

SUMMARY MINUTES

MEETING OF THE NEUROLOGICAL DEVICES ADVISORY PANEL

OPEN SESSION

November 30, 2004

**Gaithersburg Hilton
Gaithersburg, MD**

**Neurological Devices Advisory Panel Meeting
November 30, 2004**

Attendees

Chairperson

Kyra J. Becker, M.D.
University of Washington School of
Medicine

Voting Members

Jonas H. Ellenberg, Ph.D.
Westat

Stephen J. Haines, M.D.
University of Minnesota

Annapurni Jayam-Trouth, M.D.
Howard University College of Medicine

Mary E. Jensen, M.D.
University of Virginia Health Sciences
Center

Christopher M. Loftus, M.D.
Temple University

Deputized Voting Members

Alexa I. Canady, M.D.
Sacred Heart Hospital

Isabelle M. Germano, M.D.
Mount Sinai School of Medicine

David T. MacLaughlin, Ph.D.
Harvard Medical School/Massachusetts
General Hospital

Michael R. Egnor, M.D.
State University of New York at Stony
Brook

Industry Representative

Andrew K. Balo
DexCom, Inc.

Consumer Representative

Chrissy E. Wells, R.T., M.B.A., M.H.S.A.
(by speakerphone)

Food and Drug Administration

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

Janet L. Scudiero, M.S.
Executive Secretary

Stephen Rhodes
Chief, Plastic and Reconstructive Surgery
Devices Branch

Peter L. Hudson, Ph.D., Lead Reviewer

Michael J. Schlosser, M.D., Clinical
Reviewer

CALL TO ORDER

Panel Executive Secretary Janet L. Scudiero, M.S., called the meeting to order at 8:45 a.m. She read the appointment to temporary voting status statement, which appointed Drs. Canady, Egnor, Germano, and MacLaughlin as temporary voting members. She then read the conflict of interest statement. Waivers had been granted for Drs. Jensen and MacLaughlin for their interests in firms at issue that could be affected by the panel's recommendations. They may participate fully.

Celia M. Witten, M.D., Ph.D., Director, Division of General, Radiological, and Neurological Devices, noted that the terms of panel members Becker, Wells, Balo, and Diaz were ending and thanked them for their service to the panel.

Panel Chair Kyra J. Becker, M.D., stated that the purpose of the meeting was to make a recommendation to the FDA on the approvability of PMA P040034 for the Confluent Surgical DuraSeal Dura Sealant System for use as an adjunct to sutured dural repair during cranial surgery to provide watertight closure. She asked the panel members to introduce themselves, after which she noted that the voting members present constituted a quorum.

Stephen Rhodes, Chief, Plastic and Reconstructive Surgery Devices, updated the panel on matters occurring since the June 15, 2004 panel meeting. On August 11, 2004, the Agency cleared the MERCI Retriever for restoring blood flow in the neurovasculature by removing thrombus in patients experiencing ischemic stroke. The device is also indicated for use in the retrieval of foreign bodies misplaced during interventional radiological procedures in the neuro, peripheral, and coronary vasculature.

On October 24, 2004, the Agency issued a guidance document entitled "Clinical Trial Considerations: Vertebral Augmentation Devices to Treat Spinal Insufficiency Fractures."

Additionally, the guidance document and the final rule reclassifying the Neuro Embolization Device and the Vascular Embolization Device from Class III into Class II will issue soon.

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No comments were made.

SPONSOR PRESENTATION

Eric P. Ankerud, J.D., Vice President, Clinical, Regulatory and Quality, Confluent Surgical, Waltham, MA, introduced the sponsor's presenters and provided an overview of the sponsor's presentation. He summarized the regulatory history of the DuraSeal Dural Sealant System. He noted that in 2002, the Agency had consulted with a panel member to establish a suitable study design.

Patrick Campbell, Ph.D., Vice President, Research and Development, Confluent Surgical, stated that the most desirable sealants are biocompatible (e.g., polyethylene glycol [PEG] based), synthetic, absorbable, tissue adherent, strong, easy to apply, and visible. After describing the company's proprietary hydrogel technology, Dr. Campbell presented slides illustrating the syringe delivery system of the DuraSeal product along with a short video depicting its use. The device has passed all biocompatibility tests.

A canine cranial sealing study found that DuraSeal sealed the incision at all times tested. All control animals leaked at 5 cm of water pressure. A marked difference between the DuraSeal animals and the control animals was found in dural–bone flap adhesions. At 56 days, the bone flaps in the DuraSeal animals were easy to remove; those in the control animals were not . Complete and normal dural healing was found in the DuraSeal animals. In addition, canine and

rat studies evaluating DuraSeal absorption found that the material was absorbed by 8 weeks. Finally, rat brain parenchymal implant histology found no evidence of DuraSeal local irritation or neurotoxicity. In summary, DuraSeal is nontoxic, not neurotoxic, and safe; it allows dural healing as it seals, can be imaged, and is completely absorbed by 8 weeks.

John M. Tew, Jr., M.D., Professor, Department of Neurosurgery, University of Cincinnati, Mayfield Clinic, Principal Site Investigator, described the clinical study rationale. Achieving watertight dural closure is an elusive objective of neurosurgical practice. Controlling intraoperative leakage is important to preventing CSF leakage and postoperative complications. CSF leaks cause postoperative morbidity, including compression of neural structures, interference with wound healing (dehiscence), meningitis, additional surgical intervention, and prolonged hospitalization. A major unmet need exists for a product that creates watertight dural closure. All current methods have shortcomings; moreover, no FDA-approved dural sealants are on the market, so the products that are being used for this purpose, which include hemostatic agents, adhesives, and dural substitutes, are being used off label. Complicating the situation is the lack of a standard of care for sealing sutured dural closure. Dr. Tew then presented a short video to illustrate DuraSeal's intraoperative ease of use and effectiveness.

The DuraSeal pilot study was conducted at Nijmegen Medical Center, Netherlands. The objective was to evaluate the safety and performance of DuraSeal as an adjunct to standard surgical dural repair techniques in cranial and spinal procedures. The study was a prospective, single-arm, nonrandomized, single-center trial involving 47 patients (45 cranial and 2 spinal). The intraoperative sealing endpoint was defined as no CSF leakage during the Valsalva maneuver after DuraSeal application. The study resulted in 100 percent intraoperative sealing success after Valsalva; a 6.4 percent postoperative CSF leak rate; and a 4.3 percent infection rate.

No device-related adverse events occurred. Wound healing was excellent, and adverse events were consistent with procedure complexity. The results provided the basis for the U.S. pivotal trial.

G. Rees Cosgrove, M.D., Associate Professor of Surgery, Harvard Medical School/Massachusetts General Hospital, Principal Study Investigator, presented information on the DuraSeal U.S. Pivotal Study. The objective of the study was to evaluate the safety and effectiveness of DuraSeal as an adjunct to sutured dural repair during cranial surgery to provide watertight closure. The study was designed in consultation with external experts, FDA, and an FDA advisory panel member. Part of the difficulty in designing the study was the lack of a standard of care or FDA-approved control device. Using a “no treatment” group as a control would not have been medically acceptable. Most surgeons agree that a watertight seal is the desired standard. The sponsor deliberated on including a control arm using fibrin glue, which is commonly used but is unapproved. The Agency had informed the company that it would not be appropriate to compare DuraSeal to an unapproved device that has an unknown safety and effectiveness profile. Thus, the sponsor designed a prospective, multicenter, single-arm, nonrandomized study that used an intraoperative endpoint to assess device effectiveness.

The pivotal trial incorporated a prospectively defined objective performance criterion (OPC). Eleven sites participated, all of which were academic medical centers that generally attract a sicker patient population. The study population consisted of patients ages 18 to 75 undergoing a Class I/clean procedure, as defined by the Centers for Disease Control and Prevention (CDC). Patients who had penetration of air sinus or mastoid cells, prior surgery in the same area, prior or planned chemotherapy or radiation, preexisting hydrocephalus, preexisting infection, a compromised immune system, uncontrolled diabetes, or renal or hepatic dysfunction

were excluded. Intraoperative eligibility criteria were as follows: linear durotomy of at least 2 cm; dural margin from defect edges of at least 3 mm, gap ≤ 2 mm remaining after primary dural closure; and either a spontaneous CSF leak or a leak upon Valsalva maneuver following primary dural closure. Autologous duraplasty was allowed as necessary.

The primary efficacy endpoint was intraoperative sealing, defined as no CSF leakage from dural repair during Valsalva maneuver up to 20 cm water for 5 to 10 seconds. Up to two DuraSeal Sealant applications were permitted. The prospectively defined OPC was 80 percent success. Dr. Cosgrove described the sample size justification and listed the safety evaluations and endpoints: postoperative CSF leak, adverse events, laboratory evaluations, neurological assessments, wound healing, and CT imaging as assessed by an independent core lab.

Postoperative CSF leak was defined as CSF leak or pseudomeningocele-related surgical intervention (i.e., breaking of skin); CSF leak confirmation by diagnostic testing; or CSF leak confirmation by clinical evaluation, including physical examination of the surgical site. The protocol required assessments at baseline (within 2 weeks of surgery), during the procedure, at discharge or within 7 days of surgery, at 6 weeks, and at 3 months. Adverse events were collected at every time point.

One hundred thirty-two patients were enrolled in the study. The study had an exceptional compliance rate, and data on 107 patients were available at 3 months. Patient demographics were as expected. More than half of the patients had a smoking history, and 86 percent had serious cardiovascular comorbidities with high American Society of Anesthesiologists (ASA) score. Nearly 50 percent of the surgical procedures were infratentorial (unlike in the general population, in which 25 percent of procedures are infratentorial). This surgical site is considered more difficult, leading to long and involved surgery. Nearly half of the surgeons chose autologous

duraplasty material to close the wound. Intraoperatively, 60 percent of CSF leaks through suture closure were spontaneous, and 40 percent were leaks following the Valsalva maneuver. One application of DuraSeal was required in 95 percent of cases; 5 percent of cases required two applications. Ninety-five percent of surgeons rated the device “easy to use.” Among the intent-to-treat patient population, 98.2 percent were successfully sealed.

All adverse events were captured; multiple events in the same patient were reported separately. No device-related adverse events occurred. Most reported events (88 percent) were not serious, and none were inconsistent with the type and complexity of the surgery. Fifty-four serious adverse events, including eight surgical site infections, occurred in 32 patients. Each adverse event was reviewed by the clinical events committee (CEC), which consisted of three independent neurosurgeons. The CEC concluded that the events were consistent in the type and severity considering the disease state and procedures performed. No concerns were raised for patient safety, and no events were determined to be device-related. Patients experienced a significant increase in pain score immediately postoperatively, which was expected, but improvement generally occurred from baseline to the 6-week and 3-month assessments. A modified Rankin scale was used to assess patient functioning; at each follow-up visit, most patients were the same or improved compared with their baseline status. At 3 months, 84 percent of patients were the same as or improved from baseline.

Additional safety assessments included laboratory analyses, wound healing, and imaging analysis. No untoward effect on hepatic or renal function was noted. All wounds were well healed by 6 months. No unexpected findings were discerned on CT scan. At 3 months, the average reduction in extradural space at the DuraSeal application site was 75.5 percent, suggesting DuraSeal absorption.

In summary, the primary endpoint was achieved; no unanticipated adverse device effects occurred; and no device-related adverse events were observed. The 98.2 percent success rate exceeded the 80 percent OPC.

Harry van Loveren, M.D., Professor and Chairman, Director of Skull Base and Cerebrovascular Surgery, University of South Florida, and principal site investigator, presented the sponsor's safety review. Of the eight patients with deep surgical site infection (SSI), one had concurrent meningitis; the others had bone flap removal. All infections resolved. In addition, one patient had superficial SSI and one had bacterial meningitis; again, both infections resolved. The total infection rate was 9 percent.

The sponsor compared the findings from the pivotal trial to data from reports in the literature. These published studies are mostly retrospective, use less inclusive definitions, and have shorter (or unspecified) follow-up intervals than the pivotal trial. In addition, the reports contain limited information on patient follow-up compliance. The literature represents a conservative estimate for adverse event rates and potentially biases comparison against DuraSeal.

Because of the limitations in the published studies, the sponsor was only able to compare against a set of (mostly) retrospective reviews of synthetic duraplasty materials and a large prospective study undertaken to evaluate operative sepsis in neurosurgery (Narotam et al., 1994). The sponsor considered the prospective Narotam et al., 1994 study published to be the best available comparator. It involved 2,249 patients; infection rates were provided by surgery classification (i.e., clean, clean-contaminated, clean with foreign body, contaminated, and dirty). The predicted infection rate for the DuraSeal study population using the Narotam criteria was 8.3 percent. Narotam et al. (1994) found different infection rates for different classifications of

surgery. In order to compare the actual infection rate with the one predicated by the Narotam criteria, the sponsor added one patient with wound erythema and one patient with poor wound healing to the superficial wound infection group, yielding an infection rate of 10.8 percent, which was not significantly different from the predicted rate of 8.3 percent. An additional analysis comparing the infection rate observed in the DuraSeal pivotal study and the rates reported for the DuraGen (collagen sponge) Duraplasty study (Narotam et al., 1995) found comparable infection rates for both clean and clean-contaminated surgery between these two studies. The differences were not statistically significant.

The sponsor stated that patient and surgical risk factors for infection are well known; they include prolonged surgery, ASA score >2, presence of foreign implant, extent of incision, sinus penetration, and smoking. The sponsor used multiple logistic regression analysis and determined that duration of surgery and smoking status were significant independent predictors of infection in their pivotal study. In summary, the sponsor concluded that the observed DuraSeal SSI infection rate is as expected, given the patient population, risk profile, and complexity of procedures performed. The rate compares favorably to infection rates reported for duraplasty materials.

The sponsor also examined postoperative CSF leaks. Postoperative CSF leaks included both incisional leaks and pseudomeningoceles requiring surgical intervention. Five patients experienced isolated CSF leaks; one additional patient was categorized as CSF leak due to prophylactic placement of lumbar drain following DuraSeal removal in the course of wound debridement. The total leak rate, including iatrogenic leaks, was 5.4 percent. Again comparing to the literature, using the von Wild, 1999 study of DuraPatch with and without fibrin sealant, the sponsor determined that the leak rate in the pivotal study was comparable to the leak rate found

in the von Wild study. The DuraSeal leak rate for supratentorial procedures was generally lower than the rates found in the literature; for infratentorial procedures, the DuraSeal rate also was comparable to or lower than rates found in other studies, even for complicated procedures. In summary, the sponsor believes that the observed DuraSeal leak rate compares favorably to rates reported in the literature.

Dr. van Loveren noted that patients in the pivotal trial represented the worst cases with the best follow-up. The primary endpoint of intraoperative dural sealing was achieved. The wound infection rate was comparable to the literature, as was the postoperative CSF leak rate. The adverse events were consistent in nature, frequency, and severity for patients undergoing cranial surgery.

Dr. van Loveren's risk/benefit conclusion assumes that dural closure/sealing promotes wound healing and avoids the complications that follow wound failure and CSF leakage. No product has been approved by FDA for dural sealing, and none have been demonstrated effective. DuraSeal provides standardized, effective, intraoperative watertight dural closure without increased risk of adverse events. Thus he believes that the benefits of the product outweigh the risks.

Panel Questions for the Sponsor

Panel members asked the sponsor for additional information and clarification on how the Valsalva maneuver was performed; the patient population in the Narotam et al. studies; the criteria for treating pseudomeningoceles as adverse events; the clinical need for a dural sealant; the true leak rate and its relation to pseudomeningoceles; whether chemotherapy and steroid use are general exclusions for use of the product; use of DuraSeal at bone edge; the sponsor's

definition of deep wound infection; whether the sponsor was proposing use with spinal dura; whether comparison studies for infection and CSF leak used the same exclusion criteria; use of MRI versus CT in patients with CSF leaks; ease of removal of DuraSeal and data on removed product; the rationale for not using infection or other adverse events as the endpoint; findings from 23 cases excluded by the sponsor; long-term follow-up of patients, if any; and rate of seizures in study patients. The panel was particularly concerned about the sponsor's methodology and spent considerable time discussing the lack of control group; the decision not to compare the device to the current standard of care, even if just on an intrasurgeon level; and the appropriateness of the literature comparison.

FDA PRESENTATION

Peter Hudson, Ph.D., lead FDA reviewer, listed the FDA review team, and then presented preclinical data on DuraSeal. He described the device, noting that the sealant is composed of two solutions: a PEG ester solution and a trilycine amine solution. When mixed together, the precursors provide for rapid *in situ* polymerization, forming a hydrogel that is intended to assist in sealing the dura mater incision line. The mixing of the precursors takes place in the DuraSeal delivery system as the materials exit the tip of the system. Gel time is less than 3.5 seconds. DuraSeal consists of water, PEG ester, trilycine, sodium borate decahydrate, sodium phosphate, FD&C blue #1 dye, and butylated hydroxytoluene (BHT). PEG is FDA approved for a variety of uses in foods and drugs. The sponsor conducted blood chemistry evaluations (including BUN and creatinine) preoperatively, at discharge, and at 3 months during the clinical study; no abnormal blood chemistries were observed.

Trilysine consists of L-lysine, a naturally occurring amino acid. An extensive search of the toxicology literature databases found no toxicology information concerning trilysine. BHT has been generally recognized as safe for use in foods since 1959. No toxicology database or preclinical evaluation information suggests that the amount of BHT patients would be exposed to is of concern with respect to safety. FD&C blue #1 is a water-soluble dye that is FDA approved for use in foods, drugs, and cosmetics. The amount of the dye patients will be exposed to in DuraSeal is a 1000-fold lower than the acceptable daily intake (12.0 mg/kg/day). For the dye to be used in a medical device, the sponsor must submit a color additive petition to the Center for Food Safety and Nutrition. The sponsor is in the process of that submission and the topic does not have to be considered by the panel.

The sponsor also conducted standard tissue contact biocompatibility evaluations of the sealant and delivery system components in accordance with the FDA biocompatibility guidance recommendations. The device passed all tests. The sponsor conducted four mutagenicity evaluations of the product; carcinogenicity evaluations were not conducted due to the negative mutagenicity tests and what is known regarding the mutagenic potential of the product chemical constituents. The sponsor's *in vivo* studies in rat and canine models looked for product-related toxicities in the brain and used a subcutaneous implant resorption approach to determine the approximate time of degradation. The animal evaluations indicated that the device works as intended and does not cause tissue toxicity. No evidence suggests that the device can cause carcinogenesis or reproductive toxicity. The device's chemical components do not raise toxicological concerns, and the device has been demonstrated to be biocompatible.

Michael J. Schlosser, M.D., DGRND, reviewed the device's indications for use and the clinical trial design, noting that the study actually involved two groups of patients: those who

leaked spontaneously and those who only leaked following a Valsalva maneuver. The sponsor carefully defined the study population, limiting it to elective cases, autograft for dural closure, and clean approaches. CSF leaks were defined as a CSF leak or pseudomeningocele-related surgical intervention within 3 months postoperatively; CSF leak confirmed by diagnostic testing within 3 months, or CSF leak confirmed by clinical evaluation, including physical exam within 3 months.

The high success rate at achieving a watertight closure in the pilot study suggested that a high success criterion for inter operative sealing could be used as the threshold for efficacy. Complicating study design was the fact that randomization against standard of care would have resulted in a study that compared DuraSeal to a control population that included multiple off-label devices, the safety and efficacy of which have not been established by clinical studies. Therefore, FDA would have been asked to approve the device based on its being noninferior to devices for which the safety and effectiveness profile are unknown. FDA and the sponsor worked together during the IDE and pre-IDE phase to determine an appropriate study design.

No patients were excluded intraoperatively due to a lack of CSF leak: All patients leaked either spontaneously or following a Valsalva procedure. Thus, although the study design of using only patients who leaked intraoperatively was intended to select for a population more at risk, all the patients enrolled in this study leaked inter operatively. The study is therefore more representative of an “all comers” group of craniotomy patients when it comes to CSF leak risk. Patients were not selected on the basis of predilection for CSF leak.

The success criterion was 80 percent, defined as the proportion of patients with no CSF leakage from the dural repair intraoperatively. Counting two patients who were not tested at the full Valsalva pressure as failures, the observed study success rate was 98.2 percent. The lower

bound of the 95 percent confidence interval was 93.6 percent; the sponsor met the primary efficacy criterion.

The safety analysis focused on deep wound infection, CSF leak, and bacterial meningitis; other adverse events are typical of a postcraniotomy population and unlikely to be device related. Given the known association between implanted materials and infection, wound infection was of particular concern. We compared the postoperative CSF leak rate from the DuraSeal study against three studies from the literature. The rates of postoperative CSF leak range from 1.2 percent to approximately 13 percent, depending on the study population, follow-up, and definition of CSF leak. Although the DuraSeal leak rate appears to fall within the range reported in the literature, no conclusive statements about an improvement in CSF leak can be made based solely on these data.

The pivotal trial had a wound infection rate of 8.1 percent and a total infection rate of 9.0 percent. Variables that affect risk of infection in neurosurgical cases include length of procedure, implant of foreign body, and ASA score. The literature is not consistent with regard to classification of wounds as clean or clean/contaminated. The Narotam et al., 1994 study against which the sponsor compared its data used a different categorization method than the CDC criteria. This Narotam study examined some important variables for defining the clean-contaminated subgroup (i.e., entry into sinuses, fracture of cranial base, and length of surgery). The rate of infection in the >2-hour group (considered by Narotam to be clean/contaminated) was statistically higher than in the clean group, however, the difference between surgeries lasting 2 to 4 hours and >4 hours was not statistically significant.

In the Narotam et al., 1995 DuraGen study, the researchers considered clean-contaminated cases to include both procedures that involved skull base fractures or sinus

penetration and procedures lasting >2 hours. The implantation of foreign bodies was not captured on the case report forms. The power of the Narotam study is an important issue. It is not possible to draw conclusions from comparing the DuraSeal infection data against other studies in the literature because the study designs are so different. Finally, infection and postoperative CSF leak rates for intraoperative spontaneous versus Valsalva-induced leakers were not significantly different.

In conclusion, the sponsor met the primary effectiveness endpoint. Safety adverse events included a 5.4 percent postoperative CSF leak rate, an 8.2 percent wound infection rate, and a 9.0 percent procedure-related infection rate.

Panel Questions for FDA

Panel members asked for additional information about the control group in the Narotam et al. study, the leak rate, and the effects of direct application of blue dye to brain. They again discussed the pivotal study methodology, focusing on the decision to not compare the patient population to the standard of care. They asked FDA to clarify the Agency's position on comparing DuraSeal to the current sealants, all of which are products being used off label.

PANEL REVIEWS

David T. MacLaughlin, Ph.D., reported on the sponsor's preclinical data. DuraSeal has many desirable performance characteristics: It is easy to use, involves an isothermic reaction, is adherent to dura mater, is biocompatible, and is absorbable. The chemical constituents of the product are obtainable off-the-shelf, and the components have been demonstrated safe in many applications. The breakdown products are basically the same as the product itself.

One concern involves what the sponsor does once the product is in hand: How does the sponsor ensure appropriate specifications materials from so many suppliers, and what happens every time the supplier changes? In addition, it is not clear how the sponsor arrived at certain specifications for the performance characteristics. For example, why did the sponsor pick a 200 percent swelling standard when its own data show the actual swelling to be much lower? It is also unclear why the sponsor has both 25- and 37-degree accelerated degradation tests.

Dr. MacLaughlin had no concerns about the syringe delivery system integrity or toxicity, although he noted the importance of ensuring that the oxygen content of the sealed vial and buffer solution of mixing agents is appropriate. The shelf-life tests are not complete; it is important to be sure the product is stable. The fetal toxicity study and proliferation inhibition were begun at Day 4 of pregnancy; we do not know what happens if exposure occurs before Day 4. All *in vivo* studies were reasonable and approximated what happened to patients. No adverse effects were seen in extracting the material. In summary, the material was reasonably tested and does not pose an unacceptable risk.

Alexa I. Canady, M.D., commented on the clinical data. She noted that the “elephant in the room” is change from non-evidence-based practice to evidence-based practice. In the absence of historical controls, the range is 0 to 20 percent for infection and CSF leak. Comparing DuraSeal to current practices and the literature is a daunting task for this PMA.

Another issue is use of a clinical rather than an intraoperative endpoint. One must question whether a 100 percent intraoperative leak is a useful standard. Additionally, in evaluating the clinical risk of leaking, it is important to look at excluded patients since the patient population was highly selected. In addition, no appropriate comparator group for wound infection is available. Most studies involving other materials, however, have higher infection

rates. Finally, the DuraSeal material is visible on MRI. In labeling and educational materials, it is important to provide information so that clinicians do not misread MRIs.

Sponsor representatives provided additional information in response to the panel reviewers' concerns. Panel members again raised the issue of lack of control group in the clinical study and expressed their concerns with the methodology.

FDA QUESTIONS

1. . . . Please discuss whether this infection rate raises concern.

The panel was unanimous in its concern about the infection rate and the lack of data against which to compare the infection rate in the clinical study. The sponsor's attempt to find an acceptable comparison in the literature was unconvincing.

2. . . . Please discuss the observed post-operative CSF leak rate.

The panel agreed that the product is effective at stopping intraoperative leaks. It is unclear what this means for patients over the long-term and whether this product is better than other products.

3(a) Do you believe the results of the study support an adequate risk/benefit ratio in patients who exhibit spontaneous CSF leak after sutured dural closure?

3(b). Do you believe the results of the study support an adequate risk/benefit ratio in all patients with sutured dural closure (as described in the proposed indication for use)?

Panel members generally indicated that it was not possible to separate the two groups for analysis because the data shows inter operative leakage in 100 percent of the patients. Although DuraSeal is effective for closing and sealing the dura, the risks/benefit ratio is still in question based on the available information.

4. . . . Please discuss whether the data in the PMA provide a reasonable assurance of safety.

The panel was not in consensus on whether the product is safe. Many panel members agreed that the safety profile is commensurate with the current materials surgeons use to seal the dura mater, all of which are used off label. At the same time, panel members noted that although the sponsor reached the primary endpoint for effectiveness, more data on risk of infection is needed.

5. . . . Please discuss whether the data in the PMA provide a reasonable assurance of effectiveness.

Panel members concurred that the device effectively closes the dura mater in the studied patients and that the long-term clinical significance of the device is not established. The device is generally safe and may have the added benefit of reducing intraoperative time. Although approval of the device would be based on a high-risk group of subjects, the device would be used in a much wider range of patients.

6. . . . If you believe that the data in the PMA demonstrate a reasonable assurance of safety and effectiveness, but think there are specific focused questions regarding this device that still remain and can be addressed in a postapproval study, please identify those questions.

The panel concurred that postapproval studies should study the infection rate, as well as clinical outcomes in high-risk patients. Most panel members believed that safety and effectiveness were demonstrated, but several panel members had concerns. It is important to show that the device makes a difference in complicated cases, and it would be good to know the actual clinical CSF leak rates. Panel members noted that duration of surgery is not necessarily a reliable indicator for infection risk because there are so many confounding factors.

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No comments were made.

SPONSOR CLOSING REMARKS

Sponsor representatives stated that the company's intent was to label DuraSeal to match the patient population studied in the clinical trial. The study measured intraoperative sealing efficacy, and the sponsor is seeking an indication for an intraoperative watertight seal. There is a need for a first product on market so that the burden the sponsor faced in trial design cannot be placed again on other companies. The study findings are robust, and surgeons have an incredible need for the product.

VOTE

Ms. Scudiero read the voting options. The panel voted seven to two with no abstentions to recommend approval of the PMA, with the following conditions:

1. The sponsor should conduct postmarket surveillance to determine the infection rate among patients who are treated with the device.
2. The sponsor should provide data on MRI and CT imaging analyses to demonstrate DuraSeal's imaging characteristics and the duration for which the material will appear on MRI and CT images.
3. The following information should appear on the labeling:
 - A boxed warning statement that an increased infection rate was observed in the patients in the clinical study.
 - The total infection rate in the clinical study patients.
 - A statement that the device should be used only as an adjunct to standard surgical techniques for closing the dura. The device should be used when primary watertight dural closure cannot be achieved.
 - A statement that the device material appears on MRI imaging for a determined period of time after application.
 - A statement in the clinical summary that the device is effective in the studied patient cohort.

- A statement that no data are available on CSF inflammatory response with use of the device.

POLL

Panel members voting to recommend approval generally stated that the data support safety and effectiveness of the device. The DuraSeal material is in common use, and the product works as intended. Another benefit is that the product involves off-the-shelf chemical constituents. DuraSeal is at least as effective as what is currently used, and the benefits outweigh the risks. However, long-term benefits are unknown, and the clinical trial highlights the need to assess CSF leaks. The sponsor should submit the postmarket data to the Agency as soon as possible.

Panel members voting not to recommend conditional approval expressed concern over the lack of controls in assessing safety and indicated that data were not sufficient to judge the risk/benefit ratio. Some of the issues raised during the meeting should have been dealt with during trial design.

ADJOURNMENT

Dr. Witten thanked the participants on behalf of the Agency, and Dr. Becker adjourned the meeting at 4:42 p.m.

I certify that I attended this meeting of the Neurological Devices Advisory Panel Meeting on November 30, 2004, and that these minutes accurately reflect what transpired.

Janet L. Scudiero, M.S.
Executive Secretary

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

Kyra J. Becker, M.D.
Chairperson