Brand Name: Ubrelvy

Generic Name: Ubrogepant

Manufacturer[1] Allergan USA, Inc.

Drug Class[2,4]: Antimigraine agent, Calcitonin Gene-Related Peptide (CGRP) Receptor Antagonist

Uses:
> **Labeled[1,2,3,4]**: Treatment of migraine with or without aura in adults.
> **Unlabeled[1,2,3,4]**: None listed

Mechanism of Action[1,2,3,4]: Ubrogepant is a calcitonin gene-related peptide (CGRP) receptor antagonist. CGRP is dispersed throughout the nervous system and becomes concentrated at anatomical sites, such as the trigeminovascular system, which are involved in migraine pathophysiology. CGRP concentrations become elevated during acute migraine attacks and can be elevated in people with chronic migraines.

Pharmacokinetics[1,2,3,4]:
> **Absorption:**

T_{max}	1.5 hours
V_d	350 L
t ½	5-7 hours
Clearance	87 L/hr
Protein binding	Plasma: 87%
Bioavailability	Not reported

> **Metabolism**: Ubrogepant is primarily metabolized by CYP3A4. The glucuronide metabolites are not expected to contribute to the pharmacological activity of ubrogepant.   Ubrogepant is a weak substrate of OAT1, OATP1B1, and OATP1B3 and a weak inhibitor of CYP2C8, CYP2C9, CYP2C19, CYP2D6, MAO-A, OATP1B1, OATP1B3, OCT2, and UGT1A1.
> **Elimination:** Ubrogepant is primarily eliminated through the fecal route and to a minor extent through renal excretion. Following a single oral administration, 42% was recovered as unchanged drug in the feces and 6% as unchanged drug in the urine.

Efficacy:

Lipton RB, Dodick DW, Ailani J, et al. Effect of Ubrogepant vs Placebo on Pain and the Most Bothersome Associated Symptom in the Acute Treatment of Migraine: The ACHIEVE II Randomized Clinical Trial [published correction appears in JAMA. 2020 Apr 7;323(13):1318]. *JAMA*. **2019;322(19):1887-1898.**

Study design: Phase 3, multicenter, randomized, double-blind, placebo controlled, parallel-group, single attack study

Description of study: *Methods:* Participants between 18-75 years old with a history of migraine with or without aura, who experienced between 2-8 migraine attacks with moderate to severe pain in each of the 3 months prior to screening were included. In addition, patients had to have a history of migraine lasting 4-72 hours if untreated or treated unsuccessfully.   A total of 1,686 patients were randomized 1:1:1 to placebo, 25 mg ubrogepant, and 50 mg ubrogepant. Participants took 1 tablet as soon as possible within 4 hours of a qualifying migraine attack. Patients were allowed a second optional dose 2 to 48 hours after the initial dose for moderate to severe headache. Patients who didn't opt for the second dose were allowed a rescue medication which was any therapy not provided by the study for relief. *Outcomes:* The percentage of patients who reported being pain free 2 hours after the initial dose was 21.8% for the 50 mg dose (OR 1.62; P= 0.01), and 20.7% for the 25 mg dose (OR 1.56; P=0.03) compared to placebo (14.3%). The percentage of patients reporting absence of the most troublesome migraine symptoms at 2 hours was 38.9% for the 50 mg dose (OR 1.65; adjusted P=0.01) and 34.1% (OR 1.37; adjusted P=0.07) compared to placebo (27.4%). Incidence of treatment emergent adverse effects (TEAEs) reported within 48 hours of the initial or second dose were similar in the placebo (10.2%) and ubrogepant groups (9.2% 25 mg, 12.2% 50 mg). Within 30-days after any dose, TEAEs were reported by 27.3% in the 50 mg group, 22% in the 25 mg group, and 22.4% in the placebo group. The TEAEs that occurred in more than 2% in either treatment group were nausea, dizziness, upper respiratory tract infection, and nasopharyngitis.

Limitations: Patients treated their headache once it was moderate to severe which differs from the American Headache Society's guideline recommendation to treat at the first sign of headache. Therefore, the results may not reflect the treatment outcomes for those treated while their intensity is mild. Additionally, the adverse effect and tolerability data compiled in this study are based upon outcomes after a single migraine attack and thus don't reflect tolerability or efficacy after repeated use. The power for the secondary outcomes was only set at 60%. Allergan funded the study and provided editorial support and several of those involved in the study reported conflicts of interest with Allergan which could introduce bias.

Conclusion: Using ubrogepant in the treatment of acute migraine attacks compared to placebo resulted in significantly decreased pain rates at 2 hours with both the 25 and 50 mg doses and led to absence of the most bothersome migraine related symptoms at 2 hours with the 50 mg dose. This study and its data support the use of ubrogepant for treatment of acute migraine attacks. Further research is needed to assess the long-term safety of ubrogepant in unselected patient populations and in assessing its effectiveness against other acute migraine treatments.

Dodick DW, Lipton RB, Ailani J, et al. Ubrogepant for the Treatment of Migraine. *N Engl J Med*. 2019;381(23):2230-2241.

Study design: Randomized, double-blind, placebo-controlled, parallel-group trial

Description of study: *Methods:* Patients between 18-75 years old, a minimum of a 1-year history of migraine with or without aura, who experienced 2-8 migraine attacks per month, and had migraine onset prior to 50 years old were included. Additionally, patients had to have a history of migraines that lasted between 4 to 72 hours while being untreated or if treated unsuccessfully. A total of 1672 patients were randomized to receive ubrogepant 50 mg, ubrogepant 100 mg, or placebo to be taken at the time of a qualifying attack. It was optional for those experiencing a recurrent or persistent moderate to severe headache to take either an optional second dose or a rescue medication between 2-48 hours after the initial dose. Patients opting for the second dose were required to wait for 2 hours after the second dose before utilizing rescue medication. Efficacy was based on an electronic diary completed by the patients that included the pain severity as well as non-headache symptoms related to the migraine. The percentage of patients free from pain at 2 hours after the initial dose was 19.2% in the 50 mg ubrogepant group (adjusted P=0.002), and 21.2% in the 100 mg ubrogepant group (P<0.001) compared to 11.8% in the placebo group. Absence of migraine related symptoms that are troublesome was 38.6% in the 50 mg ubrogepant group (P=0.002), and 37.7% in the 100 mg ubrogepant group (P=0.002) compared to 27.8% in the placebo group. The TEAEs that occurred in more than 2% in either treatment group were nausea, somnolence, and dry mouth.

Limitations: This study lacked an active control and didn't evaluate the consistency of effect across multiple migraines which makes it difficult to compare with other available treatments or if there are consistent results with repeated use. Additionally, 21% of patients who were randomized were not included in the efficacy analysis due to not having a qualifying migraine during the 60-day period and were therefore excluded. The safety and efficacy data from this trial were based off of a single attack which means that long-term safety with repeated use can't be inferred. Lastly, some of the researchers were affiliated with Allergan which introduces the potential for bias.

Conclusion: This study supports the use of ubrogepant in patients with acute migraines, however, trials assessing consistency across multiple uses, long-term safety, and comparative efficacy are still needed to fully evaluate the clinical usefulness of ubrogepant.

Goadsby PJ, Tepper SJ, Watkins PB, et al. Safety and tolerability of ubrogepant following intermittent, high-frequency dosing: Randomized, placebo-controlled trial in healthy adults. *Cephalalgia*. 2019;39(14):1753-1761.

Study design: Phase 1, multicenter, randomized, double blind, placebo controlled, parallel group study

Description of study: *Methods:* Healthy males or females between the ages of 18-50 years old with a BMI between 18 and 30 kg/m^2 with normal alanine and aspartate aminotransferase levels and normal bilirubin levels were included. Patients were excluded if they had any significant disease state (including migraine), any medication use during the screening period (including OTCs, herbals, contraceptives, and products containing grapefruit). Patients were also required to refrain from drinking alcohol from the time of informed consent until the end of the study. Patients were randomized 1:1 to receive either two placebo tablets or 100 mg ubrogepant (2 50 mg tablets). On day 1, patients in the ubrogepant group received 2 consecutive days of 100 mg ubrogepant and then 2 days of placebo, this continued alternating for a total of 56 days. Placebo group patients received 2 tablets of placebo daily for 56 days. *Outcomes:* 518 patients were randomized and 516 of those received at least one dose and were included in the safety analysis. Incidence of (TEAEs) were similar in the placebo (45%) and ubrogepant groups (44%). Most of the TEAEs were mild (89% in both placebo and ubrogepant groups) or moderate (11% in the placebo group and 8% in the ubrogepant group) severity. The TEAEs that occurred in more than 5% in either treatment group were headache, oropharyngeal pain, and nasopharyngitis. This trial also demonstrated minimal hepatic effect due to ubrogepant with 2 cases of elevated ($\geq$ 3x ULN) aminotransferases that remained asymptomatic and had no bilirubin elevations.

Limitations: Patients in this study were healthy with a BMI $\leq$ 30 kg/m^2 and weren't allowed to take any medications during the trial. Thus, the results of this study may not be easily applied to obese patients with possible underlying liver abnormalities or in patients with migraines taking multiple medications. This study also had a limited period to collect pharmacokinetic data and were therefore not able to calculate full pharmacokinetic parameters. Lastly, this study was funded by Allergan and several of the authors were affiliated with Allergan which introduces the potential for bias.

Conclusion: This study supports that ubrogepant is well tolerated and didn't identify any serious safety concerns. Additionally, there was no indication of hepatotoxicity through the intermittent dosing utilized which mirrors how it would be used for someone with acute migraines. Further studies could be done to assess for safety in patients with comorbidities, taking multiple medications, and those with liver disease or abnormalities.

Contraindications[1,2,3]: Concomitant use of strong CYP3A4 inhibitors.

Precautions[1,2,3,4]:
    Disease- related:
- A dose reduction is recommended in hepatic impairment.
- A dose reduction is recommended in severe renal impairment and use is not recommended for patients with end-stage renal impairment.

    Concurrent drug therapy issues:

- Significant drug-drug interactions could exist, and a drug interaction database should be consulted.

Pregnancy:
- Use of ubrogepant in pregnancy may cause fetal harm and has been shown to potentially cause preeclampsia and gestational hypertension. In pregnant rabbits it was shown to cause abortion, increased embryofetal mortality, and decreased body weight at birth.

Lactation:
- Risks versus benefits should be weighed, especially in regard to the risk of infant exposure, benefit of treating the mother, and benefits of breastfeeding the infant.

Adverse effects[1,2,3,4]:

Occurring in > 1 to < 10% of patients

Central Nervous System

Drowsiness (2%-3%)

Fatigue (2%-3%)

Gastrointestinal

Nausea (4%)

Xerostomia (2%)

Drug Interactions[1,2,3,4]:

Co-administration with drugs that may increase the serum concentration of CYP3A4 Substrates

Abametapir, Clofazimine, Conivaptan, Erdafitinib, Fusidic Acid (Systemic), Idelalisib, Ivosidenib, Stiripentol,

Co-administration with drugs that may decrease the serum concentration of CYP3A4 Substrates

Dabrafenib, Deferasirox, Erdafitinib, Sarilumab, Siltuximab, Tocilizumab

Co-administration with drugs that may increase the serum concentration of ubrogepant

BCRP/ABCG2 Inhibitors, Ciprofloxacin (Systemic), Cyclosporine (Systemic), CYP3A4 Inhibitors, Fluvoxamine, P-glycoprotein/ABCB1 Inhibitors

Co-administration with drugs that may decrease the serum concentration of ubrogepant

CYP3A4 Inducers, St. John's Wort

Co-administration with drugs that may increase the serum concentration of BCRP/ABCG2 Substrates

Lasmiditan, Tafamidis, Tolvaptan, Voxilaprevir

Capmatinib

Concurrent use of Capmatinib with P-glycoprotein and BCRP substrates may result in risk of increased adverse reactions.

Dosing Administration[1,2,3,4]:

Usual adult dose:

Initial dose: 50 to 100 mg administered as a single dose; may repeat once depending on tolerability and response after $\geq$ 2 hours.

Maximum dose: 200 mg/24 hours

Geriatric dose:

Refer to adult dosing and initiate at the lower end of the dosage range.

Renal impairment dose:

CrCl $\geq$ 30 mL/min: No dose adjustment necessary

CrCl 15-29 mL/min: 50 mg as a single dose initially; may repeat once depending on tolerability and response after $\geq$ 2 hours. Maximum dose: 100 mg/24 hours

CrCl < 15 mL/min: Recommended to avoid use due to lack of study in this population.

Hepatic impairment dose:

Mild to moderate impairment (Child-Pugh Class A, B): No dose adjustment necessary

Severe impairment (Child-Pugh Class C): 50 mg as a single dose initially; may repeat once depending on tolerability and response after $\geq$ 2 hours. Maximum dose: 100 mg/24 hours

Use in special circumstances:

Overdose[1]: Ubrogepant has a half-life of 5 to 7 hours, thus monitoring of patients that overdose should continue for at least 24 hours, or while symptoms are persisting.

Conclusion:

Ubrogepant is an effective therapy for treating patients with acute migraine attacks but is not indicated for prevention. More studies need to be conducted in regard to concomitant medications, long-term safety and efficacy, and in comparison to known effective treatments. The side effects and adverse events of ubrogepant appear to be minimal. Ubrogepant has shown tolerability, minimal side effects, and effectiveness in acute migraine attacks with or without aura and therefore appears to be another clinically effective agent in the treatment of acute migraine, especially when currently available options have failed or are not tolerated.

References:
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4. Ubrogepant. Clinical Pharmacology [Internet database]. Gold Standard, Inc., 2007. Available at: http://www.clinicalpharmacology.com. Accessed: July 31, 2020.
5. Lipton RB, Dodick DW, Ailani J, et al. Effect of Ubrogepant vs Placebo on Pain and the Most Bothersome Associated Symptom in the Acute Treatment of Migraine: The ACHIEVE II Randomized Clinical Trial [published correction appears in JAMA. 2020 Apr 7;323(13):1318]. *JAMA*. 2019;322(19):1887-1898.

6. Dodick DW, Lipton RB, Ailani J, et al. Ubrogepant for the Treatment of Migraine. *N Engl J Med*. 2019;381(23):2230-2241.
7. Goadsby PJ, Tepper SJ, Watkins PB, et al. Safety and tolerability of ubrogepant following intermittent, high-frequency dosing: Randomized, placebo-controlled trial in healthy adults. *Cephalalgia*. 2019;39(14):1753-1761.

Prepared by: Marley Keister, Doctor of Pharmacy Candidate