

**Update to SIGN 155: Pharmacological management of migraine: consultation report**

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
<b>AT</b>	Dr Alok Tyagi	Consultant Neurologist, NHS Greater Glasgow and Clyde	<p><i>Individual response.</i></p> <p>Personal financial interests – topic specific:                      TEVA – financial                      Lilly – financial                      Lundbeck – financial                      Novartis – financial</p> <p>Personal non-financial interests – topic specific:                      TEVA – advisory board                      Lilly – advisory board                      Lundbeck – advisory board                      Novartis – advisory board</p> <p>Non-personal non-financial interests – topic specific:                      TEVA – clinical trials                      Lilly – clinical trials                      Lundbeck – clinical trials                      Novartis - clinical trials</p>
<b>AML</b>	Dr Anne-Marie Logan	Consultant Physiotherapist in Headache, Lead Headache Interventional Service and Headache Hub, St George’s University Hospitals NHS Foundation Trust	<p><i>Individual response.</i></p> <p>Personal financial interests – not topic specific:                      TEVA - Fees for headache nurse lecture - 2022                      Lilly - Fees for headache nurse lecture – 2022                      Pfizer - Steering committee – ongoing                      Lundbeck - Education steering committee for headache</p>

			nurse meeting – 2022  Non-personal financial interests - not topic specific: TEVA - Part time headache nurse to support all aspects of St George's headache service for 6 months – ongoing.
<b>CH</b>	Ms Christine Hepburn	Principal Pharmaceutical Analyst, Scottish Medicines Consortium	<i>Individual response.</i>
<b>DW</b>	Dr David Watson	General Practitioner, Hamilton Medical Group, Aberdeen	<i>Individual response.</i>
<b>RD</b>	Dr Richard Davenport	Consultant Neurologist (NHS Lothian), Royal Infirmary of Edinburgh	<i>Individual response.</i>  Nothing declared.
<b>FM</b>	Ms Fiona Milligan	Public Partner, Healthcare Improvement Scotland	<i>Individual response.</i>  Nothing declared.

Section	Comments received	Development group response
<b>General</b>		
	RD The first two pages are unreadable, the last three are exclusively references; SMC found a useful tabular way to present these data (crucially highlighting the modest effect on headache free days/month, which is the bottom line), can the same not be done here? The only thing of value in all 7 pages is page 3 recommendations, but I think a table highlighting just how modest these therapies are would be welcome by docs and patients.	A table has been added showing the efficacy of each therapy.
	DW I have reviewed the update and it looks excellent, good to get all the evidence in one place. The only addition is I read this weekend a summary from what I thought was a new paper about switching MABs. Apologies but I can't find it and it may be one of the papers you already have listed.	Thank you. We have looked at the evidence for switching and it is not sufficiently robust at the moment to include in the guideline. A couple of sentences have been added to highlight this.
<b>Section 4</b>		
4.14	AT The Erenumab Chronic migraine trial was a phase 2b trial so should be specified.  Perhaps clarification regarding the dosing regime of Fremanezumab used in the 675 mg arm of the HALO trials should be made.  Should the wording of 3 or more oral prophylactic treatments be changed to 4 or more prophylactic treatments? Bear in mind that Botox is injectable and is more or less standard of care for chronic migraine in Scotland and the rest of the UK.	We have stated that it is a phase 2 trial. The paper itself does not state that it is 2b.  We think this comment refers to the monthly dose where participants with chronic migraine were given a loading dose of 675 mg then the monthly doses. We have added this to the sentence describing dosing in the HALO trial along with a sentence at the end: The dose used in the trial of 675 mg then a monthly dose of 225 mg differs from the licensed monthly dose of 225 mg monthly or 675 mg quarterly.  The recommendation is in line with SMC advice. Some centres do not have access to Botox so we do not wish to preclude the use of CGRP monoclonals for those who have not been able to access and try Botox.
	FM With regards to the updated calcitonin gene-related	Thank you. No action required.

	<p>peptides. This appears fairly comprehensive and I have no concerns with the accuracy or interpretation of evidence provided or layout out of the information.</p>	
<p>AML</p>	<p>The guideline does not make clear that the studies had different refractory patient populations. ie STRIVE &gt;2 migraine preventatives, ARISE no prior or current migraine preventive treatments, HALO, failure of 2 or more prophylactics, liberty 2-4 prophylactics. It is therefore not clear to the reader that these differences have been taken into consideration when making the recommendation for not allowing erenumab for episodic migraine.</p> <p>In the real world these therapies will be used for the harder to treat group who are failing several oral therapies. The most relevant study is therefore the LIBERTY study. The functional outcomes are relevant here too and so it would be good to have this trial below referred to in the absence of evidence for the more refractory episodic migraine group.</p> <p>Lanteri-Minet M, Goadsby PJ, Reuter U, et al Effect of erenumab on functional outcomes in patients with episodic migraine in whom 2–4 preventives were not useful: results from the LIBERTY study <i>Journal of Neurology, Neurosurgery &amp; Psychiatry</i> 2021;92:466-472.</p> <p>The introduction of CGRP therapies in England has been hugely difficult for services to deliver because of the administrative burden they require.</p> <p>Legal restrictions may be different in Scotland around prescribing for home delivery but in England they mean we have to use "wet prescriptions" which are extremely resource intensive. The numbers of patients now eligible means that there is a shortage of clinical and pharmacy staff to provide the education and monitoring or prescriptions to fulfil this section of the guideline and no budgets allocated for this.</p> <p>In the 2018 SIGN guidelines there was a recognition of the</p>	<p>The rationale for the recommendation was the economic assessment and decision from the Scottish Medicines Consortium.</p> <p>A sentence and new table have been added to make clear that there are different populations, "Studies of the three CGRP monoclonal antibodies available in NHSScotland varied in the number of preventives participants were allowed to have tried prior to inclusion in the trial (<i>see Table 2</i>)."</p> <p>The number of treatment failures for inclusion criteria has been added into the new table (Table 2).</p> <p>This is one of a large number of subgroup analyses. We have focused on the main RCTs and primary outcomes (with the exception of further detail on medication overuse headache). We do not think the inclusion of this study would change the recommendation, so prefer to omit it from the review (see comments from RD that there is already too much analysis).</p>

		<p>impact on services that Botox may place. It may be sensible to recognise that CGRP may also place a similar pressure on headache specialists.</p> <p>Where will this fit into the treatment pathway that is so well described in Annex 3 of the original SIGN document? That pathway describes 50% improvement of prophylactics which is at odds with the 30% needed for continuation of CGRP or Botox.</p> <p>Also might it be useful to describe how treatment pauses may help clinicians assess ongoing need for therapy as this is regularly being used in England.</p>	<p>The paragraph discussing feasibility issues has been amended to stress that prescribing CGRPs may have workload implications for headache and neurology services.</p> <p>The final box in the pathway in Annex 3 had been changed to include 'Flunarazine, Botox or CGRP monoclonal antibodies can be considered'.</p> <p>SIGN guidance is concurrent with SMC guidance. Pauses are not evidence based, so we cannot provide definitive advice on this in the guideline.</p>
<b>Section 8</b>			
8.4	CH	The recommendations reflect the current SMC advice for these medicines and I have no other comments.	Thank you. No action required.