The Medical Letter®

on Drugs and Therapeutics

Adapted for Canada

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Suzetrigine *(Journavx)* — A Sodium Channel Blocker for Acute Pain

The FDA has approved suzetrigine (*Journavx* – Vertex; not approved in Canada), a selective sodium channel blocker, for oral treatment of moderate to severe acute pain in adults. Suzetrigine is the first sodium channel blocker to be approved in the US for this indication (in Canada, there are other sodium channel blockers approved for this indication) and the first oral nonopioid drug to be approved for treatment of pain in over 25 years.

Pronunciation Key
Suzetrigine: soo ze' tri jeen *Journavx*: jer' na vix

STANDARD TREATMENT — Nonopioid drugs are preferred for treatment of pain. In patients with moderate to severe acute pain, use of an NSAID plus acetaminophen may be at least as effective as an oral opioid combined with acetaminophen or even an injected opioid. NSAIDs can increase the risk of bleeding and can cause cardiovascular, gastrointestinal, and renal adverse effects.

As-needed use of a short-acting full opioid agonist may be required for severe acute pain. Opioids should be given in the lowest dosage and for the shortest duration possible; higher doses are associated with increased risks of motor vehicle injury, overdose, and opioid use disorder.[1,2]

PHARMACOLOGY — Suzetrigine is a selective blocker of the voltage-gated sodium channel $Na_V1.8$, which is expressed in peripheral sensory neurons such as dorsal root ganglion neurons. By stabilizing the closed state of the channel, suzetrigine inhibits the generation of action potentials that act as pain signals in the central nervous system. The drug has not been shown to cause addiction or dependence in human or animal studies.[3]

Table 1. Pharmacology

Class	Sodium channel blocker
Formulation	50 mg tablets
Route	Oral
Tmax	Suzetrigine: 3 hours (fasted); 5 hours (fed) M6-SUZ[1]: 10 hours (fasted); 24 hours (fed)
Metabolism	Hepatic by CYP3A
Elimination	Feces (49.9%; 9.1% as parent drug); urine (44.0%, primarily as metabolites)
Half-life	Suzetrigine: 23.6 hours M6-SUZ[1]: 33.0 hours

1. The major active metabolite of suzetrigine. M6-SUZ is about 3.7-fold less potent than the parent drug.

CLINICAL STUDIES — FDA approval of suzetrigine was based on the results of two double-blind trials (available only as an abstract) in a total of 2191 adults with moderate to severe pain (mean score ~7 on a 0-10 scale) following full abdominoplasty (Trial 1) or bunionectomy (Trial 2). Patients were randomized to receive 48 hours of treatment with suzetrigine (100 mg initially, then 50 mg every 12 hours), hydrocodone/acetaminophen (5/325 mg every 6 hours), or placebo. Rescue treatment with ibuprofen (400 mg every 6 hours) was permitted.

The least-squares mean time-weighted sum of pain intensity differences from baseline over the first 48 hours of treatment ($SPID_{48}$), the primary endpoint, was significantly greater with suzetrigine than with placebo in both Trial 1 (118.4 vs 70.1) and Trial 2 (99.9 vs 70.6). Compared to hydrocodone/acetaminophen, the mean $SPID_{48}$ value with suzetrigine was similar in Trial 1 (118.4 vs 111.8) but significantly smaller in

Trial 2 (99.9 vs 120.1). The median time to the onset of perceptible pain relief with suzetrigine was 30 minutes in Trial 1 and 60 minutes in Trial 2.[4]

ADVERSE EFFECTS — The most common adverse effect of suzetrigine in the two 48-hour trials (occurring more often than with placebo) was pruritus (2%). Muscle spasms, rash, increased creatine phosphokinase levels, and decreased estimated glomerular filtration rate also occurred. Similar adverse effects were observed in an unpublished open-label trial in which 256 adults took suzetrigine for up to 14 days.

PREGNANCY AND LACTATION — No data are available on the use of suzetrigine in pregnant or lactating women. In pregnant rats, exposure to suzetrigine levels 2.2 times those achieved with the maximum recommended human dose (MRHD) during organogenesis was associated with post-implantation loss and a reduced number of live fetuses, and exposure to levels 1.6 times those achieved with the MRHD during gestation and lactation was associated with increased post-natal pup mortality. Suzetrigine is secreted into animal milk.

Fertility – In a female fertility study in rats, exposure to suzetrigine levels ≥2.2 times those achieved with the MRHD was associated with a reversible increased risk of pre-implantation loss. Whether suzetrigine can reversibly affect fertility in women remains to be determined.

DRUG INTERACTIONS — Suzetrigine and its major active metabolite are CYP3A4 substrates. Concurrent use of suzetrigine and a strong CYP3A4 inhibitor, such as ketoconazole, is contraindicated. If a moderate CYP3A4 inhibitor is coadministered, the dosage of suzetrigine should be adjusted. Products containing grapefruit can inhibit CYP3A4 and should be avoided during treatment with suzetrigine.[5]

Suzetrigine is also a CYP3A4 inducer; it can decrease serum concentrations and the efficacy of sensitive CYP3A4 substrates, such as midazolam. Suzetrigine did not significantly affect the pharmacokinetics of ethinyl estradiol or levonorgestrel; patients using other contraceptive hormones should use a backup method while taking suzetrigine and for 28 days after it is discontinued. Whether suzetrigine can significantly affect exposure to buprenorphine or methadone, two CYP3A4 substrates used for treatment of opioid use disorder, remains to be determined.

Key Points: Suzetrigine (*Journavx*)

- **Description:** An oral sodium channel blocker. Not approved in Canada.
- **Indication:** Treatment of moderate to severe acute pain in adults.
- **Efficacy:** In two 48-hour double-blind trials in adults with moderate to severe acute postoperative pain, suzetrigine was more effective than placebo. Suzetrigine was not superior to hydrocodone/acetaminophen in either trial.
- **Adverse Effects:** Pruritus was most common (2%).
- **Drug Interactions:** Suzetrigine is a CYP3A4 substrate and inducer; use with strong CYP3A4 inhibitors is contraindicated.
- **Dosage:** 100 mg PO x 1 dose, then 50 mg q12 hours; dosage adjustments are required for moderate hepatic impairment and when used concurrently with a moderate CYP3A4 inhibitor.
- **Cost:** A 7-day supply costs $232.50.
- **Conclusion:** Suzetrigine may be an option for treatment of moderate to severe acute pain when an NSAID or an opioid is ineffective or undesirable.

DOSAGE AND ADMINISTRATION — The usual recommended dosage of suzetrigine is 100 mg once, followed by 50 mg every 12 hours thereafter for the shortest-possible duration. Taking the initial dose at least 1 hour before or 2 hours after food can accelerate the onset of analgesia; subsequent doses can be taken with or without food.

The recommended dosage of suzetrigine in patients with moderate hepatic impairment (Child-Pugh B) and in those taking a moderate CYP3A4 inhibitor concurrently is 100 mg initially, followed by 50 mg at 12, 24, and 36 hours and every 24 hours thereafter. Suzetrigine should not be used in patients with severe hepatic impairment (Child-Pugh C).

If a dose is missed, it should be taken as soon as possible and the next scheduled dose should generally be taken at the recommended time. Patients with moderate hepatic impairment and those taking a moderate CYP3A4 inhibitor concurrently should skip the next dose if it is scheduled to be taken within 6 hours.

COST — The wholesale acquisition cost (WAC) for a 7-day supply of suzetrigine at the usual recommended dosage is $232.50.[6] One pharmacoeconomic analysis has suggested that suzetrigine would be cost-saving relative to an opioid at this price because of a decreased risk of adverse effects such as opioid use disorder.[7]

CONCLUSION — In two 48-hour double-blind trials in adults with moderate to severe acute post-operative pain, the oral selective sodium channel blocker suzetrigine (*Journavx*; not approved in Canada) was more efficacious than placebo, but not hydrocodone/

acetaminophen. Suzetrigine appears to be well tolerated and to not cause addiction or dependence, but it is expensive. For most patients with moderate to severe acute pain, an NSAID should be tried first. Suzetrigine could be a reasonable alternative when NSAIDs or opioids are ineffective or the risk of adverse effects with their use is unacceptable. The efficacy and safety of suzetrigine for treatment of subacute or chronic pain is unknown. ■

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5. Inhibitors and inducers of CYP enzymes, P-glycoprotein, and other transporters. Med Lett Drugs Ther 2023 January 25 (epub). Available at: www.medicalletter.org/downloads/CYP_PGP_Tables.pdf.
6. Approximate WAC. WAC = wholesaler acquisition cost or manufacturer's published price to wholesalers; WAC represents a published catalogue or list price and may not represent an actual transactional price. Source: AnalySource® Monthly. February 5, 2025. Reprinted with permission by First Databank, Inc. All rights reserved. ©2025. www.fdbhealth.com/policies/drug-pricing-policy.
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Drugs for Dry Eye Disease

Disruption of tear-film homeostasis (altered composition, reduced production, rapid evaporation) and resulting ocular surface inflammation cause the discomfort and blurred vision of dry eye disease. Many cases are caused by tear evaporation due to meibomian gland dysfunction. Other precipitating factors can include lacrimal gland dysfunction, poor eyelid function, environmental factors, extended screen time, inflammatory conditions such as Sjögren's syndrome, and use of some ocular or systemic drugs such as antihistamines, retinoids, or selective serotonin reuptake inhibitors (SSRIs). Benzalkonium chloride, a preservative used in some eye drops, can cause eye irritation and exacerbate symptoms of dry eye disease; use of preservative-free ophthalmic preparations is preferred. Dry eye disease is most prevalent in females and older adults, but its incidence in young people is increasing, possibly because of increased screen time.[1]

Key Points: Drugs for Dry Eye Disease

- Artificial tears are the most cost-effective option for initial treatment of dry eye disease.
- Ophthalmic corticosteroids can be used for short-term treatment of dry eye disease. Long-term use of ophthalmic corticosteroids can cause cataract formation and glaucoma.
- Topical cyclosporine formulations *(Restasis, Cequa, Vevye; Vevye* not approved in Canada) appear to be safe and effective, but they may take up to 3 months to achieve their full effect.
- Lifitegrast ophthalmic solution *(Xiidra)* appears to be safe and modestly effective, but how it compares to other products remains to be determined.
- Perfluorohexyloctane ophthalmic solution *(Miebo)* targets tear evaporation caused by meibomian gland dysfunction; it reduces the symptoms of dry eye disease and can increase tear film and lipid layer thickness. Blurred vision and conjunctival erythema can occur.
- The nasal spray formulation of the cholinergic agonist varenicline (*Tyrvaya*; not approved in Canada) increases basal tear film production, but it can cause throat irritation and instillation-site irritation.

ARTIFICIAL TEARS — Artificial tears are generally tried first for treatment of dry eye disease. They are available over the counter and are relatively inexpensive. Artificial tears are usually administered every 4-6 hours, but can be used as often as hourly, depending on symptoms. They usually contain some form of cellulose to lubricate the eye, may contain polyethylene glycol or polyvinyl alcohol to prevent evaporation, and include a preservative if packaged in multi-use containers. Symptoms often improve within a few days of starting treatment, but it may take up to 3-4 weeks for significant improvement to occur. Ophthalmic ointment and gel formulations are generally used at night but can be used during the day in severe cases.

LOTEPREDNOL — The corticosteroid loteprednol etabonate (*Eysuvis*; not approved in Canada), an analog of prednisolone, has been approved by the FDA as a 0.25% ophthalmic suspension for short-term treatment (≤2 weeks) of dry eye disease.[2] Low-dose ophthalmic corticosteroids can reduce inflammation and relieve symptoms of dry eye disease. Their use should be limited to a few weeks.[3]

Adverse Effects – The most common adverse effects of loteprednol etabonate ophthalmic suspension in clinical trials were instillation-site discomfort and increased intraocular pressure. Long-term use of corticosteroids can cause cataract formation and glaucoma. Loteprednol etabonate ophthalmic suspension contains the preservative benzalkonium chloride.

Table 1. Some Prescription Products for Dry Eye Disease

Drug	Formulation	Usual Adult Dosage	US Cost[1]	CAN Cost[7]
Ophthalmic				
Loteprednol suspension – *Eysuvis* (Alcon)	0.25% multi-dose bottles*	1-2 drops in each eye qid for up to 2 wks[2,3]	$508.00	N.A.C.
Cyclosporine emulsion – *Restasis* (Abbvie)	0.05% single-use vials, multi-dose bottles	1 drop in each eye q12h[2-4]	645.60	$231.20
generic	0.05% single-use vials		N.A.	100.00
solution – *Cequa* (Sun)	0.09% single-use vials	1 drop in each eye q12h[3]	586.90	234.20
Vevye (Harrow)	0.1% multi-dose bottles	1 drop in each eye q12h[3]	770.00	N.A.C.
Lifitegrast solution – *Xiidra* (Novartis)	5% single-use containers	1 drop in each eye q12h[3]	701.60	263.30
Perfluorohexyloctane solution – *Miebo* (Bausch + Lomb)	100% multi-dose bottles	1 drop in each eye qid[3]	771.00	N.Y.A.
Intranasal				
Varenicline solution – *Tyrvaya* (Viatris)	0.03 mg/spray (4.2 mL bottles)	1 spray bid[5,6]	665.40	N.A.C.

*Contains the preservative benzalkonium chloride; N.A.C. = not available in Canada; N.A. = not available in the US; N.Y.A. = not yet available
1. Approximate WAC for 30 days' treatment. WAC = wholesaler acquisition cost or manufacturer's published price to wholesalers; WAC represents a published catalogue or list price and may not represent an actual transactional price. Source: AnalySource® Monthly. February 5, 2025. printed with permission by First Databank, Inc. All rights reserved. ©2025. www.fdbhealth.com/policies/drug-pricing-policy.
2. The bottle should be shaken for 2-3 seconds.
3. Contact lenses should be removed before instillation, but may be reinserted 15 minutes after administration (after 30 minutes for *Miebo*).
4. Before use, the single-use vial should be inverted repeatedly until a uniform, white, opaque emulsion forms.
5. Each actuation delivers 0.03 mg of varenicline.
6. Before use, the bottle should be primed by releasing 7 sprays; if it is not used for more than 5 days, it should be reprimed by releasing 1 spray.
7. Approximate WAC for 30 days' treatment, based on prices in Canadian dollars from a national wholesaler (prices in Ontario, February 2025).

TOPICAL CYCLOSPORINE — Ophthalmic cyclosporine reduces inflammation and increases tear production in dry eye disease. It may take up to 3 months to achieve its full effect. Three topical cyclosporine products have been approved for treatment of dry eye disease: a 0.05% emulsion *(Restasis)*, a 0.09% solution *(Cequa)*, and a 0.1% solution (*Vevye*; not approved in Canada).[4,5] Direct comparisons of their efficacy and safety are lacking.

Adverse Effects – Serum concentrations of cyclosporine following topical administration have been undetectable or negligible, and systemic or topical toxicity has not been reported. Transient burning and stinging can occur; addition of a topical corticosteroid in the first month may be helpful.

TOPICAL LIFITEGRAST — A 5% ophthalmic solution of lifitegrast *(Xiidra)*, a lymphocyte function-associated antigen-1 (LFA-1) antagonist, is Health Canada- and FDA-approved for treatment of dry eye disease. Lifitegrast is thought to reduce ocular surface inflammation. It appears to be at least modestly effective, but how it compares to other products remains to be determined.[6]

Adverse Effects – The most common adverse effects of lifitegrast in clinical trials were eye irritation, dysgeusia, and reduced visual acuity.

TOPICAL PERFLUOROHEXYLOCTANE — Perfluorohexyloctane ophthalmic solution *(Miebo)* is Health Canada- and FDA-approved for treatment of dry eye disease. Perfluorohexyloctane is a semifluorinated alkane with hydrophobic and hydrophilic properties; it forms a nonaqueous layer on the tear film surface, reducing tear evaporation.[7] Patients with meibomian gland dysfunction produce less meibum, a lipid-rich secretion that forms the outer layer of tears. In clinical trials in patients with meibomian gland dysfunction, *Miebo* was significantly more effective than saline in improving dry eyes. It has been shown to increase tear film and lipid layer thickness after a single dose; these effects increased after repeated administration.[8-10]

Adverse Effects – The most common adverse effects of perfluorohexyloctane ophthalmic solution in clinical trials were blurred vision and conjunctival erythema, which occurred in 1-3% of patients.

INTRANASAL VARENICLINE — The cholinergic agonist varenicline (*Tyrvaya*; not approved in Canada) is the only drug to be approved by the FDA as an intranasal solution for treatment of dry eye disease. Varenicline activates the trigeminal parasympathetic pathway, increasing basal tear film production.[11] In clinical trials, varenicline intranasal solution was significantly more effective in increasing tear production than its vehicle alone.[12]

Adverse Effects – The most common adverse effects of varenicline intranasal solution in clinical trials were sneezing, cough, throat irritation, and intranasal irritation.

PULSED LIGHT THERAPY — A series of in-office treatments with *Optilight*, a Health Canada- and FDA-approved device that delivers intense pulsed light, has been shown to reduce inflammation and improve meibum quality in patients with dry eye disease and meibomian gland dysfunction. How it compares to other treatments for dry eye disease is unclear and its long-term safety is unknown.

NUTRITIONAL SUPPLEMENTS — Nutritional supplements that contain a variety of ingredients are available over the counter and are widely promoted for treatment of dry eye disease. There is no convincing evidence that they are effective for this indication. ■

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5. Cyclosporine 0.09% solution (Cequa) for dry eye disease. Med Lett Drugs Ther 2019; 61:116.
6. Lifitegrast (Xiidra) for dry eye disease. Med Lett Drugs Ther 2016; 58:110.
7. Perfluorohexyloctane ophthalmic solution (Miebo) for dry eye disease. Med Lett Drugs Ther 2024; 66:13.
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10. JD Sheppard et al. NOV03 for signs and symptoms of dry eye disease associated with meibomian gland dysfunction: the randomized phase 3 MOJAVE study. Am J Ophthalmol 2023; 252:265.
11. Varenicline nasal spray (Tyrvaya) for dry eye disease. Med Lett Drugs Ther 2021; 63:198.
12. D Wirta et al. Efficacy and safety of OC-01 (varenicline solution) nasal spray on signs and symptoms of dry eye disease: the ONSET-2 phase 3 randomized trial. Ophthalmology 2022; 129:379.

Tapinarof Cream (*Vtama*) for Atopic Dermatitis

Tapinarof 1% cream (*Vtama* – Dermavant; not approved in Canada), an aryl hydrocarbon receptor (AhR) agonist, has been approved by the FDA for topical treatment of atopic dermatitis in patients ≥2 years old. Tapinarof is the first AhR agonist to be approved in the US for this indication; there are no AhR agonists approved in Canada. It was approved in 2022 for treatment of plaque psoriasis in adults.[1]

Pronunciation Key	
Tapinarof: ta pin' ar of	***Vtama*:** vee tam' uh

Table 1. Some Topical Nonsteroidal Drugs for Atopic Dermatitis

Drug	FDA-Approved Age/Dosage	US Cost[1]	CAN Cost[4]
Calcineurin Inhibitors			
Pimecrolimus 1% cream – generic *Elidel* (Bausch Health)	≥2 years[5]: bid	$301.30 598.10	N.A.C. $183.90
Tacrolimus 0.03% oint – generic *Protopic* (Leo Pharma) 0.1% oint – generic *Protopic* (Leo Pharma)	≥2 years: bid ≥16 years: bid	140.00 N.A. 120.00 N.A.	N.A.C. 212.20 N.A.C. 227.00
Phosphodiesterase-4 (PDE4) Inhibitors			
Crisaborole 2% oint – *Eucrisa* (Pfizer)	≥3 months: bid[2]	793.40	152.90
Roflumilast[6] 0.15% cream – *Zoryve* (Arcutis)	≥6 years: once/day	928.00	N.A.C.
Janus Kinase (JAK) Inhibitor			
Ruxolitinib 1.5% cream – *Opzelura* (Incyte)	≥12 years: bid[3]	2094.00	1135.20[7]
Aryl Hydrocarbon Receptor (AhR) Agonist			
Tapinarof 1% cream – *Vtama* (Dermavant)	≥2 years: once/day	1445.00	N.A.C.

oint = ointment; N.A.C. = not available in Canada; N.A. = not available in the US

1. Approximate WAC for a 60-gram tube. WAC = wholesaler acquisition cost or manufacturer's published price to wholesalers; WAC represents a published catalogue or list price and may not represent an actual transactional price. Source: AnalySource® Monthly. February 5, 2025. Reprinted with permission by First Databank, Inc. All rights reserved. ©2025. www.fdbhealth.com/policies/drug-pricing-policy.
2. Can be applied once daily once the clinical effect is achieved.
3. Should only be applied to up to 20% of body surface area. Use should be limited to one 60-gram tube per week or one 100-gram tube per two weeks.
4. Approximate WAC for a 60-gram tube, based on prices in Canadian dollars from a national wholesaler (prices in Ontario, February 2025).
5. In Canada, approved for use in children ≥3 months old.
6. In Canada, roflumilast is available as a 0.3% cream for the treatment of plaque psoriasis and a 0.3% foam for the treatment of seborrheic dermatitis.
7. Cost for 100-gram tube.

THE DISORDER — Atopic dermatitis (eczema) is a highly pruritic, chronic inflammatory skin disorder that commonly presents in infancy or early childhood; it affects about 10-20% of children and 5-10% of adults in Canada and the US. The disease has a relapsing course, often improv-ing by adolescence but sometimes persisting into or first appearing in adulthood. It is frequently associated with food allergies, allergic rhinitis, and asthma.[2]

TOPICAL TREATMENT — Topical **corticosteroids** are generally used for first-line treatment of mild to moderate atopic dermatitis when nonpharmacologic therapies such as moisturizers are ineffective, but long-term use of these drugs can cause skin atrophy, telangiectasias, and permanent striae. A topical **calcineurin inhibitor** such as tacrolimus or pimecrolimus (*Elidel*, and generics; *Elidel* only in Canada) is often added or substituted; these drugs are similar in efficacy to low- or medium-potency topical corticosteroids and can be used on the face and intertriginous areas, where use of corticosteroids can be troublesome. The topical **phosphodiesterase-4 (PDE4) inhibitors** crisaborole (*Eucrisa*) and roflumilast (*Zoryve*; in Canada *Zoryve* is not approved for treatment of atopic dermatitis) are

Key Points: Tapinarof 1% Cream *(Vtama)*

- **Description:** A 1% cream formulation of the aryl hydrocarbon receptor (AhR) agonist tapinarof. Not approved in Canada.
- **Indication:** Topical treatment of atopic dermatitis in patients ≥2 years old.
- **Efficacy:** In two randomized, 8-week trials in patients ≥2 years old with moderate to severe atopic dermatitis, significantly more patients achieved clear or almost clear skin with tapinarof cream than with its vehicle alone.
- **Adverse Effects:** Adverse effects at the application site are uncommon.
- **Dosage:** Apply to affected areas once daily.
- **Cost:** A 60-gram tube costs $1445.
- **Conclusion:** Longer-term trials with active controls are needed. Older drugs should generally be tried first.

modestly effective for treatment of mild to moderate atopic dermatitis and are often used for first-line treatment.[3,4] A topical formulation of the **Janus kinase (JAK) inhibitor** ruxolitinib *(Opzelura)* is approved for short-term treatment of mild to moderate atopic dermatitis in nonimmunocompromised patients, but its use is restricted to application on <20% of body surface area and data on its long-term efficacy and safety are lacking.[5]

MECHANISM OF ACTION — The AhR is a ligand-dependent transcription factor that regulates gene expression in many types of cells, including immune and epithelial cells. AhR signaling, which plays an important role in the development and maintenance of skin, is dysregulated in patients with atopic dermatitis. Tapinarof binds to and activates the AhR, resulting in downregulation of proinflammatory cytokines, antioxidant activity, and skin-barrier normalization.[6]

CLINICAL STUDIES — FDA approval of tapinarof 1% cream for the new indication was based on the results of two double-blind, controlled trials (ADORING 1 and ADORING 2) in a total of 813 patients ≥2 years old with moderate to severe atopic dermatitis. Patients were randomized to receive once-daily treatment with tapinarof 1% cream or its vehicle alone for 8 weeks. In both trials, significantly more patients achieved clear or almost clear skin with tapinarof cream than with its vehicle alone (45.4% vs 13.9% in ADORING 1 and 46.4% vs 18.0% in ADORING 2). Patients who applied tapinarof cream were also more likely to have a ≥75% improvement from baseline in the Eczema Area and Severity Index (EASI-75) score (55.8% vs 22.9% in ADORING 1 and 59.1% vs 21.2% in ADORING 2) and they had significantly less pruritus.[6] According to the manufacturer, a 48-week, open-label, long-term extension trial (ADORING 3) found that patients who achieved complete disease clearance with tapinarof and then stopped treatment maintained clear or almost clear skin for an average of 80 days.

ADVERSE EFFECTS — The most common adverse effects of tapinarof cream (occurring in ≥5% of patients) in the ADORING 1 and ADORING 2 trials were respiratory tract infections and folliculitis. Burning, stinging, and irritation at the application site have been uncommon with tapinarof cream, even when it was applied to sensitive areas.

PREGNANCY AND LACTATION — No data are available on use of tapinarof cream in pregnant or lactating women. Systemic absorption from the skin is minimal. Subcutaneous administration of high doses to pregnant rats did not result in embryofetal lethality or fetal malformations. Tapinarof is secreted into animal milk.

DOSAGE AND ADMINISTRATION — *Vtama* 1% cream is supplied in 60-gram tubes. A thin layer of the cream should be applied to affected areas once daily. The label does not include any restrictions on the total amount applied per week, duration of use, or use on sensitive areas.

CONCLUSION — In two clinical trials, tapinarof 1% cream (*Vtama*; not approved in Canada) was modestly efficacious for short-term treatment of moderate to severe atopic dermatitis in patients ≥2 years old. How it compares to topical corticosteroids, calcineurin inhibitors, or PDE4 inhibitors used for this indication remains to be established. Until longer-term trials with active controls become available, older drugs should generally be tried first. ■

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5. Ruxolitinib (Opzelura) for atopic dermatitis. Med Lett Drugs Ther 2022; 64:12.
6. JI Silverberg et al. Tapinarof cream 1% once daily: significant efficacy in the treatment of moderate to severe atopic dermatitis in adults and children down to 2 years of age in the pivotal phase 3 ADORING trials. J Am Acad Dermatol 2024; 91:457.

A Renal Indication for Semaglutide *(Ozempic)*

The injectable glucagon-like peptide-1 (GLP-1) receptor agonist semaglutide (*Ozempic* – Novo Nordisk) has been approved by the FDA to reduce

Table 1. Health Canada-Approved Indications for GLP-1 Receptor Agonists and SGLT2 Inhibitors for Type 2 Diabetes[1]

GLP-1 Receptor Agonists
Dulaglutide *(Trulicity)*
▶ Treatment of type 2 diabetes in adults ▶ To reduce the risk of non-fatal stroke in adults with type 2 diabetes with established CV disease or multiple CV risk factors
Liraglutide (*Victoza*)
▶ Treatment of type 2 diabetes in adults ▶ To reduce the CV death in adults with type 2 diabetes with established CV disease
Semaglutide *(Ozempic)*
▶ Treatment of type 2 diabetes in adults
Semaglutide *(Rybelsus)*
▶ Treatment of type 2 diabetes in adults
GIP/GLP-1 Receptor Agonist
Tirzepatide *(Mounjaro)*
▶ Treatment of type 2 diabetes in adults
SGLT2 Inhibitors
Canagliflozin *(Invokana)*
▶ Treatment of type 2 diabetes in adults ▶ To reduce the risk of MACE in adults with type 2 diabetes and established CVD ▶ To reduce the risk of end-stage kidney disease, doubling of serum creatinine and CV death in adults with type 2 diabetes and diabetic nephropathy with albuminuria
Dapagliflozin (*Forxiga*, and generics)
▶ Treatment of type 2 diabetes in adults ▶ To reduce the risk of heart failure hospitalization in adults with type 2 diabetes and either established CV disease or CV risk factors ▶ To reduce the risk of CV death, heart failure hospitalization and urgent heart failure visits in adults with heart failure ▶ To reduce the risk of sustained eGFR decline, end-stage kidney disease, and cardiovascular and renal death in adults with CKD
Empagliflozin *(Jardiance)*
▶ Treatment of type 2 diabetes in adults ▶ To reduce the risk of CV death in adults with type 2 diabetes and established CVD ▶ Treatment of adults with heart failure ▶ To reduce the risk of sustained eGFR decline and end-stage kidney disease and CV and renal death in adults with CKD

1. To view the FDA-approved table, go to medicalletter.org/TML-article-1723d.

the risk of sustained eGFR decline, end-stage kidney disease, and cardiovascular death in adults with type 2 diabetes and chronic kidney disease (CKD; in Canada, not approved for this indication). It is the first GLP-1 receptor agonist to be approved in the US for this indication (in Canada, there are no GLP-1 receptor agonists approved for this indication).

OTHER ANTIHYPERGLYCEMIC DRUGS WITH RENAL INDICATIONS — The sodium-glucose cotransporter 2 (SGLT2) inhibitors canagliflozin *(Invokana)*, dapagliflozin (*Forxiga; Farxiga* in the US), and empagliflozin *(Jardiance)*, which were initially approved for treatment of type 2 diabetes, have also been approved for renal and cardiovascular indications (see Table 1).[1] In clinical trials, they improved renal outcomes in patients with and without type 2 diabetes, but they can cause genital mycotic and urinary tract infections, acute kidney injury, volume depletion, hypotension, and ketoacidosis.[2-4] An increased risk of peripheral arterial disease events (lower limb amputation, stent placement, or vascular surgery) has been reported with use of SGLT2 inhibitors.[5]

CLINICAL STUDIES — FDA approval of semaglutide for the new indication was based on the results of a double-blind trial (FLOW) in 3533 patients with type 2 diabetes and CKD who were randomized to receive semaglutide 1 mg or placebo SC once weekly, each in addition to standard treatment (maximally tolerated dose of an angiotensin-converting enzyme [ACE] inhibitor or angiotensin receptor blocker [ARB]). A small number of patients were taking an SGLT2 inhibitor or mineralocorticoid receptor antagonist at baseline and were allowed to continue treatment. After a median follow-up of 3.4 years, a major kidney disease event, the primary endpoint, occurred in 18.7% of patients in the semaglutide arm and in 23.2% of those in the placebo arm, a statistically significant difference (over 3 years number need to treat [NNT] 20). Semaglutide also reduced the risk of major adverse cardiovascular events (MACE) and all-cause mortality (see Table 2).[6]

No head-to-head trials comparing semaglutide with an SGLT2 inhibitor for this indication are available.

ADVERSE EFFECTS — GI adverse effects (nausea, vomiting, diarrhea, constipation) are common with semaglutide. Acute pancreatitis, acute gall bladder

Table 2. FLOW Trial Results[1]

Endpoint	Semaglutide (n=1767)	Placebo (n=1766)
Major kidney disease event[2]	18.7%*	23.2%
MACE[3]	12.0%*	14.4%
All-cause mortality	12.8%*	15.8%

*Statistically significant difference vs placebo
eGFR = estimated glomerular filtration rate; MACE = major adverse cardiovascular event

1. After a median follow-up of 3.4 years. Patients were taking a maximally tolerated dose of an angiotensin-converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB). V Perkovic et al. N Engl J Med 2024; 391:109.
2. A composite of persistent ≥50% reduction from baseline in eGFR, persistent eGFR <15 mL/min/1.73 m², initiation of kidney-replacement therapy, death from kidney-related causes, and cardiovascular death. The primary endpoint.
3. A composite of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke.

disease including cholelithiasis, acute renal failure (possibly due to dehydration), and increases in heart rate have been reported with oral and injectable formulations of semaglutide.

The package inserts of all GLP-1 receptor agonists describe postmarketing reports of ileus associated with their use.[7] There have also been rare postmarketing reports of pulmonary aspiration with use of these drugs in patients undergoing elective procedures requiring general anesthesia or deep sedation who had residual gastric contents despite preoperative fasting.[8]

The labels of all GLP-1 receptor agonists and the GIP/GLP-1 receptor agonist tirzepatide include a boxed warning about a risk of thyroid C-cell tumors (based on animal data; no corroborating human data). These drugs are contraindicated in patients with a personal or family history of medullary thyroid carcinoma and in those with multiple endocrine neoplasia syndrome type 2.

DOSAGE, ADMINISTRATION, AND COST — *Ozempic* is available in pens that deliver 0.25, 0.5, 1, or 2 mg per injection; in Canada, *Ozempic* is available as multi-dose pens that deliver 0.25, 0.5, 1, or 2 mg doses. The recommended starting dosage of semaglutide for the new indication is 0.25 mg injected subcutaneously once weekly; the dosage should be increased in ≥4-week intervals to 0.5 mg and then to 1 mg once weekly. The wholesale acquisition cost (WAC) for a 28-day supply of *Ozempic* 1 mg once weekly is CAN$230.00[9] (US$997.60[10]).

CONCLUSION — Addition of the glucagon-like peptide-1 (GLP-1) receptor agonist semaglutide *(Ozempic)* to standard treatment reduces the risk of kidney disease progression and cardiovascular death in adults with type 2 diabetes and chronic kidney disease (CKD). Head-to-head trials comparing semaglutide with other drugs used for this indication are lacking. ■

1. Drugs for type 2 diabetes. Med Lett Drugs Ther 2022; 64:177.
2. Cardiovascular benefits of SGLT2 inhibitors and GLP-1 receptor agonists in type 2 diabetes. Med Lett Drugs Ther 2019; 61:26.
3. In brief: Dapagliflozin (Farxiga) for chronic kidney disease. Med Lett Drugs Ther 2021; 63:115.
4. In brief: Empagliflozin (Jardiance) for chronic kidney disease. Med Lett Drugs Ther 2023; 65:183.
5. KE Griffin et al. Use of SGLT2i versus DPP-4i as an add-on therapy and the risk of PAD-related surgical events (amputation, stent placement, or vascular surgery); a cohort study in veterans with diabetes. Diabetes Care 2025; 48:1.
6. V Perkovic et al. Effects of semaglutide on chronic kidney disease in patients with type 2 diabetes. N Engl J Med 2024; 391:109.
7. In brief: GI effects of GLP-1 receptor agonists. Med Lett Drugs Ther 2023; 65:191.
8. In brief: New FDA warning of pulmonary aspiration with GLP-1 receptor agonists. Med Lett Drugs Ther 2024; 66:201.
9. Approximate WAC, based on price in Canadian dollars from a national wholesaler (price in Ontario, February 2025).
10. Approximate WAC. WAC = wholesaler acquisition cost or manufacturer's published price to wholesalers; WAC represents a published catalogue or list price and may not represent an actual transactional price. Source: AnalySource® Monthly. February 5, 2025. Reprinted with permission by First Databank, Inc. All rights reserved. ©2025. www.fdbhealth.com/policies/drug-pricing-policy.

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Principal Faculty for this Activity:

Mark Abramowicz, M.D., President has disclosed no relevant financial relationships
Jean-Marie Pflomm, Pharm.D., Editor in Chief has disclosed no relevant financial relationships

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Michael P. Viscusi, Pharm.D., Associate Editor has disclosed no relevant financial relationships.
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LEARNING OBJECTIVES FOR THIS ACTIVITY:

Activity participants will read and assimilate unbiased reviews of FDA-approved and off-label uses of drugs and other treatment modalities. Activity participants will be able to select and prescribe, or confirm the appropriateness of the prescribed usage of, the drugs and other therapeutic modalities discussed in *The Medical Letter* with specific attention to clinical trials, pathophysiology, dosage and administration, drug metabolism and interactions, and patient management. Activity participants will make independent and informed therapeutic choices in their practice.

Upon completion of this activity, the participant will be able to:

1. Review the efficacy and safety of suzetrigine *(Journavx)* for treatment of moderate to severe acute pain.
2. Explain the current approach to the management of dry eye disease.
3. Discuss the treatment options for management of dry eye disease and compare them based on their mechanism of action, efficacy, and potential adverse effects.
4. Review the efficacy and safety of tapinarof 1% cream *(Vtama)* for treatment of atopic dermatitis.
5. Discuss the evidence supporting approval of semaglutide *(Ozempic)* to prevent adverse renal outcomes in patients with type 2 diabetes.

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Note: The participant should read the post-activity questions prior to beginning the activity. After careful review of the text, tables, and cited references, the participant should take time to reflect on how the newly acquired knowledge will be applied to clinical practice, affect patient care, and improve outcomes.

Issue 1723 Post-Activity Questions

(Correspond to questions #41-50 in Comprehensive Activity #92, available June 2025)

Suzetrigine *(Journavx)* – A Sodium Channel Blocker for Acute Pain

1. In Trial 2, the median time to the onset of perceptible pain relief with suzetrigine was:
   a. 15 minutes
   b. 25 minutes
   c. 45 minutes
   d. 60 minutes

2. The most common adverse effect of suzetrigine in Trials 1 and 2 was:
   a. constipation
   b. somnolence
   c. pruritus
   d. nausea

Drugs for Dry Eye Disease

3. Which of the following is generally used first for treatment of dry eye disease?
   a. artificial tears
   b. ophthalmic corticosteroids
   c. lifitegrast solution
   d. intranasal varenicline

4. In patients with dry eye disease, ophthalmic cyclosporine:
   a. reduces inflammation
   b. increases tear production
   c. may take up to 3 months to achieve its full effect
   d. all of the above

5. Ophthalmic perfluorohexyloctane:
   a. has a direct anti-inflammatory effect
   b. increases tear production
   c. reduces tear evaporation
   d. all of the above

6. In patients with dry eye disease, intranasal varenicline:
   a. has a direct anti-inflammatory effect
   b. increases tear production
   c. reduces tear evaporation
   d. all of the above

Tapinarof Cream *(Vtama)* for Atopic Dermatitis

7. Long-term use of a topical corticosteroid can cause:
   a. skin atrophy
   b. telangiectasias
   c. permanent striae
   d. all of the above

8. In the ADORING trials, approximately what proportion of patients treated with tapinarof cream achieved clear or almost clear skin after 8 weeks?
   a. 34%
   b. 45%
   c. 60%
   d. 79%

9. The most common skin-related adverse effect of tapinarof cream in the ADORING trials was:
   a. burning
   b. irritation
   c. folliculitis
   d. discoloration

A Renal Indication for Semaglutide *(Ozempic)*

10. Which of the following GLP-1 receptor agonists is FDA-approved to prevent adverse renal outcomes in patients with type 2 diabetes?
    a. exenatide
    b. dulaglutide
    c. semaglutide
    d. all of the above

ACPE UPN: Per Issue Exam: 0379-0000-25-723-H01-P; Release: February 20, 2025, Expire: February 19, 2026
Comprehensive Exam 92: 0379-0000-25-092-H01-P; Release: July 2025, Expire: July 2026

Successful completion of the post-test is required to earn AAPA Category 1 CME credit. Successful completion is defined as a cumulative score of at least 70 percent correct.