SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

I. GENERAL INFORMATION

Device Generic Name:	Sealant, Dural
Device Trade Name:	CraniSeal Dural Sealant
Device Procode:	NQR
Applicant's Name and Address:	Pramand, LLC 201 Burlington Road, Suite 210 Bedford, MA 01730
Date(s) of Panel Recommendation:	None
PMA Number:	P220014
Date of FDA Notice of Approval:	July 6, 2023

II. INDICATIONS FOR USE

The CraniSeal Dural Sealant is indicated for use in patients ≥ 18 years of age as an adjunct to sutured dural repair during cranial surgery to provide watertight closure.

III. CONTRAINDICATIONS

Do not apply the CraniSeal Dural Sealant in any surgical procedures other than those specified in the indications for use as a sealant or adhesion barrier.

Do not apply the CraniSeal Dural Sealant 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 CraniSeal Dural Sealant labeling.

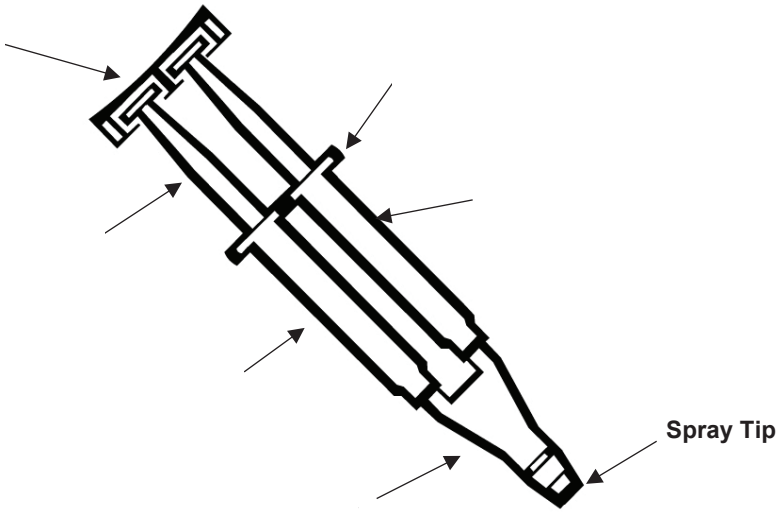
V. DEVICE DESCRIPTION

The CraniSeal Dural Sealant consists of components for preparation and delivery of an absorbable polyethylene glycol (PEG) hydrogel sealant and an applicator (i.e., Y-connector and spray tips) packaged sterile for single patient use.

The hydrogel 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 applicator as the hydrogel material exits the spray tip. The applicator (i.e., Y-connector and spray tip) allows a conformal coating that adheres to the tissue surfaces. The mixing provided by the applicator 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 hydrolysable ester bonds which enable the hydrogel to be degraded through hydrolysis after application. FD&C Blue no. 1 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, volumetrically, 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. The hydrogel implant is absorbed in approximately 4 to 8 weeks and the absorbed hydrogel components are excreted from the body. The CraniSeal Dural Sealant can be used for up to one hour following reconstitution. Figure 1 provides an overview diagram of the CraniSeal Dural Sealant.

Figure 1: Assembled CraniSeal Dural Sealant



VI. ALTERNATIVE PRACTICES AND PROCEDURES

There are several other alternatives for the correction of dural repair that consists of the direct application of sutures or the use of sutures with adjunctive dural repair materials

such as the commercially available DuraSeal Dural Sealant, fibrin glue/sealant, absorbable gelatin or collagen sponge, autologous muscle, temporalis fascia, fascia lata, pericranium, ligamentum nuchae or fat grafts. Each alternative has its own advantages and disadvantages. A patient should fully discuss these alternatives with his/her physician to select the method that best meets expectations and lifestyle.

VII. MARKETING HISTORY

The CraniSeal Dural Sealant has not been marketed in the United States or any foreign country.

VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

Below is a list of the potential adverse effects (e.g., complications) associated with the use of the device.

- Allergic reaction
- Blood and lymphatic system disorders
- Cardiac disorders
    - Arrhythmia
- Dermatologic events
- Electrolyte imbalance
- Elevated liver enzymes
- Gastrointestinal disorders
    - Nausea and/or vomiting
- General disorders
    - Delayed healing
    - Wound dehiscence
- General malaise
- Hematologic abnormality
- Hypertension
- Infections and infestations
    - Deep incisional surgical site infections
    - Superficial surgical site infections
    - Meningitis (aseptic or bacterial)
    - Late incisional surgical site infections
- Inflammatory reaction
- Musculoskeletal events
- Neoplasms benign and malignant, including cysts and polyps
- Nervous system disorders
    - Acute gait dysfunction
    - Epidural or subdural hematoma
    - Headache
    - Dizziness
    - Fever

  - Seizure
  - Stroke
  - Cerebral hemorrhage
  - CSF leak (incisional, pseudomeningocele)
  - Cranial nerve deficit
  - Motor deficit
  - Speech difficulty
  - Double vision or visual disturbance
  - Hydrocephalus
  - Cerebral edema
  - Brain tumor
  - Severe neurological deficit post-op
  - Respiratory and thoracic disorders
- Pain
- Pneumonia
- Renal compromise
- Ureterolitithiasis
- Urinary difficulty

IX. SUMMARY OF NONCLINICAL STUDIES

A. Laboratory Studies

Sterilization

The CraniSeal Dural Sealant is sterilized by E-beam irradiation sterilization, which was validated in accordance with ANSI/AAMI/ISO 11137, "Sterilization of health care products - Requirements for validation and routine control - Radiation sterilization", and EN552, "Sterilization of medical devices - Validation and routine control sterilization by irradiation," to achieve a sterility assurance level of at least 10^{-6}.

Shelf-Life

A 12-month shelf-life was established based on results from real-time (53 weeks) test evaluations for 3 CraniSeal Dural Sealant product lots. The real-time and accelerated aged devices were tested for the following attributes: visual assessment, hydrogel performance, and packaging integrity.

Biocompatibility

Biocompatibility testing was performed on the CraniSeal Dural Sealant as one system. All hydrogel samples evaluated in biocompatibility tests were prepared using the device components supplied in accordance with the Instructions for Use labeling. Biocompatibility testing (Table 1 below) of the formed CraniSeal Dural Sealant hydrogel has been performed consistent with the Good Laboratory Practices

regulations (21 CFR §58 and the FDA guidance, "Use of International Standard ISO 10993-1, "Biological evaluation of medical devices – Part 1: Evaluation and testing within a risk management process"." This biocompatibility testing conducted is based on the CraniSeal Dural Sealant hydrogel defined as a tissue/bone contacting implant of permanent contact duration.

Table 1: Summary of CraniSeal Dural Sealant Biocompatibility Tests

Test Reference	Method Reference	Results
Cytotoxicity (ISO Elution Method)	International Organization for Standardization (ISO) 10993-5, "Biological evaluation of medical devices - Part 5: Tests for in vitro cytotoxicity"	Non-cytotoxic
ISO Maximization Sensitization Study (Guinea Pigs)	ISO 10993-10, "Biological evaluation of medical devices - Part 10: Tests for skin sensitization"	Non-sensitizing
ISO Modified Intracutaneous Study	ISO 10993-10, "Biological evaluation of medical devices - Part 10: Tests for skin sensitization"	No evidence of significant irritation
USP and ISO Modified Systemic Toxicity	ISO 10993-11, "Biological evaluation of medical devices - Part 11: Tests for systemic toxicity"	No mortality or systemic toxicity
USP Pyrogenicity (Endotoxin Testing: < 2.15 Endotoxin Units (EU)/Device Limit)	Guidance for Industry: Pyrogen and Endotoxins Testing: Questions and Answers	Non-pyrogenic
USP Pyrogenicity (Material Mediated Pyrogenicity)	ISO 10993-11, "Biological evaluation of medical devices - Part 11: Tests for systemic toxicity"	Non-pyrogenic
Genotoxicity (Bacterial Reverse Mutation Assay)	ISO 10993-3: "Biological evaluation of medical devices - Part 3: Tests for genotoxicity, carcinogenicity, and reproductive toxicity"	Non-mutagenic
Micronucleus Cytogenic Assay in Mice	ISO 10993-3: "Biological evaluation of medical devices - Part 3: Tests for genotoxicity, carcinogenicity, and reproductive toxicity"	No clastogenic activity
In Vitro Hemolysis (Modified ASTM-Direct Contact Method)	ISO 10993-4: "Biological evaluation of medical devices - Part 4: Selection of tests for interactions with blood"	Non-hemolytic
Leachable Substances	ISO 10993-17: "Biological evaluation of medical devices – Part 17: Establishment of allowable limits for leachable substances"	No harmful leachables observed
Chemical Characterization	ISO 10993-18: "Biological evaluation of medical devices – Part 18: Chemical characterization of medical device materials within a risk management process"	No harmful leachables observed based on the subsequent toxicological risk assessment

Bench Studies

A series of in vitro tests were performed on the components and materials of the CraniSeal Dural Sealant (final, sterilized devices). In addition to the studies identified in Table 2 below, environmental testing was performed to assure that the product is not affected by temperature extremes during storage and transport or a maximum irradiation dose.

Table 2: 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.	CraniSeal Dural Sealant 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 < 10 mm diameter when spray tip is 2-4 cm from target tissue.

B. Animal Testing

Because the design and product specifications for the CraniSeal Dural Sealant are the same as for the commercialized DuraSeal Dural Sealant approved under PMA P040034, the CraniSeal Dural Sealant *in vivo* testing plan did not repeat all animal studies conducted for the DuraSeal Dural Sealant. A confirmatory canine dura defect study to evaluate local tissue reaction and neurological effects of the CraniSeal Dural Sealant and the DuraSeal Dural Sealant as the control was completed. Table 3 provides a summary of the tests performed and the relevant findings.

Table 3: Summary of Animal Studies – CraniSeal Dural Sealant

Test Performed	# Animals/Study Duration or Test Set-up	Summary/Relevant Findings
Cranial Dural Defect	12 CraniSeal Dural Sealants and 12 DuraSeal Dural Sealants/8 Weeks	The test article (CraniSeal Dural Sealant) was considered to elicit no adverse effects on surgical intraoperative observations, clinical observations, body weights, neurological observations, macroscopic and microscopic observations recorded at necropsy following unilateral application to dural defects of canines for 1, 4, and 8 weeks. The responses observed during in-life assessments from animals treated with the CraniSeal Dural Sealant were equivalent to those observed from animals treated with the control (DuraSeal Dural Sealant). At 1-, 4- and 8-weeks post-implantation on the dura of the dog, the test article, CraniSeal Dural Sealant, was considered to elicit no or minimal reaction in the tissue when compared to the DuraSeal Dural Sealant.

The CraniSeal Dural Sealant was shown to have a biologically equivalent response to the commercially available DuraSeal Dural Sealant (P040034) as compared in a canine dural defect safety study.

C. Additional Studies

Dye Toxicology Evaluations

The CraniSeal Dural Sealant, like the PMA approved DuraSeal Dural Sealant (P040034), contains FD&C Blue #1 colorant 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). The determination that the colorant is not present in the body for a significant amount of time is directly applicable to the CraniSeal Dural Sealant, because the same volume and concentration of FD&C Blue #1 is used in both the CraniSeal Dural Sealant and the DuraSeal Dural Sealant, and the two devices have the same design and chemical specifications. Therefore, no new studies were performed related to the dye toxicological profile for the CraniSeal Dural Sealant as the prior studies conducted on the commercialized DuraSeal Dural Sealant is applicable to the subject device.

FD&C Blue #1 is water soluble and has been evaluated in life-exposure animal studies in the PMA (P040034) of the DuraSeal Dural Sealant 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 the DuraSeal Dural Sealant 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 hydrogel 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 PRIMARY CLINICAL STUDIES

The CraniSeal Dural Sealant has not been the subject of a published clinical study. Pramand, LLC is relying on the "six-year rule" as described in Section 216 of the Food and Drug Administration Modernization Act of 1997 (FDAMA) and the FDA guidance, "Guidance on Section 216 of the Food and Drug Administration Modernization Act of 1997," to use the clinical data supporting a previous PMA application of the DuraSeal Dural Sealant (P040034) approved on April 7, 2005, to support the reasonable assurance of safety and effectiveness of the subject CraniSeal Dural Sealant because the two devices have the same chemical specifications and design. The safety and effectiveness of the DuraSeal Dural Sealant (P040034) was primarily supported by one pivotal study conducted in the United States (US) and a post-approval study (PAS) that was required as a condition of approval of the PMA. A brief overview and summary of the primary clinical studies are presented below. Additional details regarding the US pivotal study of the DuraSeal Dural Sealant can be found in the P040034 SSED.

US Pivotal Trial

A. Study Design

The pivotal study of the DuraSeal Dural Sealant was a prospective, multi-center, non-randomized, single-arm clinical investigation to evaluate the safety and effectiveness of the DuraSeal Dural Sealant as an adjunct to sutured dural repair during cranial surgery to provide watertight closure. The pivotal clinical study for P040034 included 111 patients and there were 10 investigational sites within the US and l site in Europe.

1. Clinical Inclusion and Exclusion Criteria

   Enrollment in the pivotal study of the DuraSeal Dural Sealant (P040034) was limited to patients who met the following inclusion criteria.

   a) 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.

   b) Intra-Operative Inclusion Criteria

- Surgical wound classification Class I/Clean (per Center for Disease Control and Prevention (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_20 for 5-l0 seconds.

Patients were not permitted to enroll in the pivotal study if they met any of the following exclusion criteria.

c) 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_20).
- 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., urinary tract infection (UTI), active pneumonia) or evidence of any surgical site infection (superficial, deep, or organ space), as determined by fever > 101 °F, white blood cells (WBC) > 11,000/µL, 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/µL or greater than 20,000/µL).
- Patient with uncontrolled diabetes, as determined by two or more incidences of elevated blood sugar levels (fasting glucose > 120 mg/dL) within the 6 months prior to surgery.
- Patient with creatinine levels > 2.0 mg/dL.

d) 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.

2. Follow-up Schedule

All patients were scheduled to return for follow-up examinations at discharge or within 7-days postoperatively, 6-weeks, and 3-months postoperatively. Computed tomography (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. Adverse events and complications were recorded at all visits.

3. Clinical Endpoints

With regards to safety, safety outcomes 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-operative.
- CSF leak confirmation by diagnostic testing within 3 months post-operative.
- CSF leak confirmation by clinical evaluation including physical examination of the surgical site within 3 months post-operative.

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 (mRS)) and CT imaging assessment performed by independent radiologists for evaluation of extradural collections and adverse findings.

With regards to effectiveness, the pivotal study evaluated the percent (%) success in the treatment of intra-operative CSF leakage following application of the DuraSeal Dural Sealant defined as no CSF leakage from dural repair intra-operatively after up to two DuraSeal Dural Sealant applications, during Valsalva maneuver up to 20 cm H_2O for 5 to 10 seconds.

B. Accountability of PMA Cohort

The pivotal study of the DuraSeal Dural Sealant (P040034) involved 10 investigational sites within the US and 1 site in Europe. A total of 111 patients were enrolled in the study and treated with the DuraSeal Dural Sealant. Of those 111 patients, 107 patients (> 96%) completed the three-month follow-up. Of the patients that did not complete the study, 2 patients were determined to be lost-to-follow-up following the 6-week visit, despite repeated attempts to locate the patients.

Additionally, 2 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. For the majority of the evaluation time points, the follow-up rate was 98% or greater. With the exception of the 2 patients lost-to-follow-up and the 2 patient deaths, only 1 patient missed the 6-week follow-up visit and no patients missed the 3-month follow-up visit.

C. Study Population Demographics and Baseline Parameters

The demographics of the pivotal study population are presented in Table 4 below.

Table 4: DuraSeal Dural Sealant Pivotal Study Patient 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	

Table 4 Abbreviations: AVM = Arteriovenous Malformation

D. Safety and Effectiveness Results

1. Safety Results

The analysis of safety was based on 111 patients available for the 3-month evaluation. Adverse effects observed in the pivotal study of the DuraSeal Dural Sealant (P040034) are reported in Table 5.

Table 5: Adverse Events Observed in the Pivotal Study of the DuraSeal Dural Sealant

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 • Pseudomeningocele	 2 3	 (1.8) (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) • Upper Respiratory/Bronchial • Urinary Tract	 8 4 11	 (7.2) (3.6) (9.9)
Infection, Surgical Site • Deep (re-operation required) • Superficial	 8 1	 (7.2) (0.9)
Late (>30 days) Wound Infection	3	(2.7)
Meningitis • Aseptic • Bacterial	 5 2	 (4.5) (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 -Cranial nerve deficit -Motor deficit -Neuropsychiatric disorders -Speech difficulty -Visual disturbance	 5 34 17 7 10 22	 (4.5) (30.0) (15.3) (6.3) (9.0) (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)

2. Effectiveness Results

Of the 111 patients in the pivotal study of the DuraSeal Dural Sealant (P040034), 67 patients (60.4%) experienced a spontaneous CSF leak intra-operatively (i.e., no need for Valsalva maneuver) prior to application of the DuraSeal Dural Sealant and 44 patients (39.6%) experienced a leak upon the Valsalva maneuver prior to application of the DuraSeal Dural Sealant. 105 patients (94.6%) were treated with one DuraSeal Dural Sealant application and 6 patients (5.4%) were treated with two applications. All 111 patients treated with the DuraSeal Dural Sealant showed no leakage during the intra-operative assessment. 109 of 111 patients (98.2%) met the criteria for the primary outcome, i.e., intra-operative 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.

The incidence of post-operative CSF leaks in the pivotal study of the DuraSeal Dural Sealant was 4.5% [95% confidence interval (CI): 0.65% to 8.4%]. Of these leaks, 1.8% were incisional and 2.7% were pseudomeningoceles. Time to first endpoint CSF leakage ranged from 7 to 29 days. There were 9 patients who experienced 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.

3. Pediatric Extrapolation

In this premarket application, existing clinical data was leveraged to support the reasonable assurance of safety and effectiveness of the proposed device in adolescent pediatric patients ≥ 18 years of age. This adolescent patient population is also included in the indications for use of the commercialized DuraSeal Dural Sealant (P040034). Since the pivotal clinical study data from the DuraSeal Dural Sealant PMA (P040034) was used to support the safety and effectiveness of the CraniSeal Dural Sealant based on the "six-year rule" as described in Section 216 of FDAMA and the FDA guidance, "Guidance on Section 216 of the Food and Drug Administration Modernization Act of 1997," the same patient population indicated for use with the DuraSeal Dural Sealant is also applicable to the subject device. Additional details regarding the US pivotal study of the DuraSeal Dural Sealant can be found in the P040034 SSED.

PAS Study

A. Study Design

The PAS of the DuraSeal Dural Sealant was a prospective, randomized, single-blinded (patients), multi-center study to evaluate the safety and effectiveness of the DuraSeal Dural Sealant compared to alternative usual care methods of dural repair in patients scheduled for cranial surgery that entails a dural incision at 25 sites in the

US. The PAS was required by the FDA as a condition of approval of PMA P040034 as specified in the April 7, 2005, approval order to evaluate the incidence of wound-related complications, including infection and CSF leaks associated with use of the DuraSeal Dural Sealant, that was observed in the pivotal trial.

1. Clinical Inclusion and Exclusion Criteria

   Enrollment in the PAS of the DuraSeal Dural Sealant was limited to patients who met the following inclusion criteria.

   a) Pre-Operative Inclusion Criteria
      - Patient is between 18 and 75 years of age.
      - Patient is scheduled for an elective cranial procedure that entails a dural incision.
      - Patient, or authorized representative, has been informed of the nature of the study and has provided written informed consent, approved by the appropriate Institutional Review Board (IRB) of the respective clinical site.

   b) Intra-Operative Inclusion Criteria
      - Evidence of non-watertight closure after primary dural closure, either spontaneously or upon Valsalva maneuver, at 20 cm water for 5-l0 seconds.

   Patients were not permitted to enroll in the PAS if they met any of the following exclusion criteria.

   c) 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 a known allergy (or history of intolerance) to FD&C Blue #1 dye.
      - Pregnant or breast-feeding females, or females who wish to become pregnant during the length of participation in the study.
      - Patient has traumatic injuries to the head.
      - Patient has a compromised immune system or autoimmune disease.
      - Patient is not likely to comply with the follow-up evaluation schedule.
      - Patient with diabetes, unless evidence of control.
      - Patient has a clinical diagnosis of a local site infection or a systemic infection.
      - Patient who in the surgeon's opinion should not participate.
      - Patient is participating in a clinical trial of an investigational drug or device.

d) Intra-Operative Exclusion Criteria
   - Incidental finding of any of the pre-operative exclusion criteria.
   - Dural margins from edges of bony defect is less than 3 mm throughout.
   - Patient has a gap greater than 2 mm remaining after primary dural closure.
   - Patient has a clinical diagnosis of ongoing local or systemic infection (e.g., urinary tract infection (UTI), active pneumonia).
   - Patient requires the use of non-autologous duraplasty material.

2. Follow-up Schedule

   All patients were scheduled to return for follow-up examinations at 30-days postoperatively.

3. Clinical Endpoints

   With regards to safety, the incidence of neurosurgical complications related to unplanned intervention (i.e., minimally invasive procedures) or return to the operating room and the incidence of all neurosurgical complications were assessed in addition to CSF leak, hydrocephalus, bacterial meningitis, and aseptic meningitis. In addition, the PAS evaluated the incidence of post-operative surgical site infections within 30-days post-operative, including superficial incisional, deep incisional, late incisional and organ/space infections and poor wound healing.

B. Accountability of PAS Cohort

A total of 237 subjects were enrolled in the PAS, with 117 subjects being treated with usual care methods (control) and 120 subjects treated with the DuraSeal Dural Sealant. Procedure characteristics were similar between groups with exception of location. Infratentorial procedures were less frequent among the DuraSeal Dural Sealant subjects than among the control subjects, with rates of 30.0% and 42.7%, respectively. This difference was statistically significant with a p-value of 0.044. At the final 30-day post-operative visit, there were 118 subjects treated with the DuraSeal Dural Sealant and 115 subjects in the control group available for analysis.

C. Study Population Demographics and Baseline Parameters

The baseline parameters of the PAS population are shown in Table 6 below.

Table 6: Baseline Parameters of PAS Patients

Characteristic	DuraSeal (N=120) n (%)	Control (N=117) n (%)
Duration of Surgery:		
Mean (SD)	3.19 (1.82)	3.23 (1.68)
Median	2.83	2.72
Range (Min, Max)	0.9 , 11.3	1.1 , 10.3
ASA Score:		
1	5 (4.2)	4 (3.4)
2	61 (50.8)	59 (50.4)
3	50 (41.7)	53 (45.3)
4	4 (3.3)	1 (0.9)
Indication for Surgery:		
Tumor	59 (49.2)	55 (47.0)
AVM	6 (5.0)	0 (0.0)
Aneurysm	14 (11.7)	18 (15.4)
Chiari Malformation	0 (0.0)	1 (0.9)
Cyst	2 (1.7)	6 (5.1)
Epilepsy	13 (10.8)	14 (12.0)
Nerve Decompression	22 (18.3)	20 (17.1)
Other	4 (3.3)	3 (2.6)

D. Safety and Effectiveness Results

The primary outcome of the PAS of the DuraSeal Dural Sealant was the incidence of surgical wound complications, central nervous system events, or neurosurgical complications that resulted in unplanned intervention (i.e., minimally invasive procedures) or a return to the operating room. In all of these categories, there was no significant difference between the DuraSeal Dural Sealant and control groups. The overall percentage of subjects experiencing a primary outcome complication was 5.8% in the DuraSeal Dural Sealant group and 7.7% in the control group (p=0.613).

The secondary outcome of the PAS is the incidence of post-operative surgical site infection or post-operative CSF leaks within 30 days post-operative, as well as neurological status assessments. The overall infection rate (include superficial, deep and organ/space infections) was comparable between groups of 1.7% in the DuraSeal Dural Sealant group compared to 2.6% in the control group (p=0.681). There were three CSF leaks reported during the course of this study, including one in the DuraSeal Dural Sealant group 0.8%) and two in the control group (1.7%) [p=0.619]. For each of the neurological areas assessed of neurological status, cranial nerve, and motor, reflex, sensory and gait exam, no statistically significant differences were found between groups.

There were two reports of deep surgical site infections in the DuraSeal Dural Sealant group and three reports of superficial infections in the control group. The difference was not statistically significant between groups and in both cases of deep surgical site

infections observed in the DuraSeal Dural Sealant group, the treating investigators identified the complications as being related to the procedure as a result of an infected bone flap that was subsequently removed. The following Table 7 presents any adverse event occurring at a rate of 1% or higher in the PAS. 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 7: Adverse Events in the PAS Observed at a Rate of 1% or Higher

AE category Note: Patient can experience more than one AE	DuraSeal (N=120) n(%)	Control (N=117) n(%)	p-value
Any Complication	20 (16.7)	22 (18.8)	0.735
Superficial Incisional SSI	0 (0.0)	3 (2.6)	0.119
Deep Incisional SSI	2 (1.7)	0 (0.0)	0.498
Organ/Space SSI	0 (0.0)	0 (0.0)	-----
Late Incisional SSI	3 (2.5)	1 (0.9)	0.622
Poor Wound Healing	0 (0.0)	1 (0.9)	0.494
CSF Leak	1 (0.8)	2 (1.7)	0.619
Hydrocephalus	1 (0.8)	1 (0.9)	1.000
Meningitis (Bacterial)	0 (0.0)	0 (0.0)	-----
Meningitis (Aseptic)	0 (0.0)	1 (0.9)	0.494
Pseudomeningocele	1 (0.8)	1 (0.9)	1.000
Cerebral Hemorrhage	3 (2.5)	1 (0.9)	0.622
Cerebral Edema	2 (1.7)	0 (0.0)	0.498
Cerebral Vascular Accident (stroke)	1 (0.8)	2 (1.7)	0.619
Other	13 (10.8)	14 (12.0)	0.840

p-value is based on Fisher's exact test.

1. Pediatric Extrapolation

In this premarket application, existing clinical data was leveraged to support the reasonable assurance of safety and effectiveness of the proposed device in adolescent pediatric patients ≥ 18 years of age. This adolescent patient population is also included in the indications for use of the commercialized DuraSeal Dural Sealant (P040034). Since the PAS data from the DuraSeal Dural Sealant PMA (P040034) was used to support the safety and effectiveness of the CraniSeal Dural Sealant based on the "six-year rule" as described in Section 216 of FDAMA and the FDA guidance, "Guidance on Section 216 of the Food and Drug Administration Modernization Act of 1997," the same patient population indicated for use with the DuraSeal Dural Sealant is also applicable to the subject device.

XI. SUMMARY OF SUPPLEMENTAL CLINICAL INFORMATION

A comprehensive literature review using PubMed was performed of the clinical use of the commercialized DuraSeal Dural Sealant from January 1, 2005, through January 1, 2023, to further support the safety and effectiveness of the CraniSeal Dural Sealant that has the same chemical specifications and design as the DuraSeal Dural Sealant (P040034). The literature review focused on publications related to the clinical application of the DuraSeal Dural Sealant in human patients as an adjunct to sutured dural repair during cranial surgery. The results of the literature review did not identify any new or increased risks of use of the DuraSeal Dural Sealant or issues with effectiveness.

XII. PANEL MEETING RECOMMENDATION AND FDA'S POST-PANEL ACTION

In accordance with the provisions of section 515(c)(3) of the act as amended by the Safe Medical Devices Act of 1990, this PMA was not referred to the Neurological Devices Panel, an FDA advisory committee, for review and recommendation because the information in the PMA substantially duplicates information previously reviewed by this panel. There was a prior FDA advisory committee meeting of the Neurological Devices Panel on November 30, 2004, for the review of the DuraSeal Dural Sealant PMA P040034.

XIII. CONCLUSIONS DRAWN FROM PRECLINICAL AND CLINICAL STUDIES

A. Effectiveness Conclusions

The effectiveness of the CraniSeal Dural Sealant was assessed in a direct comparison of the CraniSeal Dural Sealant to the FDA approved, commercially available DuraSeal Dural Sealant (P040034) in a canine model and nonclinical in vitro performance evaluations. In the canine animal study, each animal had unilateral cranial defects created followed by the creation of a dural defect or incision at each site. The dural defect sites were repaired with suture and either the CraniSeal Dural Sealant hydrogel or the DuraSeal Dural Sealant hydrogel was applied as an adjunct to the sutures. Valsalva maneuver was performed following sealant application for both devices to confirm the absence of CSF leakage prior to closure. All treatment sites were reported to be sealed with the appropriate thickness of hydrogel prior to wound closure. The treated defect sites were examined macroscopically, histologically processed, and microscopically evaluated by a blinded pathologist for a final report assessment. The results confirm the effectiveness of the CraniSeal Dural Sealant is comparable or equivalent to the commercialized DuraSeal Dural Sealant as an adjunct to sutured dural repair in achieving a successful watertight seal in the canine study. The nonclinical in vitro performance evaluations further support this conclusion that the CraniSeal Dural Sealant has a comparable effectiveness to the DuraSeal Dural Sealant because both devices are designed the same with the same chemical specifications.

B. Safety Conclusions

The risks of the CraniSeal Dural Sealant are based on nonclinical laboratory and animal studies as well as data collected in clinical studies assessing the safety and effectiveness of the commercialized DuraSeal Dural Sealant (P040034) since Pramand, LLC is relying on the "six-year rule" as described in Section 216 of the Food and Drug Administration Modernization Act of 1997 (FDAMA) and the FDA guidance, "Guidance on Section 216 of the Food and Drug Administration Modernization Act of 1997," to use the clinical data supporting a previous PMA application of the DuraSeal Dural Sealant (P040034) approved on April 7, 2005, to support the reasonable assurance of safety and effectiveness of the subject CraniSeal Dural Sealant because the two devices have the same chemical specifications and design. The nonclinical laboratory and animal studies demonstrate that the CraniSeal Dural Sealant is biocompatible and does not cause any toxic effects because it has an equivalent chemical formulation and specifications as the commercialized DuraSeal Dural Sealant. The responses observed during the in-life assessments in the canine study for animals treated with the CraniSeal Dural Sealant were equivalent to those observed from animals treated with the DuraSeal Dural Sealant control. At 1-, 4- and 8-weeks post-implantation on the dura of the dog, the CraniSeal Dural Sealant was considered to elicit no or minimal reaction in the tissue when compared to the DuraSeal Dural Sealant control.

C. Benefit-Risk Determination

The probable benefits of the device are also based on data collected in a clinical study conducted to support PMA approval of the DuraSeal Dural Sealant (P040034). As discussed in the P040034 SSED of the DuraSeal Dural Sealant, all 111 patients treated with the DuraSeal Dural Sealant showed no leakage during the intra-operative assessment. 109 of 111 patients (98.2%) met the criteria for the primary outcome, i.e., intra-operative 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. The incidence of post-operative CSF leaks in the pivotal study of the DuraSeal Dural Sealant was 4.5% [95% CI: 0.65% to 8.4%]. Of these leaks, 1.8% were incisional and 2.7% were pseudomeningoceles. Time to first endpoint CSF leakage ranged from 7 to 29 days.

The probable risks of the device are also based on data collected in a clinical study conducted to support PMA approval of the DuraSeal Dural Sealant (P040034) and a PAS required as a condition of approval of the P040034 PMA. As discussed in the P040034 SSED of the DuraSeal Dural Sealant, there were 9 out of 111 patients who experienced surgical wound infections (8.1%) with 7.2% identified as deep surgical site infections. The PAS for the DuraSeal Dural Sealant further investigated the safety of the DuraSeal Dural Sealant in comparison to other available methods of dural repair during cranial surgeries by evaluating the incidence of surgical wound complications, central nervous system events, or neurosurgical complications that resulted in unplanned intervention (i.e., minimally invasive procedures) or a return to

the operating room within 30 days post-operative. In all of these categories, there was no significant difference between the DuraSeal Dural Sealant and control groups. The overall percentage of subjects experiencing a primary outcome complication was 5.8% in the DuraSeal Dural Sealant group and 7.7% in the control group (p 0.613).

The secondary outcome of the PAS is the incidence of post-operative surgical site infection or post-operative CSF leaks within 30 days post-operative, as well as neurological status assessments. The overall infection rate (include superficial, deep and organ/space infections) was comparable between groups of 1.7% in the DuraSeal Dural Sealant group compared to 2.6% in the control group (p=0.681). There were three CSF leaks reported during the course of this study, including one in the DuraSeal Dural Sealant group 0.8%) and two in the control group (1.7%) [p=0.619]. For each of the neurological areas assessed of neurological status, cranial nerve, and motor, reflex, sensory and gait exam, no statistically significant differences were found between groups. There were two reports of deep surgical site infections in the DuraSeal Dural Sealant group and three reports of superficial infections in the control group. The difference was not statistically significant between groups and in both cases of deep surgical site infections observed in the DuraSeal Dural Sealant group, the treating investigators identified the complications as being related to the procedure as a result of an infected bone flap that was subsequently removed.

1. Patient Perspective

   This submission either did not include specific information on patient perspectives or the information did not serve as part of the basis of the decision to approve or deny the PMA for this device.

In conclusion, given the available information above, the data support that for the indication for use in patients ≥ 18 years of age as an adjunct to sutured dural repair during cranial surgery to provide watertight closure, the probable benefits outweigh the probable risks.

D. Overall Conclusions

The data in this application support the reasonable assurance of safety and effectiveness of the CraniSeal Dural Sealant when used in accordance with the indications for use. The CraniSeal Dural Sealant has demonstrated to have the same design and chemical specifications as the commercialized DuraSeal Dural Sealant (P040034) for the same intended use. Therefore, Pramand, LLC is relying on the "six-year rule" as described in Section 216 of the Food and Drug Administration Modernization Act of 1997 (FDAMA) and the FDA guidance, "Guidance on Section 216 of the Food and Drug Administration Modernization Act of 1997," to use the clinical data supporting a previous PMA application of the DuraSeal Dural Sealant (P040034) approved on April 7, 2005, to support the reasonable assurance of safety and effectiveness of the subject CraniSeal Dural Sealant. Results from nonclinical studies indicate that the CraniSeal Dural Sealant is functionally the same as the

commercially available DuraSeal Dural Sealant and has a comparable safety and effectiveness profile. Furthermore, the pivotal clinical study used to support PMA approval of the DuraSeal Dural Sealant (P040034), the PAS conducted as a condition of approval of P040034 as specified in the April 7, 2005, approval order for P040034, and a comprehensive literature review of the DuraSeal Dural Sealant did not identify any safety or effectiveness concerns and continue to support the reasonable assurance of safety and effectiveness of the DuraSeal Dural Sealant for its proposed indications for use.

XIV. CDRH DECISION

CDRH issued an approval order on July 6, 2023.

The final clinical conditions of approval cited in the approval order are described below.

The "CraniSeal Registry: A Multi-Center, Post-Approval Registry to Compare the CraniSeal Dural Sealant to DuraSeal Dural Sealant as an Adjunct to Sutured Dural Repair During Cranial Surgery" is a new enrollment cohort PAS that will be conducted at up to 20 sites in the United States. This PAS will collect data to investigate the safety and effectiveness of the CraniSeal Dural Sealant concurrently compared to the DuraSeal Dural Sealant. The PAS should enroll a statistically justified number of subjects indicated for infratentorial and supratentorial cranial surgical procedures with the indications for surgery clearly specified in the selection criteria. The primary effectiveness outcome of the PAS will evaluate the incidence of cerebrospinal fluid (CSF) leakage or pseudomeningocele at 90-days post-operative as confirmed by neurodiagnostic imaging [i.e., computed tomography (CT) or magnetic resonance imaging (MRI)]. The PAS will evaluate the incidence of post-operative surgical site infections as a secondary outcome. The safety outcome of the PAS will be evaluated by the collection of all new and ongoing adverse events within 90-days post-procedure.

The applicant's manufacturing facilities have been inspected and found to be in compliance with the device Quality System (QS) regulation (21 CFR 820).

XV. APPROVAL SPECIFICATIONS

Directions for use: See device labeling.

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

Post-approval Requirements and Restrictions: See approval order.