Evidence and guidance for the use of AQUIPTA▼ (atogepant) in migraine prophylaxis in adults

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Atogepant for preventing migraine [TA973] (published 15 May 2024)

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Atogepant is indicated for prophylaxis of migraine in adult patients who have at least 4 migraine days per month[2] and is recommended by NICE as an option in indicated patients if at least 3 preventive medicines have failed.[1]

Summary of guidance[1]

- NICE recommends atogepant as an option for preventing both episodic and chronic migraine in adults who have at least 4 migraine days per month, only if at least three preventive medicines have failed
- Atogepant can be used in all applicable settings (prescribed in primary or secondary care)
- Atogepant should be stopped after 12 weeks if the frequency of migraine does not reduce by:
  - at least 50% in episodic migraine
  - at least 30% in chronic migraine

Clinical burden of migraine[1]

Migraine can be a debilitating condition that substantially affects physical, social, psychological and professional aspects of life for some patients. Migraine attacks usually last between 4 and 72 hours. They involve throbbing head pain of moderate-to-severe intensity, which can be highly disabling, impacting mental wellbeing and physical activities.

Migraine can be classified as episodic or chronic, based on the frequency of headaches:

- Episodic migraine is defined as fewer than 15 headache days per month
- Chronic migraine is defined as 15 or more headache days per month, with at least 8 of those having features of migraine

Clinical management of migraine[1]

The NICE evaluation committee and external assessment group examined the evidence submitted for the appraisal. The options

available to patients with migraine prior to the assessment were discussed. People with at least 4 migraine days per month are offered a range of oral preventive medicines, including, for example, topiramate, propranolol and amitriptyline. If 3 medications have not worked or cannot be tolerated, patients may receive injectable anti-calcitonin gene-related peptide (CGRP) monoclonal antibodies: erenumab, fremanezumab, galcanezumab or eptinezumab as fourth-line treatments. Patients with episodic migraine may be treated with the oral preventive medicine rimegepant, and patients with chronic migraine may be treated with botulinum toxin type A, which is an intramuscular preventive medicine.

- Patient experts state that some people cannot have injectable medicines, for example because they have an allergy or phobia of needles. As such, people with migraines would welcome an oral medicine, particularly for chronic migraine for which no other oral medicine is available.

The NICE committee agreed that there is an unmet need for new preventive treatment options for patients who suffer from migraine and proceeded to evaluate the possible use of atogepant.

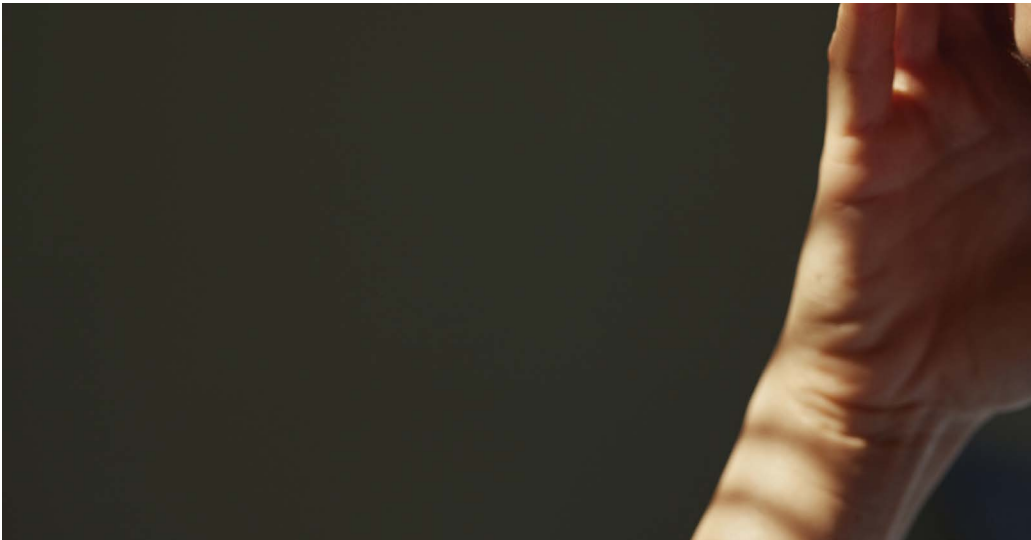
Evidence supporting use of atogepant

Clinical trial evidence – efficacy data considered by NICE[1]

Evidence from four placebo-controlled clinical trials in adults was assessed by NICE to inform their appraisal of atogepant, summarised below.

- Primary outcome was the change from baseline in monthly migraine days (MMDs)
- Secondary outcomes included the proportion or people achieving at least a 50% reduction in mean MMDs, the proportion or people achieving at least a 30% reduction in mean MMDs (chronic migraine only) and change from baseline in acute medicine use days (MUDs)

Atogepant was found to be **more efficacious than placebo in preventing episodic and chronic migraine in the study population**. For adult patients in the study with chronic migraine who had tried three preventive medicines that have failed prior to atogepant, the efficacy of atogepant was uncertain.



The ADVANCE clinical trial was a Phase III, randomised, placebo controlled trial evaluating once-daily atogepant for episodic migraine (EM). 680 adult patients with EM with a ≥1 year history of migraine (with or without aura) were randomised 1:1:1 to receive atogepant 60 mg (n=235), atogepant 10 mg (n=222) or placebo (n=223) once daily for 12 weeks; the results of the 10 mg dose are not summarised below. The primary endpoint was change from baseline in mean monthly migraine days across the 12-week treatment period.

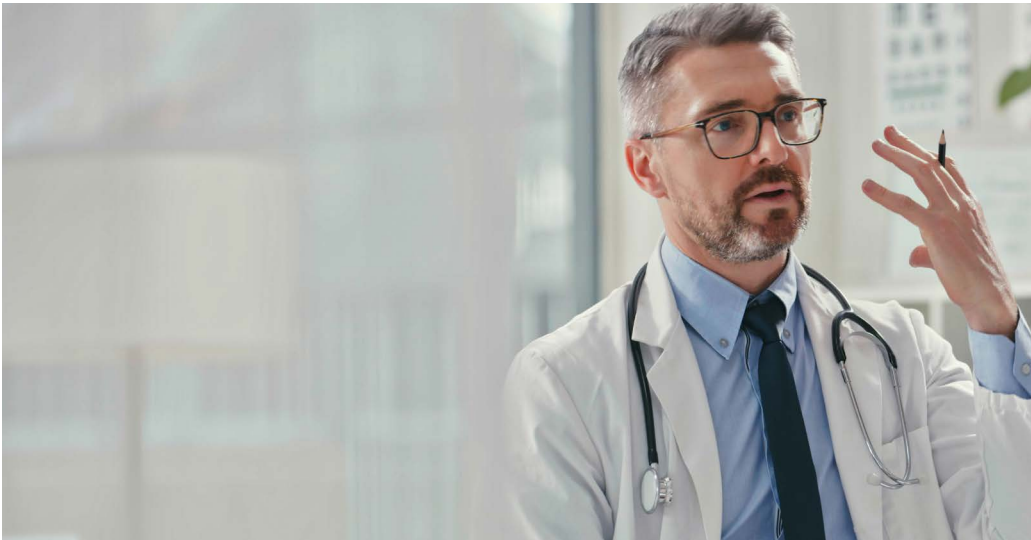
Table 1 Summary of ADVANCE clinical trial, which was considered by NICE during their appraisal

Trial name	**ADVANCE**	
Condition[1]	Episodic migraine	
	Placebo (n=214)	**Atogepant (n=222)**
Primary outcome[3] (mITT population)		
Baseline MMD	7.5 days	7.8 days
MMD change from baseline across 12 weeks	–2.5 days	–4.2 days
MMD change from baseline – difference from placebo	–1.7 days (95% CI –2.3 to –1.2, p<0.001)	
Secondary outcomes[3] (mITT population)		
Baseline acute MUDs	6.5 days	6.9 days
Acute MUD change from baseline across 12 weeks	–2.4 days	–3.9 days
Monthly acute MUDs – difference from placebo	–1.5 days (95% CI –2.0 to –1.0, p<0.001)	
Patients achieving ≥50% reduction in mean MMD from baseline across 12 weeks	62 (29.0%)	135 (60.8%)

During the PROGRESS clinical trial, a Phase III, placebo-controlled trial examining atogepant efficacy and safety in people with CM, 521 adult patients with a history of chronic migraine were randomised 1:1 to receive atogepant 60 mg (n=262) or placebo (n=259) once daily for 12 weeks; a 30 mg twice-daily group was also included, but as the dose is not licensed the results are not included here. The primary efficacy endpoint was change from baseline in mean MMDs across the 12-week treatment period.

Table 2 Summary of PROGRESS clinical trial, which was considered by NICE during their appraisal

Trial name	**PROGRESS**	
Condition[1]	Chronic migraine	
	Placebo (n=246)	**Atogepant (n=256)**
Primary outcome[4] (mITT population)		
Baseline MMD	18.9 days	19.2 days
MMD change from baseline across 12 weeks	–5.1 days	–6.9 days
MMD change from baseline – difference from placebo	–1.8 days (95% CI: –2.9 to –0.8, p=0.0009)	
Secondary outcomes[4] (mITT population)		
Baseline acute MUDs	15.4 days	15.5 days
Acute MUD change from baseline across 12 weeks	–4.1 days	–6.2 days
Monthly acute MUDs – difference from placebo	–2.1 days (95% CI: –3.1 to –1.1, p=0.0009)	
Patients with ≥50% reduction in 3-month average of MMD	26%	41%



The ELEVATE clinical trial was a 12-week, multicentre, double-blind, parallel-group, randomised, placebo-controlled Phase 3b trial to examine the efficacy and safety of AQUIPTA® 60 mg once daily for the preventive treatment of episodic migraine in patients with documented previous failure of 2–4 classes of oral preventive treatment. 309 adult patients with episodic migraine were randomised 1:1 to receive atogepant 60 mg (n=154) or placebo (n=155) once daily for 12 weeks. The primary endpoint was change from baseline in mean MMD across the 12-week treatment period.

Table 3 Summary of ELEVATE clinical trial, which was considered by NICE during their appraisal

Trial name	**ELEVATE**	
Condition[1]	Episodic migraine	
	Placebo (n=155)	**Atogepant (n=154)**
Primary outcome[5] (OTHE population)		
Baseline MMD	9.3 days	9.1 days
MMD change from baseline across 12 weeks	–1.9 days	–4.2 days
MMD difference from placebo	–2.4 days (95% CI –3.2 to –1.5, p<0.0001)	
Secondary outcomes[5] (OTHE population)		
Baseline acute MUDs	7.7 days	7.5 days
Acute MUD change from baseline across 12 weeks	–1.1 days	–3.7 days
Monthly acute MUDs – atogepant vs placebo	–2.6 days (95% CI –3.4 to –1.9, p<0.0001)	
Patients with ≥50% reduction in 3-month average of MMD	28 (18%)	78 (51%)

Table 4 Summary of CGP-MD-01 clinical trial, which was considered by NICE during their appraisal

Trial name	CGP-MD-01	
Condition[1]	Episodic migraine	
	Placebo (n=178)	**Atogepant (n=177)**
Primary outcome[6] (mITT population)		
Baseline MMD	7.8 days	7.7 days
MMD change from baseline across 12 weeks	–2.9 days	–3.6 days
MMD change from baseline – difference from placebo	–0.7 days (95% CI –14 to –0.1, p≤or= to p≤0.039)	
Secondary outcomes[6] (mITT population)		
Baseline acute MUDs	6.6 days	6.8 days
Acute MUD change from baseline across 12 weeks	–2.4 days	–3.5 days
Monthly acute MUDs – difference from placebo	–1.1 days (95% CI –1.7 to –0.5, p=0.15)	
Patients with ≥50% reduction in mean MMD across 12 weeks	72 (40%)	92 (52%)

The CGP-MD-01 clinical trial, was a multicentre, randomised, double-blind, placebo-controlled, parallel-group phase 2b /3 trial, during which 825 adult patients with a history of migraine were randomised to receive atogepant 60 mg once daily (n=186), placebo (n=186) once daily, or atogepant at a different dose or frequency (10 mg QD, 30 mg QD, 30 mg BID, 60 mg BID) for 12 weeks; as the other atogepant doses are not licensed doses, results are not summarised below. The primary endpoint was change from baseline in mean monthly migraine days across the 12-week treatment period.

Brief summary of safety of atogepant[2]

The safety of atogepant was evaluated in 2657 patients with migraine who received at least one dose of AQUIPTA. Of these, 1225 patients were exposed to atogepant for at least 6 months and 826 patients were exposed for 12 months.

The most commonly reported adverse drug 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 was nausea (0.6%). Adverse drug reactions associated with atogepant are summarised in Table 5.

There were some cases of transient, asymptomatic transaminase elevations (>3× upper limit of normal) temporally associated with atogepant treatment, which resolved within 8 weeks following discontinuation of the medication; there were no cases of severe liver injury or jaundice reported in placebo-controlled studies.[2]

Weight decreased, defined as a decrease of at least 7% at any point, was reported in 2.5% of trial subjects receiving placebo, 3.8% of subjects receiving atogepant 10 mg once daily and 5.3% of subjects receiving atogepant 60 mg once daily.[2]

Table 5 Summary of ADRs identified with atogepant[2]

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

ALT, alanine aminotransferase; AST, aspartate aminotransferase
Frequencies: Very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1 000 to <1/100), rare (≥1/10000 to <1/1000) or very rare (<1/10000).

Full safety information on atogepant is available in the summary of product characteristics.[2]

In the ELEVATE study, treatment-emergent adverse events were reported by 81 participants (52%) in the atogepant group (n=156). The most common (≥5%) treatment-emergent adverse events were constipation (10%), COVID-19 (8%), nausea (7%), and nasopharyngitis (5%). Most treatment-emergent adverse events were considered by the investigator to be mild or moderate in severity.[5]

Cost effectiveness[1]

The committee concluded that in episodic migraine, the most likely cost-effectiveness estimate for atogepant compared with rimegepant was within the range that the committee considered to be an acceptable use of NHS resources.

In chronic migraine, the costs of atogepant were lower than those of all the comparators. So, the committee recommended atogepant for preventing both episodic and chronic migraine in adults.

NICE recommendation for atogepant[1]

Atogepant is recommended as an option for preventing migraine in adults who have **at least 4 migraine days per month**, only if **at least 3 preventive medicines have failed**.

Stop atogepant after 12 weeks if the frequency of migraines does not reduce by:

- at least **50% in episodic migraine**
- at least **30% in chronic migraine**

If people with the condition and their healthcare professional consider atogepant to be one of a range of suitable treatments, the least expensive option should be used after discussing the advantages and disadvantages of all available options.

Justification of recommendations[1]

Clinical trial evidence shows that atogepant

reduces monthly migraine days more than placebo, but there is no clinical trial evidence directly comparing it with other preventive medicines. The results from indirect comparisons are uncertain and it is unclear how well atogepant works compared with other preventive medicines for episodic or chronic migraine.

- For episodic migraine, the most relevant comparator is rimegepant because it is also an oral preventive medicine. The most likely cost-effectiveness estimate for atogepant compared with rimegepant is **within the range that the committee considered an acceptable use of NHS resources**
- For chronic migraine, it is not clear whether atogepant is better or worse than the other preventive medicines, but it has lower costs. As such, **atogepant is recommended as an option for preventing episodic and chronic migraine after three or more preventive medicines**.

Implementation of NICE guidance[1]

Section 7 of the National Institute for Health and Care Excellence (Constitution and Functions) and the Health and Social Care Information Centre (Functions) Regulations 2013 requires integrated care boards, NHS England and local authorities to comply with the recommendations of the NICE evaluation within 3 months of its date of publication.

In Wales, when a NICE technology appraisal guidance recommends the use of a drug or treatment, or other technology, usually the NHS must provide funding and

resources for it within 2 months of the first publication of the final draft guidance.

What does this mean for patients?[1]
If a patient has episodic or chronic migraine and the healthcare professional responsible for their care thinks that atogepant is the right treatment, **it should be available for use, in line with NICE's recommendations**.

Prescribing in primary and secondary care[1]

Patient and professional organisations stated that availability of atogepant in primary care would improve access to treatment and reduce costs to the NHS. Atogepant can be used in all applicable settings.[1]

There is no patient access scheme (PAS) for atogepant and the list price is £182.16 for 28 tablets.[1]

Key points[1]

- NICE recommends atogepant as an option for preventing both episodic and chronic migraine in adults who have at least 4 migraine days per month, only if at least three preventive medicines have failed
- Atogepant can be used in all applicable settings (prescribed in primary or secondary care)
- Atogepant should be stopped after 12 weeks if the frequency of migraine does not reduce by:
  - at least 50% in episodic migraine
  - at least 30% in chronic migraine

References
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Atogepant Prescribing Information for the UK: https://www.emcpi.com/grp/238

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