



Australian Government
Medical Services Advisory Committee

Public Summary Document

Application No. 1358 – Vagus Nerve Stimulation Therapy

Applicant: Aurora Bioscience PTY Ltd

Date of MSAC consideration: MSAC 64th Meeting, 30-31 July 2015

Context for decision: MSAC makes its advice in accordance with its Terms of Reference, see at www.msac.gov.au

1. Purpose of application and links to other applications

An application requesting Medicare Benefits Schedule (MBS) listing of vagus nerve stimulation therapy (VNS therapy) was received from Aurora BioScience Pty Ltd. The evidence for assessment of this application was submitted in February 2015.

2. MSAC's advice to the Minister

After considering the strength of the available evidence presented in relation to safety, clinical effectiveness and cost-effectiveness of vagus nerve stimulation (VNS) therapy, MSAC did not support public funding because of uncertain cost-effectiveness. MSAC accepted there was some clinical benefit in a small patient population with a high unmet clinical need, albeit supported by limited data.

MSAC considered that any reapplication should address the issues identified with the economic evaluation by:

- providing a simple economic model with a cost utility analysis;
- including time horizon over 5 years, with sensitivity analyses for time horizons between 1 and 10 years;
- including disutility for side effects; and
- providing cost per seizure avoided.

MSAC considered that any reapplication should be made via ESC.

3. Summary of consideration and rationale for MSAC's advice

MSAC acknowledged the high unmet clinical need in a small group of patients with intractable epilepsy and agreed with the place in therapy proposed in the treatment algorithm.

MSAC noted there were multiple issues with the clinical evidence presented leading to low certainty of a clinically important benefit including imprecise estimates of effect, limited duration of the trials (3-6 months), unexplained heterogeneity in the treatment estimates observed across the studies, high risk of bias among the studies, and mixed comparators (high vs low stimulation and VNS versus anti-epileptic drugs). However, given the high unmet clinical need in a drug resistant patient population who have limited other options, MSAC agreed that low stimulation was equivalent to sham and accepted that there was likely to be modest clinical effectiveness. MSAC also noted that VNS was associated with infrequent but important complications such as vocal chord paresis, dyspnoea and hoarseness.

However, MSAC considered the economic analysis to be inappropriate. There were multiple issues with the economic model, particularly in the structure of a two-step approach. The treatment effect was uncertain due to the translation of short term clinical data of five years extrapolated to lifetime treatment effect of 20 years. MSAC noted that the therapy was not cost effective if time horizon is less than 10 years and considered that the longer term benefits are a main driver of the model. The model also inappropriately applied mortality rates and health resource to efficacy rather than the use of health states. MSAC further noted that the utilities used were inappropriately assigned to the treatment effect rather than a health state, and there was no disutility from the complications that occurred as a result of this procedure.

MSAC considered that any resubmission should include fundamental changes to the model. Any future analysis should include a simple economic model, with more appropriate utilities, include disutility for side effects and sensitivity analyses of the time horizon at one, five and ten years. The model should also use MBS fees rather than costs, though this is a minor contributor on the outcome. MSAC further noted that sensitivity analyses around the treatment effect would also be useful to investigate the direction of potential biases with respect to the ICER. MSAC considered that it would be informative to be provided with data on the cost per seizure avoided.

MSAC considered that the paediatric population could benefit more from VNS therapy, particularly in children where development can be slowed due to epilepsy. However, MSAC noted that this population had not been investigated separately with the limited clinical evidence.

4. Background

In June 2008, MSAC considered evidence for VNS therapy for patients with medically intractable epilepsy (MSAC Assessment Report 1118). MSAC did not recommend public funding for the service due to insufficient evidence to support effectiveness and net benefit.

5. Prerequisites to implementation of any funding advice

The applicant noted that VNS therapy was approved by the Therapeutic Goods Administration (TGA) 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 generalisation) or generalised seizures that are refractory to antiepileptic medications”.

6. Proposal for public funding

The applicant proposed the following five MBS items pertaining to VNS therapy.

Proposed MBS item XXX1 for placement of electrical pulse generator
Category 3 - THERAPEUTIC PROCEDURES
<p>XXXX1</p> <p>VNS Therapy ELECTRICAL PULSE GENERATOR, subcutaneous placement of, for the management of refractory generalised epilepsy, or treating refractory focal epilepsy that is not suitable for resective epilepsy surgery through stimulation of the vagus nerve</p> <p>Multiple Services Rule (Anaes.) (Assist.)</p>
Fee: \$340.60 Benefit: 75% = \$255.45
Proposed MBS item XXX2 for removal of electrical pulse generator
Category 3 - THERAPEUTIC PROCEDURES
<p>XXXX2</p> <p>VNS Therapy ELECTRICAL PULSE GENERATOR, that was inserted for the management of refractory generalised epilepsy, or treating refractory focal epilepsy that is not suitable for resective epilepsy surgery, surgical repositioning or removal of [omitted: "performed in the operating theatre of a hospital"]</p> <p>Multiple Services Rule (Anaes.)</p>
Fee: \$159.40 Benefit: 75% = \$119.55
Proposed MBS item XXX3 for surgical placement of lead
Category 3 - THERAPEUTIC PROCEDURES
<p>XXXX3</p> <p>VNS Therapy LEAD, surgical placement of, lead including connection to vagus nerve, including intraoperative test stimulation, for the management of refractory generalised epilepsy, or treating refractory focal epilepsy that is not suitable for epilepsy surgery through stimulation of the vagus nerve</p> <p>Multiple Services Rule (Anaes.) (Assist.)</p>
Fee: \$674.15 Benefit: 75% = \$505.65
Proposed MBS item XXX4 for surgical repositioning or removal of lead
Category 3 - THERAPEUTIC PROCEDURES
<p>XXXX4</p> <p>VNS Therapy LEAD, that was inserted and attached to the vagal nerve for the management of refractory generalised epilepsy, or treating refractory focal epilepsy that is not suitable for resective epilepsy surgery, surgical repositioning or removal of, [omitted: "performed in the operating theatre of a hospital"]</p> <p>Multiple Services Rule (Anaes.)</p>
Fee: \$605.35 Benefit: 75% = \$454.05

Proposed MBS item XXX5 for electrical analysis and programming of electrical pulse generator
Category 3 - THERAPEUTIC PROCEDURES
XXXX5 VNS Therapy ELECTRICAL PULSE GENERATOR, electrical analysis and programming of, VNS Therapy device using an external wand, for the management of refractory generalised epilepsy, or treating refractory focal epilepsy that is not suitable for resective epilepsy surgery.
Fee: \$189.70 Benefit: 75% = \$142.58

The applicant noted that patients with drug-resistant epilepsy are managed by Multidisciplinary Teams (MDT) in specialist epilepsy clinics. During diagnosis, the MDT evaluate all drug-resistant epilepsy patients to determine if they will benefit from epilepsy surgery. VNS therapy would be considered when all active treatment options are exhausted, or remain marginally effective, ineffective, non-feasible, failed, or cause severe complications and/or adverse events.

The delivery of VNS therapy should be restricted to neurosurgeons and neurologists with extensive experience of VNS therapy procedure.

7. Summary of Public Consultation Feedback/Consumer Issues

Overall, consumers supported the proposed intervention and noted that the low prevalence/very high impact life circumstances warrants consumer impact tests for effectiveness and efficiency.

8. Proposed intervention's place in clinical management

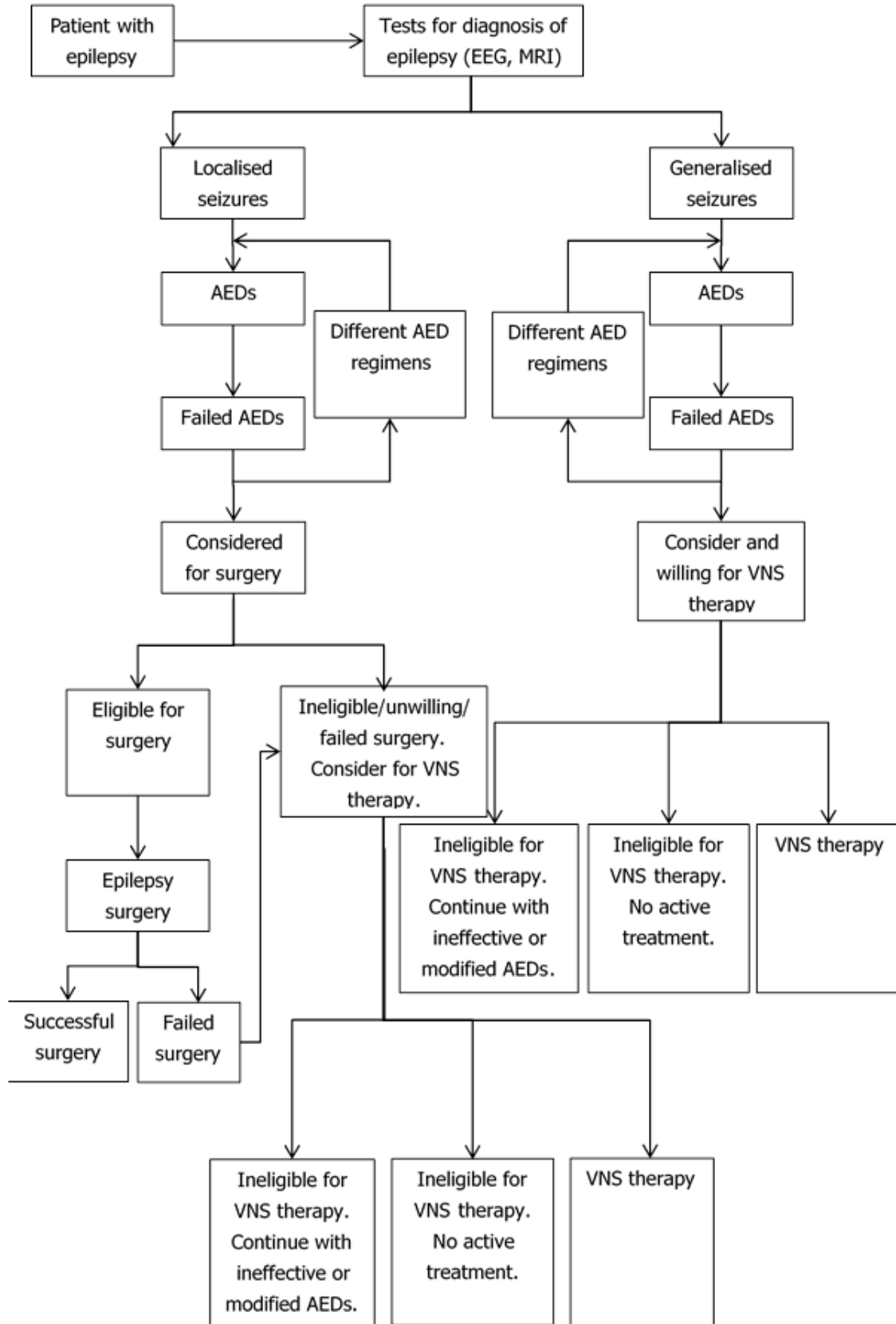
VNS therapy is an adjunctive non-pharmacologic treatment for reducing the frequency of seizures in patients with drug-resistant partial or generalised epilepsy.

The system consists of a pulse generator, lead, and external programming system. The pulse generator is an implantable, programmable pacemaker-like device which is housed in a hermetically sealed titanium case and powered by a single battery. The lead is attached to the left vagus nerve and implanted in the neck using 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, consisting of a hand-held computer, software and wand, neurologists can individualise the timing and amount of stimulation each patient receives in order to minimise seizure burden.

The applicant noted that almost 400 VNS therapy systems have been implanted in Australia since the first case in 1994. However, VNS therapy is currently not funded under the MBS.

The applicant provided a revised clinical pathway for the treatment of patients with epilepsy in the pre-ESC response. The applicant stated that the minor changes made to the clinical pathways simplify the diagram and do not alter the type of service being delivered, the defined patient population or the eligibility of patients for VNS therapy.

Proposed government funded clinical pathway for the treatment of patients with epilepsy



AED= antiepileptic drugs; EEG= electroencephalography; MRI= magnetic resonance imaging; VNS Therapy= VNS® Therapy.

9. Comparator

The comparator was 'no active intervention' based on the applicant's proposal. All patients will remain on current anti-epileptic drugs (AEDs).

10. Comparative safety

The evidence submitted consisted of five randomised controlled trials (RCTs) with maximum of 12 months follow-up. Comparator arms comprised VNS therapy with low-stimulation, best medical practice which could include a change in dosage or type of AED) and initiation of a new AED. The applicant noted that unlike AEDs which are often changed frequently, implantable therapies such as VNS therapy are intended as lifelong therapy.

Within the identified studies, the application stated that adverse events relating to the use of VNS therapy were generally well reported. However, VNS therapy in all of the studies was used in addition to AEDs, which can also cause some severe side effects. Adverse events relating to the use of AEDs were not well reported within the studies.

The application stated that comparative studies in which high stimulation VNS therapy was compared with low stimulation VNS therapy (understood to be an active control) and in which VNS therapy is compared with no active intervention both show that VNS therapy is broadly well tolerated and the rate of discontinuation due adverse events is low in both sets of studies, with seven discontinuations due to adverse events in 432 implantations (1.6%).

Complications resulting from VNS therapy were primarily attributable to either device implantation or stimulation. The randomised trials comparing VNS therapy with no active treatment reported an infection rate of 3%, while the single arm studies reported a rate of 4%. In the RCTs comparing VNS therapy at high and low stimulation the infection rate was almost 12%, but this may be related to the age of the trials, differences in infection control or surgical practices.

The critique stated that for the adverse events reported in patients receiving VNS therapy across all studies voice alteration, dyspnoea, vocal chord paresis, cough and hoarseness were the most frequent adverse events following implantation, and occurred in 5-30%. Death was reported in 48 of 2049 patients (2%) who received a VNS therapy device, although there were no deaths reported to have been directly attributable to VNS therapy.

11. Comparative effectiveness

High versus Low (active control) VNS Therapy

Two RCTs in adults (E03) and (E05) and one RCT in children (Klinkenberg, et al., 2012) presented clinical effectiveness outcomes at 3 months (in E03 and E05) and 20 weeks, respectively. The estimated effect for $\geq 50\%$ reduction in seizure frequency was relative risk (RR) of 1.61 (95% CI: 1.00 to 2.60) and a risk difference (RD) of 9% (95% CI: -1% to 20%): borderline statistically significant at the conventional $p=0.05$ level.

Studies (E03 and E05) reported the proportion of patients who achieved a $\geq 75\%$ reduction in seizure frequency. The estimated effect for $\geq 75\%$ reduction in seizure frequency was a RR of 5.09 (95% CI: 1.49 to 17.36) and a RD of 7% (95% CI: 2% to 12%) which was statistically significant.

Studies E03 and E05 also reported the number of patients achieving complete seizure freedom (100% reduction). However, in E03 no patients in either group reached a 100% reduction in seizure frequency and only one patient in the high stimulation group in the E05 study was seizure free. The estimated effect for a 100% reduction in seizure frequency in E05 was a RR of 3.25 (95% CI: 0.13 to 78.88) and a RD of 1% (95% CI: -2% to 3%), which was not statistically significant.

For seizure frequency, studies E03 and E05 reported a statistically significant change in seizure frequency from baseline to end of follow up. The mean difference was estimated at -14.66 (95% CI: -23.00 to -6.32). The application stated that these results are consistent with a moderate reduction in the seizure frequency being observed in patients receiving high stimulation VNS therapy compared with low stimulation VNS therapy.

VNS Therapy versus no active intervention

Two RCTs compared VNS therapy with no active intervention, one in adults (Ryvlin et al, 2014) and one in children (E06).

Both RCTs reported the proportion of patients who achieved a $\geq 50\%$ reduction in seizure frequency. The estimated effect was RR 1.24 (95% CI: 0.76 to 2.01) and a RD of 6% (95% CI: -8% to 20%). The application stated that although treatment benefit was observed in both studies this effect was not statistically significant.

Study E06 also reported the mean change in seizure frequency and change in seizure severity. For seizure frequency, the estimated mean difference in favour of no active intervention was 12.70 (95% CI: -29.78 to 55.18) but this difference was not statistically significant. For reduction in seizure severity, in favour of the no active intervention, the estimated mean difference was 1.30 (95% CI: (-5.83 to 8.43), which was not statistically or clinically significant.

Evidence from comparative observational studies

Four of the eight comparative observational studies (Marrosu, et al., 2003, Boon, et al., 2002, Harden, et al., 2000 and Hoppe, Wagner, Hoffmann, von Lehe, & Elger, 2013) showed a benefit of VNS therapy compared with no active intervention and in three studies this benefit was statistically significant (Marrosu, et al., 2003, Boon, et al., 2002 and Harden, et al., 2000). The summary estimate of effect for $\geq 50\%$ reduction in seizure frequency was RR 1.72 (95% CI: 1.04 to 2.84) and RD 29% (95% CI: 13% to 44%), which was statistically significant.

Two of the observational studies also reported the proportion of patients achieving a $\geq 75\%$ reduction in seizure frequency (Harden, et al., 2000 and (Hoppe, Wagner, Hoffmann, von Lehe, & Elger, 2013). The combined summary statistic was RR 3.40 (95% CI: 1.39 to 8.27) and the RD was 30% (95% CI: 11% to 48%).

Single arm studies

Thirty two single arm observational studies were presented. Twenty five studies (78.1%) reported the number of patients achieving $\geq 50\%$ reduction in seizure frequency. In all of the studies a treatment benefit was observed and in all, but one study (Muller, et al., 2010), this treatment benefit was statistically significant.

The application claimed that the evidence demonstrated that VNS therapy has a number of clinical benefits particularly with regard to increasing seizure control. In terms of seizure frequency statistically significant treatment effects were observed for key outcomes:

responder rates ($\geq 50\%$ reduction in seizure frequency, $\geq 75\%$ reduction seizure frequency and seizure freedom (100%)) and change in seizure frequency in both short and long term studies. The application stated that the available evidence showed that 10% more individuals using VNS therapy can be expected to achieve a 50% reduction in seizure frequency before one year, and 20% more individuals will achieve such a reduction before two years. Longer term comparative evidence was limited, but non-comparative evidence suggested that up to 59% of individuals may achieve a 50% reduction in seizure frequency in the longer term

The application claimed that the full effect of VNS therapy is not achieved in the short-term, and that the evidence suggested that the effect of VNS therapy increases over time, with some patients not experiencing the full effect until two years post-implantation.

The critique stated that the results from the meta-analysis of comparative trials included in the submission demonstrated a modest effect of VNS therapy. Confidence intervals (CI) indicated a wide range in the benefits of VNS therapy, from as little as a one to two per cent increases in the number of responders to as much as a 38 per cent increase, at or before two years. There were no RCTs available with more than 12 months of follow-up data. In addition, the measurement of outcomes across the RCTs varied in terms of both duration and follow-up (up to 3 months or up to 12 months) and reduction in seizures defined as an effect (50, 75 or 100 per cent reduction). Although some studies showed a benefit of VNS therapy when compared to low-stimulation or medical therapy the magnitude of the benefit attributable to VNS therapy is variable.

12. Economic evaluation

The application presented a cost-utility and cost-effectiveness analysis to assess the incremental cost of VNS therapy compared to ‘no VNS therapy’ per extra unit of health outcome achieved (e.g. life year gained (LYG) and quality adjusted life years (QALY) gained).

The modelled economic evaluation was developed in one-step – extrapolation of trial data to a lifetime time horizon. It considered the costs and consequences of the use of VNS therapy to reduce the seizure burden of patients with drug-resistant epilepsy over 20 years. An incremental cost-effectiveness ratio (ICER) for QALYs and avoided seizures was also provided. The model compared the outcomes of ‘VNS therapy’ to ‘no active intervention’.

The application stated that the model was most sensitive to the efficacy of VNS therapy and the utilisation of ICU. With all values tested, the 20-year discounted ICER for VNS therapy was less than \$45,000.

The critique performed a “trial-based” economic evaluation with no extrapolation beyond the follow-up of the clinical studies presented, which gave an ICER per QALY gain of greater than \$100,000. The critique noted that the ICER is very sensitive to the time horizon with the baseline analysis assuming a 20-year projection, for which there is limited evidence.

The critique considered that a stepped approach in which benefits are estimated for the five years covered by key RCTs and comparative observational studies would have been more informative. Noting that while a five-year period is not likely to reflect the expected benefits period for VNS therapy (e.g. the applicant notes that many patients replace batteries after seven years, therefore a 15-year period is appropriate) it does give an indication of the proportion of benefits that are captured within the period where higher-quality evidence is available.

13. Financial/budgetary impacts

The applicant noted that financial implications were estimated using an epidemiologic approach and were based on VNS therapy devices implanted during the projection period. The applicant indicated that the projections did not include patients with existing devices who would need to have batteries changed.

The applicant predicted that between 60-150 patients per year would undergo implantation of a new VNS therapy system in the first five years (private and public patients combined).

Based on the above projections, the applicant estimated that the cost of the proposed intervention to the MBS, including the implantation, removal and replacement, over five years. The total MBS costs over the first 5 years of listing (cumulative) were estimated to be less than \$250,000.

The critique noted that the financial impacts to the MBS were small and changes in the multiple service rule, projections based on five or seven year VNS Therapy implants per million Australians, increases in the population of privately insured patients and the addition of AED cost increases, have a limited impact on the budget.

14. Key issues from ESC for MSAC

ESC considered the effectiveness of the model was unacceptable and noted there were multiple issues with the economic model. Of concern was the estimates of efficacy, particularly in the longer term (>2-5 years) given it is the longer term benefits that are driving the cost effectiveness. ESC questioned whether the benefits in children should also be included as part of the child population, if the procedure is recommended for funding by MSAC. There were also issues in use of efficacy categories (of reductions in seizure frequency) rather than health states (seizure severity).

ESC agreed that the proposed item descriptor wording would need to be reviewed to consider:

- whether the procedure would be performed in an operating theatre, and consider the effect of including the term ‘unwilling’ to undergo surgery rather than ‘not suitable’;
- including whether all procedures would be performed in an operating theatre and whether this wording is necessary in the descriptor (incl. the repositioning or removal items, where the wording has been dropped by the applicant);
- whether it is appropriate to include “repositioning” of generator (this was added by applicant); and
- “treating refractory focal epilepsy that is not suitable for epilepsy surgery”, be reworded ,as epilepsy surgery technically includes VNS surgery.

15. Other significant factors

Nil.

16. Applicant’s comments on MSAC’s Public Summary Document

Whilst disappointed with the final recommendation, the applicant welcomes MSAC’s recognition that there is a clinical benefit with VNS in a population with high unmet clinical need. The high clinical need in this patient population is due to a lack of viable treatment options. These patients can endure seizures on a daily basis which profoundly impacts Their

quality of life including academic underachievement in children, learning and behavioural difficulties, employment issues in adults, restricted social activity, anxiety, and depression in both children and adults and contributes to high health care costs. The Applicant is confident the cost-effectiveness of VNS can be demonstrated and intends to continue to work with MSAC to make the necessary adjustments to the economic modelling in order to ensure a MBS listing of VNS for the benefit of this small but difficult to treat patient population.

17. Further information on MSAC

MSAC Terms of Reference and other information are available on the MSAC Website at: www.msac.gov.au.