# Drug Monograph

Drug Name: **Ubrelvy™ (ubrogepant) Tablets**
Drug Class: **Alternative Oral Anti-Migraine Agents**
Prepared For: MO HealthNet
Prepared By: Conduent

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

## Executive Summary

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| **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:** | Ubrelvy™ is available as an oral tablet in 50 mg and 100 mg tablets of ubrogepant. |
| **Manufacturer:** | Distributed by: Allergan USA, Inc., Madison, NJ 07940. |
| **Summary of Findings:** | This drug is being considered for inclusion in the state specific Preferred Drug List (PDL). |

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| **Status Recommendation:** | ☐ Clinical Edit | ☐ PA Required |
| | ☐ Open Access | ☒ PDL |
| **Type of PA Criteria:** | ☐ Appropriate Indications | ☒ Under Solicitation |
| | ☐ 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 characterized by throbbing, recurring head pain and may include symptoms like nausea, vomiting, and sensitivity to light and sound. There are no sure answers as to what causes migraine. The current school of thought is that migraine is a neurological condition that starts with activation of the trigeminovascular system. From this stimulation, vasoactive neuropeptides, including calcitonin gene-related peptides (CGRP) are released. CGRPs are thought to mediate trigeminovascular pain transmission from intracranial vessels to the central nervous system as well as contribute to neurogenic inflammation through their role as a powerful vasodilator. Migraine affects at least 28 million, or 13% of, Americans. It is more frequently seen in women than in men, and the most common age for migraine sufferers is between the ages of 20 to 45. In addition, migraine tends to run in families thus leading researchers to believe it involves a genetic component. Migraine is a major cause of disability, and it has been estimated that 157 million workdays are lost annually because of the pain and associated symptoms of migraine.

## Dosage Form [3]

Ubrelvy™ is available as an oral tablet in 50 mg and 100 mg tablets of ubrogepant.

## Manufacturer [3]

Distributed by: Allergan USA, Inc., Madison, NJ 07940.

## Indication(s) [3]

Ubrelvy™ is indicated for the acute treatment of migraine with or without aura in adults.

## Clinical Efficacy [3,4,5,6,7,8] (mechanism of action/pharmacology, comparative efficacy)

Ubrelvy™, an antimigraine agent, is a calcitonin gene-related peptide receptor antagonist.

Pharmacokinetics:

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| **Absorption** | Time to peak: 1.5 hours<br>(With high-fat meal, time to peak: 3.5 hours, 22% reduction in $C_{max}$ with no change in AUC) |
| **Metabolism** | Substrate of CYP3A4 |
| **Excretion** | Feces: 42% as ubrogepant<br>Urine: 6% as ubrogepant |
| **Half-life** | 5 – 7 hours |

 

Clinical Trials Experience

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| **STUDY 1 DESIGN** [5,6] | Randomized, double-blind, multicenter, placebo-controlled trial |
| **INCLUSION CRITERIA** | • At least a 1-year history of migraine with or without aura consistent with a diagnosis according to the International Classification of Headache Disorders, 3rd edition, beta version.<br>• Migraine onset before age 50.<br>• History of migraines typically lasting between 4 and 72 hours if untreated or treated unsuccessfully and migraine episodes are separated by at least 48 hours of headache pain freedom.<br>• History of 2 – 8 migraine attacks per month with moderate to severe headache pain in each of the previous 3 months. |
| **EXCLUSION CRITERIA** | • Difficulty distinguishing migraine headache from other headaches.<br>• Has taken medication for acute treatment of headache (including acetaminophen, nonsteroidal anti-inflammatory drugs (NSAIDs), triptans, ergotamine, opioids, or combination analgesics) on 10 or more days per month in the previous 3 months.<br>• Has a history or migraine aura with diplopia or impairment of level of consciousness, hemiplegic migraine, or retinal migraine.<br>• Has a current diagnosis of new persistent daily headache, trigeminal autonomic cephalgia (e.g., cluster headache), or painful cranial neuropathy.<br>• Required hospital treatment of a migraine attack 3 mor more times in the previous 6 months.<br>• Has a chronic non-headache pain condition requiring daily pain medication.<br>• Has a history of malignancy in the prior 5 years, except for adequately treated basal cell or squamous cell skin cancer, or in situ cervical cancer.<br>• Has a history of any prior gastrointestinal conditions (e.g., diarrhea syndromes, inflammatory bowel disease) that may affect the absorption or metabolism of investigational product, participants with prior gastric bariatric interventions which have been reversed are not excluded.<br>• Has a history of hepatitis within the previous 6 months. |
| **TREATMENT REGIMEN** | Participants were randomized in a 1:1:1 ratio to receive an initial dose of placebo, a dose of 50 mg of Ubrelvy™, or a dose of 100 mg of Ubrelvy™ for treatment of a single migraine attack, with the option to take a second dose. |
| **RESULTS** | The primary measure of efficacy was the proportion of participants who were free of pain after 2 hours had elapsed. Of the 1672 randomized participants, the percentage of participants who had freedom from pain at 2 hours was 11.8% in the placebo group, 19.2% in the 50-mg group, and 21.2% in the 100-mg group (P = 0.002). |
| **SAFETY** | Discussed in the Adverse Effects section below. |

 

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| **STUDY 2 DESIGN** [7,8] | Phase 3, randomized, double-blind, multicenter, placebo-controlled trial |
| **INCLUSION CRITERIA** | • At least a 1-year history of migraine with or without aura consistent with a diagnosis according to the International Classification of Headache Disorders, 3rd edition, beta version.<br>• Migraine onset before age 50.<br>• History of migraines typically lasting between 4 and 72 hours if untreated or treated unsuccessfully and migraine episodes are separated by at least 48 hours of headache pain freedom.<br>• History of 2 – 8 migraine attacks per month with moderate to severe headache pain in each of the previous 3 months. |
| **EXCLUSION CRITERIA** | • Difficulty distinguishing migraine headache from tension-type other headaches.<br>• Has taken medication for acute treatment of headache (including acetaminophen, nonsteroidal anti-inflammatory drugs (NSAIDs), triptans, ergotamine, opioids, or combination analgesics) on 10 or more days per month in the previous 3 months.<br>• Has a history or migraine aura with diplopia or impairment of level of consciousness, hemiplegic migraine, or retinal migraine.<br>• Has a current diagnosis of new persistent daily headache, trigeminal autonomic cephalgia (e.g., cluster headache), or painful cranial neuropathy.<br>• Required hospital treatment of a migraine attack 3 mor more times in the previous 6 months.<br>• Has a chronic non-headache pain condition requiring daily pain medication.<br>• Has a history of malignancy in the prior 5 years, except for adequately treated basal cell or squamous cell skin cancer, or in situ cervical cancer.<br>• Has a history of any prior gastrointestinal conditions (e.g., diarrhea syndromes, inflammatory bowel disease) that may affect the absorption or metabolism of investigational product, participants with prior gastric bariatric interventions which have been reversed are not excluded.<br>• Has a history of hepatitis within previous 6 months. |
| **TREATMENT REGIMEN** | Participants were randomized in a 1:1:1 ratio to receive an initial dose of placebo, a dose of 25 mg of Ubrelvy™, or a dose of 50 mg of Ubrelvy™ for treatment of a single migraine attack of moderate or severe pain intensity. |
| **RESULTS** | There were two primary measures of efficacy: pain freedom and the absence of the participant-designated most bothersome migraine-associated symptom (e.g., photophobia, phonofobia, and nausea) at 2 hours after taking the medication. Of the 1686 randomized participants, 1355 were evaluable for efficacy. Pain freedom at 2 hours was reported by 21.8% in the Ubrelvy™ 50 mg group (Ubrelvy™ 50 mg v. placebo, P = 0.01), 20.7% in the Ubrelvy™ 25 mg group Ubrelvy™ 25 mg v placebo, P = 0.03), and 14.3% in the placebo group. Absence of the most bothersome associated symptoms at 2 hours was reported by 38.9% of the Ubrelvy™ 50 mg group (Ubrelvy™ 50 mg v. placebo, P = |

 

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| | 0.01), 34.1% of the Ubrelvy™ 25 mg group(Ubrelvy™ 25 mg v. placebo, P = 0.07), and 27.4% in the placebo group. |
| **SAFETY** | Discussed in the Adverse Effects section below. |

## Contraindications [3,4]

- Ubrelvy™ is contraindicated with concomitant use of strong CYP3A4 inhibitors.

## Warnings and Precautions [3,4]

- Hepatic impairment: Dose reduction is required in patients with severe hepatic impairment.
- Renal impairment: Use of Ubrelvy™ is not recommended in patients with end-stage renal impairment. Only a dose reduction is required in patients with severe renal impairment.
- Drug-drug interactions: Potentially significant interactions may exist, requiring dose or frequency adjustment, additional monitoring, and/or selection of alternative therapy.

## Adverse Effects [3,4]

| Most common, ≥ 1% | Placebo (n = 984) % | Ubrelvy™ 50 mg (n = 954) % | Ubrelvy™ 100 mg (n = 485) % |
|---|---|---|---|
| **Nausea** | 2 | 2 | 4 |
| **Somnolence** | 1 | 2 | 3 |
| **Xerostomia** | 1 | < 1 | 2 |

## Drug Interactions [3,4]

Ubrelvy™ is a substrate of BCRP/ABCG2 (major), OATP1B1/1B3 (SLCO1B1/1B3), and P-glycoprotein/ABCB1. As such, there are a great many drug interactions caused by the use of Ubrelvy™ that are too numerous to list here. Please refer to the package insert for specific drug interactions and exceptions as well as the dosing adjustments recommended for each. Below is listed the general effect the proteins listed above may have on Ubrelvy™:

- BRCP/ABCG2 Inhibitors: May increase the serum concentration of Ubrelvy™.
- CYP3A4 Inducers (strong): May decrease the serum concentration of Ubrelvy™. Avoid this combination.
- CYP3A4 Inducers (moderate): May decrease the serum concentration of Ubrelvy™.
- CYP3A4 Inducers (weak): May decrease the serum concentration of Ubrelvy™.
- CYP3A4 Inhibitors (strong): May increase the serum concentration of Ubrelvy™. Avoid this combination.
- CYP3A4 Inhibitors (moderate): May increase the serum concentration of Ubrelvy™.
- CYP3A4 Inhibitors (weak): May increase the serum concentration of Ubrelvy™.
- P-glycoprotein/ABCB1 Inhibitors: May increase the serum concentration of Ubrelvy™.

** Exceptions and specific dosing information may be found in the prescribing information.

 

## Dosage and Administration [3,4]

The recommended dose of Ubrelvy™ is 50 mg or 100 mg taken orally with or without food. If needed, a second dose may be taken at least 2 hours after the initial dose. The maximum dose in a 24-hour period is 200 mg.
Renal Impairment: CrCl 15 – 29 ml/min: 50 mg for the initial dose followed by 50 mg at least 2 hours later if needed. CrCl < 15 ml/min: Avoid use.
Hepatic Impairment (Child-Pugh Class C): 50 mg for the initial dose followed by 50 mg at least 2 hours later if needed.
Drug-drug Interactions: This includes numerous interactions with BCRP/ABCG2, CYP3A4, and P-glycoprotein/ABCB1. Please look to the Ubrelvy™ prescribing information for specific drug-drug interactions and their subsequent dosing adjustments.

## Cost

| Generic Name | Brand Name | Manufacturer | Strength | Cost**/tablet |
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| **Ubrogepant** | Ubrelvy™ | Allergan USA, Inc. | 50 mg | $85 |
| **Ubrogepant** | Ubrelvy™ | Allergan USA, Inc. | 100 mg | $85 |

** Wholesale Acquisition Cost

## Conclusion

Ubrelvy™ is the first FDA-approved oral CGRP antagonist for the acute treatment of migraine, with or without aura. It works by inhibiting CGRP receptors and thus halting the pain transmission from the brain to the central nervous system as well as neurogenic inflammation. The efficacy of Ubrelvy™ was established in two randomized, double-blind, placebo-controlled studies consisting of 1672 and 1355 participants, both sponsored by the manufacturer, Allergan, Inc.. Treatment with Ubrelvy™ demonstrated a higher percentage of participants who were pain free at the two-hour mark than placebo, albeit neither study showed statistical significance. The most common adverse reactions in patients taking Ubrelvy™ were nausea, somnolence, and dry mouth (4 - <1%). Further studies are needed to compare this newest abortive treatment's efficacy to existing treatments already on the market.

## Recommendation

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

## References


1) Migraine facts. National Headache Foundation website. https://headaches.org/2007/11/20/migraine-facts/. Accessed February 12, 2020.
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3) Ubrelvy™ (ubrogepant) [package insert]. Madison, NJ: Allergan, Inc; 2019.


 

4) Ubrogepant: Drug information. In: *UpToDate*. Waltham, MA: UpToDate, 2020. https://www.uptodate.com/contents/ubrogepant-drug-information?search=ubrelvy&source=panel_search_result&selectedTitle=1~7&usage_type=panel&kp_tab=drug_general&display_rank=1. Accessed February 12, 2020.
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6) Dodick DW, Lipton RB, Ailani J, et al. Ubrogepant for the Treatment of Migraine. *NEngl J Med*. 2019;381:2230-2241. Doi:10.1056/NEJMoa1813049.
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