Preventative Pharmacological Management of Migraine

TARGET AUDIENCE	Primary Care
PATIENT GROUP	Adult patients with a diagnosis of migraine

Clinical Guidelines Summary

This clinical guideline focuses on local pathways for the preventative treatment of migraine and covers the following areas:

- **Introduction**
- **Prophylaxis of Migraine**
- **Preventative Treatment of Migraine**
- **Calcitonin Gene Related Peptide (CGRP) Small Molecule Antagonists (gepants) and prescribing considerations**
- **Actions Prior to Prescribing Atogepant or Rimegepant**
- **Review of efficacy and tolerance at 3 months**
- **Prescribing notes for Atogepant and Rimegepant**
- **Who to refer**
- **Prophylactic Medicines Prescribed by Secondary Care Headache Team**

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Introduction

This guideline focuses on local pathways for the preventative treatment of migraine. Further information on diagnosis and management of headache including information and guidance on the acute management of migraine in primary care can be found in the Scottish Headache Pathways. The NHS Lanarkshire formulary section Anti-Migraine Drugs – Treatment of an Acute Attack can be found here Treatment of the Acute Attack.

Prophylaxis of Migraine

The decision if or when to start oral prophylaxis should be tailored to the individual patient. As per SIGN 155, there is no specific number of migraine days or migraine attacks per month that indicates the need for prophylaxis. For example, patients with a few disabling migraine days per month may elect to start treatment, but patients with a larger number of mild headache days per month may not.

General Points

- Migraine prophylactics may take many weeks to work. Judgment of efficacy should be made once the patient has been taking the target dose or highest tolerated dose for 8-12 weeks.
- If the migraine prophylactic is ineffective at 8-12 weeks, it should be weaned over at least 2 weeks and an alternative considered.
- If it is effective (i.e. reduced monthly headache or migraine days by at least 30-50%) consider weaning the drug after 6 to 12 months (it should be weaned at the approximate rate it was increased).
- If side effects are experienced after a dosage increase, decrease to the previous dose and then attempt a dosage increase after 2 weeks.
- Patients should be warned to refrain from driving if they become drowsy.

Preventative Treatment of Migraine

The flowchart below outlines the overall treatment pathway, further details on the medicines included can be found in the prescribing notes later in the guideline.

Chronic migraine = 15 or more headache days per month for three months, at least 8 of which have migraine features
Episodic migraine = Less than 15 headache days per month (high frequency episodic migraine 8-14 days per month)

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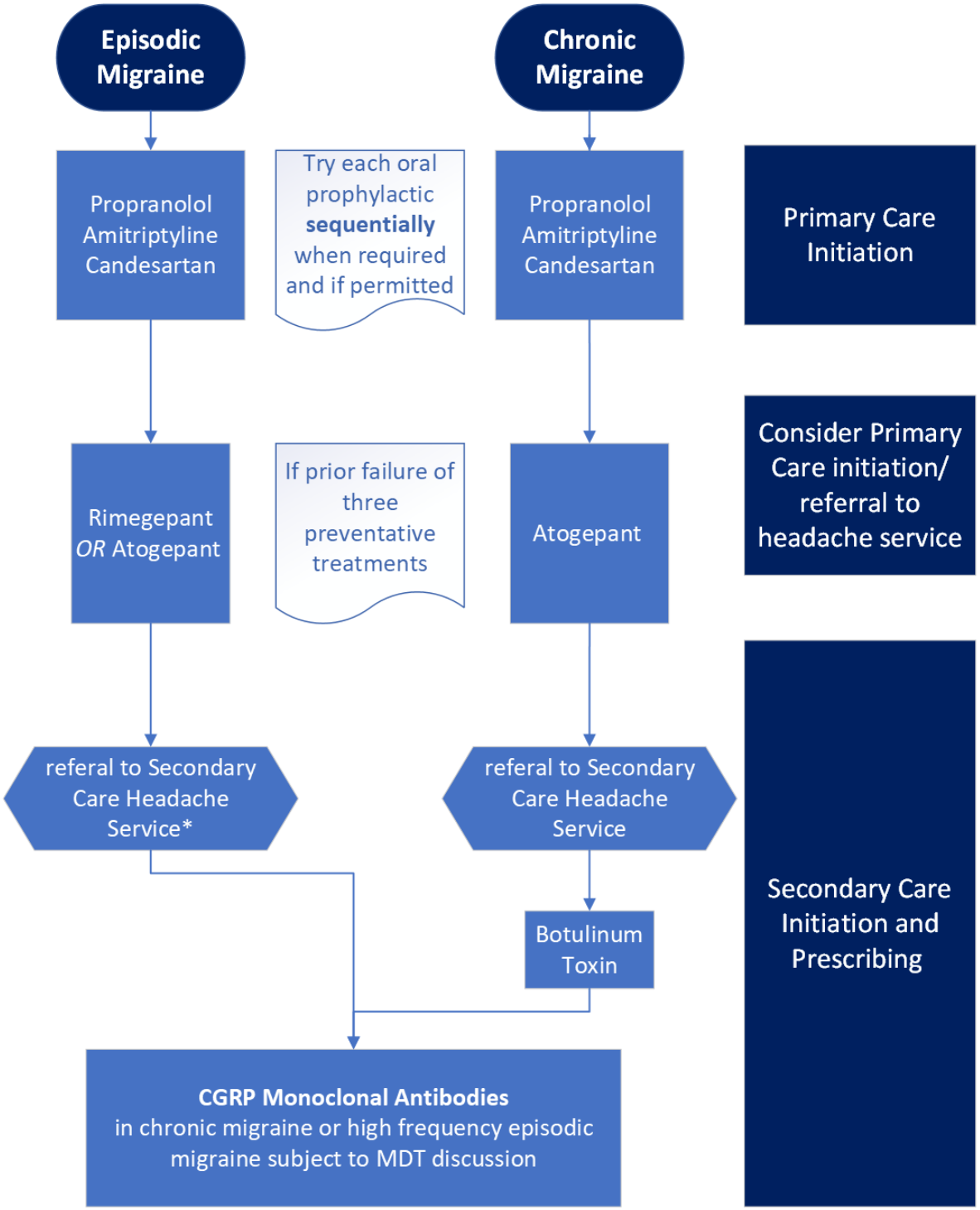

* Topiramate may be considered for specialist initiation. **It is not recommended to start topiramate in women of child bearing potential.** For further information, please see the MHRA advice regarding pregnancy prevention programme guidance Topiramate (Topamax): introduction of new safety measures, including a Pregnancy Prevention Programme and the Faculty of Sexual and Reproductive Health Guidelines for advice on contraception interactions.

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Drug & Dose	Prescribing notes
Amitriptyline	
Start at 10mg at night Increase by 10mg every 1-2 weeks. The typical first target dose is 50mg once a day in the evening. If well tolerated many patients benefit from a higher dose with further up titration up to 1mg/kg, typically a maximum of 100mg per day.	If side effects occur, alternatives include nortriptyline, or dosulepin A full list of contraindications and cautions can be found in the Summary of Product Characteristics (SPC). Contraindications include concomitant use of monoamine oxidase inhibitors, recent myocardial infarction, heart block, disorders of cardiac rhythm, and coronary artery insufficiency, and severe liver disease. Avoid use in those patients at risk of glaucoma, and QT prolongation. Caution in those patients taking serotonergic drugs. Side effects include constipation, difficulty with micturition, arrhythmias, syncope, confusion, nausea, dry mouth, drowsiness and weight gain. Patients should seek immediate medical attention if they are unable to micturate or experience visual blurring or symptoms of acute glaucoma.
Candesartan	
Start at 2-4mg per day Increase by 2-4mg every 1-2 weeks to a maximum of 16mg daily.	A full list of contraindications and cautions can be found in the Summary of Product Characteristics (SPC). Caution in patients with renal artery stenosis, hypotension and renal impairment. Candesartan is cautioned in those patients receiving lithium therapy, and in those who are taking medications which increase serum potassium such as spironolactone. Candesartan should not be used in pregnancy, and should be discontinued before planning a pregnancy. Women of child bearing age should ensure appropriate contraception is in place. Candesartan is not recommended during breast feeding. Alternative agents should be considered in those with renal impairment and those patients taking regular NSAIDS, since in such populations close monitoring of kidney function and potassium would be required. If using candesartan in older patients, monitoring of kidney function and potassium should be considered. Candesartan should be withheld if patients become acutely dehydrated (e.g. during a diarrhoea and vomiting illness) – Sick Day Rules Side effects include hypotension, renal impairment and cough Use in prophylaxis of migraine is off-label.

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Propranolol	
Start propranolol 10-20mg twice a day. Increase by 10-20mg twice a day every 1-2 weeks, to a target dose of 80mg twice a day. Some patients benefit from lower doses if they experience side effects at higher doses	A full list of contraindications and cautions can be found in the Summary of Product Characteristics (SPC). Propranolol is contraindicated in a number of conditions including asthma, severe peripheral vascular disease and should not be used in patients taking verapamil. Side effects include bradycardia, hypotension, fatigue, sexual dysfunction and wheezing. Note potential interaction with rizatriptan: rizatriptan dose should be limited to 5mg in patients prescribed propranolol and administration should be separated by at least 2 hours
Topiramate	
Start topiramate at 25mg daily Increase by 25mg every 1-2 weeks, to a target dose of 50mg twice a day. If partially effective and well tolerated further up titration to a maximum of 100mg twice a day could be considered in selected patients	**Specialist Initiation Only** **It is not recommended to start topiramate in women of child bearing potential.** For further information, please see the MHRA advice regarding pregnancy prevention programme guidance Topiramate (Topamax): introduction of new safety measures, including a Pregnancy Prevention Programme and the Faculty of Sexual and Reproductive Health Guidelines for advice on contraception interactions. A full list of contraindications and cautions can be found in the Summary of Product Characteristics (SPC). Topiramate is not recommended for use in patients who have a history of glaucoma or renal stones or who have anorexia nervosa. Caution should also be exercised in patients with a history of depression. There may be interactions with digoxin, metformin, carbonic anhydrase inhibitors, and thiazide derivatives. There is a potential for serious interaction with sodium valproate. Side effects are common and include acute glaucoma, peripheral paraesthesias, fatigue, nausea, diarrhoea or weight loss, taste change, concentration difficulties, word finding difficulties, insomnia, anxiety, and depression

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Additional prophylactic medicines that can be considered in primary care

Calcitonin Gene Related Peptide (CGRP) Small Molecule Antagonists (gepants)

Calcitonin gene-related peptide (CGRP) is associated with vasodilation, inflammation and modulation of the transmission of pain. Levels of CGRP increase significantly during migraine and return to baseline levels with headache relief.

Atogepant and rimegepant are small molecule antagonists to calcitonin gene related peptide (CGRP) antagonists.

Patients must have had prior failure of **three or more** migraine preventative treatments before atogepant or rimegepant can be considered. These medicines can be initiated and prescribed in primary care.

The licensed indications differ for these medicines

- atogepant is licensed for treatment of episodic and chronic migraine (at least 4 migraine days per month)
- rimegepant is licensed for episodic migraine only (more than four migraines per month but less than 15 headache days per month).

Prescribing Considerations

- See table overleaf for detailed prescribing notes for each drug
- Atogepant and rimegepant are new medications and therefore the long term side effects are unknown.
- It is uncertain whether adverse events associated with monoclonal antibodies to CGRP apply to the small molecule 'gepants' but until further data are available, we advise similar cautions.
- Trials of atogepant and rimegepant were not enriched with patients with significant cardiovascular or cerebrovascular disease therefore we suggest caution in these patients. We recommend particular caution in those who have suffered an acute cardiovascular or stroke event within the last 6 months.
- Blood pressure should be measured prior to starting atogepant or rimegepant
    - Atogepant or rimegepant is not recommend in patients with uncontrolled hypertension
    - Blood pressure should be monitored during treatment including measurements at 3 months and 12 months.
- Monoclonal antibodies to CGRP have been associated with de novo Raynaud's phenomenon or worsening Raynaud's phenomenon and therefore caution is advised in those with significant or uncontrolled Raynaud's phenomenon.

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Actions Prior to Prescribing Atogepant or Rimegepant

- Check patient has had prior failure of three preventative migraine treatments
- Assess whether patient has episodic or chronic migraine and select appropriate licensed treatment for indication
- Ensure blood pressure is normal – see further information below
- Screen for Raynaud's phenomenon - see further information below
- Screen for and treat constipation - see further information below
- Advise against use in pregnancy
- Recommend the use of headache diaries, with headache pain scores recorded daily
- Prescribe for three months and arrange a three-month review
- Advise to avoid driving if drowsy

Review of efficacy and tolerance at 3 months

- Screen for side effects including nausea and constipation
- Check BP and if uncontrolled hypertension is identified, discontinue atogepant or rimegepant permanently or until BP is treated.
- If medication is ineffective at 3 months, it should be discontinued.
- If it is effective:
    - continue for a period to complete a total of 6-12 months' therapy followed by a treatment holiday.
    - If headache worsens during the treatment holiday, consider restarting with a further planned treatment holiday after 12 months therapy.
- Treatment efficacy may be defined as a reduction of total monthly headache days by at least 30%, or reduction in monthly migraine days by at least 50%. Quality of life reports may also be considered.
- The optimal duration of therapy is unknown.

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Atogepant Prescribing Notes – please see the SPC for more detail	
Eligible Patient population	Patients with episodic or chronic migraine who have at least four migraine days per month and who have had prior failure of at least three previous migraine preventative treatments. We recommend targeting populations with either high frequency episodic migraine (8-14 headache days per month) or chronic migraine (15 or more headache days per month)
Starting atogepant	• Recommended dose for episodic and chronic migraine = 60mg daily ○ *10mg daily in certain patients – see below Acute treatments • If abortive therapy is required, simple analgesia such as non steroidal anti-inflammatory medications (as per SIGN 155) and prochlorperazine may be used. • If triptans are not contra-indicated, a triptan may be used for abortive therapy. The frequency of use should be less than 10 days per month • In clinical trials combinations of different gepants e.g. atogepant plus abortive rimegepant were not permitted
Cautions/ Contraindications	*Please see the BNF and summary of product characteristics for full information and see above for general considerations.* • We do not recommend Atogepant in pregnancy. • The license advises to avoid use in patients with severe hepatic failure. • In patients with severe renal impairment (creatinine clearance 15-29ml/min) and end stage renal failure (creatinine clearance <15ml/min) the recommended dose is 10mg daily. • Baseline U+Es and LFTs should be considered if clinical concern but routine monitoring is not required.
Interactions	*Please note lists of interacting drugs are not exhaustive, please check recognised sources such as BNF and discuss with pharmacy if further information required particularly for specialist medicines* The dose of atogepant should be reduced to 10mg daily in patients taking • strong inhibitors of CYP3A4 (*e.g. clarithromycin, ketoconazole, itraconazole, voriconazole, telithromycin, indinavir, nelfinavir, ritonavir, saquinavir*) • strong OATP inhibitors (*e.g. rifampicin, atazanavir, ritonavir, tipranavir, ciclosporin, telmisartan*) For short courses of a strong CYP3A4 or OATP inhibitor, if an alternative non-interacting drug is not an option, temporary discontinuation of atogepant is permitted.

	No specific advice is given regarding co-prescription of atogepant with CYP3A4 inducers but be alert to the possibility of reduced efficacy as atogepant levels may be reduced.
Side effects	Decreased appetite, constipation, drowsiness, fatigue, nausea, weight decrease. Patients should be counselled on risk of somnolence and potential effects on driving and performance of skilled tasks.

Rimegepant Prescribing Notes - please see the SPC for more detail	
Eligible Patient Population	Patients who have at least 4 migraine days per month but less than 15 headache days per month who have had prior failure of three previous migraine preventive treatments. We recommend targeting the population with high frequency episodic migraine (8-14 headache days per month)
Starting Rimegepant	• The recommended dose for prophylaxis of episodic migraine is 75mg taken on alternate days. Abortive therapy: • If abortive therapy is required, simple analgesia such as non steroidal anti -inflammatory medications (as per SIGN 155) and prochlorperazine may be used. • If triptans are not contra-indicated, a triptan may be used or abortive therapy. The frequency of use should be less than 10 days per month. • If triptans are contra-indicated, they may however take a Rimegepant tablet for abortive therapy on a day when Rimegepant has not been taken. The maximum dose is 75mg daily and this dose should not be exceeded.
Cautions/ Contraindications	*Please see the BNF and summary of product characteristics for full information and see above for additional considerations.* • We do not recommend Rimegepant in pregnancy. • Rimegepant should not be used in patients with patients with severe hepatic impairment or in patients with end-stage renal disease (CrCl < 15 ml/min).
Interactions	*Please note lists of interacting drugs are not exhaustive, please check recognised sources such as BNF and discuss with pharmacy if further information required, particularly for specialist medicines* Rimegepant is not recommended in combination with

	• Strong inhibitors of CYP3A4 (e.g. *clarithromycin, ketoconazole, itraconazole, voriconazole, telithromycin, indinavir, nelfinavir, ritonavir, saquinavir*) • Strong or moderate inducers of CYP3A4 (*e.g. carbamazepine, phenytoin, rifampicin, phenobarbital, bosentan, efavirenz, St. John's wort*) Another dose of rimegepant should be avoided within 48 hours (e.g. an additional dose could not be taken for abortive therapy) if concomitantly administered with • Moderate inhibitors of CYP3A4 or strong inhibitors of p-glycoprotein (*e.g. diltiazem, erythromycin, fluconazole, ciclosporin, amiodarone, verapamil, quinidine*) If prescription of an interacting drug is short term e.g. clarithromycin, if an alternative non-interacting drug is not an option, rimegepant could be withheld for the duration of the treatment course.
Side effects	Nausea, hypersensitivity reactions.

Who to refer:

Examples of people who may benefit from being referred to the headache clinic

- People with a headache where there is **significant diagnostic uncertainty**
  OR
- People with disabling migraine for whom at least **3 preventative medications** have been tried and have either been ineffective after 12 weeks at target dose, or have not been tolerated.

Prophylactic Medicines Prescribed by Secondary Care Headache Team

Following failure of the previously mentioned treatments, patients who are under the care of the headache team may be considered for other treatments.

For patients prescribed the above treatments, this will be communicated to primary care via letter. Please add to as an 'outside medicine' for interaction checking and awareness.

References/Evidence

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Appendices

1. Governance information for Guidance document

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Responsible Person (if different from lead author)	Kirsty MacFarlane - Lead Pharmacist, Medicines Policy and Guidance

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Consultation Process / Stakeholders:	Dr Sarah Miller – consultant neurologist NHS Lanarkshire Medicines Guidance Team
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CHANGE RECORD			
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