# Zavegepant (ZAVZPRET)
# National Drug Monograph
# August 2023

**VA Pharmacy Benefits Management Services, Medical Advisory Panel, and VISN Pharmacist Executives**

*The purpose of VA PBM Services drug monographs is to provide a focused drug review for making formulary decisions. Updates will be made if new clinical data warrant additional formulary discussion. The Product Information or other resources should be consulted for detailed and most current drug information.*

## FDA Approval Information

### Description/Mechanism of Action

- Zavegepant is a calcitonin gene-related peptide (CGRP) receptor antagonist or "gepant"

### Indication(s) Under Review in This Document

- Acute treatment of migraine with or without aura

### Dosage Form(s) Under Review

- Nasal Spray: 10mg/actuation

## Clinical Evidence Summary

### Pharmacokinetic Considerations

Zavegepant is the first gepant to be in an intranasal spray formulation. Phase 1 pharmacokinetic studies demonstrated the median time to maximum concentration (Tmax) with zavegepant 10 mg nasal spray was about 0.54 hours.[1] With both ubrogepant's and rimegepant's Tmax being about 1.5 hours[2,3], zavegepant has a faster onset than both oral gepants on the market at this time.

### Efficacy Considerations

**Phase 2/3 trial**

This was a double-blind, dose-ranging trial where patients were 1:1:1:1 randomized to zavegepant 5 mg, zavegepant 10 mg, zavegepant 20 mg, or placebo.[4] Participants could continue their current prophylaxis therapy so long as they were on a therapeutic dose for at least 3 months prior to screening and the dose was not expected to change. However, CGRP monoclonal antibody prophylaxis was not permitted and needed to be discontinued 6 months prior to screening. Only 13.6% of participants were on prophylaxis therapy at randomization, however this is likely due to the inclusion criteria that limited participation to people with episodic migraine only. Patients also could not use other nasal spray medications during the study. See table 1 for additional key inclusion and exclusion criteria. Participants could have cardiovascular (CV) risk factors like diabetes, treatment with a statin or hypertension, current smoker, or family history of coronary artery disease (CAD). Incidence of each

individual risk factor was described; however, incidence of multiple risks or identification of cumulative CV risk was not described.

The co-primary endpoints were pain freedom and freedom from the most bothersome symptom (MBS) at 2 hours post dose. Zavegepant 10 mg and 20 mg were significant for both primary endpoints. The 5 mg dose was not significant for either primary endpoint. Due to the hierarchical testing of secondary endpoints and the lack of statistical significance of the first secondary endpoint, zavegepant was not statistically superior to placebo in any of the secondary endpoints including early-onset efficacy outcomes like pain relief at 30 and 60 minutes. This lack of early-onset efficacy is contradictory to the rationale to utilize an intranasal medication with a faster Tmax than oral tablets. See Table 1 for additional data on results.

**Phase 3 trial**

From the phase 2/3 trial it was determined that zavegepant 10 mg was the optimal dose to balance risks and efficacy. Therefore, the phase 3 trial was a double-blind, randomized trial of zavegepant 10 mg nasal spray versus placebo.[5] The acute treatment phase of this study lasted up to 45 days. Inclusion and exclusion criteria were very similar to the phase 2/3 trial, see table 1 for key inclusion and exclusion criteria. This trial also prohibited the utilization of a CGRP monoclonal antibody or gepant for prophylaxis.

The co-primary endpoints were pain freedom and freedom from the most bothersome symptom (MBS) at 2 hours post dose. Zavegepant 10 mg was significant for both primary endpoints. Zavegepant was also significant for the first 13 secondary endpoints. Of note, the phase 3 study reordered the secondary endpoints compared to the phase 2/3 study "by power and clinical relevance." There were also two new secondary endpoints: pain relief at 15 minutes and ability to function normally at 15 minutes. The reordering of sustained effect outcomes prior to more early-onset outcomes seems contradictory to the desired rationale to utilize an intranasal medication over an oral tablet. Nevertheless, zavegepant had significant improvement in pain relief at 15, 30, and 60 minutes; as well as ability to return to normal function at 30 and 60 minutes. See Table 1 for additional data on results.

**Table 1: Efficacy results from clinical trials**

<table>
<tr><th>Study</th><th>Design</th><th>Results</th></tr>
<tr><td>Phase 2/3 trial (Croop et.al.)</td><td>Double-blind, randomized, placebo-controlled<br><u>Key Inclusion criteria:</u><br>- 18 years and older<br>- onset of migraine prior to age 50<br>- untreated migraine lasting 4 to 72 hours<br>- ≥ 2 but ≤ 8 migraines of moderate to severe intensity/month</td><td>Results displayed as percent incidence of outcome<br><br><u>Primary (p values are versus placebo):</u>
<table>
<tr><th></th><th>Zavegepant 5mg<br>N = 387</th><th>Zavegepant 10mg<br>N = 391</th><th>Zavegepant 20mg<br>N = 402</th><th>PBO<br>N = 401</th></tr>
<tr><td>Pain Freedom at 2 hours</td><td>19.6<br>(14.8, 24.5)<br>p = 0.1214</td><td>22.5*<br>(17.5, 27.6)<br>p = 0.0113</td><td>23.1*<br>(18.1, 28.2)<br>p = 0.0055</td><td>15.5<br>(11.1, 19.8)</td></tr>
<tr><td>MBS Freedom at 2 hours</td><td>39<br>(33.1, 45)<br>p = 0.1162</td><td>41.9*<br>(36, 47.9)<br>p = 0.0155</td><td>42.5*<br>(36.6, 48.4)<br>p = 0.0094</td><td>33.7<br>(28, 39.3)</td></tr>
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- < 15 headache days/month
- ability to distinguish migraine from tension or cluster headache

Key Exclusion Criteria:
- basilar or hemiplegic migraine
- significant or unstable medical conditions that might increase AE risk from zavegepant
- concurrent CGRP monoclonal antibody
- other nasal spray medication use

Secondary (p values not shown, no secondary endpoint met statistical significance):

| | Zavegepant 5mg N = 387 | Zavegepant 10mg N = 391 | Zavegepant 20mg N = 402 | PBO N= 401 |
|---|---|---|---|---|
| Pain Relief at 2 hours | 57.9 (51.9, 63.9) | 60.6 (54.7, 66.5) | 61.2 (55.4, 67) | 53.6 (47.7, 59.6) |
| Return to Normal Function at 2 hours | 31.7 (25.8, 37.5) | 34.5 (28.4, 40.5) | 34.7 (28.8, 40.6) | 21.4 (21.8, 32.9) |
| Rescue Medication Use Within 24 hours | 24.9 (19.7, 30.2) | 26 (20.7, 31.4) | 20.2 (15.3, 25) | 27.3 (21.9, 32.6) |
| Photophobia Freedom at 2 hours | 35 (28.8, 41.2) | 35.6 (29.4, 41.8) | 37.9 (31.7, 44) | 30.4 (24.6, 36.3) |
| Phonophobia Freedom at 2 hours | 44.2 (36.9, 51.6) | 44.8 (37.1, 52.5) | 43.3 (36, 50.7) | 34.1 (27.2, 40.9) |
| Pain Relief at 60 minutes | 47 (41, 53.1) | 46 (40, 52.1) | 49.8 (43.8, 55.7) | 41.9 (36, 47.8) |
| Return to Normal Function at 60 minutes | 22.6 (17.3, 27.8) | 18.9 (13.9, 23.9) | 18.8 (14, 23.7) | 17.1 (12.4, 21.8) |
| Pain Relief at 30 minutes | 26.6 (21.2, 32) | 29.9 (24.4, 35.5) | 26.6 (21.3, 31.9) | 24.7 (19.5, 29.8) |
| Return to Normal Function at 30 minutes | 8.8 (5.3, 12.4) | 7.6 (4.2, 11) | 9.9 (6.2, 13.7) | 5.4 (2.6, 8.2) |
| Sustained Pain Relief from 2-24 hours | 43.7 (37.6, 49.7) | 42.5 (36.5, 48.4) | 44.5 (38.6, 50.5) | 35.7 (29.9, 41.4) |
| Sustained Pain Freedom from 2-24 hours | 14.2 (10, 18.5) | 15.1 (10.8, 19.4) | 15.7 (11.3, 20) | 9 (5.6, 12.4) |
| Sustained Pain Relief from 2-48 hours | 40.1 (34.1, 46) | 39.6 (33.7, 45.6) | 38.8 (33, 44.6) | 32.7 (27.1, 38.3) |
| Sustained Pain Freedom from 2-48 hours | 12.9 (8.8, 17) | 13.8 (9.6, 18) | 13.2 (9.1, 17.2) | 7.5 (4.3, 10.6) |
| Nausea Freedom at 2 hours | 53.2 (45.4, 60.9) | 53.9 (46.3, 61.6) | 54.7 (47.4, 62) | 51 (43.3, 58.8) |
| Pain Relapse from 2-48 hours | 31.6 (18.8, 44.3) | 33 (21, 45) | 37.6 (25.6, 49.7) | 50 (34.8, 65.2) |

**Phase 3 trial (Lipton et.al.)**

Double-blind, randomized, placebo-controlled

Key Inclusion criteria:
- 18 years and older
- onset of migraine prior to age 50
- ≥ 2 but ≤ 8 migraines of moderate to severe intensity/month
- < 15 headache days/month
- ability to distinguish migraine from tension or cluster headache

Key Exclusion Criteria:
- significant or unstable medical conditions, electrocardiogram findings, or laboratory findings that

Results displayed as percent incidence of outcome

Primary:

| | Zavegepant 10mg N = 623 | PBO N = 646 |
|---|---|---|
| Pain Freedom at 2 hours | 23.6* (20.3, 26.9) | 14.9 (12.1, 17.6) |
| MBS Freedom at 2 hours | 39.6* (35.8, 43.5) | 31.1 (27.5, 34.7) |

Secondary:

| | Zavegepant 10mg N = 623# | PBO N = 646# |
|---|---|---|
| Pain Relief at 2 hours | 58.7* (54.9, 62.6) | 49.7 (45.8, 53.5) |
| Ability to Function Normally at 2 hours | 35.8* (31.9, 39.7) | 25.6 (22.1, 29.1) |
| Sustained Pain Relief from 2-24 hours | 40.6* (36.8, 44.5) | 33 (29.3, 36.6) |

might increase AE risk from zavegepant
- concurrent CGRP monoclonal antibody
- pregnancy
- history of substance use disorder

| | | |
|---|---|---|
| Sustained Pain Relief from 2-48 hours | 36.1* (32.3, 39.9) | 29.6 (26, 33.1) |
| Sustained Pain Freedom from 2-24 hours | 14.6* (11.8, 17.4) | 9.8 (7.5, 12) |
| Sustained Pain Freedom from 2-48 hours | 12.4* (9.8, 14.9) | 8.7 (6.5, 10.8) |
| Phonophobia Freedom at 2 hours | 41* (36.6, 45.8) | 32.7 (28.2, 37.2) |
| Photophobia Freedom at 2 hours | 37.1* (33.1, 41.1) | 28.5 (24.9, 32.2) |
| Pain Relief at 60 minutes | 43.3* (39.4, 47.2) | 37.3 (33.6, 41) |
| Ability to Function Normally at 60 minutes | 20.2* (16.9, 23.5) | 15.5 (12.6, 18.4) |
| Pain Relief at 30 minutes | 30.5* (26.9, 34.1) | 20.3 (17.2, 23.4) |
| Ability to Function Normally at 30 minutes | 10.5* (8, 13) | 6.1 (4.1, 8) |
| Pain Relief at 15 minutes | 15.9* (13, 18.8) | 8 (6, 10.1) |
| Ability to Function Normally at 15 minutes | 3.3 (1.9, 4.8) | 2 (0.9, 3.2) |
| No Rescue Medication Use Within 24 hours | 70.3 (66.7, 73.9) | 64.2 (60.5, 67.9) |
| Nausea Freedom at 2 hours | 52.4 (47.3, 57.4) | 50.9 (46, 55.7) |
| No Pain Relapse from 2-48 hours | 59.2 (51.2, 67.1) | 64.6 (55, 74.2) |

*Statistically significant versus placebo
# N varied on some secondary outcomes for both zavegepant and placebo groups
PBO: placebo
Additional confidence interval data obtained from clinicaltrial.gov results[6]

## Safety Considerations

**Safety Results from Clinical Trials:**

**Table 2: Safety results from clinical trials**

| Study | Results | Comments |
|---|---|---|
| **Phase 2/3 trial (Croop et.al.)** | Most ADRs appeared to be dose related. For 10 mg (FDA approved) dose:<br><br>**Common (>10% incidence):**<br>Dysgeusia (13.5%)<br><br>**Serious:**<br>1 patient experienced thrombosis (13 days after last administration of zavegepant, determined not attributed by zavegepant)<br><br>**Discontinuations:** there were no discontinuations of participants that received zavegepant<br><br>**Deaths:** none | Nasal discomfort low (1.3%) incidence. |
| **Phase 3 trial (Lipton et.al.)** | **Common (>10% incidence):**<br>Dysgeusia (21%)<br><br>**Serious:** none<br><br>**Discontinuations:** there were no discontinuations of participants that received zavegepant<br><br>**Deaths:** none | Nasal discomfort low (4%) incidence.<br><br>Six patients in the zavegepant group had a "potential drug abuse" adverse event. FDA determined that this safety data did not signal an abuse potential.[1] |

**Safety information from Package Insert:**

- **Boxed warnings:** none
- **Contraindications:** history of hypersensitivity to zavegepant or any of its components
- **Other warnings / precautions**: hypersensitivity including facial swelling and urticaria (occurred in less than 1% of patients in clinical trials)
- **Adverse reactions:** dysgeusia was the most common. Other reported side effects in at least 2% of participants include nausea, nasal discomfort, and vomiting.

## Other Considerations

**Drug-Drug Interactions:**

- Avoid administration of zavegepant with inhibitors or inducers of the organic anion transporting polypeptide 1B3 (OATP1B3) or sodium taurocholate co-transporting polypeptide (NTCP). Examples of these interacting drugs are rifampin, pretomanid, trofinetide, and voclosporin.
- Concurrent intranasal decongestant use may decrease the absorption of zavegepant. If needed, administer intranasal decongestant at least 1 hour after zavegepant administration

**Pregnancy and Lactation:** There is currently no data on developmental risk associated with zavegepant use during pregnancy. No adverse developmental effects were observed in animal studies. There is also currently no data on the presence of zavegepant or its metabolites in human milk, the effects on the infant, or zavegepant's effect on milk production.

**Hepatic Impairment:** Avoid in severe (Child-Pugh Class C) impairment

**Renal Impairment:** Avoid in CrCl less than 30 mL/min

## Other Therapeutic Options

Alternative prescription treatments for acute migraine are listed in table 3 below

**Table 3 Treatment Alternatives**

| Drug | Formulary status | Max doses per migraine / max doses per month | Indications other than acute migraine treatment |
|---|---|---|---|
| **Zavegepant nasal spray**<br><br>CGRP antagonist | TBD | 1 / 8 | None |
| **Rimegepant oral tablet**<br><br>CGRP antagonist | Nonformulary with CFU | 1 / 18 | Episodic migraine prophylaxis |
| **Ubrogepant oral tablet**<br><br>CGRP antagonist | Nonformulary with CFU | 2 / 16 | None |
| **Sumatriptan intranasal spray**<br><br>Serotonin Agonist | Formulary | 2 / 18 | None, though often used off-label for acute cluster headache |
| **Zolmitriptan intranasal spray**<br><br>Serotonin Agonist | Formulary | 2 / 18 | None, though often used off-label for acute cluster headache |
| **Dihydroergotamine nasal solution and nasal spray**<br><br>Ergot (serotonin, noradrenaline, and dopamine agonist) | Nonformulary, CFU for nasal spray | 4 / 24 | None |

## Projected Place in Therapy

- In the United States, it is estimated that 15-18% of women and 6-10% of men experience migraine or severe headache. The diagnosis of migraine occurs in 13% of all Operation Enduring Freedom/Operation Iraqi Freedom combat Veterans less than 60 years old.[8]
- The 2020 ICER report on acute migraine therapies demonstrated that triptans are similarly or more effective than gepants (only data on rimegepant and ubrogepant were available at the time of this metanalysis).[9]
- Zavegepant is the first gepant to be in an intranasal spray formulation. Phase 1 pharmacokinetic studies demonstrated the median time to maximum concentration (Tmax) with zavegepant 10 mg nasal spray was about 0.54 hours.[1] With both ubrogepant's and rimegepant's Tmax being about 1.5 hours[2,3], zavegepant has a faster onset than both oral gepants on the market at this time.
- Zavegepant demonstrated statistically significant improvement in pain freedom and freedom from most bothersome symptom at 2 hours compared to placebo. Results are mixed in the two phase III studies on earlier-onset efficacy outcomes like pain relief at 15, 30, and 60 minutes.
- Zavegepant was not studied head-to-head with any other gepant or other acute migraine treatment. Both other oral gepants for acute migraine treatment, rimegepant and ubrogepant, were also significant versus placebo for pain freedom and freedom from most bothersome symptom at 2 hours.
- Zavegepant may be an alternative for patients on oral gepants for acute migraine treatment that require a non-oral option (e.g., vomiting during migraine, severe nausea that swallowing pills aggravates). Also, in patients on other acute migraine intranasal spray medications like triptans or ergots that experience intolerance or therapeutic failure and require maintaining a non-oral route of administration.
- Unlike intranasal triptans, zavegepant currently has no evidence to support off-label use in acute cluster headache treatment.
- There is a pending trial evaluating the safety and efficacy of an oral formulation of zavegepant for migraine prophylaxis (NCT04804033).

## References


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