

ADULT HEADACHE PATHWAY

RED FLAGS - headache that is new or unexpected

- Thunderclap headache (intense headache of “explosive” onset suggest SAH).
- Jaw claudication (suggests temporal arteritis - take ESR /CRP & start steroids immediately).
- Headache with atypical aura (duration >1 hour or including significant / prolonged motor weakness).
- Headache associated with postural change (bending) or coughing (possible raised ICP).
- New onset headache in patient with history of cancer, especially if < 20 years.
- Unilateral red eye – consider angle closure glaucoma.
- Remember carbon monoxide poisoning (also causes lethargy + nausea).
- Rapid progression of sub-acute focal neurological deficit.
- Rapid progression of unexplained cognitive impairment/ behavioural disturbance.
- Rapid progression of personality changes confirmed by witness where there is no reasonable explanation.
- New onset headache in a patient with a history of HIV / immunosuppression.
- New onset headache in a patient older than 50 years.
- Headache causing patients to wake from sleep.
- Progressive headache, worsening over weeks or longer.

Patient presents with headache

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

- Do you have a headache all the time or does it come & go? (Tension Type Headache or Medicines Overuse Headache usually have pain all the time.)
- If intermittent, what do you do when you have the pain? (Patients with migraine want to lie/sit still when pain is bad, those with cluster headaches can't sit still when having an attack.)
- What tablets are you taking now and have you taken before?

Exclude red flags

Primary headache

The major types are listed below – it is important to realise however that patients may have more than one type, so can develop tension type headaches on underlying migraine, or medication overuse with tension type headaches.

NICE recommends keeping a headache diary.

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.

Secondary headache - non serious cause

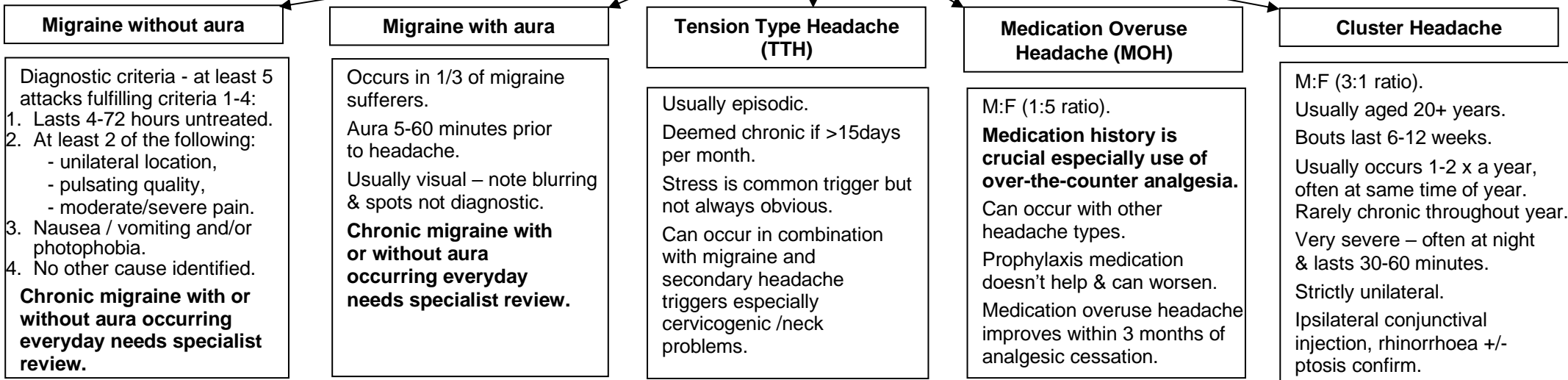
Posterior headaches often relate to cervicogenic headaches.

Unlikely to be sinus, TMJ dysfunction or teeth unless other signs /symptoms indicative of this.

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

Consider facial pain trigeminal neuralgia as a cause of 'headache'.

Consider admission, urgent MRI scan or 2ww referral as appropriate



Migraine with/ without aura

STEP 1: For acute attacks **simple analgesic & triptan** – evidence suggest combination may be best.

- Consider adding **anti-emetic**.
- Avoid opioids.

Triptans – may need to try more than one type.

Care needed – as frequent use can lead to triptan overuse headaches (a form of MOH). Aim to use <2 doses/week - [see page 3](#).

Use most cost effective first.

Also note, migraines often return 48-72 hours post use of a triptan.

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

STEP 3: If simple analgesia and 2 triptans have been tried and are ineffective, contraindicated or not tolerated, consider **oral rimegepant 75mg OD PRN** - classed AMBER 2 - following initiation/ recommendation by a Specialist only – [see page 4](#).

If headaches are frequent and acute treatment is used very frequently, consider **PROPHYLAXIS**. Titrate until symptoms controlled, it may take 6-8 weeks before beneficial effects are seen. Usually needs to be continued for at least 6 months before considering a trial without.

PROPHYLAXIS STEP 1:

β-blockers: **propranolol 80-240mg** daily in divided doses or **Topiramate*** 25mg OD titrated slowly to max 50mg BD. Contraindicated in pregnancy and in women of childbearing potential, unless [Pregnancy Prevention Programme](#) in place. Note topiramate is an enzyme inducer with potential to decrease effectiveness of OCP/POP.

PROPHYLAXIS STEP 2:

Amitriptyline initially 10mg ON titrating up to 150mg ON. Consider anticholinergic burden and risk of serotonin syndrome. **Nortriptyline** - only use if amitriptyline is effective but patient unable to tolerate side effects.

PROPHYLAXIS STEP 3:

Pizotifen - please see page 8 for more details.
If no response, consider value of MRI.

Tension type headache (TTH)

STEP 1: **Simple analgesic** (avoid opioids) along with explanation & reassurance. 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 e.g., acupuncture.

STEP 4: if headaches are severe, frequent & persist consider **amitriptyline** starting at 10mg ON, slowly increasing to 75-150mg ON.

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

Can also consider TENS and cognitive therapies.

Reconsider and exclude red flags again (page 1). Also consider mixed headaches: migraine & TTH and / or Medicine Overuse Headache.

Consider value of MRI as part of diagnostic process (where available) and refer if accepted by the patient.

MRI scan

Normal MRI scan and patient reassured – continue with Rx – consider trials of higher dosages for longer periods.

Seek further advice for diagnosis and management when:

- MRI scan not appropriate
- abnormal MRI scan
- patient not reassured despite normal MRI
- further clinical advice or specialist treatment required

REFER TO SPECIALIST

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

Rimegepant (Vydura®) and **atogepant (Aquipta®)** are classed AMBER 2 – after initiation by Specialist the ongoing prescribing may be requested from Primary Care following efficacy review of 12-week treatment.

Cluster headache

Most patients with new onset cluster headaches will require referral to a neurologist for advice.

STEP 1: Though short lived, acute treatment is nearly always needed. **Subcutaneous sumatriptan** is gold standard but consider **intranasal triptan**. **Oxygen** should only be prescribed if recommended by a neurologist ([link to guidance](#)). Usually prophylaxis is the best option.

STEP 2 PROPHYLAXIS:

Note: β-blockers should not be used for cluster headaches.

Prophylaxis dose should be increased rapidly; most sources suggest verapamil as first line.

Verapamil 80mg TDS starting dose then increase dose as prednisolone withdrawn.

Prednisolone should be started at the same time as verapamil - 60-100mg daily for 5 days then decrease by 10mg every 3 days, so that treatment is discontinued after 2-3 weeks.

Medication Overuse Headache (MOH)

Only treatment is withdrawal, but this may initially potentiate headache. Education & communication is critical. Can occur on top of other types of headaches.

Menstrual migraines

can be identified via headache diary. May respond to hormonal Rx-see [www.bash.org.uk](#)

Care needed with pregnancy - these guidelines do not apply to pregnancy or children – see NICE & BASH guidelines at [www.bash.org.uk](#)

OVERVIEW OF TREATMENT OPTIONS FOR MIGRAINE

The following information is to support prescribers regarding the medicines aspects of the pathway, please refer to the [BNF](#) and [Summary of Product Characteristics](#) for further information on contraindications, precautions, adverse effects and interactions for each relevant medication.

Acute migraine in adults (for management in pregnancy see [page 5](#))

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 or Prochlorperazine (buccal) 3-6mg (available OTC for adults 18 and over)
Diclofenac suppositories	Diclofenac 50mg or 100mg – see notes below

Notes:

1. When prescribing regular NSAIDs, consider the cardio-vascular risk and relevant contraindications ([diclofenac MHRA alert](#) and [ibuprofen MHRA alert](#)).
2. When prescribing regular metoclopramide, consider the risk of neurological adverse effects ([MHRA alert](#)).
3. Medicine should be given as soon as the onset of an attack is recognised.
4. The addition of a gastric motility agent will aid gastric emptying, as well as relieving nausea.
5. Anti-migraine medicine containing metoclopramide are not suitable for patients under the age of 20 years.
6. Since peristalsis is often reduced in migraine attacks, dispersible preparations may be helpful.
7. Suppositories are useful if vomiting or severe nausea present.

If simple analgesia fails, consider escalating to a 5HT₁ receptor agonist (triptan).

Triptans (5HT₁-receptor agonists)

Use the most cost-effective preparation first line i.e., sumatriptan 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 50, 100mg Injection 6mg per 0.5ml Nasal spray 10mg or 20mg per 0.1ml/dose	Naratriptan	Tablet 2.5mg

Zolmitriptan	Tablets and orodispersible tablets 2.5mg, 5mg Nasal spray 5mg per 0.1ml/dose	Frovatriptan	Tablet 2.5mg
Rizatriptan	Tablets and orodispersible tablets 5mg, 10mg Oral Lyophilisate 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. 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.
5. Orodispersible formulations obviate the need for water but do not get absorbed in mouth.
6. Nasal spray is useful when vomiting is a problem.

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 are ineffective or not suitable.

Acute treatment dose: 75mg as required once daily; in a form of oral lyophilisate it can be taken without liquid and should be placed on/ under the tongue to disintegrate.

Rimegepant is also recommended as AMBER 2 for the prevention of migraines – see [page 7](#) for further info. Please note the different dosing regimens for prevention and prophylaxis of migraine.

Review: To be undertaken by the initiating clinician. Consideration should be given to stop the treatment with rimegepant if there is no response after 2 to 3 acute attacks.

Contraindications: known hypersensitivity, end-stage renal disease or severe hepatic impairment.

Side effects: nausea – the most common reported. 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.

Another 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

First line	Non-pharmacological measures – avoidance of triggers, relaxation techniques and cognitive behavioural therapy
Second line	Paracetamol 1g
Third line	Sumatriptan 50-100mg

Notes:

1. Many medicines are contraindicated or have limited evidence of safety in pregnancy.
2. Risks and benefits must be discussed with the patient.
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. Ibuprofen is contraindicated in 3rd trimester and prolonged use should be avoided after 20-week of pregnancy. Some studies have suggested use of ibuprofen in early pregnancy might be linked to an increased chance of miscarriage, therefore local expert opinion is to avoid ibuprofen use in pregnancy (it is no longer locally recommended as a 3rd line).
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. The potential for teratogenic effects should be noted particularly with anti-epileptic medications.

Notes:

1. Propranolol, metoprolol and timolol are licensed, but only propranolol is on formulary for this indication.
2. 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.
3. Amitriptyline is useful with co-existent tension type headache, disturbed sleep or depression. Consider anticholinergic burden and risk of serotonin syndrome.
4. Note that gabapentin is not recommended by NICE for prophylactic treatment of migraine.
5. Note that rimegepant and atogepant for migraine prophylaxis, are to be initiated and trialed by a Specialist and only after 12 weeks review confirming the treatment effectiveness, the ongoing prescribing may be transferred into the Primary Care. One month supply is to be prescribed by the Secondary Care upon request of transfer of care, to ensure effective transition.

Topiramate

Topiramate is licensed for migraine prophylaxis, it is recommended by NICE in the headache clinical guideline for over 12's, and locally classed Amber 3 in the APC formulary. The use of topiramate during pregnancy is associated with significant harm to the fetus therefore, it should not be used in pregnancy for prophylaxis of migraine. It is also contraindicated for use in all women of childbearing potential, unless the conditions of the Pregnancy Prevention Programme 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 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 then 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.

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.

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

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 ($CrCl \leq 70$ 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).
- 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.
- Glibenclamide – possibly reduces plasma concentrations.
- 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.

Pizotifen

Pizotifen has been in use since the 1970s and is usually well tolerated. Due to inadequate evidence found for its effectiveness in the prophylaxis of migraine, the NICE guideline CG150 (September 2012) no longer recommends its use for the prevention of migraines in patients aged 12 and above. However, 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, increase in body weight. 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. Consultant neurologists may recommend use of oxygen therapy, 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 (Vyapti[®]) ▼ -concentrate for solution for infusion ([NICE TA 871](#))
- Fremanezumab (Ajovy[®]) ▼ - pre-filled Pen for Injection ([NICE TA 764](#))

Rimegepant (Vydura[®]) – AMBER 2

Licensed for acute treatment, as well, as migraine prophylaxis in adults, and it is now locally classed as AMBER 2 for both indications.

Place in therapy – prophylaxis: Recommended for use in line with corresponding [NICE TA906](#) (migraine prophylaxis) as an option for preventing migraine in adults who have at

least 4 but fewer than 15 migraine attacks per month and have tried at least 3 preventative treatments that have not worked. Considered as alternative treatment option to the injectable monoclonal antibodies erenumab, fremanezumab and galcanezumab (all are fourth-line treatments for the prevention of migraines).

Preventative treatment dose: 75mg once every other day.

Review: To be undertaken by the initiating specialist in Secondary Care (neurologist).

Discontinuation when used for migraine prophylaxis, should be considered if after 12 weeks the frequency of migraine attacks has not decreased by at least 50%.

Please see [page 4](#) for more information on rimegepant.

Atogepant (Aquipta[®]) – AMBER 2

Atogepant is locally classed as AMBER 2 and it can be prescribed following initiation by a Specialist for migraine prophylaxis for episodic (fewer than 15 headache days per month) or chronic migraine (15 or more headache days per month, with at least 8 of those having features of migraine).

Place in therapy: In line with NICE TA973 it can be considered for prevention of migraine in adults who have at least 4 migraine days per month, only if at least 3 preventive medicines have failed or cannot be tolerated. It can be used in management of episodic and chronic migraines. Considered as alternative treatment option for injectable CGRP monoclonal antibodies erenumab, fremanezumab, galcanezumab or eptinezumab, and oral rimegepant for the prevention of episodic migraine, or intramuscular injectable botulinum toxin type A or the monoclonal antibodies for the prevention of chronic migraine.

Dose: 60mg tablet once daily

Review: To be undertaken by the initiating Specialist in Secondary Care. It 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 (require dose reduction), pregnancy. With reproductive toxicity shown in animal studies any contraception method should be advised with atogepant (there is no clinically relevant interactions between hormonal/systemic contraception and atogepant) . Atogepant should be discontinued in advance of planning pregnancy.

Caution: breastfeeding patients require individual risk-benefit consideration. It is unknown whether atogepant is excreted in human milk, but data in animals confirm excretion in milk.

Side effects: In clinical trials the most commonly reported adverse drug reactions 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.

The majority 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 – these guidelines have been developed using NICE and BASH guidelines below:

1. NICE Clinical Guideline CG150: Headaches in over 12's: diagnosis and management (September 2012, updated November 2015)
<https://www.nice.org.uk/guidance/cg150>
2. NICE CKS: Migraine. Scenario: Migraine in pregnant or breastfeeding women (Last reviewed April 2019) <https://cks.nice.org.uk/migraine#!scenario:2>
3. The British Association for the Study of Headache (BASH)
<https://www.bash.org.uk/guidelines/>
4. The International Headache Society <https://ichd-3.org/evolution-of-ihs-classification-1-3/>

Self Help Resources for patients:

Patient UK – <https://patient.info/brain-nerves/headache-leaflet>

Migraine Buddy App - <https://migrainebuddy.com/>

Migraine Trust - <http://www.migrainetrust.org/>

Organization for the understanding of cluster headaches - <http://www.ouchuk.org>

NHS Choices <http://www.nhs.uk/conditions/Headache/Pages/Introduction.aspx>

