swissmedic

*Date:* 29 April 2024
Swissmedic, Swiss Agency for Therapeutic Products

# *Swiss Public Assessment Report*

# Aquipta

**International non-proprietary name:** atogepant
**Pharmaceutical form:** tablets
**Dosage strength(s):** 10 mg, 60 mg
**Route(s) of administration:** oral use
**Marketing authorisation holder:** AbbVie AG
**Marketing authorisation no.:** 69128
**Decision and decision date:** approved on 6 March 2024

**Note:**

This assessment report is as adopted by Swissmedic with all information of a commercially confidential nature deleted.

SwissPARs are final documents that provide information on submissions at a particular point in time. They are not updated after publication.

**Table of contents**

# 1 Terms, Definitions, Abbreviations

| | |
|---|---|
| ADA | Anti-drug antibody |
| ADME | Absorption, distribution, metabolism, elimination |
| AE | Adverse event |
| ALT | Alanine aminotransferase |
| API | Active pharmaceutical ingredient |
| AST | Aspartate aminotransferase |
| ATC | Anatomical Therapeutic Chemical Classification System |
| AUC | Area under the plasma concentration-time curve |
| $AUC_{0\text{-}24h}$ | Area under the plasma concentration-time curve for the 24-hour dosing interval |
| CGRP | Calcitonin gene-related peptide |
| CI | Confidence interval |
| $C_{max}$ | Maximum observed plasma/serum concentration of drug |
| CYP | Cytochrome P450 |
| DDI | Drug-drug interaction |
| EMA | European Medicines Agency |
| ERA | Environmental risk assessment |
| FDA | Food and Drug Administration (USA) |
| GI | Gastrointestinal |
| GLP | Good Laboratory Practice |
| HPLC | High-performance liquid chromatography |
| $IC/EC_{50}$ | Half-maximal inhibitory/effective concentration |
| ICH | International Council for Harmonisation |
| Ig | Immunoglobulin |
| INN | International non-proprietary name |
| ITT | Intention-to-treat |
| LoQ | List of Questions |
| MAH | Marketing authorisation holder |
| Max | Maximum |
| Min | Minimum |
| MRHD | Maximum recommended human dose |
| N/A | Not applicable |
| NO(A)EL | No observed (adverse) effect level |
| PBPK | Physiology-based pharmacokinetics |
| PD | Pharmacodynamics |
| PIP | Paediatric investigation plan (EMA) |
| PK | Pharmacokinetics |
| PopPK | Population pharmacokinetics |
| PSP | Pediatric study plan (US FDA) |
| RMP | Risk management plan |
| SAE | Serious adverse event |
| SwissPAR | Swiss Public Assessment Report |
| TEAE | Treatment-emergent adverse event |
| TPA | Federal Act of 15 December 2000 on Medicinal Products and Medical Devices (SR 812.21) |
| TPO | Ordinance of 21 September 2018 on Therapeutic Products (SR 812.212.21) |

# 2 Background information on the procedure

## 2.1 Applicant's request(s)

**New active substance status**
The applicant requested new active substance status for atogepant in the above-mentioned medicinal product.

## 2.2 Indication and dosage

### 2.2.1 Requested indication

Aquipta is indicated for the preventive treatment of migraine in adults who have at least 4 migraine attacks per month.

### 2.2.2 Approved indication

Prophylactic treatment of migraine in adults, when indicated.

### 2.2.3 Requested dosage

**Summary of the requested standard dosage:**
The recommended dosage is **60 mg** taken orally once daily, with or without food.

*Dosing modification due to interactions*
Dosing modifications for concomitant use of specific drugs are provided in Table 1 (see "Interactions").
Table 1: Dosing modifications for drug interactions

| Dosage modifications | Recommended dosage (once daily) |
|---|---|
| Strong CYP3A4 inhibitors | **10 mg** |
| Strong OATP inhibitors | **10 mg** |

…
*Patients with renal impairment*
Patients with severe renal impairment (CrCl 15–29 mL/min) and patients with end-stage renal disease (CrCl <15 mL/min): **10 mg** once daily

### 2.2.4 Approved dosage

(see appendix)

## 2.3 Regulatory history (milestones)

| | |
|---|---|
| Application | 16 September 2022 |
| Formal control completed | 28 September 2022 |
| List of Questions (LoQ) | 6 February 2023 |
| Response to LoQ | 7 May 2023 |
| Preliminary decision | 4 August 2023 |
| Response to preliminary decision | 1 September 2023 |
| Labelling corrections | 13 November 2023 |
| Response to labelling corrections | 3 December 2023 |

| | |
|---|---|
| 2nd round labelling corrections | 22 December 2023 |
| Response to 2nd round labelling corrections | 21 January 2024 |
| Final decision | 6 March 2024 |
| Decision | approval |

# 3 Medical context

Migraine is a common neurological disorder that affects around 5% of the adult population (1-year prevalence: 8% in men, 20% in women) in Western countries. It is characterised by episodic, often disabling headache, associated with sensory (aura) and autonomic symptoms (nausea, vomiting), phonophobia and photophobia, and cognitive symptoms. Migraine attacks typically last from 4 to 72 hours if untreated or unsuccessfully treated. Episodic migraine is defined as <15 headache days per month, although in clinical prophylactic trials a lower threshold of a minimum of 4 headache days is often chosen to reflect typical patients in need of prophylactic treatment. Chronic migraine is defined as 15 or more headache days per month, of which at least 8 are typical migraine days.

There are established and approved substances for the acute treatment of migraine symptoms (such as triptans) and substances for the prevention of migraine attacks (such as beta blockers, topiramate, or the CGRP antibodies). Not all patients respond to the respective treatments, and often, several substances have to be tested sequentially to find a suitable treatment option. There is still a clear need for additional options for acute treatment and prophylaxis of migraine attacks.

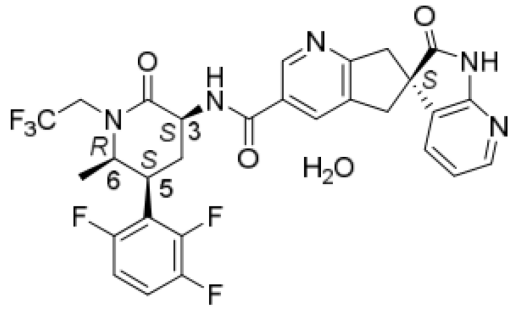
Blocking the calcitonin gene-related peptide (CGRP) or the CGRP receptor has emerged as a possible mechanism for the prevention of migraine attacks, as well as for the treatment of acute migraine attacks. Amongst others, decreasing blood flow in cerebral vessels and inhibition of pain transmission in the trigeminal ganglion are discussed as possible mechanisms for CGRP-blocking agents.

While consistent efficacy and a good safety profile have been observed for the antibodies targeting the CGRP pathway, they have to be injected subcutaneously or intravenously and have a long half-life, which makes them less flexible in case of treatment regimen changes. Oral CGRP antagonists with a shorter half-life (rimegepant, ubrogepant, atogepant) have been approved in the US and recently in the EU (rimegepant, atogepant) for the acute treatment of migraine attacks (rimegepant, ubrogepant) or for the prevention of migraine attacks (rimegepant, atogepant). Migraine therapy with a short-acting oral agent for the prevention of attacks in episodic and chronic migraine could simplify the medication regimen and offer more flexibility when adverse effects occur.

# 4 Quality aspects

## 4.1 Drug substance

| | |
|---|---|
| INN: | Atogepant |
| Chemical name: | (3'S)-N-[(3S,5S,6R)-6-methyl-2-oxo-1-(2,2,2-trifluoroethyl)-5-(2,3,6-trifluorophenyl)piperidin-3-yl]- 2'-oxo-1',2',5,7-tetrahydrospiro[cyclopenta[b]pyridine-6,3'-pyrrolo[2,3-b]pyridine]-3-carboxamide |
| Molecular formula: | $C_{29}H_{25}F_6N_5O_4$ (as free base monohydrate) |
| Molecular mass: | 621.544 g/mol |
| Molecular structure: | |




Physico-chemical properties:
Atogepant is a white to off-white powder. It has 4 chiral centres. Atogepant crystalline free base monohydrate demonstrates low solubility in water and bio-relevant media. Thus, the compound is considered a substance with low solubility in the biopharmaceutical classification system.

Synthesis:
The drug substance is manufactured by multiple-step chemical synthesis with final crystallisation resulting in the monohydrate form. The synthesis of the drug substance and the in-process controls are described in detail.

Specification:
The specifications are in line with the recommendations of the relevant ICH guidelines and are considered appropriate in order to ensure consistent quality of atogepant.

Stability:
Atogepant monohydrate drug substance is packaged in double-lined low-density polyethylene (LDPE) bags. Appropriate stability data from primary and supportive stability batches have been generated, resulting in a suitable retest period when packaged in the packaging type as described above.

## 4.2 Drug product

Description and composition:
The drug product is an immediate-release tablet intended for oral administration. The tablets are provided in 2 strengths: Atogepant 10 mg is a white to off-white, round biconvex tablet with “A10” debossed on one side. Atogepant 60 mg is a white to off-white, oval biconvex tablet with “A60” debossed on one side. The tablets consist of the pharmaceutical excipients polyvinylpyrrolidone/vinyl acetate copolymer, vitamin E polyethylene glycol succinate, mannitol, microcrystalline cellulose, sodium chloride, croscarmellose sodium, colloidal silicon dioxide, and sodium stearyl fumarate.

Pharmaceutical development:
Atogepant drug product was developed as a white to off-white immediate-release oral tablet and utilises only compendial excipients.

Manufacture:
The atogepant drug product manufacturing process comprises 4 unit operations. The manufacturing process is described with a sufficient level of detail. In order to achieve consistent quality of the tablets, appropriate in-process controls are applied.

Specification:
For the control of the finished product, adequate tests and criteria for release and at shelf-life are established. The specifications include the parameters appearance, identification, content uniformity, impurities, dissolution, water content, and microbiological purity. The test methods applied are adequately validated according to the recommendations of the current scientific guidelines.

Container closure system:
The primary container closure system used for commercial distribution of atogepant tablets is a unit-dose blister composed of an aluminium lidding foil with a thermoforming film-laminated layer.

Stability:
Appropriate stability data are presented for 3 primary stability batches for both the 10 and 60 mg tablets. Based on these data, a shelf-life was established. The storage recommendation is “Do not store above 30°C”.

## 4.3 Quality conclusions

Satisfactory and consistent quality of the drug substance and drug product has been demonstrated.

# 5 Nonclinical aspects

Regarding the marketing authorisation application for Aquipta (new active substance atogepant), the Nonclinical Assessment Division conducted an abridged evaluation based on the FDA assessment report (Integrated Review), the EMA Day 120 assessment report, and the applicant's responses to the EMA Day 120 LoQ, which were provided by the applicant.
Overall, the submitted nonclinical documentation is considered appropriate to support the approval of atogepant in the proposed indication. The pharmaco-toxicological profile has been sufficiently characterised. Since the exposure of female mice in the carcinogenicity study did not meet the requirements for a high dose, the FDA requested an additional study; the submission of this study is a post-approval requirement.
All nonclinical data that are relevant for safety are mentioned in the information for healthcare professionals.
Based on the ERA, atogepant is unlikely to represent a risk for the environment.

# 6 Clinical aspects

The evaluation of the clinical and clinical pharmacology data of this application has been carried out in reliance on previous regulatory decisions by the EMA and FDA. The available assessment reports from the EMA and FDA were used as a basis for the clinical and clinical pharmacology evaluation. For further details concerning clinical pharmacology, efficacy, and safety, please see section 8 of this report.

# 7 Risk management plan summary

The RMP summaries contain information on the medicinal products' safety profiles and explain the measures that are taken to further investigate and monitor the risks, as well as to prevent or minimise them.
The RMP summaries are published separately on the Swissmedic website. It is the responsibility of the marketing authorisation holder to ensure that the content of the published RMP summaries is accurate and correct. As the RMPs are international documents, their summaries might differ from the content in the information for healthcare professionals / product information approved and published in Switzerland, e.g. by mentioning risks that occur in populations or indications not included in the Swiss authorisations.

# 8 Appendix

## Approved information for healthcare professionals

Please be aware that the following version of the information for healthcare professionals for Aquipta was approved with the submission described in the SwissPAR. This information for healthcare professionals may have been updated since the SwissPAR was published.

Please note that the valid and relevant reference document for the effective and safe use of medicinal products in Switzerland is the information for healthcare professionals currently authorised by Swissmedic (see www.swissmedicinfo.ch).

**Note:**
The following information for healthcare professionals has been translated by the MAH. It is the responsibility of the authorisation holder to ensure the translation is correct. The only binding and legally valid text is the information for healthcare professionals approved in one of the official Swiss languages.

▼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 new or serious adverse reactions. See the "Undesirable effects" section for advice on the reporting of adverse reactions.

## AQUIPTA

### Composition

*Active substances*

Atogepant

*Excipients*

Polyvinylpyrrolidone/Vinyl acetate copolymer Type K-28, Vitamin E polyethylene glycol succinate, Mannitol (E 421), Microcrystalline cellulose, Sodium chloride, Croscarmellose sodium, Colloidal silicon dioxide, Sodium stearyl fumarate
1 tablet of 10 mg or 60 mg contains 5,26 mg of sodium or 31,48 mg of sodium, respectively.

### Pharmaceutical form and active substance quantity per unit

*AQUIPTA 10 mg tablets*

1 tablet contains 10 mg of atogepant. White to off-white, round biconvex tablet debossed with “A” and “10” on one side.

*AQUIPTA 60 mg tablets*

1 tablet contains 60 mg of atogepant. White to off-white, oval biconvex tablet debossed with “A60” on one side.

### Indications/Uses

Prophylactic treatment of migraine in adults when indicated.

### Dosage/Administration

The indication for the therapy should be made by a physician with experience in the field of migraine treatment and accompanied by them in the further treatment.

*Usual dosage*

The recommended dose for AQUIPTA is 60 mg taken orally once daily.

*Dose adjustment following interactions*

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

**Table 1: Dose modifications for interactions and for special patient groups**

| **Dosage modifications** | **Recommended once daily dose** |
|---|---|
| Strong CYP3A4 inhibitors | 10 mg |
| OATP inhibitors | 10 mg |
| Severe renal impairment and end-stage renal disease (CLcr < 30 mL/min) | 10 mg |

*Special dosage instructions*

*Elderly patients*

Population pharmacokinetic modelling suggests no clinically significant pharmacokinetic differences between elderly (≥ 65 years of age) and younger subjects. No dose adjustment of AQUIPTA is needed in elderly patients.

*Patients with hepatic disorders*

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 “Pharmacokinetics”).

*Patients with renal disorders*

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 “Pharmacokinetics”).

*Children and adolescents*

The safety and efficacy of AQUIPTA in children and adolescents below 18 years of age have not yet been established. No data are available. AQUIPTA is not authorised for use in the paediatric population.

*Delayed administration*

A missed dose should be taken as soon as it is remembered. If it is forgotten for an entire day, the missed dose should be skipped and the next dose taken as scheduled.

*Mode of administration*

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

**Contraindications**

Hypersensitivity to the active substance or to any of the excipients (listed in section “Composition”).

**Warnings and precautions**

*Hepatic disorders*

AQUIPTA is not recommended in patients with severe hepatic impairment (see "Dosage/Administration").

*Patients not studied in Phase 3 clinical trials*

Patients with clinically relevant cardiovascular or cerebrovascular disorders such as ischemic heart disease, cardiac arrhythmia or conduction disorders, myocardial infarction, transient ischemic attack, heart failure, or uncontrolled hypertension were excluded from the pivotal studies. No safety data are available for these patients.

*Medication overuse headache (MOH)*

Overuse of acute treatment medication for headaches can make them worse. Although there is no evidence that once-daily administration of atogepant for preventive treatment can cause MOH, a diagnosis of MOH should be suspected in patients who experience regular or daily headaches despite (or because of) regular use of acute treatment medication. If this is the case or suspected, the acute treatment medication should be discontinued.

*Sodium*

AQUIPTA 10 mg tablets contain less than 1 mmol sodium (23 mg) per tablet, that is to say essentially “sodium-free”.
AQUIPTA 60 mg tablets contain 31.49 mg sodium per tablet; this is equivalent to 1.6% of the WHO recommended maximum daily intake of 2 g sodium for an adult.

## Interactions

*Effect of other medicinal products on AQUIPTA*

Atogepant is mainly eliminated via the metabolism, primarily by CYP3A4.

*In vitro*, atogepant is a substrate of P-gp, BCRP, OATP1B1, OATP1B3 and OAT1. Atogepant is not a substrate of OAT3, OCT2 or MATE1.

Drug interaction studies were conducted with the coadministered drugs listed in the following table.

**Table 2. Clinical effects of other medicines on Atogepant**

| Coadministered drug (enzyme or transporter) | Dosage of the co-administered drug | Dosage of Atogepant | GMR[a] (90% CI[b]) | | Dosage recommendation for atogepant |
|---|---|---|---|---|---|
| | | | $C_{max}$ | AUC | |
| Itraconazole (strong CYP3A4 inhibitor) | 200 mg once daily for 7 days | single 60 mg dose | 2.15 (1.95, 2.37) | 5.51 (5.09, 5.96) | 10 mg once daily |
| Rifampin (OATP inhibitor) | single 600 mg dose | single 60 mg dose | 2.23 (1.99, 2.50) | 2.85 (2.60, 3.12) | 10 mg once daily |
| Rifampin (strong CYP3A4 inducer) | 600 mg once daily for 7 days | single 60 mg dose | 0.70 (0.60, 0.81) | 0.39 (0.35, 0.44) | No dose adjustment of atogepant is recommended |
| Topiramate (weak CYP3A4 inducer) | 100 mg twice daily for 5 days | 60 mg once daily for 17 days | 0.76 (0.68, 0.85) | 0.75 (0.69, 0.81) | |
| Quinidine gluconate (P-gp inhibitor) | 648 mg twice daily for 4 days | single 60 mg dose | 1.04 (0.89, 1.22) | 1.26 (1.11, 1.43) | |
| Esomeprazole (proton pump inhibitor) | 40 mg once daily for 7 days | single 60 mg dose | 0.77 (0.68, 0.86) | 0.92 (0.84, 1.01) | |
| Famotidine ($H_2$ receptor blocker) | 20 mg twice | single 60 mg dose | 0.51 (0.41, 0.63) | 0.79 (0.67, 0.93) | |
| Sumatriptan (5-HT1B/1D receptor agonist) | single 100 mg dose | single 60 mg dose | 0.78 (0.69, 0.89) | 0.95 (0.86, 1.05) | |
| Ubrogepant (CGRP receptor antagonist) | 100 mg on Day 1 and every third day on Days 7-28 | 60 mg once daily, Days 2-28 | 1.04 (0.94, 1.15) | 1.04 (0.98, 1.12) | |
| Naproxen (NSAID) | single 500 mg dose | single 60 mg dose | 1.00 (0.91, 1.11) | 0.99 (0.92, 1.06) | |
| Acetaminophen (analgesic, antipyretic) | single 1000 mg dose | single 60 mg dose | 1.00 (0.90, 1.11) | 1.13 (1.04, 1.22) | |

[a]GMR - ratio of geometric means defined as the exposure (maximum concentration or area under the curve AUC) to atogepant when used with the concomitant medication divided by the exposure to atogepant without the concomitant medication; [b]CI - confidence interval.

*Effect of AQUIPTA on other medicinal products*

*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.
*In vitro*, 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.
Drug interaction studies were conducted with the coadministered drugs listed in the following table.

**Table 3. Clinical effects of Atogepant on other drugs**

| Coadministered drug (enzyme or transporter) | Dosage of the co-administered drug | Dosage of Atogepant | GMR[a] (90% CI[b]) | | Dosage recommendation for coadministered drug |
|---|---|---|---|---|---|
| | | | $C_{max}$ | AUC | |
| Topiramate (weak CYP3A4 inducer) | 100 mg twice daily for 11 days | 60 mg once daily for 7 days | 0.94 (0.87, 1.01) | 0.94 (0.88, 1.01) | No dose adjustment of coadministered drug is recommended |
| Sumatriptan (5-HT1B/1D receptor agonist) | single 100 mg dose | single 60 mg dose | 0.95 (0.85, 1.07) | 1.02 (0.97, 1.08) | |
| Ubrogepant (CGRP receptor antagonist) | 100 mg on Day 1 and every third day on Days 7-28 | 60 mg once daily, Days 2-28 | 1.26 (1.06, 1.49) | 1.19 (1.09, 1.30) | |
| Ethinyl estradiol (estrogen) | single 0.03 mg dose | 60 mg once daily for 17 days | 0.90 (0.84, 0.96) | 1.00 (0.96, 1.05) | |
| Levonorgestrel (progestin) | single 0.15 mg dose | 60 mg once daily for 17 days | 1.09 (1.03, 1.17) | 1.19 (1.13, 1.26) | |
| Naproxen (NSAID) | single 500 mg dose | single 60 mg dose | 0.94 (0.90, 0.97) | 0.98 (0.96, 1.00) | |
| Acetaminophen (analgesic, antipyretic) | single 1000 mg dose | single 60 mg dose | 0.89 (0.81, 0.97) | 0.94 (0.89, 0.99) | |

[a]GMR - ratio of geometric means defined as the exposure (maximum concentration or area under the curve AUC) to the concomitant medication when used with atogepant divided by the exposure to the concomitant medication without atogepant; [b]CI - confidence interval.

**Pregnancy, lactation**

*Pregnancy*

There are only limited data from the use of atogepant in pregnant women. Studies in animals have shown reproductive toxicity (see section “Preclinical Data”). The use of AQUIPTA during pregnancy and in women of childbearing age who are not using contraception is not recommended..

*Lactation*

It is unknown whether atogepant is excreted in human milk. Available toxicological data in animals have shown excretion of atogepant in milk. A risk to the newborns/infants cannot be excluded. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from AQUIPTA therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

*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.

**Effects on ability to drive and use machines**

No corresponding studies have been performed. However, AQUIPTA may cause fatigue/somnolence in some patients. Patients should exercise caution before driving or using machinery until they are reasonably certain that AQUIPTA does not adversely affect performance.

**Undesirable effects**

*Summary of the safety profile*

The safety of AQUIPTA was evaluated in 2657 patients with migraine who received at least one dose of AQUIPTA. Of these, 1225 patients were exposed to AQUIPTA for at least 6 months and 826 patients were exposed for 12 months.
In 12 -week, placebo-controlled clinical studies, 678 patients received at least one dose of AQUIPTA 60 mg once daily and 663 patients received placebo.
The most commonly reported adverse drug reactions were nausea (7%), constipation (7%), and fatigue/somnolence (5%). Most of the reactions were mild or moderate in severity. The adverse reaction that most commonly led to discontinuation was nausea (0.6%).

*List of adverse reactions*

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 (≥1/1000 to <1/100),

rare (≥1/10000 to <1/1000), very rare (<1/10000), not known (frequency cannot be estimated from the available data).

| System Organ Class | Frequency | Adverse Reaction |
|---|---|---|
| Metabolism and nutrition disorders | Common | Decreased appetite, weight decreased* |
| Gastrointestinal disorders | Common | Nausea, constipation |
| Hepatobiliary disorders | Uncommon | ALT/AST increased** |
| General disorders and administration site conditions | Common | Fatigue/somnolence |

*Defined in clinical trials as weight decrease of at least 7% at any point.

**Cases of ALT/AST elevations (Defined in clinical trials as ≥ 3xULN upper limit of normal) temporally associated with atogepant were observed in clinical trials, including cases with a positive dechallenge history that resolved within 8 weeks of discontinuation. However, the overall frequency was similar in the atogepant and placebo groups.

Reporting suspected adverse reactions after authorisation of the medicinal product is very important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions online via the ElViS portal (Electronic Vigilance System). You can obtain information about this at www.swissmedic.ch.

**Overdose**

In clinical studies, atogepant was administered as single doses up to 300 mg and as multiple doses up to 170 mg once daily. Adverse reactions were comparable to those seen at lower doses, and no specific toxicities were identified. 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.

**Properties/Effects**

*ATC code*

N02CD07

*Mechanism of action/pharmacodynamics*

Atogepant is a 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.

*Cardiac Electrophysiology*

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

*Clinical efficacy*

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). Patients were randomised to 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.

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

**Table 4: Efficacy endpoints in ADVANCE**

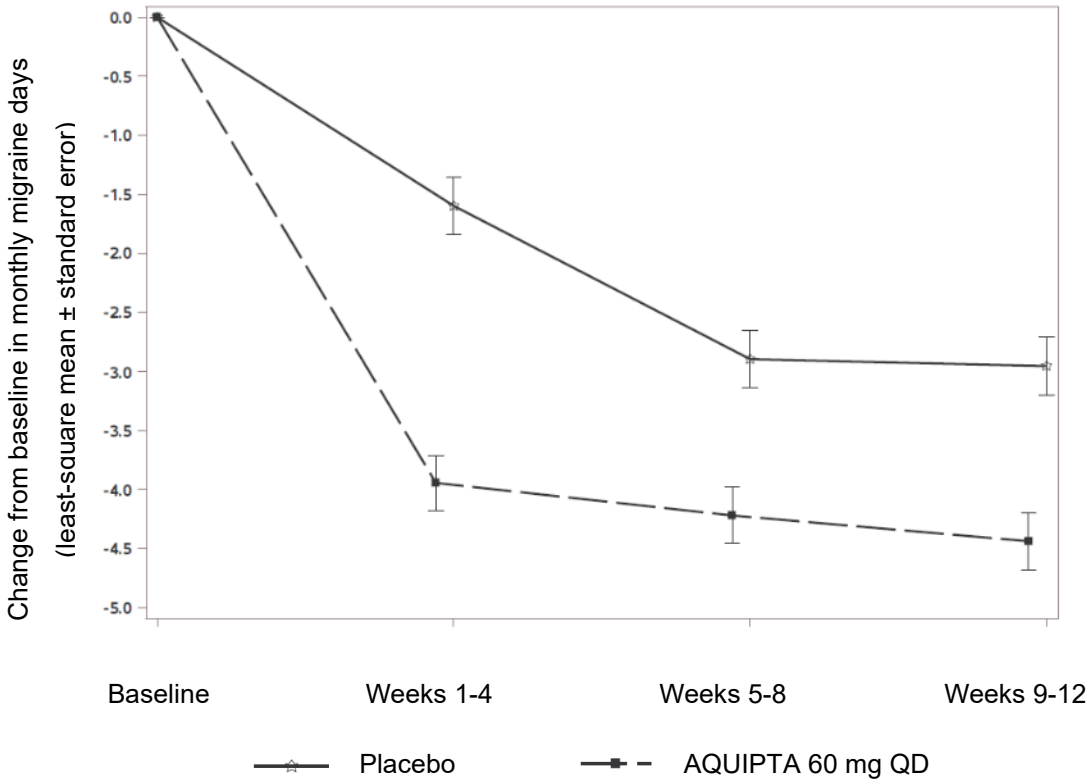
| | **AQUIPTA 60 mg N=226** | **Placebo N=216** |
|---|---|---|
| **Monthly migraine days (MMD) across 12 weeks** | | |
| Baseline | 7.8 | 7.5 |
| Mean change from baseline | -4.1 | -2.5 |
| Difference from placebo | -1.7 | |
| *p*-value | <0.001 | |
| **Monthly headache days across 12 weeks** | | |

| | | |
|---|---|---|
| Baseline | 9.0 | 8.5 |
| Mean change from baseline | -4.2 | -2.5 |
| Difference from placebo | -1.7 | |
| *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 | -1.4 | |
| *p*-value | <0.001 | |
| **≥ 50% MMD responders across 12 weeks** | | |
| % Responders | 59 | 29 |
| Odds ratio (95% CI) | 3.55 (2.39, 5.28) | |
| *p*-value | <0.001 | |
| **MSQ v2.1 RFR[a] at week 12** | | |
| Baseline | 46.6 | 46.6 |
| Mean change from baseline | 31.0 | 20.0 |
| Difference from placebo | 11.0 | |
| *p*-value | <0.001 | |

[a]Migraine Specific Quality of Life Questionnaire version 2.1 Role Function-Restrictive domain score

Figure 1 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, AQUIPTA 60 mg QD had greater mean decreases from baseline in weekly migraine days compared to placebo-treated patients.

**Figure 1: Change from baseline in monthly migraine days in ADVANCE**




*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.

*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). Patients were randomised to 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.

AQUIPTA treatment demonstrated statistically significant improvements for primary and key secondary efficacy results controlled for multiplicity compared to placebo in PROGRESS as summarized in Table 5.

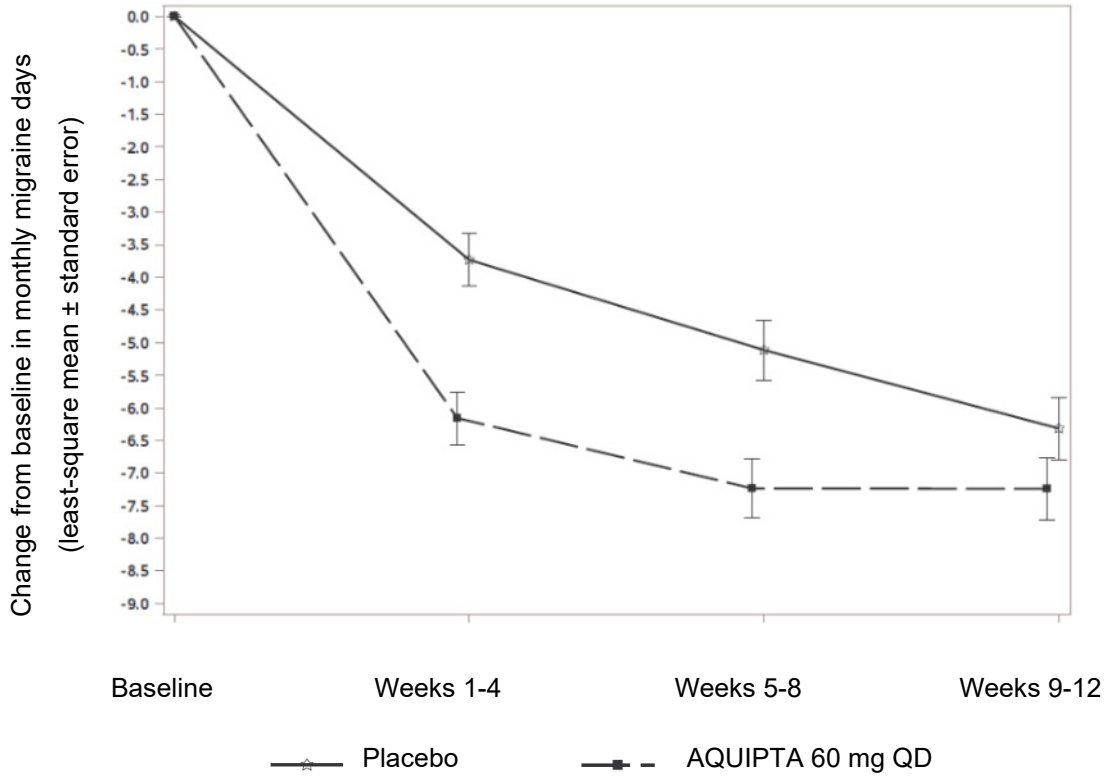
**Table 5: Efficacy endpoints in PROGRESS**

| | **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 | -1.7 | |
| *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 | -1.7 | |
| *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 | -2.1 | |
| *p*-value | 0.002 | |
| **≥ 50% MMD responders across 12 weeks** | | |
| % Responders | 40 | 27 |
| Difference from placebo (%) | 14 | |
| *p*-value | 0.002 | |
| **MSQ v2.1 RFR[a] at week 12** | | |
| Baseline | 43.3 | 44.1 |
| Mean change from baseline | 23.1 | 17.3 |
| Difference from placebo | 5.8 | |
| *p*-value | 0.002 | |

[a]Migraine Specific Quality of Life Questionnaire version 2.1 Role Function-Restrictive domain score

Figure 2 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 2: Change from baseline in monthly migraine days in PROGRESS**




*Paediatrics*

No data are available in children and adolescents under 18 years of age.

**Pharmacokinetics**

*Absorption*

Following oral administration of AQUIPTA, atogepant is rapidly absorbed with median $T_{max}$ values ranging from 1 to 2 hours. Following once daily dosing, atogepant displays dose-proportional pharmacokinetics up to 170 mg (approximately 3 times the highest recommended dose), with no accumulation.

*Influence of food*

When AQUIPTA was administered with a high-fat meal, the influence of food 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.

*Metabolism*

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.

*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.

*Kinetics in specific patient groups*

Based on a population pharmacokinetic analysis, age (18 to 78 years), sex, race (Caucasian vs Japanese or Chinese), and body weight (40.7 to 196 kg) 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.

*Renal impairment*

The renal route of elimination plays a minor role in the clearance of atogepant. Based on 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.

*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.

## Preclinical data

Based on conventional studies of safety pharmacology, repeated-dose toxicity, genotoxicity, carcinogenicity, and fertility, preclinical data do not indicate any particular hazards to humans.

*Reproductive toxicity*

Oral administration of atogepant (0, 5, 15, 125, or 750 mg/kg/day) to pregnant rats during the period of organogenesis resulted in decreased fetal body weight and an increased incidence of skeletal variations in the fetus at the two highest doses tested (125 and 750 mg/kg) which was not associated with maternal toxicity. At the no-effect dose for adverse effects on embryofetal development (15 mg/kg/day), plasma exposure (AUC) was approximately 4 times that in humans at 60 mg/day dose.
Oral administration of atogepant (0, 30, 90, or 130 mg/kg/day) to pregnant rabbits during the period of organogenesis resulted in an increased incidence of visceral and skeletal variations in rabbits at the high dose (130 mg/kg/day). At the no-effect dose for developmental effects (90 mg/kg/day) in rabbits, plasma exposure (AUC) was approximately 3 times that in humans at 60 mg/day dose.
Oral administration of atogepant (0, 15, 45, or 125 mg/kg/day) to rats throughout gestation and lactation resulted in lower offspring body weight at the highest dose (125mg/kg/day). Plasma exposure (AUC) at the highest dose tested with no effect on the offspring development (45 mg/kg/day) is approximately 5 times that in humans at 60 mg/day dose.

*Toxicity tests with juvenile animals*

Administration of atogepant by once daily oral gavage to juvenile rats from day 28 through day 70 after birth at doses of 10, 30, or 200 mg/kg/day was not associated with adverse developmental effects.

## Other information

*Shelf life*

Do not use this medicine after the expiry date ("EXP") stated on the pack.

*Special precautions for storage*

Do not store above 30°C.
Keep out of the reach of children.

## Authorisation number

69128 (Swissmedic)

## Packs

AQUIPTA 10 mg: Blisters in packs containing 28 tablets (B).
AQUIPTA 60 mg: Blisters in packs containing 28 tablets (B).

## Marketing authorisation holder

AbbVie AG, 6330 Cham

## Date of revision of the text

August 2023