ADULT HEADACHE PATHWAY

Background

The primary focus of this document is the management of chronic headache, particularly migraine.

The guidance is not targeted at acute headache / new onset headache (including thunderclap headache) or headache associated with neurological deficits, seizures, or papilloedema.

For more detailed information on both diagnosis and imaging, see the 2019 BASH headache guidelines.

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ADULT HEADACHE PATHWAY

NHS Nottinghamshire Area Prescribing Committee

Patient presents with headache

Take history & examine including BP, temporal arteries (if age > 50years) & fundoscopy

Exclude red flags

Are there potential RED FLAGS?

- Progressive subacute headache with symptoms suggestive of raised intracranial pressure - consider urgent Brain MRI.
- Thunderclap headache (sudden onset, reaching its peak instantaneously), consider SAH. Same day A&E referral or discuss with neurology, even in delayed presentation.
- If age > 50, constitutional symptoms, scalp tenderness, or jaw claudication, consider Giant Cell Arteritis. Take FBC/CRP/ESR, start steroids immediately, consider urgent discussion with rheumatology.
- Unilateral red eye – consider angle closure glaucoma.
- Consider differential diagnosis to exclude meningitis, brain abscess, cerebral venous sinus thrombosis, or pre-eclampsia.
- Overweight, snorer, catnapping – consider Obstructive Sleep Apnoea.
- Remember carbon monoxide poisoning (also causes lethargy + nausea).

The following presentations should prompt consideration of MRI brain or communication with neurology as appropriate:

- Headache with atypical aura (duration >1 hour or significant motor weakness).
- Headache precipitated (rather than aggravated) by valsalva or exercise.
- Headaches with marked postural change (consider either high or low intracranial pressure).
- New onset headache in patient with history of cancer (that can metastasise to the brain or skull).
- Associated focal neurological deficit, papilloedema, seizures, cognitive impairment, or clear behavioural / personality changes.
- New onset headache in a patient with a history of HIV / immunosuppression.
- New onset headache in a patient aged>50.
- Headache repeatedly causing patient to wake from sleep.
- Recent significant head trauma (past 3 months).
- New presentation of cluster headache.
- New headache that is daily or near-daily from onset and persists for weeks.
- Strongly suspected trigeminal neuralgia – consider neurology A&G regarding need for imaging.

Primary headache

NICE recommends a **headache diary** for a minimum of 8 weeks to aid assessment.

Most people who attend GP with recurrent/ chronic headaches have migraine. A recurrent severe headache associated with nausea and photophobia is 98% predictive of migraine.

Explain the risk of Medication Overuse Headache when initiating treatment and to those already established on acute medicine for headache.

Secondary headache - non serious cause

Posterior headaches often relate to cervicogenic headaches.

Unlikely to be sinuses, TMJ dysfunction or teeth unless other signs /symptoms.

Consider trigeminal neuralgia as a cause of 'headache'.

Consider medication – esp. combined hormonal contraception (CHC). If patient has migraines with aura, then CHC is contraindicated.

Migraine

Lasts 4-72 hours untreated • Unilateral or bilateral location • Pulsating quality • Moderate/severe pain • Nausea / vomiting and/or photophobia and/or sensitivity to sound.
No other cause identified.
Deemed **menstrual-related** if occurs between 2 days before and 3 days after the start of menstruation in ≥2 cycles.
Deemed **chronic** if >15 days per month, with ≥8 days of migraine symptoms, for >3 months.
May be with or without aura. Aura: lasts up to 60 minutes and affects 1/3 of migraine sufferers, can occur with or without headache, symptoms usually visual, also sensory or speech disturbance, and are fully reversible.

Chronic migraine with or without aura occurring every day needs specialist review.

Tension Type Headache (TTH)

Usually bilateral • Mild to moderate intensity • No other symptoms • Episodic or chronic (if >15 days per month for >3 months).
Many patients with chronic headache have a mixture of migraine and TTH. The two conditions likely lie on two ends of a spectrum.

Cluster Headache

Each attack is excruciating, unilateral, and fairly short lived (15 min-3h).
May be multiple attacks in a 24-hour period.
Most patients are agitated or restless during an attack.

Medication Overuse Headache (MOH)

Typically exacerbated chronic migraine / chronic TTH and leads to failure of preventative medication.
Medication history is crucial (including use of over-the-counter analgesia). Key risk factor is number of days per month using analgesia - high risk of MOH if >12 days per month for protracted period.
Avoid opioids altogether if frequent migrainous headaches.
Prophylaxis medication does not help and can worsen. Improves within 3 months of analgesic cessation.

Migraine with/ without aura

ACUTE TREATMENT

STEP 1: **simple analgesic with oral triptan**

Combination more effective than monotherapy.
Consider short-term **anti-emetic** even if no nausea and/or vomiting (for improved efficacy). Do not use opioids.
Triptans (see page 4 for more details):

- Sumatriptan tablets are available to buy from pharmacies with no prescription for patients with diagnosed migraine.
- May need to try more than one type and/or formulation.
- Caution – frequent use can lead to triptan overuse headaches (a form of MOH).
- Aim to use <2 doses/week.
- Use the most cost effective first i.e. sumatriptan or naratriptan tablets.
- Migraines often return 48-72 hours post use of a triptan.
- Combined with naproxen may improve efficacy.

STEP 2: consider **rectal analgesic (diclofenac)** but be aware of MHRA guidance.

STEP 3: Where simple analgesia and 2 triptans failed/ not appropriate, consider **rimegepant 75mg OD PRN** - classed Amber 2 - following A&G recommendation or initiation by a Specialist (see page 5 for more details).

PROPHYLAXIS

Consider for frequent troublesome migraines i.e. 4 or more troublesome headache days per month. Titrate up slowly and try the maximum tolerated dose for 3 months before judging its efficacy. Avoid analgesia overuse.

Riboflavin 400mg once daily is widely available over-the-counter as food-supplement and may be effective for some but not prescribed on NHS.

1st LINE: Betablocker or amitriptyline, where clinically appropriate.

- β-blockers: **propranolol 80-240mg** daily in divided doses. Caution in people with depression – risk of using for self-harm. Contraindicated in asthma or uncontrolled heart failure.
- **Amitriptyline** initially **10mg ON titrating up to 80mg ON**. Consider anticholinergic burden, risk of serotonin syndrome, dependence, CVD risk and withdrawal. If not tolerated, consider nortriptyline or imipramine, using a similar dosing regimen.

Alternative 1st line, where appropriate:

- **Topiramate tablets 25mg OD titrated slowly to max 50mg BD.** Should not be used in pregnancy and in women of childbearing potential, unless Pregnancy Prevention Programme in place. As an enzyme inducer it has potential to decrease effectiveness of OCP/POP (see page 7 for more details).
- **Candesartan** (off-label indication).
- **Pizotifen** (see page 8 for more details).

If 1st line medicines are ineffective, additional therapies i.e. acupuncture may help, but not locally available on NHS.

If no response, consider A&G or neurology referral. Explore analgesia use.

SPECIALIST TREATMENT FOR MIGRAINE MANAGEMENT

Where 3 preventative options failed/ not appropriate: oral calcitonin gene-related peptide (CGRP) receptor antagonist can be considered (see page 8 for more details – Amber 2, via A&G):

- **Atogepant** (for episodic i.e. ≥4 migraine days per month and chronic migraine prevention),
- **Rimegepant** (for episodic migraine only i.e. ≤15 migraine days per month).

Other treatment options available only via Secondary Care: **Botulinum Toxin Type A** (Botox®), **galcanezumab** (Emgality®), **erenumab** (Aimovig®), **eptinezumab** (Vyepti®), **fremanezumab** (Ajovy®).

Menstrual related migraines

Can be identified via headache diary.
If standard acute treatment fails, consider **short preventative triptan** on the days migraine is expected – this is off-label use of triptans.

- Frovatriptan 2.5 mg BD or
- Zolmitriptan 2.5 mg BD or TDS

Acute migraine in pregnancy

STEP 1: non-pharmacological measures – avoidance of triggers, relaxation techniques and cognitive behavioural therapy.

STEP 2: paracetamol 1g.

STEP 3: sumatriptan 50-100mg.

See page 6 for additional info.

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In women, **migraine WITH aura** is associated with increased risk of stroke. The risk is potentiated by **oestrogen-containing contraceptives**, which **should be avoided** in this cohort. Consider POP or alternative contraception.

Tension type headache (TTH)

STEP 1: **simple analgesic**
i.e. paracetamol, ibuprofen or aspirin
Limit the use of analgesia to a maximum of 10 days a month. Do not use opioids.
Look at triggers and consider medicine overuse headache (MOH).

STEP 2: consider alternative NSAID such as **naproxen 500mg BD**. Maybe worthwhile taking regularly for 4-6 weeks if headaches are severe (with PPI cover if needed).

STEP 3: consider additional therapies for prophylaxis i.e. acupuncture, TENS and cognitive therapies (locally not available on NHS).

STEP 4: if headaches are severe, frequent & persist consider **amitriptyline** starting at **10mg ON, slowly titrating to 80mg ON**. Consider anticholinergic burden, risk of serotonin syndrome, dependence, CVD risk and withdrawal. If not tolerated, consider nortriptyline or imipramine, using a similar dosing regimen.

Note: β-blockers not usually helpful & benzodiazepines should be avoided. SSRIs not helpful unless there is underlying depression.

Cluster headache

Most patients with new onset cluster headaches will require A&G or referral to Neurology.

ACUTE TREATMENT
Though short lived, acute treatment is nearly always needed.
Subcutaneous sumatriptan is gold standard but may consider **intranasal triptan** (off-label).
Oxygen should only be prescribed if recommended by a Neurologist (link to guidance).
Usually prophylaxis is the best option.

PROPHYLAXIS
Note: β-blockers should not be used for cluster headaches.
If ECG satisfactory, consider **verapamil** starting at 80mg TDS and increased rapidly.
Consider **prednisolone** starting in parallel with preventative at 60mg once daily (with PPI cover), then reduce by 10mg every 3 days to zero.
If absolutely no benefit after 5 days then stop prophylaxis.

Medication Overuse Headache (MOH)

Withdrawal of the causative medication is the only treatment, but this may initially potentiate headache. Education and communication are critical.
Can occur on top of other types of headaches.

If no response, consider A&G or neurology referral. Explore analgesia use.

OVERVIEW OF TREATMENT OPTIONS FOR MIGRAINE

Acute migraine in adults (for management in pregnancy see page 6)

Simple analgesia

A stepped approach is recommended commencing treatment as early as possible with an analgesic and if required an anti-emetic/pro-kinetic.

Aspirin or ibuprofen with or without paracetamol	Need to establish therapeutic levels quickly – given as single loading dose. Aspirin 600-900mg or ibuprofen 400-600mg Paracetamol 1g
Metoclopramide or prochlorperazine (buccal)	Metoclopramide 10mg as a single dose at the start of migraine or Prochlorperazine (buccal) 3-6mg up to twice a day (available OTC for adults 18 and over)
Diclofenac suppositories	Diclofenac 50mg or 100mg – see notes below

Notes:

1. Medicine(s) should be given as soon as the onset of an attack is recognised.
2. The addition of an antiemetic will aid gastric emptying, as well as relieving nausea. This can improve efficacy even in the absence of nausea and/or vomiting by improving gastric motility and aiding absorption of the co-administered oral medications.
3. Antiemetic should only be prescribed for short-term use: metoclopramide for up to 5 days, prochlorperazine for up to 2 days (as per product license). When prescribing regular metoclopramide, consider the risk of neurological adverse effects (MHRA alert).
4. Anti-migraine medicine containing metoclopramide are not suitable for patients under the age of 20 years.
5. Since peristalsis is often reduced in migraine attacks, dispersible preparations may be helpful.
6. Suppositories are useful if vomiting or severe nausea present.
7. When prescribing regular NSAIDs, consider the cardiovascular risk and relevant contraindications (diclofenac MHRA alert and ibuprofen MHRA alert).
8. Avoid opioids including codeine.

If simple analgesia fails, consider addition of triptan (5HT1 receptor agonist).

Triptans ($5HT_1$-receptor agonists)

Use the most cost-effective preparation first line i.e. sumatriptan or naratriptan tablets. Sumatriptan tablets are also available to purchase from community pharmacies without prescription and may be recommended as a self-care treatment option for patients with previously diagnosed migraines who find it effective. The current Nottinghamshire formulary choices are listed below.

Quicker onset of action, shorter half life.		**Slower onset of action. Longer half life. Lower incidence of side effects and may be useful where recurrence is a problem.**	
Sumatriptan	**Tablets 50mg or 100mg – the most cost effective of all triptans** Injection 6mg per 0.5ml Nasal spray 10mg or 20mg per 0.1ml/dose	Naratriptan	Tablet 2.5mg **– the most cost effective in this group.**
Zolmitriptan	Orodispersible tablets 2.5mg or 5mg – **the most cost effective orodispersible triptan** Nasal spray 5mg per 0.1ml/dose (Tablets 2.5mg or 5mg - more expensive than orodispersible tablets)	Frovatriptan	Tablet 2.5mg
Rizatriptan	Orodispersible tablets 10mg (5mg are significantly more expensive) Tablets 10mg (5mg are significantly more expensive) Oral lyophilizate 10mg		

Notes:

1. NICE recommends that oral triptans should be used first line and other preparations only considered if these are ineffective or not tolerated.
2. A second dose of the same triptan should not be taken if the first dose is ineffective.
3. Triptans are contraindicated in patients with uncontrolled hypertension, or risk factors for coronary heart disease or cerebral vascular disease.
4. Triptans are not licensed in > 65 years.
5. Different triptans have different profiles of 5HT site action. If the first triptan tried fails, it is worth trying alternative ones. A pragmatic approach would be to choose the cheapest one from each group as a first line.
6. Orodispersible formulations obviate the need for water but do not get absorbed in mouth.
7. Nasal spray is useful when vomiting is a problem.
8. Addition of antiemetic may improve efficacy, even in the absence of nausea/vomiting.
9. Note rizatriptan interaction with propranolol.

If simple analgesia and triptans fail to control acute migraine episodes or are not suitable – consider Rimegepant.

Rimegepant (Vydura®)

Rimegepant is locally classed as Amber 2 for migraine treatment and it can be prescribed following recommendation or initiation by a Specialist. In line with NICE TA919 it could be considered for acute treatment of migraine episodes where simple analgesia and/or at least 2 different triptans have failed or are not appropriate.
Acute treatment dose: 75mg as required once daily. In a form of oral lyophilizate it can be taken without liquid and should be placed on or under the tongue to disintegrate.
Rimegepant is also recommended as Amber 2 for the prevention of migraines – see page 9

for further info. Please note the different dosing regimens for prevention and prophylaxis of migraine.
Review: To be undertaken by the initiating clinician. Rimegepant should be stopped if there is no response to treatment after 2 to 3 acute attacks.
Contraindications: known hypersensitivity, end-stage renal disease or severe hepatic impairment.
Side effects: nausea (the most common). Hypersensitivity, including dyspnoea and severe rash, occurred in less than 1% of patients treated.
Interactions: not recommended for concomitant use with:

- strong inhibitors of CYP3A4 (e.g., clarithromycin, itraconazole, ritonavir) - increased exposure to rimegepant;
- moderate inhibitors of CYP3A4 (e.g., diltiazem, erythromycin, fluconazole) - increased exposure to rimegepant;
- strong or moderate inducers of CYP3A4 (e.g., phenobarbital, rifampicin, St John's wort, bosentan, efavirenz, modafinil) – loss of efficacy of rimegepant.

Second dose of rimegepant within 48 hours should be avoided when it is concomitantly administered with strong inhibitors of P-glycoprotein (P-gp) (e.g., cyclosporine, verapamil, quinidine).

Acute migraine in pregnancy

Notes:

1. Many medicines are contraindicated or have limited evidence of safety in pregnancy.
2. Risks and benefits must be discussed with the patient and this should be recorded.
3. If treatment with medication is necessary, consider contraindications and co-morbidities.
4. There is less evidence of safety for triptans than for paracetamol.
5. Sumatriptan is the preferred triptan in pregnancy.
6. The evidence of safety for nonsteroidal anti-inflammatories (NSAIDs) in pregnancy is limited. Local expert opinion is to avoid ibuprofen use during pregnancy, since it is contraindicated in 3rd trimester and prolonged use should be avoided after week 20 of pregnancy. Some studies have suggested use of ibuprofen in early pregnancy might be linked to an increased chance of miscarriage.
7. Pregnant patients should be encouraged to read leaflets about recommended medications, which can be found on the Best use of medicines in pregnancy website.

Prevention of migraine in adults

Prophylaxis is used to reduce the number of attacks in circumstances when acute therapy, used appropriately, gives inadequate symptom control. There are no specific guidelines as to when prophylaxis should be commenced. Considerations include frequency, impact, failure of acute therapy, avoidance of medication overuse headache. Review the need for continuing migraine prophylaxis six months after the start of prophylactic treatment.

Notes:

1. Propranolol, metoprolol and timolol are licensed, but only propranolol is on the local formulary for this indication.
2. While taking propranolol, the maximum dose of rizatriptan should be 5mg and to be taken at least 2 hours apart to reduce potential interaction.
3. Start at the lowest dose and build up gradually. Maintain the maximum tolerated dose for a minimum of 6 weeks before assessing. Discuss with patient at 6 months whether a gradual reduction and elimination of prophylactic medication might be

considered.

4. Amitriptyline is useful with co-existent tension type headache, disturbed sleep or depression. Consider anticholinergic burden and risk of serotonin syndrome.
5. Note that gabapentin is not recommended by NICE for prophylactic treatment of migraine.
6. Note that rimegepant and atogepant for migraine prophylaxis, are locally classed Amber 2 – initiated by a Specialist or a GP following Advice & Guidance recommendation.
7. To continue ongoing prescribing, a 12-week effectiveness review by the initiating clinician is recommended.

Topiramate

Topiramate is licensed for migraine prophylaxis, recommended by NICE, and classed Amber 3 in the local formulary. It should not be used during pregnancy, as it is associated with significant harm to the foetus. It is contraindicated for use in all women of childbearing potential, unless the conditions of the Pregnancy Prevention Programme (PPP) are fulfilled. This aims to ensure that all women of childbearing potential:

- are using highly effective contraception covering the period of at least four weeks after the last dose of topiramate (Cu-IUD/copper coil, LNG-IUS/Levonorgestrel Intrauterine System, DMPA/depot-medroxyprogesterone acetate plus condoms), and
- have a pregnancy test to exclude pregnancy before starting topiramate, and
- are aware of the risks from use of topiramate, have completed the Risk Awareness Form with the prescriber, and received a copy of the Patient Guide from the prescriber.

The use of topiramate in women of childbearing potential requires an annual review with annual completion of the Risk Awareness Form.
Please see prescriber guide on Topiramate Pregnancy Prevention Programme for migraine prophylaxis.
See Drug Safety Update for more information.
Place in therapy: This will be tailored to each patient, but as highlighted in the headache pathway, it should be considered when the frequency of migraines is such that regular prophylaxis is warranted.
Review: continuing therapy should be reviewed every 6 months.
Dose: Note, it can take 6-8 weeks before maximum effect gained.
Commence topiramate at 25mg nightly, and increase (see below) if required.
Titration Schedule: the dosage should be increased in increments of 25 mg/day administered at 1- week intervals. If the patient is unable to tolerate the titration regimen, longer intervals between dose adjustments can be used.

Topiramate Dosage	Morning	Evening
Week 1		25mg
Week 2	25mg	25mg
Week 3	25mg	50mg
Week 4	50mg	50mg

Some patients may experience a benefit at a total daily dose of 50 mg/day. The recommended total daily dose of topiramate as treatment for the prophylaxis of migraine headache is **100 mg/day administered in two divided doses**. No extra benefit has been shown from the administration of doses higher than 100 mg/day.

Contraindications: known hypersensitivity, breast feeding, pregnancy, women of childbearing potential unless on PPP.
Cautions: Topiramate can impair the effectiveness of hormonal contraception. See guidance from Faculty of Family Planning and Sexual Health for further information.
Avoid abrupt withdrawal. Use with caution in hepatic impairment and renal impairment.

The plasma and renal clearance of topiramate are significantly decreased in patients with moderately and severely impaired renal function (CrCl ≤ 70 ml/min) and therefore, half of the usual starting and maintenance doses are recommended for those individuals.
Topiramate has been associated with acute myopia with secondary angle closure glaucoma, typically occurring within 1 month of starting treatment. Choroidal effusions have also been reported. If raised intraocular pressures occur – seek ophthalmology advice and stop topiramate as rapidly as possible.
Side effects:

- Nausea, dyspepsia, and diarrhoea. Dry mouth and taste disturbance.
- 25% of people experience anorexia/loss of appetite.
- Drowsiness, insomnia, dizziness.
- 50% of people experience initial paraesthesia (which usually settles).
- Risk of cognitive slowing, low mood, suicidal thoughts, speech disturbance, renal stones, glaucoma.
- Rarely – reduced sweating metabolic acidosis and alopecia
- Very rarely – leucopenia, thrombocytopenia and serious skin reactions

Interactions:

- Oestrogens – metabolism accelerated – reduced contraceptive effect.
- Progestogens – metabolism accelerated – reduced contraceptive effect.
- Lithium – possibly affects plasma concentration.

Topiramate should be prescribed generically and tablets should be prescribed in preference to capsules due to price difference. In patients with swallowing difficulties, the contents of a capsule can be sprinkled on a small amount of food immediately prior to administration (tablets can be crushed but have a bitter taste and oral solution is very expensive).

Pizotifen

Pizotifen has been in use since the 1970s and is usually well tolerated. Due to inadequate evidence for its effectiveness in the prophylaxis of migraine, it is not included in NICE guidelines. However, it remains recommended by the local Specialists, as the use of pizotifen in migraine prevention was not associated with safety concerns. Therefore, it could be considered as a 4th line option for those patients who either did not respond to the preferred treatments (propranolol/ topiramate/ amitriptyline) or could not tolerate their side effects.
Review: continuing therapy should be reviewed every 6 months.
Dose: Adults and elderly: Usually start as 500 micrograms and increase in weekly intervals to 1.5mg daily. If needed the dose can be slowly increased to 3mg (either as a single or divided dose). Dosage should be adjusted according to individual patient requirements. Pizotifen should not be stopped abruptly, therefore gradual withdrawal is recommended. Withdrawal symptoms include anxiety, tremors, insomnia, nausea, and loss of consciousness.
Side effects: common side effects include nausea, dry mouth, weight gain. Pizotifen may cause drowsiness, somnolence, and dizziness. Therefore, caution should be exercised when driving or using machinery.

Specialist recommended treatment

Some patients might not respond to standard treatment and require Specialist intervention for migraine therapy. Consultant neurologists may recommend oral treatment with rimegepant or atogepant, or other injectable medications which are available through Secondary Care only and include:

- Botulinum Toxin Type A (Botox®) - injection
- Galcanezumab (Emgality®) - solution for injection in pre-filled pen (NICE TA 659)

- Erenumab (Aimovig®) - pre-filled pen for subcutaneous injection (NICE TA 682)
- Eptinezumab (Vyepti®) -concentrate for solution for infusion (NICE TA 871)
- Fremanezumab (Ajovy®) - pre-filled Pen for Injection (NICE TA 764)

Rimegepant (Vydura®)

It is licensed for adults with dual indication for acute migraine treatment and as migraine prophylaxis. Locally classed Amber 2 for both indications and it may be initiated in Primary Care on recommendation of Neurologist.
Place in therapy: Recommended for preventing migraine in line with NICE TA906 as an option for preventing **episodic** migraine (at least 4 but fewer than 15 migraine attacks per month) in adults in whom at least 3 preventative treatments have not worked, are not tolerated or are unsuitable due to safety concerns. Considered as alternative treatment option to the injectable monoclonal antibodies, which are 4th-line treatments for migraine prevention.
Preventative treatment dose: 75mg once every other day.
Review: To be undertaken by the initiating clinician.
Should be stopped after 12 weeks, if the frequency of migraine attacks does not reduce by at least 50%.
Please see page 5 for more information on rimegepant (side effects, contraindications etc).

Atogepant (Aquipta®)

Atogepant is locally classed as Amber 2 for prevention of episodic (fewer than 15 headache days per month) or chronic (15 or more headache days per month, with at least 8 of those having features of migraine) migraine.
Place in therapy: In line with NICE TA973 it can be considered for adults who have at least 4 migraine days per month, only if at least 3 preventive medicines have failed, cannot be tolerated or are deemed unsuitable due to safety concerns. Considered as alternative treatment option to oral rimegepant for the prevention of episodic migraine, or injectable CGRP monoclonal antibodies and botulinum toxin type A.
Dose: 60mg tablet once daily
Review: To be undertaken by the initiating clinician. 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.

Contraindications: severe hepatic impairment, severe renal impairment and end-stage-renal disease, pregnancy. Considering reproductive toxicity shown in animal studies any form of contraception should be advised. There are no clinically relevant interactions between hormonal or systemic contraception and atogepant. Atogepant should be discontinued in advance of planning pregnancy.
Caution: breastfeeding patients require individual risk-benefit consideration. It is unknown if atogepant is excreted in human milk, but data in animals confirm excretion in milk.
Side effects: The most commonly reported in clinical trials were:
- nausea (7%),
- constipation (7%),
- fatigue/somnolence (5%) - caution required before driving or using machinery until patients are reasonably certain that atogepant does not adversely affect their performance.

Most of the cases were mild, and none were serious. The adverse reaction that most commonly led to discontinuation was nausea (0.6%).
Interactions: Concomitant use with strong CYP3A4 inhibitors (e.g., ketoconazole, itraconazole, voriconazole, clarithromycin, telithromycin, indinavir, nelfinavir, ritonavir, saquinavir) or strong OATP inhibitors (e.g., rifampicin, atazanavir, ritonavir, tipranavir,

ciclosporin, telmisartan) requires dose reduction of atogepant (recommended dose is 10 mg once daily, not covered by NICE TA recommendation).

Useful resources:

1. Headaches in over 12's: diagnosis and management, NICE Clinical Guideline CG150 https://www.nice.org.uk/guidance/cg150
2. NICE CKS: Headache assessment and diagnosis https://cks.nice.org.uk/topics/headache-assessment/diagnosis/headache-diagnosis/
3. NICE CKS: Migraine. Scenario: Migraine in pregnant or breastfeeding women https://cks.nice.org.uk/migraine#!scenario:2
4. The British Association for the Study of Headache (BASH) https://bash.org.uk/0-0-table-of-contents/
5. The International Headache Society https://ichd-3.org/evolution-of-ihs-classification-1-3/
6. Topiramate (Topamax): introduction of new safety measures, including a Pregnancy Prevention Programme - GOV.UK https://www.gov.uk/drug-safety-update/topiramate-topamax-introduction-of-new-safety-measures-including-a-pregnancy-prevention-programme

Self Help Resources for patients:

1. Patient UK https://patient.info/brain-nerves/headache-leaflet
2. Migraine Buddy App https://migrainebuddy.com/
3. Migraine Trust http://www.migrainetrust.org/
4. Organization for the understanding of cluster headaches http://www.ouchuk.org
5. NHS Health A to Z: Headaches http://www.nhs.uk/conditions/Headache/Pages/Introduction.aspx

Appendix 1

Headache diary

Date	Day of the week	Time when headache started	Pain Score 0 - no pain 10 - worst pain	Medication (name and time taken)	Comments

Use this diary to record your headaches for at least a month. It can help you to track your headaches' pattern and can be an useful aid when consulting with your healthcare professional.
You can find more information here https://www.nationalmigrainecentre.org.uk/