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Dear ICER Review Team,

Vertex Pharmaceuticals Incorporated appreciates the opportunity to respond to the Draft Scoping Document for the ICER evaluation of suzetrigine, its investigational, oral, selective $Na_V1.8$ pain signal inhibitor for the treatment of moderate-to-severe acute pain.

There remains a high unmet need in the treatment of acute pain due to limitations of currently available therapies. The current treatment of acute pain generally consists of NSAIDs and acetaminophen, which have limited efficacy in moderate-to-severe pain, and opioids, which are effective for moderate-to-severe pain, but have tolerability concerns and carry risk of addiction. Specifically, opioids stimulate the reward pathway in the brain which can lead to misuse, addiction and opioid use disorder (OUD).[1]

The current treatment landscape for acute pain has led to the following important consequences: (1) inadequately managed acute pain, which can have a significant negative impact on patient quality of life including sleep interruption, depression, immobility, and inability to work as well as an increased risk of developing chronic pain; (2) tolerability challenges including opioid-related adverse events (ORADEs) that lead to increased morbidity and are associated with high healthcare costs; and (3) the opioid epidemic, which continues to plague the United States, with the prevalence of OUD estimated to be over 7 million people.[2, 3] Nearly 80,000 people die each year from an opioid-related overdose, and the epidemic costs the U.S. economy upwards of $160 billion per year of which $60 billion is attributed to healthcare costs.[3-5]

Racial and ethnic inequities in acute pain management, including barriers to opioid access, which lead to the undertreatment of pain in certain populations are another important area to consider in this review.[6-8] Treatments that could improve the pain management of historically underserved populations and reduce the burden of the opioid epidemic which disproportionately affects Black/African Americans are important for improving patient care and reducing health disparities.[9]

Suzetrigine is an investigational, oral, non-opioid pain signal inhibitor highly selective for $Na_V1.8$ that has the potential to provide a transformative treatment option for millions of adult patients suffering from moderate-to-severe acute pain. Suzetrigine has shown a compelling combination of efficacy and safety in its Phase 3 pivotal program. Since $Na_V1.8$ is selectively expressed in the peripheral sensory nerves and there is no $Na_V1.8$ expression in the human brain, selective inhibitors of $Na_V1.8$ channels do not have abuse or addictive potential due to this mechanism of action.[10-13] Suzetrigine has the potential to provide an important new treatment option to improve the management of moderate-to-severe acute pain, and has the potential to reduce the utilization of oral opioids.

We provide the following recommendations and clarifications to the ICER Draft Scoping Document for the review of suzetrigine for moderate-to-severe acute pain:

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Comment 1: Clarification on the population and comparators. Suzetrigine is seeking a broad label indication for adults with moderate-to-severe acute pain, based on the results from its Phase 3 program which included two randomized, double-blind, placebo-controlled, pivotal trials, one following abdominoplasty surgery and one following bunionectomy surgery, as well as a single arm safety and effectiveness study which enrolled patients with a broad range of surgical and non-surgical pain conditions.

For moderate-to-severe acute pain, opioids are the only indicated oral treatment approved despite their risks, including long-term addictive potential. While NSAIDs and acetaminophen are effective in treating mild-to-moderate pain, they have limited efficacy in treating moderate-to-severe acute pain and have an increased risk of serious cardiovascular and gastrointestinal events and renal and hepatic toxicity. Suzetrigine is looking to potentially fill the unmet need in the current moderate-to-severe acute pain treatment landscape between non-opioid analgesics (NSAIDs, acetaminophen) and oral opioids, thereby potentially reducing opioid utilization. Importantly, suzetrigine will not replace IV opioids (e.g., morphine) or impact use of opioids for those who require them.

In addition, it is unrealistic to assume that patients with moderate-to-severe acute pain will receive no systemic therapy and this should, therefore, not be included as a comparator. Treatment guidelines recommend multimodal analgesia which can include a combination of opioids and non-opioid analgesics.[14, 15] Placebo arms are included in clinical trials for pain and in the suzetrigine clinical studies, as they are important for mitigating any placebo effect which can play a role in pain trials. However, NSAIDs, acetaminophen, and opioids are commonly used as rescue medications in acute pain studies; therefore, in most cases, the placebo arm is not representative of patients not using any systemic therapy. For these reasons, oral opioids are the primary comparator of interest for suzetrigine in moderate-to-severe acute pain.

Comment 2: Limitation of an indirect treatment comparison (ITC) in pain. Analgesic trials are prone to variable placebo effects making the inclusion of a placebo arm in the trial critical for the interpretation of results, but significantly limiting the ability to use them to perform an appropriate ITC across trials.[16, 17] Further, the rescue medication used varies across analgesic trials, and pain trials are conducted in varying surgical and non-surgical patient populations and settings. Given these important factors, conducting an indirect treatment comparison (ITC) has severe limitations. The suzetrigine phase 3 trials include the most commonly prescribed oral opioid (and dosage), making an ITC unnecessary.

Comment 3: Recommendation to include opioid-related adverse events (ORADEs). ICER has acknowledged the long-term risks of opioids – persistent opioid use, OUD, and opioid misuse, however shorter-term consequences are also important. ORADEs are a common short-term complication associated with the use of opioids and have been associated with worse patient outcomes.[18-20] Patients with ORADEs in the hospital setting experience higher rates of inpatient mortality and 30-day readmission, prolonged length of stay, and increased cost of hospitalization.[18] Nausea and vomiting are common ORADEs and are significant factors in complications such as pulmonary aspiration, dehydration, and electrolyte imbalance.[21] Patients prescribed opioids who

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have nausea or vomiting claims had significantly more hospitalizations, emergency department visits, and physician office visits, amounting to 2.7 times higher adjusted 30-day healthcare costs relative to patients prescribed opioids who did not have nausea or vomiting claims.[19] Inclusion of these known side-effects of opioids is important for the economic evaluation of any therapy with the potential to reduce the use of opioids.

Comment 4: Recommendation to use a societal perspective as the base-case in the cost-effectiveness analysis. The U.S. opioid epidemic was triggered by overprescription of opioids, and prescription opioids continue to add to the crisis.[22] Numerous studies have quantified the risk of opioid misuse and opioid use disorder due to prescription opioids for the management of acute pain, as well as the increased risk of illicit drug use.[23-26] The incidence of persistent opioid use after major/minor surgery among opioid naïve patients has been reported to be 5.9%-6.5%, and nearly 85,000 acute pain patients are newly diagnosed with OUD each year.[23, 24]

The economic burden of the opioid epidemic in the United States in 2018 was estimated by the Society of Actuaries to be approximately $160 billion, of which approximately 38% ($60 billion) was attributed to healthcare costs.[5] The remaining 62% ($100 billion) were costs associated with mortality (lost lifetime earnings), criminal justice, child and family assistance, education, and lost productivity, highlighting the societal burden of the opioid epidemic. Other studies have estimated the economic toll of the opioid crisis to be over a trillion dollars.[27, 28]

Given the substantial societal burden relative to direct healthcare costs of opioids, ICER should use a societal perspective as the base-case analysis, incorporating not only patient and caregiver productivity losses but also costs associated with lost lifetime earnings due to mortality, criminal justice, child and family assistance, and education. Because suzetrigine seeks to reduce the utilization of opioids, an analysis that does not consider the societal impact of opioids will not capture the full value of suzetrigine.

Comment 5: Clarification on inclusion of short-term and long-term cost-offsets in the budget impact analysis. The use of opioids is associated with negative consequences to patient health, which are associated with significant short-term and long-term healthcare costs. Therefore, it is essential for ICER to consider cost offsets achieved from reducing opioid use in the short term, including safety and tolerability concerns (ORADEs), as well as opioid misuse/ OUD over the long term in the budget impact analysis

Sincerely,

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