

## **GammaCore external vagus nerve stimulator**

GammaCore Sapphire<sup>1</sup> (non-invasive vagus nerve stimulator) is a therapeutic medical device used in the treatment of Cluster Headache (CH). In 2019 the National Institute for Health and Care Excellence (NICE) published Medical Technologies Guidance recommending the use of gammaCore to treat CH in the National Health Service (NHS)<sup>2</sup>. Since the 1<sup>st</sup> of April 2019, gammaCore has been listed on the Innovation and Technology Payment (ITP) initiative, which provides centralised NHS England funding for the therapy<sup>3</sup>.

In January 2021, NHS England and NHS Improvement published the MedTech Funding Mandate (MTFM) policy<sup>4</sup>. The policy mandates that the clinically appropriate use of gammaCore by providers should be funded by local commissioners. Compliance with the MTFM is a condition of the NHS Standard Contract for 2021/22, with the guidance stating ‘*The NHS Standard Contract will require both commissioners and providers of NHS funded services to comply, as relevant, with their obligations under, and any recommendations contained in, the MedTech Funding Mandate*<sup>5</sup>’.

### **1. Cluster headache**

Cluster headache (CH) is a primary headache disorder characterised by recurrent attacks of severe, strictly unilateral pain, which is orbital, supraorbital, temporal or in any combination of these sites. Attacks last between 15-180 minutes and occur from once every other day to eight times a day. The pain of CH is intense. During an attack, patients are agitated and typically pace the room, the patient may beat his/her head on the wall or floor until the pain diminishes. CH is nicknamed ‘suicide headache’ and between 15-21% of patients have suicidal ideation at some point<sup>6</sup>. Patients have described their headaches like “someone’s jabbed a white-hot poker into your eye socket and is holding it there for 45 minutes to an hour and a half”; “like I just got shot in the face”; “a pain that’s so sharp and excruciating, there’s no talking or doing anything other than just screaming to try and get out of it”<sup>7</sup>. The pain is associated with ipsilateral conjunctival injection (red eye), lacrimation, nasal congestion, rhinorrhoea, forehead and facial sweating, miosis, ptosis and/or eyelid oedema, and/or with restlessness or agitation. CH is classified as a trigeminal autonomic cephalalgia; attacks which result from vascular changes in cranial circulation driven by trigeminal autonomic reflex activation<sup>8</sup>. Whilst CH does carry an ICD-10 code, it is poorly coded for both within primary care and non-elective hospital admissions. This affects young adults with a peak age of onset between 20-40 years. As few as 0.1% (one in a thousand) of the population suffer from CH, approximately the same number as for multiple sclerosis in the UK<sup>9,10</sup>. Most patients have episodic CH (eCH) where attack periods may last from seven days to several months in what is called a bout and they may have more than one bout in a year but critically they will have a pain-free period of at least three consecutive months; 10% to 20% of patients have chronic CH (cCH)<sup>2,10,11</sup> where this period of headache freedom is not maintained. Management of CH is usually via secondary/tertiary neurologists specialising in headache. Patients with CH are managed routinely in the out-patient setting, with occasional emergency admissions when they are in crisis for pain management. At present all patients with cluster headache in the wider Cambridgeshire and Peterborough CCG that do not respond sufficiently to first line oral or subcutaneous treatment options are referred to the Addenbrookes refractory headache clinic.

#### **1.1. Current medical therapeutic options for cluster headache**

There is currently no prospect of a curative treatment for either eCH or cCH. The attainable goal of treatment is total attack cessation, or attenuation of headache until the next episode. Guidelines for the

management of CH have been published by the British Association for the Study of Headache and NICE<sup>12,13</sup>. Therapies are prescribed in an attempt to prevent CH attacks (prophylaxis) and to manage pain at the time of a headache (acute / abortive treatment); the latter is rarely sufficient to achieve adequate control alone<sup>12</sup>.

Current prophylactic treatment options for CH are used outside of their licensed indication and the evidence base of robust trials limited in number and quality. The standard prophylactic treatment for CH is high dose verapamil which has both a small non-randomised and a double-blind randomised controlled trial confirming its efficacy. Other medications including anticonvulsants (topiramate, gabapentinoids, sodium valproate) and Lithium may also be tried but these therapies are not without potential significant side effects and have specific initiation requirements and the need for monitoring. Nerve blocks are also performed in the neurology clinic or on the hospital ward. There is more robust evidence for the acute treatments at the time of the attack using subcutaneous sumatriptan (nasal sumatriptan or zolmitriptan can be used for needle phobic individuals but is of lower efficacy) and high flow oxygen. In practice, single or multiple nerve blocks, pharmacological therapies and high flow oxygen may be used adjunctively to try and manage CH.

There remains a huge unmet need for safe and effective treatments for Cluster Headache. The NICE guidance and MedTech Funding Mandate for the use of gammaCore for Cluster Headache within the NHS go a long way to help address this clinical need.

## **2. What is gammaCore external vagal nerve stimulation?**

GammaCore is a CE-marked medical device indicated for the treatment and/or prevention of primary headache (migraine, cluster headache, and hemicrania continua) and medication overuse headache in adults. gammaCore is intended to provide non-invasive vagus nerve stimulation (nVNS) on the side of the neck as shown. The brief electrical current created sends signal up through the vagus nerve and this changes or modulates central pain centres in the brain. This technology has been used invasively in patient care for over 30 years for a number of different conditions including to treat epilepsy but has more recently been developed as a safer non-invasive technology for primary headache management. During use, gammaCore delivers a mild electrical stimulation to the vagus nerve. Each stimulation lasts 2 minutes. Therapy is self-administered, with the patient controlling the intensity level. gammaCore delivers up to 30 stimulations in a 24-hour period, starting when the device is turned on and the intensity level is initially increased above 3. Once the maximum daily number of treatments has been reached, the device will not deliver any more treatments until the following 24-hour period. gammaCore is rechargeable and includes a charging station to power the device. A gammaCore Sapphire Refill Card<sup>□</sup> is used to load the device with days of therapy based on a healthcare provider's (HCP) prescription. Please see the full Instructions for Use<sup>14</sup> and Important Safety Information<sup>15</sup> for more details on the appropriate use of gammaCore.

GammaCore is typically prescribed to a patient who is unable to tolerate recommended preventive pharmaceuticals, or is unresponsive to them, meaning the patient becomes reliant on dose-limited, expensive

“rescue” medications to manage their CH pain. Recent peer-reviewed publications summarise gammaCore effectiveness and suggest it be used as a first-line treatment for CH<sup>10,16</sup>. In clinical studies, the addition of GammaCore to standard of care for prevention of chronic CH significantly reduced both the number of CH attacks and the use of abortive medications (sumatriptan and oxygen)<sup>8</sup>. Addition of gammaCore to standard of care for the acute treatment of CH demonstrated a significant response in patients with episodic CH<sup>18–20</sup>.

GammaCore should be used on a prophylactic treatment regimen with patients instructed to administer three stimulations, twice a day. Acute treatments can consist of three stimulations applied consecutively at the onset of CH pain or symptoms. If pain persists 3 minutes after the first treatment, the patient may stimulate with an additional three consecutive stimulations; treatments may be applied to either side of the neck.



### 3. Proposed starting and stopping criteria

#### 3.1. Starting criteria

- Diagnosis of cluster headache or where cluster headache is high in the differential (e.g., hemicrania continua and autonomic migraine) and in chronic patients who have failed to have a marked response to maximum tolerated dose of verapamil (up to 960mg daily) and ongoing attacks on > 8 days per month. If the patient is in crisis, then gammaCore should be started during verapamil up-titration and when the maximum verapamil dose has been achieved gammaCore should be stopped (finishing the period of the card) to establish ongoing need. In patients where it is proving difficult to manage verapamil monitoring or patient/clinician concern over tolerability then gammaCore should be considered alongside greater occipital nerve blocks.
  - in episodic patients with bouts lasting >2 weeks and other options of either oral steroids or greater occipital nerve block have been explored and not pursued due to patient and clinician caution or prior lack of efficacy
  - where oxygen and subcutaneous/nasal triptan are ineffective or poorly tolerated for acute management i.e., patient in crisis
- In episodic patients first time use should be during an active cluster bout in order to be able to ascertain efficacy
- Patient should endeavour to keep a headache diary (not mandated as due to frequency of attacks and low mood during bout patients often struggle to be compliant)

#### 3.2. Exclusions

GammaCore should not be used in those:

- with an implanted device such as a pacemaker, hearing aid implant, or any implanted electronic device
- who are diagnosed with narrowing of the main artery in the neck (carotid stenosis)
- who have had surgery to cut the vagus nerve in the neck.
- who are pregnant.

#### 3.3. Stopping criteria

- No meaningful improvement in either headache severity or headache load or attack frequency or Patient global impression of improvement in response to the 3-month free of charge trial. (NICE recommendations do not stipulate the extent of response as this is recognised to be a very difficult condition to treat and even very modest impact can be of very meaningful benefit to the patient).

## 4. Summary of gammaCore benefits

### 4.1. Clinical

- The only therapy licensed for use in the prevention of Cluster Headaches<sup>12</sup>
- Safe, drug-free, portable and non-invasive intervention
- Widely accepted as being a first-line treatment option for CH<sup>16</sup>
- Can be used as both as a preventive and acute therapy
- Clinically effective; shown to reduce attack frequency, duration and severity<sup>17</sup>
- Recommended by NICE for use in Cluster headaches<sup>2</sup>
- Does not require regular monitoring activity, unlike typical “off-label” CH prevention drugs such as verapamil and Lithium which require regular ECGs and blood sampling respectively

### 4.2. Economic

- Independent evaluation by NICE highlights the use of gammaCore is cost effective and cash releasing<sup>2</sup>
- First course of therapy is supplied free of charge ensuring commissioners do not pay for non-responders
- Use significantly decreases the use of expensive acute medications/ oxygen therapy<sup>17</sup>

### 4.3. System and organisation

- No additional resources (staff, space etc.) are needed to prescribe gammaCore in the clinic (already been routinely prescribed up to this point)
- May prevent the need for more expensive and invasive procedures including multiple cranial nerve blocks and neurosurgical options of occipital nerve stimulation
- Mitigates the side-effects and safety risks associated with off-label drug use and more invasive percutaneous or surgical options
- Improved management of CH reduces the amount of NHS resource required by a patient including their direct health utilisation and crisis contacts
- The prescribing, delivery, and training on the use of gammaCore can be completed virtually without the need for a patient to enter a clinic or pharmacy during COVID times although in normal practise we would physically demonstrate this to the patient in clinic. This has however allowed business continuation throughout the COVID-19 pandemic and can help manage the escalating waiting times to access headache services.

## 5. Financial implications

The gammaCore Sapphire<sup>®</sup> device and first 93-days of therapy are supplied free of charge to the prescribing trust and relevant commissioner. ElectroCore, the supplier of gammaCore therapy, absorb this monetary loss to remove the financial risk to commissioners, of patients who do not respond to therapy. This prescribing model allows an assessment of efficacy to be made, prior to any further costs being incurred and ensures that only savings are delivered to the commissioner. Data on file from centres who have accessed gammaCore as part of the ITP initiative, suggest that approximately 50% of patients who try gammaCore go on to experience a benefit and are prescribed further refill cards (data from electroCore & manuscript under preparation).

### 5.1. NHS Cambridgeshire and Peterborough CCG financial data

The budgeting information provided below has been calculated using the resource impact template built by NICE as part of MTG46 amended to suit the **NHS Cambridgeshire and Peterborough CCG** population.

- NHS Cambridgeshire and Peterborough CCG has an estimated total adult population of **691,009** and with an estimated prevalence of cluster headache of 0.1% then it is expected there will be **691 patients with cluster headache**.
- The NICE resource impact template suggests that the current use of gammaCore plus standard care should be at a rate of 11% of patients with cluster headache and, in the future, this should rise to 25% of patients with cluster headache.
- If we were currently reaching the NICE projected population, we should have 24 patients newly started on gammaCore and 49 on continued gammaCore in the year 2020/21. At present we have not met the projected population but with more secure long term access expect our numbers to rise appropriately.

**The savings realised by the CCG are delivered through a reduction in the prescribing volume of expensive medications, therefore reducing spend from primary care prescribing budgets.**

## **5.2. Prescribing information for Addenbrooke's Hospital (historical and current)**

Addenbrooke's Hospital provides a specialised headache service and is therefore likely to treat a number of patients who travel from out of the area to access the services, as well as those residing within the boundaries of NHS Cambridgeshire and Peterborough CCG. The data demonstrate that at present a smaller proportion of patients have been treated with gammaCore than NICE would have projected but this in part reflects the caution on embarking on treatments where the long term financial provision was not guaranteed.

- In the year **2019/20** Addenbrooke's Hospital prescribed gammaCore to **4** brand new patients. No costs were incurred for this activity as the first device and 93-days of therapy are fulfilled free of charge
- In the year **2019/20** Addenbrooke's Hospital prescribed **9** refill cards for patients confirmed to be responders.
- In the current financial YTD (April 2020 – Dec 2020) Addenbrooke's Hospital has prescribed gammaCore to **4** brand new patients and authorised **13** refill cards.

With the implementation of a national adoption campaign supported by NHS England and NHS Improvement, and the Academic Health Science Network (AHSN), we foresee the Trust will likely seek to prescribe gammaCore to potentially **24** new patients in the year 2021/22 for Cambridgeshire and Peterborough CCG alone (in line with NICE 2020/21 population given current population on treatment). Taking into consideration the historical prescribing practices detailed above, and the with an anticipated responder rate of 50% for new starters (with an average of 2 cards per year), we would anticipate **37** refill cards will be prescribed by Addenbrooke's Hospital in 2021/22.

## **5.3. NICE evaluation (MTG46)**

NICE's Medical Technologies Guidance (MTG46) states that in-year cost-saving can be realised by adopting gammaCore into routine clinical practice, realised through a decrease in use of both 'triptans and/or oxygen during acute attacks. There may also be potential for a reduction in outpatient appointments or telephone consultations, as a consequence of an improvement in prophylactic control. 'Cost modelling estimates that, in the first year of treatment, adding gammaCore to standard care is cost saving compared with standard care alone.

NICE provide the following impact statement 'Adding gammaCore to standard care treatment is deemed to not have a significant resource impact' as part of the guidance.

## 6. gammaCore Sapphire□

### 6.1. Product guide (NHS Supply Chain)

As of April 2021, Trust are being encouraged to procure gammaCore products through NHS Supply Chain<sup>21</sup>. The free of charge 93-day starter kits should be bought for patients who are prescribed gammaCore for the first time. 93-day refill cards for confirmed responders are then charged. Volume based discounts on gammaCore purchases made through NHS Supply Chain are available to prescribing NHS Trusts.

Supplier Product Code	Product Description	NHS Supply Chain Code	Purchasing guide
10016-10303V	SAMPLE 93 DAY STARTER KIT (ELE)	FMA1514	For all new patients initiating gammaCore therapy (one Sample per patient only)
10016-13193	93 DAY REFILL CARD KIT UK (ELE)	FMA1515	For patients confirmed as responders requiring a refill card for continued therapy
10016-10303	93 DAY STARTED KIT UK (ELE)	FMA1511	In the event the device needs replacing for a patient who is a confirmed responder
4000-00103	ELECTROLYTE GEL (ELE)	FMA1513	If patient requests any additional gel (consumable)

## 7. References

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