INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES
[ISSN: 0975-4725; CODEN(USA): IJPS00]
Journal Homepage: https://www.ijpsjournal.com

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Review Article

Suzetrigine: A Selective NaV1.8 Sodium Channel Inhibitor for Non-Opioid Pain Management

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ARTICLE INFO

Published: 23 Nov 2026
Keywords:
Suzetrigine, NaV1.8, Non-opioid analgesics, Pain management, Voltage-gated sodium channels, Mechanism of action
DOI:
10.5281/zenodo.24457451

ABSTRACT

Suzetrigine (VX-548; Journavx) is the first approved selective $Na_V1.8$ inhibitor and the first new class of analgesic approved for moderate-to-severe acute pain in adults in more than two decades. By stabilizing the closed state of $Na_V1.8$ in peripheral nociceptors, it reduces pain-signal transmission without acting on opioid receptors. This review summarizes the role of $Na_V1.8$ in nociception, the discovery and mechanism of suzetrigine, its pharmaceutical and pharmacokinetic properties, and the clinical evidence. In two phase 3 trials of 1,118 patients after abdominoplasty and 1,073 after bunionectomy, suzetrigine reduced pain over 48 hours more than placebo, but did not show superiority over hydrocodone/acetaminophen. Common adverse reactions were pruritus, muscle spasm, increased creatine phosphokinase and rash. Evidence is limited to short-term postoperative pain; a phase 2 trial in painful lumbosacral radiculopathy did not separate suzetrigine from placebo. Suzetrigine is a promising addition to non-opioid options, but not a proven replacement for opioids or established analgesics.

INTRODUCTION

1.1 Pain

Pain is an unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage. It protects the body from harm.[1] Nociceptors detect harmful mechanical, thermal or chemical stimuli and convert them into electrical signals that travel through peripheral sensory neurons to the spinal cord and higher centres, where pain is perceived. Voltage-gated sodium channels generate and propagate these signals; $Na_V1.7$, $Na_V1.8$ and $Na_V1.9$ regulate the excitability of peripheral nociceptive pathways.[2,3] Acute pain usually resolves with healing, whereas persistent pain can impair function, sleep, mood and quality of life.

1.2 Types of Pain

Pain can be classified by duration, mechanism and clinical features.[1,4] Acute pain follows tissue injury,

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Relevant conflicts of interest/financial disclosures: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

surgery or inflammation; suzetrigine was developed and approved for moderate-to-severe acute pain in adults.[5] Chronic pain persists or recurs for more than three months.[1,4] Nociceptive pain arises from actual or threatened damage to non-neural tissue; neuropathic pain from a lesion or disease of the somatosensory nervous system, as in diabetic neuropathy;[6] and nociplastic pain from altered nociception without clear tissue damage or neural lesion, as in fibromyalgia.[7] These categories are not mutually exclusive, and a patient's pain mechanisms may change over time.[4,7]

1.3 Analgesics and Their Limitations

Analgesic choice depends on pain severity, duration and mechanism, the patient's condition and the risks of treatment.[4,8] The main groups are (i) non-opioid analgesics, including paracetamol (acetaminophen) and non-steroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen, diclofenac and naproxen;[8,9] (ii) opioids, including morphine, fentanyl, oxycodone and tramadol, which act mainly on μ-opioid receptors;[10] (iii) adjuvant analgesics such as duloxetine, amitriptyline, gabapentin and pregabalin, used in selected neuropathic conditions;[6,8] and (iv) novel agents that target specific proteins in pain signalling. In January 2025 the US Food and Drug Administration (FDA) approved suzetrigine (Journavx) for moderate-to-severe acute pain in adults, the first medicine in this fourth group.[5,11]

Each established group has limitations. NSAIDs can cause gastrointestinal, renal and cardiovascular harm, and excess paracetamol can cause serious liver injury.[8,11] Opioids relieve moderate-to-severe pain but cause constipation, nausea, sedation and respiratory depression, and repeated use can lead to tolerance, physical dependence and, in some patients, opioid use disorder.[9,10] Conventional analgesics may also control neuropathic pain poorly.[6] These limits motivate drugs that act on specific pain-signalling pathways with fewer unwanted effects, and $Na_V1.8$ has drawn particular attention as such a target.[3,5]

2. Voltage-Gated Sodium Channels

2.1 Structure and Functional States

Voltage-gated sodium (Na_V) channels produce the depolarizing phase of the action potential in excitable cells.[2,12] The pore-forming α-subunit has about 2,000 amino acids in four homologous domains (DI–DIV), each with six transmembrane segments (S1–S6). S1–S4 form the voltage-sensing domain (VSD) and S5–S6 contribute to the pore. The DIII–DIV linker carries the IFMT (isoleucine–phenylalanine–methionine–threonine) motif involved in fast inactivation. Smaller β-subunits modulate gating and trafficking.[2,12,13]

Channels cycle through resting (closed), activated (open) and inactivated (closed) states: Resting → Activated → Inactivated → Repriming/Recovery → Resting.[2,14,15] Fast inactivation follows opening within milliseconds, and slow inactivation develops over longer periods. The rate of recovery from inactivation affects how well a neuron can fire repetitively.[2,14] The contribution of the individual isoforms to the sensory-neuron action potential is illustrated in Figure 1.

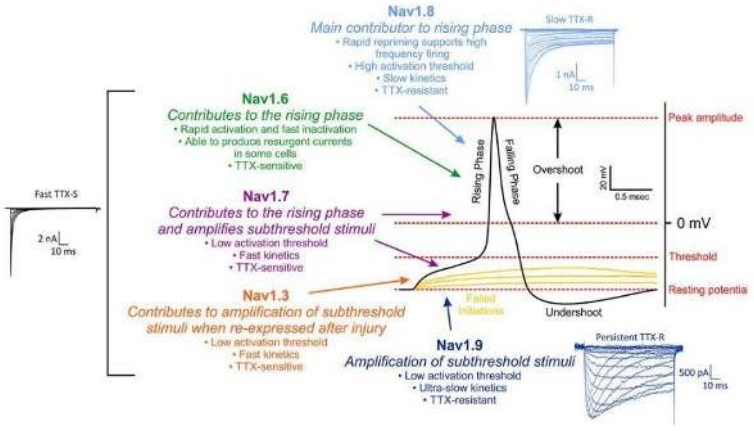

Figure 1: Contribution of $Na_V1.3$, $Na_V1.6$, $Na_V1.7$, $Na_V1.8$ and $Na_V1.9$ to the Sensory-Neuron Action Potential.[2]

2.2 Classification and Tetrodotoxin Sensitivity

The family has nine α-subunit isoforms, $Na_V1.1$–$Na_V1.9$, encoded by SCN1A–SCN11A.[2,16]

Tetrodotoxin (TTX)-resistant channels carry a non-aromatic residue (serine or cysteine) in the outer pore that sharply lowers TTX affinity.[15,17] The classification is summarized in Table 1.

Table 1: Classification of Voltage-Gated Sodium Channel Isoforms by Tetrodotoxin (TTX) Sensitivity

Sr. No.	Class	Isoforms	TTX sensitivity
1	TTX-sensitive	$Na_V1.1$, 1.2, 1.3, 1.4, 1.6, 1.7	Blocked by low-nanomolar TTX
2	TTX-resistant	$Na_V1.5$, 1.8, 1.9	Need micromolar TTX

$Na_V1.8$ and $Na_V1.9$ are expressed mainly in sensory neurons; $Na_V1.5$ mainly in the heart.[2,17]

2.3 Role in Pain Signalling

An action potential generated at a noxious stimulus travels along the sensory axon to the dorsal root ganglion and spinal cord, where it triggers neurotransmitter release onto second-order neurons.[2,14,18] After nerve injury or inflammation, altered sodium-channel function can cause spontaneous activity and hyperexcitability.[2,14]

$Na_V1.1$, 1.3, 1.6, 1.7, 1.8 and 1.9 occur in sensory neurons.[2,18–20] $Na_V1.3$ is re-expressed after nerve injury, although it is not a universal mediator of neuropathic pain;[2,18,21,22] $Na_V1.6$ is concentrated at nodes of Ranvier.[2,22] Human genetics gives the strongest evidence for $Na_V1.7$ and $Na_V1.9$: $Na_V1.7$ gain-of-function mutations cause inherited erythromelalgia and paroxysmal extreme pain disorder, loss-of-function mutations cause congenital insensitivity to pain, and $Na_V1.9$ variants are linked to both painful and painless phenotypes.[19,20,23,24] Suzetrigine does not directly inhibit these channels.

3. The NaV1.8 Channel

3.1 Expression and Electrophysiology

$Na_V1.8$, encoded by SCN10A, was first identified as a TTX-resistant channel in sensory neurons.[25–29] It is expressed mainly in small- and medium-diameter neurons of the dorsal root and trigeminal ganglia, which are rich in nociceptors, but not exclusively in nociceptors.[2,30–33] Its depolarized activation and inactivation, slow inactivation and rapid recovery keep it available during sustained or repetitive depolarization, so it contributes substantially to the action-potential upstroke and repetitive firing.[28,34–38]

3.2 Evidence That NaV1.8 Is a Pain Target

$Na_V1.8$ knockout animals show altered nociceptive responses,[27,28,37,39–42] and its expression, distribution or gating changes after inflammation and nerve injury; it is an important contributor to pathological pain, not its sole determinant.[31,32,43–47] Gain-of-function SCN10A variants occur in patients with painful peripheral neuropathy, and common variants are associated with differences in experimental pain sensitivity.[48–51] Selective or relatively selective inhibitors reduce $Na_V1.8$ currents and nociceptive behaviour in experimental pain models.[27,31,32,43,52–56]

3.3 Therapeutic Rationale

Non-selective sodium-channel blockade affects neuronal, cardiac and other tissues. Selective $Na_V1.8$ inhibition aims to suppress pathological pain signalling while sparing unrelated Na_V subtypes, which motivated selective small-molecule inhibitors and ultimately suzetrigine.[3,33,52,53,57,58]

4. History, Discovery and Development

Several programmes tried to develop selective $Na_V1.8$ inhibitors, but combining subtype selectivity with suitable pharmacokinetics was difficult. Early compounds such as A-803467 showed in animals that selective $Na_V1.8$ inhibition can be analgesic, but their pharmacokinetic properties and poor clinical translation halted progression.[2,33,53,55,59] Vertex Pharmaceuticals then developed VX-150, whose clinical activity gave proof of concept that $Na_V1.8$ inhibition can relieve pain in humans; limitations of its profile led to discontinuation of that programme and to VX-548, later named suzetrigine.[3,57,60,61] The chemical evolution of these inhibitors is shown in Figure 2.

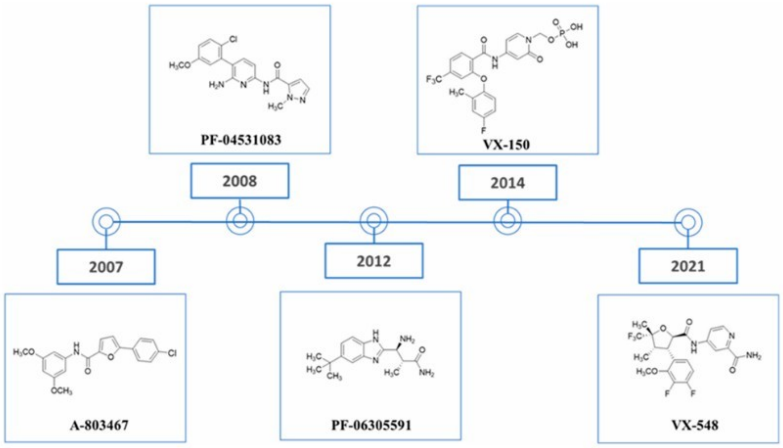

Figure 2: Chemical Evolution of $Na_V1.8$ Inhibitors, 2007–2021, From a-803467 to Suzetrigine (VX-548). Adapted from the Original Source.[62]

In phase 2 trials after abdominoplasty and bunionectomy, VX-548 reduced pain intensity more than placebo.[57] Vertex reported phase 3 results in January 2024 and submitted a New Drug Application.[63–65] The FDA approved suzetrigine on 30 January 2025 as an oral, non-opioid, selective $Na_V1.8$ inhibitor for moderate-to-severe acute pain in adults, the first approved drug of its kind.[5,63–66]

5. Structural and Pharmacological Characteristics

Suzetrigine (formerly VX-548) is an orally active small molecule: a pyridine-2-carboxamide derivative with a chiral substituted tetrahydrofuran ring, molecular formula $C_{21}H_{20}F_5N_3O_4$ and molecular weight about 473.4 g/mol.[3,33,57,67]

In recombinant human Na_V systems and primary human dorsal root ganglion (DRG) neurons, suzetrigine showed at least 31,000-fold selectivity for $Na_V1.8$ over the other Na_V subtypes tested, and no meaningful activity against 180 other molecular targets. Its half-maximal inhibitory concentration (IC_{50}) against native TTX-resistant $Na_V1.8$ current in human DRG neurons was approximately 0.68 nM.[3] Other electrophysiology work reported about 0.27 nM for human $Na_V1.8$ under different experimental conditions.[60] These potency and selectivity figures come from the suzetrigine-specific pharmacology study[3] and the state-dependence studies;[60,61] earlier $Na_V1.8$ blockers (A-803467, PF-01247324, A887826 and pyridyl carboxamides) are cited only as background on the compound class.[59,68–70]

Inhibition is state-dependent and can be partly relieved by strong depolarization, a reverse-use-dependent behaviour.[56,60,61,71,72] $Na_V1.8$ is expressed mainly in peripheral sensory neurons, and human tissue databases show no meaningful SCN10A expression in the central nervous system. Preclinical and clinical safety assessments have not shown the central effects typical of opioids,[3,48,73–75] but this does not mean adverse effects are absent.

6. Mechanism of Action

Suzetrigine is not a classical pore blocker. It binds allosterically to the second voltage-sensing domain (VSD2) of $Na_V1.8$[3,15,76] and stabilizes the channel in its closed, non-conducting state. It binds preferentially when the voltage sensors are at rest and has lower affinity once they are depolarized and activated, which reduces the number of channels available for activation.[3,60] Studies with physiological action-potential waveforms indicate that suzetrigine still inhibits substantially during normal nociceptor activity.[61,77]

The resulting fall in inward Na^+ current lowers nociceptor excitability and repetitive firing. It does not necessarily silence the neuron, because other sodium channels also contribute to excitability.[29,73,75,77] The overall sequence is: suzetrigine binds VSD2 → closed state stabilized → fewer $Na_V1.8$ channels available → reduced Na^+ current → lower nociceptor excitability and repetitive firing → less peripheral pain-signal transmission → analgesia.[2,3,60,61] The state-dependent

binding of suzetrigine to the closed state of $Na_V1.8$ is illustrated in Figure 3.

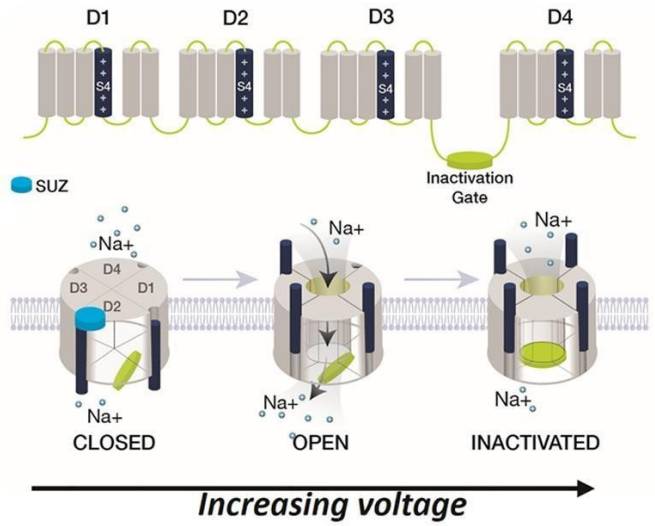

Figure 3: State-dependent Binding of Suzetrigine to the Closed State of $Na_V1.8$ with Increasing Voltage. Adapted from the Original Source.[3]

7. Pharmaceutical and Pharmacokinetic Profile

7.1 Dosage Form and Dosing

Suzetrigine (Journavx) is an oral 50 mg film-coated tablet developed by Vertex Pharmaceuticals and approved by the FDA on 30 January 2025 for moderate-to-severe acute pain, including postoperative pain, in adults.[5,66] The current US label specifies three steps:[66]

1. Dose 1: 100 mg, taken on an empty stomach at least 1 hour before or 2 hours after food, to avoid delayed onset.
2. Doses 2–4: 50 mg every 12 hours, starting 12 hours after the initial dose, with or without food.
3. Dose 5 and later: 50 mg every 24 hours, starting 12 hours after dose 4, with or without food.

Treatment should be as short as the patient's goals allow; use for acute pain has not been studied beyond 14 days.[66] Food and drink containing grapefruit should be avoided because they affect CYP3A-mediated metabolism.[66,78,79] Lower doses apply in moderate hepatic impairment (Child-Pugh B) and with moderate CYP3A inhibitors, and severe hepatic impairment (Child-Pugh C) should be avoided; the exact regimens are in sections 2.2 and 2.3 of the label and should be consulted directly.[66] The formulation and dosing are summarized in Table 2.

Table 2: Formulation and Dosing of Marketed Suzetrigine Tablets[66]

Sr. No.	Parameter	Description
1	Brand name / strength	JOURNAVX; 50 mg per tablet (film-coated, oral)
2	Appearance	Blue, oblong tablet; "VX50" on one side
3	Dose 1	100 mg on an empty stomach, at least 1 hour before or 2 hours after food
4	Doses 2–4	50 mg every 12 hours, starting 12 hours after dose 1; with or without food
5	Dose 5 and later	50 mg every 24 hours, starting 12 hours after dose 4; with or without food
6	Food precaution	Avoid grapefruit-containing food and drink
7	Dose adjustment	Moderate hepatic impairment and moderate CYP3A inhibitors: reduced dosing per label[66]

7.2 Pharmacodynamics

Suzetrigine binds VSD2 of $Na_V1.8$ and holds the channel closed, which reduces sodium conductance and the generation and propagation of action potentials in pain-sensing neurons; it does not act through opioid receptors.[3,24] In two randomized trials after abdominoplasty or bunionectomy it reduced pain more than placebo, which does not show superiority to opioids or efficacy in every pain type (Section 8).[80]

7.3 Pharmacokinetics

After oral dosing the median time to maximum concentration (T_{max}) is about 3 hours when fasting. The apparent volume of distribution is about 495 L, protein binding about 99%, and the mean effective half-life about 23.6 hours.[66,81] Suzetrigine is metabolized mainly by CYP3A.[66,82] Its major active metabolite, M6-SUZ, also inhibits $Na_V1.8$ but is about 3.7-fold less potent than the parent compound in the reported assay.[66] The pharmacokinetic parameters are summarized in Table 3.

Table 3: Pharmacokinetic Parameters of Suzetrigine and ITS Active Metabolite M6-SUZ[66]

Sr. No.	Parameter (steady state)	Suzetrigine	M6-SUZ
1	$AUC_{0–24h}$, µg·h/mL (CV%)	11.5 (25.6%)	34.7 (25.6%)
2	C_{max}, µg/mL (CV%)	0.62 (27.7%)	1.5 (24.5%)
3	Median T_{max}, h (range)	3.0 (1.50–5.03)	10.0 (4.0–48.1)
4	Protein binding	99%	96%
5	Mean effective half-life, h (CV%)	23.6 (36.2%)	33.0 (34.9%)
6	Apparent volume of distribution, L	495 (25.0%)	not applicable
7	Primary metabolic pathway	CYP3A	CYP3A
8	Excretion	Feces 49.9%; urine 44.0% (mainly as metabolites)	not reported

7.4 Drug Interactions and Special Populations

The interaction section of the label should be read in full; its main points are:[66]

- **Strong CYP3A inhibitors:** contraindicated.
- **Moderate CYP3A inhibitors:** both suzetrigine and M6-SUZ exposures rise; the dose must be reduced. Avoid grapefruit.
- **Strong and moderate CYP3A inducers:** avoid. Rifampin (strong) lowered suzetrigine AUC by 93% and M6-SUZ AUC by 85% after a single dose; efavirenz (moderate) is predicted to lower them by about 63% and 60%, which may reduce efficacy.
- **CYP3A substrates:** suzetrigine is itself a CYP3A inducer. At 50 mg every 12 hours it lowered midazolam AUC by 48% and C_{max} by 37%, so substrate doses may need adjustment when suzetrigine is started or stopped, and the substrate's own label should be consulted.
- **Hormonal contraceptives:** patients using progestins other than levonorgestrel or norethindrone need an additional non-hormonal method during treatment and for 28 days after stopping.
- **Hepatic and renal impairment:** avoid in severe hepatic impairment; reduced dosing in moderate impairment; the effect of eGFR below 15 mL/min is unknown.

8. Clinical Evidence

Suzetrigine beat placebo in both pivotal trials but did not beat hydrocodone/acetaminophen (HB/APAP) on the key secondary endpoint, and the evidence base is limited to two surgical models over 48 hours.

8.1 Pivotal Phase 3 Trials

NAVIGATE 1 (bunionectomy; NCT05553366) and NAVIGATE 2 (abdominoplasty; NCT05558410) were randomized, double-blind, placebo- and active-controlled trials in adults with moderate-to-severe pain after surgery (NPRS ≥ 4). Participants received

suzetrigine (100 mg, then 50 mg every 12 hours), HB/APAP (5/325 mg every 6 hours) or placebo for 48 hours, randomized 2:2:1. The primary endpoint was the time-weighted sum of the pain intensity difference over 0–48 hours (SPID48) versus placebo; the key secondary endpoint was SPID48 versus HB/APAP.[80] The principal results are summarized in Table 4.

Table 4: Primary and Key Secondary Results of the Phase 3 Randomized Trials[80]

Sr. No.	Item	Abdominoplasty (NAVIGATE 2)	Bunionectomy (NAVIGATE 1)
1	Participants	1,118	1,073
2	Arms (n)	Suzetrigine 447; HB/APAP 448; placebo 223	Suzetrigine 426; HB/APAP 431; placebo 216
3	SPID48 difference vs placebo (LS mean, 95% CI)	48.4 (33.6–63.1); P < 0.0001	29.3 (14.0–44.6); P = 0.0002
4	Suzetrigine vs HB/APAP (SPID48)	No significant difference	No significant difference
5	Median time to ≥ 2-point NPRS reduction, suzetrigine vs placebo	119 vs 480 min	240 vs 480 min

The investigators concluded that suzetrigine reduced pain over 48 hours more than placebo and that its effect was similar to HB/APAP.[80] Superiority over HB/APAP was not shown, and because no formal non-inferiority analysis was performed, the data do not establish equivalence either. A third, single-arm phase 3 study enrolled 256 patients with surgical and non-surgical acute pain and was consistent with the randomized trials' safety profile, but it has no control group.[83]

8.2 Earlier and Related Studies

Phase 2 trials after abdominoplasty and bunionectomy tested several doses against placebo, with hydrocodone/acetaminophen as a reference, and showed greater pain reduction than placebo.[57] In a phase 2 study of painful lumbosacral radiculopathy, pain-score reduction with suzetrigine was similar to placebo.[24]

8.3 Critical Appraisal

The strengths and limitations of the clinical evidence are summarized in Table 5.

Table 5: Critical Appraisal of the Clinical Evidence for Suzetrigine

Sr. No.	Aspect	Assessment
1	Efficacy vs placebo	Statistically significant in both trials; magnitude smaller after bunionectomy than after abdominoplasty
2	Efficacy vs active comparator	Not superior to HB/APAP 5/325 mg; no formal non-inferiority analysis; no comparison with higher-dose opioids or with NSAID combinations
3	Population	Adults without chronic pain after two elective surgeries; 98% women in the abdominoplasty trial; mean age 42 (abdominoplasty) and 48 (bunionectomy)
4	Duration	48 hours of randomized treatment; label notes no study beyond 14 days
5	Safety follow-up	Short; long-term and repeated-use safety not established
6	Generalizability	Unproven for chronic, neuropathic or severe pain (for example major orthopaedic or abdominal surgery)
7	Gaps	Head-to-head trials against NSAIDs or paracetamol-based regimens; opioid-sparing outcomes; neuropathic pain trials

9. Safety, Adverse Effects and Limitations

In trials, suzetrigine was generally well tolerated and most adverse events were mild to moderate.[80] The prescribing information lists pruritus, muscle spasms, increased creatine phosphokinase and rash as the most common adverse reactions occurring more often than with placebo; in the pooled phase 3 randomized trials pruritus occurred in 2.1% of suzetrigine, 1.6% of placebo and 3.4% of HB/APAP patients.[66] Nausea, headache, dizziness and constipation were also reported, with frequencies that varied between studies and arms.[80,83] Strong CYP3A inhibitors are contraindicated and use in severe hepatic impairment should be avoided[66] (Section 7.4).

Several limitations constrain interpretation:

- The approved indication is moderate-to-severe acute pain in adults; effectiveness and safety in long-term treatment are not established.
- The pivotal trials studied two surgical models over 48 hours, which limits generalization to other pain conditions.[80]
- Suzetrigine beat placebo but was not shown superior to HB/APAP, and was not compared with higher-dose opioids.[80]
- Evidence in chronic neuropathic pain is incomplete; the radiculopathy phase 2 study showed no separation from placebo.[24]
- The absence of opioid-like effects should not be read as absence of adverse effects.

10. Future Prospects

Ongoing research is testing suzetrigine in peripheral neuropathic pain, particularly painful diabetic peripheral neuropathy, in phase 3 studies; effectiveness in chronic neuropathic pain has not been established.[24,84] Priorities include long-term safety, effectiveness across pain conditions, combination with other analgesics, direct comparison with NSAID and paracetamol-based regimens, and any role in reducing opioid use.[24,84]

CONCLUSION

Suzetrigine is a selective $Na_V1.8$ inhibitor that offers a new, non-opioid mechanism for moderate-to-severe acute pain in adults. Randomized trials show significant benefit over placebo in two postoperative settings and acceptable short-term tolerability.[66,80] It has not been shown to outperform hydrocodone/acetaminophen, and it should not be regarded as a replacement for opioids or established analgesics. Its wider clinical role depends on results in chronic and neuropathic pain and on long-term safety data.

Acknowledgement

[Authors to add acknowledgements, if any.]

Conflicts of Interest

[Authors to declare any conflicts of interest; otherwise state that none exist.]

REFERENCES

1. Raja SN, Carr DB, Cohen M, Finnerup NB, Flor H, Gibson S, et al: The revised International Association for the Study of Pain definition of pain: concepts, challenges, and compromises. Pain 2020; 161 (9):1976-1982. doi:10.1097/j.pain.0000000000001939
2. Bennett DL, Clark AJ, Huang J, Waxman SG, Dib-Hajj SD: The role of voltage-gated sodium channels in pain signaling. Physiol Rev 2019; 99 (2):1079-1151. doi:10.1152/physrev.00052.2017
3. Osteen JD, Immani S, Tapley TL, Indersmitten T, Hurst NW, Healey T, et al: Pharmacology and mechanism of action of suzetrigine, a potent and selective $Na_V1.8$ pain signal inhibitor for the treatment of moderate to severe pain. Pain Ther 2025; 14 (2):655-674. doi:10.1007/s40122-024-00697-0
4. Treede RD, Rief W, Barke A, Aziz Q, Bennett MI, Benoliel R, et al: Chronic pain as a symptom or a disease: the IASP Classification of Chronic Pain for the International Classification of Diseases (ICD-11). Pain 2019; 160 (1):19-27. doi:10.1097/j.pain.0000000000001384
5. U.S. Food and Drug Administration: FDA approves novel non-opioid treatment for moderate to severe acute pain [Internet]. Silver Spring (MD): FDA; 2025 Jan 30 [cited 2026 Oct 19]. Available from: https://www.fda.gov/news-events/press-

announcements/fda-approves-novel-non-opioid-treatment-moderate-severe-acute-pain

6. Finnerup NB, Attal N, Haroutounian S, McNicol E, Baron R, Dworkin RH, et al: Pharmacotherapy for neuropathic pain in adults: a systematic review and meta-analysis. Lancet Neurol 2015; 14 (2):162-173. doi:10.1016/S1474-4422 (14)70251-0
7. Kosek E, Cohen M, Baron R, Gebhart GF, Mico JA, Rice ASC, et al: Do we need a third mechanistic descriptor for chronic pain states? Pain 2016; 157 (7):1382-1386. doi:10.1097/j.pain.0000000000000507
8. StatPearls Publishing: Pain management medications [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 Jan- [cited 2026 Oct 20]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK560692/
9. Imam MZ, Kuo A, Ghassabian S, Smith MT: Progress in understanding mechanisms of opioid-induced gastrointestinal adverse effects and respiratory depression. Neuropharmacology 2018; 131:238-255. doi:10.1016/j.neuropharm.2017.12.032
10. Chou R, Turner JA, Devine EB, Hansen RN, Sullivan SD, Blazina I, et al: The effectiveness and risks of long-term opioid therapy for chronic pain: a systematic review for a National Institutes of Health Pathways to Prevention Workshop. Ann Intern Med 2015; 162 (4):276-286. doi:10.7326/M14-2559
11. Dureja GP, Iyer RN, Das G, Ahdal J, Narang P: Evidence and consensus recommendations for the pharmacological management of pain in India. J Pain Res 2017; 10:709-736. doi:10.2147/JPR.S128655
12. Cardoso FC, Lewis RJ: Sodium channels and pain: from toxins to therapies. Br J Pharmacol 2018; 175 (12):2138-2157. doi:10.1111/bph.13962
13. Ahern CA, Payandeh J, Bosmans F, Chanda B: The hitchhiker's guide to the voltage-gated sodium channel galaxy. J Gen Physiol 2016; 147 (1):1-29. doi:10.1085/jgp.201511492
14. Ma RSY, Kayani K, Whyte-Oshodi D, Whyte-Oshodi A, Nachiappan N, Gnanarajah S, et al: Voltage gated sodium channels as therapeutic targets for chronic pain. J Pain Res 2019; 12:2709-2722. doi:10.2147/JPR.S207610
15. de Lera Ruiz M, Kraus RL: Voltage-gated sodium channels: structure, function, pharmacology, and clinical indications. J Med Chem 2015; 58 (18):7093-7118. doi:10.1021/jm501981g
16. Catterall WA, Goldin AL, Waxman SG: International Union of Pharmacology. XLVII. Nomenclature and structure-function relationships of voltage-gated sodium channels. Pharmacol Rev 2005; 57 (4):397-409. doi:10.1124/pr.57.4.4
17. Leffler A, Herzog RI, Dib-Hajj SD, Waxman SG, Cummins TR: Pharmacological properties of neuronal TTX-resistant sodium channels and the role of a critical serine pore residue. Pflugers Arch 2005; 451 (2):360-367. doi:10.1007/s00424-005-1463-x
18. Goodwin G, McMahon SB: The physiological function of different voltage-gated sodium channels in pain. Nat Rev Neurosci 2021; 22 (5):263-274. doi:10.1038/s41583-021-00444-w
19. Dib-Hajj SD, Waxman SG: Sodium channels in human pain disorders: genetics and pharmacogenomics. Annu Rev Neurosci 2019; 42:87-106. doi:10.1146/annurev-neuro-070918-050144
20. Kanellopoulos AH, Matsuyama A: Voltage-gated sodium channels and pain-related disorders. Clin Sci (Lond) 2016; 130 (24):2257-2270. doi:10.1042/CS20160041
21. Cummins TR, Waxman SG: Downregulation of tetrodotoxin-resistant sodium currents and upregulation of a rapidly repriming tetrodotoxin-sensitive sodium current after sciatic nerve injury. J Neurosci 1997; 17 (9):3503-3514.
22. Black JA, Frezel N, Dib-Hajj SD, Waxman SG: Expression of $Na_V1.6$ in axons and small dorsal root ganglion neurons in the adult rat. J Neurophysiol 2002; 88 (3):1497-1506.
23. Baker MD, Nassar MA: Painful and painless mutations of SCN9A and SCN11A voltage-gated

sodium channels. Pflugers Arch 2020; 472 (7):865-880. doi:10.1007/s00424-020-02419-9

24. Rajasingham R, Qi Y: Suzetrigine, a non-opioid small-molecule analgesic: mechanism of action, clinical, and translational science. Clin Transl Sci 2025; 18 (11):e70414. doi:10.1111/cts.70414
25. Akopian AN, Sivilotti L, Wood JN: A tetrodotoxin-resistant voltage-gated sodium channel expressed by sensory neurons. Nature 1996; 379:257-262. doi:10.1038/379257a0
26. Sangameswaran L, Delgado SG, Fish LM, et al: Structure and function of a novel voltage-gated, tetrodotoxin-resistant sodium channel specific to sensory neurons. J Biol Chem 1996; 271 (11):5953-5956. doi:10.1074/jbc.271.11.5953
27. Akopian AN, Souslova V, England S, et al: The tetrodotoxin-resistant sodium channel SNS has a specialized function in pain pathways. Nat Neurosci 1999; 2:541-548. doi:10.1038/9195
28. Renganathan M, Cummins TR, Waxman SG: Contribution of $Na_V1.8$ sodium channels to action potential electrogenesis in DRG neurons. J Neurophysiol 2001; 86:629-640. doi:10.1152/jn.2001.86.2.629
29. Han C, Huang J, Waxman SG: Sodium channel $Na_V1.8$: emerging links to human disease. Neurology 2016; 86:473-483. doi:10.1212/WNL.0000000000002333
30. Shields SD, Ahn HS, Yang Y, et al: $Na_V1.8$ expression is not restricted to nociceptors in mouse peripheral nervous system. Pain 2012; 153:2017-2030. doi:10.1016/j.pain.2012.04.022
31. Gold MS, Weinreich D, Kim CS, et al: Redistribution of $Na_V1.8$ in uninjured axons enables neuropathic pain. J Neurosci 2003; 23:158-166.
32. Joshi SK, Mikusa JP, Hernandez G, et al: Involvement of the TTX-resistant sodium channel $Na_V1.8$ in inflammatory and neuropathic, but not postoperative, pain states. Pain 2006; 123:75-82. doi:10.1016/j.pain.2006.02.011
33. Wang H, Huang J, Zang J, Jin X, Yan N: Drug discovery targeting $Na_V1.8$: structural insights and therapeutic potential. Curr Opin Chem Biol 2024; 83:102538. doi:10.1016/j.cbpa.2024.102538
34. Blair NT, Bean BP: Roles of tetrodotoxin-sensitive Na+ current, TTX-resistant Na+ current, and Ca2+ current in the action potentials of nociceptive sensory neurons. J Neurosci 2002; 22:10277-10290. doi:10.1523/JNEUROSCI.22-23-10277.2002
35. Han C, Estacion M, Huang J, Vasylyev D, Zhao P, Dib-Hajj SD, Waxman SG: Human Nav1.8: enhanced persistent and ramp currents contribute to distinct firing properties of human DRG neurons. J Neurophysiol 2015; 113 (9):3172-3185. doi:10.1152/jn.00113.2015
36. Dib-Hajj SD, Cummins TR, Black JA, Waxman SG: Sodium channels in normal and pathological pain. Annu Rev Neurosci 2010; 33:325-347.
37. Rush AM, Dib-Hajj SD, Liu S, Cummins TR, Black JA, Waxman SG: A single sodium channel mutation produces hyper- or hypoexcitability in different types of neurons. Proc Natl Acad Sci U S A 2006; 103 (21):8245-8250. doi:10.1073/pnas.0602813103
38. Cummins TR, Sheets PL, Waxman SG: The roles of sodium channels in nociception: implications for mechanisms of pain. Pain 2007; 131 (3):243-257. doi:10.1016/j.pain.2007.07.026
39. Nassar MA, Levato A, Stirling LC, Wood JN: Neuropathic pain develops normally in mice lacking both $Na_V1.7$ and $Na_V1.8$. Mol Pain 2005; 1:24.
40. Laird JMA, Souslova V, Wood JN, Cervero F: Deficits in visceral pain and referred hyperalgesia in $Na_V1.8$-null mice. J Neurosci 2002; 22:8352-8356. doi:10.1523/JNEUROSCI.22-19-08352.2002
41. Yoshimura N, Seki S, Novakovic SD, et al: The involvement of the tetrodotoxin-resistant sodium channel $Na_V1.8$ in a rat model of visceral pain. J Neurosci 2001; 21:8690-8696. doi:10.1523/JNEUROSCI.21-21-08690.2001
42. Hudmon A, Choi JS, Tyrrell L, et al: Phosphorylation of sodium channel $Na_V1.8$ by p38 MAP kinase increases current density in dorsal root ganglion neurons. J Neurosci 2008; 28:3190-3201. doi:10.1523/JNEUROSCI.4403-07.2008

43. Thakor DK, Lin A, Matsuka Y, et al: Increased peripheral nerve excitability and local $Na_V1.8$ mRNA up-regulation in painful neuropathy. Mol Pain 2009; 5:14.
44. Xiao Y, Barbosa C, Pei Z, et al: Increased resurgent sodium currents in $Na_V1.8$ contribute to nociceptive sensory neuron hyperexcitability associated with peripheral neuropathies. J Neurosci 2019; 39:1539-1550. doi:10.1523/JNEUROSCI.0468-18.2018
45. Huang CP, Chen HN, Su HL, et al: Electroacupuncture reduces carrageenan- and CFA-induced inflammatory pain accompanied by changes in $Na_V1.7$ and $Na_V1.8$ expression. Evid Based Complement Alternat Med 2013; 2013:312184. doi:10.1155/2013/312184
46. Lv MD, Wei YX, Chen JP, et al: Melatonin attenuated chronic visceral pain by reducing $Na_V1.8$ expression and nociceptive neuronal sensitization. Mol Pain 2023; 19:17448069231170072. doi:10.1177/17448069231170072
47. Gold MS, Flake NM: Inflammation-mediated hyperexcitability of sensory neurons. Neurosignals 2005; 14 (4):147-157.
48. Faber CG, Lauria G, Merkies ISJ, Cheng X, Han C, Ahn HS, et al: Gain-of-function Nav1.8 mutations in painful neuropathy. Proc Natl Acad Sci U S A 2012; 109 (47):19444-19449. doi:10.1073/pnas.1216080109
49. Huang J, Yang Y, Zhao P, et al: Small-fiber neuropathy $Na_V1.8$ mutation shifts activation to hyperpolarized potentials and increases excitability of dorsal root ganglion neurons. J Neurosci 2013; 33:14087-14097. doi:10.1523/JNEUROSCI.2710-13.2013
50. Duan G, Han C, Wang Q, Guo S, Zhang Y, Ying Y, et al: A SCN10A SNP biases human pain sensitivity. Mol Pain 2016; 12:1744806916666083. doi:10.1177/1744806916666083
51. Duan G, Sun J, Li N, Zheng H, Guo S, Zhang Y, et al: A variant in the SCN10A enhancer may affect human mechanical pain sensitivity. Mol Pain 2018; 14:1744806918763275. doi:10.1177/1744806918763275
52. Urru M, Muzzi M, Coppi E, et al: Dexpramipexole blocks $Na_V1.8$ sodium channels and provides analgesia in multiple nociceptive and neuropathic pain models. Pain 2020; 161:831-841. doi:10.1097/j.pain.0000000000001774
53. Brown AD, Bagal SK, Blackwell P, et al: The discovery and optimization of benzimidazoles as selective $Na_V1.8$ blockers for the treatment of pain. Bioorg Med Chem 2019; 27:230-239. doi:10.1016/j.bmc.2018.12.002
54. Zhang F, Zhang C, Xu X, et al: Naja atra venom peptide reduces pain by selectively blocking the voltage-gated sodium channel $Na_V1.8$. J Biol Chem 2019; 294:7324-7334. doi:10.1074/jbc.RA118.007370
55. Qin H, Wei A, Wang Y, Wang L, Xu H, Zhan Y, et al: Discovery of selective $Na_V1.8$ inhibitors based on 5-chloro-2-(4,4-difluoroazepan-1-yl)-6-methyl nicotinamide scaffold for the treatment of pain. Eur J Med Chem 2023; 254:115371.
56. Gilchrist J, et al: Pharmacologic characterization of LTGO-33, a selective small molecule inhibitor of the voltage-gated sodium channel $Na_V1.8$ with a unique mechanism of action. Mol Pharmacol 2024. doi:10.1124/molpharm.123.000789
57. Jones J, Correll DJ, Lechner SM, et al: Selective inhibition of $Na_V1.8$ with VX-548 for acute pain. N Engl J Med 2023; 389 (5):393-405. doi:10.1056/NEJMoa2209870
58. Abd-Elsayed A, Hashimoto N, Reilly M, Kohr D, Sahin MZ: Selective $Na_V1.8$ inhibition for pain management: current evidence and future potential of suzetrigine. Curr Pain Headache Rep 2026; 30 (1):35. doi:10.1007/s11916-026-01472-w
59. Jarvis MF, Honore P, Shieh CC, Chapman M, Joshi S, Zhang XF, et al: A-803467, a potent and selective $Na_V1.8$ sodium channel blocker, attenuates neuropathic and inflammatory pain in the rat. Proc Natl Acad Sci U S A 2007; 104 (20):8520-8525. doi:10.1073/pnas.0611364104
60. Vaelli P, Fujita A, Jo S, Zhang HXB, Osorno T, Ma X, Bean BP: State-dependent inhibition of $Na_V1.8$ sodium channels by VX-150 and VX-548.

Mol Pharmacol 2024; 106 (6):298-308. doi:10.1124/molpharm.124.000944

61. Jo S, Fujita A, Osorno T, Stewart RG, Vaelli PM, Bean BP: Differential state-dependent Nav1.8 inhibition by suzetrigine, LTGO-33, and A887826. J Gen Physiol 2025; 157 (4). doi:10.1085/jgp.202413719
62. Medhat RM, Kotb OA, Baecker D: Suzetrigine, a $Na_V1.8$ inhibitor as a novel approach for pain therapy: a medicinal and chemical drug profile. Molecules 2026; 31 (2):358.
63. Vertex Pharmaceuticals Incorporated: Vertex announces positive results from the VX-548 Phase 3 program for the treatment of moderate-to-severe acute pain [Internet]. Boston: Vertex; 2024 Jan 30 [cited 2026 Oct 19]. Available from: https://investors.vrtx.com/news-releases/news-release-details/vertex-announces-positive-results-vx-548-phase-3-program
64. Vertex Pharmaceuticals Incorporated: Vertex announces advancements of suzetrigine (VX-548) in acute and neuropathic pain [Internet]. Boston: Vertex; 2024 Apr 18 [cited 2026 Oct 19]. Available from: https://investors.vrtx.com/news-releases/news-release-details/vertex-announces-advancements-suzetrigine-vx-548-acute-and
65. Vertex Pharmaceuticals Incorporated: Vertex announces FDA acceptance of New Drug Application for suzetrigine for the treatment of moderate-to-severe acute pain [Internet]. Boston: Vertex; 2024 Jul 30 [cited 2026 Oct 19]. Available from: https://investors.vrtx.com/news-releases/news-release-details/vertex-announces-fda-acceptance-new-drug-application-suzetrigine
66. U.S. Food and Drug Administration: Journavx (suzetrigine) tablets: prescribing information [Internet]. Silver Spring (MD): FDA; revised 2026 [cited 2026 Oct 29]. Available from: https://dailymed.nlm.nih.gov/dailymed/lookup.cfm?setid=f0976da4-1d20-4517-945c-b60ed2f41c12
67. Cho EB, Jiang C, Wang Z, Yu Y, Jiang J: Suzetrigine for moderate to severe acute pain. Trends Pharmacol Sci 2025; 46 (5):480-481. doi:10.1016/j.tips.2025.02.008
68. Payne CE, Brown AD, Theile JW, Loucif AJC, Alexandrou AJ, Fuller MD, et al: A novel selective and orally bioavailable Nav1.8 channel blocker, PF-01247324, attenuates nociception and sensory neuron excitability. Br J Pharmacol 2015; 172 (10):2654-2670. doi:10.1111/bph.13092
69. Zhang XF, Shieh CC, Chapman ML, Matulenko MA, Hakeem AH, Atkinson RN, et al: A-887826 is a structurally novel, potent and voltage-dependent $Na_V1.8$ sodium channel blocker that attenuates neuropathic tactile allodynia in rats. Neuropharmacology 2010; 59 (3):201-207. doi:10.1016/j.neuropharm.2010.05.009
70. Poslusney M, Ernst G, Huang Y, Gerlach AC, Chapman ML, Santos S, et al: Development and characterization of pyridyl carboxamides as potent and highly selective Nav1.8 inhibitors. Bioorg Med Chem Lett 2025; 117:130059. doi:10.1016/j.bmcl.2024.130059
71. Jo S, Zhang HXB, Bean BP: Use-dependent relief of inhibition of Nav1.8 channels by A-887826. Mol Pharmacol 2023; 103 (4):221-229. doi:10.1124/molpharm.122.000593
72. Huang X, Jin X, Huang G, Huang J, Wu T, Li Z, et al: Structural basis for high-voltage activation and subtype-specific inhibition of human $Na_V1.8$. Proc Natl Acad Sci U S A 2022; 119 (30):e2208211119. doi:10.1073/pnas.2208211119
73. Djouhri L, Fang X, Okuse K, Wood JN, Berry CM, Lawson SN: The TTX-resistant sodium channel Nav1.8 (SNS/PN3): expression and correlation with membrane properties in rat nociceptive primary afferent neurons. J Physiol 2003; 550 (Pt 3):739-752. doi:10.1113/jphysiol.2003.042127
74. Matthews EA, Wood JN, Dickenson AH: Na (v)1.8-null mice show stimulus-dependent deficits in spinal neuronal activity. Mol Pain 2006; 2:5. doi:10.1186/1744-8069-2-5
75. Klein AH, Vyshnevska A, Hartke TV, De Col R, Mankowski JL, Turnquist B, et al: Sodium channel Nav1.8 underlies TTX-resistant axonal action

potential conduction in somatosensory C-fibers of distal cutaneous nerves. J Neurosci 2017; 37 (20):5204-5214. doi:10.1523/JNEUROSCI.3799-16.2017

76. Catterall WA, Lenaeus MJ, Gamal El-Din TM: Structure and pharmacology of voltage-gated sodium and calcium channels. Annu Rev Pharmacol Toxicol 2020; 60:133-154. doi:10.1146/annurev-pharmtox-010818-021757
77. Stewart RG, Osorno T, Fujita A, Jo S, Ferraiuolo A, Carlin K, Bean BP: Modulation of human dorsal root ganglion neuron firing by the Nav1.8 inhibitor suzetrigine. Proc Natl Acad Sci U S A 2025; 122 (22):e2503570122. doi:10.1073/pnas.2503570122
78. U.S. Food and Drug Administration: Drug Trials Snapshots: JOURNAVX [Internet]. Silver Spring (MD): FDA; 2025 [cited 2026 Oct 19]. Available from: https://www.fda.gov/drugs/drug-trials-snapshots/drug-trials-snapshots-journavx
79. U.S. Food and Drug Administration, Center for Drug Evaluation and Research: Approval package for application number 219209: Journavx (suzetrigine) [Internet]. Silver Spring (MD): FDA; 2025 [cited 2026 Oct 19]. Available from: https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&ApplNo=219209
80. Bertoch T, D'Aunno D, McCoun J, Solanki D, Taber L, Urban J, et al: Suzetrigine, a nonopioid $Na_V1.8$ inhibitor for treatment of moderate-to-severe acute pain: two phase 3 randomized clinical trials. Anesthesiology 2025; 142 (6):1085-1099. doi:10.1097/ALN.0000000000005460
81. National Center for Biotechnology Information: PubChem compound summary for suzetrigine, CID 156445116 [Internet]. Bethesda (MD): National Library of Medicine; [cited 2026 Oct 20]. Available from: https://pubchem.ncbi.nlm.nih.gov/compound/156445116
82. ClinicalTrials.gov: A study to evaluate the relative bioavailability and food effect of a new tablet formulation and strength of suzetrigine. Identifier NCT06336096 [Internet]. Bethesda (MD): National Library of Medicine; 2024 [cited 2026 Oct 19]. Available from: https://clinicaltrials.gov/study/NCT06336096
83. McCoun J, Winkle P, Solanki D, Urban J, Bertoch T, Oswald J, et al: Suzetrigine, a non-opioid $Na_V1.8$ inhibitor with broad applicability for moderate-to-severe acute pain: a phase 3 single-arm study for surgical or non-surgical acute pain. J Pain Res 2025; 18:1569-1576. doi:10.2147/JPR.S509144
84. Vertex Pharmaceuticals Incorporated: Quarterly report for the period ended December 31, 2025 [Internet]. Boston (MA): Vertex Pharmaceuticals Incorporated; 2026.

HOW TO CITE: Sanidhya Meti, Pankaj Chaudhary, Suzetrigine: A Selective NaV1.8 Sodium Channel Inhibitor for Non-Opioid Pain Management, Int. J. of Pharm. Sci., 2026, Vol 4, Issue 11, 4105-4117. https://doi.org/10.5281/zenodo.24457451