NICE National Institute for Health and Care Excellence

NICE guidance

gammaCore for cluster headache

Medical technologies guidance
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Your responsibility

This guidance represents the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, healthcare professionals are expected to take this guidance fully into account, and specifically any special arrangements relating to the introduction of new interventional procedures. The guidance does not override the individual responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.

All problems (adverse events) related to a medicine or medical device used for treatment or in a procedure should be reported to the Medicines and Healthcare products Regulatory Agency using the Yellow Card Scheme.

Commissioners and/or providers have a responsibility to implement the guidance, in their local context, in light of their duties to have due regard to the need to eliminate unlawful discrimination, advance equality of opportunity, and foster good relations. Nothing in this guidance should be interpreted in a way that would be inconsistent with compliance with those duties. Providers should ensure that governance structures are in place to review, authorise and monitor the introduction of new devices and procedures.

Commissioners and providers have a responsibility to promote an environmentally sustainable health and care system and should assess and reduce the environmental impact of implementing NICE recommendations wherever possible.

Contents

This guidance replaces MIB162.

1 Recommendations

1.1 Evidence supports the case for adopting gammaCore to treat cluster headache in the NHS. gammaCore reduces the frequency and intensity of cluster headache attacks and improves quality of life.

1.2 gammaCore is not effective in everyone with cluster headache. Treatment with gammaCore should only continue for people whose symptoms reduce in the first 3 months.

1.3 Cost modelling estimates that, in the first year of treatment, adding gammaCore to standard care is cost saving compared with standard care alone by an average of £450 per person. This cost saving:

- assumes that the first 3-month period of gammaCore use is offered by the company free of charge
- largely results from less use of subcutaneous sumatriptan.

Why the committee made these recommendations

gammaCore is a non-invasive vagus nerve stimulator that can be used to treat cluster headaches. Existing medications for cluster headaches are often only partially effective and may cause serious side effects.

Clinical evidence shows that, for some people, using gammaCore as well as standard care reduces the frequency and intensity of cluster headache attacks and reduces the need for medication. This is likely to lead to significant quality of life benefits for people living with this condition.

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.

2 The technology

Technology

2.1 gammaCore (electroCore) is a non-invasive vagus nerve stimulator used to treat and prevent cluster headaches. It is self-administered by the person or their carer. After applying conductive gel, gammaCore is held against the neck (over the cervical branch of the vagus nerve) and delivers a small electric current for about 2 minutes. This stimulation should be repeated 3 times. The device is small and portable. gammaCore requires RFID (radio frequency identification) card activation which is renewed every 3 months (93 days). The RFID card activation allows gammaCore to deliver a maximum of 30 stimulations in each 24-hour period. Conductive gel is provided with each new RFID card. Additional gel can be provided at no extra cost.

Innovative aspects

2.2 gammaCore is currently the only technology that uses non-invasive stimulation of the vagus nerve to treat cluster headache.

Intended use

2.3 The instructions for using gammaCore state that it should be used regularly throughout the day to prevent cluster headache attacks and acutely to reduce pain during an attack. gammaCore is intended to be self-administered, or treatment can be administered by a carer. Using gammaCore requires brief training and some manual dexterity. Training for patients and staff is provided by the company for free. gammaCore should not be used by people with an active implantable medical device, people with heart disease, during pregnancy or in children.

Costs

2.4 gammaCore is provided free of charge for the first 3 months (93 days). Subsequent treatment costs £625 for 93 days (excluding VAT).

For more details, see the website for gammaCore.

3 Evidence

Clinical evidence

The clinical evidence comprises 8 published studies

3.1 The published studies comprise:

- 3 randomised trials: 2 sham-controlled (ACT1, Silberstein et al. 2016, and ACT2, Goadsby et al. 2018) and 1 open label (PREVA, Gaul et al. 2016)
- 1 post-hoc analysis of a randomised trial (Gaul et al. 2017)
- a pooled analysis of 2 randomised trials (de Coo, 2019)
- 3 non-comparative cohort studies (Nesbitt et al. 2015, Marin et al. 2018, and Trimboli et al. 2018).

The evidence includes 410 patients with cluster headache. For full details of the clinical evidence, see section 3 of the assessment report.

The evidence includes the preventative and acute use of gammaCore and treatment refractory cluster headache

3.2 gammaCore was used in different ways in the studies. In the ACT1 and ACT2 studies, gammaCore was used as an acute treatment only. In all the other studies, gammaCore was used as a preventative and an acute treatment. Two cohort studies (Marin et al. 2018 and Trimboli et al. 2018) reported on gammaCore used for people classified as refractory to 1 or more standard treatments for cluster headache. In all other studies gammaCore was used in addition to standard of care treatments.

The studies show that gammaCore can reduce the frequency of

cluster headache attacks and the intensity of pain during an attack

3.3 The evidence for gammaCore comprises a small number of studies which include comparative, non-comparative and observational studies. The external assessment centre (EAC) noted, however, that large randomised trials are not likely to be possible given the very low prevalence of cluster headaches. All but one of the studies was sponsored by the company. The studies had short follow-up times so there is no evidence for the long-term benefits of using gammaCore. The trials showed that some but not all people benefit from using gammaCore. When gammaCore was used preventatively, it reduced the frequency of cluster headache attacks (Gaul et al. 2016). When gammaCore was used acutely it reduced the intensity of attacks (ACT1 and ACT2). Using gammaCore improved measures of quality of life (Gaul et al. 2016).

The degree of clinical benefit is uncertain

3.4 In the 2 sham-controlled trials (ACT1 and ACT2), gammaCore worked better as an acute treatment for people with episodic cluster headache than for people with chronic cluster headache. The EAC noted, however, that these studies were not powered to allow such sub-group analysis. The EAC concluded that the published evidence suggests that people with cluster headache may benefit from using gammaCore (either preventatively or acutely) although the degree of benefit is uncertain.

Adverse events are mild to moderate

3.5 The reported adverse events were mild to moderate in all studies. No-one stopped using gammaCore because of adverse events. The clinical experts told the EAC that gammaCore is safe and easy to use and that there was no need for safety monitoring. The EAC concluded that there is enough evidence that gammaCore does not cause any serious device-related adverse events in people with cluster headache. For full details of the adverse events, see section 4.8 about adverse effects.

Cost evidence

The cost evidence comprises 3 published studies

3.6 There were 3 published studies: Morris et al. 2016 used data from the PREVA trial, Mwamburi et al. 2017 used data from ACT 1 and ACT 2 and Pietzsch et al. 2015 used data from a randomised, sham-controlled study (Schoenen et al. 2013).

The company says using gammaCore saves £450 per person in the first year

3.7 The company created a de novo cost analysis using a Markov model with a 1-month cycle and 1-year time horizon. The model only considered people with chronic cluster headache and did not include anyone with episodic cluster headache. The model considered gammaCore in addition to standard care acute treatments (oxygen, zolmitriptan and sumatriptan). Preventative medication (for example, verapamil) was not included in the model because it was assumed to be the same in both treatment arms. Data from the PREVA trial was used in the model to estimate the proportion of people whose cluster headaches responded to treatment with gammaCore; this study defined a treatment response as cluster headache frequency reduced by 50% or more. For full details of the cost evidence, see section 4 of the assessment report.

3.8 The company's model, which was unchanged by the EAC, reported that using gammaCore in addition to standard care would lead to cost savings of £450 per patient in the first year.

Cost savings depend on a free 3-month initial period and reduced sumatriptan use

3.9 In the model gammaCore is free for the first 3 months, and it assumes that only people whose condition responds to treatment with gammaCore continue to use it. This is called a trial; however, this refers to the user trialling the technology for 3 months and does not mean that people using gammaCore will be automatically

enrolled in a clinical trial. The model included less acute medication use by people in the gammaCore responder arm, based on data from the PREVA trial. The EAC's sensitivity analyses showed that the cost savings associated with gammaCore depend on the initial 3-month period being free of charge and less sumatriptan use in the gammaCore responder arm.

The cost analysis has limitations because of lack of evidence

3.10 The model does not include costs for:

- inpatient, outpatient or primary care
- psychological support
- invasive surgical procedures such as implanted sphenopalatine nerve stimulators
- unlicensed medications used for treatment refractory cluster headaches, which might be avoided if gammaCore treatment is successful.

These costs could not be included in the model for gammaCore because there is no evidence to base assumptions on. The EAC noted that gammaCore is likely to lead to a reduced need for care resources, and their associated costs, because people who it is effective for will have fewer, less severe cluster headaches. The EAC also noted that the data underpinning the economic model is part of a single small data set and post-hoc analysis that was only partially based in the UK. However it did not identify any other data that could be used to improve the analysis.

4 Committee discussion

Clinical-effectiveness overview

gammaCore is effective in some people

4.1 The evidence base for gammaCore is small. But cluster headache is a rare condition, and the quality of the studies was good. The committee concluded that gammaCore appears to be effective in some but not all people. In people whose condition responds, it can make a significant difference to their symptoms and quality of life. The clinical experts said that, in their experience, 25% to 50% of people have cluster headaches that respond to gammaCore.

Cluster headache significantly worsens day to day life

4.2 The published evidence of efficacy was supported by evidence from people with cluster headache that was submitted to the committee. Sixty people with cluster headache were surveyed. They described the impact of the condition on their lives, and how it responded to gammaCore. Two patient organisations also submitted reports. The committee understood the devastating impact that this condition can have on the lives of sufferers and the desperation that can result from ineffective treatment. For example, the submission from OUCH (Organization for the Understanding of Cluster Headache) reported that on average 5 people a year in the UK end their lives because they are no longer able to live with the pain of cluster headaches. The committee noted the life-changing effects that gammaCore had had for many people in the survey.

Vagus nerve stimulation with gammaCore could plausibly reduce pain in people with cluster headache

4.3 gammaCore is the only device available that treats cluster headache by non-invasive vagus nerve stimulation. The clinical experts described the results of

studies that supported the mechanism of action of gammaCore. They explained that, patho-physiologically, vagus nerve stimulation could plausibly reduce pain in people with cluster headache. The clinical experts also explained that, while a placebo effect is likely in all treatments for chronic pain conditions, it is unlikely that the benefits of gammaCore can be explained by this alone. They said that gammaCore's response rate is higher and its therapeutic benefits more sustained than would be expected for a placebo treatment. The committee was also convinced by the experts' argument that people with such a debilitating condition welcome a treatment response regardless of its mode of action as long as it is safe and has no adverse effects.

The free initial 3-month period means gammaCore is worth trying if there is a possibility it can reduce attacks and medication

4.4 Although the evidence for gammaCore is subject to some uncertainty, the committee noted that gammaCore would only be used in people who find it effective after the first 3 months of treatment. Cluster headache attacks have a profound negative impact on everyday life so any treatment that can help reduce this is worth trying. The committee also noted that gammaCore, as a non-drug treatment, is unlikely to interact with any other treatments and may help reduce the number of drugs that are prescribed to this patient group.

A doctor should decide if treatment with gammaCore has been successful after 3 months, after consulting the patient

4.5 The clinical experts stated that the definitions of a successful response to 3 months of treatment with gammaCore vary and are subjective. This was also the case in the published evidence. However, they explained that it's usually clear within 3 months if someone's cluster headaches have reduced meaningfully in frequency and severity, leading to reduced medication use that justifies continuing treatment with gammaCore. The clinical experts said that people do not generally want to continue with treatments if they're not helping. The committee concluded that the decision about whether or not to continue with

gammaCore after the first 3 months of treatment should be made by a doctor after consulting the patient.

There is enough evidence of clinical benefit for people with chronic and episodic cluster headache to recommend gammaCore for both groups

4.6 The experts explained the different patterns of symptoms that people with cluster headaches have. There is a difference in particular between people with chronic and episodic cluster headache. They also explained that some people with episodic cluster headache later become chronic sufferers and vice versa. But the natural history of the condition is unpredictable. This means it's uncertain how the condition is likely to respond to an intervention. The sham-controlled randomised clinical trials (ACT1 and ACT2) were not powered to examine therapeutic benefits separately in episodic and chronic cluster headache, and they only considered acute use of gammaCore. But people with episodic cluster headache had particular benefit. In the open-label randomised controlled trial (PREVA), people with chronic cluster headache had clinical benefit. The patient survey included responses from 12 people with episodic cluster headaches, and 9 of them said they had received substantial clinical benefits from gammaCore. The clinical experts said they most often use gammaCore for people with chronic cluster headache. They said that treatment effects were more difficult to measure in episodic cluster headache. The committee concluded that overall there was enough evidence of clinical benefit for people with chronic and episodic cluster headache to recommend adopting gammaCore if treatment is successful in the first 3 months. It said it could not reliably make a therapeutic distinction between the 2 based on current evidence.

People using gammaCore should have regular follow ups at specialist headache centres

4.7 The clinical experts said that clinical follow up of people is essential because response to treatment with gammaCore is unpredictable. People should be reassessed after the first 3 months of treatment to review attack frequency and

intensity, and use of treatments to stop acute attacks (oxygen, sumatriptan, zolmitriptan). The experts advised that only people whose cluster headaches respond to treatment with gammaCore should carry on using it. The experts recommended follow up again at 12 months and every year afterwards to determine long-term benefits and to give an opportunity to stop gammaCore if it's no longer effective.

Adverse events

gammaCore is a non-pharmacological treatment that has no serious side effects

4.8 There are no published reports of serious adverse events with gammaCore. The experts and manufacturer representative said none had been reported to them. The patient survey confirmed that the device is well tolerated and easy to use. People with cluster headache risk side effects from conventional pharmacological treatment. Sometimes they need invasive treatment such as implanted stimulators. gammaCore could help some people avoid or delay the need for these treatments. The safety and efficacy of using gammaCore has not been evaluated in people with an implanted medical device, people with heart conditions, people who are pregnant, lactating or aged under 18 years.

NHS considerations overview

gammaCore should be offered in addition to standard care

4.9 The clinical experts described their experience of using gammaCore in their NHS practice. They reported that it was usually used as a second or third-line treatment option to prevent chronic cluster headache attacks after verapamil, and possibly lithium, had been tried. They also explained that verapamil and lithium can have adverse effects, they need careful monitoring, and they may be contraindicated in some people. The experts said that if people benefit therapeutically from gammaCore – and around 25% to 50% do – they usually

carry on benefiting from it. They said that some of their patients have been using the technology for 3 years or more. It has been difficult for clinical services to get funding for gammaCore. The experts explained that they get it through individual patient funding requests to commissioners.

Training is simple

4.10 People are trained to use gammaCore by specialist headache nurses. The manufacturer provides training resources free of charge. The clinical experts explained that training was simple, and that most people were able to learn how to use the device in one session. The manufacturer representative explained that if someone cannot use the device themselves because they have problems with manual dexterity, someone else can give treatment.

Cost modelling overview

There are limitations in the cost model but there are cost savings linked to clinical benefits

4.11 The company's cost model showed a potential £450 saving per patient over 1 year if gammaCore is used with standard treatment in people with chronic cluster headache. It noted that the cost savings were largely from a reduced need for sumatriptan to stop the symptoms of acute attacks. It also noted that they depended on the first 3 months of treatment being free of charge.

gammaCore may reduce the need for medications and invasive procedures

4.12 The data used in the cost modelling was from one open-label randomised controlled trial (PREVA) that included patients from the UK. The committee discussed uncertainties in the cost modelling but acknowledged that they cannot be resolved by the available evidence. For example, the impact of gammaCore on other outpatient, community or inpatient services – such as occipital nerve

blocks, intravenous dihydroergotamine or implanted nerve stimulators – is unclear. Reduced cluster headache symptoms could mean other treatments or care could be reduced or stopped. But with no evidence to support this, it could not be considered in the cost modelling.

The study definition of a successful response to gammaCore may differ from a clinically meaningful response

4.13 The trial used to inform the cost model classified a successful response to gammaCore as cluster headache frequency reduced by 50% or more. The experts explained that, in clinical practice, several treatments may be needed to reduce cluster headache attacks to this degree. The clinical experts also advised that people classified as non-responders on this basis may still receive clinically meaningful benefits from gammaCore that would not be captured in the cost modelling.

Main cost drivers

The free 3-month initial period is a key driver of cost savings

4.14 gammaCore is offered for a free 3-month initial period. The external assessment centre (EAC) identified this as a key driver of the cost savings. The company representatives assured the committee that the free period is a fixed part of its business model which would not change. They also clarified that there are no extra costs for conductive gel, training resources, or replacing the gammaCore device if it is broken, lost or stops working. The committee concluded that the technology costs used in the model are accurate.

Cost savings also depend on reduced subcutaneous sumatriptan use

4.15 The experts explained to the committee the importance of the treatments that people use to stop the symptoms of an acute attack of cluster headache. These

include inhaled oxygen, sumatriptan and zolmitriptan. The committee considered it plausible that, if gammaCore reduces the frequency and severity of attacks, then medication use is also likely to reduce. More than half the people in the patient survey had reduced their medication use since starting treatment with gammaCore. Reduced sumatriptan use was another key driver of the cost savings for gammaCore in the model. The committee concluded that the clinical evidence would support this.

Cost savings

Cost modelling for gammaCore has limitations but cost savings are likely if it is only used by people who it is effective for

4.16 The committee accepted the EAC's rationale for not changing the model because there was no relevant additional evidence. The model had a 1-year time horizon because this was the duration of the relevant study. The annual cost of gammaCore treatment increases after the first year because the free period no longer applies. But the committee considered that this could continue to be offset by savings from reduced medications used to stop the pain of an attack, as well as reduced or avoided care or treatments not captured in the cost modelling. The committee noted that it was important that only people who benefited clinically from gammaCore should use it. People who do not benefit should stop treatment with it to avoid incurring additional costs. Overall, the committee concluded that the model's cost saving of £450 per patient in the first year is plausible.

Further research

Further research will help reduce uncertainty and should include long-term outcomes data

4.17 Further evidence to address the uncertainties in the current clinical evidence, including the impact of gammaCore on all treatments and care as well as its long-term benefits, would be welcome.

5 Committee members and NICE project team

Committee members

This topic was considered by the medical technologies advisory committee which is a standing advisory committee of NICE.

Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that evaluation.

The minutes of each committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

NICE project team

Each medical technologies guidance topic is assigned to a team consisting of 1 or more technical analysts (who act as technical leads for the topic), a technical adviser and a project manager.

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