Drug Monograph

Drug Name: **Qulipta™ (atogepant) tablets**
Drug Class: **Central Nervous System: Calcitonin Gene-Related Peptide (CGRP) Receptors**
Prepared For: MO HealthNet
Prepared By: Conduent

☒ **New Criteria** ☐ **Revision of Existing Criteria**

Executive Summary

Purpose:	The purpose of this monograph is to provide a review of new therapy to determine whether the reviewed drug should be made available on an open access basis to prescribers, require a clinical edit or require prior authorization for use.
Dosage Forms:	Qulipta is available in 10 mg, 30 mg, and 60 mg tablets.
Manufacturer:	Distributed by: Allergan Pharmaceuticals/AbbVie, North Chicago, IL 60064.
Summary of Findings:	Qulipta was approved based on the results of 2 multicenter, randomized, double-blind, placebo-controlled clinicals trials, ADVANCE Study 1 and Study 2. ADVANCE (N=795) evaluated the efficacy and safety of 10 mg, 30 mg, and 60 mg daily doses of Qulipta or placebo. Across the 12-week treatment period, all five Qulipta groups showed significant least-squares mean (SE) change from baseline in mean monthly migraine days (MMDs) versus placebo: Qulipta 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). Additional secondary endpoints included the change from baseline in mean monthly headache days and mean monthly acute medication use days, and the proportion of patients achieving ≥50% reduction from baseline in mean MMDs (3-month average).
Status Recommendation:	☐ Clinical Edit ☐ PA Required ☐ Open Access ☒ PDL
Type of PA Criteria:	☐ Appropriate Indications ☒ Non-Preferred ☐ No PA Required ☐ Preferred

Purpose

The purpose of this monograph is to provide a review of new therapy to determine whether the reviewed drug should be considered a prior authorization drug, a clinical edit drug or an open access drug. While prescription expenditures are increasing at double-digit rates, payers are evaluating ways to control these costs by influencing prescriber behavior and guide appropriate medication usage. This review will assist in the achievement of qualitative and economic goals related to health care resource utilization. Restricting the use of certain medications can reduce costs by requiring documentation of appropriate indications for use, and where appropriate, encourage the use of less expensive agents within a drug class.

Introduction [1,2]

- Migraine is a chronic neurologic disease characterized by attacks of throbbing, often unilateral headache that are exacerbated by physical activity and associated with photophobia, phonophobia, nausea, vomiting, and, in many patients, cutaneous allodynia.
- Migraine has an estimated prevalence of 12% in the U.S. and occurs most commonly between the ages of 25 and 55 years. Family history of migraines is present in 90% of patients.
- Migraines are classified into three types:
  - **Episodic migraine (EM)** is characterized by 0 to 14 headache days per month; represents 90% of migraine sufferers
  - **Chronic migraine (CM)** is characterized by 15 or more headache days per month; represents 10% of those with migraine
  - **Cluster headaches (CH)** are recurrent, severe headaches on one side of the head, typically around the eye. The duration of a typical CH attack ranges from about 15 to 180 minutes. Most untreated attacks (about 75%) last less than 60 minutes, Attacks can occur every day for weeks, or even months, then disappear for up to one year.

Dosage Form [3]

Qulipta is available in 10 mg, 30 mg, and 60 mg tablets.

Manufacturer [3]

Distributed by: Allergan Pharmaceuticals/AbbVie, North Chicago, IL 60064.

Indication(s) [3]

Qulipta is indicated for the preventive treatment of episodic migraine in adults.

Clinical Efficacy [3,4,5] (mechanism of action/pharmacology, comparative efficacy)

Qulipta is a calcitonin gene-related peptide (CGRP) receptor antagonist.

Pharmacokinetics:

Absorption	T_{max}= 1-2 hours
Metabolism	Hepatic (CYP3A4)
Excretion	Fecal (42%); Renal (5%)
Half-life	11 hours

Clinical Trials Experience

STUDY DESIGN (ADVANCE; NCT03777059)	Two randomized, multicenter, double-blind, placebo-controlled studies [Study 1 (N=910), Study 2 (N=652)]
INCLUSION CRITERIA	• 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, 4-14 monthly migraine days (MMDs) • Age of the participant at the time of migraine onset < 50 years
EXCLUSION CRITERIA	• History of migraine accompanied by diplopia or decreased level of consciousness or retinal migraine • Current diagnosis of chronic migraine, new persistent daily headache, CH, or painful cranial neuropathy • Myocardial infarction, stroke, or TIA within 6 months prior to screening • Inadequate response to at least 3 (Study 2) or more than 4 (Study 1) medications prescribed for migraine prevention (including at least 2 from different therapeutic classes) • Study 2 only: o History of malignancy in the prior 5 years, except for adequately treated basal cell of squamous cell skin cancer, or in situ cervical cancer o History of gastric or small intestinal surgery, or has a disease that causes malabsorption o History of hepatitis within previous 6 months o Usage of opioids or barbiturates ≥ 2 days/month, triptans or ergots ≥ 10 days/month, or simple analgesics (e.g., aspirin, NSAIDS, acetaminophen) ≥ 15 days/month in the 3 months prior to Visit 1 o Pregnant or nursing females
TREATMENT REGIMEN	• Randomization: o Study 1- 1:1:1:1 to receive Qulipta 10 mg (N=222), Qulipta 30 mg (N=230), Qulipta 60 mg (N=235) or placebo (N=223) once daily for 12 weeks o Study 2- 1:2:2:2 to receive Qulipta 10 mg (N=94), Qulipta 30 mg (N=185), Qulipta 60 mg (N=187) or placebo (N=186) once daily for 12 weeks • Patients were allowed to use acute headache treatments (i.e., triptans, ergotamine derivatives, NSAIDs, acetaminophen, and opioids) as needed, but the use of a concomitant CGRP medication was not permitted.
RESULTS	• **ADVANCE (Study 1) Results:** • A total of 805 patients completed the 12-week double-blind study period. The modified intent-to-treat (mITT) population included all randomized participants who received at least one dose of the study drug, had evaluable Baseline period of eDiary data, and had at least one evaluable post-baseline 4-week period of eDiary data during the double-blind treatment period. • The primary efficacy endpoint was the change from baseline in MMDs across the 12-week treatment period • Secondary endpoints included: o The change from baseline in mean monthly headache days o The change from baseline in mean monthly acute medication use days o The proportion of patients achieving at least a 50% reduction from baseline in mean MMD (3-month average)

Commented [AA1]: AbbVie does have a long term, open arm safety study in the works. They will only be looking at the 60 mg daily dose compared to "standard of care." The purpose of the study is to contextualize liver safety data collected over 52 weeks. There were 13 cases of postbaseline ALT or AST elevations ≥3 x ULN in the Qulipta group vs. 6 in the standard of care group. A total of 68.4% of all randomized subjects completed the 52-week study. 5.7% of the Qulipta patients discontinued the study due to experiencing an TEAE. Graphic shows that change in # of migraine days and reduction of acute migraine days stays relatively consistent from 16 to 52 weeks.

- 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
- 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 treated with Qulipta had greater mean decreases from baseline in MMD across the 12-week treatment period compared to patients who received placebo.
- The change from baseline in mean monthly acute medication use days achieved statistical significance in all Qulipta treatment groups. Also, Qulipta groups achieved statistically significant improvements in MSQ v2.1 RFR domain scores compared to placebo and the 30 mg and 60 mg groups achieved statistical significance in improvements in AIM-D PDA and PI domain scores.

Efficacy Endpoints in Study 1

	Qulipta 10 mg (N=214)	Qulipta 30 mg (N=223)	Qulipta 60 mg (N=222)	Placebo (N=214)
Monthly Migraine Days (MMD) Across 12 Weeks				
Baseline	7.5	7.9	7.8	7.5
Mean change from baseline	-3.7	-3.9	-4.2	-2.5
Difference from placebo	-1.2	-1.4	-1.7	
p-value	<0.001	<0.001	<0.001	
Monthly Headache Days Across 12 Weeks				
Baseline	8.4	8.8	9.0	8.4
Mean change from baseline	-3.9	-4.0	-4.2	-2.5
Difference from placebo	-1.4	-1.5	-1.7	
p-value	<0.001	<0.001	<0.001	
Monthly Acute Medication Use Days Across 12 Weeks				
Baseline	6.6	6.7	6.9	6.5
Mean change from baseline	-3.7	-3.7	-3.9	-2.4
Difference from placebo	-1.3	-1.3	-1.5	
p-value	<0.001	<0.001	<0.001	
≥ 50% MMD Responders Across 12 Weeks				
% Responders	56	59	61	29
Difference from Placebo	27	30	32	
p-value	<0.001	<0.001	<0.001	
MSQ v2.1 RFR Domain* at Week 12				
Baseline	44.9	44.0	46.8	46.8
Mean change from baseline	30.4	30.5	31.3	20.5
Difference from placebo	9.9	10.1	10.8	
p-value	<0.001	<0.001	<0.001	
AIM-D PDA Domain Across 12 Weeks**				
Baseline	15.5	16.9	15.9	15.2
Mean change from baseline	-7.3	-8.6	-9.4	-6.1
Difference from placebo	-1.2	-2.5	-3.3	
p-value	NS†	<0.001	<0.001	
AIM-D PI Domain* Across 12 Weeks**				
Baseline	11.7	13.0	11.6	11.2
Mean change from baseline	-5.1	-6.0	-6.5	-4.0
Difference from placebo	-1.1	-2.0	-2.5	
p-value	NS†	0.002	<0.001	

Commented [PM2]: Do these numbers differ from the randomization numbers listed previously as some patients we lost before the endpoints? Previously reported Qulipta 10 mg (N=222), Qulipta 30 mg (N=230), Qulipta 60 mg (N=235) and placebo (N=223)

	* Migraine Specific Quality of Life Questionnaire version 2.1 Role Function-Restrictive domain score- scores ranging from 0 to 100; higher scores indicate lesser impact of migraine on daily activities, and increases from baseline indicate improvement ** Activity Impairment in Migraine-Diary Performance of Daily Activities domain score- scores ranging from 0 to 100; higher scores indicate greater impact of migraine, and reductions from baseline indicate improvement *** Activity Impairment in Migraine-Diary Physical Impairment domain score † Not statistically significant **ADVANCE (Study 2) Results:** • A total of 541 patients completed the 12-week double-blind study period. The mITT population included all randomized participants who received at least one dose of the study drug, had evaluable Baseline period of diary data, and had at least one evaluable post-baseline 4-week (Weeks 1-4, 5-8, and 9-12) period of diary data. • The primary efficacy endpoint was the change from baseline in mean monthly migraine days across the 12-week treatment period o There was a significantly greater reduction in mean monthly migraine days across the 12-week treatment period in all three Qulipta treatment groups, compared with placebo. • None of the once-daily Qulipta groups achieved statistically significant results in any of the secondary endpoints.
SAFETY	Discussed in the Adverse Effects section below.

Efficacy Endpoints in Study 2

	Qulipta 10 mg (N=92)	Qulipta 30 mg (N=182)	Qulipta 60 mg (N=177)	Placebo (N=178)
Monthly Migraine Days (MMD) Across 12 Weeks				
Baseline	7.6	7.6	7.7	7.8
Mean change from baseline	-4.0	-3.8	-3.6	-2.8
Difference from placebo	-1.1	-0.9	-0.7	
p-value	0.024	0.039	0.039	
Monthly Headache Days Across 12 Weeks				
Baseline	8.9	8.7	8.9	9.1
Mean change from baseline	-4.3	-4.2	-3.9	-2.9
Difference from placebo	-1.4	-1.2	-0.9	
p-value	0.024	0.039	0.039	

Commented [PM3]: Same comment as above on total numbers vs. randomization (attrition before study completion?)

Contraindications (3,4)

- None

Warnings and Precautions (3,4)

- Based on animal data, may cause fetal harm.
- Avoid use in patients with severe hepatic impairment.

Adverse Effects [3,4]

Most common, ≥ 2%	Placebo (N=408) %	Qulipta 10 mg (N=314) %	Qulipta 30 mg (N=411) %	Qulipta 60 mg (N=417) %
Nausea	3	5	6	9
Constipation	1	6	6	6
Fatigue/Somnolence	3	4	4	6
Decreased Appetite	<1	2	1	2

Drug Interactions [3,4]

- CYP3A4 Inhibitors: The recommended dosage of Qulipta with concomitant use of strong CYP3A4 inhibitors (e.g., ketoconazole, itraconazole, clarithromycin) is 10 mg once daily.
- CYP3A4 Inducers: The recommended dosage of Qulipta 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. No dosage adjustment of Qulipta is needed with concomitant use of weak CYP3A4 inducers.
- OATP Inhibitors: The recommended dosage of Qulipta with concomitant use of OATP inhibitors (e.g., cyclosporine) is 10 mg or 30 mg once daily.

Dosage and Administration [3,4]

The recommended dosage of Qulipta is 10 mg, 30 mg, or 60 mg taken orally once daily with or without food.

Dosage Modifications for Drug Interactions and for Specific Populations

Dosage Modifications	Recommended Once Daily Dosage
Concomitant Drug	
Strong CYP3A4 Inhibitors	10 mg
Strong and Moderate CYP3A4 Inducers	30 mg or 60 mg
OATP Inhibitors	10 mg or 30 mg
Renal Impairment	
Severe Renal Impairment and End-Stage Renal Disease (CrCl <30 mL/min)	10 mg

Cost

Generic Name	Brand Name	Manufacturer	Dose	Cost**
Atogepant	Qulipta™	Allergan/AbbVie	10 mg, 30 mg, or 60 mg orally once daily	$990.90 per month
Eptinezumab-jjmr	Vyepti®	Lundbeck Pharmaceuticals	100 mg IV every 3 months	$1,495 per 100 mg
Erenumab-aooe	Aimovig®	Amgen, Inc.	70 mg SC once monthly	$603.18 per month
Fremanezumab-vfrm	Ajovy®	Teva Pharmaceuticals	225 mg SC monthly or 675 mg every 3 months	$603.20 per month
Galcanezumab-gnlm	Emgality®	Eli Lilly and Co.	240 mg SC loading dose, followed by monthly doses of 120 mg	$603.60 per month
Rimegepant	Nurtec® ODT	Biohaven	75 mg orally every other day	$2,008.08 per 18 tablets

** Wholesale Acquisition Cost

Conclusion

Qulipta will compete with other medications for the prevention of migraine, such as the other oral CGRP antagonist, Nurtec® ODT, which originally was approved for acute treatment of migraine. Other preventive medications recommended by American Academy of Neurology (AAN) and American Headache Society (AHS) include the antiepileptic drugs (divalproex sodium, sodium valproate, topiramate), beta blockers (metoprolol, propranolol, timolol, atenolol, nadolol), and antidepressants (amitriptyline, venlafaxine). Due to a lack of effectiveness and poor tolerability of these older agents, there is a significant opportunity for growth of both oral and injectable CGRP inhibitors for preventive therapy. Although most patients prefer oral products over injectables, Qulipta lacks the indication for chronic migraine prevention compared to injectable CGRP inhibitors. Patients with 15 or more headache days per month should use an injectable CGRP inhibitor for prevention of migraines. Coverage strategies for CGRP inhibitors for preventive and acute treatment may need to be evaluated together now that there is some cross-over between agents.

Commented [PM4]: These abbreviations/organizations should be defined somewhere (I might have missed it).

Recommendation

This drug is being considered for inclusion in the state specific Preferred Drug List (PDL) as non-preferred.

References

1) American Headache Society. AHS Consensus Statement: The American Headache Society Position Statement on Integrating New Migraine Treatments into Clinical Practice. https://headachejournal.onlinelibrary.wiley.com/doi/10.1111/head.13456. Accessed September 29, 2021.
2) IPD Analytics [Qulipta New Drug Review]. Available at: https://secure.ipdanalytics.com. Accessed January 7, 2022.
3) Qulipta [package insert]. North Chicago, IL: AbbVie; 2021
4) Clinical Pharmacology. [Drug reference database]. https://www.clinicalkey.com/. Accessed January 7, 2022.
5) U.S. National Library of Medicine. 12-Week Placebo-controlled Study of Atogepant for the

Preventive Treatment of Migraine in Participants with Episodic Migraine. https://clinicaltrials.gov/ct2/show/study/NCT03777059?term=atogepant%2C+ADVANCE&draw=2&rank=1. Accessed January 7, 2022.

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