Hertfordshire and West Essex Integrated Care System

NHS Hertfordshire and West Essex Integrated Care Board

Treatment of migraine in adults in primary care

Contents

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Treatment of migraine in adults in primary care - summary flow chart

Patient presents with headache → History & examination → Exclude Red Flags requiring immediate referral → Diagnosis of migraine?

Yes

1st Line

Simple analgesia

NSAIDs +/- paracetamol 1g
Aspirin 900mg
Ibuprofen 400mg to 600mg

Contraindication to NSAIDs
Paracetamol 1g

OR

Triptan

Sumatriptan tablets
50mg to 100mg

OR

Triptan

AND

Simple analgesia

ALL +/-

Antiemetic

Metoclopramide 10mg orally#
Prochlorperazine 10mg orally

#Metoclopramide should not be used regularly due to the risk of extrapyramidal side effects MHRA Drug Safety Update

Advise all patients to keep a Headache Diary to allow assessment of response

Inadequate response [adequate symptom relief in 3 out of 4 migraine attacks is considered a good response] OR patient has N&V^ OR intolerance

2nd Line

Patients **WITH** contraindication to triptans

Simple analgesia with antiemetic
(if not already trialled)

Inadequate response

Patients with **NO** contraindication to triptans

Alternative triptan
(see guidance below on choice)

OR

Triptan with antiemetic* (if not already trialled)
Consider this combination **1st line** in those with N&V

^For patients with early profuse vomiting consider:
- an alternative non-oral triptan e.g. nasal zolmitriptan 5mg
-an alternative non-oral NSAID e.g. im diclofenac 75mg
- an alternative non-oral antiemetic e.g. buccal prochlorperazine 3-6mg

2 triptans ineffective/not tolerated and administration route and use in combination with other treatments have been considered

3rd Line

Gepants (CGRP antagonists)

Rimegepant 75mg

OR

Alternative triptan
(see guidance below on choice)

At any stage of acute treatment - Consider prophylaxis:

If headaches are frequent &/or acute medication is used very frequently, prophylaxis should be considered
(e.g. migraine headache on more than 4 days in a month, acute medications taken on 10 days or more in a month)

Migraine Prophylaxis

This should be titrated until control is gained and may take 8-12 weeks at the target dose before beneficial effects are seen.
When choosing a preventative treatment from the list below consider: patients past medical history, co-morbidities (including depression/ anxiety /suicidal ideation), and whether they have child-bearing potential. The order in which the treatments are chosen should be individualised to the patient based on these factors.
Refer to BNF or SmPC for full prescribing details

	Medication	General considerations & contraindications
Green	**Propranolol (immediate release)** (*Beta blocker*) ***Start***: 10mg twice daily ***Dose increment***: 10-40mg weekly ***Target***: 40-80mg twice daily ***Max***: 120mg twice daily	• Switch to a long-acting formulation, as desired, once a maintenance dose is achieved • Possible side effects: dizziness, fatigue, cold extremities, vivid dreams, lowers blood pressure. • Cautions: asthma, peripheral vascular disease or depression. • Avoid abrupt withdrawal as causes rebound headache.
Green	**Amitriptyline**[Δ] (*Tricyclic*) ***Start***: 10-25mg at night ***Dose increment***: 5-10mg weekly ***Target***: 30-50mg at night ***Max***: 100mg at night	• Possible side effects: dry mouth, sedation, blurred vision, constipation and urinary retention. • Contraindications: heart disease/arrythmias. Can cause QT interval prolongation • Caution in the elderly, consider a lower starting dose. Doses above 75mg should be used with caution. [Δ] If effective but cannot tolerate side-effects a less sedating TCA can be considered e.g. **nortriptyline** (unlicensed) with same dosing schedule
Green	**Topiramate** (*Antiepileptic*) ***Start***: 15- 25mg at night ***Dose increment***: 15-25mg two weekly ***Target***: 50mg twice daily ***Max***: 100mg twice daily	• Possible side effects: somnolence, angle-closure glaucoma, loss of verbal fluency, tingling/numbness in extremities, weight loss, renal stones (ensure adequate fluid intake), depression or behavioural change, foetal malformations. • Use of topiramate in pregnancy for migraine prophylaxis is **contraindicated** [Drug safety Update Jun 2024] • C/I in women and girls of childbearing potential unless conditions of Pregnancy Prevention Programme are met. [HCP guide] [Risk awareness form] – They should be using at least one highly effective method of contraception (preferably a user independent form such as a copper intrauterine device or levonorgestrel intrauterine system) or two complementary forms of contraception including a barrier method throughout treatment. – Consider the possibility of decreased contraceptive efficacy and increased breakthrough bleeding in patients taking systemic hormonal contraceptive products with topiramate (it is an enzyme inducer so care is needed and women using systemic hormonal contraceptives should also use a barrier method).
Green	**Candesartan** (*Angiotensin II Receptor Antagonist*) ***Start***: 2-4mg at night ***Dose increment***: 4mg two weekly ***Target***: 16mg at night ***Max***: 16mg at night	Unlicensed indication • Possible side-effects: bodily pain, tiredness, tingling; lowers blood pressure. • Monitoring: regular blood tests for urea & electrolytes (NICE CKS) • Not recommended in pregnancy, ensure highly effective contraception.
Green*	**Pizotifen** (*Serotonin antagonist*) ***Start***: 500micrograms at night ***Dose increment***: 500micrograms weekly ***Target***: 3mg (1mg tds) ***Max***: 4.5mg (1.5mg tds)	***Should be considered only when alternative treatments have failed or are unsuitable** • Possible side-effects: weight gain, dry mouth. • Evidence for use is limited and weight gain and sedation are often unacceptable side effects of this drug. • Pizotifen should not be stopped abruptly, therefore gradual withdrawal is recommended. Withdrawal symptoms include anxiety, tremors, insomnia, nausea and loss of consciousness. • Use in pregnancy should be avoided unless potential benefit outweighs risk.

- Some UK guidelines advise that **Riboflavin 400mg at night** may be useful in preventing migraine but there is no licensed riboflavin product available in the UK and no cost-effectiveness data to justify its use on NHS prescription. It is available as a food supplement and patients should be advised to self- purchase OTC from a reputable source.
- **Acupuncture** is not routinely available on the NHS but if pursued privately recommendations are that it should be 10 sessions over 5-8 weeks.
- **Gabapentin** should **NOT** be used for migraine prevention as there is now good evidence that it is not effective.

Medication for migraine prophylaxis should be trialled at or above the target dose for at least 3 months, in the absence of analgesia overuse, to be considered a sufficient trial.

Response at 3 months?
[A reduction of 50% or more in severity and frequency of attacks is considered a good response in episodic migraine.
A reduction of 30% or more in severity and frequency of attacks is considered a good response in chronic migraine].

No → Switch to an alternative

Yes → Continue. If the patient responds well to prophylactic treatment the need for continuing prophylaxis should be reviewed and a trial of gradual drug withdrawal should be considered after 6 to 12 months.

Sufficient trial of at least 3 oral preventatives but inadequate response

Secondary care referral for consideration of specialist preventative treatment

Options for consideration:

Alternative oral preventatives for specialist initiation only (Amber initiation)
- flunarizine, sodium valproate

Botulinum toxin A (chronic migraine only)

Oral anti-CGRP medications: rimegepant (episodic migraine only); atogepant
Note: these treatments are AMBER INITIATION (initiation & response assessment by specialists then ongoing prescribing in primary care)

Injectable anti-CGRP medications: erenumab; galcanezumab; fremanezumab; eptinezumab
Note: These treatments are RED drugs (specialist prescribing & monitoring)

Refer to additional notes below for details

Acute treatment of migraine in adults in primary care

Diagnosis of migraine

Confirm diagnosis through history taking and examination
See Appendix 1 for further details

Management of acute migraine

Self-care

Advise on lifestyle and over the counter medications.

Avoidance of known triggers and lifestyle changes such as stress management, good sleep hygiene, adequate hydration, avoidance of caffeine and alcohol, regular meals, exercise, and maintenance of a healthy weight can help.

Consider activities that encourage relaxation such as mindfulness, yoga or meditation.

Simple pain killers such as NSAIDs [e.g. aspirin, ibuprofen] and/or paracetamol are available over the counter and should be taken when the headache comes on. If response to these treatments is inadequate, then prescription of triptans (e.g. sumatriptan) can be considered.

Advise patients that **medication overuse headache (MOH)** is common in people with migraine and can be avoided by restriction of acute medication to a maximum of 2 days per week. Local specialists have advised that MOH can occur with 10 or more days per month use of simple analgesics (such as aspirin, ibuprofen and paracetamol) or 8 or more days use per month of triptans or combination analgesics.

Opioid prescriptions should be avoided as there is a higher risk of resistant medication overuse and other medications generally target migraine better. This includes, but is not exhaustive, any which contain codeine, dihydrocodeine, tramadol, morphine or fentanyl. Caution is needed when recommending over the counter products as these may contain codeine or caffeine which should generally be avoided e.g., Migraleve® preparations (typically containing paracetamol 500 mg and codeine phosphate 8 mg) or Anadin Extra® (typically containing aspirin 300 mg, paracetamol 200 mg and caffeine 45 mg).

Headache diaries

Patients should be asked to keep a headache diary to record details of their migraine attacks or headache. This can help to confirm the diagnosis and can be used to assess whether acute or preventative medication is working. It can also help the patient to recognise any triggers and warning signs and to show any patterns to attacks.

A headache diary should be simple and record basic information which should include:
Date / day of the week / duration (how long the attack lasted) / severity (how bad the attack was using a severity scale of 0-10 where 0 is no pain and 10 is the worst possible and patient is bed-bound) / other symptoms (e.g., dizziness, vertigo, sensitivity to light, sound, smells) / medication taken / any side effects from medication / any potential triggers.

Example headache diary template: Keeping a headache diary - The Migraine Trust

Acute treatment

Advise the patient that:

- Acute medication should be taken early while pain is mild.
- If they have aura, triptans should be taken at the start of the headache and not at the start of the aura (unless the aura and headache start simultaneously).
- If a medication does not work in treating an attack, there is no point in repeating the same treatment unless you are then using in a new combination with other painkillers or anti-emetics.

- Headache diary must be used.
- Arrange follow up within 2–8 weeks of starting treatment but advise the person to attend for review sooner if headache changes in nature or adverse effects develop.

First line

- Depending on the severity of attacks, associated symptoms, contraindications and comorbidities:
  1. Offer **simple analgesia** (+/- an anti-emetic) such as:

     Ibuprofen (400 mg; if ineffective, consider increasing to 600 mg) OR Aspirin (900 mg) AND/OR Paracetamol (1g)

     OR
  2. Offer a **triptan, alone or in combination** with, paracetamol or an NSAID (+/- an anti-emetic): Oral sumatriptan (50–100 mg) is first choice
  3. Consider offering an **anti-emetic** (such as metoclopramide 10mg or prochlorperazine 10mg) in addition to other acute medication even in the absence of nausea and vomiting. Limited exposure to anti-emetics is recommended and patients should not take regularly for more than 5 days at a time (MHRA indicate that these should be dose restricted and not used regularly to mitigate concerns [Metoclopramide risk of extrapyramidal side effects]).
- Opioid medications should NOT be used to treat migraine headache.
- Oral triptans should be used first line but if vomiting restricts oral treatment, consider a non-oral formulation (such as intra-nasal zolmitriptan or subcutaneous sumatriptan; oro-dispersible formulations obviate the need for water but do not get absorbed in mouth).
- Combinations of acute treatments can be helpful if individual treatments are not adequately effective.
- Paracetamol doses may need to be adjusted in patients weighing <50kg.

Second line

- Patients with contraindications to triptans – offer a combination of simple analgesia and anti-emetic (if not already trialled first line).
- Patients with an inadequate response or intolerance to sumatriptan - an alternative triptan should be offered (see below) or combination treatment of triptan with analgesia/anti-emetics

Third line

- Patients with contraindications or significant intolerance to triptans – consider rimegepant in those who have had inadequate response to simple analgesia (with or without anti-emetics)
- In patients without contraindications to triptans consider rimegepant if 2 different triptans have been ineffective or not tolerated and administration route and use in combination with other treatments have all been considered. Additional trials of alternative triptans may also be considered in these patients.

Follow up/Review

- Review headache diary and discuss frequency of attacks, effectiveness of treatment, adverse effects and lifestyle improvements. It is important to also evaluate the most bothersome symptom of migraine as this may not be well captured on a pain diary and can sometimes reflect the mismatch between reporting of significant benefit but pain diaries seemingly not reflecting this.
- If treatment has been effective (noting that functional gain is important), is being used appropriately and is well tolerated, continue it (with appropriate medication reviews). Ask the person to reconsult if they experience problems in the future (for example increasing severity or frequency of migraine or side effects of medication).
- If previous acute treatments have proven ineffective or poorly tolerated:
  - Reconfirm the diagnosis — consider the need for referral.
  - Reassess lifestyle advice, check correct usage of treatment and rule out MOH.
  - Consider alternative triptans (see table below) or combination therapy with an oral triptan and an NSAID or an oral triptan and paracetamol, if not tried previously and no contraindications.

- Consider need for preventative therapy in patients with 4 or more migraine days a month.
- If the patient has tried two or more triptans unsuccessfully (or triptans are contraindicated) consider a switch to rimegepant
- Reiterate advice on avoidance of MOH (i.e. restriction of use of acute medications to a max of 2 days per week)

Treatment of acute migraine in pregnancy

First line: Non-pharmacological measures – avoidance of triggers, relaxation techniques and cognitive behavioural therapy
Second line: Paracetamol 1g
Third line: Ibuprofen 200-400mg (must be stopped and not used in the 3rd trimester)
Sumatriptan 50-100mg

Notes:
- Many medicines are contraindicated or have limited evidence of safety in pregnancy.
- Risks and benefits must be discussed with the patient.
- If treatment with medication is necessary, consider contraindications and co- morbidities.
- There is less evidence of safety for NSAIDs and triptans than for paracetamol.
- Sumatriptan is the preferred triptan in pregnancy.
- Pregnant patients should be encouraged to read leaflets about recommended medications, which can be found on the *best use of medicines in pregnancy* website (https://www.medicinesinpregnancy.org/Medicine--pregnancy/).
- Seek specialist advice if prophylactic treatment for migraine is needed during pregnancy.

Triptans (5HT1-receptor agonists)

Cautions and contraindications:
Triptans are contraindicated in people with:
- cardiovascular disorders including: ischaemic heart disease, uncontrolled hypertension, previous myocardial infarction, coronary vasospasm, uncontrolled arrhythmias or peripheral vascular disease, cerebrovascular disorders, including previous transient ischaemic attack or ischaemic stroke (seek advice for haemorrhagic stroke).
- Severe peripheral vascular disease.
- Severe hepatic impairment

Triptans should not be taken concurrently (in the same 24-hour period) with other triptans, ergotamine derivatives, monoamine oxidase inhibitors.

Triptans should be prescribed with caution in people:
- With risk factors for cardiovascular disease — cardiovascular assessment required prior to prescription. Hypertension if treated is not a contraindication but good control needs to be established and if blood pressure measurements are consistently above 140/90mmHg then this is inadvisable.
- With a history of, or risk factors for, seizures.
- With renal or hepatic impairment — dose adjustment may be required.
- Who are elderly (unlicensed). Triptans are not licensed in adults older than 65 years, but in practice, if patients do not have vascular risk factors, then triptans may be considered if alternative simple analgesics are ineffective. Patients should be warned to stop the triptans in future if they develop any of the cardiovascular or cerebrovascular issues cited in the list of contraindications.

Drug Interactions (not exhaustive):
Please check individual SmPCs or BNF for full details.
- Triptans should not be combined with monoamine oxidase inhibitors or ergotamine derivatives.
- Triptans are not contra-indicated with Selective Serotonin Reuptake Inhibitors (SSRIs).

Although all UK summary of product characteristics caution against the concomitant use of triptans and SSRI / serotonin – norepinephrine reuptake inhibitor (SNRI) anti-depressants due to the risk of serotonin syndrome, in practice this combination can be taken safely in most patients. The authors of the SIGN guideline suggest this combination is not contraindicated. Nonetheless, patients should be monitored for signs of serotonin syndrome if this combination is used.

- In patients taking propranolol, limit rizatriptan to the 5mg dose, and ensure a minimum separation of 2h between taking propranolol and rizatriptan. No more than 2 doses of rizatriptan should be taken in a 24h period.
- Check individual drug listings for drug interactions including in those taking antibiotics, antifungal agents, cimetidine, antiretroviral agents, and verapamil – interactions vary between triptans.

Choice of triptan:

Both NICE and SIGN guidelines advise that the lowest cost triptan should be used first line but that if this is ineffective other triptans should be offered. Sumatriptan is specified as the recommended first line treatment, but further guidance is not given on subsequent choices.

The table below is in line with guidance for use of sumatriptan first line but then lists other potential options for patients who fail sumatriptan or cannot tolerate it. The second line drugs are listed in order of cost with £ signs indicating the comparative costs.

First line	Green	Sumatriptan 50-100mg tablet	£
Second and subsequent line choices		Naratriptan 2.5mg tablet	£
		Rizatriptan 10mg oro disp	£
		Frovatriptan 2.5mg tablet	££
		Zolmitriptan 5mg oro disp	£££
		Almotriptan 12.5mg tablet	£££
		Eletriptan 40mg tablet	£££
		Zolmitriptan 5mg nasal spray	££££
		Sumatriptan 3mg injection	£££££
		Sumatriptan 6mg injection	£££££

Some preparations are significantly more expensive than equivalent or comparable preparations, so use of these items is restricted and they should only be initiated by, or on the advice of, a specialist. The formulations below should only be trialled if the patient only responds to one specific triptan and the recommended formulations are not tolerated or when a nasal spray is required but zolmitriptan is not tolerated.

Restricted triptan preparations	Rizatriptan 10mg tablets	££
	Rizatriptan oro disp (Maxalt MELT) 10mg	££££
	Zolmitriptan 5mg tablets	££££
	Sumatriptan nasal sprays 10mg & 20 mg	££££

Situations where a particular triptan may be considered as preferred second- or subsequent-line choices:

- In patients with profuse early vomiting a non-oral triptan (e.g. nasal zolmitriptan or subcutaneous sumatriptan) with a non-oral antiemetic.
- In patients who experience headache recurrence (i.e. patients who consistently have a significant response to a triptan, but the headache rebounds or recurs) a longer lasting triptan may provide a more sustained response e.g. naratriptan or frovatriptan
- For women with predictable menstrual-related migraine that does not respond adequately to standard acute treatment (e.g. NSAIDs), treatment with frovatriptan or zolmitriptan could be considered.

If more than one triptan is considered suitable the least expensive should be chosen

Adverse effects:
Patients should be warned that triptan sensations and / or sedation may occur.
Symptoms may include tightness/burning in the jaw, throat, or chest, or pins and needles in the face.

Taking triptans:
- Triptans should be taken at the onset of the headache pain, as they are more effective when taken early in an attack.
- If the first dose is ineffective, a second dose should not be taken for the same attack (unless taken with a new additional therapy e.g. NSAID). If there is response to the first dose, but symptoms recur, a second dose may be taken provided there is a minimum of 2 hours between doses (or 4 hours between doses for naratriptan).
- Treatment frequency should be *limited to no more than two days per week* (up to 2 doses can still be taken in any one day if needed) – more frequent use can result in MOH.
- The combination of triptan and an NSAID is more effective than taking either of these medicine types separately. Anti sickness medication can also be taken in combination with a triptan and can enhance the effectiveness of oral medications.

Prescribing triptans:
Triptans should be prescribed generically.
Ask the person to make a follow-up appointment after the first pack of triptans has been used (typically three to six doses).

How to assess effectiveness:
The European Headache Federation (EHF) consensus on the definition of effective treatment of a migraine attack by a triptan is adequate symptom relief in 3 out of 4 headaches.
Response to different triptans is variable, and people who fail to respond to one triptan may respond to another. Therefore, if the patient does not respond to one triptan after use in three separate attacks, an alternative triptan may be considered.

Gepants (CGRP antagonists)
Rimegepant
Rimegepant is an oral calcitonin gene-related peptide (CGRP) small molecule antagonist targeting the receptor.
Rimegepant has been approved for *acute treatment* of migraine attacks (Green RAG rating) and for *prevention* of episodic migraine attacks (Red RAG rating) (i.e. more than 4 migraine attacks per month but less than 15 headache [including migraine] days per month).

Before initiation:
Before rimegepant is considered patients must have tried *at least 2 triptans* which did not work well enough or triptans are contraindicated or not tolerated, and NSAIDs and paracetamol were tried but did not work well enough or were unsuitable.
[NICE TA919: Rimegepant for treating migraine]

Before considering rimegepant the prescriber should confirm:
- triptans have been taken early in the headache phase
- the correct route of administration has been considered, e.g. use of nasal or subcutaneous injections in patients with early vomiting
- combination use of triptan with simple painkillers/anti-sickness medication has been considered
- full and accurate drug history
- the patient is not pregnant

Cautions and contra-indications:
Rimegepant is not recommended in those with severe liver disease or end-stage kidney disease.
It is not recommended if a patient is pregnant and local specialists have advised rimegepant should be stopped at least 4 weeks before trying to conceive.

CGRP is a potent vasodilator and blocking its vasodilatory action may have other effects within the body. Whilst there are no specific cautions or contraindications listed in the SmPC, patients with clinically significant cardiovascular or cerebrovascular disease were excluded from trials (e.g. Myocardial Infarction (MI), Acute Coronary Syndrome (ACS), Percutaneous Coronary Intervention (PCI), cardiac surgery, stroke or Transient Ischemic Attack (TIA) during the 6 months prior to enrolment in the trial). The potential risk of use in these cohorts is therefore uncertain and specialist advice should be sought if needed.

Drug interactions (not exhaustive):

Please check SmPC or BNF for full details.

- Rimegepant is metabolised by liver enzymes from the CYP family, primarily CYP3A4, and other enzymes so has potential interactions with other medications. Use with strong inhibitors of CYP3A4 (e.g. clarithromycin, itraconazole, ritonavir) or strong or moderate inducers of CYP3A4 (e.g., phenobarbital, rifampicin, St John's wort [*Hypericum perforatum*]*, bosentan, efavirenz, modafinil) is not recommended.
- If patients are also taking a moderate inhibitor of CYP3A4 (e.g., diltiazem, erythromycin, fluconazole*) or a strong inhibitor of P-glycoprotein (P gp) (e.g., cyclosporine, verapamil, quinidine) another dose of rimegepant within 48 hours should be avoided.

  *It is therefore important to ask patients about medications bought over the counter from a pharmacy, herbal remedies etc
- Patients should be advised to avoid drinking grapefruit juice on the day of treatment as this can also interact with rimegepant.

Adverse effects:

Rimegepant is generally very well tolerated. In the clinical trials, nausea developed in 2% of people who received rimegepant compared to less than 0.4% of patients who received placebo. Allergic hypersensitivity reactions have been reported as an uncommon reaction (occurring in <1% of patients in clinical studies). If a hypersensitivity reaction occurs, rimegepant should be discontinued and appropriate therapy should be initiated.

Taking rimegepant for acute migraine:

Rimegepant is available as an oral tablet that melts in the mouth and should be placed on or under the tongue and allowed to dissolve. It will disintegrate in the mouth and can be taken without liquid.
A single dose of 75mg can be taken for an acute migraine attack. 75mg is the maximum daily dose so repeat doses should not be taken.
Note – there is a different schedule of dosing for prevention of episodic migraine – use for this indication is restricted to specialist initiation.

Prescribing rimegepant:

Prescribers should issue an initial prescription for 4 x 75 mg doses (available pack sizes 2 tablets and 8 tablets).
Patients should be advised to keep a headache diary to help evaluate response to treatment. It may also be helpful to ask patients to evaluate each of the 4 attacks treated against the following statements:

- It significantly improved my migraine pain or most bothersome migraine symptom within 2 hours
- I did not need or want to reach for additional rescue painkillers
- I remained free of bothersome migraine symptoms for 24 hours
- I had no concerning side effects

A patient questionnaire is available which can be completed by the patient following each attack and used to evaluate treatment.

A follow up review should be arranged in 2 to 4 weeks, (depending on frequency of migraine attacks) to assess response & tolerability.

How to assess effectiveness:

- Rimegepant costs £12.90 per dose. It is important that it is only continued when there has been a satisfactory response.
- A satisfactory response is one where the patient's well-being has been significantly improved within 2 hours and this is maintained for 24 hours, and this is achieved by:
    a) improvement of headache
    b) relief of non-pain symptoms (e.g. nausea, vomiting, sensitivity to light sound, smell and aggravation of symptoms on physical exertion)
    c) absence of adverse events.
- If a response to rimegepant is not clear, then treatment should be stopped, and further options explored (e.g. alternative simple analgesia approaches or further trials of triptans if appropriate).
- If migraine has responded well to rimegepant treatment on at least 3 out of 4 occasions, further supply of 4 x 75mg doses may be provided on prescription. These should be issued as acute prescriptions initially and usage should be assessed before re-issue.
- If the patient is using frequent doses (4 or more a month) then preventative medications should be considered if the patient is not already taking them. If the patient is already on preventative medication this should be reviewed due to lack of effectiveness.

When ongoing rimegepant treatment is no longer suitable and should be stopped:

- If the patient reports hypersensitivity to or intolerance of the drug
- If the patient reports a worsening of migraine and is no longer responding
- If the patient develops severe renal or liver failure
- If the patient becomes pregnant or is trying to conceive
- If the patient starts a new medication that is a strong inhibitor of CYP3A4 or a strong or moderate inducer of CYP3A4 (see interactions)
- If the patient develops a new vascular condition whilst on treatment the risk/benefit should be reassessed, and specialist advice sought if needed (see cautions)
- If the patient starts an injectable calcitonin gene-related peptide (CGRP) receptor antagonist as a specialist preventive the specialist will advise on appropriate ongoing acute treatment

Standard oral preventative treatments for migraine in adults

Preventative treatment aims to make migraine less severe or less frequent. It may also reduce the risk of getting medication overuse headache from taking medication for acute attacks too frequently.

The standard oral preventatives included in this guideline are those supported by NICE &/or SIGN guidelines with target doses advised by local specialists.

Please refer to table in flowchart for recommended therapies in primary care.

Note: Topiramate is C/I in pregnancy and in women and girls of childbearing potential unless conditions of Pregnancy Prevention Programme are met, and the healthcare professional and patient complete an Annual Risk Acknowledgement Form. [HCP guide] [Risk awareness form]

- Prescribing decisions should be made with reference to the patient's current clinical situation and their future plans (e.g., pregnancy or contraception). As there are relatively few head-to-head comparative studies, the choice of preventive depends primarily upon co-existing morbidities and the patient's priorities.
- Preventive treatment should be offered as an option to patients with 4 or more migraine days a month as this frequency is associated with significant disability.
- Such an approach will also mitigate the risk of escalation of acute treatment and consequent development of MOH. Acute treatment on more than 2 days per week is associated with medication overuse, which renders preventive treatment less effective.
- Preventive medications must be titrated slowly to an effective or maximum tolerable dose and continued for at least 8-12 weeks to adequately assess effect. A headache diary will help evaluate response to treatment.

- A reduction of 50% or more in severity and frequency of attacks is considered a good response in episodic migraine, and a reduction of 30% or more is considered a good response in chronic migraine**.**
- Consider gradual withdrawal after 6-12 months of effective preventive treatment.
- If there is treatment failure (defined as a lack of response to the highest tolerated dose after 3 months) consider an alternative option.
- If three separate preventative treatments have failed at target dose and for sufficient duration, or patient has contraindications to recommended treatments, consider referral for specialist advice or review.
- While preventative migraine therapies aim to achieve a clinically meaningful reduction in migraine attacks, the vast majority of patients will use acute medications to manage breakthrough events.
- Some preventative therapies are contraindicated in pregnancy due to potential harmful effects and the need for highly effective contraception must be discussed with women before starting treatment.

Refer to BNF or SmPC for full prescribing details

Specialist neurology services

- Consider admission or urgent referral if a serious cause of headache is suspected (see the section on Red Flags)

When to consider referral for specialist advice:

- if there is any doubt about the diagnosis
- if there is a change in the patient's circumstances which may affect treatment (e.g. pregnancy, new health condition)
- if optimal treatment in primary care does not adequately control the symptoms (MOH should be considered and addressed).
- if a patient has had three or more trials of different oral preventative therapies at target dose and for sufficient duration with inadequate response (or if these treatments are contra-indicated) - specialist preventative treatments may be suitable at this point

Specialist preventative treatments for migraine

Standard oral preventatives requiring specialist initiation

Refer to BNF or SmPC for full prescribing details

	Medication	General considerations & contraindications
Amber Initiation	**Flunarizine** (*Calcium channel blocker*) ***Start***: 5mg at night ***Dose increment***: 5mg two weekly ***Target***: 10mg at night ***Max***: 10mg at night	Not marketed or licensed in the UK but it is in many other countries. Should be avoided in people with depression, Parkinson's disease or movement disorders. • Possible side effects: tiredness, drowsiness, weight gain, low mood • Flunarizine should be avoided during pregnancy
Amber Initiation	**Sodium valproate** (*Antiepileptic)* ***Start***: 200mg at night ***Dose increment***: 200mg two weekly ***Target***: 1200mg (600mg BD) ***Max***: 1200mg (600mg BD)	**New patients:** Valproate should **not** be prescribed for migraine prophylaxis in females or males of reproductive age (younger than 55 years) **Existing patients:** If valproate is being used in under 55s for this indication use should be reviewed by a specialist team to assess if ongoing use is appropriate. In patients under the age of 55 years, two specialists must independently consider and document that there is no other effective or tolerated treatment at their next annual review. In women and girls of childbearing potential the conditions of the pregnancy prevention programme must be fulfilled, and the specialist must complete and sign an Annual Risk Acknowledgement Form with the patient. [HCP guide] [Patient guide] [Risk acknowledgment form] Male patients under 55 need to be made aware of the risk of male infertility or potential testicular toxicity and a risk acknowledgement form must be completed by specialists at the time of initiation. [Risk Acknowledgement form] All male patients and/or carers should be made aware potential risk to children born to men treated with valproate in the 3 months before conception. [MHRA Sept 24] [PIL] Valproate is not licensed for migraine prophylaxis • Side effects: weight gain, somnolence, tremor, tiredness, haematological and hepatic abnormalities, risk of foetal malformations • Monitoring: FBC and LFTs at baseline and during treatment.

Specialist preventive treatments

Specialists may prescribe a number of specialist preventative treatments for chronic and episodic migraine in line with the recommendations for use from the National Institute for Health and Care Excellence and local ICS guidelines. More information is available from the ICB clinical guidance website.

To be considered for any of the below treatments patients need to have a diagnosis of episodic or chronic migraine and have trialled 3 standard oral preventative treatments at target dose and for sufficient duration, without achieving an adequate response (unless there have been issues with intolerance).

- The injectable calcitonin gene-related peptide (CGRP) receptor antagonists **erenumab** (Aimovig®), **galcanezumab** (Emgality®)**, fremanezumab** (Ajovy®) **& eptinezumab** (Vyepti®) may be used for prevention of either chronic or episodic migraine if a patient has more than 4 migraine days per month on a recurring basis.
  These treatments are all **RED** drugs with prescribing and monitoring undertaken by specialists.
- The oral CGRP antagonists have different approved indications. **Atogepant** (Aquipta®) may be used for prevention of either chronic or episodic migraine if a patient has more than 4 migraine days per month on a recurring basis. **Rimegepant** (Vydura®) can be used at a different dosing schedule for prevention of episodic migraine (episodic migraine defined as having at least 4 migraine attacks per month but less than 15 total headache days per month).
  These treatments are both **AMBER INITIATION** drugs with initiation & response assessment by specialists then ongoing prescribing in primary care.
- **Botulinum toxin A** injections may also be used in the prevention of chronic migraine (chronic migraine defined as more than 15 total headache days per month, of which at least 8 are with migraine and this has been the case for 3 or more months).

Information for patients

- Migraine from Patient Info UK: Migraine leaflet
- Treatment of migraine from Patient Info UK: Migraine treatment-medication and prevention
- NHS Health A-Z: Migraine
- The Migraine Trust: Migraine
- British Association for the Study of Headache Guidelines (BASH): For headache sufferers

References:

- NICE guidance CG150. Headaches in over 12s: diagnosis and management. Last updated 2021 - https://www.nice.org.uk/guidance/cg150
- SIGN 155 Pharmacological management of migraine 2023 update - https://www.sign.ac.uk/media/2077/sign-155-migraine-2023-update-v3.pdf
- BASH Guideline: National Headache management system for adults 2019 - https://headache.org.uk/wp-content/uploads/2023/02/bash-guideline-2019.pdf
- NICE CKS Migraine - https://cks.nice.org.uk/migraine
- NICE CKS Headache- https://cks.nice.org.uk/topics/headache-assessment/
- EHF Consensus on the definition of effective treatment of a migraine attack and of triptan failure - https://thejournalofheadacheandpain.biomedcentral.com/articles/10.1186/s10194-022-01502-z

Appendix 1

Diagnosis of migraine
Confirm diagnosis through history taking and examination

Diagnostic criteria for migraine:

- Recurrent episodes (at least 5 attacks) of headache lasting between 4 and 72 hours untreated
- One or both of the following:
  - Nausea/vomiting
  - Photophobia/Phonophobia
- At least two of the following:
  - Site of pain: unilateral
  - Pulsating in character
  - Aggravated by routine physical activity
  - Moderate or severe in intensity
- No other cause identified

Examination should include:

- Vital signs (including blood pressure and BMI)
- Mental state and alertness
- Examination of the neck, facial and extracranial structures
- Neurological examination- including fundoscopy

Check if female patients with a confirmed/suspected diagnosis of migraine with aura are taking the combined oral contraceptive (COC) pill. Migraine with aura is a contraindication for taking COC for contraceptive reasons therefore an alternative contraception such as the progesterone only pill should be prescribed.

Exclude Red Flags – consider admission, urgent MRI scan or 2ww referral as appropriate

- **New severe or unexpected headache**
  - New-onset headache in >50 years (may indicate temporal arteritis or a space-occupying lesion)
  - Sudden onset severe ('thunderclap') headache reaching maximum intensity within 5 minutes (may indicate subarachnoid haemorrhage or other intracerebral haemorrhage, venous sinus thrombosis, malignant hypertension, vertebral artery dissection, or intracranial hypertension)
- **Progressive or persistent headache, or headache that has changed dramatically.** (If there is evolution of headache over days to weeks, particularly with focal neurological signs, consider a space-occupying lesion or subdural haematoma).
- **Associated features such as:**
  - Fever, impaired consciousness, seizure, neck pain/stiffness, or photophobia (may indicate central nervous system (CNS) infection such as meningitis or encephalitis; neck stiffness may indicate subarachnoid haemorrhage).
  - Papilloedema (may indicate a space-occupying lesion, cerebral venous sinus thrombosis, or benign intracranial hypertension).
  - New-onset focal neurological deficit, change in personality, cognitive impairment, and/or altered consciousness (may indicate a stroke or transient ischaemic attack (TIA), malignancy, CNS infection, or other cause of space-occupying lesion such as subacute or chronic subdural haematoma).
  - Atypical aura (duration greater 60 minutes, or including motor weakness, double vision, visual symptoms affecting only one eye, or impaired balance) or aura occurring for the first time in a person using the COC pill (consider a stroke or TIA).
  - Dizziness can be associated with migraine, check for hearing loss (Meniere's' disease) and consider ischaemic or haemorrhagic stroke).

  - Visual disturbance (can be associated with migraine but also with serious causes such as angle-closure glaucoma and temporal arteritis).
  - Vomiting (can be associated with migraine but also with serious causes such as a mass lesion including brain abscess or carbon monoxide poisoning).
- **Contacts with similar symptoms:**
  - Consider serious causes such as carbon monoxide poisoning.
- **Precipitating factors such as:**
  - Preceding recent head trauma [usually within the past 3 months] (consider subacute or chronic subdural haematoma).
  - Headache triggered by a Valsalva manoeuvre [such as coughing, sneezing, bending, or exertion] (consider a Chiari malformation type 1 (a herniation of the cerebellar tonsils), a posterior fossa lesion, or other space-occupying lesions).
  - Headache that worsens on standing and fully resolves within 30 minutes of lying flat (consider a cerebrospinal fluid leak).
  - Headache that worsens on lying down (consider a space-occupying lesion or cerebral venous sinus thrombosis).
- **Comorbidities such as:**
  - A condition causing immunocompromise [such as HIV or immunosuppressive drugs] (consider CNS infection (including abscess) or malignancy).
  - Current or past malignancy (especially if age under 20 years); a history of malignancy known to metastasize to the brain [such as lung, breast, and malignant melanoma] (consider cerebral metastases).
- **Current or recent pregnancy:**
  - Consider pre-eclampsia.

Classification of migraine

- Chronic migraine: 15 or more headache days per month, of which at least 8 are with migraine
- Episodic migraine: fewer than 15 headache days per month

Version	1.1
Developed by	Pharmacy and Medicines Optimisation Team, Hertfordshire and West Essex (HWE) ICB with relevant HWE ICS stakeholders.
Approved by	Hertfordshire & West Essex Area Prescribing Committee
Date approved / updated	June 2025
Review Date	This HWE APC recommendation is based upon the evidence available at the time of publication. This recommendation will be reviewed upon request in the light of new evidence becoming available.
Superseded version	Treatment of migraine in adults in primary care. v1.0 HWE APC, Nov 2024