Australian Government

Medical Services Advisory Committee

Public Summary Document

Application No. 1491 - Vagus Nerve Stimulation (VNS) for chronic major depressive episodes

Applicant: **LivaNova Australia Pty Ltd**

Date of MSAC consideration: **MSAC 73rd Meeting, 26-27 July 2018**

Context for decision: MSAC makes its advice in accordance with its Terms of Reference, visit the MSAC website

1. Purpose of application

An application requesting Medicare Benefit Schedule (MBS) listing for Vagus Nerve Stimulation (VNS) for chronic major depressive episodes was received from LivaNova Australia Pty Ltd by the Department of Health.

2. MSAC's advice to the Minister

After considering the strength of the available evidence in relation to comparative safety, clinical effectiveness and cost-effectiveness, MSAC did not support MBS funding of VNS for chronic major depressive episodes. MSAC accepted that there was a clinical need for more treatment options for this patient population. However, MSAC had concerns regarding the comparative safety, limited evidence of clinical effectiveness, and resulting uncertainty regarding comparative cost-effectiveness for VNS.

MSAC advised that any resubmission should include further clinical effectiveness data from sham-controlled randomised trials and also studies that explore (a) the mechanistic basis for how VNS achieves its antidepressant effects and (b) whether VNS interacts negatively with ongoing treatment with pharmacological antidepressant agents.

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

MSAC noted that the proposed population is people with a major depressive disorder (MDD) who have not had an adequate response to four or more appropriate antidepressant treatments. VNS involves a pulse generator that is implanted under the skin below the patient's clavicle. The generator is connected to a lead that tracks under the skin and delivers electrical stimuli to the left vagus nerve at level of the carotid sheath. The device is purported to increase regional cerebral blood flow to multiple brain areas. VNS settings are adjusted using a magnetic wand placed on the skin surface overlying the pulse generator. The estimated battery life is 10 years.

MSAC noted that the applicant had agreed to amend the item descriptor to 'four or more classes of antidepressants', but also considered that it was unclear what defined an 'adequate'

response. MSAC also considered that, of the six proposed MBS items for VNS implantation, it was unclear who would be responsible for programming the device – a psychiatrist or a non-medical professional.

The intervention is proposed to be delivered under specialist care through accredited 'centres of excellence', and the application named six centres in New South Wales and Victoria. MSAC considered that this delivery model would create issues relating to equity of access. It was questioned whether a 'centres of excellence' model was clinically necessary, although it was noted in consultation comments from a professional organisation that this model was reasonable to ensure that VNS is offered in a multidisciplinary environment.

MSAC acknowledged that there was a high unmet clinical need in this population and noted comments received during consultation:

- that there is no standard treatment for this population, making it difficult to demonstrate clinical superiority over treatment as usual (TAU)
- that patients are likely to exhaust all other options before selecting VNS (clinical expert), as it is an invasive procedure
- that although the number of patients who meet the criteria for MDD is large, the group eligible for and agreeable to VNS is small (clinical expert).

The clinical trial data in the application focused on two meta-analyses, both sponsored by the applicant. Only two randomised controlled trials were included:

- Aaronson (2013) was a 3-arm trial using low, medium and high VNS regimes. This trial showed no dose-response curve over a 22-week follow-up.
- Rush (2005a) was a 2-arm trial comparing VNS with sham treatment. This trial showed no significant difference between VNS and sham up to 10 weeks.

A further non-randomised study by Aaronson (2017) had significant loss to follow-up at 5 years (39% in the VNS group and 54% in the TAU group). MSAC considered that this may indicate that VNS is unacceptable to patients.

MSAC considered that the observational studies had a high risk of bias because the VNS generator is visible after implantation.

MSAC also noted a meta-analysis (Martin 2012) that was not included in the application. The included studies were highly heterogeneous (I^2 91%), and 84% of the variance was explained by severity of depression at the start of treatment (demonstrating regression to the mean). MSAC concluded that the evidence for clinical effectiveness was weak and suggested that VNS had little or no effect.

MSAC considered that comparative safety was unfavourable. The Aaronson trial (2013) found that, after 1 year, 72% of participants had voice alteration, 32% had dyspnea, 32% had pain and 25% had cough. The FDA database (MAUDE) recorded 120 adverse events relating to VNS, including lead fracture, high impedance and corrosion. In the pre-MSAC response, it was acknowledged that 19 issues were detected with VNS devices between 2007 and 2018, for which corrections or removals of the product were voluntarily initiated. Four of these issues were related to the generator and leads under consideration in this application, none required device explant.

MSAC considered that the comparative cost-effectiveness was uncertain. The economic model included uncertain costs due to mixed data from several sources, and the model parameters favoured VNS. The time horizon was extrapolated beyond the clinical evidence (5 years) to 10 years (the battery life of the VNS device). The utilities attributed to different

health states were also uncertain, particularly regarding remission. The ICER was sensitive to reasonable changes in underlying assumptions, including time horizon and health utilities (especially remission).

Regarding financial implications, MSAC noted that the 'centres of excellence' model would result in a net cost to the MBS of $305,000 over 5 years, and that an epidemiological approach would result in a net cost to the MBS of $781,000 over 5 years.

MSAC acknowledged that there is a clinical need for treatment for this debilitating condition, and the numbers of eligible patients would likely be small. However, MSAC concluded that the uncertain comparative safety, lack of evidence of clinical effectiveness, uncertain cost-effectiveness, and issues relating to implementation were grounds to not support listing for this application.

For any resubmission, MSAC considered that it would require higher-quality studies and data inputs. This would include:

- for comparative safety, a justification for the 'centres of excellence' model and details on training implications
- appropriate comparative clinical effectiveness data, MSAC considered this could be data from sham-controlled randomised trials, as well as studies that explore the mechanistic basis for how VNS achieves its antidepressant effects, and whether VNS interacts negatively with ongoing treatment with pharmacological antidepressant agents
- for comparative cost-effectiveness, better quality data for model inputs.

MSAC noted that any resubmission would need to be considered via ESC.

4. Background

MSAC has not previously considered VNS therapy for chronic major depressive episodes.

VNS therapy is currently listed on the MBS for use in refractory epilepsy.

5. Prerequisites to implementation of any funding advice

The requested MBS listing for VNS therapy is consistent with the TGA approved indication – see Table 1.

Table 1 Relevant ARTG listings

ARTG no.	Product no.	Product description	Product category	Sponsor
Implantable				
168817	Model 103	VNS Therapy Demipulse Generator - Stimulator	Medical Device AIMD	LivaNova Australia Pty Ltd
192080	Model 303 Lead (303.2 and 303.3)	VNS Therapy	Medical Device AIMD	LivaNova Australia Pty Ltd
192081	Model 304 Lead (304.2 and 304.3)	VNS Therapy PerenniaFLEX -	Medical Device AIMD	LivaNova Australia Pty Ltd
Non-implantable portions of the VNS Therapy System				
277451	Model 250	VNS Therapy® Programming Software	Medical Device Included Class 3	LivaNova Australia Pty Ltd
298408	NA	Stimulator control magnet	Medical Device Included Class 1	LivaNova Australia Pty Ltd

The SBA proposed that the intervention is delivered under specialist care through six accredited 'Centres of Excellence' in New South Wales and Victoria. This may create issues around equity of access if adopted.

6. Proposal for public funding

There are six proposed MBS items for VNS implantation, relating to the placement of the generator, repositioning or removal of the generator, placement of the lead, repositioning or removal of the lead, device programming and replacement of the battery.

These items mirror the same items that were approved for VNS in the treatment of refractory epilepsy.

The proposed MBS item descriptors are presented in Table 1.

Table 2 Proposed MBS item descriptors, as per the ratified PICO Confirmation

Category 3 - THERAPEUTIC PROCEDURES
Vagus nerve stimulation using an ELECTRICAL PULSE GENERATOR (subcutaneous placement of) to stimulate the left vagus nerve, for management of patients (aged 18 years of age or older) with a chronic major depressive episode who have not had an adequate response to four or more appropriate antidepressant treatments (i.e. at least four medications have been tried for sufficient time to stabilise dose and manage side effects, before an assessment of failure of therapeutic effect is made) Multiple Services Rule (Anaes.) (Assist.) Fee: $340.60 Benefit: 75% = $255.45 (In-hospital/admitted patient only)
Category 3 - THERAPEUTIC PROCEDURES
Vagus nerve stimulation using an ELECTRICAL PULSE GENERATOR (surgical re-positioning or removal of), for management of patients (aged 18 years of age or older) with a chronic major depressive episode who have not had an adequate response to four or more appropriate antidepressant treatments (i.e. at least four medications have been tried for sufficient time to stabilise dose and manage side effects, before an assessment of failure of therapeutic effect is made) Multiple Services Rule (Anaes.) Fee: $159.40 Benefit: 75% = $119.55 (In-hospital/admitted patient only)
Category 3 - THERAPEUTIC PROCEDURES
Vagus nerve stimulation LEAD (surgical placement of), which must include connection of lead to left vagus nerve and intraoperative test stimulation, for management of patients (aged 18 years of age or older) with a chronic major depressive episode who have not had an adequate response to four or more appropriate antidepressant treatments (i.e. at least four medications have been tried for sufficient time to stabilise dose and manage side effects, before an assessment of failure of therapeutic effect is made) Multiple Services Rule (Anaes.) (Assist.) Fee: $674.15 Benefit: 75% = $505.65 (In-hospital/admitted patient only)
Category 3 - THERAPEUTIC PROCEDURES

Category 3 - THERAPEUTIC PROCEDURES
Vagus nerve stimulation LEAD (surgical re-positioning or removal of), that was inserted and attached to left vagal nerve for management of patients (aged 18 years of age or older) with a chronic major depressive episode who have not had an adequate response to four or more appropriate antidepressant treatments (i.e. at least four medications have been tried for sufficient time to stabilise dose and manage side effects, before an assessment of failure of therapeutic effect is made) Multiple Services Rule (Anaes.) Fee: $605.35 Benefit: 75% = $454.05 (In-hospital/admitted patient only)
Category 3 - THERAPEUTIC PROCEDURES
Vagus nerve stimulation ELECTRICAL PULSE GENERATOR (electrical analysis and programming of device, using an external wand), for management of patients (aged 18 years of age or older) with a chronic major depressive episode who have not had an adequate response to four or more appropriate antidepressant treatments (i.e. at least four medications have been tried for sufficient time to stabilise dose and manage side effects, before an assessment of failure of therapeutic effect is made) Fee: $189.70 Benefit: 75% (In-hospital) = $142.30 Benefit: 85% (Out-of-hospital) = $161.25
Category 3 - THERAPEUTIC PROCEDURES
Vagus nerve stimulation ELECTRICAL PULSE GENERATOR (subcutaneous replacement of battery), for management of patients (aged 18 years of age or older) with a chronic major depressive episode who have not had an adequate response to four or more appropriate antidepressant treatments (i.e. at least four medications have been tried for sufficient time to stabilise dose and manage side effects, before an assessment of failure of therapeutic effect is made) Multiple Services Rule (Anaes.) (Assist.) Fee: $340.60 Benefit: 75% = $255.45 (In-hospital/admitted patient only)

7. Summary of Public Consultation Feedback/Consumer Issues

Responses were received from the two professional organisations, clinical experts and a researcher. The feedback stated:

- "The difficulty in demonstrating the applicant's clinical claim of VNS superiority over TAU, given patients are unique in their clinical profiles, and there is no standard treatment" (professional organisation).

- "VNS implantation is an invasive surgical service, which may limit the number of eligible patients who choose the intervention. Patients are likely to exhaust all other treatment options, before selecting VNS therapy" (clinical expert).

- "While the number of patients who meet criteria for MDD is large, the group eligible for and agreeable to VNS is small" (clinical expert).

- "It is reasonable to limit VNS introduction to accredited centres and offered in a multi-disciplinary environment (i.e. psychiatrist, neurosurgeon/neurologist working closely together) with the initial rollout targeting one to two centres per state" (professional organisation).

8. Proposed intervention's place in clinical management

Major depressive disorder (MDD) is a common and debilitating psychiatric disorder associated with low mood, loss of interest and enjoyment, and a number of other psychological and somatic symptoms including reduced energy, concentration/attention, and self-esteem; ideas of guilt/unworthiness; bleak or pessimistic views of the future; ideas or acts of self-harm/suicide; and disturbed sleep and appetite. The lowered mood varies little on a day to day basis, and is often unresponsive to circumstances.

VNS therapy involves a small implantable device that delivers mild, intermittently pulsed signals to the vagus nerve, which then activates various areas of the brain for patients

suffering from MDD. It consists of a pacemaker-like device usually implanted in the left chest area during an outpatient procedure that does not involve brain surgery. The implantation procedure requires two small incisions – just under the skin below the collar bone and in a natural crease in the left side of the neck.

The proposed listing of VNS therapy targets a small subgroup of patients with MDD referred to as having TRD.

The current clinical management of chronic major depressive episodes typically involves persisting with the pharmacological strategies as described above, but ECT, rTMS and/or psychotherapeutic approaches may also be considered in this difficult-to-treat population.The proposed treatment algorithm of MDD with VNS therapy is presented in Figure 1.

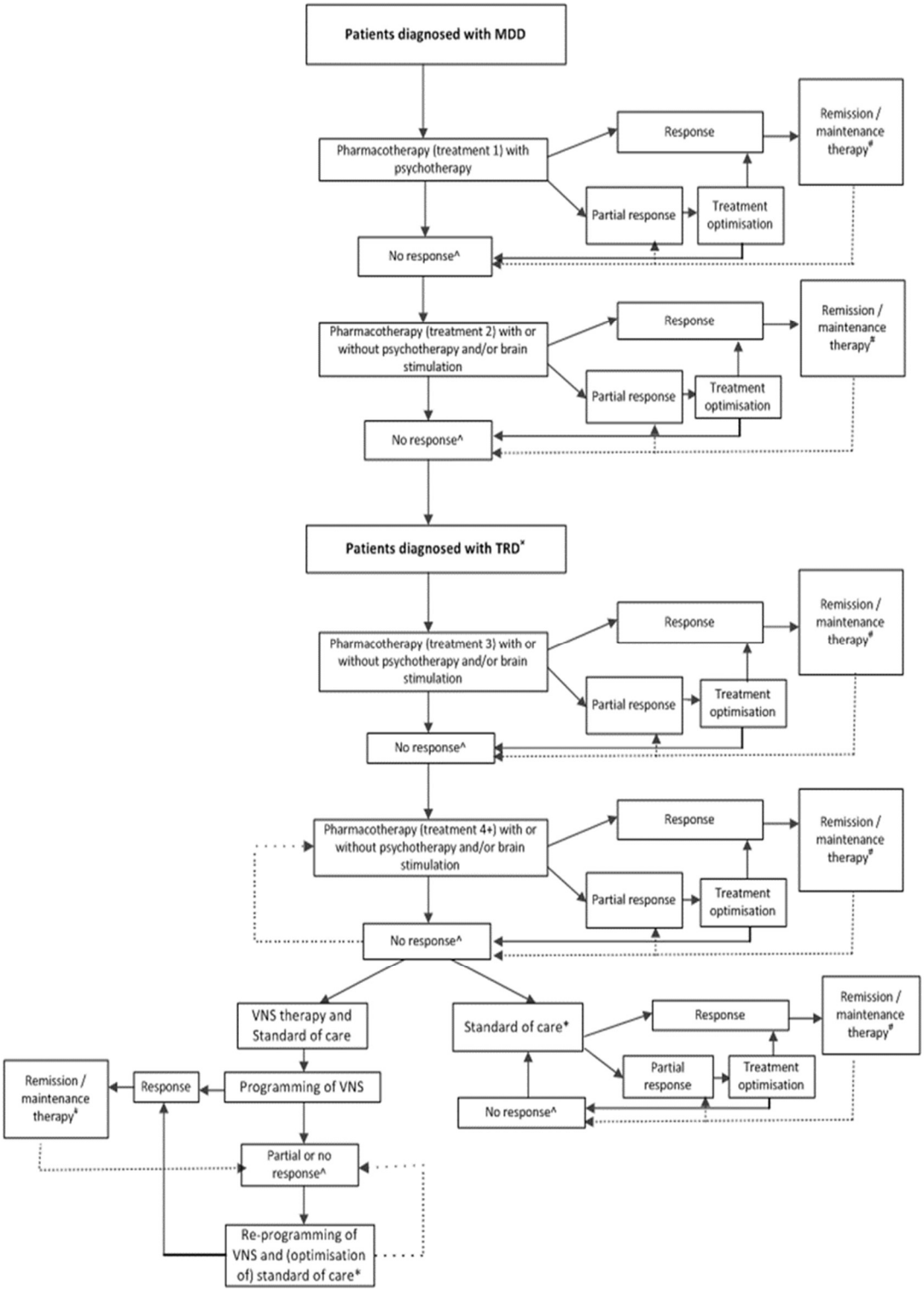

Figure 1 Proposed treatment algorithm for chronic major depressive episodes including VNS therapy

Source: Figure 4, PICO confirmation (based on Malhi et al 2015). MDD=major depressive disorder; TRD=treatment-resistant depression. #While patients may achieve remission, it is possible for them to subsequently experience a relapse, where patients then re-enter the management algorithm at "no response" or "partial response". ^When no response to an adequate course of treatment the patient's diagnosis is re-evaluated considering any new comorbidity, adherence to treatment is monitored and a second opinion sought. An appropriate clinical response is a significant reduction in signs/symptoms, which is quantified as a 50 per cent reduction in the total score on a standardised rating scale, such as the Hamilton Depression Rating Scale. ×TRD is defined as lack of improvement following adequate trials of two or more antidepressants. *Standard of care includes pharmacotherapy, psychological therapy, and brain stimulation strategies. Pharmacotherapy may involve optimisation, switching, combination of antidepressants, and augmentation with a non-antidepressant agent. Common psychological therapies are cognitive-behavioural therapy, interpersonal psychotherapy, acceptance and commitment therapy and mindfulness-based cognitive therapy. Electroconvulsive therapy and repetitive transcranial magnetic stimulation may also be used.

The clinical management algorithm shows that VNS therapy is targeted to highly-resistant and hard-to-treat patients. "Treatment resistant" for the purpose of the MBS eligibility is

defined as failure to show an adequate response to four or more appropriate antidepressant treatments.

9. Comparator

TAU, otherwise referred to as standard of care, is proposed as the main comparator for VNS. TAU in MDD typically comprises alternative pharmacological strategies (switching, augmentation or combination), psychotherapeutic strategies or brain stimulation therapies such as ECT. The treatment is necessarily individualised reflecting the individual patient needs and previous treatment history. VNS is to be added onto TAU (i.e., complementary and adjunctive).

10. Comparative safety

The Sponsor MA (2016) and Berry et al (2013) meta-analyses were the primary evidence sources used to determine the comparative safety of VNS+TAU to TAU. The SBA stated that high to moderately high heterogeneity was observed in the safety data. The number of events in mortality, suicides (completed) and suicides (attempted) were low. Comparisons between VNS+TAU and TAU were only possible for the drop outs (all causes) outcome which showed benefit of VNS+TAU over TAU. Results for VNS+TAU showed a manageable safety profile.

In the Berry meta-analysis (2013), the most common adverse events were voice alteration, dyspnoea, pain, cough, and incision pain. In addition, there was a trend towards diminishing adverse events (AE) over the 2 years of VNS treatment. This decrease of side effects over time was also seen in the extended assessment of harm which was based on 5-year follow-up data from study D-23, and long-term (up to 3 years) safety outcomes of VNS therapy in a patient population with refractory epilepsy.

The critique stated that there is no direct comparative data comparing safety outcomes of VNS+TAU to TAU beyond 10 weeks. The safety data reported in the SBA were primarily from single-arm trials of VNS+TAU, non-randomised studies of VNS+TAU versus TAU, and naïve comparisons of these study designs.

Due to the absence of direct comparative data, the critique stated that it is not possible to separate the treatment effects of VNS therapy from TAU for the safety outcomes (e.g. hospitalisation, mania, serious adverse events etc.). A conservative approach to interpreting the safety data is to assume all adverse effects are related to VNS therapy, which represent additional harms not otherwise borne in the TAU group. Across time points, the rates of all-cause mortality (range 0.0-1.4%), suicide fatal (range 0.0-0.2%), and suicide attempts (range 0.0-3.7%) were low in the VNS+TAU group. Serious adverse events were common (~18.5% at 12 months, 39.1% at 24 months). It is unclear if discontinuations due to adverse events were reported correctly, due to the high degree of unexplained study withdrawals in the primary data.

The critique stated that VNS is associated with device-specific adverse events such as voice alteration (69% at 12 months), pain (28% at 12 months), incision pain (26% at 12 months), incision-site reaction (16% at 12 months),device-site pain (14% at 12 months) and device-site reaction (12% at 12 months) (Berry 2013). These adverse event rates show some reduction at 24 months. Importantly, 16% of the VNS patient withdrawals from the analysis were unexplained, and may have been caused by adverse events.

11. Comparative effectiveness

The SBA stated that in the Sponsor MA 2016, 22 comparative analyses were possible. The sponsor pooled available data from multiple studies of VNS+TAU and used two studies for the TAU arm, D-04 and D-23 (which included a direct head-to-head comparison). Two psychometric instruments, one measuring specific depressive symptoms (MADRS) and another, a more general measure of clinical outcomes in depression, CGI-I, were used across all studies included in the analysis. The sponsor advised that both measures are validated and widely used in the field.

VNS+TAU was statistically significantly better compared to TAU in 12 analyses (10 efficacy and 2 safety outcomes), and numerically superior in 10 analyses (9 efficacy and 1 safety outcome). There was no measure in which TAU was superior to VNS+TAU. Exclusion of non-sponsored studies did not change these findings, as sample sizes of these studies were small, and therefore did not influence results greatly. There was an improvement in outcomes over time across all 7 efficacy measures. The pooled rate typically increased over 12 months and often remained stable at 24 months. This is analogous to findings with VNS therapy in treatment resistant epilepsy patients.

In the Berry meta-analysis (2013), a consistent superiority of VNS + TAU over TAU was found, with the odds of response in VNS + TAU patients three times that for patients who received TAU alone, and the odds of remission in VNS + TAU patients were almost five times as likely as that for TAU patients.

The critique noted that there is only one direct comparative study comparing effectiveness outcomes of VNS+TAU to sham VNS+TAU, with outcomes to 10 weeks. The remaining evidence presented was from a meta-analysis combining single-arm studies and non-randomised comparative studies.

The critique considered that the Sponsor MA (2016) did not use an appropriate methodology to evaluate comparative effectiveness of the VNS therapy. Further, although the Berry (2013) meta-analysis was conducted using appropriate methods, it had several key limitations due to the available data used. Some key issues from both the primary evidence and data synthesis included:

- A high rate of patient attrition was observed throughout the course of the VNS treatment, according to primary studies included. The SBA did not provide an adequate explanation or make appropriate adjustments to mitigate the issue. It is possible there was a correlation between patient attrition and safety and effectiveness outcomes, as the rationale for these losses was not adequately explained in the included studies. The discounting effect of attrition potentially made the safety and effectiveness outcomes more favourable to VNS therapy.
- A number of different psychometric measures were inconsistently utilised. . This resulted in substantial clinical heterogeneity which made the comparative results difficult to interpret. The SBA did not address the issue or make any adjustment to mitigate any potential impact.
- The Sponsor MA (2016) pooled available outcome data from multiple studies of VNS+TAU (the intervention), and then compared with results of TAU from two non-randomised studies to produce comparative effectiveness with no adjustment of confounding. This was not appropriate. The effectiveness results in the SBA were highly likely to be biased and confounded.

The critique considered that the clinical claims on VNS+TAU being superior over TAU alone could not be substantiated. There were significant uncertainties with how VNS could

influence remission rate for eligible patients. The comparative effectiveness of VNS+TAU was not clear, and likely to be biased in favour of VNS therapy. Therefore interpretations of clinical effectiveness results on VNS therapy in the SBA should be considered with caution.

Clinical Claim

The SBA's clinical claim on the basis of the benefits and harms reported in the evidence base, was relative to TAU, VNS+TAU has inferior safety (because VNS therapy is used as an adjuvant treatment to TAU, and it is invasive, although minimally, in nature) and superior effectiveness.

12. Economic evaluation

The economic evaluation presented a cost-utility analysis that used a Markov approach, and health states defined by MADRS scores, to compare the incremental costs and health benefits of VNS+TAU against TAU in patients with MDD. The model horizon was 10 years to match the expected battery life of the VNS device in the MDD application.

Table 3 Summary of the economic evaluation

Perspective	Australian healthcare system
Comparator	Standard of care (or treatment as usual)
Type of economic evaluation	Cost-utility analysis
Sources of evidence	D-23 trial for clinical inputs (supported by systematic review).
Time horizon	10 years (the average battery life of VNS generator)
Outcomes	Quality-adjusted life years (QALYs)
Methods used to generate results	Markov cohort model
Health states	MADRS 35-60 MADRS 20-34 MADRS 10-19 MADRS 0-9 Dead
Cycle length	6 months
Discount rate	5% per annum
Software packages used	TreeAge

Abbreviations: MADRS, Montgomery–Åsberg Depression Rating Scale; VNS, vagus nerve stimulation.

The overall costs and outcomes, and incremental costs and outcomes as calculated for the intervention and comparator in the model, with the base case assumptions, are shown in Table 4. The incremental cost-effectiveness ratio (ICER) of VNS+TAU compared to TAU was estimated to be $26,633 per QALY gain, calculated for 10 years.

Table 4 Incremental cost-effectiveness of VNS plus SoC versus SoC alone in treatment resistant depression

	Cost	Incremental cost	QALYs	Incremental QALYs	ICER
VNS + TAU	$38,975	$13,418	4.3652	0.5038	$26,633
TAU alone	$25,557		3.8614		

Abbreviations: ICER, incremental cost-effectiveness ratio; TAU, treatment as usual; VNS, vagus nerve stimulation; QALYs, quality-adjusted life years.
Note: All results discounted at 5% per annum.

The critique noted that when only 5 years of clinical benefits were included the ICER is estimated to be $65,586.

The SBA included a number of sensitivity scenarios around clinical effectiveness. The results of the base case model were most sensitive to shortening of time horizon and adverse event-related disutility sensitives.

13. Financial/budgetary impacts

The SBA used an epidemiological approach to estimate the patient population potentially eligible for VNS on the MBS. While the epidemiological evidence may suggest a sizeable potentially eligible patient population for VNS, the actual usage will be limited by the capacity to provide the treatment. An analysis of likely local caseload capacity is performed to inform more realistic budget estimates to the MBS.

The estimated total financial impact on the MBS with and without VNS therapy is shown in Table 5. The total estimated MBS costs were associated with **redacted** private implantation procedures in Year 1, increasing to **redacted** by Year 5. The estimated total MBS cost was estimated to be $**redacted** in Year 5 using the centre based (case load) approach.

Table 5 Total costs to the MBS associated with VNS for the management of TRD – caseload capacity approach

Table redacted

14. Key issues from ESC for MSAC

ESC Key ISSUES	ESC ADVICE
Strength of evidence	All data rests essentially on 2 RCTs: • The only RCT vs sham shows no significant difference at 10 weeks • The other shows no dose response effect • All other data are observational and not strong enough to support efficacy • High likelihood of regression to the mean
Poor quality record	19 issues were detected with VNS devices between 2007 and 2018
ICER likely to be higher than estimated	VNS involves a substantial initial cost, therefore continued clinical benefits from years 5-10 in the base model have a large impact on the economic attractiveness of the intervention. Based on SA conducted in critique more conservative ICER in range $65,586 up to -$95,560/QALY
Uncertainty in financial estimates	The high rate of patient attrition in the evidence base (raising questions around patient acceptability), and competition with other treatment alternatives could place a downward pressure on utilisation. Equally, in the event that VNS delivers better than expected clinical benefits, service volumes may increase to meet patient demand.

ESC Discussion

ESC noted that VNS is an invasive therapy for chronic major depressive episodes in which a device that electrically stimulates the vagus nerve is implanted under the skin in the upper chest of a patient.

ESC noted that due to the invasive nature of this treatment, the item descriptor proposes that it be restricted to people with severe depression who have not responded to an adequate trial of at least four medicines. ESC suggested the wording of the item descriptor could be changed to restrict VNS use to people who have not responded to at least four different classes of antidepressants. ESC noted that based upon the US STAR*D study, 2.4% of patients do not respond to a fourth line medicine (Rush AJ et al 2006).

ESC noted that the comparator for VNS is TAU. However, ESC considered that TAU is difficult to accurately define in a patient group with depression that is treatment resistant (TRD) because it could include pharmacological strategies, psychotherapeutic therapies, brain stimulation and other miscellaneous non-evidence based treatments. ESC also noted that the evidence for VNS in treatment resistant depression was limited.

ESC queried how the PBAC defines treatment resistance in MDD to recommend ongoing treatment when considering anti-depressant medicines for PBS listing, as this would assist defining 'treatment resistant patients' for VNS therapy. ESC also queried whether PBAC assessed relapse treatment for antidepressant drugs. ESC noted that the CA submitted no evidence on relapse and thereby requested evidence on whether VNS is effective the second time, if it fails to be effective the first time.

ESC noted that while there had been two randomised controlled trials (RCTs) of VNS, only one of these had used a sham control arm in which the device was implanted but not turned on (Rush AJ et al 2005). In the other RCT, all patients were treated with VNS, but were randomised to differing dose levels (Aaronson ST et al 2013). ESC noted that the submission also heavily relied upon a non-randomised observational study, the D-23 study (Aaronson ST et al 2017).

With regards to safety, ESC noted that 19 issues were detected with VNS devices between 2007 and 2018 with 120 adverse events logged on the FDA's Manufacturer and User Facility Device Experience (MAUDE) database between 2015 and 2018. The adverse events recorded included lead fracture, high impedance and corrosion. ESC considered that the FDA data was likely to be of concern to consumers.

ESC noted that in the Aaronson 2013 trial, voice alterations were reported in 72% of patients while dyspnoea, pain and paraesthesia were all reported in 32% of patients.

With regards to clinical effectiveness, ESC considered that as patients can see the implanted device there is likely to be a placebo effect. However, ESC acknowledged that it may be difficult to adequately blind patients as to whether they have an active device even in trials using sham controls given the high prevalence of adverse effects on the voice.

ESC considered that the randomised evidence to support the clinical effectiveness of VNS was weak. ESC noted that the Rush trial (n = 235) reported no improvements in depression between the VNS arm and the sham arm after 10 weeks of treatment. In addition, in the Aaronson 2013 trial (n = 331) there was no evidence of a dose response at any follow-up time point over 22 weeks when patients were randomised to a 'low', 'medium' or 'high' stimulation group.
ESC considered that the observational D-23 study (n = 795) result to support the clinical effectiveness of VNS was very weak, and highly likely to be at high risk of bias. Patients enrolled in this study could choose their own treatment (VNS or TAU), there were significant

differences in demographics between the two arms and the VNS group had more severe depression at baseline. ESC also noted that while the D-23 study provided graphs comparing the cumulative proportions of participants who had responded to treatment in the VNS and TAU arms, these graphs did not include confidence intervals or error bars and provided no indication of how many people remained in the study as time progressed.

ESC noted that while there had only been two randomised trials of VNS in treatment resistant depression, there were three meta-analyses (and another three systematic reviews). ESC noted that two of the meta-analyses were undertaken by the sponsor (Berry SM et al 2013; Sponsor 2016) while another was undertaken by authors independent of the company (Martin JL & Martin-Sanchez E 2012). The Martin meta-analysis had been largely ignored in the submission despite being the only meta-analysis that did not pool randomised studies with observational studies. The Martin meta-analysis treated these observational studies as pre-post intervention studies. Pooling these observational studies suggested that there had been an improvement in depression after VNS. However, there was considerable heterogeneity among the pooled studies ($I^2 = 91\%$) and a meta-regression analysis indicated 84% of this variance was due to the severity of depression at baseline. ESC suggested that as such any improvements in depression outcomes seen in the observational studies may simply be regression to the mean.

ESC noted that due to the weakness of the evidence for effectiveness, the results of the economic evaluation were highly uncertain. ESC considered that the base case incremental cost effectiveness ratio (ICER) of approximately $26,600 per QALY was highly uncertain. ESC noted that the economic model has flaws in the structure. For non-responders, the model allows patients to restart on BSC or lithium or ECT or TMS over 3 cycles, however no evidence was presented to justify the loop.

ESC noted that uncertainty had been introduced into the model:

- by extending the time horizon beyond the five years of observational data seen in the D-23 study to 10 years. ESC noted as implantation of a VNS device has a high upfront cost, extending the time horizon made VNS look more cost-effective. ESC noted that reducing the time horizon to five years increased the ICER to approximately $65,500 per QALY;
- because of the choice of utility values for various depression states. While the literature identified three reviews which estimated utility values (Kolovos S et al 2017; Mohiuddin and Payne 2014; Sapin C et al 2004), the model took the highest utility value for remission from the Sapin review and the lowest utility values for mild, moderate and severe depression from the Mohiuddin and Payne review. The Kolovos review which included values for all four of these states was not used. ESC considered that the way utility values were selected in the model favoured VNS because the model assigned fewer VNS patients to the more severe depression states. ESC noted that if all utility values were taken from the Kolovos review, the ICER increased to approximately $57,800 per QALY (using EQ-5D values) or approximately $95,500 per QALY (using SF-36 values);
- the proportion of patients who achieved remission at six months and 12 months in the modelling (14.3% and 18.8%, respectively) differed slightly from that reported in the Sponsor meta-analysis (11.0% and 21.6%) and that seen in the D-23 study (11.9% and 11.1%);
- it was assumed that the proportion of patients in the various health states would remain stable after five years; and

- it was assumed that the costs for moderate and severe depression hospital admissions would be the same.

ESC also queried whether using a six-month cycle in the modelling was too long for depression. ESC considered that the financial estimates were also highly uncertain due to uncertainties around the acceptability of VNS to patients, patients' preferences for other treatments, levels of patient uptake and health system capacity. ESC further noted that the patient out of pocket expenses for VNS are high.

ESC was also concerned regarding the high incidence of voice changes noted in patients receiving this treatment (72%), potentially implying an adverse electrical conduction effect on the recurrent laryngeal nerve with a subsequent impairment of vocal cord function.

Overall, ESC considered this listing as a high risk listing due to several uncertainties discussed above.

15. Other significant factors

Nil

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

LivaNova Australia is disappointed with MSACs decision not to support MBS funding of VNS for chronic major depressive episodes. The available 5-year comparative data, supported by other clinical trials, demonstrates VNS's clear effectiveness. The proposed listing targeted patients who have effectively exhausted all available treatment options yet continue to suffer from uncontrolled depression. Whilst acknowledging the main body of clinical evidence was not RCT, the available 5-year comparative data in a "real world" setting should have been given more positive consideration, especially considering the lack of standardised treatment strategies at this "last line" setting (thus difficult / unethical to capture in a long-term RCT). Against the significant unmet clinical needs experienced by these patients, the presented clinical and cost-effectiveness evidence was believed to be sufficient and adequate.

17. Further information on MSAC

MSAC Terms of Reference and other information are available on the MSAC Website: visit the MSAC website