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Joan Claybrook, President

September 6, 2006

Daniel Schultz, M.D.
Director, Center for Devices and Radiologic Health
Food and Drug Administration
9200 Corporate Blvd.
Rockville, MD 20850

Dear Dr. Schultz:

Public Citizen, a consumer advocacy group with 98,000 members, hereby petitions the Food and Drug Administration (FDA), pursuant to the Medical Device Amendments to the Federal Food, Drug and Cosmetic Act, 21 U.S.C. §§ 360d, 360f, and 352, and 21 C.F.R. §§ 10.30 and 861, to reverse the approval of the vagus nerve stimulation (VNS) device for the management of treatment-resistant depression (TRD) because the device has not demonstrated a "reasonable assurance that the device is safe and effective," the standard under the law, 21 CFR 860.7(4)(c)(1).

Today, we are also filing a request for a National Coverage Determination with the Center for Medicare & Medicaid Services (CMS) in which we ask that the device not be considered appropriate for reimbursement by the Medicare program. That letter is attached to this letter and is incorporated by reference. We also incorporate by reference our letter to you of May 11, 2005 (available at: <http://www.citizen.org/publications/release.cfm?ID=7385>), in which we argued that the device should not have been approved in the first place.

A. Action Requested

The revocation of FDA's prior approval of VNS for TRD

B. Statement of Grounds

We will not reiterate our arguments as to why we consider VNS ineffective for TRD, as they are reviewed in the letter to CMS as well as in our earlier letter to you. Moreover, the company has generated no significant new data since its submission to the FDA. The only new information of relevance is the report by the Senate Finance Committee on the approval process for VNS (Committee on Finance, United States Senate. Review of the FDA's approval process for the

vagus nerve stimulation therapy system for treatment-resistant depression. February 2006. Available at: http://finance.senate.gov/press/Gpress/02_2006%20report.pdf).

The investigation concluded that, in approving VNS, you overruled the more than twenty FDA officials who had reviewed the data. Every one of them recommended against FDA approval. The report concluded further that "The facts and circumstances ... raise legitimate questions about the FDA's decision to approve that device for the treatment of TRD." Elsewhere, the report again questions the appropriateness of FDA's approval, concluding that "instead of relying on the comprehensive scientific evaluation of its scientists and medical officers, it appears that the FDA lowered its threshold for evidence of effectiveness." Among the report's more specific findings were these:

- On October 3, 2003, CDER officials notified CDRH that had a sponsor submitted to CDER data similar in quality to those submitted for VNS, the CDER would not even have allowed the filing of the New Drug Application.
- When you were director of the Office of Device Evaluation, you ordered staff to issue a Major Deficiency Letter (instead of the non-approvable letter the staff favored) without even reviewing the sponsor's data. The letter was sent on March 4, 2004.
- An advisory committee meeting took place on June 15, 2004, despite the objections of FDA staff, and was described by the committee's executive secretary as "very unusual, emotional, not data driven." The committee recommended device approval in a 5-2 vote.
- After the August 11, 2004, non-approvable letter, the FDA received hundreds of letters and phone calls urging the agency to approve the device.
- FDA relations with the sponsor were described in the report as "not collegial." FDA staff described such interactions as "terrible" and at times "abus[ive]."
- Certain key management staff and reviewers were excluded from a critical meeting between FDA staff and the sponsor in December 2004.
- On January 6, 2005, one month prior to the approvable letter, the entire review team, including the new director of the Office of Device Evaluation, recommended against approval. The director of the Office of Device Evaluation is not typically involved in device approval decisions.
- Typically, device approval decisions are made at the division level and signed at the office level (the next level up). In this case, the decision was made at the center level in CDRH (the next step up from the office level).
- Several FDA staff, including you, agreed that the CDRH director was involved "very rarely" in decisions regarding device approval.

Given these highly irregular aspects of the approval process at the FDA, it is appropriate that the FDA revisit its ill-advised decision to approve VNS for TRD. To have an ineffective device on the market (and an expensive,

surgically implanted one at that) does no favors for those suffering from TRD. To allow the continued marketing of this device is to perpetrate a cruel hoax on those patients.

C. Environmental Impact

The actions requested by this petition are covered by categorical exclusions from the preparation of an environmental assessment or environmental impact statement under 21 C.F.R. §§ 25.34 (c) and 25.30(k). In addition, the actions requested would not have any substantial impact on the environment.

D. Certification

The undersigned certify that, to the best of their knowledge and belief, this petition includes all information and views on which the petition relies, and that it includes representative data and information known to the petitioners, which are unfavorable to the petition.

Yours sincerely,

Peter Lurie, MD, MPH
Deputy Director

Nicholas Stine
Research Associate

Sidney M. Wolfe, MD
Director
Public Citizen's Health Research Group



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Steve E. Phurrough, MD, MPA
Director
Coverage and Analysis Group
Office of Clinical Standards and Quality
Centers for Medicare & Medicaid Services
7500 Security Boulevard
Mailstop: C1-09-06
Baltimore, MD 21244-1850

Re: Formal Request for a National Coverage Determination for Vagus Nerve Stimulation for Treatment-resistant Depression (Track #1; Coverage Topic: Surgical Services)

Dear Dr. Phurrough:

We are writing to request that the Center for Medicare & Medicaid Services (CMS) issue a National Coverage Determination (NCD) that would deny Medicare reimbursement for Cyberonics' Vagus Nerve Stimulation (VNS) device for treatment-resistant depression (TRD). Although the device was approved for this purpose by the Food and Drug Administration (FDA) on July 15, 2005, CMS has made clear that this does not automatically guarantee reimbursement under the Medicare program. Indeed, while under the Food, Drug, and Cosmetic Act, a device must be proved safe and effective to gain FDA approval, the Social Security Act provides for reimbursement under Medicare only if the device is "reasonable and necessary." In our view, neither standard has been met, and for this reason today we are also filing a petition with the FDA urging the reversal of FDA's scientifically meritless previous decision to approve VNS.

On July 24, 2006, Cyberonics filed a request for an NCD with CMS. This is an act of desperation on the part of a flailing company. Instead of the direct route to reimbursement offered by the NCD (the obvious route if one was confident of a favorable NCD), the company sought approval from ten individual CMS contractors in 19 separate applications. Having completely failed with that strategy (see below), it is now turning to the NCD as a last resort for saving a product with disappointing sales.

Legal Background

FDA regulations require that a device demonstrate a "reasonable assurance that the device is safe and effective"¹ before the device can be marketed.² While it is clear that this standard has not

¹ 21 CFR 860.7(4)(c)(1)

been met (see “Background on VNS,” below), the FDA approved the device on July 15, 2005, making it eligible for reimbursement under Medicare. However, as CMS has made clear on multiple occasions, while it does defer to the FDA’s determinations of safety and efficacy, it operates under a different, more restrictive, standard in determining eligibility for reimbursement:

Whereas the FDA must determine that a product is safe and effective as a condition of approval, CMS must determine that the product is reasonable and necessary as a condition of coverage under section 1862(a)(1)(A) of the [Social Security] Act. CMS adopts FDA determinations of safety and effectiveness, and CMS evaluates whether or not the product is reasonable and necessary for the Medicare population. Although an FDA-regulated product must receive FDA approval or clearance ... for at least one indication to be eligible for Medicare coverage, ... FDA approval/clearance alone does not generally entitle that device to coverage.³

CMS uses a two-track approach to determining whether it will reimburse for a device. In the first, a company seeks a favorable NCD from CMS itself. CMS then initiates an evidence-based process to determine whether the criteria for reimbursement have been met. This may include an outside technology assessment and/or referral to CMS’ Medicare Coverage Advisory Committee. However, CMS regulations provide for the filing of NCDs by entities other than the manufacturer. Indeed a Track #1 request for an NCD can be made by “any party”:

A request to make an NCD can be received from an individual or entity who identifies an item or service as a potential benefit (or to prevent potential harm) to the Medicare population; this requestor can be either an aggrieved party as defined by section 522 of [the Benefits Improvement and Protection Act], or a nonaggrieved party.⁴

In general, any payment change that results from an NCD will take effect within a year of the filing of the NCD. On May 16, 2006, CMS issued a negative NCD for the Charite lumbar artificial disc for patients over the age of 60 on the grounds that it was not reasonable and necessary. *As far as we are aware, our application is the first by an advocacy group (and one of very few by anyone) to seek an NCD denying reimbursement under Medicare.*

The second track for securing Medicare reimbursement proceeds from Medicare’s contracting with carriers and fiscal intermediaries to process Medicare claims. Together with Quality Improvement Organizations, these groups can make their own Local Coverage Determinations (LCDs) that govern reimbursement in the dozens of Medicare regions in the country. LCDs

² This is a lower standard than for drugs which must demonstrate “substantial evidence of effectiveness for the claimed indications.” (21 CFR 314.50(d)(5)(v)) It defies logic to have a lower standard for a device that makes a disease claim (“treats depression”) than a drug making a similar claim.

³ 68 Fed Reg 55636 (September 26, 2003). See 67 Fed Reg 66755 (November 1, 2002) for essentially identical language.

⁴ 68 Fed Reg 55638 (September 26, 2003).

cannot be in conflict with NCDs, but may supplement them. This offers manufacturers two routes to reimbursement. As we will see, Cyberonics has now attempted both.⁵

Background on VNS

The VNS device is implanted beneath the left clavicle in an outpatient procedure that typically costs \$25,000 (including the device).⁶ A lead runs to the vagus nerve and generates 30-second electrical pulses every five minutes. The device was approved in 1997 for refractory epilepsy, but Cyberonics pursued the additional indication of TRD, perhaps because the company estimated that the market for the latter was 4.4 million people in the U.S. alone. In a May 11, 2005, letter to the FDA urging the agency to not approve the device, we described the inadequacies in the data supporting the efficacy of VNS for TRD.⁷ Here, we summarize those data and incorporate the entire letter by reference.

Expecting to demonstrate the efficacy of VNS over the short-term, Cyberonics conducted an appropriately designed randomized, controlled trial (Study D02 Acute Phase) of three months' duration in which all TRD patients were implanted with the device, but only half had the device turned on. The other half did not have the device turned on, and so received "sham therapy". The study was a failure. On the primary outcome measure (the Hamilton Rating Scale for Depression, or HRSD), VNS showed no efficacy compared to sham therapy; the same was true for nine of ten secondary analyses.⁸ This remains the best-designed study of VNS to date.

Following Study D02, the company offered sham therapy patients the chance to have their device turned on (Study D02 Long-term Phase). Predictably, the patients improved over time. This is a near-ubiquitous finding in studies of depression patients due to both the placebo effect and the tendency of patients enrolled into studies of relapsing conditions to improve over time (regression to the mean) because their condition is typically worse at the time of enrollment than at other times. In this and the follow-up to Study D02, patients were unblinded and, unlike in the acute phase of Study D02, were permitted to change concomitant therapies including other antidepressants and even electroshock therapy.

Facing rejection of their application by the FDA, the company opted to add a comparison group for Study D04, which merely compared the Study D02 Long-term Phase patients to this hastily assembled comparison group. Like Study D02 Long-term Phase, there was no blinding, concomitant therapies were permitted to change over time and the comparison patients were recruited from overlapping, but different, sites. Indeed, the authors of a published report on VNS acknowledge that the comparison arm "had not originally been intended to serve as the [control]; it was intended to describe health care costs."⁹ A modest benefit was reported by the

⁵ On rare occasions, an insurer may reimburse for a service that has neither an NCD nor an LCD, depending on the circumstances of the particular patient.

⁶ Kelly S. Profits elusive for Cyberonics, shares plunge. Reuters, August 1, 2006.

⁷ Stine N, Lurie P, Wolfe S. Letter to FDA urging that the Vagus Nerve Stimulator not be approved for treatment of depression (HRG Publication #1741). Available at: <http://www.citizen.org/publications/release.cfm?ID=7385>.

⁸ Rush AJ, Marangell LB, Sackeim HA, George MS, Brannan SK, Davis SM et al. Vagus nerve stimulation for treatment-resistant depression: a randomized, controlled acute phase trial. *Biological Psychiatry* 2005;58:347-354.

⁹ George MS, Rush AJ, Marangell LB, Sackeim HA, Brannan SK, Davis SM et al. A one-year comparison of vagus nerve stimulation with treatment as usual for treatment-resistant depression. *Biological Psychiatry* 2005;58:364-373.

researchers, but only after the only (secondary) outcome that was positive in Study D02 was hand-picked to be the primary outcome for Study D04. Moreover, in an analysis mandated by the FDA, adjusting for overlapping sites and concomitant treatment produced no statistically significant finding on any primary or secondary outcome.

A weaker package of studies is difficult to imagine. Yet, inconceivably, the FDA issued an approvable letter on February 2, 2005, and approved the device on July 15, 2005, overruling an August 12, 2004, non-approvable letter the FDA had sent to the company.

Developments since FDA approval

Senate Finance Committee Report

So unusual were these circumstances, that the Senate Finance Committee launched an investigation into the VNS approval process.¹⁰ The investigation concluded that, in approving VNS, the director of FDA's Center for Devices and Radiological Health, Dr. Daniel Schultz, had overruled the more than twenty FDA officials who had reviewed the data. Every one of them recommended against FDA approval. The report concluded further that, "The facts and circumstances ... raise legitimate questions about the FDA's decision to approve that device for the treatment of TRD." Elsewhere, the report again questions the appropriateness of FDA's approval, concluding that "instead of relying on the comprehensive scientific evaluation of its scientists and medical officers, it appears that the FDA lowered its threshold for evidence of effectiveness." Among the report's more specific findings were these:

- On October 3, 2003, CDER officials notified CDRH that, had a sponsor submitted to CDER data similar in quality to those submitted for VNS, CDER would not even have allowed the filing of the New Drug Application.
- Dr. Schultz, who was then director of the Office of Device Evaluation, ordered staff to issue a Major Deficiency Letter (instead of the non-approvable letter the staff favored) without even reviewing the sponsor's data. The letter was sent on March 4, 2004.
- An advisory committee meeting took place on June 15, 2004, despite the objections of FDA staff, and was described by the committee's executive secretary as "very unusual, emotional, not data driven." The committee recommended device approval in a 5-2 vote.
- After the August 11, 2004, non-approvable letter, the FDA received hundreds of letters and phone calls urging the agency to approve the device.
- FDA relations with the sponsor were described in the report as "not collegial." FDA staff described such interactions as "terrible" and at times "abus[ive]."

¹⁰ Committee on Finance, United States Senate. Review of the FDA's approval process for the vagus nerve stimulation therapy system for treatment-resistant depression. February 2006. Available at: http://finance.senate.gov/press/Gpress/02_2006%20report.pdf.

- Certain key management staff and reviewers were excluded from a critical meeting between FDA staff and the sponsor in December 2004.
- On January 6, 2005, one month prior to the approvable letter, the entire review team, including the new director of the Office of Device Evaluation, recommended against approval. The director of the Office of Device Evaluation is not typically involved in device approval decisions.
- Typically, device approval decisions are made at the division level and signed at the office level (the next level up). In this case, the decision was made at the center level in CDRH (the next step up from the office level).
- Several FDA staff, including Dr. Schultz himself, agreed that the CDRH director was involved "very rarely" in decisions regarding device approval.

Given these highly irregular aspects of the approval process at the FDA, it is appropriate that CMS review the data themselves rather than depending upon the demonstrably corrupted FDA process.

Articles in Biological Psychiatry

After VNS was approved, and considerably after the failed Study D02 was unblinded in 2002, the VNS researchers saw fit to publish reports of the three studies mentioned above in *Biological Psychiatry*.^{8,9,11} In general, the studies downplay the weaknesses in the data, use graphics to emphasize isolated positive findings and conclude, with respect to Study D04 Long-term Phase that "The primary analysis found a significant between-group difference favoring VNS + [treatment-as-usual] over TAU alone that grew over time."⁹

In a recently published letter in *Biological Psychiatry*,¹² we outline the same problems (different sites, lack of blinding, concomitant therapies, lack of randomization, regression to the mean, etc.) with the Study D04 Long-term data that we have identified in this letter. Our letter notes that the FDA's statistical review repeatedly stated that aspects of the comparison were "questionable." The FDA statistician concluded that "it is unclear whether the effectiveness claim . . . has been demonstrated."¹³ It is worth noting that Dr. Rush, the lead author on two of the articles and the second author on the third, is one of only five Deputy Editors and is also on the Editorial Committee of the journal.

Article in Neuropsychopharmacology

¹¹ Rush AJ, Sackeim HA, Marangell LB, George MS, Brannan SK, Davis SM et al. Effects of 12 months of vagus nerve stimulation in treatment-resistant depression: a naturalistic study. *Biological Psychiatry* 2005;58:355-63.

¹² Lurie P, Stine N. Responding to three articles regarding vagus nerve stimulation (VNS) for depression. *Biological Psychiatry* 2006;Aug 23 (electronic publication prior to print).

¹³ Food and Drug Administration (2004): Final Statistical Summary Review for PMA P970003/S50 (Original and Various Amendments), Vagus Nerve Stimulator (VNS) Therapy System for Depression, Cyberonics, Inc. Accessed 9/4/06 at

http://www.fda.gov/ohrms/dockets/ac/04/briefing/4047b1_00_a_FDA%20Statistical%20Review%20Memo.pdf.

A typical part of any campaign for a drug or device these days is to get favorable articles reviewing your treatment into the medical literature. A particularly crass version of this occurred when Cyberonics organized for an article reviewing the efficacy of VNS to be written.¹⁴ It hired a ghost-writer and arranged for Charles Nemeroff, the chair of Emory University's Department of Psychiatry and Behavioral Sciences, to be first author. The article was published in *Neuropsychopharmacology*, a journal Dr. Nemeroff edits. The article concluded that VNS "appears to be a valuable addition to existing treatments" for TRD and described the therapy as "promising" and "effective in a subset of patients with treatment-resistant depression." The authors were eight leading academics and one Cyberonics employee. (One of the academics, Dr. Dennis Charney, is also the editor of *Biological Psychiatry*.) Although all of the academics had received consultancy fees from Cyberonics, none of them (including Dr. Nemeroff) disclosed this, even though journal policy requires such disclosure.¹⁵ Dr. Nemeroff was forced to resign as editor of the journal.¹⁶

Article in British Journal of Psychiatry

Just recently, another article touting the purported benefits of VNS for TRD appeared in the medical literature.¹⁷ Funded by Cyberonics, it involved just 11 patients, was unblinded, allowed concomitant therapies, and had no control group whatsoever. The authors do not even mention the *Biological Psychiatry* articles (or the FDA review documents), even though their article was submitted after those articles were published. They did not add them in their final revision, which was submitted four months after the *Biological Psychiatry* articles.

Failure to secure reimbursement

Although an NCD was the most straightforward route to obtaining Medicare reimbursement, the company embarked on the more time-consuming but, they may have reasoned, more fruitful strategy of applying for a series of LCDs. It appears that the current application for an NCD is the result of the total failure of that strategy. The Medicare Coverage Database¹⁸ lists 19 applications for LCDs, involving ten separate contractors and 14 states (see Table 1).¹⁹ In each case, the contractor rejected the LCD, often in striking terms. For example, Blue Cross Blue Shield of Arkansas stated:

At present, the available evidence is not sufficient to determine the efficacy of vagus nerve therapy for treatment resistant depression, or to define precisely the

¹⁴ Nemeroff CB, Mayberg HS, Krahl SE, et al. VNS therapy in treatment-resistant depression: clinical evidence and putative neurobiological mechanism. *Neuropsychopharmacology* 2006;31:1345-55.

¹⁵ Armstrong D. Medical reviews face criticism over lapses. *Wall Street Journal*, July 19, 2006, p. B1.

¹⁶ Armstrong D. Medical journal editor to quit in wake of disclosure oversight. *Wall Street Journal*, August 25, 2006.

¹⁷ Corcoran CD, Thomas P, Phillips J, O'Keane V. Vagus nerve stimulation in chronic treatment-resistant depression. *British Journal of Psychiatry* 2006;189:282-3.

¹⁸ <http://www.cms.hhs.gov/mcd/search.asp>.

¹⁹ Medicare contractors have coverage areas that can extend over several states. One state may have several contractors. Our count of negative LCD determinations includes those formally listed as such in the Medicare coverage database (these have the prefix "L") as well as clearly non-duplicative "articles" addressing reimbursement these have the prefix "A").

patient population that might be helped by this modality. Therefore, coverage is not extended²⁰ to allow depression on the basis that it is an investigational treatment.²¹

In each of its four rejections of reimbursement of VNS for depression, the National Heritage Insurance Company uses this language:

Much of the data reviewed by the FDA has yet to be published in peer-reviewed journals. Of the few studies published, only one is a randomized control [sic] trial which found the data "did not yield definitive evidence of short-term efficacy for adjunctive VNS in treatment-resistant depression." (citing Rush⁸)

After review of the FDA approval letter, published literature, and other pertinent sources, NHIC, Medicare Part B, has decided **not to cover VNS for the treatment of depression** at this time. (emphasis in original)²²

These findings are consistent with those of the BlueCross BlueShield Technology Evaluation Center. Its exhaustive report on VNS reached the conclusion that "The available evidence is not sufficient to permit conclusions of the effect of VNS therapy on health outcomes."²³ In August 2006, BlueCross BlueShield rejected an appeal from Cyberonics that sought to reverse the insurer's prior decision to not reimburse for VNS for TRD.²⁴ In April, Aetna also denied reimbursement for VNS for TRD.²⁵ Although the company had previously estimated the TRD market at 4.4 million people, by the end of July 2006 only 1600 TRD patients had received VNS and 2 ½ times as many had been turned down for reimbursement by their insurers.²⁶

On July 24, 2006, Cyberonics altered its previous strategy and filed an NCD application with CMS. Comments are due by September 6, 2006. We are filing this letter as a public comment on that NCD application as well.

Securities and Exchange Commission investigation

Cyberonics is also under investigation by the Security and Exchange Commission (SEC) and has received a subpoena from the U.S. Attorney's Office for the Southern District of New York.²⁷ The probe relates to the timing of stock options granted to company executives, without any

²⁰ Many Medicare contractors do reimburse for VNS use in epilepsy, the only other condition for which the device is approved by the FDA.

²¹ Blue Cross and Blue Shield of Arkansas. LCD for Vagal Nerve Stimulation (L21950), December 1, 2005.

Available at: <http://www.cms.hhs.gov/mcd/search.asp>.

²² National Heritage Insurance Company. LCD for Vagal Nerve Stimulation (L21629). July 16, 2006. Available at: <http://www.cms.hhs.gov/mcd/search.asp>.

²³ Mark D. Vagus nerve stimulation for treatment-resistant depression. Technology Evaluation Center, Vol. 20, No. 8, August 2005. Available at: http://www.bcbs.com/tec/vol20/20_08.html.

²⁴ Clarke T. Blue Cross to again reject Cyberonics device. Reuters, August 8, 2006.

²⁵ Anon. Blue Cross rejection sends Cyberonics stock tumbling. Houston Business Journal, August 8, 2006.

²⁶ Cyberonics. Cyberonics revises guidance for FY07 and confirms receipt of NASDAQ staff determination letter. Cyberonics press release, August 1, 2006.

²⁷ Cyberonics. Cyberonics announces delay in filing annual report on Form 10-K. Cyberonics press release, July 11, 2006.

involvement of corporate management.⁶ It has been alleged that the directors authorized the stock options in the evening after the FDA advisory committee recommended VNS approval for TRD. When the markets reopened in the morning, the chief executive realized a paper profit of \$2.3 million. As a result of the options probe, the company failed to file its Form 10-K with the SEC, and the company now faces delisting by NASDAQ.²⁸ Public Citizen has also filed a letter with the FDA pointing out ten false or misleading aspects of an advertisement for VNS.²⁹

Conclusion

Despite various attempts to resuscitate this failing therapy, VNS continues to struggle. And it is doing so for the appropriate reason. Even the full-court press of misleading advertising, training sessions in its use for physicians, presentations at the American Psychiatric Association annual meeting, case managers to help secure reimbursement for individual patients, abuse of FDA employees, misleading clinical trial write-ups, ghost-written review articles and company-generated favorable local media coverage cannot disguise what is lacking and what insurers are increasingly realizing: There are no convincing data of the device's effectiveness, let alone, in CMS terms, that it is "reasonable and necessary." To reimburse for an ineffective device (and an expensive, surgically implanted one at that) does no favors for those suffering from TRD. Ten contractors in 14 states have reached the unanimous conclusion that the Medicare program in their jurisdiction will not reimburse for this unproven device, a reasonable decision given scarce Medicare resources. It is time for the national program to follow in these well-trodden footsteps.

Yours sincerely,

Peter Lurie, MD, MPH
Deputy Director

Nicholas Stine
Research Associate

Sidney M. Wolfe, MD
Director
Public Citizen's Health Research Group

Cc: Mark McClellan

²⁸ Cyberonics. Form 8-K. Filed with U.S. Securities and Exchange Commission July 31, 2006.

²⁹ Lurie P, Stine N, Wolfe SM. Letter to FDA requesting the immediate halt of Cyberonics ads for vagus nerve stimulation devices. May 18, 2006. Available at:

<http://www.citizen.org/publications/release.cfm?ID=7434&secID=1163&catID=126>.

Table 1: Local Coverage Decisions (LCDs) Regarding Vagus Nerve Stimulation

LCD Number	Contractor	Primary Geographic Distribution	LCD Decision
A40451	First Coast	Florida	Denied
A40486	First Coast	Connecticut	Denied
A37719	AdminaStar Federal	Indiana	Denied
A37722	AdminaStar Federal	Illinois	Denied
A37723	AdminaStar Federal	Kentucky	Denied
A37724	AdminaStar Federal	Ohio	Denied
A37687	Associated Hospital Service	Maine	Denied
A37690	Associated Hospitals of Maine	Connecticut, Massachusetts, Maine, New Hampshire, Rhode Island, Vermont	Denied
A37689	Associated Hospital Service	Massachusetts, Maine	Denied
L21950	BCBS Arkansas	Arkansas	Denied
L21629	National Heritage	Maine	Denied
L21659	Anthem	New Hampshire, Vermont	Denied
L21683	National Heritage	Massachusetts	Denied
L21685	National Heritage	New Hampshire	Denied
L21687	National Heritage	Vermont	Denied
L21583	Group Health (NY)	New York-Queens	Denied
L21552	Empire Medicare Services	New York-Downstate	Denied
L21554	Empire Medicare Services	New Jersey	Denied
L22678	HealthNow	New York-Upstate	Denied



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Joan Claybrook, President

May 11, 2005

Daniel Schultz, M.D.
Director, Center for Devices and Radiologic Health
Food and Drug Administration
9200 Corporate Blvd.
Rockville, MD 20850

Dear Dr. Schultz:

We strongly urge you to reject the pending Premarket Approval (PMA) application for Cyberonics' NeuroCybernetic Prosthesis (NCP) System, more commonly known as Vagus Nerve Stimulation (VNS) Therapy, for the new indication of treatment-resistant depression (TRD), because the safety and efficacy of this medical device have not been established. The only randomized trial conducted (study D02) failed to demonstrate the efficacy of the VNS device for TRD, and the nonrandomized efficacy analysis submitted by the sponsor was deemed "highly questionable" by the FDA statistician.¹ The sponsor also has not demonstrated long-term safety in the TRD patient population, nor have concerns over numerous reports in clinical trials of worsening depression, suicides and sudden deaths with VNS treatment been adequately investigated. The FDA issued a non-approvable letter to Cyberonics in August 2004,² but, in a highly unusual reversal of position, the FDA sent the sponsor an approvable letter in February 2005.³

The VNS device consists of a pulse generator implanted in the base of the neck that delivers electrical signals to the left cervical vagus nerve, a major nerve with connections to the heart, the gastrointestinal tract, the brain, and many other parts of the body. An external device used by the physician adjusts the settings of the pulse generator, but the device is typically programmed to be on for 30 seconds and off for 5 minutes. No definitive mechanism of action has been established for the depression indication.⁴ The manufacturer estimates that about 30,000 epilepsy patients are currently using the device, and have accumulated about 79,000 patient-years of experience. By expanding into the TRD market, Cyberonics hopes to gain access to over 4 million new customers with depression.³

Regulatory Background

In July 1997, VNS therapy was approved by the FDA for the treatment of refractory epilepsy in adults and adolescents 12 years and older. During follow-up visits in the early epilepsy trials, many of the participants stayed in the same Florida hotel. The hotel clerk supposedly observed that the mood of the VNS patients seemed to improve over time.⁵ Eyeing a potentially huge expansion of their market, Cyberonics began to conduct a series of studies to investigate VNS therapy for depression.

On October 27, 2003, Cyberonics submitted a PMA requesting approval for patients 18 years or over with chronic or recurrent depression who had failed to respond to two or more antidepressant treatments.⁴ Much of the correspondence between FDA and the sponsor concerning VNS treatment for depression is not accessible to the public, but the available FDA documents and company press releases provide an outline.

On March 1, 2004, the FDA completed an initial review of the PMA Supplement for the depression indication and responded to the sponsor with a Major Deficiency letter, citing serious flaws in the data submitted. Cyberonics was permitted to respond to these concerns, and a meeting of the Neurological Devices Panel of the Medical Devices Advisory Committee was called for June 15, 2004.⁴

The advisory committee panel had very mixed feelings about the VNS data. After the panel discussed the risk-benefit ratio of the device, Chairperson Dr. Kyra Becker concluded prior to the vote:

In summary ... it sounds like the panel believes that the device is generally safe but based on what is questionable efficacy, it's unclear whether the safety benefit ratio rises to the point that make it something that we should achieve to use.⁶

Two panelists voted against approval. "I voted against because I thought it should not have been approved, because I didn't think they demonstrated efficacy," commented Dr. Richard Malone. Similarly, Dr. Jonas Ellenberg concluded that "I don't believe that a standard for efficacy has been met."⁶

Five panelists voted to recommend conditional approval (conditions are explained below). However, in their explanations of their votes, only two panelists expressed, somewhat cautiously, the belief that the data demonstrated efficacy. "Although I would have liked to have seen a more rigorous study," said Dr. Laura Fochtman, "I think there has been evidence shown that this is efficacious" Dr. Phillip Wang based his vote on the D02 randomized controlled trial primary endpoint, claiming a trend toward efficacy despite the actual lack of a statistically significant difference between VNS and control: "I'm voting for this on the basis of mainly the acute phase D02 data which supports that there is some efficacy, although albeit not particularly robustly (T)his is probably an improvement over, say, fourth line, fifth line sort of treatments."⁶

The other three panel members recommending approval expressed discomfort with the quality of the efficacy data, but were willing to look past this because of the few treatment options available for patients who don't respond to other depression treatments. "Although it would be nice to have randomized controlled data for the efficacy," remarked Dr. Mary Lee Jensen, "I believe this is a difficult patient population ... And I think [VNS] should at least be available to this group of patients."⁶

Dr. Annapurni Jayam-Trouth concluded:

The reason I'm voting for approval with conditions is that I mean this is a very tough group of patients, and it's difficult to treat them. The death rate is very high, it's almost a terminal type of condition, more or less, and I think that there's very little that we can offer at this time, and I think we have shown that this is relatively safe. There have been studies on epilepsy showing that it is efficacious in this group of patients and the efficacy seems to improve over time. So I think that for the reasons I mentioned, I'm voting for approval.⁶

Similarly, Dr. Irene Ortiz explained that "I'm voting in favor because I feel that treatment-resistant depression does have a very high incidence of suicide. The data was not ideal, but safety I think was established."⁶ In essence these three panel members implied that it didn't matter so much whether the device worked, since these patients were suffering so much already and VNS didn't appear to be unsafe.

The final vote was thus 5-2 in favor of recommending approval with the following conditions:

1. Patients must fail four or more adequate trials of antidepressant therapy.
2. Surgeons implanting the device must have skills operating within the carotid sheath.
3. Clinicians caring for VNS patients must receive training in setting device parameters.
4. Patients must be educated about device complications.
5. The sponsor must establish a registry to collect clinical data on safety and efficacy, as well as stimulation levels and prognostic factors.
6. The labeling must reflect the questionable efficacy data, including that the "positive" efficacy study was an open-label trial and not a randomized, controlled trial.⁶

In an unusual step, on August 12, 2004, the FDA went against these Advisory Committee recommendations and sent a letter to Cyberonics stating that its PMA was not approvable. The letter is not available to the public, but according to the company it cited reasons for this decision that included 1) Concerns over data showing worsening depression in many VNS patients, 2) Potential biases stemming from a nonrandomized control, and 3) An inability to distinguish VNS effects from the placebo effect and concomitant treatment effects in the nonrandomized data. Cyberonics responded that it

was "shocked and bewildered" by this decision, announcing that it was "in the process of arranging a meeting with senior FDA management to discuss their letter."² The sponsor claims to have then submitted more data to the FDA, but as best can be determined from Cyberonics' press releases this adds little more than a one-year extension of the nonrandomized data already submitted and described below.⁷

In the meantime, the FDA has also reprimanded Cyberonics for not adequately investigating deaths and other adverse events in VNS patients with epilepsy. In a Warning Letter sent on December 22, 2004, the FDA cites Cyberonics for a long list of violations including "failure to completely investigate and evaluate the cause of each medical adverse event."⁸ Cyberonics has since responded to this Warning Letter and claims to have satisfied the FDA's concerns.⁹

In a mysterious reversal of the FDA's earlier non-approvable letter, the FDA sent another letter to the sponsor on February 2, 2005 declaring the device approvable. This letter is also not public but according to Cyberonics it states that approval would be conditional upon the development of a postmarketing study to evaluate proper voltage levels for the device, new labeling revisions, and the establishment of a 1,000-patient registry. Cyberonics expects full approval by May 2005.³

Studies submitted to the FDA

D01 Pilot Study

This was a non-randomized, open-label trial of 60 TRD patients acting as their own controls. After a baseline assessment period, patients were surgically implanted with the VNS device and then entered a 12-week acute phase. With two weeks to recover and two more weeks to adjust stimulation, this really amounted to eight weeks of sustained stimulation. Patients maintained a stable concomitant antidepressant/mood disorder medication regimen. Responders were defined as those with an over 50% improvement in their Hamilton Rating Scale for Depression (HRSD, also known as HAM-D) scores from baseline to the end of the acute phase.

Eighteen of 59 patients (31%) who completed the acute phase were classified as responders. The researchers followed the patients for two more years, finding that 25/55 patients (45%) were responders at one year, and 18/42 (43%) were responders at two years. Seventeen of 59 patients (29%) were lost to follow-up at two years, meaning that the response rate may actually have been as low as 18/59 patients (31%) at two years.⁴ Given the lack of a control group for these data, it is impossible to separate these response rates from the placebo effect, regression to the mean, or any secular effects.

Over the course of the up-to-two years for which patients were monitored, a total of 77 "serious" adverse events (a category including worsening depression, suicide attempts, and mania) were reported among the 60 patients, and every implanted patient reported at least one treatment-emergent adverse event. In total, 34 patients (57%) reported adverse mood alteration, including worsening depression. Twelve patients (20%)

attempted suicide.⁴ These rates are cause for concern, but impossible to definitively attribute to VNS because of the lack of a control group.

D02 Pivotal Study

Acute Phase

This was a 12-week double-blind, randomized, placebo-controlled phase III study of TRD patients. Two-hundred and thirty-five patients were implanted with the VNS device, 119 of whom were randomized to therapy and 116 to sham treatment (no stimulation). As in the pilot study, after two weeks to recover and two more weeks to adjust stimulation, the patients underwent eight weeks of sustained stimulation in combination with a constant concurrent antidepressant/mood disorder medication regimen. Responders were again defined as those with at least a 50% improvement in HRSD scores from baseline to the end of the acute phase. When the acute phase was unblinded, 17/111 treatment patients (15%) and 11/110 placebo patients (10%) had responded according to the HRSD criteria, a difference that was not statistically significant ($p=0.238$). Of four depression assessment test endpoints designated by the sponsor as secondary prior to the study, three were negative and only one (Inventory of Depressive Symptomatology Self-Report, or IDS-SR, which is not physician-administered) showed a statistically significantly better rate of response for VNS (19/109) over placebo (8/106, $p=0.032$). There was one suicide in the treatment group and none in the placebo group.⁴

It is also interesting to note here the difference between the HRSD response rates of VNS-treated patients at 12 weeks in the unblinded D01 study (31%) and the blinded D02 study (15%).⁴ (Even this randomized, controlled phase of the D02 study does not achieve the level of blinding that would be ideal. Many patients receiving VNS stimulation can sense that the device is active, thereby exaggerating efficacy.¹⁰) These data suggest that at least some of the apparent effectiveness of VNS is due to patients' knowing if they were receiving treatment.

Long-Term Phase

This was a 12-month, open-label follow-up to the D02 acute phase, in which all implanted patients from the acute phase could elect to receive stimulation. Of 205 patients participating at the onset of the long-term phase, a total of 177 completed the entire 12 months of treatment. Adjustments in patients' medication regimen were allowed, as was concurrent Electroconvulsive Therapy (14 patients). After 12 months of therapy, 52/174 patients (30%) met the response criteria of at least a 50% improvement in HRSD scores. Thirty-one of 205 patients (15%) were lost to follow-up, meaning that the response rate may actually have been as low as 52/205 (25%). A total of 96 serious adverse events were reported during the long-term phase, including 62 patients reporting worsening depression (30%) and 11 suicide attempts.⁴ As in the D01 trial, the lack of a proper control group limits the meaning of these data, due to the difficulty separating response rates from placebo effect, regression to the mean, and other secular effects.

Comparison of D02 Long-Term Outcomes to an Observational Study (D04)

Despite the failure of VNS to demonstrate efficacy with respect to the primary outcome in the randomized, controlled D02 Acute Phase trial, Cyberonics asserted that there might be a pattern of increasing response over time, as demonstrated, they claimed, by the long-term follow-up phase of D02. Therefore efficacy might only be detectable in longer-term data.⁴ But instead of conducting a longer-term randomized controlled trial, the logical response to this assertion, the sponsor elected to generate a new control. It took the 12-month D02 Long-Term data of VNS-treated patients it already had and decided to collect new "usual care" data (i.e., medication, ECT, etc. administered at the physician's discretion to unimplanted patients). Thus, instead of attempting to prove its claim of efficacy over the long-term by collecting data on implanted patients in a randomized controlled trial over the long-term, the sponsor collected more data on unimplanted patients.⁵

In its protocol for this new comparison, the sponsor also elected to redefine the primary endpoint. In the D02 acute phase, the only one of the five primary and secondary endpoints to suggest efficacy was the self-administered IDS-SR.⁴ Cyberonics then used IDS-SR as the primary endpoint in its revised D02-D04 analysis, instead of HRSD. While the HRSD is one of the standard assessment tools used in depression trials, IDS-SR is obscure. A review of the labels of the ten most recent antidepressant drugs approved by the FDA reveals no mention of IDS-SR as an outcome variable whatsoever. In contrast, the HRSD was cited eight times. The FDA has raised serious questions about the validity of using IDS-SR as a predictor of HRSD scores. The FDA statistical review's analysis found that there was "questionable concordance" between IDS-SR and HRSD in the D02 study. The FDA review added that "we do not agree that concordance studies reported in the published literature are sufficient to support IDS-SR as a 'good predictor' of HRSD-24."¹ In addition to this switch to a more favorable assessment tool, the sponsor switched from a dichotomous outcome variable to a continuous one. All other things being equal, analyses of continuous outcome variables are more likely to reach statistical significance; the differences thus detected may not be clinically meaningful.

¹ The company initially claimed at the Advisory Committee meeting that to conduct a longer-term randomized controlled trial with fixed medications would have been unethical. However, as pointed out by several Advisory Committee panelists, there are many potential ways around this problem. These include allowing medication changes according to a fixed protocol; censoring the data if a medication is changed and using last-observation-carried-forward; using multivariate analysis to adjust for concomitant treatment effects; analyzing the need for additional therapy as an outcome; and not allowing concomitant treatment changes, but allowing for an escape if symptoms worsen. When Advisory Committee panelists suggested such alternative study designs, the company acknowledged that such a trial was possible.

In the D04 observational study, 112 patients completed 12 months of usual care. In the D02-D04 primary endpoint comparison, using linear regression analyses, a statistically significant difference ($p < 0.001$) was found between the change in IDS-SR scores per month in favor of D02 patients at 12 months (-0.397 estimated average difference per month, IDS-SR scale is 0-84). However, if these data are censored for changes in concomitant antidepressant treatment (i.e., the patient's last IDS-SR score before the concomitant antidepressant treatment was changed is used for subsequent assessment points, a last-observation-carried-forward approach), there is no statistically significant difference between usual care and VNS plus usual care. For the HRSD secondary endpoint response analysis, 13/104 patients (13%) in the D04 study were responders as defined by a greater than 50% improvement in HRSD scores between baseline and 12 months. This was statistically significantly lower than the HRSD response rate for VNS-treated patients in D02 (30%). Again, however, when the data were censored for changes in concomitant antidepressant treatment, statistical significance is lost.⁴

This long-term D02-D04 analysis is extremely problematic for a number of reasons. The purpose of a randomized controlled trial is to ensure that the groups to be compared are as close to identical as possible, to eliminate confounding. But there were very significant differences between the two groups in this non-randomized comparison.

First, the illness and treatment histories of the two groups were not the same. As the FDA's statistical review points out: "There were significant differences in baseline demographics between D02 and D04, including those patients who received ECT during their lifetimes, patients who received ECT during the current major depressive episode, and patients in the control population with greater than 10 lifetime episodes of depression."⁶ These factors limit the ability to isolate the effect of the VNS treatment on these patients.

Second, the studies were not conducted on an identical timeline, meaning there may be differences in seasonal effects on depression, or in responses to news events.

Third, only 12 of the 22 study sites in D02 participated in D04 ("overlapping sites"), meaning the "usual care" may not always have meant the same thing. The FDA's statistical reviewer was very concerned about this, concluding that "the validity of statistical inferences from comparison of two proportions of Responses pooled over all non-overlapping and overlapping sites, without any appropriate statistical modeling approach, such as meta-analysis, is highly questionable."¹

Fourth, both the long-term phase of D02 and D04 allowed for changes in concomitant antidepressant therapy and ECT, which, themselves, could cause improved depression symptoms. As mentioned, when the primary endpoint data were censored for concomitant treatment changes, statistical significance was lost.

Fifth, the long-term D02-D04 comparison was by its nature unblinded. D02 VNS-treated patients were surgically implanted with a device they knew was being investigated as a

novel depression treatment. By the long-term phase, they all knew the device was turned on. This could have an enormous psychological impact, increasing patients' expectations of clinical improvement. By contrast, D04 patients did not undergo surgery. In depression, the placebo effect and regression to the mean are known to be unusually large. The response rate for long-term D02 VNS-treated patients was about 30% according to the initial endpoint criteria of at least a 50% improvement in HRSD scores. During the past 30 years, antidepressant drug trials have shown placebo response rates of around 30%.¹¹ Granted, the D02 and D04 populations were by design treatment-resistant and may have experienced smaller placebo-response rates than otherwise expected. But one might also suspect that an implant would have a greater placebo effect than a drug. In any case, there is reason to suspect a substantial role for a placebo effect and regression to the mean in the implanted patients. Particularly given the modest magnitude of efficacy differences measured, these are crucial flaws in the study design.

The FDA statistical review of the D02-D04 efficacy data concludes with skepticism:

Due to above statistical issues, such as questionable concordance between HRSD-24 and IDS-SR, questionable pooling of multi-center data for comparison of proportions of responses, statistically insignificant findings from censored and overlapping sites ... for IDS-SR primary effectiveness endpoint (Slope) and HRSD-24 secondary effectiveness endpoint (Response proportions), it is unclear whether the effectiveness claim of [VNS-treated] D-02 over [standard-of-care] D-04 group patients has been demonstrated.¹

Safety

Cyberonics did not systematically collect safety data in the D04 "usual care" study, meaning a D02-D04 safety comparison is not possible. The result of this, and the lack of long-term randomized controlled data, is that there are a lot of unanswered questions about the safety of the VNS device in TRD patients.

Of course, there is a risk of complications for any surgical procedure in a delicate area such as that around the left cervical vagus nerve in the neck, with the immediate vicinity including the carotid artery and jugular vein. Beyond this, after the point of stimulation, the vagus nerve goes on to innervate the larynx, heart, lungs, abdominal viscera, and brain, meaning all of these areas are potential sites for adverse effects from VNS. A review of the literature reveals case reports of vocal chord paralysis,¹² loss of sensation in the pharynx,¹³ and breathing problems during sleep induced by VNS.¹⁴ Several cases of complete heart block with the initiation of stimulation have been reported, with Ali *et al.* hypothesizing a mechanism of VNS-induced ventricular asystole (lack of contraction of the heart).^{15,16}

Cyberonics asked the FDA to consider long-term safety data from clinical trials for epilepsy instead of providing controlled data specific to the TRD patient population to be targeted. Dr. Michael Schlosser, the FDA medical officer who reviewed the safety of the

device, was dissatisfied with this submission. "The safety of the device in another population doesn't necessarily mean that that device is safe in this different population," he noted. Even Cyberonics' own scientist, Dr. John Rush, acknowledged that the epilepsy data did not determine safety for the TRD population when he defended the sponsor's decision not to conduct a longer-term randomized controlled trial. "At the time that we started [the D02 trial, i.e. long after VNS was approved for epilepsy], where we were going we had no evidence of long-term safety or efficacy of VNS," said Dr. Rush. "...We couldn't do a long-term. We didn't even have an idea of safety in the short run."⁶ Patients with severe epilepsy and severe depression are very different populations. Especially when some of the most common serious adverse events in the depression studies were psychiatric (worsening depression, suicide attempts, etc.), it is irresponsible not to conduct long-term, controlled safety studies for this group.

Even without long-term randomized controlled safety data, there were red flags identified by the FDA in the depression data submitted. The occurrence of worsening depression in VNS-treated patients (the most common serious adverse event in the D02 study, reported in 30% of long-term patients) is very troubling, especially in light of questionable efficacy data. An FDA analysis combined safety data from D01, D02, and a postmarketing depression registry from Europe found an incidence of 24 suicide attempts in 689 patient-years (3.5% per year). The FDA summary and analysis cites as a comparator Khan *et al.*, who report an incidence of suicide attempt per patient year of 2.7% in patients receiving placebo in depression drug trials. At the Advisory Committee meeting, the FDA's Dr. Schlosser commented that the data are "enough to make us concerned that there might be something to precipitation of suicide by this device, or at least to look at it more carefully."⁶

The FDA also raised questions about the role of the VNS device in sudden death. "There is a concern that this might be due to cardiac events due to the direct vagal nerve stimulation," said the FDA's Dr. Schlosser at the Advisory Committee meeting. "Could this be causing a cardiac event that led to sudden death?" he asked. At best, the safety data for VNS in depression are incomplete.

Conclusion

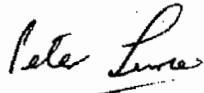
The approval of VNS for this indication would represent a dramatic expansion of the market for VNS, from the current pool of roughly 30,000 epilepsy patients to the 4.4 million TRD patients Cyberonics often cites as desperately needing this new treatment.² We strongly oppose this approval because there are no randomized controlled data demonstrating efficacy for the primary endpoint. The nonrandomized efficacy analysis is riddled with the potential for bias and confounding. The FDA statistical review repeatedly called Cyberonics' analysis "questionable," and concluded that it was not clear that efficacy had been established. The FDA Advisory Committee members agreed that a safety-benefit ratio could not be established with the data available. The FDA has raised questions about increased suicides, worsening depression, and sudden death, all of which deserve further investigation. The FDA would never approve a drug under these conditions. With so many uncertainties and red flags, it is a serious mistake

for the FDA to be prepared to approve this device for use in millions more people for whom it has not been proved to work. Do not let justified empathy for this patient population lead to the unjustified approval of a device that does not come close to meeting FDA's approval standards, and may well do more harm than good.

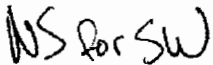
Sincerely,



Nicholas Stine
Research Associate



Peter Lurie, MD, MPH
Deputy Director



Sidney Wolfe, MD
Director
Public Citizen's Health Research Group

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