National Institute for Health and Care Excellence

Medical technologies evaluation programme

MT323 gammaCore for cluster headache

Consultation comments table

Final guidance MTAC date: 13 September 2019

There were 21 consultation comments from 5 consultees:

- 2 comments from NHS Professionals
- 19 comments from the company

The comments are reproduced in full, arranged in the following groups:

- patient response
- new evidence
- draft recommendations
- wording changes

#	Consultee ID	Role	Section	Comments	NICE response
Patient response					
1	1	NHS Professional	general	This device has changed the way we practice - it has huge implications beyond the results of headache diaries. This has saved a lot of NHS clinic time compared with other standards of care (verapamil is costly and timely in requiring such close monitoring with ECGs and even 24 hour ECGs). Lithium monitoring has patients coming to clinic every two weeks or so for up to 3-4 months to ensure safe management. In addition, these medications may cause significant side effects (I have had 1 patient who had a cardiac arrest on verapamil when a GP unwittingly added an antibiotic and it was prescribed and reacted). I have seen seizures and confusional states with lithium. The majority of topiramate users can not tolerate it because of severe depression, suicidal ideation/action, severe cognitive dysfunction, aphasia etc. Most other drugs are highly ineffective in the majority of patients. Treatments like gammaCore will potentially improve patient's symptoms, their quality of life, the cost of their care, reduce morbidity, see fewer side effects and adverse outcomes. It only works in a proportion of patients, but for this in whom it works, we have shown excellent compliance (which is interesting when studies looking at compliance in the US for other drugs in headache disorders such as migraine have shown compliance to be less than 20% at a year into treatment. Patients will naturally select and they will only wish to continue stimulating for 20 minutes or more a day if treatment is providing enough benefit.	Thank you for your comment.
2	1	NHS Professional	general	I am highly supportive of the draft guidance as it stands and in its entirety. I would comment however that I have personally treated over 300 people with gammaCore in addition to evaluating and following over 100 people who have received gammaCore within a clinical trial context (as UK Chief Investigator and Principal Investigator) and therefore had a lot of experience with seeing clinical response and the meaningful and significant impact this treatment can commonly have on people's lives. In addition, my 3 headache specialist neurologist colleagues also prescribe gammaCore and have commented on similar responses to treatment. I am informed by Electrocore that I have the single largest group of patients treated to date with this technology.	Thank you for your comment.

				In my practice I see predominantly highly refractory patients as we are the second largest UK headache group and we receive referrals from around the UK, especially to my own clinic. All of our patients (whether treated for cluster headache (the majority), other TACs (especially hemicrania continua) or refractory chronic migraine, have had extensive outcome measures performed with headache monitoring packs filled in for at least 1-2 months before starting, and they have continued prospective monitoring throughout their treatment. No patients have been allowed in our practice to remain on tretament without such monitoring. The monitoring included: - patient diaries (looking at headache-free days, mild-moderate days and severe headache days) - for cluster headache patients we have also recorded number of cluster attacks and number of sumatriptan injectors per month (for all our successful IFR requests, we have also looked at cost savings comparing gammaCore cost vs sumatriptan s/c injector costs alone and I have been informed that this equated in our group to approximately £6000 saving per patient per year - the company Electrocore looked at this data). - monthly HIT6 and modified MIDAS scores (to look at quality of life and level of functioning) - weekly VAS score. With regards to Cluster Headache, we have seen life changing responses including in patients who have failed occipital nerve stimulation. We have seen useful responses in episodic and chronic cluster headache and for both acute attack and preventative treatment. Although we have not yet analysed our database (we do plan to do so), we consider that the response rate sees approximately half of our patients demonstrate clinically significant resposne (eg at least a moderate response) and this response is in terms of frequency and severity of the headache. We have also seen huge changes in all the other non-headache features that we assess that typically accompany the headache and lead to considerable additional suffering (eg depression, suicidal ideation and attempted suicide, fatigue, family-social-work stresses, etc). The number of patients we see each week who truly comment that this has changed their lives is significant. We clearly see a group of super-responders who are at least 90-95% better.	

				I have seen no significant adverse reactions in all the time using this. The worst side effect has been rare - pain at site of stimulation (usually sorted out by retraining to ensure better device positioning). In addition to its role in cluster headache, we see similar approx 50% clinically significant responses in hemicrania continua but slightly less response in our most refractory chronic migraine patients. I would point out that from the outset, we have used a higher dose setting - typically 3 stimulations three times a day in all our clinical patients. I am not sure if this explains differences between different patient populations.	
3	4	Company	Page 8	(4.1) electroCore shipping data suggests that the responder rate for cluster headache patients is closer to 50% in the real world. We anticipate that patients and clinicians will comment on this value and cite their experience as being closer to our estimation.	Thank you for your comment. The committee discussed typical responder rates with the clinical experts who stated that in their experience, between 25 and 50% of patients responded to gammaCore. The committee decided to update section 4.1.
New evidence					
4	4	Company	Page 6	(3.4) Whilst ACT1 and ACT2 were not powered to allow sub-group analysis, the recently published de Coo, Goadsby et. al. meta-analysis did allow sub-group analysis to be performed.	Thank you for your comment. The EAC had seen an abstract of this study and were aware that it was going to be published however it was not available for inclusion in the assessment report before the committee meeting. Critical appraisal of the study and results from the study were subsequently added to the assessment report in June 2019 following publication of the study in a peer reviewed journal. The EAC highlighted some key points for consideration. This version of the

					assessment report was made available for public consultation. The EAC does not consider that the results of this publication would change the conclusions of the report. The committee decided not to change the guidance.
5	4	Company	general	Since the draft guidelines were produced, an independent peer-reviewed study has been published discussing the possibly active signal used in some of the sham devices used in our RCTs. The conclusion made by the authors was that the sham device is likely to be activating the vagus nerve causing the sham group to have a larger than expected 'placebo' effect. These results suggest that both the regular nVNS and the sham device used in some of the clinical nVNS trials modulate the trigeminal-autonomic reflex. This could explain the high sham effect in these trials and suggests that stimulation of the posterior neck may be considered as a real sham condition. The paper can be provided by electroCore on request, or is available online at the following link: https://www.ncbi.nlm.nih.gov/pubmed/?term=nVNS+sham+significantly+affects+the+trigeminal-autonomic+reflex	Thank you for your comment. The EAC note that this study was carried out in healthy volunteers and not patients with cluster headache and therefore would likely have been excluded from the report as the population does not fit with the scope. The EAC have not formally appraised this study and have not made any changes to the assessment report at this time, however the EAC note that this publication does provide some insight into the mechanism of action of gammaCore and gammaCore sham devices and the possible reason for high sham treatment responses noted in clinical trials. The committee decided not to change the guidance.
6	4	Company	general	Since the draft guidelines were produced, an independent review article has been published discussing how to manage Cluster Headache in clinical practice. The authors advise that gammaCore can be utilised as both an acute and preventive therapy in both episodic and chronic cluster headache. The review is in agreement with the recommendations made in the draft consultation document. The paper can be provided by electroCore on request, or is available online at the following link: https://pn.bmj.com/content/early/2019/07/05/practneurol-2018-002124.long	Thank you for your comment. This article is a narrative review, describing the general clinical experience in one centre and therefore would not meet criteria for inclusion in the clinical evidence review.

					The EAC suggest that it provides a useful background and context to the condition (cluster headaches) and overview of the current evidence and clinical management of the condition. The committee decided not to change the guidance.
Draft recommendations					
7	4	Company	Page 2	(1.1) electroCore consider recommendation 1.1 to be a sound recommendation and a suitable basis for guidance to the NHS.	Thank you for your comment.
8	4	Company	Page 2	(1.2) electroCore agrees with recommendation 1.2, stating that only patients who gain benefit should continue with therapy beyond the evaluation period. However, we would respectfully note that the first sentence of recommendation 1.2 is unnecessary, with language like this not typically found in guidance. It is generally acknowledged that no drug or device is effective in all people and this sentence could be interpreted as discounting gammaCore efficacy due to it being a device.	Thank you for your comment. The committee discussed this statement and decided it was factually correct and did not change the recommendations.
9	4	Company	general	electroCore believes that the summaries of the clinical and resource savings are a reasonable interpretation of the evidence that is available. We support the findings of the MTAC and welcome the positive guidance and recommendations in their draft form.	Thank you for your comment.
10	2	NHS Professional	general	I am glad of NICE's endorsement of the GammaCore device; although it only seems to help about half my Cluster Headache patients it is a modestly priced intermediate treatment to offer before more invasive options. The company's free trial scheme is very helpful. I have to say I do not use S/C sumatriptan for cluster attack, relying on nasal sprays and oxygen, which might weaken the cost advantage of the device. I see little point in comparing it to Botox, which has no place for Cluster Headache; there has been some 'leakage' of the GammaCore device in chronic migraine patients, though to my knowledge there is no trial evidence to support this. Your opening pages do not make clear that your neurological advisors are Doctors.	Thank you for your comment.

11	5	NHS Professional	general	The Faculty of Pain Medicine of the Royal college of Anaesthetists thinks that this is overall a balanced evaluation and is a welcome recommendation. Our only comment would be to question what qualifies as a 'successful' trial of what ultimately could be quite an expensive on-going therapy.	Thank you for your comment. The committee discussed with the clinical experts how they determine whether or not a trial of gammaCore has been successful for the patient. The committee decided to add section 4.5 to describe this.
12	3	NHS Professional	general	The Association of British Neurologists does not recommend any substantial changes to the consultation document. We consider that gammacore is an appropriate treatment for both episodic and chronic cluster headache. Gammacore may be considered as a second/ third line option after non-oral triptans and high flow oxygen for acute treatment, and verapamil , and possibly greater occipital nerve blocks and lithium for preventative treatment. Whilst the treatment may not have high efficacy, it is safe to use and very few other non-invasive treatment options are available for this devastating pain condition.	Thank you for your comment.
Wording changes					
13	4	Company	Page 4	(Table 2) In the description of the technology electroCore thinks it would be valuable to highlight the fact that each treatment regimen (acute or preventive) comprises of three, 2-minute stimulations ,so that potential gammaCore users do not feel they only need to use the device for 2 minutes in total.	Thank you for your comment. The committee decided to update this section.
14	4	Company	Page 4	(Table 2) In 'Intended use' electroCore suggests changing the wording from 'The company recommends' to 'The clinical data suggests'	Thank you for your comment. The statement has been modified to 'The instructions for use state'. The committee noted that this was the most factually accurate description.
15	4	Company	Page 5	(3.1) electroCore would like to highlight that the economic analysis of PREVA (Morris et al. 2016) is not mentioned in the summary of the published clinical evidence and is a post-hoc analysis of a randomised trial.	Thank you for your comment. The committee decided to add section 3.6 to reference this study.

16	4	Company	Page 5	(3.2) electroCore would respectfully argue that patients recruited into the PREVA study are treatment refractory. These patients had tried and failed multiple lines of treatment prior to study inclusion, were experiencing more than 2 cluster attacks per day despite the best possible care at tertiary care headache centre, and carried a confirmed diagnosis of chronic cluster headache for several years.	Thank you for your comment.
17	4	Company	Page 5	(3.3) All of the studies are described as having short follow-up times. electroCore would like to highlight that the duration of our studies was consistent with IHS and ICHD guidelines and in many cases substantially longer than many other published cluster headache studies.	Thank you for your comment.
18	4	Company	Page 6	The way in which the 'trial period' is discussed throughout the document still implies some room for uncertainty. For example, we find the following statement on page 3 misleading: 'Cost analysis suggests that using gammaCore may lead to cost savings because people use medication less. But this depends on a free 3-month period to identify people who benefit.' We would encourage the use of more neutral form of words in various sections of the document where cost savings are discussed.	Thank you for your comment.
19	4	Company	Page 6	(3.6) electroCore challenges the statement 'The company says using gammaCore saves £450 per person in the first year'. As a company, we believe that the economic model is conservative in it's cost-saving estimates due to the limitations in the evidence available. The EAC has supported the economic model and throughout the document acknowledges these limitations in the available evidence, and how the model most likely underestimates the potential savings. A more appropriate and neutral statement therefore could be 'The economic model suggests that using gammaCore saves £450 per person in the first year. The available evidence is limited and therefore the economic modelling may underestimate the potential savings that gammaCore could deliver.'	Thank you for your comment. The committee noted that some elements of the care pathway could not be included in the cost analysis because of the lack of evidence. It noted there were other uncertainties in the cost modelling and did not think it was appropriate to state that the cost saving estimates are conservative.
20	4	Company	Page 11	(4.7) electroCore would like to highlight that there are no published reports of device-related adverse events.	Thank you for your comment.
21	4	Company	Page 12	(4.10) electroCore would like to see the following sentence included in this section 'The company acknowledge that there is limited robust evidence that could be utilised in the submitted economic model. Therefore the company suggests the estimated saving of £450 per patient, per year, is likely the minimum annual savings that gammaCore could deliver to the NHS.'	Thank you for your comment. Please see the response to comment 19.

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