Suzetrigine for Acute Pain

Revised Background and Scope

August 26, 2024

Background

While definitions and estimates of prevalence vary, one consensus working definition of acute pain is "the physiologic response to and experience of noxious stimuli that can become pathologic, is normally sudden in onset, time limited, and motivates behaviors to avoid potential or actual tissue injury." The meaning of "time limited" also varies, and in the prior working definition the following was noted: acute pain typically lasts up to seven days; prolongations up to 30 days are common; prolongations beyond 90 days reflect chronic pain; between 30 and 90 days, pain may be "subacute" but this is not well defined.[1]

Acute pain is ubiquitous though it frequently does not require specific treatment or drug therapy. In medical care settings, pain is particularly common. In a series of surgical patients, only 10% had no pain, while 12% had severe-to-extreme pain at discharge and 54% had moderate-to-severe pain at discharge.[2] Pain is also common in emergency department settings and on inpatient medical services.[3,4]

Particularly in the postoperative setting, many patients are treated with opioid analgesics.[5] Opioids can have important side effects including sedation, confusion, falls, and constipation, but a primary concern with opioid prescriptions for acute pain is the risk of developing persistent opioid use and/or opioid use disorder (OUD).[6] This risk is uncertain and can vary widely, in part based on the definition used and underlying patient and medication risk factors.[7-9] One series of surgical patients found that 3.1% of patients who had not previously used opioids continued to use opioids for more than 90 days after major elective surgery.[10]

Given concerns about opioids, safer analgesic medications could be beneficial. Generally, however, nearly all other systemic analgesics used for acute pain are either nonsteroidal anti-inflammatory medications (NSAIDs) or acetaminophen, and use of more than one pain medication to allow for greater analgesia with fewer side effects is typically recommended.[5] Suzetrigine (VX-548; Vertex

Pharmaceuticals) is an oral small-molecule inhibitor of the voltage-gated sodium channel $Na_v1.8$ that has been studied for the treatment of acute post-surgical pain and represents a new class of analgesic medication.[11] The drug is administered every 12 hours. Suzetrigine is currently undergoing FDA priority review with a target action date of January 30th, 2025.[12]

Stakeholder Input

This revised scoping document was developed with input from diverse stakeholders, including patients, patient groups, clinicians, researchers, and the manufacturer of the agent of focus in this review. This document incorporates feedback gathered during preliminary calls with stakeholders and open input submissions from the public.

Stakeholders emphasized the need for safer medications to treat moderate-to-severe acute pain while preserving access to opioids for those who require them. The efficacy of pain medications can vary based on the type of pain, such as bony versus soft-tissue injuries. New analgesics may enhance the efficacy of multimodal strategies in reducing opioid use while effectively managing acute pain. However, some patients are likely to continue to need opioid analgesics, and the development of OUD remains a concern. Efforts have been made to predict the risk of OUD for an individual, considering factors such as opioid type, dosing, patient education, and follow-up. Even in patients at low risk for OUD, there may be preference for pain medications that avoid this risk. We spoke with one patient with recent acute pain who, despite receiving good pain relief with opioids after various surgeries, and despite having no side effects from opioids or difficulties with discontinuation, would have preferred a medication with no addiction risk even if it were somewhat less effective for pain control.

When evaluating pain medications, stakeholders felt that important considerations include functional improvement, patient satisfaction, organ system effects, and long-term risks. Further research is needed to optimize acute pain management protocols, especially in diverse clinical settings and patient populations.

ICER looks forward to continued engagement with stakeholders throughout its review and encourages comments to refine our understanding of the clinical effectiveness and value of preventive treatments.

Report Aim

This project will evaluate the health and economic outcomes of suzetrigine for acute pain. The ICER value framework includes both quantitative and qualitative comparisons across treatments to ensure that the full range of benefits and harms – including those not typically captured in the clinical evidence such as innovation, public health effects, reduction in disparities, and unmet medical needs – are considered in the judgments about the clinical and economic value of the interventions.

Scope of Clinical Evidence Review

The scope for this assessment is described on the following pages using the PICOTS (Population, Intervention, Comparators, Outcomes, Timing, and Settings) framework. Evidence will be abstracted from randomized controlled trials as well as high-quality systematic reviews; high-quality comparative cohort studies will be considered, particularly for long-term outcomes and uncommon adverse events. Our evidence review will include input from patients and patient advocacy organizations, data from regulatory documents, information submitted by manufacturers, and other grey literature when the evidence meets ICER standards (for more information, see ICER's grey literature policy).

All relevant evidence will be synthesized qualitatively or quantitatively. Wherever possible, we will seek out head-to-head studies of the interventions and comparators of interest. Data permitting, we will also consider combined use of direct and indirect evidence in network meta-analyses of selected outcomes. Full details regarding the literature search, screening strategy, data extraction, and evidence synthesis will be provided after the revised scope in a research protocol published on the Open Science Framework website (https://osf.io/7awvd/).

Populations

The population of focus for the review is adult patients with acute pain that is not adequately controlled with non-systemic therapies (e.g. heat therapy, local anesthetic).

Interventions

The full list of interventions is as follows:

- Suzetrigine in addition to non-systemic therapies, if any

Comparators

We intend to compare the intervention to:

- No systemic therapy for pain
- Non-opioid analgesics including NSAIDs, acetaminophen, and the combination of NSAIDs and acetaminophen
- Opioid analgesics alone or in combination with acetaminophen

Outcomes

A 2023 consensus core outcome set for acute pain recommended outcomes of pain (including pain intensity and pain interference with the patient's life), physical function, and quality of life.[13]

These and other outcomes of interest are described in the list below.

- Patient-Important Outcomes
    - Pain control
    - Pain interference in daily life (including activities of daily living)
    - Time to clinically important reduction in pain
    - Time until pain medication is no longer needed
    - Quality of life
    - Physical functioning
    - Short-term adverse events, including:
        - Undesired sedation
        - Gastrointestinal side effects including nausea, abdominal pain, constipation
        - Headache
        - Confusion
        - Clinically-important renal dysfunction
        - Gastrointestinal bleeding
    - Long-term adverse events, including:
        - Chronic pain
        - Need for chronic pain medication
        - Opioid use disorder and/or opioid misuse
- Other Outcomes
    - Adverse events including:
        - Laboratory evidence of renal dysfunction

Timing

Evidence on intervention effectiveness and harms will be derived from studies of any duration.

Settings

All relevant settings will be considered, with a focus on settings where concerns around acute pain are likely to arise, including post-surgical, medical inpatient, emergency department, urgent care, and primary care settings in the United States.

Benefits Beyond Health and Special Ethical Priorities

Our reviews seek to provide information on benefits beyond health and special ethical priorities offered by the intervention to the individual patient, caregivers, the delivery system, other patients, or the public that would not have been considered as part of the evidence on comparative clinical effectiveness. These general elements (i.e., not specific to a given disease) are listed in the table below.

Table 1.1. Benefits Beyond Health and Special Ethical Priorities

Benefits Beyond Health and Special Ethical Priorities*
There is substantial unmet need despite currently available treatments.
This condition is of substantial relevance for people from a racial/ethnic group that have not been equitably served by the health care system.
The treatment is likely to produce substantial improvement in caregivers' quality of life and/or ability to pursue their own education, work, and family life.
The treatment offers a substantial opportunity to improve access to effective treatment by means of its mechanism of action or method of delivery.

* Benefits beyond health and special ethical priorities shape to some extent how the value of any effective treatments for a particular condition will be judged and are meant to reflect the broader effects of a specific treatment on patients, caregivers, and society. For additional information, please see the ICER Value Assessment Framework.

ICER encourages stakeholders to provide input on these elements in their public comment submissions.

Scope of Comparative Value Analyses

A detailed economic model analysis plan with proposed methodology, model structure, model parameters, model inputs, and model assumptions will be published on October 22, 2024. This scoping document provides early thoughts about the overall model structure.

As a complement to the evidence review, we will develop an economic model to assess the lifetime cost-effectiveness of suzetrigine compared to relevant comparator treatments. The model structure

will be based in part on a literature review of prior published models of acute postoperative moderate-to-severe pain.[14-19] Analyses will be conducted from the health care system perspective and a modified societal perspective. The base case analysis will take a health care system perspective (i.e., focus on direct medical care costs only). Societal impacts from both the beneficial effects and adverse events of treatment (e.g., patient and caregiver productivity, interactions with the criminal justice system) and other indirect costs will be considered in a separate modified societal perspective analysis. This analysis will be considered as a co-base case when (a) direct data on indirect costs are available, (b) the societal costs of care are large relative to direct health care costs, and (c) the impact of treatment on these costs is substantial. This will most often occur in cases where the incremental cost-effectiveness ratio changes by greater than 20%, by more than $200,000 per evLY gained (evLYG) and/or when the result crosses the threshold of $100,000-$150,000 per evLYG. If direct data are lacking on patient and/or caregiver productivity, we will implement a method to capture the potential impacts of suzetrigine on productivity (patient and caregiver) as well as certain other impacts (e.g., patient time in treatment).

The target population will consist of adult patients with acute pain that is not adequately controlled with non-systemic therapies. Data permitting, the model will consist of health states including postoperative pain levels, short-term adverse events (e.g., undesired sedation, headache, confusion, gastrointestinal side effects, and renal dysfunction) and long-term adverse events (e.g., chronic pain, incident opioid use disorder, and/or opioid misuse).[20] A cohort of patients will transition between states during predetermined cycles over a lifetime time horizon, modeling patients from treatment initiation until death. We will consider a short-term decision tree model to estimate immediate acute pain outcomes including quality of life and costs followed by a long-term model to capture any potential lifetime outcomes. In addition, cost-effectiveness will be estimated for shorter time horizons in scenario analyses.

Key model inputs will include clinical probabilities, quality of life values, and health care costs. Probabilities, costs, and other inputs will differ to reflect varying effectiveness between interventions. Treatment effectiveness will be estimated using evidence from Phase II and Phase III trials and network meta-analyses where appropriate.

Health outcomes and costs will be dependent on time spent in each health state, clinical events, adverse events (AEs), and direct medical costs. The health outcome of each intervention will be evaluated in terms of the immediate quality of life changes from acute pain, life-years gained, quality-adjusted life years (QALYs) gained, and equal value of life years gained (evLYG). Quality of life weights will be applied to each health state, including quality of life decrements for serious adverse events. The model will include direct medical costs, including but not limited to costs related to drug administration, drug monitoring, condition-related care, and serious adverse events. In addition, patient and caregiver productivity changes and other indirect costs will be included in a separate analysis, as available data allow. In particular, patient and caregiver productivity changes

and other societal costs related to opioid use disorder and/or opioid misuse will be included, data permitting. Relevant pairwise comparisons will be made between treatments, and results will be expressed in terms of the marginal cost per QALY gained, cost per evLY gained, cost per life-year gained, and cost per postoperative pain days averted or a similar measure. Costs and outcomes will be discounted at 3% per year.

In separate analyses, we will explore the potential health care system budgetary impact of suzetrigine treatment over a five-year time horizon, utilizing published or otherwise publicly-available information on the potential population eligible for treatment and results from the economic model for treatment costs and cost offsets. This budgetary impact analysis will indicate the relation between treatment prices and level of use for a given potential budget impact, and will allow assessment of any need for managing the cost of such interventions. More information on ICER's methods for estimating potential budget impact can be found here.

Identification of Low-Value Services

ICER includes in its reports information on wasteful or lower-value services in the same clinical area that could be reduced or eliminated to create additional resources in health care budgets for higher-value innovative services (for more information, see ICER's Value Assessment Framework). These services are ones that would not be directly affected by suzetrigine (e.g., need for treatment of opioid overdose), as these services will be captured in the economic model. Rather, we are seeking services used in the current management of acute pain beyond the potential offsets that arise from a new intervention. ICER encourages all stakeholders to suggest services (including treatments and mechanisms of care) that could be reduced, eliminated, or made more efficient.

References

1. Kent ML, Tighe PJ, Belfer I, et al. The ACTTION-APS-AAPM Pain Taxonomy (AAAPT) Multidimensional Approach to Classifying Acute Pain Conditions. *Pain Med*. May 1 2017;18(5):947-958. doi:10.1093/pm/pnx019
2. Buvanendran A, Fiala J, Patel KA, Golden AD, Moric M, Kroin JS. The Incidence and Severity of Postoperative Pain following Inpatient Surgery. *Pain Med*. Dec 2015;16(12):2277-83. doi:10.1111/pme.12751
3. Cordell WH, Keene KK, Giles BK, Jones JB, Jones JH, Brizendine EJ. The high prevalence of pain in emergency medical care. *Am J Emerg Med*. May 2002;20(3):165-9. doi:10.1053/ajem.2002.32643
4. Dix P, Sandhar B, Murdoch J, MacIntyre PA. Pain on medical wards in a district general hospital. *Br J Anaesth*. Feb 2004;92(2):235-7. doi:10.1093/bja/aeh052
5. Tighe P, Buckenmaier CC, 3rd, Boezaart AP, et al. Acute Pain Medicine in the United States: A Status Report. *Pain Med*. Sep 2015;16(9):1806-26. doi:10.1111/pme.12760
6. Benyamin R, Trescot AM, Datta S, et al. Opioid complications and side effects. *Pain Physician*. Mar 2008;11(2 Suppl):S105-20.
7. Jivraj NK, Raghavji F, Bethell J, et al. Persistent Postoperative Opioid Use: A Systematic Literature Search of Definitions and Population-based Cohort Study. *Anesthesiology*. Jun 2020;132(6):1528-1539. doi:10.1097/aln.0000000000003265
8. Hamilton GM, Ladha K, Wheeler K, Nguyen F, McCartney CJL, McIsaac DI. Incidence of persistent postoperative opioid use in patients undergoing ambulatory surgery: a retrospective cohort study. *Anaesthesia*. Feb 2023;78(2):170-179. doi:10.1111/anae.15900
9. Deyo RA, Hallvik SE, Hildebran C, et al. Association Between Initial Opioid Prescribing Patterns and Subsequent Long-Term Use Among Opioid-Naïve Patients: A Statewide Retrospective Cohort Study. *J Gen Intern Med*. Jan 2017;32(1):21-27. doi:10.1007/s11606-016-3810-3
10. Clarke H, Soneji N, Ko DT, Yun L, Wijeysundera DN. Rates and risk factors for prolonged opioid use after major surgery: population based cohort study. *BMJ (Clinical research ed)*. Feb 11 2014;348:g1251. doi:10.1136/bmj.g1251
11. Jones J, Correll DJ, Lechner SM, et al. Selective Inhibition of Na(V)1.8 with VX-548 for Acute Pain. *The New England journal of medicine*. Aug 3 2023;389(5):393-405. doi:10.1056/NEJMoa2209870
12. Vertex Announces FDA Acceptance of New Drug Application for Suzetrigine for the Treatment of Moderate-to-Severe Acute Pain. 2024. https://investors.vrtx.com/news-releases/news-release-details/vertex-announces-fda-acceptance-new-drug-application-suzetrigine
13. Bova G, Domenichiello A, Letzen JE, et al. Developing consensus on core outcome sets of domains for acute, the transition from acute to chronic, recurrent/episodic, and chronic pain: results of the INTEGRATE-pain Delphi process. *EClinicalMedicine*. Dec 2023;66:102340. doi:10.1016/j.eclinm.2023.102340
14. Carter JA, Black LK, Deering KL, Jahr JS. Budget Impact and Cost-Effectiveness of Intravenous Meloxicam to Treat Moderate-Severe Postoperative Pain. *Adv Ther*. Aug 2022;39(8):3524-3538. doi:10.1007/s12325-022-02174-6
15. Kwong WJ, Ozer-Stillman I, Miller JD, Haber NA, Russell MW, Kavanagh S. Cost-effectiveness analysis of tapentadol immediate release for the treatment of acute pain. *Clin Ther*. Sep 2010;32(10):1768-81. doi:10.1016/j.clinthera.2010.09.011
16. Seagle BL, Miller ES, Strohl AE, Hoekstra A, Shahabi S. Transversus abdominis plane block with liposomal bupivacaine compared to oral opioids alone for acute postoperative pain after

laparoscopic hysterectomy for early endometrial cancer: a cost-effectiveness analysis. *Gynecol Oncol Res Pract*. 2017;4:12. doi:10.1186/s40661-017-0048-7
17. Simpson KN, Fossler MJ, Wase L, Demitrack MA. Cost-effectiveness and cost-benefit analysis of oliceridine in the treatment of acute pain. *J Comp Eff Res*. Oct 2021;10(15):1107-1119. doi:10.2217/cer-2021-0107
18. Wang X, Penm J, Patanwala AE. Cost-effectiveness of tapentadol immediate release versus oxycodone immediate release for acute post-operative pain after major hip surgeries. *Curr Med Res Opin*. Jan 2022;38(1):115-121. doi:10.1080/03007995.2021.1993161
19. Xie H, Chen SH, Li L, Ge WH. The cost-effectiveness analysis of analgesic treatment options for postoperative pain following laparotomy surgeries. *Int J Clin Pharm*. Apr 2023;45(2):355-363. doi:10.1007/s11096-022-01473-w
20. Fairley M, Humphreys K, Joyce VR, et al. Cost-effectiveness of Treatments for Opioid Use Disorder. *JAMA Psychiatry*. Jul 1 2021;78(7):767-777. doi:10.1001/jamapsychiatry.2021.0247