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Horizon scanning prioritising summary

Update Number 3

VNS therapy system for the treatment of depression

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UPDATE PRIORITISING SUMMARY

REGISTER ID: **000176**

NAME OF TECHNOLOGY: **VNS THERAPY™ SYSTEM**

PURPOSE AND TARGET GROUP: **TREATMENT OF CHRONIC OR RECURRENT TREATMENT-RESISTANT DEPRESSION IN ADULTS**

STAGE OF DEVELOPMENT (IN AUSTRALIA):

☐	Yet to emerge	☐	Established
☐	Experimental	☒	Established *but* changed indication or modification of technique
☐	Investigational	☐	Should be taken out of use
☐	Nearly established		

AUSTRALIAN THERAPEUTIC GOODS ADMINISTRATION APPROVAL

☒	Yes	ARTG number	114995
☐	No		
☐	Not applicable		

The VNS Therapy™ System is approved by the Australian Therapeutic Goods Administration (TGA) for the treatment of epileptic seizures.

INTERNATIONAL UTILISATION:

COUNTRY	LEVEL OF USE		
	Trials Underway or Completed	Limited Use	Widely Diffused
United States	✓		

IMPACT SUMMARY:

This summary provides a 12 month update on the VNS Therapy™ System, manufactured by Cyberonics Inc. The original Prioritising Summary for this device was compiled in December 2005. The VNS Therapy™ System is an implantable, pulse generated device for treating chronic or recurrent treatment-resistant depression. At the time of preparing the original prioritising summary a clinical trial was beginning at the Prince of Wales hospital in conjunction with the University of Sydney.

BACKGROUND

The vagus nerve is the tenth cranial nerve with fibres carrying efferent (motor) and afferent (sensory) information. The largest component (80%)of the left vagus nerve is the afferent sensory input, which relays information from extracranial sources to parts of the brain stem that modulate the activity of cortical and limbic structures relevant to depression (Matthews and Eljamel 2003, Groves and Brown 2005).

Vagus nerve stimulation (VNS) refers to the electrical stimulation of the cervical portion of the left vagus nerve. A bipolar stimulating electrode is wrapped around the vagus nerve and connected subcutaneously to an implantable, programmable pulse generator located under the skin of the left chest wall (Matthews and Eljamel 2003). The device is programmed to automatically stimulate the afferent fibres of the vagus nerve for 30 seconds every five minutes. VNS therapy is an established treatment modality for refractory epilepsy. The observation of changes in mood in participants of clinical trials of VNS on epilepsy was a precursor to research of VNS in depression (Elger et al 2000).

The VNS Therapy™ System is indicated as an adjunct for the long-term treatment of chronic or recurrent depression for patients over the age of 18 who are experiencing a major depressive episode and have not had an adequate response to four or more antidepressant treatments (VNS Therapy 2005).

The VNS Therapy™ System consists of an implantable VNS Therapy™ Pulse Generator, the VNS Therapy™ Lead and the external programming system used to change stimulation settings. The lead and the pulse generator make up the surgically implanted portion of the VNS Therapy™ System (Figure 1). Electrical signals are transmitted intermittently (30 seconds on and five minutes off) from the pulse generator to the vagus nerve by the lead. The software allows a physician to identify, read and change device settings such as pulse treatment, output current, signal frequency and stimulation duration. The pulse generator is surgically placed in the left chest and the lead is then connected to the pulse generator and attached to the left vagus nerve (Figure 2.).

Figure 1 VNS™ Therapy System Pulse Generator
(Printed with permission, Cyberonics Inc. 2005)

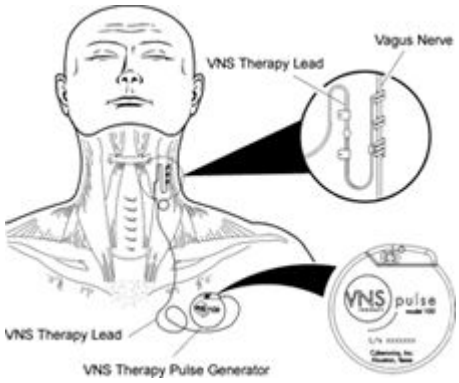

Figure 2 Implantation of VNS™ Therapy System

Patients are provided with magnets which if placed over the implanted pulse generator can deactivate programmed stimulation. Programmed stimulation resumes when the magnet is removed. The device is inactivated for 10-14 days post-implantation to avoid the risk of nerve damage (Matthews and Eljamel 2005). The VNS device can be programmed to provide therapy for up to ten years.

CLINICAL NEED AND BURDEN OF DISEASE

In the 2001 Australian Bureau of Statistics (ABS) National Health Survey, nearly 850,000 Australians reported symptoms of depression depression. However, the ABS did not publish the number of individuals reporting a specific diagnosis of depression (AIHW 2005a).

An earlier ABS survey, the 1997 National Survey of Mental Health and Wellbeing, used internationally recognised diagnostic interview schedules to assess the prevalence of mental disorder through the measurement of symptoms (AIHW 2005a). This survey found that approximately 700,000 Australian adults (6% of the population) aged 18 years and over, had experienced depression during the 12 month period prior to the survey. Depression was more prevalent amongst females with a rate of 9%, compared to 5% in males. Depression was also diagnosed in approximately 3% of children (aged 6-12 years) and 5% of adolescents (aged 13-17 years).

It is estimated that one in five people in Australia will experience depression at some point in their lifetime, with around one million adults in Australia and 100,000 young people living with depression each year (DHA 2005). Depression is currently the leading cause of non-fatal disability in Australia, with less than 50% of affected people receiving medical care (DHA 2005). In New Zealand a recent survey of general practitioners found approximately 50% of patients had experienced psychological problems in the past year, with 10%classifed as moderate or severe (MaGPIe Research Group 2003).

In 2003-04 there were 53,186 and 26,926 for principal diagnoses, F32 depressive episodes and F33 recurrent depressive episodes, respectively (AIHW 2005b).

DIFFUSION

The VNS Therapy™ System received United States Food and Drug Administration (FDA) approval for the indication of treatment-resistant depression in July 2005 (FDA 2005a). The device has been commercially available for the treatment of resistant partial onset seizures in Europe since 1994, and in the United States since 1997.

COMPARATORS

There are currently three major treatment modalities for which there is substantial evidence of effectiveness in the treatment of a major depressive episode: pharmacotherapy with antidepressant drugs (ADDs), specific forms of psychotherapy (including cognitive behavior and interpersonal therapy), and electroconvulsive therapy (ECT). ADDs are the usual first line treatment for depression (FDA 2005a). Clinical trials have demonstrated efficacy for a number of pharmacologic classes of ADDs. Physicians usually reserve ECT for treatment-resistant cases or when it is determined that a rapid response to treatment is desirable.

DECEMBER 2005 EFFECTIVENESS AND SAFETY ISSUES

The initial feasibility study (level IV intervention evidence) of the VNS Therapy™ System was conducted in 60 patients with treatment–resistant major depressive episodes (Sackheim et al 2001b). This study builds on a previous study on the effect of VNS Therapy™ on 30 patients and includes this data (Rush et al 2000). Patients with a nonpsychotic major depressive or bipolar disorder experiencing a major depressive episode (MDE) > 2 years, or patients who had experienced 4 MDE and had not responded to at least two medication trials during the current MDE were included in this study. The median duration of the current MDE was 6.6 years and patients had received an average of 16 different interventions aimed at treating the current MDE. These included nine traditional antidepressant medications and seven other mood disorder treatments. In terms of treatment resistance, 30% had failed two treatments; 7% had failed three; 20% had failed four; and 43% had failed more than five treatments during the current MDE (George et al 2002). Almost two thirds had received Electric Convulsive Therapy (ECT) within the current episode. Ten weeks of VNS therapy were provided with medication held constant.

Fifty-nine of the 60 subjects completed the 12-week acute phase (one patient improved during the recovery period), and were available for evaluation of effectiveness (Sackeim et al 2001b). Primary efficacy analysis of the 28-item Hamilton Rating Scale for Depression[1] ($HRSD_{28}$) at the end of 12 weeks demonstrated 18/60 (30%) patients met response criteria of a ≥ 50% reduction in score compared to baseline values. At baseline the mean $HRSD_{28}$ score was 37. The most common side-effect was voice alteration or hoarseness reported in 36/60 (60%) patients, which was related to the intensity of the output current. The study concluded that patients' history of treatment resistance and intensity of concurrent antidepressant treatment during the VNS trial were related to VNS therapy outcome. There were no improvements in depression in the 13 patients who had not responded adequately to

[1]A recognised, validated tool for categorising levels of depression for patients already diagnosed with the condition. Higher scores indicate more sever depression (Hamilton 1960). The higher the total score the more severe the depression.

more than seven antidepressant regimes, while 18/59 patients who completed the acute phase (30%, p=0.0057) did improve (Sackeim et al 2001b).

The first 30 patients continued treatment with the VNS Therapy™ System for a further nine months (Marangell et al 2002). In this follow-up study VNS therapy response rates in 12 (40%) patients originally reported by Rush et al (2000) were maintained. The FDA approval for the VNS Therapy™ System includes additional data for 25 patients from the Sackheim (2001b) trial and reports on effectiveness after one and two years (FDA 2005a). After one year 25/55 (45%) patients were responders, and 18/42 (43%) after two years. At two years 17/59 (29%) patients were lost to follow-up. Of the 18 patients who responded in the Sackheim study, 13 (72%) maintained their response while 12/41 of the non-responders in the acute phase (29%) became responders after one year of treatment. Of the subjects available for evaluation, 15%, 27% and 21% reached remission ($HRSD_{28} \leq 10$) at 12 weeks, one and two years, respectively (FDA 2005a).

The feasibility study formed the basis for the following 10-week study (level II intervention evidence) of the VNS Therapy™ System compared to sham-controlled treatment (Rush et al 2005a). The study included 235 outpatients with nonpsychotic major depressive disorder (n=210) or nonpsychotic, depressed phase, bipolar disorder (n=25), who had not responded adequately to between two and six medication regimes. A two-week, single-blind recovery period (no stimulation) was followed by 10 weeks of masked active (n=119) or sham (n=116)[2] VNS Therapy™ System treatment followed implantation. Clinical assessments were made weekly in the first four weeks after the device was turned on and fortnightly in the final six weeks. Outcome assessors and clinical management staff were blinded to treatment (Rush et al 2005a).

The primary efficacy outcome was a response rate of ≥ 50% reduction after 10 weeks relative to the mean $HRSD_{28}$ score obtained at two baseline visits (Rush et al 2005a). Active VNS treatment failed to show a statistically significant difference (p= 0.251) in acute response (15% response rate) from the sham control group (10% response rate) (Rush et al 2005a).

Two major adverse events occurred in the active VNS group causing withdrawal from the trial: one patient had the device removed due to infection and the second patient committed suicide after five weeks of treatment. A third participant withdrew from the study due to voice hoarseness (Rush et al 2005a). The four most common adverse events in patients originally implanted with the device were: voice alteration in

[2] The study reports that many participants experience no sensations when the device is operated at low stimulus intensity, or at higher intensities for some participants. These facts were communicated to participants to help preserve blinding.

124/235 (53%), increased cough in 44/235 (18%), dyspnea in 27/235 (16%) and dysphagia in 37/235 (15%) patients. It is unclear whether these symptoms were caused by the stimulation or device implantation.

After completion of the initial 3-month study, 205 participants (110 from the original treatment group and 95 from the sham group) continued in a long-term phase where those receiving VNS therapy (n=103) in the treatment group continued VNS therapy for a further nine months and patients in the control group (n=74) were offered VNS treatment for 12 months (Rush et al 2005b).

The primary outcome measure was change over time in the $HRSD_{24}$ scores[3]. Twelve months of VNS therapy was completed by 177/205 patients. There was a positive response rate (≥50% reduction in $HRSD_{24}$ score) of 30% with a mean reduction of 0.45 points per month ($p<0.001$) on the $HRSD_{24}$ and a complete remission rate (defined as a score ≤ 9 $HRSD_{24}$ of 17% (Rush et al 2005b).

After 12 months of treatment, 99/177 (56%) of patients available for evaluation achieved a meaningful clinical benefit, however 27% of patients had minimal or no benefit and 18% of patients were reported to be worse than baseline values (Rush et al 2005b, FDA 2005a). A sustained response was reported in 47/177 (27%) patients.

A poor quality study by George et al (2005) (level III-3 intervention evidence) compared 124 patients receiving standard of care (SOC) enrolled in a separate, unpublished, observational study for treatment-resistant depression, to the 205 patients available for evaluation who had received VNS therapy in the study by Rush et al (2005b). SOC treatment was defined as the treatment strategy chosen by patients' physicians. The primary outcome was the comparison of monthly data of the estimated mean change from baseline between groups according to scores of the 30-item Inventory of Depressive Symptomatology-Self-Report ($IDS\text{-}SR_{30}$).[4] The IDS-SR scores were chosen for the primary efficacy analysis rather than the HRSD-24 scores because the linear regression analysis required multiple post-baseline observations and the only HRSD-24 observations available for the SOC patients were a baseline and a 12-month observation (FDA 2005b). This study reported that patients receiving VNS treatment experienced greater improvement per month in $IDS\text{-}SR_{30}$ scores compared to the SOC patients across 12 months ($p<0.01$).

[3] Both Sackheim et al 2001 and the RCT (Rush et al 2005a) trials employed the 28 item (HRSD28) instrument while this trial employed a modified 24 item scale, the HRSD24. One of the authors was contacted to provide an explanation for the difference. According to the author the reason was that the missing 4 items largely tap atypical symptoms and those with atypical features were excluded from the trials.

[4] The IDS-SR is a 30-item, patient self-report rating of the symptoms of mood and depression.

COST IMPACT

It is estimated that depression-associated disability costs the Australian economy $14.9 billion annually, with more than six million working days lost each year, over $600 million each year in treatment costs (DHA 2005). These costs are likely to rise as the number of patients requiring treatment continues to rise due to improved diagnostic techniques employed by clinicians.

The current cost of the VNS Therapy™ System device is $12,300 for the pulse generator and $3,770 for the VNS Therapy™ System Lead. Private health insurance companies do provide rebates for the cost of the device and implant procedure for the epilepsy indication (personal communication, VNS Therapy™ product distributor, 17th October 2005).

There was no available data on the cost impact of treating depression with the VNS Therapy™ System at the time of preparing this summary.

ETHICAL, CULTURAL OR RELIGIOUS CONSIDERATIONS

Patients suffering from treatment resistant depression who have been eligible for trialling the device are a particularly vulnerable group, who are difficult to treat and experience high death rates. The introduction of new devices or treatments for these groups needs to be based on evidence that demonstrates *both* safety and effectiveness and not offered as a "last" resort or simply because standard treatments have not proved successful. The available data for the VNS Therapy™ System raises concerns over patients displaying worsening depression, patients who died while receiving treatment and other adverse events. The issue of informed consent needs to be carefully examined for future studies and/or before introducing this device into clinical practice.

OTHER ISSUES

No issues were identified/raised in the sources examined.

DECEMBER 2005 RECOMMENDATION:

It is well recognised that mental health and associated disorders impact greatly on both patients and their families' physical, emotional and social health in addition to the economic costs of medical treatment and welfare services. Mental Health is a current National Health Priority by the Australian, State and Territory governments with increased focus on initiatives to improve outcomes for people with mental health conditions. Although there are numerous treatment options for depression, there is still a need for alternatives that are safe and effective in both the short and long term. The higher quality data to date suggest that the VNS Therapy™ System may provide limited relief as an adjunctive treatment for long-term depression patients.

Given that the device is about to be trialled in Australia HealthPACT recommended that this technology be monitored.

LIST OF STUDIES INCLUDED	TOTAL
Total number of studies	
Level II intervention	1
Level II intervention	1
Level III-3 intervention	1
Level IV intervention	1

DECEMBER 2005 SOURCES OF FURTHER INFORMATION:

AIHW (2005a). *Incidence and prevalence of risk factors* [Internet]. Available from: http://www.aihw.gov.au/cdarf/data_pages/incidence_prevalence/index.cfm#Depression [Accessed 1st September 2005].

AIHW (2005b). *National Hospital Morbidity Database* [Internet] AIHW. Available from: http://www.aihw.gov.au/cognos/cgi-in/ppdscgi.exe?DC=Q&E=/AHS/principaldiagnosis0304 [Accessed 1st September 2005].

DHA (2005). *beyondblue - the National Depression Initiative* [Internet]. Australian Government Department of Health and Ageing. Available from: http://www.health.gov.au/internet/wcms/publishing.nsf/Content/mental-beyond [Accessed 15th September 2005].

Carpenter, L. L., Friehs, G. M. & Price, L. H. (2003). 'Cervical vagus nerve stimulation for treatment-resistant depression', *Neurosurg Clin N Am*, 14 (2), 275-282.

Elger, G., Hoppe, C.et al (2000). 'Vagus nerve stimulation is associated with mood improvements in epilepsy patients', *Epilepsy Res*, 42, 203–210.

George, M. S., Rush, A. J. et al (2005). 'A one-year comparison of vagus nerve stimulation with treatment as usual for treatment-resistant depression', *Biol Psychiatry*, 58 (5), 364-373.

George, M. S., Rush, A. J. et al (2003). 'Vagus nerve stimulation (VNS): utility in neuropsychiatric disorders', *Int J Neuropsychopharmacol*, 6 (1), 73-83.

Groves, D. A. & Brown, V. J. (2005). 'Vagal nerve stimulation: a review of its applications and potential mechanisms that mediate its clinical effects', *Neurosci Biobehav Rev*, 29 (3), 493-500.

Hamilton M (1960) A rating scale for depression. Journal of Neurology Neurosurgery and Psychiatry 23,56-62.

MaGPIe Research Group (2003). 'The nature and prevalence of psychological problems in New Zealand primary healthcare: a report on Mental Health and General Practice Investigation (MaGPIe)', *N Z Med J*, 116 (1171), U379.

Marangell, L. B., Rush, A. J. et al (2002). 'Vagus nerve stimulation (VNS) for major depressive episodes: one year outcomes', *Biol Psychiatry*, 51 (4), 280-287.

Matthews, K. & Eljamel, M. S. (2003). 'Vagus nerve stimulation and refractory depression: please can you switch me on doctor?' *Br J Psychiatry*, 183, 181-183.

Rush, A. J., George, M. S. et al (2000). 'Vagus nerve stimulation (VNS) for treatment-resistant depressions: a multicenter study', *Biol Psychiatry*, 47 (4), 276-286.

Rush, A. J., Marangell, L. B. et al (2005a). 'Vagus nerve stimulation for treatment-resistant depression: a randomized, controlled acute phase trial', *Biol Psychiatry*, 58 (5), 347-354.

Rush, A. J., Sackeim, H. A. et al (2005b). 'Effects of 12 months of vagus nerve stimulation in treatment-resistant depression: a naturalistic study', *Biol Psychiatry*, 58 (5), 355-363.

Sackeim, H. A., Keilp, J. G. et al (2001a). 'The effects of vagus nerve stimulation on cognitive performance in patients with treatment-resistant depression', *Neuropsychiatry Neuropsychol Behav Neurol*, 14 (1), 53-62.

Sackeim, H. A., Rush, A. J. et al (2001b). 'Vagus nerve stimulation (VNS) for treatment-resistant depression: efficacy, side effects, and predictors of outcome', *Neuropsychopharmacology*, 25 (5), 713-728.

United States Food and Drug Administration (2005a). *VNS Therapy System - P970003s050* [Internet]. FDA. Available from: http://www.fda.gov/cdrh/PDF/p970003s050a.pdf [Accessed 15th September 2005].

United States Food and Drug Administration (2005b). *Executive Summary and Discussion of the Vagus Nerve Stimulation (VNS) Therapy Depression Indication Clinical Data* [Internet]. FDA.Available from: http://www.fda.gov/ohrms/dockets/ac/04/briefing/4047b1_01_Clinical%20Executive%20Summary-FINAL.htm [Accessed September 15th 2005].

VNS Therapy (2005).*What is VNS Therapy?* [Internet]. Cyberonics. Available from: http://www.vnstherapy.com/depression/whatisvnstherapy/default.aspx [Accessed August 31st 2005].

SEARCH CRITERIA TO BE USED:

Cognition Disorders/etiology/ psychology/therapy
Depressive Disorder/complications/ psychology/therapy
Electric Stimulation
Vagus Nerve/ physiology

JANUARY 2007 – UPDATE - EFFECTIVENESS AND SAFETY ISSUES

There have been no further studies with *new* patients reporting clinical outcomes since the publication of the original prioritising summary, however a long-term follow-up of one study included in the 2005 summary has since been published. This study (level IV Intervention evidence) described a subset of 11 patients from the same hospital, who were included in the long-term phase safety and effectiveness trial of VNS previously described by Rush et al 2005b. This study reported an overall reduction in mean depression scores at 1 year ($p<0.05$) defined as a 50% decrease in the $HRSD_{24}$ scores from the baseline $HRSD_{24}$ scores. This includes three patients who had gone into remission (defined as $HRSD_{24} \leq 10$) at 12 months (Corcoran et al 2006).

A study reports on patients from the original case series study (Rush et al 2000) at 2 years (Nahas et al 2005). There were substantial losses to follow-up at this time (n=42/59). The study authors included all 59 participants in the last observation carried forward (LOCF) analyses. At 2 years it is reported that 42% (25/59) patients demonstrated a 50% improvement in $HRSD_{28} \leq 10$ score (non-significant $p=0.648$) and 22% (13/59, non-significant $p=0.549$) reported a remission rate as defined by a final score of $HRSD_{28} \leq 10$ (Nahas et al 2005). As outcome rates are only reported for the 42 patients that were assessed at 2 years, it is difficult to know whether the losses to follow-up affect the results reported.

The Blue Cross Blue Shield published a non-systematic technology report presenting the same studies included in the original ANZHSN summary and this updated prioritising summary. The authors of this report concluded that there was insufficient available evidence to permit conclusions regarding the effectiveness of VNS therapy on health outcomes or its effect iveness compared to alternative therapies (Technology Evaluation Center 2006).

OTHER ISSUES

A clinical trial of VNS therapy is currently being conducted at the Prince Wales Hospital in Sydney. The trial coordinator was contacted to advise on progress of this trial and reported that to date there are only two patients enrolled (personal email communication, Prince of Wales Hospital, NSW 1st November 2006).

JANUARY 2007 – CONCLUSION:

There is no new evidence for safety and effectiveness for the VNS Therapy™ System.

HEALTHPACT ACTION:

Given the lack of new evidence HealthPACT has recommended that further assessment of this technology is no longer warranted.

JANUARY 2007 - SOURCES OF FURTHER INFORMATION:

Corcoran, C.D., Thomas, P.et al.(2006). 'Vagus nerve stimulation in chronic treatment-resistant depression: preliminary findings of an open-label study.' *Br J Psychiatry*, 189:282-3.

Nahas, Z., Marangell, L.B. et al. (2005). 'Two-year outcome of vagus nerve stimulation (VNS) for treatment of major depressive episodes. ' *J Clin Psychiatry*, 66:1097-104.

Technology Evaluation Center Assessment Program (2006). *Vagus nerve stimulation for treatment-resistance depression.* August 21(7):1-21. [Internet] Blue Cross Blue Shield Association. Available from: http://www.bcbs.com/tec/Vol20/20_08.pdf [Accessed 1st November 2006].

LIST OF STUDIES INCLUDED

Level IV intervention	2