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Technology Assessment Review Report

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Name of the Technology:
Vagus Nerve Stimulation (VNS) for Treatment-Resistant Depression

Description of the Technology:
Vagus Nerve Stimulation (VNS) is a seizure-free, stimulation-based therapy currently being explored for the treatment of depression and has already been widely used in the treatment of epilepsy in the United States since 1997. In VNS therapy, a mild electrical pulse is applied to the left vagus nerve via an implantable device positioned under the skin of the neck during an outpatient surgery with the patient under either general anesthesia or regional cervical block. Specifically, a pulse generator (IPG) is implanted in the left chest and a lead (wire) is connected to the IPG and wrapped around the left vagus nerve. Electrical signals are sent from the IPG to the nerve via the lead. To turn the stimulator off, the patient holds a magnet over the pulse generator.

The device is programmed to automatically stimulate the afferent fibers of the vagus nerve for 30-90 seconds every 5-10 minutes or upon demand by patients or family by placing a magnet against the subclavicalur implant site. Stimulator settings are programmed to deliver intermittent stimulation with current of 0.25-5.0mA, frequency of 20-50 HZ, and pulse width of 500 nanoseconds. This stimulation typically occurs 24 hours a day, 7 days a week and last for as long as the life of the battery within the implant – usually about 10 years.

It is thought that VNS elicits its antidepressant effects indirectly; the vagus nerve stimulates the nucleus of the solitary tract through direct afferent connection, and this area in turn, stimulates limbic structures – the same structures associated with animal models of depression. Research has shown that VNS increases turnover rates in a number of neurotransmitters implicated in depression including serotonin, norepinephrine and dopamine.

1. Technology must have final approval from the appropriate government regulatory bodies.

VNS Therapy System has been approved for the treatment of epilepsy in the United States since 1997. On July 15, 2005, the Centers for Devices and Radiological Health (CDRH) of the Food and Drug notified the manufacturer, Cyberonics, Inc., that it was approved for use for the adjunctive long-term treatment of chronic or recurrent depression for patients 18 years of age or older who are experiencing a major depressive episode and have not had an adequate response to four or more adequate

antidepressant treatments. This approval allows Cyberonics, Inc. to begin commercial distribution of the devise for this intended use.

This FDA approval came with requirements for two postapproval studies to further characterize the optimal stimulation dosing and patient selection criteria for the VNS Therapy System for treatment resistant depression (TRD) : (1) a prospective, multi-center, randomized, double-blind comparison of different output comparisons in 450 new subjects with TRD and (2) a prospective, observational registry study of 1000 implanted subjects with TRD with follow-up extending to 5 years – designed to evaluate the long-term outcomes as well as predictors of response to therapy.

2. The scientific evidence must permit conclusions about the effects of the technology on health outcomes. (Conclusive evidence in peer-reviewed medical literature to enable the evaluation of the effectiveness and efficacy of the procedure or drug.)

Levels of Evidence are defined as follows:

Level 1: *Randomized trials that had enough power to demonstrate a statistically significant health outcome.*
Level 2: *Randomized trials with results that were not statistically significant but where a larger trial might have shown a clinically important difference.*
Level 3: *Nonrandomized concurrent cohort comparisons between contemporaneous patients.*
Level 4: *Nonrandomized historical cohort comparisons between current patients and former patients (from the same institution or from the literature).*
Level 5: *Case series without control subjects.*

Few studies have been conducted on VNS since the Magellan issued its initial Technology Assessment in 2001and subsequent revisions in 2005 and 2006. The two studies discussed below were submitted to the FDA for review and formed the basis for the decision of the FDA Advisory Panel of Experts to approve its use in treating treatment resistant depression:

Marangell LB, Rush AJ, George MS, et. al (2002) – Level 5
An open-label trial of VNS therapy tracked **60** subjects over an 8-week, fixed-dose period. The subjects were considered very treatment resistant at baseline (mean Hamilton Rating Scale for Depression (HRSD $_{28}$) was 36.8, and they had a mean length of current depressive episode of 9.9 years. In this study group, 66% of the subjects had experienced ECT treatment during the current depressive episode. At 3 months, 31% of subjects showed response (reduced HRSD $_{28}$ >/=50) and 15% of responders were in remission (HRSD $_{28}$ </= 10). Follow-up at 1 year found an increase in response (45% response rate, 27% remission) and a decrease in reported adverse events.

George MS, Rush AJ, Sackeim HA, Marangell LB (2003) – Level 1
This was a blinded and placebo-controlled study of **222** subjects where those considered "extremely treatment resistant" based on large numbers of previous treatment failures were excluded. However, these subjects were considered similarly ill in that the mean HRSD $_{24}$ scores = 27.9. Only 10% of subjects were bipolar, the remaining suffered from unipolar depression. Findings demonstrated a 15% response rate to VNS treatment (reduction in HRSD $_{24}$) and 10% response rate for those receiving sham treatment.

Long-term follow-up at 12 months found 29.8% response rate, with 17.1% of subjects in full remission. These response rates were not statistically significant when compared with the sham-control response rates.

An additional literature search through August 2006 was conducted to update Magellan's second revision of this Technology Assessment which was released on 7/26/05. The search returned the following studies:

Sponsor (Cyberonics) commissioned ECT study (2004) – Level 4
Cyberonics commissioned an analysis from a previously published study of ECT by Prudic (2004) et al. where a subset of patients that would have qualified for the VNS trials was assembled. The VNS patients had several characteristics associated with a greater severity of treatment-resistant depression. Fifty-eight percent of patients receiving ECT achieved at least 50% reduction in Hamilton Rating Scale for Depression (HRSD) score. At 6 months following ECT, 41% of patients still had at least a 50% reduction in HRSD score. Comparing this informally to the results of the VNS patients in the sponsors D-02 (pivotal) and D-04 (comparative) studies, ECT appears to be a much more effective treatment for depression – 41% response and 21% remission. After 12 months of VNS therapy plus standard of care treatment 27% met the response criterion and 15% met the remission criteria.

Carpenter LL, Moreno FA, King MA, Anderson GM et al. (2004) – Level 5
Carpenter et al conducted a clinical trial to show that VNS alters concentrations of monoamines and gamma-aminobutyric acid (GABA), neurotransmitter systems possibly involved in the pathogenesis of depression. Twenty-one (**21**) adults with treatment-resistant, recurrent, or chronic major depression underwent standardized lumbar puncture for collection of 12 ml cerebrospinal fluid (CSF) on three separate but identical procedure days during participation in the VNS D-02 (pivotal study) clinical trial. All subjects remained on stable regimens of mood medications. Collections were made at baseline (2 weeks after surgical implantation but before devise activation), week 12 (end of the acute-phase study), and week 24. Cerebrospinal fluid concentrations of norepinephrine (NE), 5-hydroxyindoleascetic acid (5-HIAA), homovanillic acid (HVA), and 3 methoxy-4-hydroxyphenylglycol (MHPG) were determined with high performance liquid chromatography. Concentration of GABA was assayed with mass spectrometry. Comparison of sham versus active VNS revealed a significant (mean 21%) VNS-associated increase of CSF HVA. Mean CSF concentrations of NE, 5-HIAA, MHPG and GABA did not change significantly. Higher baseline HVA/5-HIAA ratio predicted worse clinical outcome. The authors reached a conclusion that although several of the CSF neurochemical effects observed in this VNS study were similar to those described in the literature for antidepressants and electroconvulsive therapy, the results do not suggest a putative antidepressant mechanism of action for VNS.

Nahas Z, Marangell LB, Husain NM, Rush AJ, Sackeim HA, Lisanby SH, Martinez JM, George (2005) – Level 5
This study is an initial open, acute phase pilot study of **59** participants (adult outpatients with chronic or recurrent major depressive or bipolar I or II disorder) in a treatment-resistant major depressive episode (MDE) examining the effects of adjunctive VNS over a 24 month period. Changes in psychotropic medications and VNS were allowed only after the first 3 months. Response was defined as > or = 50% reduction from the baseline 28-item Hamilton Rating Scale for Depression (HAM-D-28) total score, and remission was defined as a HAM-D-28 score < or= 10. Based on last observation carried forward analyses, results were as follows: HAM-D-28 response rates were 31% (18/59) after 3 months, 44% (26/59) after 1 year, and 42% (25/59) after 2 years of

adjunctive VNS. Remission rates were 15% (9/59) at 3 months, 27% (16/59) at 1 year and 22% (13/59) at 2 years. By 2 years, 81% (48/59) were still receiving VNS.

Rush AJ, Sackeim HA, Marangell LB, George MS, Brannan SK, Davis SM, Lavori P et al. (2005) –Level 4

This is a naturalistic follow-up study describing outpatients (**n=205**) with non-psychotic major depressive (n=185) or bipolar I or II disorder, depressed phase (n=20) who initially received 10 weeks of active (n=110) or sham vagus nerve stimulation (n=95). The initial active group received another 9 months, while the initial sham group received 12 months of VNS. Participants received antidepressant treatments and VNS, both of which could be adjusted. Results of the primary analysis using repeated measures of linear regression revealed a significant reduction in 24-item Hamilton Rating Scale for Depression (HRSD 24) – average improvement was .45 points (SE+.05) per month ($p<.001$). At exit HRSD 24 response rate was 27.2% (55/202); remission rate (HRSD 24 < or = 9 was 15.8% (32/202). Montgomery Asberg Depression Rating Scale (28.2% - 57/202) and Clinical Global Impression-Improvement was 34% (68/220) showing similar response rates. Voice alteration, dyspnea, and neck pain were the most frequently reported adverse events. Data from this one year open trial found VNS to be well tolerated in the treatment of treatment-resistant depression – albeit in the context of changes in depression treatments. Comparative long-term data are still needed to determine whether these benefits can be attributed to VNS.

Rush AJ, Marangell LB, Sackeim HA, George MS, Brannan SK, Davis SM, Howland R, et al. (2005) - Level 1

This is a 10-week acute, randomized, controlled, masked trial comparing adjunctive VNS with sham treatment in **235** outpatients with non-psychotic, depressed phase (n=210); bipolar disorder (n=25). In the current episode, participants had not responded adequately to between two and six research-qualified medication trials. A two-week, single-blind recovery period (no stimulation) and then 10 weeks of masked active or sham VNS followed implantation. Medications were kept stable. Primary efficacy outcome among 222 evaluable participants was based on response rates defined as >/= 50% reduction from baseline on the 24 item HRDS. The results showed that at 10 week, HRSD 24 response rates were 15.2% for the active and 20% for the sham group ($p=.251$), last observation carried forward (LOCF). While VNS was well tolerated (1% left the study because of adverse events), this study did not yield definitive evidence of short-term efficacy for adjunctive VNS in treatment-resistant depression.

3. The technology is as safe and effective as existing alternative treatments.

VNS has been established to be safe, well tolerated, and efficacious in treatment-refractory epilepsy.

In the VNS studies for treatment-resistant depression, there were adverse events that could be divided into two categories: those related to the surgical implantation of the device, and those related to the stimulation. In the case of the former, 30% reported pain at the incision site, which usually dissipated within 1-2 weeks. The most common adverse events associated with the stimulation included hoarseness or voice alteration (60%), headache (30%), throat pain (27%), shortness of breath (23%), general pain (23%), and neck pain (17%). These rates of adverse events were consistent with those reported in previous studies of epilepsy. Particular adverse events from other treatments of depression have been induction of mania, hypomania, suicidality and worsening of the depression. There has not been evidence of a greater risk of these adverse events with VNS.

In conclusion, there has not been sufficient evidence to determine that VNS is as safe and effective as existing treatments. One important reason is that the studies to date have not totaled a sufficient number of patients and there have been no direct comparison studies to the established alternative – ECT.

4. The technology improves the net health outcome, i.e., there is conclusive evidence that the benefits outweigh the risks.

Conclusive evidence that benefits outweigh risks can only be satisfactorily determined after larger studies have occurred over longer time frames. There currently is not conclusive evidence that the benefits outweigh the risks.

5. The improvement in health outcomes is reliably obtainable outside investigational settings.

Evidence to date is not even conclusive that this technology benefits health outcomes in an investigational setting. Therefore, it has not been determined that this technology would be beneficial outside of investigational settings.

Conclusion (Is the new technology proven or experimental, and summary of why):

While the technology of VNS appears promising, evidence thus far remains limited and does not yet clearly demonstrate that this is an established treatment for depression. For the reasons stated in this document, Vagal Nerve Stimulation for Treatment-Resistant Depression remains investigational at this time.

Determination: **Investigational** **Effective Date:** September 26, 2006

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