Drug Use Research & Management Program
Oregon State University, 500 Summer Street NE, E35
Salem, Oregon 97301-1079
Phone 503-947-5220 | **Fax** 503-947-2596

New Drug Evaluation: Suzetrigine (JOURNAVX) 50 mg tablet

Date of Review: June 2025
Generic Name: Suzetrigine

End Date of Literature Search: 04/13/2025
Brand Name (Manufacturer): Journavx™ (Vertex)

Dossier Received: yes

Plain Language Summary:

- Many patients experience pain due to different causes. Pain can last a short amount of time (acute) or last longer (chronic).
- The Food and Drug Administration recently approved suzetrigine for acute pain. Suzetrigine is not an opioid, such as hydrocodone, and evidence from short-term studies shows that it is probably not addictive. It works differently than acetaminophen or non-steroidal anti-inflammatory drugs (NSAID) such as ibuprofen to control pain.
- Based on 2 studies lasting 48 hours, suzetrigine may work better than a placebo to relieve moderate to severe pain after a surgery. There is no evidence that suzetrigine works better than low-dose hydrocodone/acetaminophen. Nearly all patients in these studies also took ibuprofen for breakthrough pain, and patients who received suzetrigine took ibuprofen at similar amounts as patients who took a placebo.
- One study allowed patients to take suzetrigine for up to 14 days (average 9.8 days). There were no major concerns for safety shown, but this study did not compare suzetrigine to another group and patients knew what they were taking.
- Suzetrigine is not studied or approved by the Food and Drug Administration for chronic pain. It has not been compared to a non-steroidal anti-inflammatory drug or taken simultaneously with an opioid. Suzetrigine is being studied for nerve pain from diabetes.
- We recommend requests for suzetrigine follow labeled age requirements and limit quantities beyond the time period where there is quality evidence to show it may help acute pain. This process is called prior authorization.

Research Questions:

1. What is the comparative efficacy or effectiveness suzetrigine in people acute pain?
2. What is the comparative safety of suzetrigine in people with acute pain?
3. Is there evidence to show that suzetrigine is more effective or safer in certain populations of people (based on diagnoses, disease characteristics, race, comorbidities [renal or hepatic impairment, history of opioid abuse], concomitant drug therapies, or socioeconomic status)?

Conclusions:

- Suzetrigine a sodium channel blocker the Food and Drug Administration (FDA) approved for moderate to severe acute pain in adults. It is not expected to have risk of addiction and is not classified as a controlled substance by the Drug Enforcement Agency.

Author: Sara Fletcher, PharmD, MPH, BCPS

- Suzetrigine was approved based on the findings of two fair-quality, phase 3, double-blind, randomized, multicenter, active- and placebo-controlled studies for moderate to severe acute postsurgical pain after abdominoplasty or bunionectomy.[1] Publication of results is available as a preprint, and full publication is pending.
    - There is moderate quality evidence that suzetrigine is superior to placebo by decreasing time-weighted sum of the pain intensity between hours 0 to 48 (SPID48) on the numeric pain rating scale (NPRS) in patients after bunionectomy (NAVIGATE 1: least squares mean [LSM] difference 29.3, 95% confidence interval [CI] 14.0 to 44.6, p=0.0002) and abdominoplasty (NAVIGATE 2: LSM difference 48.4, 95% CI 33.6 to 63.1, p<0.0001).[1]
    - There is moderate quality evidence that suzetrigine is not superior to low dose hydrocodone 5 mg/acetaminophen 325 mg given every 6 hours using the SPID48 after bunionectomy (NAVIGATE 1: LSM difference -20.2, 95% CI -32.7 to -7.7, p=0.0016 [favors hydrocodone/acetaminophen]) or abdominoplasty (NAVIGATE 2: LSM difference 6.6, 95% CI -5.4 to 18.7, p=0.281).[1]
- There is moderate quality evidence that suzetrigine is safe for use for 48 hours. Most side effects were mild and severe adverse events were generally not attributed to suzetrigine. Nausea and vomiting was less likely to occur with suzetrigine than hydrocodone/acetaminophen (number needed to harm [NNH] 7-13).[1]
- There is insufficient evidence based on one open-label, single arm study that suzetrigine is safe for use up to 14 days (mean 9.8 days).[2]
- Most patients included in clinical trials were White women after outpatient surgery. Abdominoplasty is often performed for cosmetic reasons and may not be representative of Medicaid post-operative patients.

Recommendations:

- Implement prior authorization for use beyond 48 hours and limit use to no more than 14 days.

Background:

Pain management is an important aspect for a variety of acute and chronic conditions. Acute pain is generally defined as pain lasting up to 30 days, usually in response to some form of tissue injury, such as surgery or trauma.[3] Both non-pharmacologic treatments (such as rehabilitative therapy, chiropractic or osteopathic manipulation, and acupuncture) and pharmaceutical analgesics play an important role in management of pain. Evidence supporting specific interventions varies depending on the condition, but current guidelines routinely recommend non-opioid pharmaceuticals and non-pharmacologic treatments for the initial treatment of acute or chronic pain. Most guidelines, medical societies, and public health agencies have recently recommended against routinely prescribing opioids due to increasing evidence of harms reported in observational and epidemiologic studies. These harms include increased mortality, development of opioid use disorder, overdose, sexual dysfunction, fractures, myocardial infarction, constipation, and sleep-disordered breathing.[4] Opioids have also been implicated in impaired cognitive function and development of new onset depression.[4]

Non-opioid pharmaceutical options currently available for pain management include acetaminophen, NSAIDs, certain antidepressants, topical agents, muscle relaxants, and some anticonvulsants (e.g., gabapentin, pregabalin). Acetaminophen and some NSAIDs are available over-the-counter without the need for a prescription. There has been interest in development of new pain medications which utilize non-addictive modalities and provide adequate pain relief.[3] The FDA issued non-binding industry guidance in February 2022 for the development of non-opioid analgesics for acute pain and recommended against the use of non-inferiority study designs because pain intensity can be influenced by study design factors (e.g., placebo effect, rescue medications) and the result of “no difference” could occur in a situation where neither product worked.[3]

Improvement in pain severity or intensity is one of the most commonly reported efficacy outcomes for pain studies. However, outcomes evaluating the impact of treatment on disability, function, and quality of life are equally important. Pain intensity measurements used in clinical trials include the visual analog scale (VAS; range 0-100 or 0-10) and numeric pain rating scale (NPRS; range 0-10).[5] The NPRS and VAS are highly correlated and can be interpreted equally. For acute pain, the minimum clinically important difference (MCID) in the 11-point VAS is 1.4 (95% CI, 1.2 to 1.6).[6] Similar MCID values have been shown with 100-point scales (correlating to about a 14 point change on a 100 point scale).[7] The Sum of Pain Intensity Difference (SPID) over a specified time period (often 24-48 hours) has been used in acute pain studies including tramadol and NSAIDs. A specific minimum clinically important difference (MCID) has not been established.[1,3,8,9]

See **Appendix 1** for **Highlights of Prescribing Information** from the manufacturer, including Boxed Warnings and Risk Evaluation Mitigation Strategies (if applicable), indications, dosage and administration, formulations, contraindications, warnings and precautions, adverse reactions, drug interactions and use in specific populations. Pharmacology and pharmacokinetic properties are listed in **Appendix 2**.

Clinical Efficacy:

Suzetrigine, a sodium channel blocker, works by selective inhibition of $Na_v1.8$, which is not expressed in the human brain or spinal cord. This presumably limits addictive potential.[10] It is approved for the treatment of moderate to severe acute pain in adults.[10] Use for acute pain has not been studied beyond 14 days.[10] It is dosed as 100 mg followed by 50 mg every 12 hours and is available in a 30-count bottle (~ 14 day supply) and a 100-count bottle.[10]

Suzetrigine has been studied in two, phase 3, double-blind, randomized, multicenter, active- and placebo-controlled studies for moderate to severe acute postsurgical pain after abdominoplasty (NAVIGATE 2; NCT05558410) or bunionectomy (NAVIGATE 1; NCT05553366).[1] Studies are currently published as a pre-print. Included adults were aged 18 to 80 years, had a moderate or severe verbal categorical rating scale (VRS; 4 levels ranging from “no pain” to “severe pain”), and pain of 4 or greater on the numeric pain rating scale (NPRS, a numerical version of the visual-analogue scale; range 0 to 10, higher score indicate more pain).[1] Patients in NAVIGATE 2 were assessed for pain within 4 hours of surgical completion after standard abdominoplasty under general anesthesia.[1] Surgical duration was less than 3 hours and those with liposuction were excluded.[1] In NAVIGATE 1, patients underwent primary unilateral bunionectomy with local blockade and regional anesthesia and were assessed for pain within 9 hours after removal of popliteal sciatic block on day 1.[1] All patients were required to stop chronic use of opioids or NSAIDS at least 5 half-lives or 2 days (whichever was longer) before admission.[1] Full inclusion and exclusion details are included in **Table 2**. Patients were randomized 2:1:2 to receive suzetrigine 100 mg followed by 50 mg every 12 hours plus dummy placebo every 12 hours (to mimic every 6 hour dosing), placebo every 6 hours, or hydrocodone 5 mg/acetaminophen 325 mg every 6 hours.[1]

Pain intensity was assessed using the NPRS at 19 timepoints (0.5, 1.0, 1.5, 2, 3, 4, 5, 6, 8 hours, then every 4 hours up to 48 hours) after the first dose of study drug.[1] Ibuprofen 400 mg orally every 6 hours was allowed as rescue medication after first dose of study drug, though all patients were encouraged to wait 90 minutes after the first study drug administration before requesting rescue medication to allow time for effect and reduce confounding from rescue medication. The primary endpoint in both studies was time-weighted sum of the pain intensity difference for suzetrigine versus placebo on NPRS from hours 0 to 48 hours (SPID48). Positive SPID48 scores indicate reduction in pain from baseline while larger numbers indicate greater pain reduction.[1] The expected MCID for SPID48 was not stated. Suzetrigine was superior to placebo using SPID48 (NAVIGATE 1: LSM difference 29.3, 95% CI 14.0 to 44.6, p=0.0002; NAVIGATE 2: LSM difference 48.4, 95% CI 33.6 to 63.1, p<0.0001).[1] The first key secondary endpoint was SPID48 of suzetrigine compared to hydrocodone/acetaminophen, and suzetrigine did not have superior pain improvement in either trial (NAVIGATE 1: LSM difference -20.2, 95% CI -32.7 to -7.7, p=0.0016 [favoring hydrocodone/acetaminophen]; NAVIGATE 2: LSM difference 6.6, 95% CI -5.4 to 18.7, p=0.281).[1] Due to hierarchical testing plan and failure to meet first key secondary endpoint, additional secondary endpoints are considered exploratory.[8] Additional endpoints are included in **Table 2**.

Rescue use of ibuprofen was similar between groups in NAVIGATE 1 (suzetrigine n=364, 85.4%, 800 mg total; placebo n=185, 85.6%, 800 mg total; hydrocodone/acetaminophen n=345, 80.0%, 400 mg total), and NAVIGATE 2 (suzetrigine n=362, 81.0%, 800 mg total; placebo n=196, 87.9%, 1200 mg total; hydrocodone/acetaminophen n=360; 82.6%, 800 mg total).[1] Efficacy of suzetrigine beyond 48 hours for acute pain is not known, and there is currently insufficient evidence for use in chronic pain. Combination use with an opioid has not been studied, and it is unclear if suzetrigine would reduce opioid exposure with concomitant use. Most participants were generally healthy females and based on surgical type and may not be representative of the Medicaid population. Suzetrigine was not superior to a low dose of hydrocodone/acetaminophen and the difference was more defined in the bunionectomy study. There was a large amount of attrition (>10%) due to perceived lack of efficacy in all groups for a short term (48 hour) study intervention.

Clinical Safety:
Suzetrigine is contraindicated with strong CYP3A inhibitors (e.g., ketoconazole, clarithromycin) which increase exposure to suzetrigine and the M6-SUZ active metabolite.[10] The medication is an inducer of CYP3A and should be used with caution in those taking other CYP3A substrates, including certain hormonal birth contraceptives.[10] FDA labeling includes a warning/precaution for use in moderate to severe hepatic impairment. Use of suzetrigine should be avoided in Child-Pugh Class C and used only with dose modification for in people with Child-Pugh Class B.[10]

In NAVIGATE 1 and 2 the most common side effects were nausea, constipation, headache, dizziness, hypotension, and vomiting. These were mostly mild and usually occurred at lower rates than the placebo or hydrocodone/acetaminophen group. However, administration of the medication lasted only 48 hours. Those that occurred at greater rate than placebo are in **Table 1**.

Table 1. Adverse events of suzetrigine occurring in at least 1% of patients and greater than placebo[10]

Adverse event	**Placebo** (N=438) n (%)	**Suzetrigine** (N=874) n (%)	**Hydrocodone/acetaminophen** (N=879) n (%)
Pruritus	7 (1.6)	18 (2.1)	30 (3.4)
Muscle spasms	2 (0.5)	11 (1.3)	6 (0.7)
Increased blood creatine phosphokinase	2 (0.5)	10 (1.1)	7 (0.8)
Rash	2 (0.5)	10 (1.1)	6 (0.7)

In addition to the randomized controlled trials, suzetrigine has been studied in a published, phase 3, single-arm trial (NCT05661734) for moderate to severe surgical or non-surgical acute pain (n=256) in 15 United States centers.[11] The trial had high risk of bias due to lack of blinding, randomization, and a control group, and only the primary endpoint of safety will be detailed in this document. Suzetrigine 100 mg then 50 mg every 12 hours was given for up to 14 days or until pain resolution occurred in adult participants (age 18 to 80 years) with BMI between 18 and 40 kg/m^2 who were post-surgical or presenting to a medical facility with acute pain of new origin within 48 hours of onset.[11] Patients were anticipated to require less than a 24-hour admission.[11] Those with alcohol or illicit drug use within the past 3 years were excluded.[11] Pain was rated as moderate to severe on the VRS and 4 or higher on the NPRS.[11] Rescue with 650 mg acetaminophen or 400 mg ibuprofen every 6 hours was allowed and required by most patients who underwent surgery (n=187; 82.4%). In the total cohort 73% used both acetaminophen and ibuprofen.[11] Concomitant ibuprofen and acetaminophen was more common in surgical (177/222; 79.7%) than non-surgical (10/34; 29.4%) patients.[11] No other pain medications were permitted, and the specific amount of rescue medication was not reported.[11]

Patients were primarily female (n=173; 67.6%) and White (n=214; 83.6%) with a mean age of 43.9 years for females and 44.0 years for male participants.[11] The mean baseline NPRS was 6.7 and most patients were post-surgical (n=222; 86.7%).[11] In the post-surgical patients, orthopedic (n=93; 41.9%) and plastic surgery (n=83; 37.4%) were the most common types of surgery, and otorhinolaryngologic surgeries and hernia repairs each accounted for about 10% surgeries.[11] Non-surgical patients (n=34) most commonly presented with an upper extremity (n=25; 44.1%) or lower extremity (n=12; 35.3%) pain after an acute injury.[11] Three patients presented with pain in multiple regions.[11]

Treatment was completed prior to day 14 in 105 patients (41.0%) due to pain resolution, and the entire 14-day regimen was completed by 137 patients (53.5%). Differences in duration based on patient type (surgical or non-surgical) was not reported. The mean overall exposure of suzetrigine was 9.8 days.[11] A total of 14 patients discontinued suzetrigine, 5 (2.0%) due to adverse event (accidental overdose, arrhythmia, nausea, rash, somnolence), 4 (1.6%) due to lack of efficacy, 1 (0.4%) by sponsor decision, and the remaining 4 (1.6%) due to "other" reason.[11] The arrhythmia (n=1) resulting in discontinuation of suzetrigine did not resolve by the end of the study period and the affected patient had a history of sinus arrhythmia and cardiac murmur.[11]

Headache was the most common adverse event (n=18; 7.0%).[11] Constipation, nausea, fall, and rash were the other adverse events occurring in more than 2% of patients.[11] Those with falls had lower extremity surgeries prior to the event and did not report syncope or dizziness.[11] There were 94 patients who experienced any AE. Mild events (n=71; 27.7%) were more common than moderate (n=21; 8.2%) or severe events (n=2, cellulitis and suicidal ideation; 0.8%).[11]

There are no phase 3 data beyond 14 days of use. A 12-week, phase 2 study versus pregabalin or placebo for diabetic peripheral neuropathy has been conducted, and a phase 3 study is currently in progress (NCT06628908) in patients with pain associated with diabetic peripheral neuropathy.

Comparative Endpoints:

Clinically Meaningful Endpoints:

1) Improvement in pain severity or intensity
2) Avoidance of opioid use disorder
4) Serious adverse events
5) Study withdrawal due to an adverse event

Primary Study Endpoint:

1) Time-weighted sum of the pain intensity difference for suzetrigine versus placebo on NPRS from hours 0 to 48 (SPID48)

Table 2. Comparative Evidence Table.

Ref./ Study Design	Drug Regimens/ Duration	Patient Population	N	Efficacy Endpoints	ARR/ NNT	Safety Outcomes	ARR/ NNB	Risk of Bias/ Applicability
1. NAVIGATE 2[1] NCT05558410 MC, DB, PC/AC	1. Suzetrigine 100 mg orally once, then 50 mg every 12h with alternating placebo every 6h 2. Placebo orally every 6h	Demographics: -Mean Age 42 y -Ethnicity White 70% Black 27% -34% Hispanic/Latino -Female 98% -Mean baseline NPRS score 7.4	ITT: 1. 447 2. 223 3. 448 Attrition: 1. 51 (11.4%) 2. 55 (24.7%) 3. 66 (14.7%)	Primary Endpoint: SPID48 (LSM) 1. 118.4 2. 70.1 3. 111.8 LSM Difference 1 vs. 2 = 48.4 (95% CI 33.6 to 63.1) P<0.0001	NA	Discontinued due to AE: 1. 6 (1.3%) 2. 1 (0.4%) 3. 5 (1.1%) Discontinued due to lack of efficacy: 1. 42 (9.4%) 2. 48 (21.5%) 3. 59 (13.2%)	NA	**Risk of Bias (low/high/unclear)**: Selection Bias: (Low) Stratified by clinical site and baseline NPRS score (<8 or ≥8) using block size of 5. Random allocation sequence by independent randomization vendor and enrollment with IWRS. Baseline characteristics well balanced. Performance Bias: (Unclear) Placebo dummy used to make all interventions dosed every 6 hours. Method of blinding not described.

	3. HB/APAP orally 5mg/325mg every 6h Duration: 48 hours 2:1:2 randomization	<u>Key Inclusion Criteria</u>: -Age 18-80 y -Moderate to severe acute pain after full abdominoplasty -Abdominoplasty lasted ≤ 3 hours -Lucid and able to follow commands -Able to swallow oral medications <u>Key Exclusion Criteria</u>: -Hx of previous abdominoplasty -Hx of recent surgery -Hx of intra-abdominal or pelvic surgery with complications -BMI <18 or >40 kg/m^2 -Hx of cardiac dysrhythmias within past 2 y -Non-standard abdominoplasty, collateral procedures (e.g., liposuction) or any surgical complication -Medical complication during surgery	Overall 84.6% completed treatment	<u>First Key Secondary Endpoint</u>: SPID48 (LSM) Difference: 1 vs. 3 = 6.6 (95% CI -5.4 to 18.7) P=0.2781 <u>Second Key Secondary Endpoint* (exploratory)</u>: Median time to meaningful pain relief (≥ 2 point reduction in NPRS) 1. 119 minutes 2. 480 minutes 3. NR 1 vs. 2 P<0.0001 Rescue Medication Use 1. 362 (81.0%) 2. 196 (87.9%) 3. 370 (82.6%)[8] Total Ibuprofen Use time 0-48 hours (median in mg) 1. 800 2. 1200 3. 800[8]		<u>SAE:</u> 1. 2.5% 2. 2.3% 3. 1.6% <u>Death:</u> 1. 0 2. 1 (pulmonary embolism following cardiogenic shock and DIC) 3. 0 <u>Vomiting or Nausea:</u> 1. 91 (20.3%) 2. NR 3. 150 (33.5%) P<0.0001	13.2%/ 7	<u>Detection Bias</u>: (Unclear) Method of blinding not described. Patients completed a pain assessment training video prior to surgical procedure. <u>Attrition Bias</u>: (Unclear) Greater than 10% attrition on short term study. Missing data and score imputation for primary and key secondary endpoints were as follows: 1) scores during the rescue period (within 6 hours after rescue medication) were replaced by the pre-rescue score; 2) missing scores following treatment discontinuation were imputed using the baseline score when discontinuation was due to an AE and with the last score prior to discontinuation when discontinuation was due to other reasons; 3) missing scores for subjects who completed the treatment but with missing data from a certain time point to 48 hours were imputed with the last score; and 4) intermittently missing scores were imputed using linear interpolation. <u>Reporting Bias</u>: (Unclear) Full protocol not published (similarly designed phase 2 protocol is available), extensive use and reporting of post-hoc analyses, and secondary endpoints generally only reported vs. placebo (HB/APAP data included in FDA review). <u>Other Bias</u>: (Unclear) Trials supported by manufacturer, multiple authors are manufacturer employees and own stock and/or options in the company. **Applicability**: <u>Patient</u>: Most patients were female and study included patients having outpatient surgical interventions. Abdominoplasty is typically a cosmetic procedure and not representative of the Medicaid population. <u>Intervention</u>: Frequent pain assessment during 48-hour post-operative period mirrors inpatient but not outpatient real-world use. No evidence for longer term acute or chronic therapy. Frequent use of rescue medication and high attrition for lack of efficacy may be indication inadequate early pain relief.

								Comparator: Placebo and opioids are appropriate comparators, though HB/APAP dosing was on low end of dosing range. Future studies using NSAID comparison would help define place in therapy. Outcomes: SPID48 is an acceptable outcome measurement for acute pain per FDA guidance. Setting: 12 US locations
2.NAVIGATE 1[1] NCT05553366 MC, DB, PC/AC	1. Suzetrigine 100mg orally once, then 50mg every 12h with alternating placebo every 6h 2. Placebo orally every 6h 3. HB/APAP orally 5mg/325mg every 6h Duration: 48 hours 2:1:2 randomization	Demographics: -Mean Age 48 y -Ethnicity White 71% Black 24% -35% Hispanic/Latino -Female 85% -Mean NPRS score 6.8 Key Inclusion Criteria: -Age 18-80 y -Moderate to severe acute pain on VRS after bunionectomy and NPRS score ≥4 after procedure -Primary unilateral bunionectomy with distal first metatarsal osteotomy and internal fixation under regional anesthesia -Lucid and able to follow commands Key Exclusion Criteria: -Hx of bunionectomy -BMI <18 or >40 kg/m^2 -Hx of cardiac dysrhythmias within past 2 y -Hx of recent surgery	ITT: 1. 426 2. 216 3. 431 Attrition: 1. 54 (12.7%) 2. 39 (18.1%) 3. 42 (9.7%) Overall 87.4% completed treatment	Primary Endpoint: SPID48 (LSM) 1. 99.9 2. 70.6 3. 120.1 LSM Difference 1 vs. 2 = 29.3 (95% CI 14.0 to 44.6) P=0.0002 First Key Secondary Endpoint: SPID48 (LSM) Difference: 1 vs. 3 = -20.2 (95% CI -32.7 to -7.7) P=0.0016 (in favor of HB/APAP) Second Key Secondary Endpoint* (exploratory): Median time to meaningful pain relief (≥ 2-point reduction in NPRS) 1. 240 minutes 2. 480 minutes 3. NR 1 vs. 2 P=0.0016 Secondary Endpoints: Rescue Medication Use 1. 364 (85.4%) 2. 185 (85.6%) 3. 345 (80.0%)[8]	NA	Discontinued due to AE: 1. 0 2. 0 3. 1 (0.2%) (pretreatment hypotension) Discontinued due to lack of efficacy: 1. 51 (12.0%) 2. 35 (16.2%) 3. 34 (7.9%) SAE: None Vomiting or Nausea: 1. 39 (9.2%) 2. NR 3. 71 (16.5%) P=0.0014	NA 7.3%/ 13	**Risk of Bias (low/high/unclear)**: Selection Bias: See NAVIGATE 2 Performance Bias: See NAVIGATE 2 Detection Bias: See NAVIGATE 2 Attrition Bias: See NAVIGATE Reporting Bias: See NAVIGATE 2 Other Bias: See NAVIGATE 2 **Applicability**: Patient: Most patients were female and study included patients having outpatient surgical interventions. Intervention: See NAVIGATE 2 Comparator: See NAVIGATE 2 Outcomes: See NAVIGATE 2 Setting: 21 US locations

		-Type 3 deformity requiring a base wedge osteotomy or concomitant hammertoe repair -Medical complication during surgery		Total Ibuprofen Use time 0-48 hours (median in mg) 1. 800 2. 800 3. 400[8]				

Abbreviations: AC = active-controlled; AE = adverse event; ARR = absolute risk reduction; BMI = body mass index; CI = confidence interval; DIC = disseminated intravascular coagulation; FDA = Food and Drug Administration; h = hours; HB/APAP = hydrocodone bitartrate/acetaminophen; hx = history; ITT = intention to treat; IWRS = interactive web response system; LSM = least squares mean; MC = multicenter; mITT = modified intention to treat; N = number of subjects; NA = not applicable; NNB = number needed to benefit; NNT = number needed to treat; NPRS = 11-point numeric pain rating scale [range 0-10]; NR = not reported; NS = not significant; PC = placebo-controlled; PP = per protocol; SPID48 = time-weighted sum of the pain intensity difference from 0-48 hours; US = United States; VRS = verbal rating scale; y = years.

*based on hierarchical nature of secondary endpoints, after failure to meet the first key secondary endpoint, all subsequent endpoints were considered exploratory by the FDA.

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Appendix 1: Prescribing Information Highlights

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use JOURNAVX safely and effectively. See full prescribing information for JOURNAVX.

JOURNAVX (suzetrigine) tablets, for oral use
Initial U.S. Approval: 2025

----------INDICATIONS AND USAGE----------

JOURNAVX is a sodium channel blocker indicated for the treatment of moderate to severe acute pain in adults. (1)

----------DOSAGE AND ADMINISTRATION----------

- Swallow JOURNAVX tablets whole and do not chew or crush. (2.1)
- Recommended starting JOURNAVX oral dose is 100 mg. Take the starting dose on an empty stomach at least 1 hour before or 2 hours after food. Clear liquids may be consumed during this time (e.g., water, apple juice, vegetable broth, tea, black coffee). (2.1)
- Starting 12 hours after the starting dose, take 50 mg of JOURNAVX orally every 12 hours. Take these doses with or without food. (2.1)
- Use JOURNAVX for the shortest duration, consistent with individual patient treatment goals. Use of JOURNAVX for the treatment of acute pain has not been studied beyond 14 days. (2.1)
- See the full prescribing information for the recommended dosage in patients with hepatic impairment (2.2), for JOURNAVX dosage modifications with concomitant use of CYP3A inhibitors (2.3), and recommendations regarding missed dose(s). (2.4)
- Avoid food or drink containing grapefruit during treatment with JOURNAVX. (2.3)

----------DOSAGE FORMS AND STRENGTHS----------

Tablets: 50 mg (3)

----------CONTRAINDICATIONS----------

- Concomitant use with strong CYP3A inhibitors is contraindicated. (4)

----------WARNINGS AND PRECAUTIONS----------

Moderate and Severe Hepatic Impairment: Avoid use in patients with severe hepatic impairment (Child-Pugh Class C). Use in patients with moderate hepatic impairment may increase the risk of adverse reactions. The recommended dosage is lower in patients with moderate hepatic impairment (Child-Pugh Class B) than those with normal hepatic function. (5.4)

----------ADVERSE REACTIONS----------

The most common adverse reactions (greater incidence in JOURNAVX-treated patients compared to placebo-treated patients) were pruritis, muscle spasms, increased creatine phosphokinase, and rash. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Vertex Pharmaceuticals Incorporated at 1-877-634-8789 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------

- *Strong and Moderate CYP3A inhibitors*: Concomitant use with strong CYP3A inhibitors is contraindicated. Reduce the JOURNAVX dose when used concomitantly with moderate CYP3A inhibitors. Avoid food or drink containing grapefruit. (2.3, 7.1, 12.3)
- *Strong and Moderate CYP3A inducers*: Avoid JOURNAVX use with strong or moderate CYP3A inducers. (7.1, 12.3)
- *CYP3A substrates*: If JOURNAVX is used concomitantly with sensitive CYP3A substrates or CYP3A substrates where minimal concentration changes may lead to loss of efficacy, refer to the Prescribing Information for the CYP3A substrates for dosing instructions. Dosage modification of the concomitant CYP3A substrates may be required when initiating or discontinuing JOURNAVX. (7.2, 12.3)
- *Hormonal contraceptives*: JOURNAVX-treated patients using hormonal contraceptives containing progestins other than levonorgestrel and norethindrone should use an additional nonhormonal contraceptive method or an alternative hormonal contraceptive during concomitant use and for 28 days after JOURNAVX discontinuation. (7.2)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 1/2025

Appendix 2: Pharmacology and Pharmacokinetic Properties.[10]

Parameter	
Mechanism of Action	Selective blocker of the NaV1.8 voltage-gated sodium channel. NaV1.8 is expressed in peripheral sensory neurons including dorsal root ganglion neurons, where its role is to transmit pain signals (action potentials). By selectively inhibiting NaV1.8 channels, suzetrigine inhibits transmission of pain signals to the spinal cord and brain. M6-SUZ, a major active metabolite, is a less potent inhibitor of NaV1.8 than suzetrigine by 3.7-fold.
Oral Bioavailability	Max absorption: 3 hours (active drug), 10 hours (M6-SUZ active metabolite)
Distribution and Protein Binding	Volume of distribution: 495 L (active drug) Protein binding: 99% (active drug), 96% (M6-SUZ active metabolite)
Metabolism	CYP3A (active drug and M6-SUZ active metabolite)
Half-Life	23.6 hours (active drug), 33.0 hours (M6-SUZ active metabolite)
Elimination	Feces: 49.9% (9.1% as active drug) Urine: 44.0% (primarily as metabolites)

Appendix 3: Proposed Prior Authorization Criteria

Suzetrigine (Journavx™)

Goal(s):

- Allow use in accordance with available medical evidence for safety and efficacy.

Length of Authorization:

- Up to 14 days per acute injury/surgery

Requires PA:

- Suzetrigine quantities greater than 5 tablets total (50 mg tablets, a 48-hour supply) within 30 days

Covered Alternatives:

- Current PMPDP preferred drug list per OAR 410-121-0030 at www.orpdl.org
- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	
2. Is the patient an adult 18 years or older?	**Yes**: Go to #3	**No:** Pass to RPh. Deny; medical appropriateness.
3. Is the request for treatment of acute pain? Note: Acute pain is generally considered to last less than 30 days.	**Yes**: Go to #4	**No:** Pass to RPh. Deny; medical appropriateness.
4. Is the pain documented to be moderate to severe?	**Yes**: Go to #5 Record pain rating_____ using visual analogue scale (VAS), numeric pain rating scale (NPRS) or other validated measure.	**No:** Pass to RPh. Deny; medical appropriateness.
5. Has the patient already received 14 days of suzetrigine for this indication?	**Yes:** Pass to RPh. Deny; medical appropriateness.	**No:** Go to #6
6. Is there documentation that the patient is failing to receive adequate pain relief from, or have contraindications to, both acetaminophen and a non-steroidal anti-inflammatory agent?	**Yes:** Approved requested doses up to maximum 30 tablets (total includes any doses received before prior authorization requirement).	**No:** Pass to RPh. Deny; medical necessity.

P&T/DUR Review: 6/25 (SF)
Implementation: 8/1/25