evidence does **not** support an increased risk of suicide, self-harm, or suicidal/self-harm ideation with use of GLP-1 RAs in those with type 2 diabetes.
- In patients using GLP-1 RAs for **obesity** regardless of diabetes status, results were **inconclusive** requiring further investigation.
- No updates to product monographs were made.
- Report any suspected reactions to the Canada Vigilance Program

Provera and Depo-Provera warning: risk of meningioma

Product monograph update: warning for the risk of meningioma with long-term administration of progestins, including medroxyprogesterone acetate (MPA). Discontinue MPA if a meningioma is found. Caution is advised before use in patients with a history of meningioma.[16] Does not apply to IUS/IUD.

Highlights from the two case-control studies:[17,18]

- Associated with use of injectable MPA **beyond one year**; strong association with longer duration
- 90% of cases occurred in women ≥40 years old
- Injectable MPA was associated with 53% increased odds of cerebral meningiomas specifically, but the absolute risk remains low (0.05% in cases vs. 0.01% in controls).

CEP academic detailing updates – New topic: ADHD in adults

Adult ADHD: Learn how a six-question screener can help in diagnosing ADHD, reducing the need for psychiatry referrals, wait times, and multiple visits to your office. Discuss differences in treatment options and troubleshooting adverse effects. **Link to ADHD tool**

Did you know? 75% of patients with ADHD have comorbid conditions – anxiety, depression, and insomnia are common.

Many other topics are still available!

Pharmacotherapy for obesity: Did you know that only four medications have an indication for weight loss in Canada? Learn about the 4M framework for assessing, initiating and managing treatment.

Heart failure: Not sure if it's heart failure? NT-proBNP can help rule out heart failure with a high degree of confidence. Learn about the four standard therapies for HFrEF.

Accredited detailing visits are open to physicians and nurse practitioners. Reach out to your TVFHT pharmacist or **to CEP** if you are not at a TVFHT site.

Quick summaries: New products on the market

Ixchiq (chikungunya vaccine)[20]

The chikungunya virus is transmitted by mosquitoes. Outbreaks have occurred in countries in Africa, Asia, and the Americas.[19]

Indication: Prevent disease caused by the chikungunya virus in adults ≥18 years old.

Dose: Single IM dose of a **live attenuated vaccine**.

Contraindications and precautions: Contraindicated if immunocompromised or pregnant. Avoid pregnancy for one month following vaccination.

Lactation: Unknown if it is excreted into breast milk.

Adverse effects: Most common: tenderness, headache, fatigue, myalgia. Serious: reports of hospitalization post-vaccination are under investigation.[21]

Efficacy: 98.9% seroresponse rate at 28 days and 96% after 6 months in Phase III trial.

Place in therapy: Canadian recommendations are in development. Mosquito bite prevention is key.[21]

Cost: ~225 per dose

Veozah® (fezolinetant, 45 mg tablets)[22]

First-in-class NK3 receptor antagonist that targets the hypothalamic thermoregulatory centre.

Indication: **Non-hormonal** treatment of moderate to severe menopausal vasomotor symptoms (VMS).

Dose: 45 mg once daily. **Monitor ALT, AST, ALP, and bilirubin** at baseline and at 1, 2, 3, 6, and 9 months after starting. No hepatic or renal dosing.

Contraindications: Child-Pugh Class B or C, eGFR <30, with concomitant moderate or strong CYP1A2 inhibitors, and pregnancy.

Smoking: ↓ fezolinetant AUC by 50% but no clinical difference and no dose adjustment.

Adverse effects: Headache, abdominal pain, diarrhea, nausea, ↑ LFTs, insomnia, and hot flushes occurred more than placebo. **FDA warning: rare but serious liver injury**.[23] **Endometrial cancer**: one case of this adverse effect.[24]

Efficacy: 2 fewer hot flashes per day at 4 and 12 weeks vs. placebo. Slight ↓ in severity of hot flashes but unclear if clinically significant.

Place in therapy: Expensive option with frequent monitoring due to risk of liver injury and no comparison to standard of care.

Cost: >$200 per month

Winlevi® (clacoterone, 1% cream)[25]

First-in-class androgen receptor inhibitor that decreases sebum production and inflammation.

Indication: Treatment of acne vulgaris in patients >12 years old.

Dose: A thin layer twice daily on the area prone to acne (do not spot treat). Max 1 gram per application.

Contraindications: Hypersensitivity

Special populations: No data in pregnant or lactating people or in patients ≥65 years old.

Adverse effects: Most common: erythema and scaling/dryness, similar rate as vehicle-only group. Reversible hypothalamic-pituitary-adrenal **(HPA) axis suppression**. **Hyperkalemia** in 3.6% of patients (similar rate in vehicle-only group).

Efficacy: Trials included mostly **female Caucasian patients with moderate acne** (only 16% with severe acne). ↓ in acne severity scores and 4-7 fewer lesions at 12 weeks but unclear if clinically significant.[26] There was a trend of less benefit in racialized subgroups after stratifying by Fitzpatrick skin type, ethnicity, and race.

Place in therapy: Expensive option with no evidence comparing to gold standard treatment.[27] **Possibly less benefits in skin of colour**.

Cost: $250 per 30 gram tube

Reminder: Pharmacotherapy for VMS (menopausal vasomotor symptoms)[28]

- **First line**: Hormone therapy is the most effective option for moderate to severe VMS
- **Second line**: Non-hormonal therapy (antidepressants, gabapentinoids, clonidine, and oxybutynin) are options when hormonal therapy is contraindicated or declined.
- The SOCG has not released any statements on fezolinetant.
- **MenopauseandU.ca**, created by the SOGC, contains many patient-focused resources

Case: optimizing meds post NSTEMI

This bread-and-butter case shows the value of post-discharge medication reviews and collaboration between primary care and specialists.

74M recently discharged from hospital. Medication reconciliation and review were initiated by the pharmacist.

Medical history: NSTEMI two weeks ago with PCI x 2 to LAD and diagonal, hypertension, dyslipidemia, history of duodenal ulcer with bleed, GERD, osteoarthritis, ankylosing spondylitis, generalized anxiety disorder

Allergies: tetracycline – SOB, chest pain; **perindopril – angioedema**

Social history: ex-smoker, rare EtOH. Sees naturopath

Relevant vitals/labs: BP 180/71 mmHg, HR 43 bpm (in office one month before NSTEMI), eGFR 66 mL/min/1.73m^2, calculated CrCL (using ideal body weight) 55 mL/min, A1C 5.9%

Discrepancies found during med reconciliation:

1. Ticagrelor: Patient reduced dose to 90 mg once daily due to GI upset
2. Perindopril: Stopped during ER visit one week ago due to suspected angioedema
3. Atenolol: Stopped in hospital due to bradycardia

Medication list:

1. ASA 81 mg PO daily (NEW)
2. Ticagrelor 90 mg PO BID x one year (NEW)
3. Indapamide 1.25 mg PO daily (NEW)
4. Perindopril 8 mg PO daily (NEW, STOPPED)
5. Atenolol 50 mg PO daily (STOPPED)
6. Amlodipine/atorvastatin 10 mg/80 mg PO daily (NEW)
7. Nitroglycerin 0.4 mg SL spray PRN q5min chest pain (NEW)
8. Omeprazole 20 mg PO daily
9. Lactulose 15 mL PO daily for constipation since starting ticagrelor

Actions taken by the care team:

- The family physician was advised of the above discrepancies and booked a follow up appointment with the patient to discuss medication adherence and side effects.
- The pharmacist sent a letter to the cardiologist to advise of meds that were stopped or changed and provided recommendations:
  - Restart ticagrelor 90 mg BID, or if not tolerated switch to clopidogrel 75 mg daily
  - Start candesartan – as per chart patient had tolerated this in past
  - Consider a low dose beta blocker (i.e. metoprolol 12.5 mg BID) with close monitoring
- The cardiologist also discussed adherence with the patient and started clopidogrel and candesartan. The patient had also stopped his statin and an alternate statin was started.

Question: My patient had angioedema with an ACEI, what should be prescribed instead?

Answer: Patients who have had ACEI angioedema can safely be prescribed ARBs as the risk of cross reactivity is low.

- Risk of angioedema with ACEi is estimated at 0.2-2.5%.[29] While rare, this reaction can be fatal.
- Multiple studies found that ARBs have half the risk of angioedema (0.1%) as ACEIs and the incidence of cross reactivity is <10%.[29]
- In adults with a history of ACEi angioedema, there is no increased risk of angioedema associated with switching to an ARB.[30]

Question: Why is it important that patients are on full dual antiplatelet therapy (DAPT) after PCI?

Answer: DAPT post-PCI prevents early complications, readmission and improves long-term outcomes including mortality.

- Benefit of DAPT is front-loaded: 50% of recurrent cardiovascular events happen within 90 days of the initial acute event.[31]
- Patients with early recurrent MI have worse prognosis: one study found 50% of these patients die within 5 years.[32]
- The optimal duration of DAPT is not known.[33] This is an individualized decision balancing risks of thrombosis vs. risks of bleeding.

PCI = percutaneous coronary intervention; ACEI = angiotensin-converting enzyme inhibitors; ARB = angiotensin II receptor blocker

Lp(a) and ApoB continued: what are they and when to order?

What are Lp(a) and ApoB?

Test	Explanation[3]	Clinical relevance[3]
Lipoprotein a Lp(a)	An LDL-like particle. Up to 90% of Lp(a) concentration is influenced by genetics.	ASCVD risk increases with increasing Lp(a) levels. Statins do not decrease Lp(a).
Apoprotein B ApoB	A more accurate measure than LDL-C of the total concentration of atherogenic particles, especially when triglycerides (TG) >1.5 mmol/L.	In patients with TG >1.5 mmol/L, non-HDL-C or ApoB are alternative markers to LDL-C for predicting CV risk. In Ontario, non-HDL-C is routinely reported but ApoB is not covered.

Question: Do I HAVE to order Lp(a) and ApoB?

Answer: No. The PEER 2023 Simplified Lipid guideline recommends **against** ordering Lp(a) or ApoB.[1]

Two Canadian guidelines differ in approach to Lp(a) and ApoB

See The Dose Winter 2024 for a full lipid guideline comparison

1. PEER Simplified Lipid Guideline 2023
   - no industry conflicts of interest
   - aim to make practical recommendations for primary care based on best evidence
2. Canadian Cardiovascular Society (CCS) Dyslipidemia Guideline 2021

		PEER 2023[1]	CCS 2021[3]
Initial screening	WHO to screen	Only patients without known ASCVD. Men ≥40 years, women ≥50 years. Can screen earlier if risk factors present.	All patients ≥40 years old AND patients of any age with ≥1 CV risk factor
	WHAT to screen	History (validated risk calculator) Non-fasting lipid profile: TC, LDL-C, HDL-C, non-HDL-C, TG	History (validated risk calculator) Lipid profile: TC, LDL-C, HDL-C, non-HDL-C, TG
	Lipoprotein A	Do not check	Check **once,** only during initial screen
	Apoprotein B	Do not check	Optional, alternative to LDL-C
Rescreening	WHO to rescreen	Low-risk patients not on statin Do not repeat any lipid testing for any patient after starting statin	Low-risk patients not on statin Primary prevention patients on statin Secondary prevention patients on statin
	WHEN to rescreen	Earliest every 5 years, preferably every 10 years. Sooner if risk factors change.	Every 5 years. Sooner if risk factors change.
	WHAT to rescreen	History (validated risk calculator) Non-fasting lipid profile as above Do not check Lp(a) or ApoB	History (validated risk calculator) Lipid profile as above Use non-HDL-C or ApoB as preferred alternatives for LDL-C to titrate statin, particularly if TG >1.5 mmol/L,

Lp(a) = lipoprotein a; ApoB = Apoprotein B; TC = total cholesterol; TG = triglycerides

References

1. Kolber MR, Klarenbach S, Cauchon M, et al. PEER simplified lipid guideline 2023 update: Prevention and management of cardiovascular disease in primary care. *Can Fam Physician*. 2023;69(10):675-686. doi:10.46747/cfp.6910675
2. Hong SJ, Lee YJ, Lee SJ, et al. Treat-to-Target or High-Intensity Statin in Patients With Coronary Artery Disease: A Randomized Clinical Trial. *JAMA*. 2023;329(13):1078-1087. doi:10.1001/jama.2023.2487
3. Pearson GJ, Thanassoulis G, Anderson TJ, et al. 2021 Canadian Cardiovascular Society Guidelines for the Management of Dyslipidemia for the Prevention of Cardiovascular Disease in Adults. *Can J Cardiol*. 2021;37(8):1129-1150. doi:10.1016/j.cjca.2021.03.016
4. NACI. Updated recommendations on human papillomavirus vaccines. Published Jul 2024. Accessed Apr 9, 2025. https://www.canada.ca/en/public-health/services/publications/vaccines-immunization/national-advisory-committee-immunization-updated-recommendations-hpv-vaccines.html#table3
5. Forbes N, Montroy J, Salvadori MI, Dubey V. Summary of the National Advisory Committee on Immunization (NACI) Statement: Updated guidance on human papillomavirus (HPV) vaccines. *Can Commun Dis Rep*. 2024;50(12):419-425. Published 2024 Dec 5. doi:10.14745/ccdr.v50i12da01
6. World Health Organization. WHO updates recommendations on HPV vaccination schedule. Published Dec 2022. Accessed Apr 9, 2025. https://www.who.int/news/item/20-12-2022-WHO-updates-recommendations-on-HPV-vaccination-schedule
7. Getting the HPV vaccine. Ontario Ministry of Health. Updated Apr 2024. Accessed Apr 9, 2025. https://www.ontario.ca/page/getting-hpv-vaccine#section-4
8. Publicly funded immunization schedules for Ontario. Ontario Ministry of Health. Published Jun 2022. Accessed Apr 9, 2025. https://www.ontario.ca/files/2024-01/moh-publicly-funded-immunization-schedule-en-2024-01-23.pdf
9. Lambourg EJ, Fu EL, McGurnaghan S, et al. Stopping Versus Continuing Metformin in Patients With Advanced CKD: A Nationwide Scottish Target Trial Emulation Study. *Am J Kidney Dis*. 2025;85(2):196-204.e1. doi:10.1053/j.ajkd.2024.08.012
10. Lalau JD, Kajbaf F, Bennis Y, Hurtel-Lemaire AS, Belpaire F, De Broe ME. Metformin Treatment in Patients With Type 2 Diabetes and Chronic Kidney Disease Stages 3A, 3B, or 4. *Diabetes Care*. 2018;41(3):547-553. doi:10.2337/dc17-2231
11. Diabetes Canada Clinical Practice Guidelines Expert Working Group, Shah BR, Bajaj HS, et al. Pharmacologic Glycemic Management of Type 2 Diabetes in Adults---2024 Update. *Can J Diabetes*. 2024;48(7):415-424. doi:10.1016/j.jcjd.2024.08.002
12. Renal dosing chart. Diabetes Canada. Accessed Apr 9, 2025. https://guidelines.diabetes.ca/reduce-complications/renal-dosing-chart
13. Mounjaro® monograph. Eli Lilly. Updated Sept 2024. Accessed Apr 9, 2025. https://pdf.hres.ca/dpd_pm/00077180.PDF
14. Suissa S et al. Exploration of the risk of suicidality and self-harm with glucagon-like peptide-1 receptor agonists. Published May 2024. Accessed Apr 9, 2025. https://www.cda-amc.ca/exploration-risk-suicidality-and-self-harm-glucagon-peptide-1-receptor-agonists
15. Health Product InfoWatch: December 2024. Health Canada. Updated Dec 2024. Accessed Apr 9, 2025. https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/health-product-infowatch/december-2024.html#a2.1.1
16. Health Product InfoWatch: October 2024. Health Canada. Updated Oct 2024. Accessed Apr 9, 2025. https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/health-product-infowatch/october-2024.html#a13
17. Roland N, Neumann A, Hoisnard L, et al. Use of progestogens and the risk of intracranial meningioma: national case-control study [published correction appears in BMJ. 2024 Mar 28;384:q776. doi: 10.1136/bmj.q776.]. *BMJ*. 2024;384:e078078. Published 2024 Mar 27. doi:10.1136/bmj-2023-078078
18. Griffin RL. The Association between Medroxyprogesterone Acetate Exposure and Meningioma. *Cancers (Basel)*. 2024;16(19):3362. Published 2024 Sep 30. doi:10.3390/cancers16193362
19. Chikungunya. World Health Organization. Updated Dec 2022. Accessed Apr 9, 2025. https://www.who.int/news-room/fact-sheets/detail/chikungunya
20. Valneva Austria GmbH. Ixchiq monograph. Published Jun 2024. Accessed Apr 9, 2025. https://pdf.hres.ca/dpd_pm/00076049.PDF
21. For health professionals: Chikungunya. Health Canada. Updated Mar 10, 2025. Accessed Apr 9, 2025. https://www.canada.ca/en/public-health/services/diseases/chikungunya/health-professionals-chikungunya.html
22. Astellas Pharma Canada. Veozah® monograph. Published Dec 2024. Accessed Apr 9, 2025. https://pdf.hres.ca/dpd_pm/00077931.PDF
23. FDA adds warning about rare occurrence of serious liver injury with use of Veozah (fezolinetant) for hot flashes due to menopause. Federal Drug Association. Updated Dec 2024. Accessed Apr 9, 2025. https://www.fda.gov/drugs/drug-safety-and-availability/fda-adds-warning-about-rare-occurrence-serious-liver-injury-use-veozah-fezolinetant-hot-flashes-due
24. Neal-Perry G, Cano A, Lederman S, et al. Safety of Fezolinetant for Vasomotor Symptoms Associated With Menopause: A Randomized Controlled Trial. *Obstet Gynecol*. 2023;141(4):737-747. doi:10.1097/AOG.0000000000005114. Appendix 1.
25. Sun Pharma Canada. Winlevi® monograph. Updated Jun 2023. Accessed Apr 9, 2025. https://pdf.hres.ca/dpd_pm/00071308.PDF
26. Clinical Review Report: Dupilumab (Dupixent): (Sanofi-Aventis Canada Inc.): Indication: Moderate-to-severe atopic dermatitis (AD). Ottawa (ON): Canadian Agency for Drugs and Technologies in Health; 2018 Jul. Appendix 5, Validity of Outcomes Measures. Available from: https://www.ncbi.nlm.nih.gov/books/NBK539234/
27. CADTH reimbursement recommendation. Clascoterone (Winlevi). Canada's Drug and Health Technology Agency. Published Oct 2024. Accessed Apr 9, 2025. https://www.cda-amc.ca/sites/default/files/DRP/2024/SR0863_Draft_Recommendation.pdf
28. Yuksel N, Evaniuk D, Huang L, et al. Guideline No. 422a: Menopause: Vasomotor Symptoms, Prescription Therapeutic Agents, Complementary and Alternative Medicine, Nutrition, and Lifestyle [published correction appears in J Obstet Gynaecol Can. 2022 Feb;44(2):227. doi: 10.1016/j.jogc.2021.12.005.]. J Obstet Gynaecol Can. 2021;43(10):1188-1204.e1. doi:10.1016/j.jogc.2021.08.003
29. Brown T, Gonzalez J, Monteleone C. Angiotensin-converting enzyme inhibitor-induced angioedema: A review of the literature. *J Clin Hypertens (Greenwich)*. 2017;19(12):1377-1382. doi:10.1111/jch.13097
30. Rasmussen ER, Pottegård A, Bygum A, von Buchwald C, Homøe P, Hallas J. Angiotensin II receptor blockers are safe in patients with prior angioedema related to angiotensin-converting enzyme inhibitors - a nationwide registry-based cohort study. *J Intern Med*. 2019;285(5):553-561. doi:10.1111/joim.12867
31. Nedkoff L, Briffa T, Murray K, et al. Risk of early recurrence and mortality in high-risk myocardial infarction patients: A population-based linked data study. *Int J Cardiol Cardiovasc Risk Prev*. 2023;17:200185. Published 2023 Apr 6. doi:10.1016/j.ijcrp.2023.200185
32. Nair R, Johnson M, Kravitz K, et al. Characteristics and Outcomes of Early Recurrent Myocardial Infarction After Acute Myocardial Infarction. *J Am Heart Assoc*. 2021;10(16):e019270. doi:10.1161/JAHA.120.019270
33. Mourikis P, Polzin A. Dual-Antiplatelet Therapy After Percutaneous Coronary Intervention: How Short Is Too Short?. *J Am Heart Assoc*. 2023;12(2):e028775. doi:10.1161/JAHA.122.028775