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Joan Claybrook, President

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Office of Clinical Standards and Quality
Centers for Medicare & Medicaid Services
7500 Security Boulevard
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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)

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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

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[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

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[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]."

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[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

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[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 Database[18] 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

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[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 extended[20] 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 Rush[8])
>
> 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

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[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

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[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