Update to SIGN Guideline 155: Pharmacological management of migraine consultation

COMMENTS RECEIVED FROM EXTERNAL REFEREES AND OTHERS

All reviewers submitted declarations of interests which were viewed prior to the addressing of comments.

Invited reviewers			**Type of response and declared interests**
AT	Arina Tamborska	Neurology Specialist Registrar, Department of Clinical Neurosciences, Royal Infirmary of Edinburgh	*Individual response.* <u>Non-financial personal interests</u> Ongoing research projects on prescribing practices in novel migraine therapeutics in England.
FA	Fayyaz Ahmed	Consultant Neurologist and Hon Professor in Neurology, Hull University Teaching Hospitals NHS Trust	*Individual response.* <u>Personal financial interests</u> 1. Treasurer International Headache Society. 2. Trustee Anglo-Dutch Migraine Association. 3. Trustee British Association for the Study of Headache. 4. Chair of the Association of British Neurologist Headache Specialty Interest Group. 5. Received honorarium for being on the advisory board of Abbvie, TEVA, Lundbeck, Pfizer, Dr Reddy laboratory. <u>Non-personal financial interests</u> 1. Received grant from Pfizer for service improvement. 2. Received grant from Lundbeck to organise the British Association for the Study of Headache biennial meeting on headache disorders.
SD	Sabine Dedner	GP with special interest in Neurology (working in Epilepsy and Headache Clinic), University of Coventry and Warwickshire Neurology Department, Castle Medical Centre, Kenilworth	*Individual response.* <u>Personal financial interests</u> Working as a GPwSI as mentioned above.

			I did 2 talks so far for Abbvie but not on their products only about migraine in general.
Open consultation			**Type of response and declared interests**
AG	Amanda Gotch	Consultant Midwife, NHS Grampian	*Individual response.* Nothing declared.
GD	Gordon Drummond	Person with lived experience, Edinburgh	*Individual response.* Person with lived experience. I have participated in previous SIGN guidelines and written on the inadequacy of medical textbooks. <u>Voluntary organisations</u> Not related, other than a group that campaigns for evidence-based government. <u>Other organisation involvement</u> Senior fellow, RCPEd
LS	Laura Stobo	Senior Pharmacist, Public Health Scotland	*Individual response.* <u>Non-financial personal interests</u> I have contributed to a number of migraine guidelines in NHSGGC where I also work as a pharmacist. I have contributed to the anti-seizure medicines in pregnancy report and dashboard within Public Health Scotland.
MT	Migraine Trust	Pippa Coulter, Information Manager, commenting on behalf of Migraine Trust	*Group response.* <u>Nature and purpose of your group</u> Charity. <u>How might the statements and recommendations in the draft SIGN guideline impact on your organisation's functions/status/productivity?</u>

			Draft recommendations in this SIGN guideline will have no discernible impact on the function or productivity of our organisation.
NHSAA	NHS Ayrshire & Arran	Roisin Kavanagh, Director of Pharmacy, commenting on behalf of NHS Ayrshire & Arran	*Group response.* Nature and purpose of your group NHS Health Board How might the statements and recommendations in the draft SIGN guideline impact on your organisation's functions/status/productivity? Draft recommendations in this SIGN guideline will support prescribers and patients to make evidence-based choices for the management of migraine. They provide clarity on the use of topiramate and sodium valproate in accordance with updated MHRA guidance.
NHSG	NHS Grampian	Lesley Coyle, Associate Director of Pharmacy, commenting on behalf of NHS Grampian	*Group response.* Nature and purpose of your group NHS Health Board How might the statements and recommendations in the draft SIGN guideline impact on your organisation's functions/status/productivity? Implementation feasibility regarding CRGP therapies - concerns due to cost and specialist capacity, and appropriate use if extend use beyond specialists. Difference between SMC and local position – need to utilise other agents better before bring in CGRPs i.e. learning for effective use of triptans.

			Pathways/formulary will require review and update for acute, preventative, menstrual, and pregnancy-related migraine. Costs expected to increase due to oral CGRP therapies and monitoring requirements (Primary Care workload - BP monitoring recommendation).
PL	Pfizer Limited	Rowena Randall, Medical Team Leader Internal Medicine, commenting on behalf of Pfizer Limited	*Group response.* Nature and purpose of your group Pfizer Ltd. are a pharmaceutical manufacturer with a licensed product, which is contained in the SIGN 155 Guidelines. How might the statements and recommendations in the draft SIGN guideline impact on your organisation's functions/status/productivity? We are inputting in to this draft guideline to ensure clinicians are able to make informed decisions which reflect the quality and quantity of evidence, which includes rimegepant, a medicine for which Pfizer Ltd. holds the marketing authorisation in the United Kingdom.
SMC	Scottish Medicines Consortium	Sharon Hems, Principal Pharmaceutical Analyst, commenting on behalf of Scottish Medicines Consortium	*Group response.* Nature and purpose of your group Health technology assessment. How might the statements and recommendations in the draft SIGN guideline impact on your organisation's functions/status/productivity? The remit of the Scottish Medicines Consortium (SMC) is to provide advice to NHS Boards and their Area Drug and Therapeutics Committees across Scotland about the clinical and cost effectiveness of newly licensed medicines, and new indications for established products.

			When SMC accepts a new medicine, NHS boards are expected to make it, or an equivalent SMC-accepted medicine, available. Note that Health boards may make decisions about the continued application of ‘not recommended’ advice for the reference product when generic, branded generic or hybrid medicines (or biosimilar medicines) become available. SMC does not issue advice on unlicensed or off-label use of medicines.

General/Additional comments:			
Section	*Reviewer*	*Comment*	*Development group response*
	AG	This is an excellent source of information and easy to read.	Thank you
	GD	See my first comment: my wider point is that gaps, or holes, in evidence, are not seen if you start by asking "what is the evidence" - because you look at what other people have looked at, and not for what is missing. You should start by asking "what should we know?" rather than "what have other people thought of to report?"	The remit of a SIGN guideline is built upon areas where there is uncertainty and where there are variations in practice in NHSScotland. We start from the perspective of a clinical or care focused key question that makes no assumptions about whether or not evidence exists to answer it. These are evidence-based guidelines, so we use the evidence to answer those gaps. Where there is insufficient evidence to support a recommendation, this is highlighted as an area for further research.
	NHSG	Overall structure is clear and evidence-based. Implementation challenges should be acknowledged – regarding capacity and affordability Menstrual migraine section is valuable Valuable to include reference to local formularies for positioning of treatments, particularly for CGRPs where threshold may differ. For acute treatment lack of head-to-head data for CGRPs versus alternatives Problems with all pain studies – high placebo response Minor formatting issues re numbering to be resolved prior to publications – contents and Section numbering, misnumbering of subsections within 4.17.	Thank you. The group did not consider that there were significant challenges to implementation. The therapies are already in use. We are providing advice at a national level to inform local formularies. Agree. We have removed the statement on Rimegepant from the section on comparison on therapies. The positioning of Rimegepant is in accordance with SMC advice. We have used the best available evidence to inform the guideline and included data on effect sizes. This will be resolved in the desktop publishing version.
	MT	No comments on any sections within the survey. However, Intro - We would suggest reviewing and updating statistics around how migraine ranks in the GBD causes of disability, as this appears to be out of date. We believe this is the latest GBD study looking at	Amended to: Migraine is the most common severe form of primary headache.[8] The Global Burden of Disease study ranks migraine as the fourth most common cause worldwide of years lived with disability in all ages and second in people under the age of 50.[9] Prevalence is highest in women but prevalence of migraine in young men is also increasing.[152]

		migraine as a disability, which ranks migraine as 4th for YLD, 2nd for under 50s: https://pmc.ncbi.nlm.nih.gov/articles/PMC11145804/ Similarly we'd suggest reviewing and updating estimates on cost of migraine, which we put as £8.8 billion (Society's Headache. The socioeconomic impact of migraine. The Work Foundation 2018).	It is estimated that migraine costs the UK public economy around £12.2 billion a year. (ref Martins R, Large S, Russell R, Surmay G, Connolly MP. The Hidden Economic Consequences of Migraine to the UK Government: Burden-of-Disease Analysis Using a Fiscal Framework. J Health Econ Outcomes Res. 2023 Oct 3;10(2):72-81.)
	AT	Introduction (1.1): It is worth referencing the most recent edition of neurological GBD from Jamie Steiner: 2024 instead of 2019. (migraine is the leading cause of neurological disability in children and teenagers aged 5-19; Migraine prevalence still remains approx. 1 in 7. at 14 or so %; this varies and is stratified by the age group)	We have updated with studies with information on prevalence in adults.
	AT	3.1 Phrasing suggestion: "complete treatment response IS DEFINED as (...). A table of NNT to achieve (...). In addition, some studies define treatment response reduction in pain or headache (e.g. from moderate to mild).	Amended to: Treatment response is defined as pain free at two hours and sustained pain free at 24 hours. A table of numbers needed to treat (NNTs) to achieve pain free at two hours for some acute therapies can be found in section 3.10. In addition, pain relief or headache relief (from severe or moderate to mild or no pain) is reported in some studies.
	AT	Recommendation re MOH (section 3.1): "When starting acute treatment, healthcare professionals should warn patients about the risk of developing medication-overuse headache." It is worth highlighting that this is determined by the number of days of using acute therapies rather than the doses of medicines used on those days.	MOH is covered in section 5, which was not part of this update. We have added (see Section 5) to the good practice point.
	AT	Section 3.6: Triptans (new recommendations): Re triptans: We say: "Triptans are contraindicated in patients with uncontrolled hypertension and in symptomatic	The following good practice point has been added. Triptans should not be used in patients at high risk of ischaemic cardiovascular disease, including uncontrolled hypertension.

		cardiovascular and cerebrovascular disease" - this should also enter the recommendations/ summary points as many people will only read this.	
	MT	Section 4 - A slight variation between this and NICE guideline, CG150, has been noted in terms of preventative treatment options. NICE guidelines put propranolol on an equal weighting with amitriptyline and topiramate, and recognised the risk of using propranolol for self-harm in people with depression and migraine. While the risks of topiramate and restrictions on use are noted, we wondered whether the risks associated with propranolol highlighted by NICE have been considered? We wondered if further clarity is needed in the guidance around which treatments should be offered first-line - propranolol is currently the only preventative where the guidance specifically states that it is recommended first-line. If other treatments could also be considered first-line, should this be stated? Our hope is that clarification in guidance will give doctors the confidence in prescribing a broad range of treatments, allowing people with migraine access to treatment that best meets their individual needs. P33 - An error in one of the experts listed; Professor Alison Sinclair should be Alex Sinclair.	We did not review evidence on propranolol for this update. We have included a link to the national headache pathway that provides advice on first and second-line therapies. We agree, we hope that prescribers will refer to the guideline and the national headache pathway. Expert's name has been taken out as they did not submit a response.
	AT	Section 4.2: Candesartan: "The evidence base for candesartan is small." Has this recent trial been included? https://www.thelancet.com/journals/laneur/article/PIIS1474-4422(25)00269-8/abstract 2025 Oct, Lancet Neurology - high quality new evidence to expand candesartan section.	We have looked at this study. As the findings do not change the original recommendation, we did not extend the remit of this update to include a review of candesartan. We have deleted the sentence that states the evidence base is small.
	SMC	Section 4.2: suggest note as per BNF that: Candesartan is used for migraine prophylaxis, but is not licensed for this indication.	Added.

	AT	Section 4.7: CGRP antibodies: The table of the studies is no longer up to date. We should either update it with most recent large trials or remove it into the appendix so that it is not understood as the most recent review of evidence. Examples: The evidence base for some CGRP infusions has expanded since the table has last been published Frenuzumab for patients with depression: https://jamanetwork.com/journals/jamaneurology/fullarticle/2833452 Erunumab for MOH: https://jamanetwork.com/journals/jamaneurology/fullarticle/2823594 https://pubmed.ncbi.nlm.nih.gov/40542538/	This is outside the remit of this update. Both examples given would not be included in the table as they are outside the inclusion criteria for the research question for this section. We will note your points to inform the next update to the guideline.
	SD	I miss that you mention in your recommendation alternatives (you have mentioned it partially in the evidence bit) e.g. use Propranolol OR Metoprolol or Amitriptyline or Nortriptylinel) I miss that propranolol should NOT be given to suicidal patients the BNF refers to this website https://www.hssib.org.uk/patient-safety-investigations/potential-under-recognised-risk-of-harm-from-the-use-of-propranolol/ I love to use Lamotrigine and think this is particular effective. I think the guidelines (like ALL guidelines unfortunately) misses the importance to review also comorbidities and treat this as they have an impact on the migraine. if looking at the comorbidities you will suddenly see that actually SSRI/SNRI may be very useful for treatment in migraine if they tackle also anxiety/depression/ocd/insomnia to mention a few (further comorbidities may be obesity, overactive	The risk in propranolol is in patients who may be prescribed propranolol for management of anxiety, rather than those with migraine. The risk is therefore lower in the migraine population, and we would encourage prescribers to check for all potential risks. Thank you for your comments. These prophylactics were not part of the remit for this update. We will note your points to inform future updates of the guideline.

		bladder, cognitive impairment etc. or recommendation of migraine tx in pregnancy. I also miss the specific treatment aspects in migraine variants e.g. vestibular migraine, or hemiplegic migraine (you have partially overed PMP).	
	MT	Section 4.7 - a new line has been added that refers to 'oral' CGRP mAbs - believe oral has been added in error.	Removed.
	SMC	Section 4.7: SIGN guidance refers to ‘four headaches’ where SPC and SMC advice refer to ‘4 migraine days’. Suggest amend SIGN guidance by stating: Fremanezumab, galcanezumab and eptinezumab are accepted for restricted use by SMC for use in NHSScotland for prophylaxis of migraine in adults who have at least 4 migraine days per month. Use is restricted to the treatment of patients with chronic and episodic migraine who have had prior failure on three or more migraine preventive treatments.	Amended.
	SMC	Section 8.4: Advice for NHSScotland from the Scottish Medicines Consortium: several of the links to SMC advice do not work.	All links will be checked in the final version prior to publication.

Section 3.3: Non-steroidal anti-inflammatory drugs			
	AT	Re ibuprofen We say: "Ibuprofen may be considered under specialist recommendation up to week 20." But then we recommend: "During pregnancy ibuprofen should be used with caution and only up to 20 weeks, if paracetamol or sumatriptan, or a combination of both, are ineffective in reducing pain."	We have removed ‘under specialist recommendation’ from the evidence statement. Primary care prescribers can make this decision.

		--> should our recommendation re pregnancy include "under specialist recommendation" or are we happy for primary care prescribers to make this decision? Current recommendation is more liberal than the evidence we quote.	
	FA	I support cautious use of Ibuprofen in pregnancy and under specialist recommendation up to 20 weeks. The section should also include cautious use in patients with chronic renal disease particularly in those with a GFR less than 45.	Thank you. We have removed the need for specialist recommendation as in practice this is unlikely to happen and can be managed by primary care prescribers. This is a specific assessment that would be considered by the GP using appropriate prescribing guidance.
	GD	I have only one comment to make. I personally suffered with migraine which was debilitating until I tried diclofenac, given rectally. There is no mention at all in the guideline, presumably because no studies have been done. of this route of administration. This deficiency of evidence should be acknowledged. Gastric stasis makes oral administration, in many patients, hit or miss and evidence for other routes, far more reliable, has not been gained. I now take one diclofenac suppository and can abort in one hour what used to be at least a day of misery. A lifechanging discovery.	Thank you for reflecting your personal experience. This is outside the remit of this update. When we reviewed NSAIDs when the guideline was originally published we did not identify evidence specific to this formulation. The guideline includes a link to the Scottish Headache Pathway which includes this. It can be considered on an individual patient basis rather than a recommendation across the population.
	AG	Up to date information regarding use of ibuprofen in early pregnancy.	Thank you. No action required.
	LS	No comments.	No action required.
	NHSAA	Do the recommendations reflect the evidence? YES Are there any relevant studies that we have missed? NO Are the recommendations appropriate for use in NHSScotland? YES Is the language and presentation of the evidence and recommendations appropriate? YES	Thank you. No action required.
	NHSG	Recommendations reflect strong evidence (Cochrane reviews).	Thank you. No action required.

		Aligns with current practice. Clear language and presentation.	
	PL	No comments.	No action required.
	SD	Do the recommendations reflect the evidence? YES Are there any relevant studies that we have missed? Please supply references to support your comments. NO Are the recommendations appropriate for use in NHSScotland? YES Is the language and presentation of the evidence and recommendations appropriate? YES	Thank you. No action required.
	SMC	No comments.	No action required.
Section 3.7: Oral calcitonin gene-related peptide receptor antagonists			
	AT	Re CGRP blockers: Phrasing suggestions "It was also superior for remaining pain free from 2 to 24 hours (OR 2.43, 95% CI 1.59 to 3.71) and SUSTAINING pain relief for 2 to 24 hours (OR 2.24, 95% CI 1.89 to2.65).1" "reported an ABSOLUTE risk difference" - this precisely indicates that difference rather than ratio was calculated Should we make a comment on whether we consider a combination of anti-CGRP with NSAIDs/ paracetamol/ triptans appropriate or withhold from a comment based on limited evidence?	Thank you. Amended to sustaining. We don't think this is necessary. Cited direct from the SMC summary. There is a lack of evidence for this.
	FA	As there is no alternative following failure or intolerance to triptan, the use of Rimegepant should be recommended rather than considered.	We have reviewed and added the new RCTs to the evidence statement. They were appraised as 1+

			The group agreed that the recommendation should stay as ‘should be considered’ due to the evidence level.
	NHSG	Evidence well presented; includes RCTs and SMC advice. Noted rimegepant studies versus placebo – no published head to head comparative trials. Appropriate for NHS Scotland with access caveats. Cardiovascular caution well noted – but need to consider how translated into practice. BP monitoring requirements and capacity/workload will require to be considered.	We have removed the good practice point for blood pressure monitoring. Hypertension has been added to the good practice point advising to give careful consideration to risks and benefits before prescribing.
	SMC	Suggest amend 'Rimegepant should be considered as second-line treatment for patients with acute migraine who have had an inadequate response to two or more triptans' to read 'Rimegepant should be considered as a third-line treatment for patients with acute migraine who have had an inadequate response to two or more triptans.'	Amended to: Rimegepant should be considered for patients with acute migraine who have had an inadequate response or poor tolerability to two or more triptans, and paracetamol/NSAIDS have been considered to be ineffective or unsuitable.
	PL	Since the publication of the meta-analysis conducted by Puledda et al in 2023, reference 155, additional randomised-controlled trials for rimegepant in the acute treatment of migraine have been published. These trials include: • Study 301 [1] • Study 310 [2] • Study 313 [3] • Study 406 [4] We believe that the quality and quantity of randomised clinical trials in acute treatment of migraine for rimegepant is more befitting of a strong recommendation as per the definitions provided on Page 2 of the Draft Guidelines.	We have reviewed and added the new RCTs to the evidence statement. The group agreed that the recommendation should stay as ‘should be considered’ because: • the correct alternative may be a triptan with an alternative mode of delivery, or combination treatment. Rimegepant should be an option in this situation. • there were some issues with the studies highlighted at critical appraisal, so they are graded as 1+ rather than a robust 1++.

		We therefore believe rimegepant should be recommended as second-line treatment for patients with acute migraine who have had: • inadequate response to two or more triptans • poor tolerability or contraindications to triptans With regards to the good-practice point 'Careful consideration should be given to the potential risks and benefits for patients at high risk of ischaemic cardiovascular disease before prescribing oral CGRP receptor agonists', Pfizer acknowledges that those with an ischaemic cardiovascular event within the past 6 months were excluded from our pivotal clinical trial for acute treatment of migraine [5]. However, there are no cardiovascular contraindications, precautions for use, or side-effects listed in the summary of product characteristics for rimegepant [6]. True et al [7] conducted a post-hoc analysis of adverse events in individuals treated with rimegepant which demonstrated the medicine to be well tolerated in individuals with a Framingham Risk Score ≥ 10% and those with ≥ 2 cardiovascular risk factors. The available evidence and summary of product characteristics for rimegepant are thus in contrast to the expert opinion regarding ischaemic cardiovascular disease. It is notable that a warning on patients' cardiovascular risk, including ischaemic heart disease, is not present in the summary for the triptans section of the guideline. Triptans have cardiovascular contraindications, including ischaemic heart disease [8]. The cardiovascular contraindications of triptans are well documented in the main body of the triptan section, but are not included in the summary at the bottom of the section like with oral CGRP antagonists in Section 3.7.	All the RCTs have excluded people with active CV disease, including the phase 4 study. Therefore there is no evidence it is safe in people with active CV disease. It is the opinion of the guideline development group that in practice clinicians would not risk prescribing to someone with CV disease without evidence that it is safe to do so. We have moved poor tolerability to the recommendation above, as 'should be considered' but have retained the good practice point advising careful consideration of risks and benefits for pts with CV disease. We have added a good practice point to the triptans section to reflect this.

		We therefore have reservations that the ischaemic heart disease good practice point might encourage busy healthcare professionals who skim the summaries of the guideline to prescribe triptans off-label in those at high risk of ischaemic heart disease. Although the triptan section was out of scope of this update, we believe the ischaemic heart disease good-practice point in section 3.7, if retained, warrants an update to the summary of the triptan section to clarify that triptans are contraindicated in ischaemic heart disease. The next practice-point 'Treatment with rimegepant in patients with uncontrolled hypertension is cautioned...' is factually inaccurate given no such formal contraindications or cautions exist in the rimegepant summary of product characteristics [6]. Triptans are contraindicated in uncontrolled hypertension [8], but no such warning appears in the summary of the triptan section in the draft guidelines. We therefore believe, if retained, the language in this good practice point should be softened and a good practice point on uncontrolled hypertension with stronger wording should be added to the triptans section summary for balance. In summary, we believe the following amends are needed: • Rimegepant should be recommended for second-line treatment for patients with acute migraine who have had an inadequate response to two or more triptans. • Rimegepant should be recommended for patients with acute migraine who have poor tolerability or contraindications to triptans. • Good practice point on ischemic heart disease should either be removed or the language softened, and a stronger warning on ischaemic heart disease added to the summary of the triptan section for	This good practice point has been removed and uncontrolled hypertension has been added to the other good practice point: Careful consideration should be given to the potential risks and benefits for patients at high risk of ischaemic cardiovascular disease, including uncontrolled hypertension, before prescribing oral CGRP receptor antagonists.

		balance given triptans are contraindicated in this cohort. Section 3.7 we had one additional recommendation: • Good practice point on uncontrolled hypertension should either be removed or the language softened given rimegepant is not cautioned in this cohort as per the summary of product characteristics, and a stronger warning added to the summary of the triptan section for balance given triptans are contraindicated in uncontrolled hypertension. Section 3.7 References 1. Lipton RB et al. Efficacy and safety of rimegepant 75 mg oral tablet, a CGRP receptor antagonist, for the acute Treatment of migraine: a randomized, double-blind, placebo-controlled trial. Journal of Pain Research. 2024: 17. https://doi.org/10.2147/JPR.S453806 2. Yu S et al. Safety and efficacy of rimegepant orally disintegrating tablet for the acute treatment of migraine in China and South Korea: a phase 3, double-blind, randomised, placebo-controlled trial. Lancet Neurology. 2023; 22(6): 476-484. https://doi.org/10.1016/S1474-4422(23)00126-6 3. Ikeda K et al. Efficacy and safety of rimegepant for the acute treatment of migraine in Japan: a dose-ranging, double-blind, randomized controlled trial. Headache. 2025; 00: 1-10. https://doi.org/10.1111/head.14994 4. Ashina M et al. A phase 4, randomized, double-blind, placebo-controlled, efficacy and tolerability trial of rimegepant for the acute treatment of migraine in adults unsuitable for triptan use. American Headache Society 67th Annual Scientific Meeting.19-22 June 2025; Minneapolis, US; oral presentation IOR-09. 5. Biohaven Pharmaceutical Holding Company. BHV-3000-303 Study Protocol, v4.0, Jan 2018. Available	

		from: https://cdn.clinicaltrials.gov/large-docs/57/NCT03461757/Prot_000.pdf 6. Vydura 75mg Oral Lyophilisate Summary of Product Characteristics. Pfizer Ltd. Last Updated May 2025. https://www.medicines.org.uk/emc/product/13928/smpc 7. True D et al. Safety of rimegepant in adults with migraine and cardiovascular risk factors: analysis of a multicenter, long-term, open-label study. Pain and Therapy. 2024; 13(5): 1203-18. https://doi.org/10.1007/s40\122-024-00626-1 8. Imigran 100mg Tablets Summary of Product Characteristics. GSK. Last updated October 2025. Available from: https://www.medicines.org.uk/emc/product/3355/smpc	
	SD	Do the recommendations reflect the evidence? YES Are there any relevant studies that we have missed? Please supply references to support your comments. NO Are the recommendations appropriate for use in NHSScotland? YES Is the language and presentation of the evidence and recommendations appropriate? YES	Thank you. No action required.
	LS	No comments.	No action required.
	AG	Nothing to add	No action required
	NHSAA	Do the recommendations reflect the evidence? YES Are there any relevant studies that we have missed? NO Are the recommendations appropriate for use in NHSScotland? YES Is the language and presentation of the evidence and recommendations appropriate? YES	Thank you. No action required.

Section 3.8: Combined therapies			
	FA	The NNT for combination is significantly better than individual treatments with Naproxen and Sumatriptan. Hence a combination treatment should be recommended rather than considered if the response to single agent is inadequate.	The recommendation has been strengthened from 'can be considered' to 'should be considered'.
	NHSG	Strong evidence supports triptan + NSAID combination. Appropriate and already practiced in NHS Grampian. Clear and practical presentation.	Thank you.
	LS	There is a minor typo in practice point 1 - triptan rather than triptans and I wonder if it should read non-steroidal agent rather than therapy for consistency with rest of section.	Amended, thank you.
	AG	Nothing to add	No action required.
	NHSAA	Do the recommendations reflect the evidence? YES Are there any relevant studies that we have missed? NO Are the recommendations appropriate for use in NHSScotland? YES Is the language and presentation of the evidence and recommendations appropriate? YES	Thank you. No action required.
	PL	No comments.	No action required.
	SD	Do the recommendations reflect the evidence? yes Are there any relevant studies that we have missed? Please supply references to support your comments. no Are the recommendations appropriate for use in NHSScotland? yes Is the language and presentation of the evidence and recommendations appropriate? yes	Thank you. No action required.

	SMC	The dose of naproxen in Suvexx is incorrect. Suvexx contains naproxen 457mg (not 475mg)	Amended to 457 mg.
Section 3.10: Comparison of therapies			
	AT	Suggestion for acute therapies: A table of summarising a number of triptan & other acute treatment options, with route of administration, doses, time to response, pregnancy safety and other considerations would extremely useful as a quick point of reference for any busy primary care physician. - This would be an excellent extension to Table 1 in 3.10: one stop for all the relevant information, not just NNTs.	Unfortunately we do not have the data to do this. It would be more appropriate for the National Headache Pathway.
	FA	The table should include NNT for Rimegepant as well.	This data was not available in the studies reviewed.
	LS	I note rimegepant is not included in table 1 which I assume is because NNT is not available for rimegepant, should this be stated in the paragraph at the start of this section as it does for some triptans which do not have NNT available?	This data was not available in the studies reviewed.
	NHSG	Useful NNT table and network meta-analysis. Appropriate for NHS Scotland. Treatment algorithm was useful, assume will be updated and remain available.	Thank you Rather than duplicating work, we are including a link to the National Headache Pathway, which incorporates the advice in the SIGN guideline.
	PL	We note the following sentence which reflects on the Karlsson et al [1] systematic review and meta-analysis 'Rimegepant was comparatively less effective than the triptans (18%) and was similar to ibuprofen (20%)'. The positioning of rimegepant with NHS Scotland is when triptans are contraindicated, poorly tolerated, and when simple analgesia and two or more triptan have provided insufficient response. This means comparison of rimegepant with triptans or simple analgesics like ibuprofen is therefore not relevant to clinical practice in NHS Scotland. We therefore believe that this sentence should be removed.	Agree. Information on rimegepant removed.

		The additional context below is provided for more balance should this sentence be retained. The quality of a systematic review or meta-analysis is only as good as the studies it includes [2]. If the primary studies are flawed or biased, the synthesis will reflect those limitations. In Karlsson et al [1] rimegepant versus placebo was the only comparison within the meta-analysis that was rated as high degree of certainty as per the CINeMA framework for all primary outcomes. Every comparison involving ibuprofen was rated as low or very low certainty for pain freedom at 2 hours, all comparisons also had concerns of within-study bias [1]. It is therefore simplistic to say that rimegepant is similarly effective to ibuprofen for acute treatment of migraine, given the uncertainty and risk of bias in the ibuprofen data. As per Professor Lipton and Professor Goadsby [3]: “This NMA comparing triptans, gepants, and ditans summarises studies sometimes conducted decades apart. The assumption of NMA is that adjustment for differences in the placebo arm corrects for differences among studies. Large differences in placebo rates among studies, supported by data in the appendix of the current report, suggest that this fundamental assumption may not be valid. In recent studies, triptans underperform relative to earlier pivotal efficacy studies. For example, in the recent studies of rizatriptan 2-hour pain free rates were 17.4% (placebo 6.7%), far lower than the 40% rate (placebo 9%) reported in older studies [4,5]. In a phase II adaptive study [6], pain free rates at 2-hours were 31% for rimegepant 75 mg (n = 86) and 35% for sumatriptan 100 mg (n = 100); the difference was 4% (95% confidence interval: -10% to + 17%). Though limited by sample size and the adaptive design, these data show no differences between rimegepant and sumatriptan.”	

		In summary, given the positioning of rimegepant where triptans and simple analgesics are not suitable, we believe the sentence 'Rimegepant was comparatively less effective than the triptans (18%) and was similar to ibuprofen (20%)' should be removed as this comparison is not relevant to clinical practice in NHS Scotland. 3.10 References 1. Karlsson WK et al. Comparative effects of drug interventions for the acute management of migraine episodes in adults: systematic review and network meta-analysis. BMJ. 2024; 386: e080107. https://doi.org/10.1136/bmj-2024-080107 2. Lockett A. Systematic review and meta-analysis in clinical trials. Medicine. 2025; 53(6): 364-7. https://doi.org/10.1016/j.mpmed.2025.04.004 3. Lipton RB, Goadsby PJ. Rapid response to: comparative effects of drug interventions for the acute management of migraine episodes in adults: systematic review and network meta-analysis. BMJ. 2024; 386: e080107. Submitted: 10th January 2025. Available from: https://www.bmj.com/content/386/bmj-2024-080107/rr-4 4. Jones A et al. Efficacy and Safety of AXS-07 (MoSEIC™ Meloxicam/Rizatriptan) in the Acute Treatment of Migraine: Results from the MOMENTUM Phase 3 Trial. 2020 American Academy of Neurology. September 23, 2020. Accessed November 09, 2025. Available from: https://www.axsome.com/wp-content/uploads/2024/11/Axsome_AXS-07-Presentation_AAN-Emerging-Science-2020.pdf 5. Tfelt-Hansen P et al. Oral rizatriptan versus oral sumatriptan: a direct comparative study in the acute treatment of migraine. Headache. 1998;38:748-55. https://doi.org/10.1046/j.1526-4610.1998.3810748.x 6. Marcus R et al. BMS-927711 for the Acute Treatment of Migraine: A Double-Blind, Randomized, Placebo Controlled, Dose-ranging Trial. Cephalalgia. 2014;34:114-25.	

	SD	I would very much appreciate if in the Triptan part (so also 3.6) the effectivity of the orodispersible triptans are mentioned. I think this is quite essential particular for GPs. (I work in England)	This is outside the remit of this guideline update. It is included in the original text that they are not better than other formulations.
	SD	Do the recommendations reflect the evidence? YES Are there any relevant studies that we have missed? Please supply references to support your comments. NO Are the recommendations appropriate for use in NHSScotland? yes Is the language and presentation of the evidence and recommendations appropriate? YES	Thank you. No action required.
	NHSAA	Do the recommendations reflect the evidence? YES Are there any relevant studies that we have missed? NO Are the recommendations appropriate for use in NHSScotland? YES Is the language and presentation of the evidence and recommendations appropriate? YES	Thank you. No action required.
	AG	Nothing to add	No action required.
	SMC	No comments.	No action required.
Section 4.5: Oral calcitonin gene-related peptide receptor antagonists			
	NHSG	Comprehensive evidence base; aligns with SMC guidance. Noted rimegepant studies versus placebo – no published head to head comparative trials. Appropriate for specialist use in NHS Scotland. Could benefit from summary table of indications	Thank you. This is outwith remit of this guideline update. Prescribers are encouraged to check indications in the BNF. SMC advice is included signposted in each section and in section 8.4.
	PL	As per page 2 of the draft guidelines, the word “recommended” conveys a stronger degree of certainty that the medicine in question will do more harm than good for the majority of patients than the term “consider”.	We have added the new evidence and agree that there is similar evidence for both therapies for episodic migraine. The recommendation for rimegepant has been changed for ‘consider’ to ‘recommended’.

		The draft guideline “recommends” atogepant for the prevention of migraine and “considers” rimegepant for prevention of episodic migraine, creating an implication that the quality of evidence for rimegepant in prevention of episodic migraine is inferior to that for atogepant. As referenced in the main body of the text, both gepants have grade 1++ evidence. Rimegepant is also the only gepant which has a direct head-to-head randomised controlled trial with a CGRP targeted monoclonal antibody [1]. Direct head-to-head randomised controlled trials are the gold standard in evidence-based medicine. We therefore believe, in balance of the available evidence, parity on the strength of recommendations for rimegepant and atogepant would be more appropriate. Since the publication of the systematic reviews referenced in the draft guidelines, references 172 and 173, the following additional randomised controlled trials for rimegepant 75mg every other day in prevention of episodic migraine have been published: • Study 309 [2] • Study 407 [3] We therefore believe the following change is more representative of the evidence: • Rimegepant should be recommended for the prophylactic treatment of patients with episodic migraine (4 to 14 days per month), where medication overuse headache has been addressed and patients have been appropriately treated with three or more oral migraine prophylactic treatments. Like in Section 3.7, we note that there are no contraindications, precautions for use, or cardiovascular side-effects relating to ischemic heart disease or uncontrolled hypertension in the summary of product characteristics for rimegepant [4]. Additionally, there are no blood pressure monitoring	We have removed the good practice point on blood pressure monitoring and added uncontrolled hypertension to the good practice point on consideration of benefits and risks in cardiovascular disease.

		requirements listed in the rimegepant summary of product characteristics [4]. Removal of the sentence 'Treatment with these agents in patients with uncontrolled hypertension is cautioned' would retain the expert opinion, but remove any unintended sentiment of a formal precaution for use. In summary, we believe the following amends are needed: • Rimegepant should be recommended for the prophylactic treatment of patients with episodic migraine (4 to 14 days per month), where medication overuse headache has been addressed and patients have been appropriately treated with three or more oral migraine prophylactic treatments. • Removal of the word 'cautioned' from the uncontrolled hypertension good practice given there are no formal precautions for use in the rimegepant summary of product characteristics. References 1. Schwedt T et al. Comparing the efficacy and safety of galcanezumab versus rimegepant for prevention of episodic migraine: results from a randomized, controlled clinical Trial. Neurol Ther. 2024;13(1):85-105. https://doi.org/10.1007/s40120-023-00562-w 2. Kitamura S et al. Efficacy and safety of rimegepant for the preventive treatment of migraine in Japan: a double-blind, randomized controlled trial. Headache. 2025;65(8):1403-1412. https://doi.org/10.1111/head.14995 3. Pozo-Rosich P et al. A phase 4, randomised, double-blind, placebo-controlled study to evaluate the efficacy and tolerability of rimegepant for the prevention of migraine in adults with a history of inadequate response to oral preventive medications. Oral presentation at the 22nd Congress of the International Headache Society; 10-13 September 2025; São Paulo, Brazil.	

		4. Vydura 75mg Oral Lyophilisate Summary of Product Characteristics. Pfizer Ltd. Last Updated May 2025. https://www.medicines.org.uk/emc/product/13928/smpc	
	SD	I think there is pending evidence that Atogepant may be exceptionally helpful for Medication overuse headache, I believe the same applies for Galcanezumab by the way.	Thank you for the information. Any new publications will be considered in the next update.
	SMC	Suggest amend reference to SMC advice for atogepant to read: Atogepant is accepted for restricted use by the SMC for use in NHSScotland for the prevention of migraine in adults who have at least 4 migraine days per month. Use is restricted to patients with chronic and episodic migraine who have had prior failure on three or more migraine preventive treatments. Suggest amend reference to SMC advice for rimegepant to read: Rimegepant is accepted for restricted use by the SMC for use in NHSScotland for the preventive treatment of episodic migraine in adults who have at least four migraine attacks per month. Use is restricted to patients with episodic migraine who have at least 4 migraine attacks per month, but fewer than 15 headache days per month and who have had prior failure on three or more migraine preventive treatments.	Wording amended. Wording amended.
	AG	Up to date information regarding avoidance in pregnancy and washout period.	Thank you. No action required.
	FA	No comments. I feel the use of term consideration for Rimegepant and recommendation for Atogepant is appropriate.	Thank you. No action required.
	LS	Typo: galcenezumab but correct spelling is galcanezumab Section 4.7 - states eptinezumab is not available in NHS Scotland but it was approved for restricted use by SMC in February 2023. I think this might be an old version as the current version of this guideline on the	Amended, thank you. This is in the published version and will not change with this update. The draft version has been updated to reflect what is already published.

		SIGN website has the updated information on eptinezumab.	
	SD	Do the recommendations reflect the evidence? yes Are there any relevant studies that we have missed? Please supply references to support your comments. no Are the recommendations appropriate for use in NHSScotland? yes Is the language and presentation of the evidence and recommendations appropriate? yes	Thank you. No action required.
	NHSAA	Do the recommendations reflect the evidence? YES Are there any relevant studies that we have missed? NO Are the recommendations appropriate for use in NHSScotland? YES Is the language and presentation of the evidence and recommendations appropriate? YES	Thank you. No action required.
Section 4.8: Topiramate			
	AG	Up to date information regarding avoidance in pregnancy, I could not find evidence of a suggested washout period before attempting a pregnancy.	We have added the following good practice point: A washout period of at least 4 weeks after the last dose of topiramate is advised before trying for a pregnancy.
	AT	Topiramate: "It should not be considered in women of childbearing potential unless the conditions of a pregnancy prevention programme are fulfilled" --> change to it should not be PRESCRIBED in women (....) - certainly it can be considered and risk/benefits be discussed with patients	Amended.
	FA	Support the recommendations. How about in male patients below the age of 55 ?	There is no MHRA safety advice for use of topiramate in men.
	LS	There are a few slight differences in the text with the MHRA information that may warrant review of wording:	

		The MHRA drug safety update wording regarding developmental disorders is: 'topiramate may be associated with an approximately 2 to 3 times increased risk of intellectual disability, autistic spectrum disorders and attention deficit hyperactivity disorder compared with children born to mothers with epilepsy not taking antiseizure medication.' The current text does not include the word 'may', however, I do note that the risk awareness form does not include the word 'may' therefore it is consistent with that. The text states that cardiac malformations are the most common type, however, I cannot find reference specifically to cardiac malformations in the MHRA documentation. The healthcare professional guide states 'The most common types of malformation included: cleft lip and cleft palate, hypospadias and anomalies involving various body systems.' In Recommendation 2 bullet point 5 I wonder if it should specify highly effective contraception for consistency with the rest of the text. For bullet point 6, the MHRA advice states 'if you think you are pregnant and are taking topiramate for migraine prevention, stop taking topiramate straight away and contact your GP' I wonder if this needs to be specified as it is different than for those planning a pregnancy (and for those prescribed topiramate for epilepsy).	Amended to: The risk of intellectual disability, autistic spectrum disorder and attention deficit hyperactivity disorder (ADHD) may be around 2–3 times that of the general population. The sentence on cardiac malformations has been removed. We have added' in line with the MHRA Topiramate Pregnancy Prevention Programme. Revised bullet points: • the need to seek urgent advice on migraine prophylaxis and stopping topiramate if planning a pregnancy • the need to stop taking topiramate (for migraine prevention) straight away if they do become pregnant, and contact their GP for advice.
	NHSAA	Do the recommendations reflect the evidence? YES Are there any relevant studies that we have missed? NO Are the recommendations appropriate for use in NHSScotland? YES	Thank you. No action required.

		Is the language and presentation of the evidence and recommendations appropriate? YES	
	NHSG	Strong evidence and MHRA safety alerts included. Appropriate for NHS Scotland with restrictions. Clear contraception guidance and presentation.	Thank you. No action required.
	PL	No comments.	No action required.
	SD	Do the recommendations reflect the evidence? YES Are there any relevant studies that we have missed? Please supply references to support your comments. NO Are the recommendations appropriate for use in NHSScotland? YES Is the language and presentation of the evidence and recommendations appropriate? YES	Thank you. No action required.
	SMC	No comments.	No action required.
Section 4.10: Sodium valproate			
	LS	The text does not mention that there is a possible association between valproate use in men and neurodevelopmental disorders in their children which my understanding forms the basis of the new sentence regarding the recommendation for males to use contraception (Drug safety update September 2024) and therefore may be worth adding for context. The update in February 2025 to the requirements for males currently receiving valproate which now differs from females currently receiving valproate and is not reflected in the current text. (drug safety update February 2025)	The section has been revised to be clearer about the risks in males.
	AG	Nothing to add.	No action required.
	FA	No comments.	No action required.
	NHSAA	Do the recommendations reflect the evidence? YES	Thank you. No action required.

		Are there any relevant studies that we have missed? NO Are the recommendations appropriate for use in NHSScotland? YES Is the language and presentation of the evidence and recommendations appropriate? YES	
	NHSG	Limited efficacy and strong safety concerns well addressed. Appropriate restrictions for NHS Scotland. Clear safety warnings and guidance	Thank you. No action required.
	PL	No comments.	No action required.
	SD	Do the recommendations reflect the evidence? YES Are there any relevant studies that we have missed? Please supply references to support your comments. NO Are the recommendations appropriate for use in NHSScotland? YES Is the language and presentation of the evidence and recommendations appropriate? YES	Thank you. No action required.
	SMC	No comments.	No action required.