

**SUMMARY MINUTES**

**OF THE**

**NEUROLOGICAL DEVICES**

**ADVISORY PANEL MEETING**

**OPEN SESSION**

**March 31, 2000**

**DoubleTree Hotel  
Plaza Ballroom  
1750 Rockville Pike  
Rockville, MD**

**Neurological Devices Advisory Panel Roster  
March 31, 2000**

Alexa I. Canady, M.D.  
Chairperson

Everton A. Edmondson, M.D.  
Voting Member

Richard G. Fessler, M.D., Ph.D.  
Voting Member

Steve G. Massaquoi, M.D., Ph.D.  
Voting Member

Cedric F. Walker, Ph.D., P.E.  
Voting Member

Mark Hallett, M.D.  
Consultant, deputized to vote

Marc R. Nuwer, M.D., Ph.D.  
Consultant, deputized to vote

Lucia J. Zamorano, M.D., Ph.D.  
Consultant, deputized to vote

Steven Piantadosi, M.D., Ph.D.  
Consultant, deputized to vote

Sally L. Mahler, Esq.  
Industry Representative

Catalina E. Garcia, M.D.  
Consumer Representative

Perry D. Cohen, Ph.D.  
Patient Representative

**FDA Participants**

Janet L. Scudiero, M.S.  
Panel Executive Secretary  
Division of General and Restorative Devices (DGRND)

Celia M. Witten, M.D., Ph.D.  
Director, DGRND

Heather S. Rosecrans  
Director, Premarket Notification Staff

Captain Marie Schroeder, M.S., P.T.  
Clinical Reviewer

John M. Dawson, J.D., M.S.  
Statistical Reviewer

**OPEN SESSION—MARCH 31, 2000**

**Panel Executive Secretary Ms. Janet L. Scudiero** called the meeting to order at 10:05 a.m. and read appointments to temporary voting status for Drs. Hallett, Nuwer, Zamorano, and Piantadosi. She also read the conflict of interest statement, noting that waivers had been granted to Drs. Fessler and Piantadosi for their interest in firms at issue; these waivers allowed their full participation. Matters involving Drs. Edmondson, Fessler, and Walker had been considered but deemed unrelated to the topic at hand, and their full participation was allowed. Patient Representative Dr. Perry Cohen had also declared personal financial interests in the firm at issue.

**Panel Chair Dr. Alexa I. Canady** stated that the panel would make a recommendation on the approvability of premarket approval application (PMA) P960009 Supplement 7 for the Medtronic Activa Parkinson's Control System. She noted that the panel members constituted a quorum and asked the panel members to introduce themselves.

**FDA Presentation--Least Burdensome Provisions of the FDA Modernization Act**

**Ms. Heather S. Rosecrans, Director of the Premarket Notification Staff,** discussed the meaning of the "least burdensome" provisions of the FDA Modernization Act of 1997 (FDAMA). She read the provisions applicable to PMA and premarket notification (510(k)) submissions. She stated that FDAMA did not change the clearance standard for PMAs, which remains a demonstration of reasonable assurance of safety and effectiveness, or for 510(k)s, which remains a determination of substantial equivalence. FDA has implemented of these provisions via a January 1999 public meeting, a draft

guidance document, and an industry task force. Based on these efforts, FDA is tentatively defining least burdensome as “a successful means of addressing a premarket issue that involves the smallest investment of time, effort, and money for both the sponsors and FDA.” She noted that the agency has considered possible changes that might result in changes in FDA culture and whether the least burdensome provisions were in conflict with scientific integrity. Ms. Rosecrans stated that good science includes resource cost-effectiveness considerations and that compromise is necessary. Possible mechanisms to lessen the regulatory burden include reliance on nonclinical testing when possible, reliance on recognized standards, alternatives to randomized controlled trials, and use of surrogate endpoints. She concluded by stating that FDA remains open-minded to alternative proposals for satisfying regulatory requirements.

#### **OPEN PUBLIC HEARING**

**Dr. Anthony Arthur**, a study patient whose expenses were paid by Medtronic, spoke in favor of the Activa device, which he stated had given him a quality of life he could not have had without it. He gave his personal history as a person with Parkinson’s disease (PD), describing the overwhelming side effects he had experienced with other treatment modalities and his good experiences as a study participant with the device. Dr. Arthur’s son, **Mr. Michael Arthur**, also spoke in favor of the device, which he said had given him his father back.

**Mr. Larry Wistrom**, another study patient whose way was paid by the sponsor, also spoke in support of the device. He said that the device had made him a new man. His wife also spoke favorably of the device, saying that without it, he would not be appearing before the panel today.

**Mr. Jeffrey Martin, Esq.**, a person with PD and an advocate for those with the disease, spoke in favor of the device, saying that it should be available as a treatment option. He stated that existing drug treatments only alleviate symptoms and have significant side effects. Mr. Martin stated that deep brain stimulation (DBS) provides hope for the most promising treatment of PD. Nonetheless, in his opinion, the device should be restricted to study centers, and not be approved for widespread distribution to all neurosurgeons.

**Mr. Robin Elliott, Executive Director of the Parkinson's Disease Foundation**, spoke on behalf of people with PD, stating that the consensus of scientific opinion strongly supports the use of DBS by competent and experience surgeons, as a valuable option for those with PD. He noted that while this procedure is not for all PD patients and should only be used by those medical centers that have resources and personal dedicated to the procedure, it is an excellent option for some PD patients. He concluded that prompt approval of the device is clearly merited.

**Consumer Representative Dr. Catalina Garcia** read two statements mailed to the panel. The first, from Drs. Michael Dogali and Robert R. Young at the University of Southern California, stated their belief that DBS would be a significant therapy for control of advanced PD and that the Medtronic device is safe. However, they also expressed concern about insufficient information on the device's efficacy and the study's morbidity and mortality data. They summarized their own DBS research and data from overseas DBS studies. Drs. Dogali and Young stated that while general approval of DBS in additional nuclei for advanced PD may result in improved short-term outcomes, it might also subject a substantial number of patients to a procedure for which indications

and efficacy are not understood. It also it might place them in the hands of surgeons not technically competent to perform the procedure. They urged the panel to exercise due caution until additional scientific data are available.

The second letter, by **Ms. Joan Samuelson, President of the Parkinson's Action Network**, spoke of the extremely urgent need for effective therapies for PD and the great suffering and economic loss this disease causes. She described the disease, its effects both personally and economically, and the limited treatment options now available. She concluded requesting that if DBS is found to be safe and effective, it should be approved as soon as possible because those with PD do not have the time to await for potential life-enhancing therapies.

#### **OPEN COMMITTEE DISCUSSION—MEDTRONIC INC.'S PMA 960009/S7**

#### **ACTIVA PARKINSON'S CONTROL SYSTEM**

##### **Sponsor Presentation**

**Ms. Lisa Pritchard, Principal Product Regulation Manager**, read the device's proposed indications for use and reviewed its regulatory history. FDA approved the Activa device for treatment of unilateral essential and PD tremor in 1997. She then summarized the Activa device's regulatory history from approval of the investigational device exemption in 1995 to the present time. She described the device as an implantable, programmable neurostimulator that applies controlled electrical stimulation to specified target locations within the brain. Diagrams of the device components and its placement were shown.

**Dr. C. Warren Olanow** presented data from the Activa DBS clinical investigation of the subthalamic nucleus (STN) and the globus pallidus pars interna

(GPi). He provided statistics on the extent to which PD is a public health concern and described the clinical features of the disease. Dr. Olanow listed the currently available medical therapies, with particular focus on the advantages and disadvantages of levodopa therapy. Levodopa therapy provides an excellent initial therapeutic effect, but after prolonged use it produces significant side effects and fails to address new features of PD that develop as the disease progresses. Dr. Olanow discussed the few alternative treatments available when medical therapy fails and the advantages of DBS over them.

Dr. Olanow described the study design, which was a prospective, non-randomized 12-month multicenter clinical trial. A double-blind, randomized (to a sequence of stimulation off then stimulation on or vice versa), crossover assessment of the effect of stimulation in the medication-off state was used only at three month timepoint for both the STN and GPi groups. He explained the primary and secondary endpoints, which involved improvements in the motor subscores and activities of daily living subscores of the Unified Parkinson's Disease Rating Scale (UPDRS), as well as home diary assessments. Dr. Olanow described inclusion/exclusion criteria, assessment schedule, and randomized evaluation procedures, as well as methods of statistical analysis (Wilcoxon Rank Sum and Signed Rank Tests). Analysis of results by center showed benefits in 90% of the centers.

Dr. Olanow also discussed the effectiveness of bilateral DBS. Key findings for STN patients were that bilateral DBS improves the motor features of PD, decreases occurrence of dyskinesias, increases "on" time, allows patients to regain independence and functional ability, allows most patients to reduce PD medication, and decreases overall disability. Most of these findings were also true for GPi patients, with the

exception of allowing patients to reduce PD medication. Overall, 87% of patients experienced at least one adverse event. No deaths were attributed to any aspect of study. The most frequently reported adverse events were confusion, intracranial hemorrhage, and infection, most of which resolved in most patients. Dr. Olanow attributed these events to the surgical procedure, the device, or the stimulation, and then analyzed these events by category. He concluded that the incidence of the adverse events experienced in the study is consistent with the incidence of adverse events in other stereotactic neurosurgical procedures and tremor control therapy. After listing the benefits of the device, he compared Activa therapy and some recently approved for PD medications. He then showed a video demonstrating the device's effect on a patient "frozen" with PD. He concluded that implantation of the device improves the features of PD in patients who cannot be satisfactorily controlled with medical treatment options, has an acceptable safety profile, and is reversible.

Questions from the panel to the sponsors concerned the necessary experience of the surgeon and the availability of the device, the reason for the statistical methodology chosen, and the length of the device's battery lifetime.

### **FDA Presentation**

**Captain Marie A. Schroeder, M.S., P.T.**, introduced the FDA review team and summarized the original 1997 PMA application and its conditions for approval. She then discussed the PMA supplement's new indications for use and the study objectives, scope, duration, and inclusion/exclusion criteria. The trial design followed two different protocols, one in Europe and one in the United States, Australia, and Canada. Both used prospective designs. It was double-masked, randomized, and had crossover assessment

only at three months. She discussed the treatment and follow-up schedules, noting that the effectiveness measures were assessed with various combinations of medications and the device stimulus off and on. She stated that the primary efficacy endpoint of the device was defined as the motor examination portion of the UPDRS with medication off/stimulation off compared to medication off/stimulation on. She also discussed the other effectiveness measures listed in the protocol. She stated that no secondary efficacy or safety criteria were specified. She also discussed differences and discrepancies between the protocols, case report forms, and concomitant therapies, such as medications.

Captain Schroeder briefly outlined the sponsor's statistical methods, noting that data were analyzed separately by target site but pooled across centers on an intent-to-treat basis. She discussed the lack of study masking except at three months, the lack of a prospectively defined patient population, and study success and failure criteria.

After reviewing patient demographics, Captain Schroeder discussed attempted lead implantations and adverse events. She noted that 87% of enrolled patients experienced one or more adverse events and then summarized these adverse events. She observed that some adverse events were inappropriately categorized. She discussed the extent of exposure to the implanted devices, the etiology of the adverse events, the reliability of the device, and the patient tolerability of the device. She also noted that the sponsor's summary of explanted and replaced devices did not list all of the clinical consequences of complications and did not include pharmacological or other clinical interventions.

Captain Schroeder noted some qualifications of the primary effectiveness total motor score data. For example, effectiveness was assessed without medications, although

the device will be used with medication in clinical practice. Because effectiveness of permanent implants was assessed at three months only, the study did not address how clinical outcome varies over time and whether it's effects may diminish over time or remain. She noted that the doses of medications were reduced in most patients, although the reasons for most medication reductions were uncertain. In at least one case, the medication was reduced in response to an adverse event; the patient experienced increased dyskinesias and required medication reduction to treat this adverse event. Captain Schroeder showed comparisons of the various effectiveness scores in the "stimulation off" to "stimulation on" states. She also summarized the overall motor exam scores, and then the subscores for tremor, rigidity, bradykinesia, and postural instability for STN and GPi patients when off and on medications and with stimulation off and on.

Captain Schroeder concluded that it is difficult to get a clear picture of the device's safety profile. No total UPDRS effectiveness score analysis was provided. She noted that there were multiple confounding variables, such as electrode site placement, imaging techniques, and medication changes. The claimed clinical relevance of the effectiveness measures evaluated in the medication off state was not substantiated. Masking was another problem in the study because patients could tell when the device was operational. Captain Schroeder asked the panel to consider whether the sponsor's analyses provided to justify the pooling of data were clinically meaningful.

**Mr. John Dawson, FDA statistician,** noted that his review was based entirely on the sponsor's data for support of the primary effectiveness endpoint as the sponsor defined it. Results were assessed for most patients at three months only; this assessment

was not a truly blinded assessment because patients knew when the device was activated. He observed that this study is basically part of an open-label study.

Mr. Dawson said that the principal question was how much of the change in total motor examination levels was a result of a placebo effect versus a device effect. He read the sponsor's claims for the device and raised questions about the ability of patients to know when the device was activated, thus triggering a placebo effect. Mr. Dawson concluded that all the endpoints showing improvement over time are vulnerable to the placebo effect, and that performance beyond 12 months was unknown.

**Panel Clinical Review—Dr. Lucia J. Zamorano**

Dr. Zamorano reviewed the history of surgical treatments for PD, observing that stereotactic surgery has been commonly used to treat tremors for 30 years. She noted that thalamotomy has a high response rate but can produce serious complications, such as hemorrhage, pulmonary embolism, and confusion. An alternative treatment is pallidotomy or pallidal stimulation, a second-line treatment against PD with fewer complications. The benefits of thalamic stimulation are its reversibility and its ability to change the parameters of the disease's effects. The drawbacks include cost, the implantation of a foreign material in the brain, and the need for replacement. Dr. Zamorano concluded that there is no question that GPi stimulation is a very important treatment option.

**Panel Clinical Review—Dr. Mark R. Nuwer**

In answer to the first four FDA questions, Dr. Nuwer stated that he saw some evidence of a positive clinical effect for the device. He was concerned about concurrent decreases in medication and about the possibility of a placebo effect. He thought the

global disability rating showed the least impressive results. He was also concerned about safety issues, particularly the high rate of significant adverse effects, such as hemorrhages. The autopsy results lessened his concern about long-term effects from stimulation. Dr. Nuwer was concerned about how long the stimulation effect would really last and about the extrapolation of results from 50-60-year-old patients to 70-80-year-old patients.

#### **Statistical Review—Dr. Steven Piantadosi**

Dr. Piantadosi made six points in his review. First the framework for the investigation, as a feasibility study was initially good, but then was over extended without modification to take advantage of what was learned in the preliminary investigation. He thought the data collection plan showed notable deficiencies, such as control of random error, bias, and selection of relevant endpoints. The investigational plan was inconsistent with study goals. The clinical benefit also was not well served by the choice of a relevant endpoint. In terms of the regulatory overlay, he thought the hurdle could be set high because it is not the first-of-a-kind device. Dr. Piantadosi concluded that the study had significant signs of methodological problems: it is not a robust design, and it did not control for extraneous factors, such as investigational centers effects, prognostic factors, patient ages, baseline scores, and the site of the brain chosen for stimulation (GPi or STN). The clinical effectiveness outcome criteria were poorly chosen, with longitudinal effects and major bias considerations. He thought the data in its current form were poorly suited to regulatory purpose because the trial was not well- controlled. A new use of data or a new trial might provide evidence, but as a crossover trial it was not well-designed.

He thought the device of marginal benefit because it did not meet the needs of the patients.

### **Panel Discussion of the FDA Questions**

In discussing the FDA questions, the panel chose to make general comments at the beginning of its discussion rather than addressing each question specifically. Panel members first asked for whom this device was primarily intended. The sponsor replied that the intended population is the 30-40% of those PD patients for whom medications are no longer working consistently. There is no evidence or data on how the device would function for patients with typical PD or with early to mild PD.

The panel then discussed the difficulty of analyzing “on” and “off” time as a function of whether the patient was responding to levodopa or not versus whether the patient was responding somewhat, i.e., not now frozen but still suffering from debilitating excessive movement or highly limited movement. They noted that the global scale does not show impressive gains with device use, although the data do reflect an improvement in function in daily living. In discussing improvement of rigidity, the panel noted that as the disease progresses and patients are less responsive to levodopa, it is difficult to reduce rigidity without producing dyskinesia. The panel did see a difference in the “off” state with this device versus levodopa, in that “off” time is reduced by the device and the quality of that “off” time is improved by the device.

The panel consensus was that the device appeared safe and effective, although there were concerns about long-term use in elderly patients and the quality of the data in the supplement. In answer to a question from the panel to the study investigators, the

physicians all replied that they would not hesitate to use this device for their own elderly mothers.

In individual panel comments, **Dr. Catalina Garcia, the Consumer Representative**, commented that efficacy was more important than safety in this context, because of the lack of options patients with PD have. **Ms. Sally Maher, Esq., the Industry Representative**, noted that the sponsor came forward with good information in the course of a feasibility study, which should be considered during the risk/benefit analysis.

**Dr. Edmondson** thought that the limitations of the data regarding the efficacy claims should be stated in the labeling. **Dr. Hallett** commented that despite the fact that the study was poorly designed and the wrong primary outcome measure was chosen, the benefit of the device is clear even when the statistics describe the effect poorly. He noted that some published small studies also describe a positive outcome for the device. He recommended that the key outcome should be how many “on” hours/day the subject experiences. The panel agreed that the instructions to physicians need more detailed information, particularly those involving GPi or STN placement, anatomical location of the IPG, and adjustment of the stimulation parameters. Concern over credentialing was voiced, but it was noted this is a problem throughout all medicine. The labeling should include a statement that only highly trained physicians experienced in stereotactic procedures should the implant the device.

#### **OPEN PUBLIC HEARING**

There were no requests to address the panel.

**FDA Remarks**

There were no additional comments.

**Sponsor Remarks**

The sponsor's primary investigators, Drs. Olanow, Jerrold Vitek, Steven Wilkinson, Andres Lozano, and Erwin Montgomery, all spoke briefly in support of the device as being an advance in treatment for PD. It can restore bed-ridden patients to the on state without motor complications. Other procedures are more destructive and have more adverse events. The biological basis for the device is well established, i.e., that the STN and the GPi sites are interconnected, and that the bilateral therapy can be modified as necessary allowing more flexibility than surgical procedures. They strongly requested that the panel recommend approval of the PMA supplement.

**Panel Recommendations and Vote**

**Panel Executive Secretary Ms. Scudiero** read the three panel voting options. A motion to recommend the PMA as approvable with conditions was made and seconded.

The conditions were as follows:

- 1) That the physician instructions for use should include a written protocol for the selection of electrodes and for the optimization of all stimulation parameters.
- 2) That the labeling should be revised to state "Bilateral Activa PD control therapy is safe and effective in controlling the symptoms of advanced levodopa responsive PD that are not controlled with medications."
- 3) That there should be long-term study of effectiveness over a period of three years, including for cognitive and neuropsychological factors.

- 4) That the word “patient” in the other indications would be replaced with “those with advanced levodopa responsive PD.”
- 5) That the last indication “Allowing most patients to reduce their anti-parkinsonian medication consumption” would be deleted.
- 6) That the fifth indication would be reworded to state that it allows many patients with advanced levodopa responsive PD to improve their independence and functional ability.
- 7) That the labeling should note that safety and effectiveness have not been demonstrated for the exclusion criteria conditions.
- 8) That specific training in the procedure is recommended for physicians.

(A condition that complete answers to all statistical questions and further analysis of the existing data should be submitted to the FDA prior to approval the device was moved. Upon discussion of possible unforeseen circumstances that could arise after submission and analysis of these data, Dr. Hallett withdrew the motion with the assumption that the statistical analysis of existing data would be completed.)

The motion to recommend the PMA supplement as approvable with the conditions listed above passed unanimously.

**Dr. Perry Cohen, the Patient Representative**, stated that he was pleased with the panel’s recommendation of approval with conditions.

**Panel Chair Dr. Canady** thanked the panel and all presenters and adjourned the meeting.

I certify that I attended the Open Session of the Neurological Devices Advisory Panel Meeting on March 31, 2000, and that this summary accurately reflects what transpired.

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Janet L. Scudiero, M.S.  
Panel Executive Secretary

I approve the minutes of this meeting as recorded in this summary.

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Alexa I. Canady, M.D.  
Panel Chairperson

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Summary minutes revised by  
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based on comments of FDA staff.