CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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RISK ASSESSMENT and RISK MITIGATION REVIEW(S)

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Application Type	NDA
Application Number	219209
PDUFA Goal Date	January 30, 2025
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Reviewer Name(s)	Timothy Bernheimer, Pharm.D
Team Leader	Carolyn Tieu, Pharm.D, MPH
Division Director	Cynthia LaCivita, Pharm.D
Review Completion Date	January 21, 2025
Subject	Evaluation of Need for a REMS
Established Name	suzetrigine
Trade Name	Journavx
Name of Applicant	Vertex Pharmaceuticals Incorporated
Therapeutic Class	Sodium channel blocker
Formulation	Oral tablets
Dosing Regimen	(b) (4)

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EXECUTIVE SUMMARY

This review by the Division of Risk Management (DRM) evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity Journavx (suzetrigine) is necessary to ensure the benefits outweigh its risks. Vertex Pharmaceuticals Incorporated submitted a New Drug Application (NDA 219209) for Journavx with the proposed indication for the treatment of moderate to severe acute pain in adults. There were no serious risks associated with Journavx identified by the clinical review team that rise to the level of a Boxed Warning. Draft labeling currently includes concomitant use of Journavx with strong CYP3A inhibitors as a contraindication. The risks of interactions with drugs affecting CYP enzymes described in the *Warnings and Precautions* section are risks that are commonly managed by healthcare providers likely to prescribe or dispense Journavx. The risks associated with use in patients with severe hepatic impairment and /or severe renal impairment have not been studied, *Warnings and Precautions* section of labeling will include to avoid use in these patient populations.

The applicant did not submit a proposed REMS or risk management plan with this application.

DRM has determined that a REMS is not needed to ensure the benefits of Journavx outweigh its risks. The likely prescribers are likely to have experience in managing the aforementioned risks. These risks will be communicated through labeling.

1. Introduction

This review by the Division of Risk Management (DRM) evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity (NME) Journavx (suzetrigine) is necessary to ensure the benefits outweigh its risks. Vertex Pharmaceuticals submitted a New Drug Application (NDA) 219209 for Journavx with the proposed indication for the treatment of moderate to severe acute pain in adults. This application is under review in the Division of Anesthesiology, Addiction Medicine, and Pain Medicine (DAAP). The applicant did not submit a proposed REMS or risk management plan with this application.

2. Background

2.1. Product Information

Journavx (suzetrigine), a NME,[a] is a sodium channel blocker proposed for the treatment of moderate to severe acute pain in adults. Journavx tablets, for oral use, are proposed as two 50 mg tablets followed by one 50 mg tablet every 12 hours, with use for the shortest duration, consistent with individual patient treatment goals.[b] Use of Journavx for the treatment of acute pain has not been studied beyond 14 days. Journavx was granted priority review and is not currently approved in any jurisdiction.

2.2. Regulatory History

[a] Section 505-1 (a) of the FD&C Act: *FDAAA factor (F): Whether the drug is a new molecular entity.*

[b] Section 505-1 (a) of the FD&C Act: *FDAAA factor (D): The expected or actual duration of treatment with the drug.*

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The following is a summary of the regulatory history for NDA 219209 relevant to this review:

- 03/05/2020: IND 146185 granted Fast Track Designation
- 06/30/2022: IND 146185 granted Breakthrough Therapy designation for moderate to severe acute pain.
- 03/18/2024: IND 146185 granted Rolling Review designation and Breakthrough Therapy designation is rescinded.
- 03/28/2024: NDA 219209 submission received for the treatment of moderate to severe acute pain in adults.
- 10/02/2024: A Post Mid-cycle meeting was held between the Agency and the Applicant via teleconference. The Agency informed the Applicant that based on the currently available data, there were no safety issues that require a REMS for Journavx
- 12/05/2024: A Late-cycle meeting was held between the Agency and the Applicant via teleconference. The Agency reiterated that, at this time, no issues related to risk management have been identified to date.

3. Therapeutic Context and Treatment Options

3.1. Description of the Medical Condition

Acute pain is sudden, sharp or intense pain, that is caused by injury or trauma and generally lasts from a few minutes to less than six months.[1] Acute pain can consist of both somatic and visceral pain which differs in where the pain originates and travels to the spinal cord.[2]

Acute pain is a common condition associated with many medical conditions. Inadequately controlled pain negatively affects quality of life, function, functional recovery, risk of post-surgical complications, and the risk of persistent postsurgical pain.[3,c] It is estimated that the prevalence for acute pain in the United States is 12.2% of the population[4] and pain is one of the top reasons for consultation in general practice.[5,d]

Acute pain is a serious condition that has other societal and global health implications as untreated acute pain can result in chronic pain if untreated. The impact of untreated pain includes social isolation, dependence on care givers, disrupted social relationships, depression, anxiety as well as financial burdens due to income loss due to the inability to work, and the healthcare costs of treatment.[6,7]

[c] Section 505-1 (a) of the FD&C Act: FDAAA factor (B): *The seriousness of the disease or condition that is to be treated with the drug.*

[d] Section 505-1 (a) of the FD&C Act: *FDAAA factor (A): The estimated size of the population likely to use the drug involved.*

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3.2. Description of Current Treatment Options

Non-pharmacologic management of acute pain includes rest, ice, compression and elevation (RICE), physical therapy, acupuncture, massage, hypnosis and relaxation techniques.

Journavx, if approved, would be the first selective blocker of the Nav1.8 voltage-gated sodium channel compared to other known voltage-gated sodium channels (Nav1.1 through 1.9). Other pharmacologic options for acute pain management include acetaminophen, nonsteroidal anti-inflammatory drugs (NSAIDs), topical agents (e.g., local anesthetics), and opioids. Acetaminophen and NSAIDS are frequently used as first-line therapy for mild to moderate acute pain. Opioids are frequently used for moderate to severe acute pain, but are associated with the risks of respiratory depression, addiction, overdose, and death. Opioids should be reserved for when non-opioid options are inadequate and when the benefits of the opioids are expected to outweigh the risks.[8]

There is an unmet medical need for more non-opioid treatment options for acute pain. Opioid use disorder (OUD) has reached epidemic proportions in the United States. According to the 2022 National Survey on Drug Use and Health, an estimated 5.6 million people in the United States have OUD.[9] Although commonly prescribed opioids are no longer driving the opioid overdose epidemic, the number of drug overdose deaths involving prescription opioids in 2022 was 14,716.[10] As with other patients being treated for pain, maximizing multimodal opioid sparing therapy in patients with a history of OUD before moving to opioids is important because opioid use may place OUD patients at risk for returning to uncontrolled OUD.[11]

A summary of the most common classes of acute pain medications is described in Table 1 in the Appendix.

4. Benefit Assessment

Substantial evidence of effectiveness for Journavx in adults with moderate to severe acute pain was established using data from two adequate and well-controlled trials. Studies 104 and 105 were two randomized, double-blind, placebo and active-active controlled Phase 3 studies using two different acute pain models (Study 104 used a bunionectomy pain model and Study 105 used an abdominoplasty pain model) to assess the efficacy of Journavx. Both studies evaluated a 100 mg loading dose followed by 50 mg every 12 hours for a 48-hour treatment period. Both studies used hydrocodone bitartrate/acetaminophen (HB/APAP) as the active comparator with a dose regimen of 5 mg/325mg every 6 hours. The primary efficacy endpoint in both studies was time-weighted sum of the pain intensity difference as recorded on the numeric pain rating scale (NPRS) from 0 to 48 hours (SPID48) compared to placebo. In each trial pain intensity was measured using a patient reported 11-point NPRS, ranging from 0 to 10, where zero corresponds to no pain and 10 corresponds to the worst pain imaginable. The key secondary efficacy endpoints in both studies were SPID48 compared to HB/APAP and time to ≥2-point reduction in NPRS from baseline compared to placebo. In each study, males and

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females 18 to 80 years of age were randomized. Study 104 randomized 1075 subjects to 426 subjects in the Journavx arm, 431 subjects in the HB/APAP arm and 216 subjects in the placebo arm. Study 105 randomized 1118 subjects to 447 subjects in the Journavx arm, 448 subjects in the HB/APAP arm and 223 subjects in the placebo arm.

In both studies, Journavx demonstrated a statistically greater reduction in pain than did placebo as measured by the SPID48 with a least squares (LS) mean difference of 29.3 for Study 104 and 48.4 for Study 105. In either study, Journavx did not demonstrate greater pain reduction than did HB/APAP as measured by the SPID48. The clinical reviewer concludes that compared to placebo, there is replicate evidence of efficacy of Journavx 100 mg followed by 50 mg every 12 hours.[e]

For more details, refer to the Efficacy (Evaluation of Benefit) section of the Integrated Review for Journavx.[12]

5. Risk Assessment & Safe-Use Conditions

A total of 18 clinical studies were used for the safety database. The trials that were used to compile the safety database are Phase 3 studies 104 and 105 and an open-label, uncontrolled Phase 3 study 107. Additional data are available from phase 2 studies 101 and 102. Studies 101 and 104 were conducted in patients after bunionectomy, while studies 102 and 105 were conducted in patients after abdominoplasty. Study 107 was an open-label evaluation of Journavx in patients with acute pain resulting from a variety of surgical or non-surgical conditions. Additionally, 13 Phase 1 studies evaluated Journavx in healthy subjects and special populations. A total of 1883 unique subjects received at least 1 dose of Journavx.

There were no deaths in subjects treated with Journavx.

There was no substantial difference in overall incidence of serious adverse events (SAE) experienced by subjects in the Journavx compared to the HB/APAP and placebo arms and there were no substantial differences between the treatment arms for any specific SAE. No SAEs were considered to be related or possibly related to Journavx by the study investigators.[f] Most of the SAEs were known risks with surgical procedures and would not be unexpected considering the surgical acute pain models used in the studies. There was no substantial difference in the incidence of any adverse event (AE) leading to discontinuation between treatment arms. Similarly, the AEs leading to discontinuation are known to be associated with surgical procedures and are not unexpected considering the pain model used in the studies.

There were two SAEs in study 107. A SAE of cellulitis in a subject who underwent a surgical procedure was observed, however, this risk is a known risk associated with surgical procedures. An SAE of suicidal ideation occurred in a subject with situational social stressors that appeared unrelated to study

[e] Section 505-1 (a) of the FD&C Act*: FDAAA factor (C): The expected benefit of the drug with respect to such disease or condition.*

[f] Section 505-1 (a) of the FD&C Act: *FDAAA factor (E): The seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug.*

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treatment. There were no AEs occurring in Journavx treated patients at a frequency higher than placebo by ≥ 1%.

The clinical review team did not identify any major safety concerns and concluded that the demonstrated safety profile of Journavx administered in subjects with moderate to severe acute pain is acceptable for the indicated doses. At the time of this review, the proposed label for Journavx does not contain a Boxed Warning. The proposed labeling will contain risks of interactions with drugs affecting cytochrome P450 (CYP) enzymes, risk of use in patients with severe hepatic impairment, and risk of use in patients with severe renal impairment in the *Warnings and Precaution* section of labeling. These risks are detailed in the subsections below.

5.1. Risks of Interactions with Drugs Affecting CYP enzymes

Journavx and its major metabolite, M6-SUZ, are CYP3A substrates. Journavx is an inducer of CYP3A. Based on the safety database, no serious adverse reactions of Journavx had been identified related to interactions with strong CYP3A inhibitors. However, the labeling will advise healthcare providers who prescribe that strong and moderate CYP3A inhibitors may increase Journavx and M6-SUZ exposures which may cause adverse reactions. The labeling advises healthcare providers that concomitant use of Journavx with strong CYP3A inhibitors is contraindicated and to reduce the Journavx dosage with moderate and strong CYP3A inhibitors. Labeling also communicates that Journavx efficacy and CYP3A substrate efficacy may be reduced with concomitant use with strong and moderate CYP3A inducers.

The labeling advises healthcare providers and patients that using hormonal contraceptives containing progestins other than levonorgestrel and norethindrone should use additional nonhormonal contraceptives or use alternative contraceptives during treatment with Journavx and for 28 days after discontinuation of Journavx.

5.2. Risk of Use in Patients with Severe Hepatic Impairment

Journavx has not been studied in patients with severe hepatic impairment. The effect of severe hepatic impairment on Journavx pharmacokinetics is unknown. Labeling will advise healthcare providers to avoid use of Journavx in severe hepatic impairment.

5.3. Risk of Use in Patients with Severe Renal Impairment

Journavx has not been studied in patients with renal impairment of estimated glomerular filtration rate (eGFR) < 15 mL/min. The effect of renal impairment with eGFR < 15 mL/min on Journavx pharmacokinetics is unknown. Labeling will advise healthcare providers to avoid use of Journavx in severe renal impairment.

6. Expected Postmarket Use

Journavx is proposed as an oral analgesic therapy for patients with acute moderate to severe pain. Acute pain is very common and treated in a wide variety of settings. Additionally, treatment of pain is multimodal, and preference is given to non-opioid therapies. Therefore, Journavx is expected to be used in a wide variety of inpatient and outpatient settings.

7. Risk Management Activities Proposed by the Applicant

The Applicant did not propose any risk management activities for Journavx beyond routine pharmacovigilance and labeling.

7.1. Other Proposed Risk Management Activities

The following postmarketing requirements (PMR) will be issued at the time of approval.

The Applicant will:

A. Conduct randomized, controlled trials evaluating the pharmacokinetic, safety, tolerability, and efficacy profiles of Journavx in pediatric patients with moderate to severe acute pain
    - aged 12 to less than 17 years
    - aged 6 to less than 12 years
    - from birth to less than 1 year
B. Conduct juvenile animal studies in the rodent model to characterize the impact of Journavx on the developing brain to support clinical studies in pediatric patients from
    - birth to less than 3 years of age
    - 3 to less than 12 years of age
C. Conduct a pregnancy exposure registry study, complementary pregnancy study, and lactation study

Reviewer's Comments: *We note that these other activities proposed by the applicant are outside of the scope of the REMS program and defer to Division of Epidemiology for review and input.*

8. Discussion of Need for a REMS

The Clinical Reviewer recommends approval of Journavx on the basis of the efficacy and safety information currently available.

There were no serious risks associated with Journavx identified by the clinical review team that rise to the level of a Boxed Warning. Draft labeling currently includes concomitant use of Journavx with strong CYP3A inhibitors as a contraindication. The risks of interactions with drugs affecting CYP enzymes described in the *Warnings and Precautions* section are risks that are commonly managed by healthcare providers likely to prescribe or dispense Journavx. The risks associated with use in patients with severe hepatic impairment and /or severe renal impairment have not been studied, *Warnings and Precautions* section of labeling will include to avoid use in these patient populations.

Based on the available data, this reviewer is not recommending a REMS for Journavx therapy.

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9. Conclusion & Recommendations

Based on the clinical review, the benefit-risk profile is favorable therefore, a REMS is not necessary for Journavx to ensure the benefits outweigh the risks. At the time of this review, evaluation of safety information and labeling was ongoing. Please notify DRM if new safety information becomes available that changes the benefit-risk profile; this recommendation can be reevaluated.

10. Appendices

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Table 1: Summary of Treatment Options Relevant to Acute Pain[13,14,15]			
Drug	**Suggested Use**	**Summary of Class Risks**	**Risk Evaluation Mitigation Strategy (REMS)**
Acetaminophen	Often preferred first-line therapy in the treatment of mild to moderate pain	hepatotoxicity[16]	No REMS
NSAIDs	Often preferred first-line therapy in some pain-related disease states such as osteoarthritis. Useful for pain associated with inflammation.	Gastrointestinal bleeding and ulceration, renal dysfunction, worsening asthma or bronchospasm, increase risk of bleeding, cardiovascular events	No REMS
Opioids	Often the next step in management of acute pain. Initially give around-the-clock for acute pain. As pain subsides, as needed schedules can be used. Consider the patients risks factors for opioid use disorder or overdose.	Respiratory depression, potential for addiction and abuse, sedation, nausea and vomiting, constipation	Opioid Analgesic (OA) REMS* Dsuvia REMS
Gabapentinoids	Considered first-line medications for the treatment of neuropathic pain. Other roles for gabapentinoids include perioperative pain management	Dizziness, sedation, peripheral edema, weight gain, reduce dose with renal dysfunction, increase risk of suicidal thoughts and behavior	No REMS
Skeletal Muscle Relaxants	Spasm and spasticity Recommended for patients with acute or subacute low back pain	Risks dependent on agent include: respiratory depression, withdrawal syndrome, renal dosing adjustments, hepatic dose adjustments, hepatoxicity, hypotension, physical dependence potential, anticholinergic effects, avoid in older patients	No REMS
Ketamine	As adjuvant in acute pain, in perioperative period in individuals with refractory pain, and in opioid-tolerant patients[17]	Hallucinations, dissociative symptoms, contraindicated in patients with history of psychosis	No REMS

Local anesthetics	Positioned by injection (e.g., joints, epidural or intrathecal space, along nerve roots), used for regional nerve blocks by specialized skillful application	Myocardial depression, hypotension, decreased cardiac output, heart block, bradycardia, arrhythmias, cardiac arrest, CNS-excitation and depression, dizziness, tinnitus, drowsiness, disorientation, muscle twitching, seizures, and respiratory arrest	No REMS
Topical anesthetics	Temporary relief of minor aches and pains of muscles, joints, neuropathic pain, osteoarthritis, strains, sprains, bruises	See local anesthetics; also local pain, infection, bleeding, rash	No REMS
* The OA REMS include extended-release or long-acting, and immediate-release opioid analgesic products intended for use in the outpatient setting			

11. References

[1] Acute Pain | International Association for the Study of Pain. Published January 12, 2023. https://www.iasp-pain.org/resources/topics/acute-pain/

[2] Boezaart AP, Smith CR, Chembrovich S, et al. Visceral versus somatic pain: an educational review of anatomy and clinical implications. Reg Anesth Pain Med. 2021;46(7):629-636. doi:10.1136/rapm-2020-102084

[3] Chou R, Gordon DB, de Leon-Casasola OA, et al. Management of Postoperative Pain: A Clinical Practice Guideline From the American Pain Society, the American Society of Regional Anesthesia and Pain Medicine, and the American Society of Anesthesiologists' Committee on Regional Anesthesia, Executive Committee, and Administrative Council [published correction appears in J Pain. 2016 Apr;17(4):508-10. doi: 10.1016/j.jpain.2016.02.002. Dosage error in article text]. J Pain. 2016;17(2):131-157. doi:10.1016/j.jpain.2015.12.008

[4] Riskowski JL. Associations of socioeconomic position and pain prevalence in the United States: findings from the National Health and Nutrition Examination Survey. Pain Med. 2014;15(9):1508-1521. doi:10.1111/pme.12528

[5] Leung L. From ladder to platform: a new concept for pain management. J Prim Health Care. 2012;4(3):254-258. Published 2012 Sep 1.

[6] Goldberg DS, McGee SJ. Pain as a global public health priority. BMC Public Health. 2011;11:770. Published 2011 Oct 6. doi:10.1186/1471-2458-11-770

[7] King NB, Fraser V. Untreated pain, narcotics regulation, and global health ideologies. PLoS Med. 2013;10(4):e1001411. doi:10.1371/journal.pmed.1001411

[8] FDA's Opioid Analgesic REMS Education Blueprint for Health Care Providers Involved in the Treatment and Monitoring of Patients with Pain | Food and Drug Administration. Published October 31, 2024. https://www.accessdata.fda.gov/drugsatfda_docs/rems/Opioid_Analgesic_2024_10_31_FDA_Blueprint.pdf

[9] 2022 NSDUH Detailed Tables | Substance Abuse and Mental Health Services Administration. Published November 13, 2023. https://www.samhsa.gov/data/report/2022-nsduh-detailed-tables

[10] Drug overdose deaths: Facts and figures | National Institute on Drug Abuse. National Institutes of Health. Published September 30, 2024. https://nida.nih.gov/research-topics/trends-statistics/overdose-death-rates#Fig4

[11] Mitra S, Sinatra RS. Perioperative management of acute pain in the opioid-dependent patient. Anesthesiology. 2004;101(1):212-227. doi:10.1097/00000542-200407000-00032

[12]Integrated Review: NDA 219209 Journavx (suzetrigine) tablets. Review in progress, Accessed January 14, 2025.

[13] Chou R, Gordon DB, de Leon-Casasola OA, et al. Management of Postoperative Pain: A Clinical Practice Guideline From the American Pain Society, the American Society of Regional Anesthesia and Pain Medicine, and the American Society of Anesthesiologists' Committee on Regional Anesthesia, Executive Committee, and Administrative Council [published correction appears in J Pain. 2016 Apr;17(4):508-10. doi: 10.1016/j.jpain.2016.02.002. Dosage error in article text]. J Pain. 2016;17(2):131-157. doi:10.1016/j.jpain.2015.12.008

[14] Herndon CM, Kominek CM, Mullins AM. Pain Management. In: DiPiro JT, Yee GC, Haines ST, Nolin TD, Ellingrod VL, Posey L. eds. *DiPiro's Pharmacotherapy: A Pathophysiologic Approach, 12th Edition*. McGraw Hill; 2023. Accessed December 04, 2024. https://accesspharmacy.mhmedical.com/content.aspx?bookid=3097&sectionid=266106683

[15] Knags RD, Hobbs GJ. Pain. In: Whittlesea C, Hodson K. eds. *Clinical Pharmacy and Therapeutics, 6th Edition*. Elsevier; 2019.

[16] Chou R, Gordon DB, de Leon-Casasola OA, et al. Management of Postoperative Pain: A Clinical Practice Guideline From the American Pain Society, the American Society of Regional Anesthesia and Pain Medicine, and the American Society of Anesthesiologists' Committee on Regional Anesthesia, Executive Committee, and Administrative Council [published correction appears in J Pain. 2016 Apr;17(4):508-10. doi: 10.1016/j.jpain.2016.02.002. Dosage error in article text]. J Pain. 2016;17(2):131-157. doi:10.1016/j.jpain.2015.12.008

[17] Schwenk ES, Viscusi ER, Buvanendran A, et al. Consensus Guidelines on the Use of Intravenous Ketamine Infusions for Acute Pain Management From the American Society of Regional Anesthesia and Pain Medicine, the American Academy of Pain Medicine, and the American Society of Anesthesiologists. Reg Anesth Pain Med. 2018;43(5):456-466. doi:10.1097/AAP.0000000000000806

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