Atogepant (Qulipta)
National Drug Monograph
November 2021
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
- Atogepant is a calcitonin gene-related peptide receptor antagonist. CGRP is a neuropeptide that is especially common in trigeminal ganglia but is also widely distributed throughout the central and peripheral nervous systems. It is a potent vasodilator and pain-signaling neurotransmitter. Serum levels of CGRP appear to increase during migraine attacks and IV injection of CGRP has induced migraine-like headaches in patients with a history of migraines.

Indication(s) Under Review in This Document
- Atogepant is indicated for the preventive treatment of episodic migraine in adults.

Dosage Form(s) Under Review
- Atogepant is available as 10, 30, and 60 mg tablets, taken orally once daily with or without food.
- Dosing modifications for drug interactions and for specific populations; with concomitant use of strong CYP3A4 inhibitors (e.g., ketoconazole, itraconazole, clarithromycin) is 10 mg once daily, with concomitant use of strong or moderate CYP3A4 inducers (e.g., rifampin, carbamazepine, phenytoin, St. John’s wort, efavirenz, etravirine) is 30 mg or 60 mg once daily, concomitant use of OATP inhibitors (e.g., cyclosporine) is 10 mg or 30 mg once daily and in severe renal impairment (CrCl 15-29 mL/min), and in patients with end-stage renal disease (ESRD) (CrCl <15 mL/min), the recommended dosage of 10 mg once daily.

Clinical Evidence Summary

Efficacy Considerations
- The efficacy of atogepant was evaluated in two large, randomized, double blinded clinical trials. A primary outcome of monthly migraine days relative to placebo for participants with episodic migraine across 12 weeks of treatment was employed in both trials. In secondary analyses, atogepant was associated with significant reductions in the number of headache days compared with placebo, and a significantly greater proportion of participants had at least a 50% reduction in monthly migraine days compared with the placebo group.
- Efficacy data are summarized in Table 1
### Table 1; Key Clinical Outcomes of Clinical trials of atogepant

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Change from baseline in mean monthly migraine days (MMD)</th>
<th>Proportion of patients with ≥50% reduction in MMD, N(%)</th>
<th>Comments</th>
</tr>
</thead>
</table>
| **Goadsby³**  | double-blind, placebo-controlled, randomized, multicenter, parallel-group, phase 2b/3 study to evaluate the safety, tolerability, and efficacy of atogepant doses during 12 weeks of treatment followed by a 4-week safety follow-up period | 10 mg -4.0  
30 mg -3.8  
60 mg -3.6  
Placebo -2.9 | 10 mg 53(58)*  
30 mg 97(58)*  
60 mg 92(52)* | Excluded History of inadequate response to ≥3 medications prescribed for migraine prevention (including 2 from different classes: |
| **ADVANCE⁴**  | A double-blind, placebo-controlled, randomized, multicenter, parallel-group, phase 3 study to evaluate the safety, tolerability, and efficacy of atogepant doses during 12 weeks of treatment followed by a 4-week safety follow-up period | 10 mg -3.7#  
30 mg -3.9#  
60 mg -4.2#  
Placebo -2.5# | 10 mg 56%#  
30 mg 59%#  
60 mg 61%# | Excluded; History of inadequate response to >4 oral medications prescribed for migraine prevention (including 2 with different mechanisms of action)  
• Used opioids or barbituates >2 days/month, triptans or ergots ≥10 days/month, or simple analgesics (eg, aspirin, NSAIDs, or acetaminophen) ≥15 days/month in the 3 months before visit 1 or during the 28-day screening period |

*P<0.05, **P<0.01 versus placebo, P<0.0001

The efficacy of atogepant (A) for the preventive treatment of episodic migraine in adults was demonstrated in two randomized, multicenter, double-blind, placebo-controlled studies. The studies enrolled patients with at least a 1-year history of migraine with or without aura, according to the International Classification of Headache Disorders (ICHD-3) diagnostic criteria.

Goadsby³, et al evaluated 910 patients who were randomized 1:1:1:1 to receive A10 mg (N = 222), A30 mg (N = 230), A60 mg (N = 235), or placebo (N = 223), once daily for 12 weeks. Patients were allowed to use acute headache treatments (i.e., triptans, ergotamine derivatives, NSAIDs, acetaminophen, and opioids) as needed. The use of a concomitant medication that acts on the CGRP pathway was not permitted for either acute or preventive treatment of migraine. The
studies excluded patients with myocardial infarction, stroke, or transient ischemic attacks within six months prior to screening and those who had a history of inadequate response to ≥3 medications prescribed for migraine prevention (including 2 from different classes). The primary efficacy endpoint was the change from baseline in mean monthly migraine days (MMD) across the 12-week treatment period. Secondary endpoints included the change from baseline in mean monthly headache days, the change from baseline in mean monthly acute medication use days, the proportion of patients achieving at least a 50% reduction from baseline in mean MMD (3-month average), the change from baseline in mean monthly Activity Impairment in Migraine–Diary (AIM-D) Performance of Daily Activities (PDA) domain scores, the change from baseline in mean monthly AIM-D Physical Impairment (PI) domain scores, across the 12-week treatment period, and the change from baseline at Week 12 for Migraine Specific Quality of Life Questionnaire version 2.1 (MSQ v2.1) Role Function-Restrictive (RFR) domain scores. Patients had a mean age of 42 years (range 18 to 73 years), 89% were female, 83% were White, 14% were Black, and 9% were of Hispanic or Latino ethnicity. The mean migraine frequency at baseline was approximately 8 migraine days per month and was similar across treatment groups. A total of 805 (88%) patients completed the 12-week double-blind study period.

Results for the secondary endpoints showed that participants randomly assigned to all atogepant groups also had significantly greater decreases in mean monthly headache days across the 12-week treatment period, all five atogepant groups showed significant least-squares mean (SE) change from baseline in mean monthly migraine days versus placebo: atogepant 10 mg once daily -4.0 (0.3; p=0.024), 30 mg once daily -3.8 (0.2; p=0.039), 60 mg once daily -3.6 (0.2; p=0.039), 30 mg twice daily -4.2 (0.4; p=0.0034), and 60 mg twice daily -4.1 (0.3; p=0.0031); placebo -2.9 (0.2), days across the 12-week treatment period than placebo (least-squares mean difference ranged from -0.9 to -1.4; p=0.039; table 2). The mean change from baseline in monthly headache days ranged from -3.9 to -4.3 days in the atogepant groups compared with -2.9 days in the placebo group, with no apparent dose-related trend in the responses. The proportions of participants with at least a 50% reduction in monthly migraine days across 12 weeks in all atogepant dose groups ranged from 52% (92/177) to 62% (54/87). The proportions of participants with at least a 50% reduction in monthly migraine days across the 12-week treatment period were significantly different from placebo in the atogepant 30 mg twice-daily group (odds ratio [OR] 1.8, 95% CI 1.2 to 2.9; p=0.034) and 60 mg twice-daily group (OR 2.0, 1.3 to 3.2; p=0.0097) but not in the once-daily atogepant groups. Reductions in the number of acute medication use days ranged from -3.5 days to -3.9 days in the atogepant groups compared with placebo group, with no apparent dose-related trend in the responses. The proportions of participants with at least a 50% reduction in monthly migraine days across 12 weeks in all atogepant dose groups ranged from 52% (92/177) to 62% (54/87). The proportions of participants with at least a 50% reduction in monthly migraine days across the 12-week treatment period were significantly different from placebo in the atogepant 30 mg twice-daily group (odds ratio [OR] 1.8, 95% CI 1.2 to 2.9; p=0.034) and 60 mg twice-daily group (OR 2.0, 1.3 to 3.2; p=0.0097) but not in the once-daily atogepant groups. Reductions in the number of acute medication use days ranged from -3.5 days to -3.9 days in the atogepant groups (table 2). The difference from placebo in the reduction of acute medication use days reached significance in the atogepant 30 mg twice-daily group (least-squares mean difference ranged from -0.6 to -1.4 days (95% CI -2.1 to -0.6; p=0.034) and the 60 mg twice-daily group (-1.2 days, -1.9 to -0.5; p=0.0097). In addition, atogepant was effective one day after the initial dose: a significantly lower proportion (p≤0.0071) of atogepant-treated patients (range, 10.8%-14.1%) had a migraine compared to placebo-treated patients (25.2%).

The ADVANCE trial evaluated A in a Phase 3, randomized, double-blind, placebo-controlled study in 910 patients with chronic migraine (≥15 migraine days per month). Patients were randomized to A10 mg, A30 mg, A60 mg and placebo taken once daily. A key exclusion criterion was participants who had an inadequate response to more than four oral medications prescribed for the preventive treatment of migraine, two of which needed to have different mechanisms of action. Patients had a mean age of 40 years (range: 18 to 74 years), 87% were female, 76% were white, 20% were Black, and 15% were of Hispanic or Latino ethnicity. The mean migraine frequency at baseline was approximately 8 migraine days per month. A total of 541 (83%) patients completed the 12-week double-blind study period.

The primary endpoint was the change from baseline in mean monthly migraine days across 12 weeks. The change from baseline in mean monthly migraine days was -4.2 days with atogepant 60 mg, -3.86 days with atogepant 30 mg, -3.69 days with atogepant 10 mg (p < 0.0001 for all atogepant strengths vs placebo) and -2.48 days with placebo. The percentage of patients with ≥50% reduction in mean monthly migraine days at week 12 was 60.8% with atogepant 60 mg, 58.7% with atogepant 30 mg, 55.6% with atogepant 10 mg (p < 0.0001 for all atogepant strengths vs placebo) and 29% with placebo. Secondary endpoints included data from additional health outcome measures were collected. The Activity Impairment in Migraine–Diary (AIM-D) is an 11-item daily diary measure that assesses the effect of migraine on two domains: Performance of Daily Activities (7 items) and Physical Impairment (4 items). Results for the secondary endpoints favored atogepant over placebo with the exceptions of the AIM-D Performance of Daily Activities score and the AIM-D Physical Impairment score for the 10-mg dose.
**Safety Results from Clinical Trials:**

The safety of atogepant was evaluated in 1958 patients with migraine who received at least one dose of atogepant. Of these, 839 patients were exposed to atogepant once daily for at least 6 months, and 487 patients were exposed for 12 months.

In the 12-week, placebo-controlled clinical studies\(^3\)\(^4\) 314 patients received at least one dose of A 10 mg once daily, 411 patients received at least one dose of A 30 mg once daily, 417 patients received at least one dose of A 60 mg once daily, and 408 patients received placebo. Approximately 88% were female, 80% were White, 17% were Black, and 12% were of Hispanic or Latino ethnicity. The mean age at study entry was 41 years (range 18 to 74 years).

The most common adverse reactions (incidence at least 4% and greater than placebo) are nausea, constipation, and fatigue.

The adverse reactions that most commonly led to discontinuation were constipation (0.5%), nausea (0.5%), and fatigue/somnolence (0.5%).

The rate of hepatic transaminase elevations over 3 times the upper limit of normal was similar between patients treated with atogepant (1.0%) and those treated with placebo (1.8%). However, there were cases with transaminase elevations over 3 times the upper limit of normal that were temporally associated with atogepant treatment; these were asymptomatic and resolved within 8 weeks of discontinuation. There were no cases of severe liver injury or jaundice.

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

<table>
<thead>
<tr>
<th></th>
<th>Placebo N=408</th>
<th>A 10 mg N=314</th>
<th>A 30 mg N=411</th>
<th>A 60 mg N=417</th>
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</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>3%</td>
<td>5%</td>
<td>6%</td>
<td>9%</td>
</tr>
<tr>
<td>constipation</td>
<td>1%</td>
<td>6%</td>
<td>6%</td>
<td>6%</td>
</tr>
<tr>
<td>Fatigue/Somnolence</td>
<td>3%</td>
<td>4%</td>
<td>4%</td>
<td>6%</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>&lt;1%</td>
<td>2%</td>
<td>1%</td>
<td>2%</td>
</tr>
</tbody>
</table>

**Safety Considerations**

- **Boxed warnings:** none
- **Contraindications:** none
Other Therapeutic Options
Alternative treatments for headache prevention are listed in Table 3 below

<table>
<thead>
<tr>
<th>Drug</th>
<th>Formulary status</th>
<th>Clinical Guidance</th>
<th>Other Considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atogepant</td>
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<td>Oral</td>
<td></td>
</tr>
<tr>
<td>Rimegepant</td>
<td>NF</td>
<td>CFU</td>
<td>oral</td>
</tr>
<tr>
<td>Erenumab</td>
<td>NF</td>
<td>CFU</td>
<td>National Contract Subcutaneous injection</td>
</tr>
<tr>
<td>Eptinezumab</td>
<td>NF</td>
<td>Intravenous infusion</td>
<td></td>
</tr>
<tr>
<td>Fremanezumab</td>
<td>NF</td>
<td>Subcutaneous injection</td>
<td></td>
</tr>
<tr>
<td>Galcanezumab</td>
<td>NF</td>
<td>CFU</td>
<td>Subcutaneous injection</td>
</tr>
</tbody>
</table>

Projected Place in Therapy

- Atogepant has demonstrated efficacy in two large randomized, controlled clinical trials. It demonstrated superiority over placebo for all three doses trialed (10, 30 and 60 mg).
- The FDA has approved four monoclonal antibodies targeting the CGRP pathway (erenumab, galcanezumab, fremanezumab, and eptinezumab) for the preventive treatment of migraine.
- Although effective, monoclonal antibodies exhibit a long half-life (21–48 days) and require parenteral administration (subcutaneous or intravenous injection). An orally administered CGRP-targeted medication might be preferable for some patients and could alleviate initial apprehension to start CGRP-targeted preventive therapy. Additionally, the shorter half-life compared with monoclonal antibodies might be of benefit to patients who need to reduce therapeutic concentrations more quickly because of an adverse event or life event (eg, pregnancy).
- The role of CGRP in migraine pathophysiology suggests its importance as a target for preventive treatment. Given the preference of some patients for oral medications and the ability to adjust treatments quickly to manage side-effects, oral medications such as atogepant might provide meaningful advantages over the available monoclonal antibodies with regard to convenience and safety.

References

1 Qulipta™ [Package Insert]. AbbVie/ Allergan Pharmaceuticals; 2021
2 Qulipta™ (atogepant) AMCP Formulary Dossier. Prepared by AbbVie Inc, North Chicago, IL ;2021