SUMMARY OF PRODUCT CHARACTERISTICS

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1 NAME OF THE MEDICINAL PRODUCT

AQUIPTA 60 mg tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

AQUIPTA 60 mg tablets

Each tablet contains 60 mg of atogepant.

Excipients with known effect

This medicinal product contains 31.5 mg sodium per dose. This is equivalent to 1.6% of the WHO recommended maximum daily intake of 2 g sodium for an adult.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

AQUIPTA 60 mg tablets

White to off-white, oval biconvex tablet debossed with “A60” on one side.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

AQUIPTA is indicated for:

- Acute treatment of migraine with or without aura in adults
- Prophylaxis of migraine in adults who have at least 4 migraine days per month.

4.2 Posology and method of administration

Posology

The maximum dose per day for AQUIPTA is 60 mg.

For acute treatment of migraine as needed, the recommended dose for AQUIPTA is 60 mg.

For prophylaxis of migraine, the recommended dose for AQUIPTA is 60 mg taken orally once daily with or without food. A missed dose should be taken right away. If it is almost time for the next dose, patients should be instructed to skip the missed dose and take the next dose as scheduled.

Dose modifications

Dosing modifications for concomitant use of specific drugs are provided in Table 1 (see section 4.5).

Table 1: Dose modifications for drug interactions

Dosage modifications	Recommended once daily dose
Strong CYP3A4 inhibitors	10 mg
Strong OATP inhibitors	10 mg

Special populations

Elderly (³65 years)

There is limited data available in the elderly with no data available in patients over 80 years of age. Population pharmacokinetic modelling suggests no clinically significant pharmacokinetic differences between elderly and younger subjects. No dose adjustment of AQUIPTA is needed in elderly patients.

Hepatic impairment

Avoid use of AQUIPTA in patients with severe hepatic impairment. No dose adjustment is recommended for patients with mild or moderate hepatic impairment (see section 5.2).

Renal impairment

In patients with severe renal impairment (CLcr 15-29 mL/min), and in patients with end-stage renal disease (ESRD) (CLcr <15 mL/min), the recommended dosage of AQUIPTA is 10 mg once daily. For patients with ESRD undergoing intermittent dialysis, AQUIPTA should preferably be taken after dialysis. No dose adjustment is recommended for patients with mild or moderate renal impairment (see section 5.2).

Paediatric population

The safety and efficacy of atogepant in children have not yet been established. No data are available.

Method of administration

AQUIPTA is to be taken orally once daily with or without food.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1 (see section 4.4).

4.4 Special warnings and precautions for use

Hypersensitivity reactions, including anaphylaxis, dyspnoea, rash, pruritus, urticaria, and facial oedema, have been reported with use of AQUIPTA (see section 4.8). Some hypersensitivity reactions can occur days after administration. If a hypersensitivity reaction occurs, discontinue AQUIPTA and institute appropriate therapy (see section 4.3).

Excipients

AQUIPTA 60 mg tablets contain 31.5 mg sodium per dose; this is equivalent to 1.6% of the WHO recommended maximum daily intake of 2 g sodium for an adult.

4.5 Interaction with other medicinal products and other forms of interaction

CYP3A4 Inhibitors

Co-administration of AQUIPTA with itraconazole, a strong CYP3A4 inhibitor, resulted in a significant increase in exposure of atogepant in healthy subjects. The recommended dosage of AQUIPTA with concomitant use of strong CYP3A4 inhibitors (e.g., ketoconazole, itraconazole, voriconazole, clarithromycin, telithromycin, indinavir, nelfinavir, ritonavir, saquinavir) is 10 mg once daily. No dosage adjustment of AQUIPTA is needed with concomitant use of moderate or weak CYP3A4 inhibitors.

OATP Inhibitors

Co-administration of AQUIPTA with single dose rifampicin, an OATP inhibitor, resulted in a significant increase in exposure of atogepant in healthy subjects. The recommended dosage of AQUIPTA with concomitant use of strong OATP inhibitors (e.g., rifampicin, atazanavir, ritonavir, tipranavir, ciclosporin, telmisartan) is 10 mg once daily.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are limited data from the use of atogepant in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). AQUIPTA is not recommended during pregnancy.

Breast-feeding

In a study of 12 breast-feeding women administered a single oral dose of atogepant 60 mg, transfer of atogepant into breast milk was minimal. The relative infant dose was approximately 0.19% of the maternal weight-adjusted dose with a milk-to-

plasma ratio of 0.08. The cumulative amount of atogepant excreted in breast milk over 24 hours was minimal, at less than 0.01 mg.

There are no data on the effects of atogepant on the breastfed infant or the effects of atogepant on milk production.

The developmental and health benefits of breast-feeding should be considered along with the mother's clinical need for atogepant and any potential adverse effects on the breastfed infant from atogepant or from the underlying maternal condition.

Fertility

No human data on the effect of atogepant on fertility are available. Animal studies showed no impact on female and male fertility with atogepant treatment (see section 5.3).

4.7 Effects on ability to drive and use machines

AQUIPTA has no or negligible influence on the ability to drive and use machines. However, it may cause somnolence in some patients. Patients should exercise caution before driving or using machinery until they are reasonably certain that atogepant does not adversely affect performance.

4.8 Undesirable effects

Summary of the safety profile

The safety of AQUIPTA was evaluated in 3 852 patients with migraine who received at least one dose of AQUIPTA. Of these, 1 225 patients were exposed to AQUIPTA for prophylaxis daily for at least 6 months and 826 patients were exposed for 12 months. 895 patients were exposed during 24 weeks on an as-needed basis for treatment of acute migraine attacks.

In 12-week, placebo-controlled prophylaxis clinical studies, 314 patients received at least one dose of AQUIPTA 10 mg once daily, 411 patients received at least one dose of AQUIPTA 30 mg once daily, 343 patients received at least one dose of AQUIPTA 30 mg twice daily, 678 patients received at least one dose of AQUIPTA 60 mg once daily, 91 patients received at least one dose of AQUIPTA 60 mg twice daily, and 663 patients received placebo. In the placebo-controlled clinical study for acute treatment of migraine, 1 195 patients received at least one dose of AQUIPTA 60 mg, and 1 177 patients received placebo; patients received both AQUIPTA and placebo to treat qualifying migraines.

In placebo-controlled prophylaxis studies, the most commonly reported adverse reactions were nausea (7%), constipation (7%), and fatigue/somnolence (5%). The majority of the cases were mild, and none were serious. The adverse reaction that most commonly led to discontinuation for prophylaxis was nausea (0.6%). Nausea (1.3%) was the most commonly reported adverse reaction for acute treatment.

Tabulated list of adverse reactions

Table 2 lists adverse reactions for which a causal relationship between AQUIPTA and the adverse event is at least a reasonable possibility. Given the lower exposure in the

setting of acute treatment of migraine, adverse drug reactions may not occur or may not be as frequent as when used for the prophylaxis of migraine.

The adverse reactions are listed below by system organ class and frequency. Frequencies are defined as follows: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1 000 to <1/100), rare (≥1/10 000 to <1/1 000) or very rare (<1/10 000).

Table 2: Adverse drug reactions identified with AQUIPTA*

System Organ Class	Frequency	Adverse Reaction
Immune system disorders	Common	Hypersensitivity (e.g., dyspnoea, rash, pruritus, urticaria, facial oedema)
	Rare	Anaphylaxis
Metabolism and nutrition disorders	Common	Decreased appetite
Gastrointestinal disorders	Common	Nausea, constipation
General disorders and administration site conditions	Common	Fatigue/somnolence
Investigations	Common	Weight decreased
	Uncommon	ALT/AST increased

* Frequency categories are based on once daily administration. Given the lower exposure in the setting of acute treatment of migraine, adverse drug reactions may not occur or may not be as frequent as when used for the prophylaxis of migraine.

Description of selected adverse reactions

Liver enzyme elevations

In placebo-controlled prophylaxis studies, the rate of transaminase elevations over 3 times the upper limit of normal was similar between patients treated with AQUIPTA (0.9%) and those treated with placebo (1.2%). In the placebo-controlled period of the study for acute treatment of migraine, transaminase elevations over 3 times the upper limit of normal were not seen in patients treated with AQUIPTA, though cases with a possible relationship to AQUIPTA were seen in the open-label period. There were cases with transaminase elevations over 3 times the upper limit of normal that were temporally associated with AQUIPTA treatment; these were asymptomatic and resolved within 8 weeks of discontinuation. There were no cases of severe liver injury or jaundice in these clinical studies.

Changes in body weight

In placebo-controlled prophylaxis studies, the proportion of patients with a weight decrease of at least 7% at any point was 2.5% for placebo, 3.8% for AQUIPTA 10 mg once daily, 3.2% for AQUIPTA 30 mg once daily, 5.3% for AQUIPTA 30 mg twice daily, 5.3% for AQUIPTA 60 mg once daily, and 6.8% for AQUIPTA 60 mg twice daily.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions

via the Yellow Card Scheme: Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

There is no known antidote for AQUIPTA. Treatment of an overdose of AQUIPTA should consist of general supportive measures including monitoring of vital signs and observation of the clinical status of the patient.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: {Analgesics, antimigraine preparations}, ATC code: N02CD07

Mechanism of action

Atogepant is an orally administered, small molecule, selective calcitonin gene-related peptide (CGRP) receptor antagonist that blocks the binding of the CGRP to the receptor and antagonizes CGRP receptor function. CGRP is a neuropeptide that has been associated with migraine pathophysiology. In the trigeminovascular system, CGRP modulates nociceptive signaling and inflammation, and also functions as a vasodilator.

Pharmacodynamic effects

At a dose 5 times the maximum recommended daily dose, AQUIPTA does not prolong the QT interval.

Clinical efficacy and safety

Acute treatment of migraine

The efficacy of AQUIPTA for the acute treatment of migraine with or without aura in adults was studied in a randomised, double-blind, placebo-controlled study (ECLIPSE). In the 16-week blinded treatment period, 1 328 subjects were randomised to 1 of 4 sequence groups to treat 4 qualifying migraine attacks of moderate or severe headache pain intensity with either AQUIPTA 60 mg (3 attacks) or placebo (1 attack) in a prespecified order. Subjects who completed the blinded period of the study treated subsequent attacks with open-label AQUIPTA 60 mg until the end of week 24. Approximately 22% of subjects were using concomitant migraine-prophylaxis medication (e.g., topiramate, amitriptyline, propranolol). Rescue medication was permitted beginning 2 hours after taking study drug. The use of a concomitant medicinal product that acts on the CGRP pathway was not permitted for either acute or preventive treatment of migraine.

Approximately 84% subjects who received study drug treated 4 qualifying migraine attacks during the double-blind study period. Patients had a mean age of 42 years (range: 18 to 74 years), 2% were 65 years or older, 85% were female, 59% were white, and 40% were Asian. Mean migraine frequency was approximately 4 moderate to severe migraine attacks per month over the 3 months prior to enrolment.

The primary efficacy endpoint was pain freedom (defined as reduction in headache severity from moderate/severe to no pain) at 2 hours during Attack 1 (Table 3).

Secondary endpoints included absence of patient-identified most bothersome symptom at 2 hours, pain relief (defined as reduction in headache severity from moderate/severe to mild/no pain) at 2 hours, sustained pain relief from 2 hours to 48 hours, use of rescue medication within 24 hours, ability to function normally at 2 hours, and sustained pain freedom from 2 hours to 48 hours. AQUIPTA demonstrated statistically significant improvement for these endpoints compared to placebo.

Table 3: Efficacy endpoints during Attack 1 in ECLIPSE

	AQUIPTA 60 mg	**Placebo**
Pain-free at 2 hours		
Responders, n/N (%)	146/602 (24.3)	80/612 (13.1)
Model-based Response Rate[a], %	24.5	12.1
Risk Difference, % (95% CI)	12.42 (8.31, 16.52)	
Relative Risk (95% CI)	2.02 (1.53, 2.52)	
Odds ratio (95% CI)	2.36 (1.76, 3.15)	
p-value	<0.0001[b]	
Freedom from most bothersome symptom[c] at 2 hours		
Responders, n/N (%)	263/602 (43.7)	200/612 (32.7)
Model-based Response Rate[a], %	43.7	30.5
Risk Difference, % (95% CI)	13.25 (7.95, 18.56)	
Relative Risk (95% CI)	1.44 (1.22, 1.65)	
Odds ratio (95% CI)	1.77 (1.41, 2.24)	
p-value	<0.0001[b]	
Pain relief at 2 hours		
Responders, n/N (%)	434/602 (72.1)	333/612 (54.4)
Model-based Response Rate[a], %	73.0	53.6
Risk Difference, % (95% CI)	19.47 (14.18, 24.76)	
Relative Risk (95% CI)	1.36 (1.24, 1.48)	
Odds ratio (95% CI)	2.35 (1.85, 2.98)	
p-value	<0.0001[b]	
Sustained pain relief from 2 to 48 hours		
Responders, n/N (%)	311/602 (51.7)	142/612 (23.2)
Model-based Response Rate[a], %	51.9	22.3
Risk Difference, % (95% CI)	29.63 (24.51, 34.75)	
Relative Risk (95% CI)	2.33 (1.95, 2.71)	
Odds ratio (95% CI)	3.77 (2.95, 4.82)	
p-value	<0.0001[b]	
Use of rescue medication within 24 hours		
Responders, n/N (%)	91/602 (15.1)	327/613 (53.3)
Model-based Response Rate[a], %	14.1	53.1
Risk Difference, % (95% CI)	-39.04 (-43.98, -34.10)	
Relative Risk (95% CI)	0.27 (0.21, 0.32)	
Odds ratio (95% CI)	0.14 (0.11, 0.19)	
p-value	<0.0001[b]	
Normal function at 2 hours		
Responders, n/N (%)	288/602 (47.8)	245/613 (40.0)
Model-based Response Rate[a], %	47.1	34.7
Risk Difference, % (95% CI)	12.40 (6.18, 18.62)	
Relative Risk (95% CI)	1.36 (1.15, 1.57)	

Odds ratio (95% CI)	1.68 (1.29, 2.18)	
p-value	<0.0001[b]	
Sustained pain freedom from 2 to 48 hours		
Responders, n/N (%)	100/602 (16.6)	35/612 (5.7)
Model-based Response Rate[a], %	16.7	5.2
Risk Difference, % (95% CI)	11.43 (8.09, 14.76)	
Relative Risk (95% CI)	3.18 (2.02, 4.35)	
Odds ratio (95% CI)	3.62 (2.43, 5.39)	
p-value	<0.0001[b]	

n=number of responders/N=number of subjects for Attack 1 in the efficacy analysis population

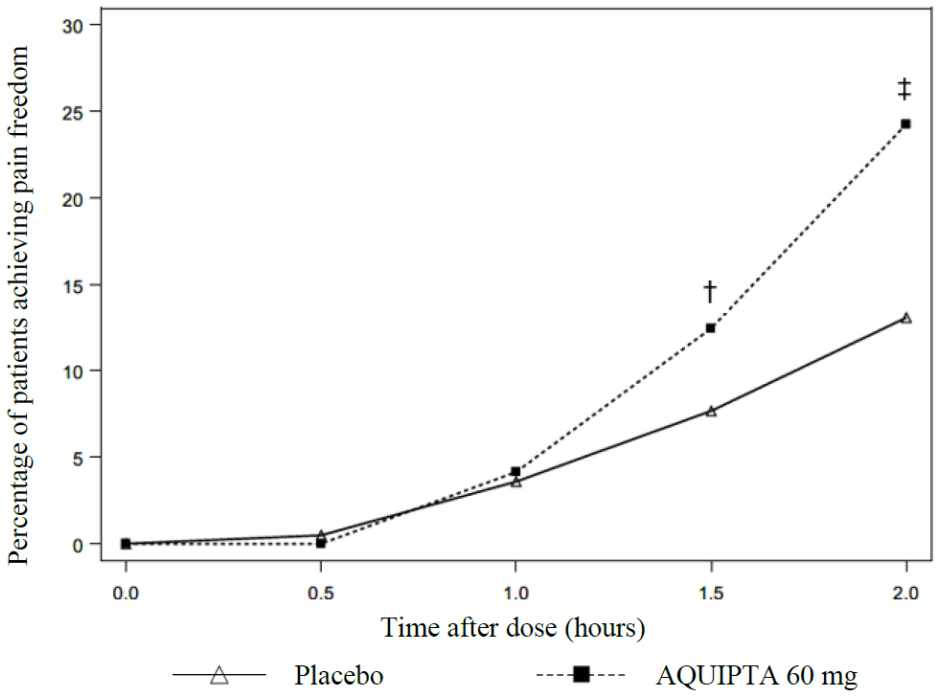
[a] Model-based response rates were calculated from a generalized linear mixed model with a logit link function to analyse primary and key secondary endpoints

[b] p-values were calculated for model-based odds ratios and adjusted for multiple comparisons

[c] Patient-identified as nausea (31%), photophobia (44%), or phonophobia (25%)

A greater percentage of patients treated with AQUIPTA 60 mg achieved pain freedom beginning at 1.5 hours during Attack 1 compared to patients who received placebo (Figure 1). AQUIPTA also demonstrated consistent effect with 26.3% of patients achieving pain freedom at 2 hours in at least 2 of 3 migraine attacks.

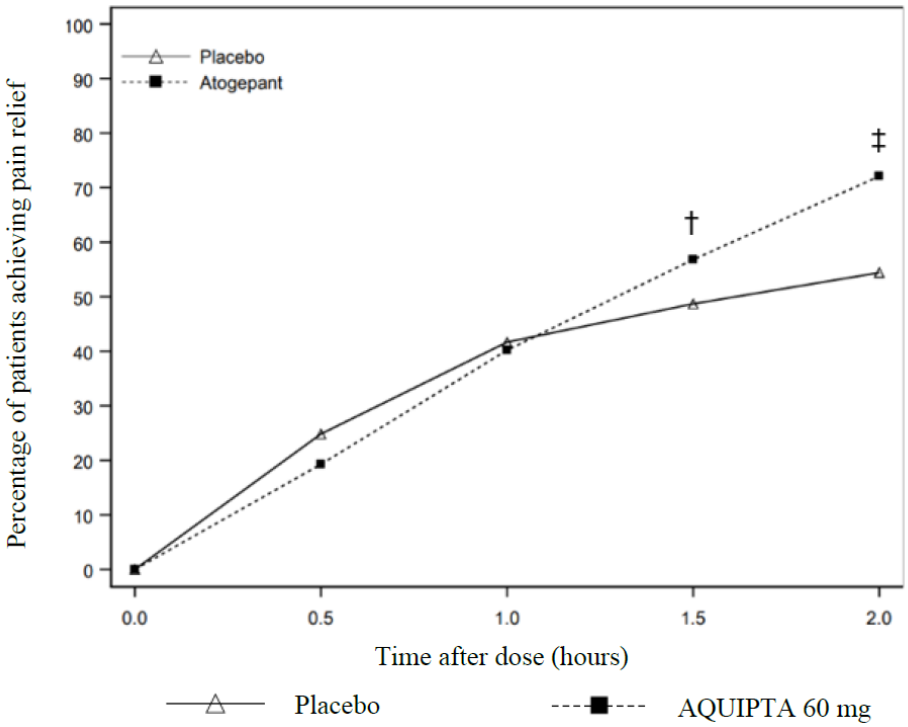
Figure 1: Percentage of patients achieving pain freedom within 2 hours for Attack 1 in ECLIPSE



† $p < 0.001$ (not adjusted for multiple comparisons)
‡ $p < 0.0001$ (adjusted for multiple comparisons)

A greater percentage of patients treated with AQUIPTA 60 mg achieved pain relief beginning at 1.5 hours during Attack 1 compared to patients who received placebo (Figure 2). AQUIPTA also demonstrated consistent effect with 79.3% of patients achieving pain relief at 2 hours in at least 2 of 3 migraine attacks.

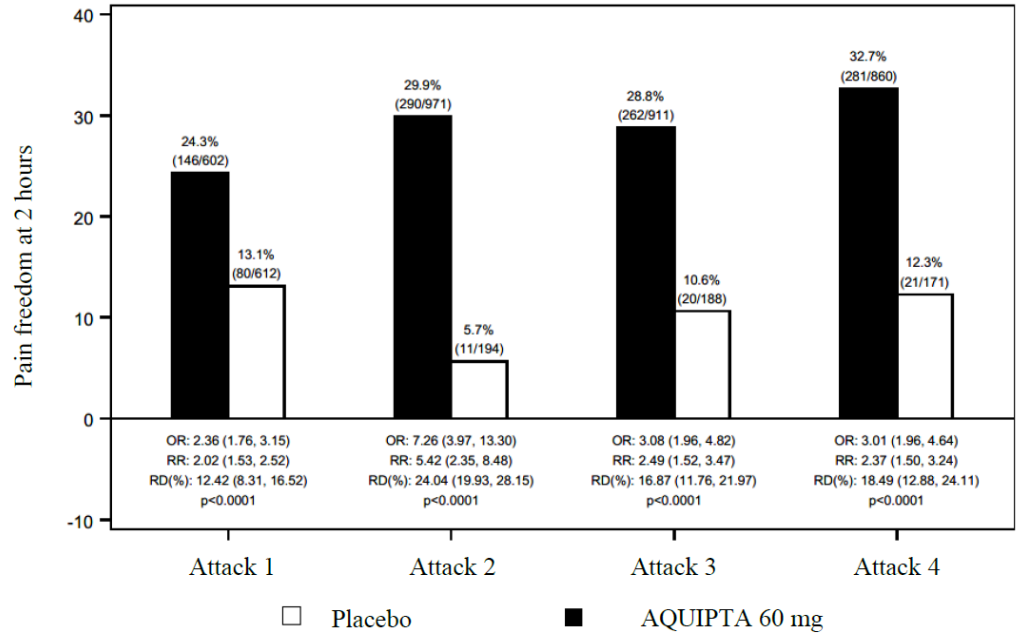
Figure 2: Percentage of patients achieving pain relief within 2 hours during Attack 1 in ECLIPSE



† $p < 0.001$ (not adjusted for multiple comparisons)
‡ $p < 0.0001$ (adjusted for multiple comparisons)

AQUIPTA 60 mg showed higher response rates than placebo for pain freedom at 2 hours for each of the 4 single attacks during the double-blind period (nominal p-value < 0.0001 for Attacks 2 to 4) as shown in Figure 3. The AQUIPTA response rates for Attacks 2 to 4 were similar to Attack 1.

Figure 3: Percentage of patients achieving pain freedom at 2 hours for Attacks 1 to 4 in ECLIPSE



Prophylaxis of migraine

AQUIPTA was evaluated for the prophylaxis of migraine in two pivotal studies across the migraine spectrum in chronic and episodic migraine. The episodic migraine study (ADVANCE) enrolled patients who met International Classification of Headache Disorders (ICHD) criteria for a diagnosis of migraine with or without aura. The chronic migraine study (PROGRESS) enrolled patients who also met ICHD criteria for chronic migraine. Both studies excluded patients with myocardial infarction, stroke, or transient ischemic attacks within six months prior to screening.

Episodic Migraine

AQUIPTA was evaluated for the prophylaxis of episodic migraine (4 to 14 migraine days per month) in a randomised, multicentre, double-blind, placebo-controlled study (ADVANCE). A total of 458 patients were randomised 1:1 to receive AQUIPTA 60 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.

A total of 88% patients completed the 12-week double-blind study period. Patients had a mean age of 42 years (range: 18 to 73 years), 89% were female, and 83% were white. The mean migraine frequency at baseline was approximately 8 migraine days per month and was similar across treatment groups.

The primary efficacy endpoint was the change from baseline in mean monthly migraine days (MMD) across the 12-week treatment period. Additional 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% and 75% reduction from baseline in mean MMD (3-month average), and change from baseline at week 12 for Headache Impact Test (HIT-6) total score and Migraine Specific Quality of Life Questionnaire version 2.1 (MSQ v2.1) Role Function-Restrictive (RFR) domain score.

The HIT-6 measures the impact of headache on participants' ability to function at work, school, home, and in social situations. A reduction in scores from baseline

indicates improvement. The MSQ v2.1 RFR domain score assesses how often migraine impacts function related to daily social and work-related activities. An increase in scores from baseline indicates improvement.

AQUIPTA treatment demonstrated statistically significant improvements for key efficacy endpoints compared to placebo in ADVANCE, as summarized in Table 4.

Table 4: Efficacy endpoints in ADVANCE

	AQUIPTA 60 mg N=226	**Placebo N=216**
Monthly Migraine Days (MMD) across 12 weeks		
Baseline	7.8	7.5
Mean change from baseline	-4.1	-2.5
Difference from placebo (95% CI)	-1.7 (-2.2, -1.1)	
p-value	<0.001	
Monthly Headache Days across 12 weeks		
Baseline	9.0	8.5
Mean change from baseline	-4.2	-2.5
Difference from placebo (95% CI)	-1.7 (-2.3, -1.0)	
p-value	<0.001	
Monthly Acute Medication Use Days across 12 weeks		
Baseline	6.9	6.5
Mean change from baseline	-3.8	-2.3
Difference from placebo (95% CI)	-1.4 (-1.9, -0.9)	
p-value	<0.001	
≥ 50% MMD Responders across 12 weeks		
% Responders	59	29
Difference from placebo (%)	30	
p-value	<0.001	
≥ 75% MMD Responders across 12 weeks		
% Responders	38	11
Difference from placebo (%)	27	
p-value	<0.001[a]	
HIT-6[b] at week 12		
Baseline	63.8	64.6
Mean change from baseline	-9.1	-5.2
Difference from placebo (95% CI)	-3.9 (-5.4, -2.5)	

	AQUIPTA 60 mg N=226	**Placebo N=216**
p-value	<0.001[a]	
MSQ v2.1 RFR[c] at week 12		
Baseline	46.6	46.6
Mean change from baseline	31.0	20.0
Difference from placebo (95% CI)	11.0 (6.6, 15.3)	
p-value	<0.001	

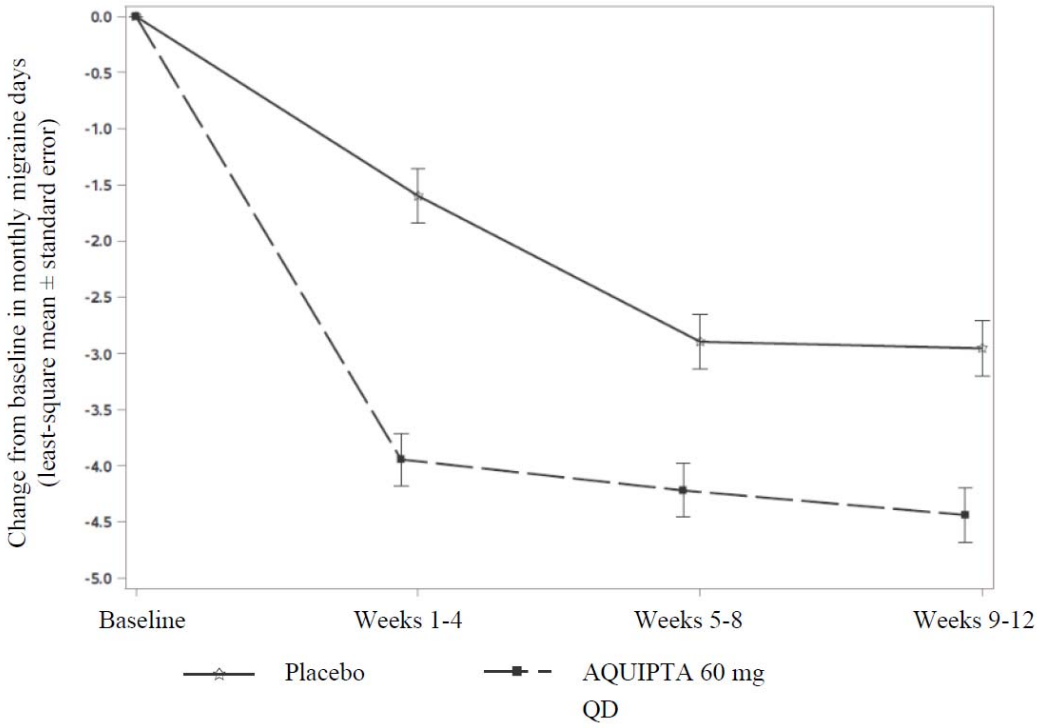
[a] Not adjusted for multiple comparisons
[b] Headache Impact Test total score
[c] Migraine Specific Quality of Life Questionnaire version 2.1 Role Function-Restrictive domain score

Additional pre-specified endpoints included the Activity Impairment in Migraine-Diary (AIM-D) domains and the MSQ v2.1 Role Function-Preventive (RFP) and Emotional Function (EF) domains. The AIM-D evaluates difficulty with performance of daily activities (PDA domain) and physical impairment (PI domain) due to migraine. A reduction in scores from baseline indicates improvement. MSQ v2.1 assesses how migraine prevents daily social and work-related activities (RFP domain) and the emotions associated with migraine (EF domain). An increase in scores from baseline indicates improvement.

The mean change from baseline for the AIM-D PDA domain (placebo: -6.1, 60 mg: -9.1) and AIM-D PI domain (placebo: -4.0, 60 mg: -6.4) demonstrated greater improvements with AQUIPTA 60 mg QD across the 12-week treatment period. The change was significant when adjusted for multiple comparisons. At week 12, the mean change from baseline for the MSQ v2.1 RFP domain (placebo: 16.9, 60 mg: 23.9) and EF domain (placebo: 18.2, 60 mg: 28.8) demonstrated greater improvements with AQUIPTA 60 mg QD (not controlled for multiple comparisons).

Figure 4 shows the mean change from baseline in MMD in ADVANCE. Patients treated with AQUIPTA 60 mg QD had greater mean decreases from baseline in MMD across the 12-week treatment period compared to patients who received placebo. During the first month of treatment (starting the first day after the initial dose), AQUIPTA 60 mg QD had greater mean decreases from baseline in weekly migraine days compared to placebo-treated patients.

Figure 4: Change from baseline in monthly migraine days in ADVANCE



In patients failing one or more prophylactic medications, the treatment difference for the reduction of MMD observed as compared to placebo across the 12-week treatment period was -2.2 (95% CI: -3.0, -1.3) for AQUIPTA 60 mg.

The proportions of participants with ≥ 50%, ≥ 75%, and 100% reduction in monthly migraine days was greater in the AQUIPTA 60 mg QD treatment group than in the placebo treatment group for each of the 4-week intervals assessed (weeks 1 to 4, 5 to 8, and 9 to 12), and the percentage of responders at each threshold increased over time.

Table 5: Reduction of ≥ 50%, ≥ 75%, and 100% from baseline in MMD by 4-week interval[a]

	AQUIPTA 60 mg (%)	**Placebo (%)**
≥ 50% MMD Responders		
Weeks 1-4	59	27
Weeks 5-8	66	46
Weeks 9-12	71	44
≥ 75% MMD Responders		
Weeks 1-4	39	10
Weeks 5-8	40	17
Weeks 9-12	49	22
100% MMD Responders		

	AQUIPTA 60 mg (%)	**Placebo (%)**
Weeks 1-4	19	4
Weeks 5-8	24	8
Weeks 9-12	27	12

[a] $p < 0.001$ for all comparisons between AQUIPTA 60 mg and placebo (not adjusted for multiple comparisons)

Long-term efficacy

Efficacy was sustained for up to one year in an open-label study in which patients with episodic migraine received AQUIPTA 60 mg once daily. 68.4% of patients completed the treatment period. The reduction in the least-squares mean number of monthly migraine days in the first month (weeks 1-4) was -3.8 days and improved to a least-squares mean reduction of -5.2 days in the last month (weeks 49-52). Approximately 84%, 70%, and 48% of patients reported ≥ 50%, ≥ 75%, and 100% reduction in monthly migraine days at weeks 49-52, respectively.

Patients with previous failure to 2 to 4 classes of oral prophylactic treatments

In the ELEVATE study, 315 adult patients with episodic migraine who previously failed 2 to 4 classes of oral prophylactic treatments (e.g., topiramate, tricyclic antidepressants, beta-blockers) based on efficacy and/or tolerability were randomised 1:1 to receive either atogepant 60 mg (N = 157) or placebo (N = 158) for 12 weeks. Results in this study were consistent with the main findings of previous episodic migraine efficacy studies and statistically significant for primary and secondary efficacy endpoints including several patient-reported outcome measures assessing functioning. Atogepant treatment led to a reduction of 4.2 days in mean MMD compared to 1.9 days in the placebo group ($p<0.001$). 50.6% (78/154) of patients in the atogepant group achieved at least a 50% reduction from baseline in MMD compared to 18.1% (28/155) in the placebo group (odds ratio [95% CI]: 4.82 [2.85, 8.14], $p<0.001$).

Chronic Migraine

AQUIPTA was evaluated for the prophylaxis of chronic migraine (15 or more headache days per month with at least 8 migraine days) in a randomised, multicentre, double-blind, placebo-controlled study (PROGRESS). A total of 521 patients were randomised 1:1 to receive AQUIPTA 60 mg (N = 262) or placebo (N = 259) once daily for 12 weeks. A subset of patients (11%) was allowed to use one concomitant migraine prophylaxis medication (e.g., amitriptyline, propranolol, topiramate). Patients were allowed to use acute headache treatments (i.e., triptans, ergotamine derivatives, NSAIDs, acetaminophen and opioids) as needed. Patients with acute medication overuse and medication overuse headache also were enrolled.

A total of 463 (89%) patients completed the 12-week double-blind study. Patients had a mean age of 42 years (range: 18 to 74 years), 87% were female, and 59% were white. The mean migraine frequency at baseline was approximately 19 migraine days per month and was similar across treatment groups.

The primary efficacy endpoint was the change from baseline in mean MMD across the 12-week treatment period. Additional 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% and 75%

reduction from baseline in mean MMD (3-month average), and change from baseline at week 12 for HIT-6 total score and MSQ v2.1 RFR domain score.

Key efficacy results of PROGRESS are summarized in Table 6.

Table 6: Efficacy endpoints in PROGRESS

	AQUIPTA 60 mg N=257	**Placebo N=249**
Monthly Migraine Days (MMD) across 12 weeks		
Baseline	19.2	19.0
Mean change from baseline	-6.8	-5.1
Difference from placebo (95% CI)	-1.7 (-2.7, -0.6)	
p-value	0.002	
Monthly Headache Days across 12 weeks		
Baseline	21.5	21.4
Mean change from baseline	-6.9	-5.2
Difference from placebo (95% CI)	-1.7 (-2.8, -0.7)	
p-value	0.002	
Monthly Acute Medication Use Days across 12 weeks		
Baseline	15.5	15.3
Mean change from baseline	-6.2	-4.1
Difference from placebo (95% CI)	-2.1 (-3.1, -1.1)	
p-value	0.002	
≥ 50% MMD Responders across 12 weeks		
% Responders	40	27
Difference from placebo (%)	14	
p-value	0.002	
≥ 75% MMD Responders across 12 weeks		
% Responders	18	6
Difference from placebo (%)	13	
p-value	<0.001[a]	
HIT-6[b] at week 12		
Baseline	64.4	63.8
Mean change from baseline	-7.8	-5.2
Difference from placebo (95% CI)	-2.7 (-4.0, -1.3)	
p-value	<0.001	

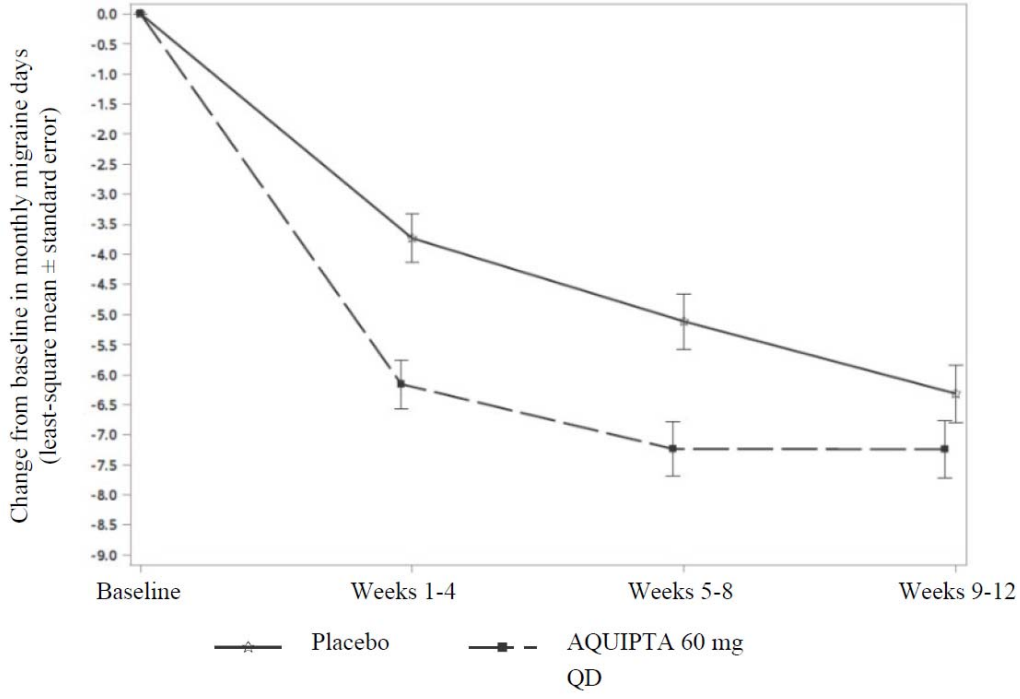
	AQUIPTA 60 mg N=257	Placebo N=249
MSQ v2.1 RFR[c] at week 12		
Baseline	43.3	44.1
Mean change from baseline	23.1	17.3
Difference from placebo (95% CI)	5.8 (2.2, 9.4)	
p-value	0.002	

[a] Not adjusted for multiple comparisons
[b] Headache Impact Test total score
[c] Migraine Specific Quality of Life Questionnaire version 2.1 Role Function-Restrictive domain score

Additional pre-specified endpoints included the MSQ v2.1 RFP and EF domains. The mean change from baseline for the MSQ v2.1 RFP domain (placebo: 13.6, 60 mg: 19.9) and EF domain (placebo: 15.7, 60 mg: 22.4) demonstrated greater improvements with AQUIPTA 60 mg QD at week 12 (not controlled for multiple comparisons).

Figure 5 shows the mean change from baseline in MMD in PROGRESS. Patients treated with AQUIPTA 60 mg QD had a greater mean decrease from baseline in MMD across the 12-week treatment period compared to patients who received placebo.

Figure 5: Change from baseline in monthly migraine days in PROGRESS



In patients failing one or more prophylactic medications with the same mechanism of action, the treatment difference for the reduction of MMD observed between AQUIPTA 60 mg and placebo across the 12-week treatment period was -1.5 (95%

CI: -3.3, 0.4). In patients failing two or more prophylactic medications with different mechanisms of action, the treatment difference was -2.4 (95% CI: -4.2, -0.6).

The proportions of participants with ≥ 50%, ≥ 75%, and 100% reduction in monthly migraine days was greater in the AQUIPTA 60 mg QD treatment group than in the placebo treatment group for each of the 4-week intervals assessed (weeks 1 to 4, 5 to 8, and 9 to 12), and the percentage of responders at each threshold increased over time.

Table 7: Reduction of ≥ 50%, ≥ 75%, and 100% from baseline in MMD by 4-week interval

	AQUIPTA 60 mg (%)	**Placebo (%)**
≥ 50% MMD Responders		
Weeks 1-4	39[a]	18
Weeks 5-8	43[a]	31
Weeks 9-12	44	38
≥ 75% MMD Responders		
Weeks 1-4	17[a]	5
Weeks 5-8	24[a]	10
Weeks 9-12	28[a]	15
100% MMD Responders		
Weeks 1-4	4[b]	0
Weeks 5-8	6[a]	<1
Weeks 9-12	7[b]	3

[a] p<0.01 for comparison between AQUIPTA 60 mg and placebo (not adjusted for multiple comparisons)

[b] p<0.03 for comparison between AQUIPTA 60 mg and placebo (not adjusted for multiple comparisons)

5.2 Pharmacokinetic properties

Absorption

Following oral administration of AQUIPTA, atogepant is rapidly absorbed with plasma concentrations >14 nM (EC_{90} based on capsaicin induced dermal vasodilation model [CIDV]) within 0.5 hours and median T_{max} values ranging from 1 to 2 hours. Atogepant displays dose-proportional pharmacokinetics through 300 mg single dose with no accumulation upon once daily dosing.

Effect of food

When AQUIPTA was administered with a high-fat meal, the food effect was not significant (AUC and C_{max} were reduced by approximately 18% and 22%,

respectively, with no effect on median time to maximum atogepant plasma concentration). AQUIPTA was administered without regard to food in clinical efficacy studies.

Distribution

Plasma protein binding of atogepant was not concentration-dependent in the range of 0.1 to 10 µM; the unbound fraction of atogepant was approximately 4.7% in human plasma. The mean apparent volume of distribution of atogepant (V_z/F) after oral administration is approximately 292 L.

Biotransformation

Atogepant is eliminated mainly through metabolism, primarily by CYP3A4. The parent compound (atogepant), and a glucuronide conjugate metabolite (M23) were the most prevalent circulating components in human plasma.

In vitro studies

Enzymes

In vitro, atogepant is not an inhibitor for CYPs 3A4, 1A2, 2B6, 2C8, 2C9, 2C19, or 2D6 at clinically relevant concentrations. Atogepant does not inhibit MAO-A or UGT1A1 at clinically relevant concentrations. Atogepant is not anticipated to be a clinically significant perpetrator of drug-drug interactions through CYP450s, MAO-A, or UGT1A1 inhibition.

Atogepant is not an inducer of CYP1A2, CYP2B6, or CYP3A4 at clinically relevant concentrations.

Transporters

Atogepant is a substrate of P-gp, BCRP, OATP1B1, OATP1B3, and OAT1. Dose adjustment for concomitant use of AQUIPTA with strong inhibitors of OATP is recommended based on a clinical interaction study with a strong OATP inhibitor.

Co-administration of atogepant with BCRP and/or P-gp inhibitors is not expected to increase the exposure of atogepant. Atogepant is not a substrate of OAT3, OCT2, or MATE1.

Atogepant is not an inhibitor of P-gp, BCRP, OAT1, OAT3, NTCP, BSEP, MRP3, or MRP4 at clinically relevant concentrations. Atogepant is a weak inhibitor of OATP1B1, OATP1B3, OCT1, and MATE1. No clinical drug interactions are expected for atogepant as a perpetrator with these transporters.

In vivo studies

CYP3A4 inhibitors

Co-administration of AQUIPTA with itraconazole, a strong CYP3A4 inhibitor, resulted in a clinically significant increase (C_{max} by 2.15-fold and AUC by 5.5-fold) in the exposure of atogepant in healthy subjects.

Physiologically based pharmacokinetic (PBPK) modeling suggested co-administration of AQUIPTA with moderate (e.g., ciclosporin, ciprofloxacin, fluconazole, fluvoxamine, grapefruit juice) or weak (e.g., cimetidine, esomeprazole) CYP3A4 inhibitors increases atogepant AUC by 1.7- and 1.1-fold, respectively. The changes in atogepant exposure when coadministered with weak or moderate CYP3A4 inhibitors are not expected to be clinically significant.

CYP3A4 inducers

Co-administration of AQUIPTA with rifampicin, a strong CYP3A4 inducer, decreased atogepant AUC by 60% and C_{max} by 30% in healthy subjects. No dedicated

drug interaction studies were conducted to assess concomitant use with moderate CYP3A4 inducers. Moderate inducers of CYP3A4 can decrease atogepant exposure. Clinically significant interaction was not observed with concomitant administration of AQUIPTA and topiramate, a weak inducer of CYP3A4.

BCRP/OATP/P-gp inhibitors

Co-administration of AQUIPTA with single dose rifampicin, a strong OATP inhibitor, increased atogepant AUC by 2.85-fold and C_{max} by 2.23-fold in healthy subjects.

Co-administration of AQUIPTA with quinidine, a P-gp inhibitor, increased atogepant AUC by 26% and C_{max} by 4% in healthy subjects. The changes in atogepant exposure when co-administered with P-gp inhibitors are not expected to be clinically significant.

PBPK modeling suggests that co-administration of AQUIPTA with BCRP inhibitors increases atogepant exposure by 1.2-fold. This increase is not expected to be clinically significant.

OCT1 substrates

Co-administration of sumatriptan, an OCT1 substrate, with AQUIPTA did not result in significant change in the systemic exposure of either drug.

Other drug interaction evaluations

Co-administration of AQUIPTA with oral contraceptive components ethinyl estradiol and levonorgestrel, famotidine, esomeprazole, acetaminophen, naproxen, sumatriptan, topiramate, or ubrogepant did not result in significant pharmacokinetic interactions for either atogepant or co-administered drugs.

Elimination

The elimination half-life of atogepant is approximately 11 hours. The mean apparent oral clearance (CL/F) of atogepant is approximately 19 L/h. Following single oral dose of 50 mg ^{14}C-atogepant to healthy male subjects, 42% and 5% of the dose was recovered as unchanged atogepant in faeces and urine, respectively.

Specific populations

Patients with renal impairment

The renal route of elimination plays a minor role in the clearance of atogepant. Based on PBPK and population pharmacokinetic analysis, there is no significant difference in the pharmacokinetics of atogepant in patients with mild or moderate renal impairment (CLcr 30-89 mL/min) relative to those with normal renal function (CLcr >90 mL/min). As patients with severe renal impairment or end-stage renal disease (ESRD; CLcr <30 mL/min) have not been studied, use of atogepant 10 mg is recommended in those patients.

Patients with hepatic impairment

In patients with pre-existing mild (Child-Pugh Class A), moderate (Child-Pugh Class B), or severe hepatic impairment (Child-Pugh Class C), total atogepant exposure was increased by 24%, 15% and 38%, respectively. However, unbound atogepant exposure was approximately 3-fold higher in patients with severe hepatic impairment. Avoid use of AQUIPTA in patients with severe hepatic impairment.

Other specific populations

Based on a population pharmacokinetic analysis, age, sex, race, and body weight did not have a significant effect on the pharmacokinetics (C_{max} and AUC) of atogepant. Therefore, no dose adjustments are warranted based on these factors.

5.3 Preclinical safety data

Carcinogenicity

Atogepant was administered orally to mice (0, 5, 20, or 75 mg/kg/day in males; 0, 5, 30, or 160 mg/kg/day in females) and rats (0, 10, 20, or 100 mg/kg in males; 0, 25, 65, or 200 mg/kg in females) for up to 2 years. There was no evidence of drug-related tumours in either species. Plasma exposures at the highest doses tested in mice and rats were approximately 8 and 20-35 times, respectively, that in humans at the maximum recommended human dose (MRHD) of 60 mg/day.

Mutagenicity

Atogepant was negative in in vitro (Ames, chromosomal aberration test in Chinese Hamster Ovary cells) and in vivo (rat bone marrow micronucleus) assays.

Impairment of fertility

Oral administration of atogepant (0, 5, 20, or 125 mg/kg/day) to male and female rats prior to and during mating and continuing in females to Gestation Day 7 resulted in no adverse effects on fertility or reproductive performance. Plasma exposures (AUC) at the highest dose tested are approximately 15 times that in humans at the MRHD.

Reproductive and developmental toxicology

Oral administration of atogepant to pregnant rats and rabbits during the period of organogenesis resulted in decreased foetal body weight in rats and an increased incidence of foetal visceral and skeletal variations at doses associated with minimal maternal toxicity. At the no-effect dose for adverse effects on embryofoetal development, plasma exposure (AUC) was approximately 4 times in rats and 3 times in rabbits that in humans at the MRHD of 60 mg/day.

Oral administration of atogepant to rats throughout gestation and lactation resulted in decreased pup body weight at the highest dose tested which persisted into adulthood. At the no observed effect dose, plasma exposure (AUC) was approximately 5 times that in humans at the MRHD.

In lactating rats, oral dosing with atogepant resulted in levels of atogepant in milk approximately 2-fold higher than those in maternal plasma.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Polyvinylpyrrolidone/Vinyl acetate copolymer

Vitamin E polyethylene glycol succinate

Mannitol

Microcrystalline cellulose

Sodium chloride

Croscarmellose sodium

Colloidal silicon dioxide

Sodium stearyl fumarate

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Aluminium foil and PVC/PE/PCTFE blisters in packs containing 2, 7, 28 or 98 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

AbbVie Ltd

Maidenhead
SL6 4UB
UK

8 MARKETING AUTHORISATION NUMBER(S)

PLGB 41042/0089

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

30/08/2023

10 DATE OF REVISION OF THE TEXT

22/04/2026