1358

Protocol to guide the assessment of vagus nerve stimulation therapy for patients with refractory epilepsy

September 2014

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MSAC and PASC

The Medical Services Advisory Committee (MSAC) is an independent expert committee appointed by the Australian Government's Minister for Health to strengthen the role of evidence in health financing decisions in Australia. MSAC advises the Minister on the evidence relating to the safety, effectiveness, and cost-effectiveness of new and existing medical technologies and procedures and under what circumstances public funding should be supported.

The Protocol Advisory Sub-Committee (PASC) is a standing sub-committee of MSAC. Its primary objective is the determination of protocols to guide clinical and economic assessments of medical interventions proposed for public funding.

Purpose of this document

This document is intended to provide a draft protocol that will be used to guide the assessment of an intervention for a particular population of patients. The draft protocol will be finalised after inviting relevant stakeholders to provide input. The final protocol will provide the basis for the assessment of the intervention.

The protocol guiding the assessment of the health intervention has been developed using the widely accepted "PICO" approach. The PICO approach involves a clear articulation of the following aspects of the research question that the assessment is intended to answer:

Patients – specification of the characteristics of the patients in whom the intervention is to be considered for use;
Intervention – specification of the proposed intervention
Comparator – specification of the therapy most likely to be replaced by the proposed intervention
Outcomes – specification of the health outcomes and the healthcare resources likely to be affected by the introduction of the proposed intervention

Purpose of application

In May 2013 Aurora BioScience Pty Ltd applied for Medicare funding of vagus nerve stimulation (VNS), an adjunctive therapy used to reduce the frequency of seizures in patients whose epileptic disorder is dominated by focal seizures or generalised seizures, which are refractory to antiepileptic medications.An original application for Medicare funding of VNS therapy for epilepsy was considered by MSAC in June 2008 (MSAC Assessment Report 1118, Department of Health and Ageing 2008). At this time MSAC found there was insufficient evidence of effectiveness and net benefit of VNS for patients with medically refractory epilepsy.The Medicare funding arrangement for VNS for epilepsy remained unchanged.

For the current application the applicant has provided a number of publications reporting the safety and effectiveness of VNS therapy, which have become available since the completion of MSAC Assessment Report 1118 (see Appendix A). In addition, two cost-effectiveness studies have been published (Bernstein & Hess 2007; Helmers et al. 2011). The applicant claims that this body of evidence of VNS therapy supports this resubmission.

Intervention

Description of the medical condition

Epilepsy is a disorder characterised by unprovoked recurrent seizures. It is a neurological state in which a region of the brain or the entire brain develops abnormal, hyper-synchronous neuronal discharges (Sander & Shorvon 1996). Due to technological and scientific advances in the understanding and treatment of epilepsy, the classification of epilepsies and seizures are constantly changing. Currently, epilepsy are classified as seizures of generalised (whole brain involved) onset, focal (or regional) onset or mix. The disorder can also be divided into primary epilepsy (due to genetic or inherited factors) and secondary epilepsy (due to outside aetiology such as trauma or tumours).

More than half of people with epilepsy have epilepsy with focal seizures, which can be subtle and unnoticed at onset, and which may be mistaken for such things as intoxication or daydreaming (Epilepsy Action Australia 2014, Kwan et al. 2010).

Whole brain seizures, also known as generalised seizures, are caused by abnormal neuro-electrical activities in both hemispheres of the brain simultaneously. Patients lose consciousness at the onset of the seizure and go into extensive spasms which may lead to trauma or brain tissue damage (Beyenburg, Stavem & Schmidt 2012). The generalised 'tonic clonic' seizure is the most recognised (Bagla & Skidmore 2011), manifested by body stiffness (tonic), shortly followed by jerking of the muscles (clonic). Breathing is shallow or temporarily suspended, causing lips and complexion to turn grey; saliva may come from the mouth; and there may be loss of bladder control (Epilepsy Action Australia 2014). Seizures can last two minutes or longer, followed by confusion, agitation, extreme tiredness, headache or soreness (National Health Service 2012).

Epilepsy has many known causes. Triggers for seizures could include alcohol drinking, emotional stress, head trauma and light stimulations. Secondary causes for epilepsy include stroke, tumours, metabolic problems or brain disorders such as Alzheimer's diseases. Many patients suffer from epilepsy due to inherited conditions (Sander & Shorvon 1996).

Description of the current treatment for epilepsy

For most patients, seizures are adequately controlled with anti-epileptic drugs (AEDs) (National Health Service 2012), which are classified according to chronological parameters or by their mechanisms of action. Generally, AEDs modulate voltage-gated ion channels of neurons to enhance synaptic inhibition or reduce synaptic excitations (Mula 2013). There are three generations of AEDs, and there are newly emerging drugs under trial (for example, NCT01281293).

Due to the neurological action of AEDs, side effects are common and occur with varying severity. Side effects upon the central nervous system include dizziness, headache, drowsiness, mood change and unsteadiness of gait. Other side effects include liver toxicity, rashes or suppression of the bone marrow, bone demineralisation, teratogenicity(Beyenburg, Stavem & Schmidt 2012). Normally, patients require AEDs for life; stopping or interrupting their administration may lead to recurrence of seizures, an increase in their severity, or other health problems (Epilepsy Action Australia 2014). Severe side effects due to drug toxicity or interaction with other medicationsmay, however, compel patients to adjust or even discontinue AEDs. In addition, approximately 30 per cent of epilepsy patients do not respond well to AEDs. This type of epilepsy is termed 'refractory epilepsy' and is difficult to treat. If a patient fails treatment with the principal AEDs used at appropriate doses for a reasonable period of time, the remaining therapy options include AED combinations, use of second- and third-line AEDs and trial of experimental AEDs. The International League Against Epilepsy (ILAE) has a consensus definition of drug-resistant epilepsy as 'failure of adequate trials of two tolerated and appropriately chosen and used AED schedules (whether as monotherapies or in combination) to achieve sustained seizure freedom'(Kwan et al. 2010). This definition is broadly adopted by most available guidelines, including the National Institute for Health and Care Excellence (NICE) (National Health Service 2012).Polytherapy regimens are often only marginally effective and are usually associated with more serious side effects. According to certain models approximately 35 per cent of patients either cannot tolerate any of the available AEDs or have recurrent seizures despite optimal medical therapy, usually involving multiple AEDs(Mohanraj & Brodie 2006).

In clinical practice, however, the actual number of trials of AEDs is higher than that recommended by guidelines. Clinical advice from the HESP suggests that patients would normally attempt at least five cycles of different AEDs, and possibly up to 10. Data shows that prior to the prescription of certain AEDs such as lacosamide which are considered later during drug therapy, patients would have tried at least three, and up to 12 different AEDs(Stephen et al. 2011).

PASC advised that the Protocol does not need to be explicit on the exact number of different AEDs trialled prior to considering VNS therapy.

Surgery is one of the treatment options for patients who are refractory to treatment with AEDs, if this can be undertaken without significant risk (Miller & Hakimian 2013; National Health Service 2004).Epileptic surgeries include surgeries which involve the removal or disconnection of the brain tissue causing the abnormality(Georgiadis, Kapsalaki & Fountas 2013). Resective surgery for treatment of epilepsy is indicated in only patients where a discrete focus for the seizures can be identified and then accessed during surgery. In these patients surgery can result in seizure freedom. Not all patients have a discrete and accessible focal lesion and therefore these patients are not considered as surgical candidates. Moreover, resective surgery is not always successful, even when repeated after initial failure (Jehi 2010 and Germano 1994). There are also general contraindications for any elective surgical procedures that need to be considered, these are not specific to resective surgery.

An epilepsy-free status is the main motivation for eligible candidates to undergo surgery. In surgically curable patients, it is suggested that surgery should be considered as an early treatment option, even prior to the use AEDs (Duncan 2007). The applicant provided a number of reasons for a patient to be deemed unsuitable for epilepsy surgery including inability to localise seizures; multifocal or generalised seizures; lack of an epileptogenic lesion (i.e. non-lesional); involvement of critical cortex; risks of surgery outweigh the benefits. The decision regarding eligibility for surgery involves a range of tests. Tests include electroencephalography (EEG), nuclear magnetic resonance imaging (MRI) and positionemission tomography (PET)(Kwan et al. 2010). The tests are used to identify the region of the brain which causes the seizure and evaluate whether the excision will interfere with normal brain functions.

Clinical advice from the HESP has advised that the ketogenic diet, as an adjunctive therapy, is currently used in certain patients. However, due to its highly restricted and unpalatable nature, it is unlikely to be effective in adult patients. Currently this adjunctive therapy is practised only in the paediatric setting.

Description of the proposed intervention

Vagus Nerve Stimulation (VNS® Therapy) Therapy is an adjunctive non-pharmacologic treatment for patients with drug-resistant partial or generalised epilepsy, manufactured by Cyberonics Inc. The VNS pulse generator is an implantable, programmable pacemaker-like device. It is housed in a hermetically sealed titanium case and is powered by a single battery. A lead is attached to the left vagus nerve in the neck through a percutaneous approach. Electrical signals are transmitted from the pulse generator to the vagus nerve via the lead, which delivers precisely timed and measured electrical stimulation to the left vagus nerve. Using an external programming system (hand-held computer, software and wand), neurologists can adjust the timing and amount of stimulation the patient receives.

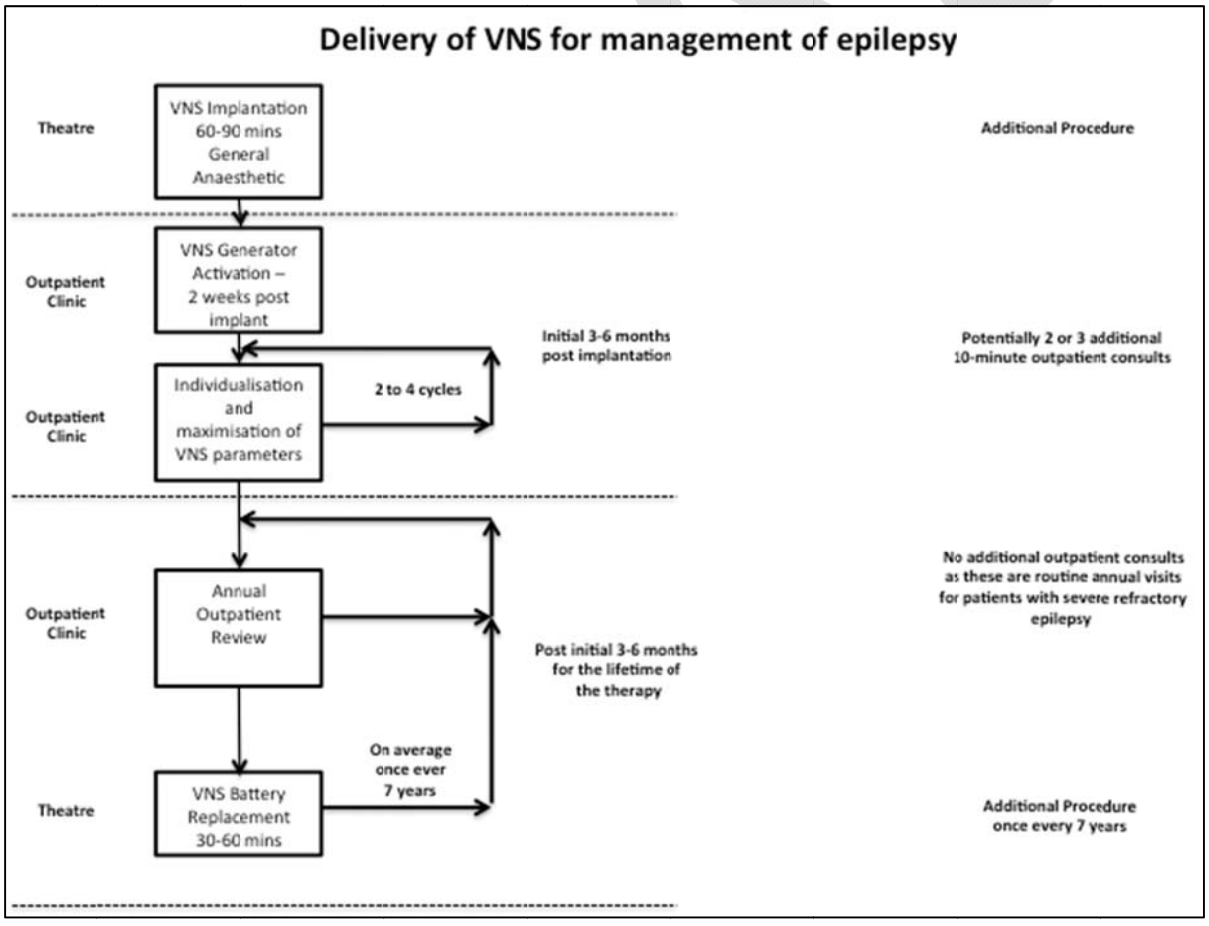
Administration, dose, frequency of administration, duration of treatment

The applicant has advised that all patients with refractory epilepsy have by the time of consideration for VNS therapy been referred to a neurologist specialising in epilepsy at a comprehensive epilepsy centre at a major tertiary hospital. In addition, the patient would have received all necessary tests,

including but not limited to EEG, seizure monitoring, MRI or PET, and investigations to confirm their eligibility for surgery. Once the patient is considered eligible for VNS therapy, there will be no additional investigations prior to receiving the VNS therapy device and its leads. Generally, only neurosurgeons (or rarely, ENT or vascular surgeons) with necessary experience will perform the implantation procedure.

The pulse generator is implanted below the clavicle in a subcutaneous pocket in the left upper chest. The lead is attached to the left vagus nerve half-way between the clavicle and the mastoid process, with the lead subcutaneously tunnelled between the incision site in the neck and the pocket formed in the upper chest. The pulse generator and lead are implanted at the same time.The procedure is provided under general anaesthesia and takes approximately 60 to 90 minutes. The surgery is performed as a day case or with an overnight stay, in either a public or private hospital.The implanted device is tested at the end of the implantation procedure to ensure full compliance and functionality. The delivery of VNS therapy for the management of epilepsy is illustrated in Figure 1.

Figure 1 Delivery of VNS therapy for management of epilepsy



The applicant stated that the patient would have a post-implant follow-up with the neurosurgeon within 7 to 14 days for wound assessment. The neurologist would then take over patient management.

At two weeks following implantation the pulse generator is activated, and device parameters are adjusted using an external computer and a programming wand to maximise patient outcomes.Parameters that can be adjusted include output current (0-3.5mA), signal frequency (20/30Hz), pulse width (250/500μsecs), signal-on time (14-30seconds), signal-off time (0.5-5minutes) and magnet settings.Patients receive a small discharge of current in the range of 1.5 to 2.5 mA once every 1.8 to 5 minutes for a 30 second period. This is continual. Magnet settings are used by the patient for self-management of oncoming seizures and are 0.25 mA higher than the routine setting. Patients can use the magnet to activate additional stimulation to arrest or minimise an oncoming seizure.

Individualisation of VNS therapy will take place after the activation of the pulse generator. This will occur in the initial three to six months after surgery, with approximately two to four 10 to 15 minutes meetings to finalise the parameters. The exact timing and number of cycles of these visits would be patient-dependant based upon the severity of their condition. In the paediatric setting patient reviews may be more frequent, especially in the early stage after the implantation.

Currently it is recommended that patients have 6- to 12-monthly check-ups. It is anticipated that this would be undertaken as part of the patient's routine outpatient review with their regular neurologist. At this visit, their VNS therapy would be analysed and its programming optimised based on seizure reduction rates. HESP members indicated that the regular check-ups may be more frequent than 6 to 12 monthly.

The applicant claims that device monitoring and re-programming is relatively simple. Trainingcan be provided as needed, including through the use of online resources.

All patients receiving VNS therapy will remain on their current AEDs. About 5-10% of patients are deemed seizure free after the implantation of a VNS Therapy device. Some of these patients may withdraw medication.The decision to continue or withdraw medication should be taken by the patient (child, young person, adult, family and/or carer as appropriate) and the specialist after a full discussion of the risks and benefits of withdrawal. At the end of the discussion there should be clear understanding of their risk of seizure recurrence on and off medications. This discussion should take account of the child, young person or adult's epilepsy syndrome, prognosis and lifestyle. For the sake of this review it would be appropriate to assume there is no significant change in patients AEDs after implantation of the VNS device.

The battery/generator of current devices requires changing approximately once every seven years, although this may vary depending on stimulation parameters. Replacement requires an exchange of the entire battery/generator in a theatre.

The applicant noted that while implantation would need to be carried out at Comprehensive Epilepsy Centres, once the device was activated and parameters maximised, satellite outpatient clinics may be suitable for annual reviews on an as needed basis if the patient numbers were suitable. Rural equity of access is potentially achieved once the device is activated and delivering benefit. The reduced

likelihood of rural patients needing to access specialist medical care in a major hospital should helpkeeprural patients and the families at home rather than in a major capital city."

Co-administered interventions

VNS therapy is proposed as an adjunctive intervention for patients with epilepsy who in the expert opinion of their treating neurologist have been evaluated for all appropriate AEDs and other treatment options including resective surgery. The applicant recommended that the dosage of AEDs should not be changed in the initial 12–24 months after receiving the VNS therapy. In some successful cases, AED dosage maybe reduced over time. The PBS lists all currently available AEDs by categorising them into seven groups based on their chemical origins. There are 18 publicly funded drugs available (Appendix F).

The applicant stated that a patient who is eligible for VNS therapy would already have received the necessary tests (e.g. MRI, EEG and seizure monitoring) to determine if the patient is a potential candidate for epilepsy surgery.

Background

Current arrangements for public reimbursement

There are currently no MBS items for VNS therapy.

Three MBS items are available surgeries for epilepsy (see Table 1).MBS items 40700, 40703 and 40706 represent surgical resections or disconnections of brain lesions.

Table 1: Current MBS items for surgeries for epilepsy

Category 3 - THERAPEUTIC PROCEDURES
40700 CORPUS CALLOSUM, anterior section of, for epilepsy Multiple Services Rule (Anaes.) (Assist.) Fee: $1,744.65 Benefit: 75% = $1,308.50
Category 3 - THERAPEUTIC PROCEDURES
40703 CORTICECTOMY, TOPECTOMY or PARTIAL LOBECTOMY for epilepsy Multiple Services Rule (Anaes.) (Assist.) Fee: $1,466.30 Benefit: 75% = $1,099.75
Category 3 - THERAPEUTIC PROCEDURES
40706 HEMISPHERECTOMY for intractable epilepsy Multiple Services Rule (Anaes.) (Assist.) Fee: $2,143.10 Benefit: 75% = $1,607.35 85% = $2,066.90

There are five MBS items related to neurostimulator implantation for chronic intractable neuropathic pain or pain from refractory angina pectoris, numbered from 39134 to 39138 (see Appendix B). Among MBS items for chronic intractable neuropathic pain or pain from refractory angina pectoris, there are two items, numbered 39134 and 39135, which relate to implantation and removal of the neurostimulator. The rest of the items, numbered 39136, 39137 and 39138, are for insertion, reversion and removal of the leads.

These five items have been identified by the applicant as being the most relevant to the proposed VNS therapies as the implantation process is targeted at specific peripheral nerves. The time, complexity and costs of these services are suggested as being comparable to the proposed services.

The applicant also provided five MBS items related to deep brain stimulation as a further comparison (MBS items 40852 to 40862, Appendix C). Specifically, MBS item 40862(neurostimulator analysis and programming) was proposed by the applicant as being relevant for VNS therapy system analysis and programming.

Current use of VNS therapy in Australia

The applicant states that Vagus Nerve Stimulation (VNS® Therapy) Therapy is currently managed by expert neurologists in 12 specialised epilepsy treatment centres across the country.

According to the applicant, 24 patients were implanted with a VNS therapy device and 10 patients received battery replacement in Australia during 2012. It is claimed that over 300 patients in Australia have received VNS therapy implantation. The applicant said that the average implantation rate in developed countries (excluding the USA) was between five and six units per one million people, based on a population of 70,000 people that have received VNS worldwide. The rate has been consistent over several years. The applicant expected that in Australia 1.3 patients per million per year, or 30 patients per year,would currently receive VNS therapy for epilepsy. The total population estimated in the previous MSAC Assessment Report 1118 was 30 (range of 30 to 75) patients per year (Department of Health and Ageing 2008).

Currently, VNS devices implanted in Australia have been funded through public hospital funds, private health insurance or patients' payment.

The applicant provided a list of clinical centres implanting VNS therapy in Australia: there are five centres in Victoria, four in Queensland, two in Western Australia and one each in New South Wales (POW Adults and Sydney Children's), South Australia and Tasmania.

Regulatory status

The electric pulse generator and associated leads of the VNS therapy, distributed by Aurora Bioscience Pty Ltd, are approved by the TGA and are already listed on the Prosthesis List. The pulse generator is listed at $12,670.00 and the leads at $3,400.00. HESP confirmed that the device for follow-up programming VNS therapy pulse generator will be provided to neurologists by the manufacture at no cost, where only one programming wand is needed for all patients.Further information regarding VNS therapy devices on the TGA and Prosthesis List, including leads and accessories, is provided in Appendices D and E.

The ARTG-approved intended purpose is: "The VNS Therapy System is indicated for use as an adjunctive therapy in reducing the frequency of seizures in patients whose epileptic disorder is dominated by partial seizures (with or without secondary generalization) or generalized seizures that are refractory to antiepileptic medications".

No other devices or therapies comparable to VNS therapy are available.

PASC suggested that the delivery of VNS therapy should be restricted to neurosurgeons and neurologists with extensive experience and that surgeries be performed only at specialised epilepsy centres.

Patient population

The population is patients with epilepsy who are refractory to AEDs, suffering ongoing severe and frequent seizures, and unsuitable for or having failed surgery. The population would include all ages, including children.

In detail, an eligible patient should be:

1. Under neurologists' care at a comprehensive epilepsy centre at a major tertiary hospital.
2. On maximal tolerated medical management with AED(s) and managed by a specialist epileptologist who is aware of ongoing medical needs.
3. Suffering from ongoing high seizure burden (frequency and occurrence).
4. Already worked up for potential epilepsy surgery (including but not limited to EEG, seizure monitoring and MRI) and aware of previous surgical history.
5. Either:
    a) Unsuitable for epilepsy surgery;
    b) experiencing burdensome seizures despite prior epilepsy surgery.

Clinical advice from the HESP suggested that there are little differences between adult and paediatric settings in terms of VNS therapy. The implanted lead is long enough to allow for growth; therefore ongoing care for children is the same as for adults and mainly involves regular maintenance and battery change.Paediatric patients are often the best candidates for VNS therapy.

The applicant provided certain contraindications and limitations for VNS therapy. VNS therapy should not be used for patients who have received bilateral or left cervical vagotomy.Shortwave diathermy, microwave diathermy or therapeutic ultrasound diathermy should not be used on patients implanted with a VNS Therapy System,however routine Surgical Diathermy (monopolar and bipolar) requires some precautions but can be used on patients implanted with a VNS Therapy System. MRI scans should be performed with caution and under specific therapy settings. Safety issues on pregnant women such as potential interactions between VNS therapy devices and foetal monitoring systems are not well studied and reported.

Proposed MBS listing

The applicant suggested that the proposed MBS items for VNS therapy for the treatment of epilepsy could be aligned with the current neurostimulators implantation and its associated items (items 39134 to 39138, Appendix B). This range of MBS items includes separate services for implantation of stimulation devices and their leads as well as maintenance, repositioning and removal of the device. The applicant also provided the MBS items of deep brain stimulation for the treatment of Parkinson's disease as a further comparison. Particularly, MBS item 40862 for neurostimulator analysis and programming was proposed to be relevant for the VNS device analysis and programming. PASC agreed that new MBS items should be proposed new items rather than making amendments on any current MBS items. The proposed new MBS items are listed below:

Table 2: Proposed MBS item descriptor for VNS therapy

Category 3 - THERAPEUTIC PROCEDURES
XXXX1 ELECTRICAL PULSE GENERATOR, subcutaneous placement of for the management of refractory generalised epilepsy, or treating refractory focal epilepsy that is not suitable for epilepsy surgery Multiple Services Rule (Anaes.) (Assist.) Fee: $340.60 Benefit: 75% = $255.45

Category 3 - THERAPEUTIC PROCEDURES
XXXX2 ELECTRICAL PULSE GENERATOR, that was inserted for the management of refractory generalised epilepsy, or treating refractory focal epilepsy that is not suitable for epilepsy surgery, removal of, performed in the operating theatre of a hospital Multiple Services Rule (Anaes.) Fee: $159.40 Benefit: 75% = $119.55

Category 3 - THERAPEUTIC PROCEDURES
XXXX3 LEAD, surgical placement of, including intraoperative test stimulation, for the management of refractory generalised epilepsy, or treating refractory focal epilepsy that is not suitable for epilepsy surgery Multiple Services Rule (Anaes.) (Assist.) Fee: $674.15 Benefit: 75% = $505.65

Category 3 - THERAPEUTIC PROCEDURES
XXXX4 LEAD, that was inserted for the management of refractory generalised epilepsy, or treating refractory focal epilepsy that is not suitable for epilepsy surgery, surgical repositioning or removal of, performed in the operating theatre of a hospital Multiple Services Rule (Anaes.) Fee: $605.35 Benefit: 75% = $454.05

Category 3 - THERAPEUTIC PROCEDURES
XXXX5 ELECTRICAL PULSE GENERATOR, electrical analysis and programming of, for the management of refractory generalised epilepsy, or treating refractory focal epilepsy that is not suitable for epilepsy surgery. Fee: $189.70Benefit:75% = $142.58

Clinical place for proposed intervention

VNS therapy is indicated for use as an adjunctive therapy in reducing the frequency of seizures in patients with epilepsy who are refractory to antiepileptic medications and who are not suitable for epilepsy surgeries. This would include patients with epilepsy with both focal and generalised seizure. The use of VNS therapy would be a later-line treatment when all other conventional treatment options are exhausted and remain marginally effective, ineffective, non-feasible and/or with severe complications and adverse events. The decision to use VNS therapy will be made by reviewing patients' medication history and its effectiveness, as well as whether patients are suitable for surgical interventions. Factors and criteria which may lead to the use of VNS therapy may include:

- Failed treatment with the principle AEDs used in an appropriate doses for a reasonable period of time;
- Failed treatment with appropriately selected AEDs (polytherapy); second- or later-line AEDs;
- Being unsuitable for epilepsy surgery.

In those refractory patients who are not considered candidates for epilepsy surgery there is currently no other treatment available to help reduce the seizure burden for these patients. It is this subgroup of patients where VNS therapy is proposed for use – for patients with ongoing seizure activity despite maximal medical treatment and where epilepsy neurosurgery is not suitable.

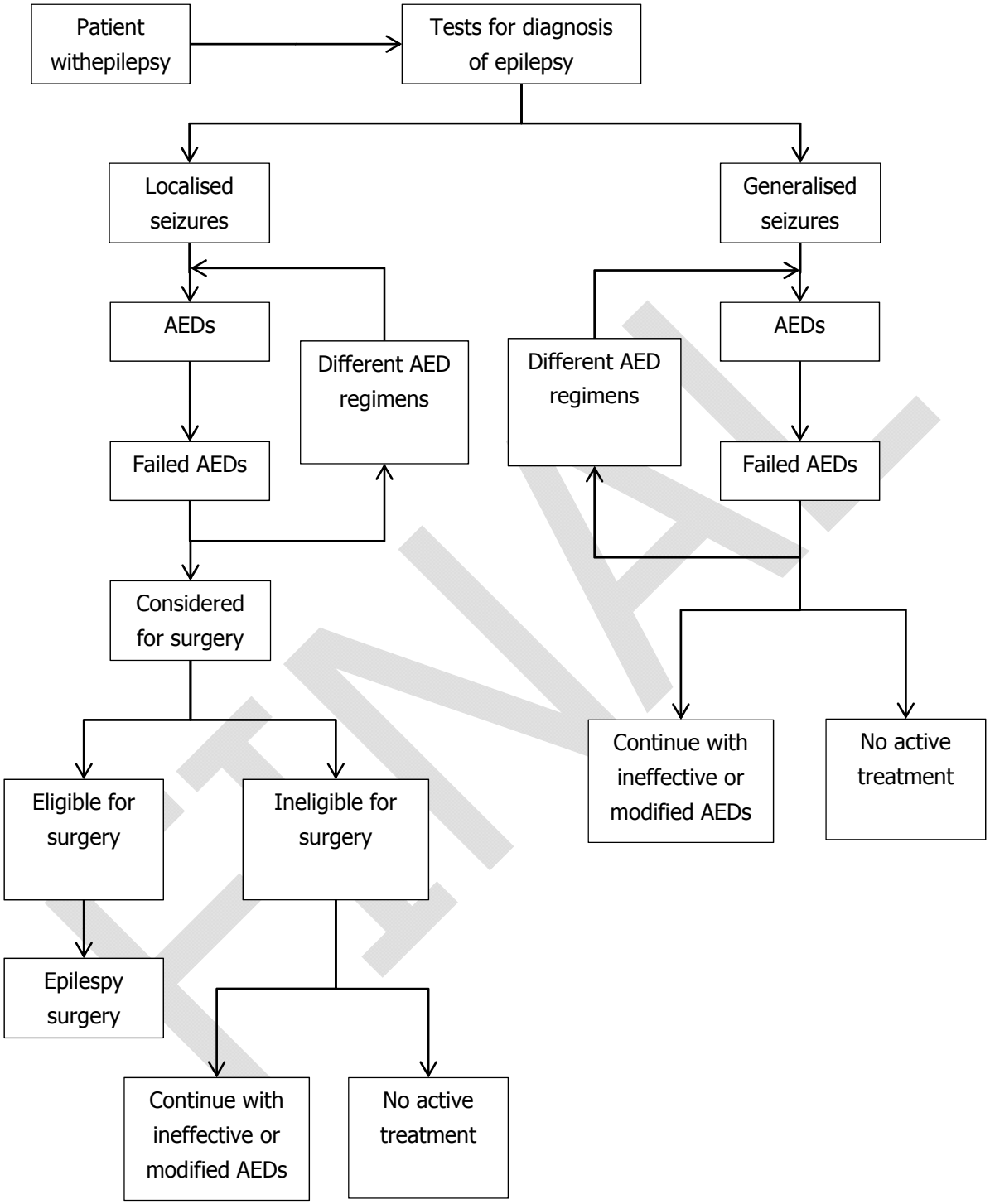
The clinical management algorithms are created based on the applicant's proposal (Figure 2 and Figure 3).The applicant also provided an algorithm of epilepsy management with and without VNS therapy, with clinical outcomes (Appendix G).

In regard to the definition of the failure of AEDs, only nine per cent of patients with three or more AEDs become seizure free, 91 per cent still have uncontrolled seizures and refractory epilepsy. According to this model, 35 per cent of patients with epilepsy will be categorised as having refractory or difficult-to-treat epilepsy (Mohanraj & Brodie 2006). The applicant's estimation of proportions of refractory epilepsy is attached in Appendix G. Clinical advice from the HESP has suggested that these models do not accurately reflect clinical practice in Australiaand are likely to overestimate the patients refractory to AEDs and those eligible for VNS. A detailed estimation of the eligible population in Australia should be undertaken at the assessment phase, using local data and clinical expert advice.

According to the Australian Institute of Health and Welfare (AIHW) in financial year 2009-10 there were 15,826 separations for the diagnosis of epilepsy (ICD-10, G40). Of these, 1,967 were localisation-related (focal/partial) epilepsy (G40.0, G40.1, G40.2), and 5,343 were generalised and

other generalised epileptic syndromes (G40.3, G40.4) (AIHW 2009). Public hospital data is not available for the number of neurosurgical procedures provided for patients with epilepsy.

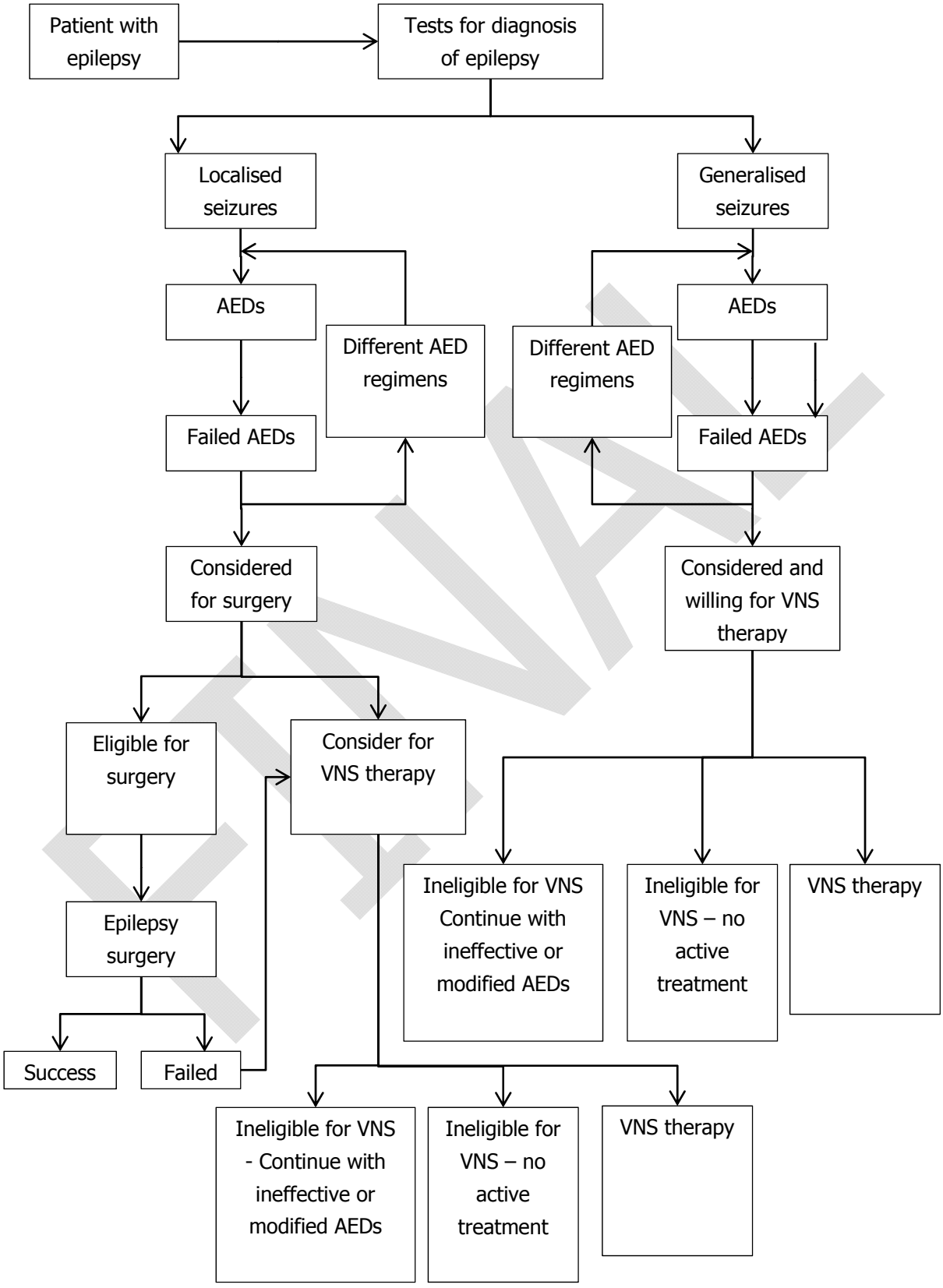
Figure 2 Current clinical pathway for the treatment of patients with epilepsy



Note: AEDs: anti-epileptic drugs

Different AED regimens = in the expert opinion of their treating neurologist, patients have been evaluated for all appropriate AEDs

Figure 3 Proposed clinical pathway for the treatment of patients with epilepsy



Note: AEDs=anti-epileptic drugs; VNS=vagus nerve stimulation; Different AED regimens = in the expert opinion of their treating neurologist, patients have been evaluated for all appropriateAEDs.

The proposed pathway includes the VNS therapy as the treatment option for refractory patients when all other treatment options remain ineffective. As specified in the application, patients with refractory epilepsy, even if receiving VNS therapy as the adjunctive treatment, will be mostly like to continue using AEDs.

Comparator

The comparator is "no active intervention" based on the applicant's proposal. All patients will remain on current AEDs.

The applicant stated that "currently there is no effective treatment option for patients who suffer from drug-resistant epilepsy and who have limited tolerance to AEDs". Surgical treatment for epilepsy will be considered prior to VNS therapy, therefore is not a comparator. Patients will not be eligible for VNS unless they have been considered for epileptic surgery. Though there should be no requirement for the clinical studies of VNS included in the submission to MSAC to have specifically included this information.

This is in line with MSAC Application 1118.

Clinical claim

VNS is an adjunctive non-pharmacologic treatment for patients with drug-resistant focal or generalised epilepsy which can improve seizure control and quality-of-life for patients with epilepsy. VNS therapy results in a decrease in both the rate and severity of seizure for patients where no other therapy is available. VNS therapy will achieve an epilepsy-free status in approximately 5% of patients.

The applicant acknowledged that there are few clinical trials solely in the population of patients who are refractory to AEDs and for whom intracranial surgery is either unsuitable or has been unsuccessful. Clinical trials nominated by the applicant have demonstrated that post-implantation, seizure frequency was reduced by an average of 45 per cent, with a 36 per cent reduction in seizures at 3–12 months post-surgery and a 51 per cent reduction after more than 1 year of therapy. At the last follow-up, seizures were reduced by 50 per cent or more in approximately half of all patients (Englot, Chang & Auguste 2011). Similar efficacy is seen in patients with either focal or generalised seizures. Patients with generalised epilepsy and children benefited to a greater extent.

Other issues suggested by the applicant include:

- Effectiveness is seen in more difficult to control seizure types such as drop attacks or Lennox Gastaut syndrome.
- VNS therapy is not typically associated with the common systemic and neurological side effects of AEDs such as drowsiness, lethargy, weight gain and cognitive impairment. Rather, studies have shown that VNS therapy is associated with increased alertness, reduced daytime sleepiness, improved mood and improved memory.
- VNS therapy is well tolerated and associated with quality-of-life benefits.

- Continuation rates with VNS therapy are high. 97 per cent of patients continue with VNS therapy at one year, and approximately 75 per cent at three years. These rates are much higher than typically observed with AEDs.
- The effectiveness of VNS therapy does not diminish over time. In clinical studies, seizure control and quality-of-life benefits with VNS therapy have been shown to increase over time. Furthermore, over time some patients are able to reduce the dosage or number of AEDs.

In addition to MSAC Assessment Report 1118 there have been other high level reports and guidance on VNS for epilepsy. A Cochrane systematic review concluded that VNS therapy for focal seizures appears to be an effective and well tolerated treatment (Privitera et al. 2002). NICE has published two guidelines on VNS therapy regarding epilepsy treatment. The NICE guideline published in 2012 recommended that VNS can be an effective adjunctive therapy for patients refractory to AEDs (National Health Service 2012). A NICE guideline specifically on children with epilepsy is also available and states that current evidence on the safety and efficacy of VNS therapy appeared adequate to support the use of this procedure (National Health Service 2004). In addition, two guidelines published by the National Guideline Clearinghouse stated that VNS therapy may be considered for epilepsy patients, although the optimal settings of VNS therapy remain uncertain(National Guideline Clearinghouse 2012a, 2012b).

The applicant confirmed that VNS therapy is superior in terms of safety and effectiveness. For the economic evaluation, a cost-effectiveness or a cost-utility analysis should be conducted (Table 3). The latter is the most appropriate because there is limited evidence that a decrease in seizure frequency of around 50% (as the primary outcome of several studies including those mentioned by the applicant) is associated with an improvement in quality of life (because it is also about the severity of seizure).

Given the cost of changing batteries/generators (and its likely impact on the findings of economic evaluation), the stated replacement rate—about once every seven years, depending on stimulation parameters—should be firmly supported with appropriate sensitivity analyses.

Table 3: Classification of an intervention for determination of economic evaluation to be presented

<table>
<tr><td colspan="2" rowspan="2"></td><td colspan="4">Comparative effectiveness versus comparator</td></tr>
<tr><td colspan="2">Superior</td><td>Non-inferior</td><td colspan="2">Inferior</td></tr>
<tr><td rowspan="5">Comparative safety versus comparator</td><td rowspan="3">Superior</td><td colspan="2" rowspan="3">CEA/CUA</td><td rowspan="3">CEA/CUA</td><td>Net clinical benefit</td><td>CEA/CUA</td></tr>
<tr><td>Neutral benefit</td><td>CEA/CUA*</td></tr>
<tr><td>Net harms</td><td>None^</td></tr>
<tr><td>Non-inferior</td><td colspan="2">CEA/CUA</td><td>CEA/CUA*</td><td colspan="2">None^</td></tr>
<tr><td rowspan="3">Inferior</td><td>Net clinical benefit</td><td>CEA/CUA</td><td rowspan="3">None^</td><td colspan="2" rowspan="3">None^</td></tr>
<tr><td>Neutral benefit</td><td>CEA/CUA*</td></tr>
<tr><td>Net harms</td><td>None^</td></tr>
</table>

Abbreviations: CEA = cost-effectiveness analysis; CUA = cost-utility analysis

* May be reduced to cost-minimisation analysis. Cost-minimisation analysis should only be presented when the proposed service has been indisputably demonstrated to be no worse than its main comparator(s) in terms of both effectiveness and safety, so the difference between the service and the appropriate comparator can be reduced to a comparison of costs. In most cases, there will be some uncertainty around such a conclusion (i.e., the conclusion is often not indisputable). Therefore, when an assessment concludes that an intervention was no worse than a comparator, an assessment of the uncertainty around this conclusion should be provided by presentation of cost-effectiveness and/or cost-utility analyses.

^ No economic evaluation needs to be presented; MSAC is unlikely to recommend government subsidy of this intervention

Outcomes and health care resources affected by introduction of proposed intervention

Outcomes

Effectiveness outcomes to be measured include:

Primary effectiveness:

- Seizure onset frequency;
- Seizure duration / severity ; and
- Health related quality of life.

Secondary effectiveness:

- Outpatient visits, hospitalisation and length of stay due to epilepsy;
- Seizure related injuries and trauma;

Safety:

- Adverse events due to implantation of device;
    - Infection;
    - Cough;
    - Dyspnoea;
    - Pharyngitis;
    - Voice alteration;
    - Sleep apnoea (new onset);
    - Interference with medical imaging diagnostics; and
    - Lead or device repositioning.

Health care resources

The health care resources used in VNS therapy will include the implantation procedure, the cost of VNS devices including the pulse generator and the leads, and associated cost from any follow-up appointments and adjustment of the device.

Specific resources include:

- General anaesthesia and surgical time for one off implantation of the device;
- 4-6 additional outpatient clinic visits to allow for the initial programming of the VNS parameters;
- General anaesthetic and surgical time for routine battery change (approximately once every 7 years);
- Emergency department presentations as a result of seizures;

- Hospital inpatient episodes as a result of seizures;
- Dosage of AEDs;
- The VNS generator and leads;
- The VNS programming device is provided by the manufacturer at no cost;
- The proportion of patients receiving VNS as a day patient or with overnight stay;
- All relevant tests required to determine eligibility for VNS would have already been undertaken as part of the consideration of the patient as a candidate for epilepsy surgery.

Table 4: List of resources to be considered in the economic analysis

	Provider of resource	Setting in which resource is provided	Number of units of resource per relevant time horizon per patient receiving resource	Source of information of number of units*
Resources provided to identify the eligible population that would vary from current clinical practice (from Step 2, e.g., diagnostic and other investigative medical services, prior therapeutic interventions). *Identify variations where these may vary across different decision options.*				
-				
No extra cost as patient work up already undertaken during the diagnosis and assessment of their epilepsy. No additional EEG or other tests. No extra MRI or CTs. (Relevant MBS items include 11000 to 11006). Clinicians would have already had programming devices provided by the manufacture at no cost.				
Resources provided in association with the proposed medical service to deliver the proposed intervention (from Step 1, e.g., pre-treatments, co-administered interventions). *Identify variations where these may vary across different decision options.*				
- Anaesthetic review	Anaesthetist	Outpatient clinic	1 per life time	Current practice/ clinicians
- Consultation with neurosurgeons	Neurosurgeon	Outpatient clinic	1 per life time	Current practice/ clinicians
- Implantation	Surgeon/ Anaesthetics	Hospital	1 per life time	Current practice/ clinicians
- Setting of VNS parameters for individual patients	Neurologist	Outpatient clinics	3-6 additional visits in first year following implantation	Current practice/ clinicians
- Emergency department presentations	Hospital	Emergency department	Variable	
- Inpatient admissions	Hospital	Inpatient	Variable per year and variable length of stay	
- AEDs				
Resources provided to deliver the comparator to deliver the current intervention (from Step 4, e.g., pre-treatments, co-administered interventions). *Identify variations where there may be more than one comparator or where these may vary across different decision options.*				
- Annual review	Neurologist	Outpatient clinic	1-2 per year	Current practice/ clinicians
- Emergency department presentations	Hospital	Emergency department	Variable	
- Inpatient admissions	Hospital	Inpatient	Variable per year and variable length of stay	
- AEDs				

Proposed structure of economic evaluation (decision-analytic)

The PICO table is summarised in Table 5.

Table 5: Summary of extended PICO to define research question that assessment will investigate

Patients	Intervention	Comparator	Outcomes to be assessed	Healthcare resources to be considered
Patients with epilepsy who are refractory to AEDs, suffer from ongoing severe and frequent seizures, and are unsuitable for or have failed epilepsy surgery.	VNS therapy, with continued AEDs	No active intervention (Patients remain on current AEDs)	Primary effectiveness: • Seizure onset frequency and duration; • Health related quality of life; Secondary effectiveness: • Seizure related injuries and trauma; • Hospitalisation and emergency department presence;	•General anaesthesia and surgical time for one off implantation of the device •2-4 additional outpatient clinic visits to allow for the initial programming of the VNS parameters •General anaesthetic and surgical time for routine battery change - approximately once every 7 years •Emergency department presentations as a result of seizures •Hospital inpatient episodes as a result of seizures •Dosage of AEDs

Primary questions for public funding

Is VNS therapy and continued optimum AEDs a safe, effective and cost-effective intervention for patients with epilepsy with generalised and focal seizures who are refractory to conventional treatment?

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Appendix A

Supporting evidence published since MSAC Application 1118, provided by the applicant:

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Appendix B

MBS items associated with the implantation, adjustment and removal of neurostimulators and leads for chronic intractable neuropathic pain or pain from refractory angina pectoris.

Category 3 - THERAPEUTIC PROCEDURES
39134 NEUROSTIMULATOR or RECEIVER, subcutaneous placement of, including placement and connection of extension wires to epidural or peripheral nerve electrodes, for the management of chronic intractable neuropathic pain or pain from refractory angina pectoris Multiple Services Rule (Anaes.) (Assist.) Fee: $340.60 Benefit: 75% = $255.45

Category 3 - THERAPEUTIC PROCEDURES
39135 NEUROSTIMULATOR or RECEIVER, that was inserted for the management of chronic intractable neuropathic pain or pain from refractory angina pectoris, removal of, performed in the operating theatre of a hospital Multiple Services Rule (Anaes.) Fee: $159.40 Benefit: 75% = $119.55 85% = $135.50

Category 3 - THERAPEUTIC PROCEDURES
39136 LEAD, epidural or peripheral nerve that was inserted for the management of chronic intractable neuropathic pain or pain from refractory angina pectoris, removal of, performed in the operating theatre of a hospital Multiple Services Rule (Anaes.) Fee: $159.40 Benefit: 75% = $119.55

Category 3 - THERAPEUTIC PROCEDURES
39137 LEAD, epidural or peripheral nerve that was inserted for the management of chronic intractable neuropathic pain or pain from refractory angina pectoris, surgical repositioning to correct displacement or unsatisfactory positioning, including intraoperative test stimulation, not being a service to which item 39130, 39138 or 39139 applies Multiple Services Rule (Anaes.) Fee: $605.35 Benefit: 75% = $454.05

Category 3 - THERAPEUTIC PROCEDURES
39138 PERIPHERAL NERVE LEAD, surgical placement of, including intraoperative test stimulation, for the management of chronic intractable neuropathic pain or pain from refractory angina pectoris, to a maximum of 4 leads Multiple Services Rule (Anaes.) (Assist.) Fee: $674.15 Benefit: 75% = $505.65

Appendix C

MBS items associated with the implantation, adjustment and removal of deep brain stimulation neurostimulators for Parkinson's disease, essential tremor or dystonia.

Category 3 - THERAPEUTIC PROCEDURES
40852 DEEP BRAIN STIMULATION (unilateral) subcutaneous placement of neurostimulator receiver or pulse generator for the treatment of: Parkinson's disease where the patient's response to medical therapy is not sustained and is accompanied by unacceptable motor fluctuations; or Essential tremor or dystonia where the patient's symptoms cause severe disability. Multiple Services Rule (Anaes.) (Assist.) Fee: $340.60 Benefit: 75% = $255.45

Category 3 - THERAPEUTIC PROCEDURES
40854 DEEP BRAIN STIMULATION (unilateral) revision or removal of brain electrode for the treatment of: Parkinson's disease where the patient's response to medical therapy is not sustained and is accompanied by unacceptable motor fluctuations; or Essential tremor or dystonia where the patient's symptoms cause severe disability. Multiple Services Rule (Anaes.) Fee: $526.40 Benefit: 75% = $394.80

Category 3 - THERAPEUTIC PROCEDURES
40856 DEEP BRAIN STIMULATION (unilateral) removal or replacement of neurostimulator receiver or pulse generator for the treatment of: Parkinson's disease where the patient's response to medical therapy is not sustained and is accompanied by unacceptable motor fluctuations; or Essential tremor or dystonia where the patient's symptoms cause severe disability. Multiple Services Rule (Anaes.) Fee: $255.45 Benefit: 75% = $191.60

Category 3 - THERAPEUTIC PROCEDURES
40860 DEEP BRAIN STIMULATION (unilateral) target localisation incorporating anatomical and physiological techniques, including intra-operative clinical evaluation, for the insertion of a single neurostimulation wire for the treatment of: Parkinson's disease where the patient's response to medical therapy is not sustained and is accompanied by unacceptable motor fluctuations; or Essential tremor or dystonia where the patient's symptoms cause severe disability. Multiple Services Rule (Anaes.) Fee: $2,022.70 Benefit: 75% = $1,517.05

Category 3 - THERAPEUTIC PROCEDURES
40862 DEEP BRAIN STIMULATION (unilateral) electronic analysis and programming of neurostimulator pulse generator for the treatment of: Parkinson's disease where the patient's response to medical therapy is not sustained and is accompanied by unacceptable motor fluctuations; or Essential tremor or dystonia where the patient's symptoms cause severe disability. Multiple Services Rule (Anaes.) Fee: $189.70 Benefit: 75% = $142.30 85% = $161.25

Appendix D

TGA approved VNS devices and leads with ARTG codes

Neurostimulators

- Class AIMD - 131044 - VNS Therapy Pulse Generator Model 102 - Stimulator, electrical, vagus nerve, antiseizure
- Class AIMD – 131045 - VNS Therapy Pulse Generator Model 102R (Replacement) - Stimulator, electrical, vagus nerve, antiseizure
- Class AIMD - 168817 - VNS Therapy DemiPulse Generator Model 103 - Stimulator, electrical, vagus nerve, antiseizure
- Class AIMD - 169837 - VNS Therapy DemiPulse Generator Model 104 (Replacement) - Stimulator, electrical, vagus nerve, antiseizure

Leads

- A single electrical lead that transmits stimulation from the Vagus Nerve Stimulation (VNS® Therapy) Therapy Generator to the left vagus nerve in the patient's neck.
- Class III – 131047 – VNS Therapy Lead Model 302.2 / 302.3 - Electrode/lead, stimulator, implantable, neurological
- Class III – 192080 – VNS Therapy Lead Model 303.2 / 303.3 - Electrode/lead, stimulator, implantable, neurological
- Class III – 192081 – VNS Therapy Lead Model 304.2 / 304.3 - Electrode/lead, stimulator, implantable, neurological

Accessories

- VNS Computer - User-friendly computer and software program which can interrogate the VNS generator and modify the stored
- Stimulation parameters
- Class III – 131046 – VNS Therapy Handheld Computer Model 250 - Computer, palmtop

VNS Tunneler

- A disposable surgical tool used for subcutaneous tunnelling of the lead assembly from the nerve site in the neck to the VNS generator site in the chest.
- Class IIb – 130202 - VNS Therapy Tunneler Model 402 - Tunneller, vascular

VNS Accessories Pack

- A pack including back-up sterile test resistor, lead tie-downs and hex screwdriver.
- Class IIb – 130203 – VNS Therapy Accessories Pack Model 502 - Stimulator, electrical, vagus nerve, antiseizure

Appendix E

Prosthesis list for VNS pulse generators and leads:

- RA001 VNS Pulse Generator
- RA002 VNS Lead

Appendix F

Currently available AEDs from the Pharmaceutical Benefits Schedule, categorised by drug types:

Type	Drug names
Barbiturates and derivatives	Phenobarbitone[b], Primidone
Hydantoin derivatives	Phenytoin[b]
Succinimide derivatives	Ethosuximide[a]
Benzodiazepine derivatives	Clonazepam, nitrazepam
Carboxamide derivatives	Oxcarbazepine, Carbamazepine[a]
Fatty acid derivatives	Valproate[a], Bigabatrin, Tiagabine[b]
Other antiepileptics	Zonisaminde, Lamotrigine[b], Levetiracetam[b], Lacosamide, gabapentin[b], Sulthiame, Topiramate[b]

[a] First-line treatment; [b] Second-line treatment(Schachter 2007)

Appendix G

Figure 4 Clinical management outcomes proposed by the applicant

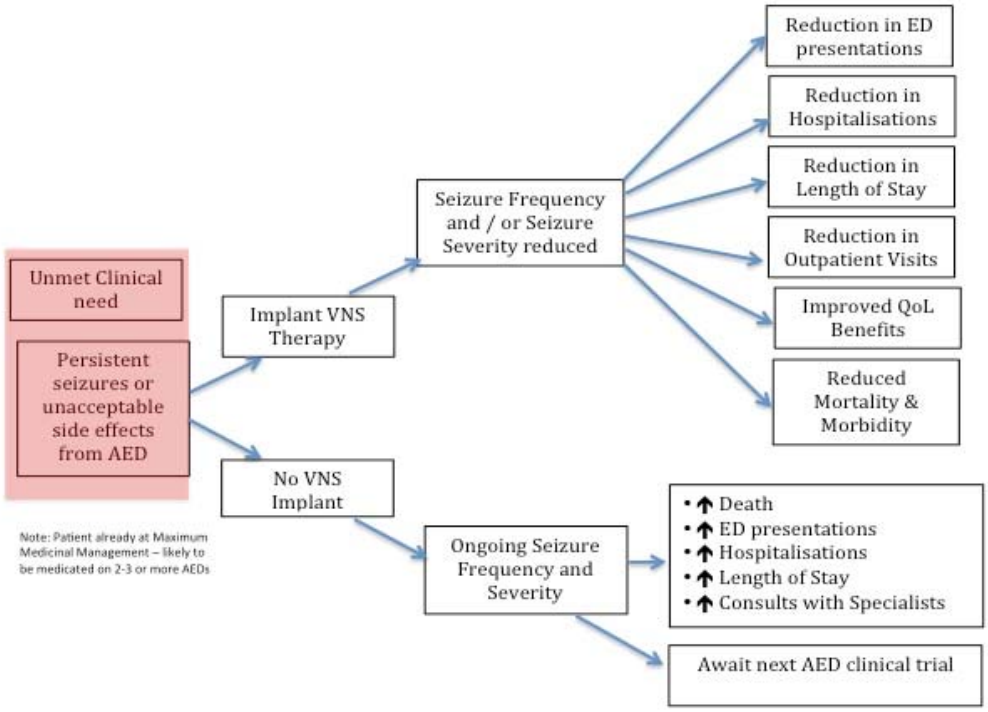
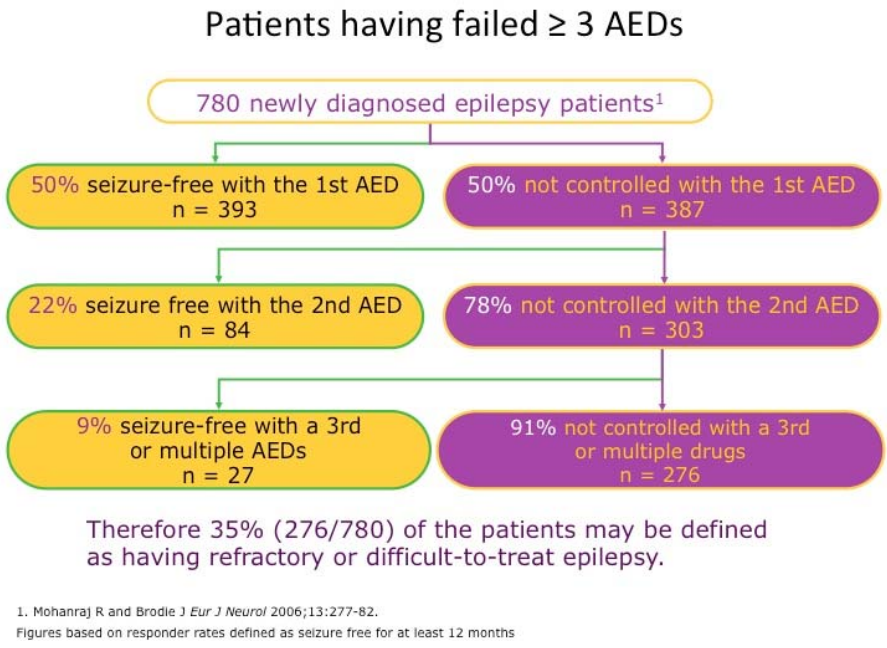


Figure 5 Estimation of refractory or intractable epilepsy



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