SUMMARY OF SAFETY AND EFFECTIVENESS DATA

I. GENERAL INFORMATION

Device Generic Names:	Sealant, Dural
Device Trade Names:	DuraSeal Dural Sealant System
Applicant's Name and Address:	Confluent Surgical, Inc. 101A First Avenue Waltham, MA 02451
PMA Number:	P040034
Date of Panel Recommendation:	November 30, 2004
Date of Notice of Approval to the Applicant:	APR 7 2005

II. INDICATIONS FOR USE

The DuraSeal™ Dural Sealant System is intended for use as an adjunct to sutured dural repair during cranial surgery to provide watertight closure. DuraSeal should only be used with autologous duraplasty material.

III. CONTRAINDICATIONS

Do not apply the DuraSeal Dural Sealant System to confined bony structures where nerves are present since neural compression may result due to hydrogel swelling. The hydrogel may swell up to 50% of its size in any dimension.

IV. WARNINGS AND PRECAUTIONS

The warnings and precautions can be found in the DuraSeal™ Dural Sealant System labeling.

V. DEVICE DESCRIPTION

The DuraSeal Dural Sealant System consists of components for preparation of an absorbable polyethylene glycol (PEG) hydrogel sealant and a delivery system (i.e., applicator, spray tips and plunger cap) packaged in a sterile single use kit. The sealant is composed of two solutions, a PEG ester solution and a trilysine amine solution which are referred to as the "blue" and "clear" precursors, respectively. When mixed together, the precursors rapidly polymerize *in-situ* to form the hydrogel sealant. The mixing of the

precursors is accomplished in the DuraSeal delivery system as the materials exit the tip of the delivery system. The delivery system allows a conformal coating that adheres to the tissue surfaces. The mixing provided by the delivery system also ensures a complete reaction of the precursors. The polymerization requires no external energy requirements, such as light or heat, and takes place by a nucleophilic substitution reaction. The PEG component contains hydrolyzable ester bonds which enable the hydrogel to be degraded through hydrolysis after application. FD&C Blue no. 1 dye provides the color of the blue solution and enables the user to discern the thickness of the hydrogel layer and the area of hydrogel application. The gel swells, volummetrically, no more than 200%. For a 2 mm thick hydrogel that isotropically swells 200%, the maximum linear dimensional change in any direction is <1 mm. There is very little or no heat evolution during the polymerization reaction.

The cross linked solid hydrogel is more than 90% water at application. Due to this high water content, the hydrogel has physical properties similar to tissue. The hydrogel implant is absorbed in approximately 4 to 8 weeks and the absorbed hydrogel components are excreted from the body. The DuraSeal Dural Sealant can be used for up to one hour following reconstitution.

VI. ALTERNATIVE PRACTICES OR PROCEDURES

The current methods of dural repair consist of the direct application of interrupted sutures, possibly with the use of dural replacement materials (i.e., duraplasty) to cover significant dural gaps. Adjunct dural repair techniques used today entail the application of absorbable gelatin or collagen sponge, autologous muscle, temporalis fascia, fascia lata, pericranium, ligamentum nuchae or fat grafts.

VII. MARKETING HISTORY

The DuraSeal Dural Sealant System is approved for commercial sale in the European Economic Area (EEA) since June 2003 (CE Mark), in South Africa since January 2004, in the United Arab Emirates since March 2004, and in Australia since August 2004. The DuraSeal System has not been withdrawn in any country due to reasons related to safety and effectiveness of the device.

VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

The DuraSeal Dural Sealant System was evaluated in 111 investigational patients in the pivotal clinical study. The following table presents any adverse event occurring at a rate of 1% or higher in these patients. Adverse event rates presented are based on the number of patients having at least one occurrence of a particular adverse event divided by the total number of patients treated.

Table 1

Adverse Event Category Note: Patient can experience more than one AE	# of patients n	 %
Arrhythmia	6	(5.4)
Bleeding	4	(3.6)
Cerebral Edema	4	(3.6)
CSF Leak (protocol definition)		
• Incisional	2	(1.8)
• Pseudomeningocele	3	(2.7)
Dermatologic Events (e.g. rash, skin breakdown, steroid related acne, etc.)	11	(9.1)
Dizziness	8	(7.2)
Edema (non-systemic)	19	(17.1)
Electrolyte Imbalance	11	(9.9)
Elevated Liver Enzymes	11	(9.9)
Fever Post-op (>38.5°C for 48 hours)	6	(5.4)
Fever (<38.5°C for <48 hours)	5	(4.5)
General Malaise	9	(8.1)
General - Other: Corneal abrasion, chemotherapy, complication, hiccoughs	3	(2.7)
GI Disturbance (e.g. abdominal pain, diarrhea, reflux, heartburn, etc.)	16	(14.4)
Headache (not responding to standard therapy)	5	(4.5)
Headache (responding to standard therapy)	9	(8.1)
Hematologic Abnormality	7	(6.3)
Hydrocephalus	4	(3.6)
Hypertension	5	(4.5)
Infection (non-incisional)		
• General (Thrush, otitis media, keratitis, catheter-related infection)	8	(7.2)
• Upper Respiratory/Bronchial	4	(3.6)
• Urinary Tract	11	(9.9)
Infection, Surgical Site		
• Deep (re-operation required)	8	(7.2)
• Superficial	1	(0.9)
Late (>30 days) Wound Infection	3	(2.7)
Meningitis		
• Aseptic	5	(4.5)
• Bacterial	2	(1.8)
Musculoskeletal Events (e.g. facial pain, left arm pain, difficulty with head movement, abdominal hernia, throat pain, etc.)	21	(18.9)
Nausea and/or Vomiting	24	(21.6)
Neurological Symptoms		
-Cognitive	5	(4.5)
-Cranial nerve deficit	34	(30.0)
-Motor deficit	17	(15.3)
-Neuropsychiatric disorders	7	(6.3)
-Speech difficulty	10	(9.0)
-Visual disturbance	22	(19.8)
Pain, Incisional	2	(1.8)
Peripheral edema	2	(1.8)
Pneumonia	3	(2.7)
Pseudomeningocele (responding to conservative therapy)	2	(1.8)
Respiratory Difficulties (e.g. bronchospasms, hypoxia, respiratory distress, difficulty breathing, etc.)	6	(5.4)
Seizure	3	(2.7)
Stroke/CVA/Cerebral Hemorrhage	5	(4.5)
Subdural Hematoma	2	(1.8)
Ureterolilithiasis	2	(1.8)
Urinary Difficulty	9	(8.1)
Urogenital Other	2	(1.8)
Wound erythematic/inflammation	2	(1.8)

The incidence and nature of adverse events observed in this patient population are consistent with the type and complexity of the surgery performed and the co-morbid state of the treated patients. There were two patient deaths (out-of-hospital). In both cases, the deaths were attributed to the patients' prior condition. Potential, but not observed, risks and adverse events that could occur from the use of the DuraSeal Dural Sealant System include, but are not limited to, renal compromise, inflammatory reaction, neurological compromise, allergic reaction and/or delayed healing.

The DuraSeal Dural Sealant System was also clinically evaluated in an additional 47 patients during a European Pilot Trial. The nature and severity of events reported in this study were consistent with the results presented in Table 1.

IX. SUMMARY OF PRECLINICAL STUDIES

Biocompatibility

Biocompatibility testing was performed on the device as one system. All hydrogel samples evaluated in biocompatibility tests were prepared using the kit components supplied, in accordance with the Instructions for Use. Additional studies evaluated the DuraSeal delivery system (i.e., applicator, spray tips and plunger cap) for biocompatibility.

Biocompatibility testing (Table 2) of the formed DuraSeal hydrogel has been performed consistent with Federal Good Laboratory Practices Regulations (21 CFR § 58) and FDA's Blue Book memorandum G95-1 "Use of ISO-10993 Biological Evaluation of Medical Devices Part 1: Evaluation and Testing". This document defines the DuraSeal hydrogel as a tissue/bone contacting implant of permanent contact duration.

Table 2 Summary of DuraSeal Sealant Biocompatibility

Test Reference	Method Reference	Results
Cytotoxicity (Agarose Overlay Method)	International Organization for Standardization: Biological Evaluation Medical Devices, Part 5. 10993-5: *Tests for Cytotoxicity*	Non cytotoxic
ISO Maximization Sensitization Study (Guinea Pigs)	International Organization for Standardization: Biological Evaluation Medical Devices, Part 10. 10993-10: *Tests for Irritation and Sensitization*	Non sensitizing
ISO Modified Intracutaneous Study	International Organization for Standardization: Biological Evaluation Medical Devices, Part 10. 10993-10: *Tests for Irritation and Sensitization*	No evidence of significant irritation.
USP and ISO Modified Systemic Toxicity	International Organization for Standardization: Biological Evaluation Medical Devices, Part 11. 10993-11: *Tests for Systemic Toxicity*	No mortality or systemic toxicity
USP Pyrogenicity	International Organization for Standardization: Biological Evaluation Medical Devices, Part 11. 10993-11: *Tests for Systemic Toxicity*	Non-pyrogenic
Subchronic toxicity	This test evaluates the potential systemic toxicity of the test material following implantation in the rat. Test in accordance with portions of the International Organization for Standardization: Biological Evaluation Medical Devices, Part 11. 10993-11: *Tests for Systemic Toxicity*	No Systemic Toxicity
Bacterial Reverse Mutation Assay	International Organization for Standardization: Biological Evaluation Medical Devices, Part 3. 10993-3: *Tests for Genotoxicity, Carcinogenicity, and Reproductive Toxicity*	Non-mutagenic
In Vitro Mammalian Chromosome Aberration Test	*In vitro* Chromosomal Aberrations Test evaluates the potential clastogenic properties of a test material solution.	Non-mutagenic
Micronucleus Cytogenic Assay in Mice	International Organization for Standardization: Biological Evaluation Medical Devices, Part 3. 10993-3: *Tests for Genotoxicity, Carcinogenicity, and Reproductive Toxicity*	No clastogenic activity
In Vitro Mammalian Cell Gene Mutation Test	International Organization for Standardization: Biological Evaluation Medical Devices, Part 3. 10993-3: *Tests for Genotoxicity, Carcinogenicity, and Reproductive Toxicity*	Non-mutagenic
ISO Muscle Implantation Study (2 Weeks)	International Organization for Standardization: Biological Evaluation Medical Devices, Part 6. 10993-6: *Tests for Local Effects after Implantation*	Slight Irritant
ISO Subcutaneous Implantation Study in the Rat (10 days)	International Organization for Standardization: Biological Evaluation Medical Devices, Part 6. 10993-6: *Tests for Local Effects after Implantation*	No significant macroscopic reaction. Microscopically material classified as non-irritant.
In Vitro Hemolysis (Modified ASTM-Direct Contact Method)	International Organization for Standardization: Biological Evaluation Medical Devices, Part 4. 10993-4: *Selection of Tests for Interactions with Blood*	Non-hemolytic
In Vitro Proliferative Effects of DuraSeal in Various Human Cancer Cell Lines	This test assessed whether DuraSeal could stimulate or inhibit the proliferation of 4 human cancer cell lines (HT29 Colon Cancer, OVCAR3 Ovarian Cancer, A549 Lung Cancer, and U-87 MG Gliobastoma) in *in vitro* culture. Cells were cultured in the presence of gel fragments for four days, after which time cell proliferation was assessed via the MTT assay.	No proliferative or anti-proliferative effects observed.

In Vitro Product Testing

A series of *in vitro* tests were performed on the components and materials of the DuraSeal System (final, sterilized devices). In addition to the studies identified in **Table 3**, environmental testing was performed to assure that the product is not affected by temperature extremes or maximum irradiation dose.

Table 3 In Vitro Product Testing

Design Characteristic	Test Description	Results
Gel Time and Pot Life	Test evaluates the time it takes for a hydrogel to form when the two precursor components are mixed (gel time), and 1 hour after reconstitution of the blue precursor with buffer (pot life).	Upon mixing precursors, a gel is formed in ≤ 3.5 seconds.
Swelling	Evaluates the percent weight gain resulting after a 24-hour immersion of the hydrogel in 37°C phosphate buffered saline (PBS).	In vitro swelling is ≤ 200%.
In vitro absorption - disappearance	Hydrogel time of dissolution when placed in PBS at 60.4°C.	DuraSeal hydrogel is visibly dissolved in 1.2 to 4 days after immersion into PBS, pH 7.4, at 60.4°C.
Gel application-pressure integrity	Test evaluates the mechanical joints of the applicator to ensure that the device is sufficiently robust to withstand anticipated use.	Applicators did not leak or fail when pressurized to 68 psi for a minimum of 4 seconds.
Uniform gel application	Evaluates proper function of the applicator and mixing of the precursors to the target area to assure uniform sealant application.	Applicator disperses gel in a pattern <10mm diameter when Spray Tip is 2-4cm from target tissue.

Sterilization

E-beam irradiation sterilization validated in accordance with "*Sterilization of health care products – Requirements for validation and routine control – Radiation sterilization*", ANSI/AAMI/ISO 11137 – 1994 and "*Sterilization of medical devices – Validation and routine control sterilization by irradiation*", EN552.

Shelf Life

A 12-month shelf life was established based on results from real-time (53 weeks) test evaluations for 3 DuraSeal product lots. The devices were tested for the following attributes following real-time and accelerated aging:

- Visual assessment
- Hydrogel performance
- Packaging assessment

Animal Testing

A series of animal studies were conducted to evaluate the *in vivo* performance and safety of the DuraSeal Dural Sealant System. Table 4 provides a summary of the tests performed and the relevant findings.

Table 4 Summary of Animal Studies

Test Performed	# Animals/ Study Duration or test set-up	Summary/Relevant Findings
Heat of polymerization	Muscle tissue with temperature probe	A temperature probe was inserted into temperature-controlled (37°C) muscle just under the site of device application. The temperature was measured during and after hydrogel application and polymerization. The hydrogel components were at room temperature and a small decrease (5.4°C) in surface temperature was observed. The tissue temperature re-equilibrated quickly.
Canine Cranial Sealing Study	13 test and 13 control/56 days	Study performed to demonstrate both safety and effectiveness of the DuraSeal Sealant in a canine cranial durotomy model. Study endpoints included sealing capability of CSF leaks after treatment with DuraSeal (suture plus hydrogel application) when compared with control (suture) following challenge with a Valsalva maneuver, and confirmation of normal healing (tolerance) following application of the DuraSeal Sealant. Animals were observed to qualitatively assess normal behavior, general health signs (e.g., incision healing, appetite), and for possible CNS abnormalities. Marked peridural adhesions were encountered in 3/3 control dogs at 7 days, and 1/3 control dogs at 56 days; no dural adhesions were observed in the treated group. Valsalva at 1, 4, 7 and 56 days showed mean leakage pressures of, respectively: 5, 5, 7 and 13 cm H_2O in controls and 53, 37, 42 and 48 cm H_2O in treated animals. Histopathology of controls showed thick dural fibroplasias with little or no injury to the underlying brain; in hydrogel treated animals, both dura-arachnoid complex and brain displayed minimal changes. Evidence of residual implant material was less evident at the 7 day re-explorations, and had completely disappeared by 56 days. The results obtained from this controlled study suggest that the DuraSeal is effective as a tissue sealant to achieve optimal dural closure and repair, and that the hydrogel material is well tolerated.
DuraSeal MR and CT Imaging Evaluation: Canine Craniotomy Model	2 test/14 weeks	Following a craniotomy in 2 dogs, DuraSeal was sprayed onto the dura (3 mm in thickness), i.e., the dura was not incised, and the bone flap was then replaced. Following recovery, both animals underwent MR and CT imaging at 3 days, and at 2, 4, 6, 8, and 10 weeks. Gel appearance at each time point was characterized, and compared with pathological findings obtained 14 weeks following implantation. Both dogs remained neurologically intact. DuraSeal Sealant was readily apparent with all imaging techniques out through 6 weeks. The sealant could be viewed with MRI and CT and could be distinguished from CSF. Histopathology examination revealed minimal changes, with tissue compatibility with the gel noted. Histological examination found an unremarkable response with no neurotoxicity, or space-filling defect. With MRI/CT imaging, a rapid reduction in hydrogel volume between weeks 2 and 4 simultaneous with a reduction in marginal enhancement intensity was observed. This was followed by a gradual ongoing reduction in the volume of hydrogel and an associated adjoining-hydrogel image enhancement, until the 10 week time point, when there was near total resorption with virtually no residual image enhancement. With regard to differentiating the appearance of the gel in contrast to CSF, inflammatory collections or an infected surgical bed, the gel collection image is hyperintense with respect to CSF, inflammatory collections and would be expected to have greater signal heterogeneity. The symmetric and homogenous circumferential marginal enhancement may help in image interpretation.
Rat Brain Parenchymal Implant Study	8 test and 8 control/42 days	The DuraSeal Sealant was evaluated for the potential to cause local irritation or toxicity at the implant site. Micro forceps were used to implant pieces of DuraSeal into brain parenchyma in test animals, and to create sham injuries in controls. Examinations for clinical signs of disease or abnormality and a neurological assessment were conducted prior to treatment, and at days 4, 14, 28, and 42 post-treatment. No neurologic deficits were noted and no adverse reactions were observed for any of the test sites at explant. There was no evidence of a local effect or a neurotoxicity effect in association with the test article implanted within the neuropil of the brain in rats.
Study in the Rat Following Injection of Test Extracts into the Brain	13 test and 13 control/2 weeks	The potential neurotoxicity of the DuraSeal Sealant compared to a control solution was evaluated following injection of prepared extracts into the lateral ventricle and the cisterna magna of the brain of a rat. Detailed health examinations and neurologic assessments were conducted at prespecified intervals, i.e., 4 days and 2 weeks following injection. No macroscopic encapsulation was observed at any test or control cannulation site. The microscopic evaluation of the tissues revealed no

Test Performed	# Animals/ Study Duration or test set-up	Summary/Relevant Findings
		evidence of a treatment related response. Under the conditions of the study, there was no significant evidence of neurotoxicity from the test extract injected into the brain of rats.
Evaluation of DuraSeal Persistence Following Subcutaneous Implantation in the Rat	21 test and 21 control/14 weeks	Study performed to evaluate the in-vivo persistence and degradation of the DuraSeal Sealant over a period of 14 weeks following subcutaneous implantation in the rat. Results demonstrate that the DuraSeal hydrogel sealant persists essentially in its initial form for 2 weeks, becomes noticeably softer at 4 weeks and is predominantly degraded by 6 weeks. Degradation was complete within 8 weeks of implant.
Study for Effects on Embryo-Fetal Development with DuraSeal in Rats Following Intraperitoneal Administration	25 test and 25 control/2 weeks	Study performed to determine the developmental toxicity, including the teratogenic potential of the DuraSeal Sealant in rats following subcutaneous administration on Day 6 of gestation. Detailed clinical observations were performed daily up through 20 days of gestation. Dams were subjected to necropsy including uterine examination and fetuses were evaluated for malformations and developmental variations. No toxic or teratogenic observations were noted comparing DuraSeal to a control substance. Based on the results of this study, the No Observable Effect Level (NOEL) for maternal and developmental effects is >0.1mL (0.3909 mL/kg) of DuraSeal, which represents almost 5.5 times the anticipated exposure under normal conditions of use. Under the conditions of this study, the DuraSeal sealant was found to be non-teratogenic in rats.

Dye toxicology evaluations

The DuraSeal Sealant contains FD&C Blue #1 dye for visualization of the hydrogel during application. The dye is a certified color listed in 21 CFR 82 and it has been approved for use in foods (21 CFR 74.101), drugs (21 CFR 74.1101) and cosmetics (21 CFR 2101). FD&C Blue #1 is water soluble and has been evaluated in life-exposure animal studies that determined an acceptable daily intake (ADI) for the dye of 12 mg/kg/day. Calculations comparing the amount of dye absorbed by ingestion, and the amount of dye a patient will be exposed to in one application of DuraSeal, indicate that the absorbed amount of ingested dye would be much greater. *In vitro* and *in vivo* determinations found low microgram/mL concentrations after 9 hours of elution from polymerized gel in a saline bath or undetectable amounts (low microgram detection sensitivity) of the dye at 7-8 days, post-implantation in a dog model. The dye was determined to not be present in the body for a significant amount of time.

X. SUMMARY OF CLINICAL STUDIES

European Pilot Trial

A prospective, single center, non-randomized clinical investigation to evaluate the safety and performance of the DuraSeal Dural Sealant System in patients scheduled for elective cranial or spinal surgery was performed in the Netherlands.

A total of 47 patients were treated with the DuraSeal Dural Sealant System; 45 (95.7%) cranial and 2 (4.3%) spinal intra-dural procedures.

The primary endpoint of this study was a reduction in the incidence of intra-operative cerebrospinal fluid (CSF) leakage following dural sealant application defined as no CSF leakage from dural repair intra-operatively during Valsalva maneuver (20 cm H_20).

None of the 47 patients treated with the DuraSeal System demonstrated a CSF leak during the post application Valsalva maneuver, thus demonstrating a 100% success rate in holding a watertight seal. The incidence of clinically diagnosed post-op CSF leaks was 4.7%, the incidence of pseudomeningocele was 2.3%.

The primary safety endpoint was defined as procedure-related complications and adverse events. There were a total of 51 adverse events reported in 28 patients; there were 14 serious adverse events in 11 patients or an overall incidence of 29.8% in the study. None of the reported adverse events were deemed related to the DuraSeal System.

US Pivotal Trial

A prospective, multi-center, non-randomized, single arm clinical investigation to evaluate the safety and effectiveness of the DuraSeal Dural Sealant System as an adjunct to sutured dural repair during cranial surgery to provide watertight closure was conducted. Current standard of care for prevention of CSF leaks following surgeries involving incision of the dura includes a variety of approaches. There was no approved dural sealant that could be included in the clinical study design as a control. The study involved 10 investigational sites within the United States and 1 site in Europe. A total of 111 patients were treated with the DuraSeal Sealant.

Key Inclusion/Exclusion criteria for the study included the following:

Pre-Operative Inclusion Criteria

- Patient is scheduled for an elective cranial procedure that entails a dural incision using any of the following approaches (or combination): Frontal, Temporal, Parietal, Occipital and/or Suboccipital
- Patient requires a procedure involving surgical wound classification Class I/Clean

Pre-Operative Exclusion Criteria

- Patient requires a procedure involving translabyrinthine, transsphenoidal, transoral and/or any procedure that penetrates the air sinus or mastoid air cells; superficial penetration of air cells are not excluded
- Patient has had a prior intracranial neurosurgical procedure in the same anatomical location
- Patient has had chemotherapy treatment within 6 months prior to, or planned during the study (until completion of last follow-up evaluation)
- Patient has had prior radiation treatment to the surgical site or planned radiation therapy within one month post procedure
- Patient has hydrocephalus (e.g. elevated intracranial pressure > 22 cm H_2O)
- Patient has a known malignancy or another condition with prognosis shorter than 6 months (patients with stable systemic disease can be included, extent of disease will be documented)
- Patient has pre-existing external ventricular drainage or lumbar CSF drain
- Patient is not able to tolerate multiple Valsalva maneuvers or an intra-operative CSF shunt does not allow for transient elevation of CSF pressure during Valsalva maneuvers

- Patient has a systemic infection (e.g. UTI, active pneumonia) or evidence of any surgical site infection (superficial, deep, or organ space), as determined by fever > 101°F, WBC > 11,000/uL, positive blood culture, positive urine culture, and/or by a positive chest x-ray.
- Patient has been treated with chronic steroid therapy unless discontinued more than 6 weeks prior to surgery (standard acute perioperative steroids are permitted)
- Patient has a compromised immune system or autoimmune disease (WBC count less than 4000/uL or greater than 20,000/uL)
- Patient with uncontrolled diabetes, as determined by two or more incidences of elevated blood sugar levels (fasting glucose >120mg/dL) within the 6 months prior to surgery
- Patient with creatinine levels > 2.0 mg/dL

Intra-Operative Inclusion Criteria

- Surgical wound classification Class I/Clean (per CDC criteria)
- Linear extent of durotomy is at least 2 cm
- Dural margin from edges of bony defect is at least 3 mm throughout
- Patient must have a CSF leak after primary dural closure, either spontaneous or upon Valsalva maneuver, up to 20 cm H_2O for 5-10 seconds

Intra-Operative Exclusion Criteria

- Patient required use of synthetic or non-autologous duraplasty material
- Patient has a gap greater than 2 mm remaining after primary dural closure
- Incidental finding of any of the Pre-operative Exclusion Criteria

Safety and Effectiveness Parameters

The primary effectiveness endpoint for the study was the percent (%) success in the treatment of intra-operative CSF leakage following DuraSeal Sealant application defined as no CSF leakage from dural repair intra-operatively after up to two DuraSeal Sealant applications, during Valsalva maneuver up to 20 cm H_20 for 5 to 10 seconds. The study success definition was met if the two-sided 95% confidence limit of the CSF leak rate (expected to be at least 90%) was greater than a minimally clinically acceptable success rate of 80%.

Safety endpoints include the incidence of CSF leaks within 3 months of the index procedure as determined from clinical diagnosis by one of the following methods:

- CSF leak or pseudomeningocele related surgical intervention (i.e., breaking skin) within 3 months post-op; or
- CSF leak confirmation by diagnostic testing within 3 months post-op; or
- CSF leak confirmation by clinical evaluation including physical examination of the surgical site within 3 months post-op.

Additional safety evaluations include the incidence of adverse events and device-related adverse events diagnosed by physical examination, protocol-specified diagnostic

laboratory tests, neurological assessments (including pain and modified Rankin Scale) and CT imaging assessment performed by independent radiologists for evaluation of extradural collections and adverse findings.

Treatment and Follow-up Procedures

Prior to initiation of enrollment, all study neurosurgeons were trained on the proper use of the DuraSeal Dural Sealant System. Patients requiring elective cranial surgery were screened for eligibility based on pre-operative eligibility criteria and were treated with the DuraSeal Dural Sealant System only if specific intra-operative criteria were met. Patients who did not meet the intra-operative eligibility criteria were considered screening failures and withdrawn from the study without additional follow-up. Treated patients were evaluated at discharge or within 7-days post procedure, 6-weeks and 3-months post procedure.

The Investigator conducted the appropriate cranial procedure according to the standard procedures and practices at the institution and the sutured dural repair was completed to the Investigator's satisfaction. If necessary, autologous grafts were harvested to augment dural closure. Upon completion of the sutured dural repair, the closure was evaluated for cerebrospinal fluid (CSF) leakage with a baseline Valsalva maneuver to 20 cm H_2O. If a spontaneous leak was already apparent immediately after dural closure, no Valsalva was performed. If a leak was present, either spontaneously or upon Valsalva, the Dural Sealant was applied to the closure site and a subsequent Valsalva maneuver was conducted to evaluate the effectiveness of the device to hold a watertight seal.

Patients were clinically assessed for the primary effectiveness endpoint and safety endpoints throughout the duration of the trial. CT scans were performed at baseline, at discharge or within 7-days post-procedure and at 3 months post-procedure and reviewed by independent neuroradiologists for an evaluation of extradural measurements and unexpected findings.

Patient Accountability and Demographics

The study involved 10 investigational sites within the United States and 1 site in Europe. A total of 111 patients were enrolled in the study and treated with the DuraSeal Dural Sealant System. Of those, 107 patients (>96%) completed the three-month follow-up. Patient demographics are provided in Table 5.

Of the patients that did not complete the study, two (2) patients were determined to be lost-to-follow-up following the 6-week visit, despite repeated attempts to locate the patients. Additionally, two patients died during the study follow-up period. The deaths were unrelated to the study treatment. The deaths were due to complications related to cerebral edema following surgical resection of a brain tumor. In the second case, the subject died due to progression of the malignancy. Forty-five per cent of the patients had primary dura repairs that included autologous duraplasty materials.

For the majority of the evaluation time points, the follow-up rate was 98% or greater. With the exception of the two patients lost-to follow-up and the 2 patient deaths, only one patient missed the 6-week follow-up visit and no patients missed the 3-month follow-up visit.

Table 5 Subject Demographics

Characteristic	*DuraSeal Study Population*
N	111
Men/Women	35/76
Age (range)	49.3 ± 13.2 (20-75)
Height (cm)	169.5 ± 10.6 (152-199)
Weight (kg)	80.5 ± 23.0 (45.0-202.8)
Current Smoker	
Never	52 (46.8%)
History	26 (23.4%)
Yes	33 (29.7%)
Duration of surgery	
< 2 hours	7 (6.3%)
≥ 2 hours	102 (91.8%)
unknown	2 (1.8%)
ASA (American Society of Anesthesia) **Scores (n, %)**	
I	14 (12.6%)
II	59 (53.2%)
III	36 (32.4%)
IV	1 (0.9%)
unknown	1 (0.9%)
Indication for Surgery:	
AVM	7 (6.3%)
Aneurysm	12 (10.8%)
Chiari Malformation	6 (5.4%)
Cyst	3 (2.7%)
Epilepsy	10 (9.0%)
Nerve Decompression	21 (18.9%)
Tumor	51 (45.9%)
Acoustic Neuroma	6
Cerebellopontine angle	5
Dermoid/Epidermoid	2
Frontal	5
Meningioma	12
Parietal/parietotemporal/temporal	9
Other **	12
Incidental right posterior artery communicating artery stenosis	1 (0.9%)
**includes brain/brainstem, cavernous sinus, intraventricular/ventricular tumors, occipital metastasis, chordoma and medullobastoma	

A poolability analysis was performed to ensure that data across all sites could be combined for analysis. "Site" was not found predictive for key safety variables and no variability among sites was seen with respect to the primary endpoint, intraoperative sealing success.

Effectiveness and Safety evaluations

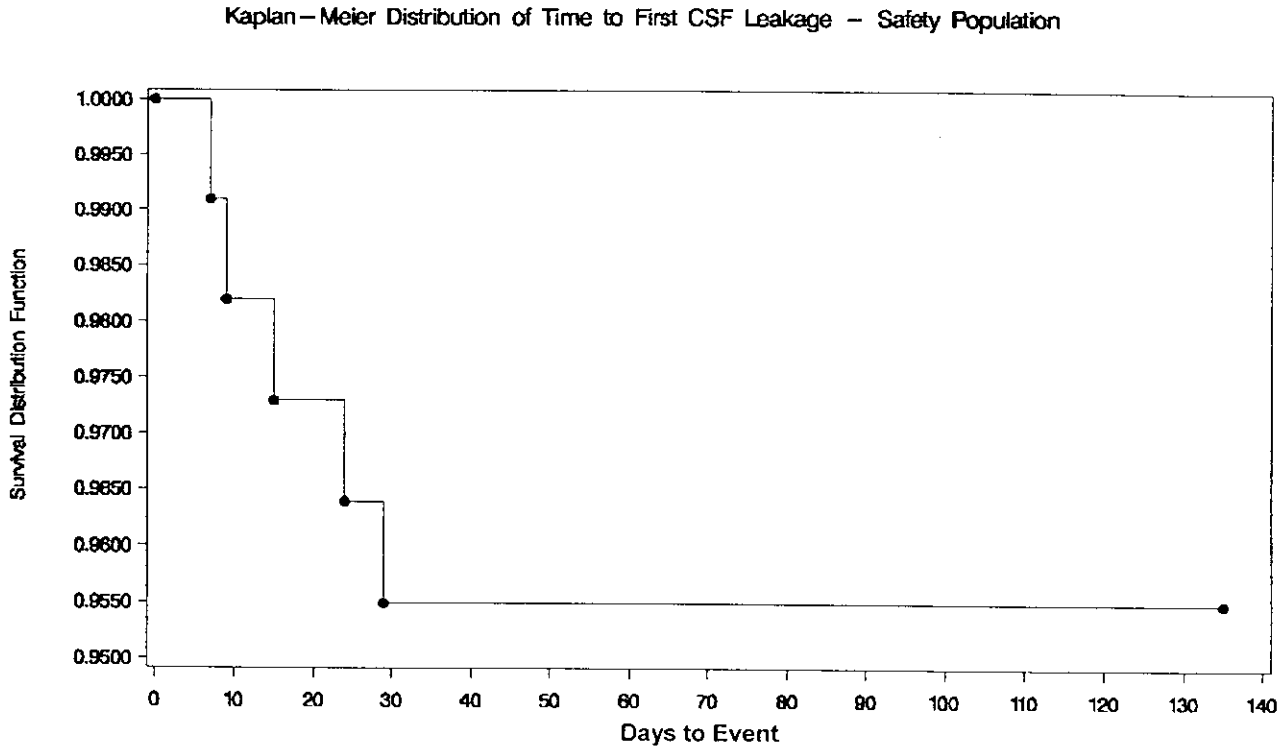
Of the 111 patients in this study, 67 patients (60.4%) experienced a spontaneous CSF leak intra-operatively (i.e., no need for Valsalva maneuver) prior to DuraSeal application, and 44 patients (39.6%) experienced a leak upon the Valsalva maneuver prior to DuraSeal application. One hundred five (105) patients (94.6%) were treated with one DuraSeal Sealant application, and 6 patients (5.4%) were treated with two applications. All 111 patients treated with the DuraSeal Sealant showed no leakage during the intra-operative assessment. One hundred nine of 111 patients (98.2%) met the criteria for primary endpoint success; i.e., intraoperative sealing. Two (2) patients were considered not evaluable for purposes of the primary effectiveness analysis, as the pressure applied during the post-treatment Valsalva maneuver only reached 10 cm H_2O.

Safety was assessed based on evaluation of wound healing, the occurrence of post-operative CSF leaks, the nature and severity of other adverse events, and device-related adverse events diagnosed by physical examination, protocol-specified diagnostic laboratory tests, neurological assessments (including pain and modified Rankin Scale) and CT imaging performed by independent neuroradiologists for evaluation of extradural collections and adverse findings.

There were no unanticipated adverse device effects. There were two patient deaths (out-of-hospital). In both cases, the deaths were attributed to the patients' prior condition or neurosurgical procedure. The incidence and nature of adverse events observed in this patient population (see Table 1) are consistent with the type and complexity of the surgery performed and the co-morbid state of the treated patients. Thirty-two patients (29%) experienced a total of 54 serious adverse events (SAE). Relationship to the study-device was "not related" for 78% of SAE reports and 22% were "unable to determine" including 6 patients with events of deep surgical site infections, 3 patients with cerebrospinal fluid (CSF) leaks and 1 patient with headaches that did not respond to standard therapy which preceded a CSF leak.

The Kaplan-Meier estimate (Fig. 1) for freedom from CSF Leakage at 135 days following surgery is 95.5%, which corresponds to a leak rate of 4.5% [95% C.I: 0.65% to 8.4%]. Time to first endpoint CSF leakage ranged from 7 to 29 days.

Figure 1. Kaplan-Meier Analysis: Freedom from CSF Leakage



The incidence of post-operative CSF leaks in this study was 4.5%. Of these leaks, 1.8% were incisional and 2.7% were pseudomeningoceles. Reports in the published literature of CSF leaks for craniotomy procedures range from 0 to 20%[1-4]. Based upon comparison to published literature of clinical studies investigating CSF leak rates, the observed CSF leak rate of the study was found to be comparable.

There were 9/111 surgical wound infections (8.1%) with 7.2% identified as deep surgical site infections. All 8 deep surgical site infections were treated with surgical debridement. The clinical protocol specified only clean surgical cases and contained an intra-operative exclusion criterion for cases in which a clean case became a clean-contaminated case (e.g., sinus penetration). History of smoking and prolonged surgery were found to be independent predictors for infection. Based on the clinical characteristics and risk factors for wound infections of the studied population, e.g., high ASA scores (>2) and long operative times (more than 38% of cases greater than 4 hours), the observed infection rate is within the range of rates (0-13.4%) published in the literature for similar patients[5-9].

All wounds were well healed by the 3-month post-operative visit. There was no untoward effect on hepatic or renal function associated with product use and absorption. Additionally, there were no unexpected findings based on CT imaging assessment by independent neuroradiologists.

XI. CONCLUSIONS DRAWN FROM STUDIES

Preclinical studies were conducted to evaluate product safety and included biocompatibility and toxicology studies. Device safety and effectiveness was also assessed in animal models. Product specifications have been identified and validated to ensure the manufacture of product of consistent quality. The specifications are product benchmarks that assess product characteristics which are essential to device performance.

The clinical study observed a 98% rate of water tight closure as tested by a Valsalva maneuver to 20 cm of water pressure after DuraSeal application. The results demonstrate that the device is effective at providing a water-tight dural closure in cases where suturing alone, or in combination with autologous grafting is not successful. Achieving a watertight closure of the dura is recognized as an important step in preventing post-operative CSF leaks. The overall rate of surgical wound infection was 9/111 (8.1%) with a 7.2% rate of deep surgical infection, all requiring repeat surgery. The overall rate of CSF leak was 4.5% (5/111). The rates of these complications were within the ranges reported in the literature for patients with similar risk factors who underwent craniotomies. The rates of other serious adverse events shown in Table 1 are comparable to expected outcomes of intracranial surgeries. Further evaluation of risk factors for these events will be assessed in the post-approval study.

In conclusion, results from preclinical studies indicate that the DuraSeal Dural Sealant System meets or exceeds safety and performance specifications. Data collected from a multi-center clinical investigation of the performance of the DuraSeal Dural Sealant System provides a reasonable assurance of product safety and effectiveness when the device is used, in accordance with the labeling, as an adjunct to sutured dural repair during cranial surgery to provide watertight closure.

Therefore, it is reasonable to conclude that the benefits of use of the device for the target population outweigh the risk of illness or injury when used as indicated in accordance with the directions for use.

XII. PANEL RECOMMENDATIONS

At an advisory meeting held on November 30, 2004, the Neurological Devices Panel recommended that Confluent Surgical's PMA for the DuraSeal Dural Sealant System be approved subject to submission to, and approval by, the Center for Device and Radiological Health (CDRH) of the following:

1. A post-approval study to evaluate the incidence of wound related complications including infection and CSF leak rates associated with use of the device.

2. Data regarding MRI and CT imaging analyses to demonstrating the characteristics of the implant image viewed upon MRI and CT and the duration of time it will be seen.

3. A revised product label reflecting observations of the clinical evaluation as recommended by the Neurological Devices Advisory Panel.

XIII. CDRH DECISION

CDRH concurred with the Neurological Devices Advisory Panel's recommendation of November 30, 2004. To address these conditions, Confluent Surgical has agreed to conduct a post-approval clinical study to further evaluate the incidence of wound related complications including infection and CSF leak rates associated with use of the device. The study will be initiated within 6 months of approval. The protocol will enroll patients using the same inclusion and exclusion criteria as the pivotal study and will randomize patients to treatment with either DuraSeal or a standard of care. Patients will be followed for 30 days after treatment. The study will involve approximately 25 sites within the U.S. Summary data will be presented on the incidence of post-operative surgical site infections and the presence or absence of CSF leaks within 30 days post-op. Data from all neurological status assessments will be summarized.

In addition, Confluent Surgical has provided MRI and CT evaluations and a revised product label in accordance with Panel recommendations. FDA finds the responses, including the post-approval study design acceptable.

FDA issued an approval order on APR 7 2005

The applicant's manufacturing facilities were inspected on August 25th and September 1st, 2004 and were found to be in compliance with the Quality System Regulation (21 CFR 820).

XIV. APPROVAL SPECIFICATIONS

Directions for use: See the labeling.

Hazards to Health from Use of the Device: See Indications, Contraindications, Warnings, precautions and Adverse Events in the labeling.

Postapproval Requirements and Restrictions: See approval order.

XV. REFERENCES

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