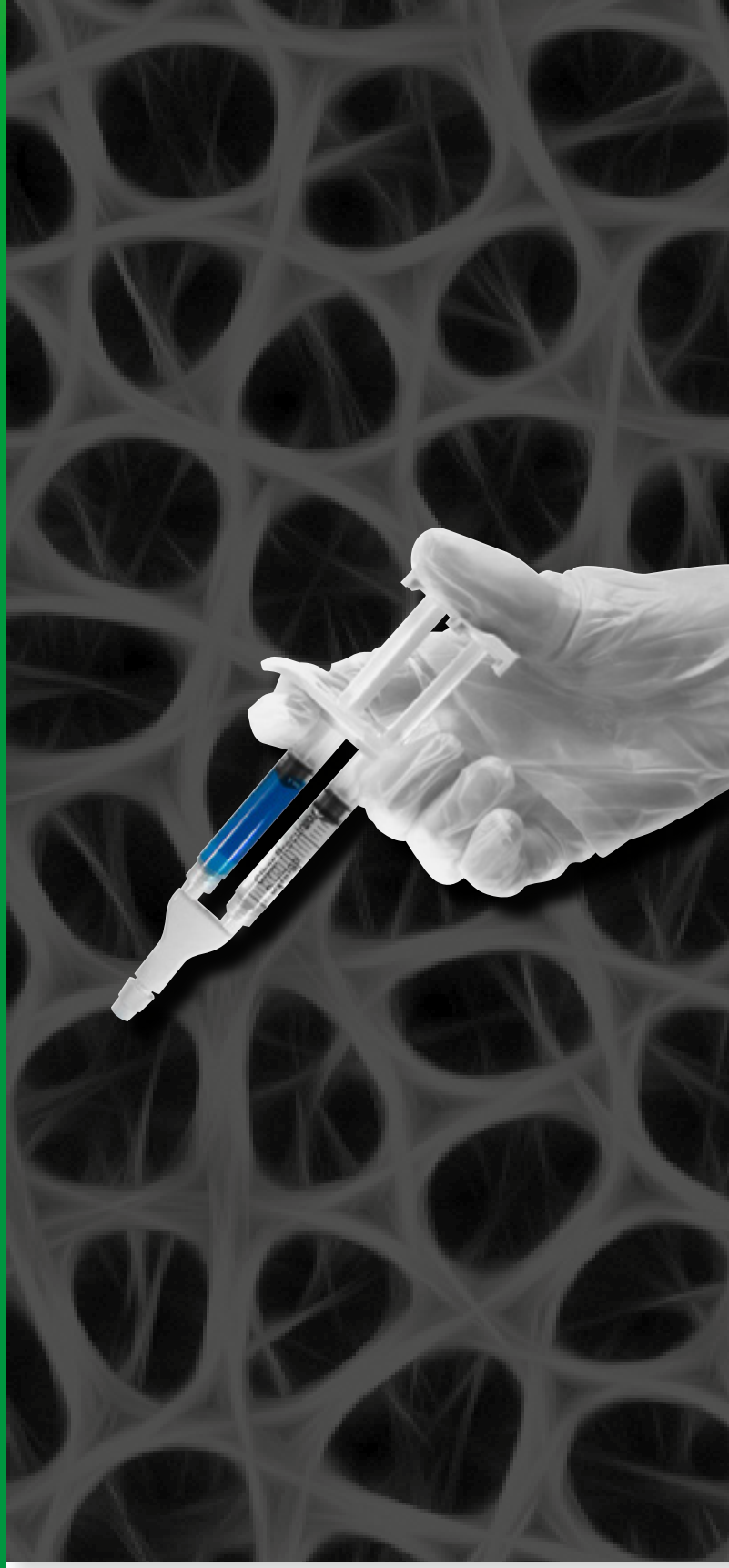
Integra®

DuraSeal® Dural Sealant System
Tender Package

Limit uncertainty by using the quick and easy to use DuraSeal® dural sealant system to ensure a watertight closure.



INTEGRA®
LIMIT UNCERTAINTY

Table of Content

1. Regulatory Information

1.1 Requirement Designator

The DuraSeal® dural sealant system is a class III medical device according to Rule 8 Annex IX of the European council Directive 93/42/ECC and its relatives. The Notified Body is TÜV Product Service (0123).

A copy of the current certificates and declarations of conformity relative to the DuraSeal® dural sealant system and to its application accessories (Extended Tip Applicator, MicroMyst® Applicator and Flow Regulator) are included in the Appendix.
Please note that regulatory documents for DuraSeal® dural sealant system might be updated. A copy of these updated documents will be provided when available.

1.2 Indications

The DuraSeal® dural sealant system is intended for use as an adjunct to standard methods of dural repair, such as sutures, to provide watertight closure.
The Extended Tip Applicator is intended for use in the simultaneous delivery of two non-homogenous solutions onto a surgical site.
The MicroMyst® Applicator is intended for use in the delivery of two non-homogenous solutions onto a surgical site.
The Flow Regulator is intended to provide pressurized gas (air or nitrogen) to gas-assisted applicators.

1.3 Contraindications

Do not apply the DuraSeal® Dural Sealant in abdominopelvic surgical procedures for use as a sealant or adhesion barrier.
Do not use Extended Tip Applicator, MicroMyst® Applicator and Flow Regulator for other indications than ones provided in the instructions for use.

2. Description and Presentation

2.1 Description

The DuraSeal® dural sealant system consists of components for preparation and delivery of a synthetic absorbable surgical sealant. The surgical sealant is composed of two solutions: a polyethylene glycol (PEG) ester solution and a trilysine amine solution (referred to as the blue and the clear precursors, respectively).
When mixed together, the precursors link to form the surgical sealant. The mixing of the precursors is accomplished as the materials exit the tip of the applicator. DuraSeal® dural sealant system should be used within 1 hour of preparing the blue precursor.
The DuraSeal® dural sealant system is absorbed in a timeframe of 4 to 8 weeks, sufficient to allow for normal wound healing, is fully synthetic and has no human or animal derived products. All components are provided sterile.

2.2 Presentation

Powder Vial

Blue Precursor Syringe

Clear Precursor Syringe

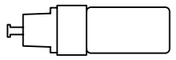
3 Spray Tips

Syringe Holder

Dual Liquid Applicator

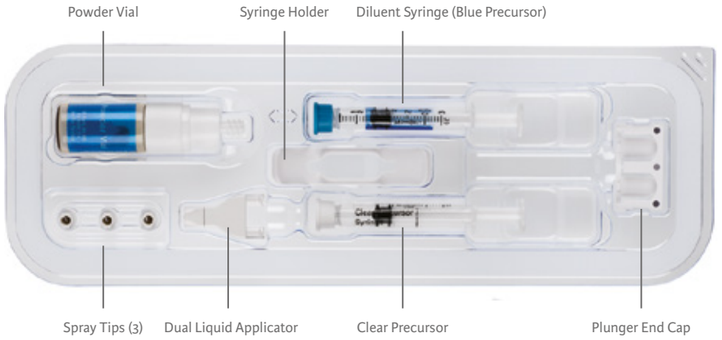
Plunger Cap

DuraSeal® dural sealant system: Kit Components Description - 5 mL kit

Component	Description		Quantity
Hydrogel powder and syringes			
Powder Vial		10ml vial containing ester N-hydroxy Succinimide (PEG) powder (with BHT conservative) and combined with FD&C #1 blue colorant as visualization agent	1 vial Approx 0.5 g
Diluent Syringe		Sodium phosphate buffer	1 syringe Approx 2.5 ml
Clear Precursor Syringe		Trilysine acetate in a 0.075m sodium borate decahydrate buffer	1 syringe Approx 2.5 ml
Distribution devices			
Syringe Holder		Holds the bodies of the syringes	1
Application Device	Dual Liquid Applicator	Permits the application of gel on the operating site	1
	Plunger End Cap	Positions onto syringe plungers	1
	Spray Tips (3)	Used for combining and delivering the 2 precursors onto the referred site	3

Packaging

Each DuraSeal® dural sealant system kit includes materials for the preparation and delivery of 5 mL of hydrogel. The kit is supplied in a double sterile packaging (sealed pouch containing the blister pouch with vial and diluent syringes).



DuraSeal® dural sealant system
(ref. DSD5001, box of 1 - DS-D-5005, box of 5)

Traceability Labels

Six traceability labels indicating the product reference, lot number and expiry date are included with each system on the Tyvek®* lid of the blister pouch.

Storage

The DuraSeal® system should be stored at or below 25° C and has a shelf life of 18 months.

Sterilization

The kit is sterilized by E-Beam radiation at a dose of 25kGy minimum.

*Registered trademark of its respective owner.

2.3 Applicators

Extended Tip Applicator - to be ordered separately

The Extended Tip Applicator is intended for use in the simultaneous delivery of two non-homogenous solutions onto a surgical site.
It is a sterile single use device consisting of a malleable shaft manual applicator with extended reach and added visibility.
The Extended Tip Applicator is available in 8 cm and 15 cm length and does not require the Flow Regulator.

Extended Tip Applicator - 8 cm length (ref. 205108)

MicroMyst® Applicator - to be ordered separately

The MicroMyst® applicator consists of a 14 cm long, dual lumen, stainless steel cannula with an outer sheath to provide a path for two non-homogenous fluids and filtered air or nitrogen gas. The MicroMyst® applicator is intended for use in the delivery of two non-homogenous solutions onto a surgical site.

Extended Tip Applicator - 15 cm length (ref. 205115)

The distal end of the stainless steel cannula is designed to permit delivery, mixing and atomization of the non-homogenous liquids. The applicator shaft is bendable to provide access to hidden or difficult to reach surfaces. The distal tip of the applicator is beveled; each cannula is angled to 45° (90° total included angle). The 3.3mm diameter of the cannula helps reduce fluid flow to a volume that can be atomized and mixed by a gentle airflow.

The proximal end of the MicroMyst® Applicator is designed to allow for the attachment of two syringes containing the non-homogenous fluids that will make up the sealant for application to the surgical site. Also attached to the proximal end of the applicator is poly (vinyl chloride) (PVC) tubing with an integral 0.2µm filter. The free end of this tubing connects to the Flow Regulator.

MicroMyst® Applicator - 14 cm length (ref. 20-5000)

Features Summary

- Packed in double-sterile protection
- Single patient, single use
- Cannula: working length = 14cm
- Diameter = 3.3mm
- Filter of diameter 0.2 micron
- Gas hose 3.65m in length

DuraSeal® system with Extended Tip applicator

Precision & Control:

- Unique design coupled with air or nitrogen assistance.
- Provides a fine mist for a precise and controlled application.
- **Minimal Invasive Surgery compatibility:**
14 cm cannula for increased access.
- **Optimized visualization:** the malleable shaft can be curved in order to improve the visualization of the operating area.

DuraSeal® system with MicroMyst® applicator

Flow Regulator - to be ordered separately

The Flow Regulator is a reusable medical device intended to deliver low pressure air or nitrogen to the gas-assisted MicroMyst® applicator.

The Flow Regulator is a stainless steel enclosure that houses a pressure regulator and a 0.40mm diameter orifice. The inlet of the Flow Regulator is a 3.65m flexible tubing with a male Schrader fitting on the distal end that will connect into a wall fitting in an operating room.

The proximal end of the flexible tubing connects to the stainless steel housing, which contains an in-line filter and an off-the-shelf pressure regulator. The outlet of the Flow Regulator mates with the male fittings on the end of the MicroMyst® applicator.

The stainless steel enclosure has four rubber feet to sit on a tabletop, and a clamp on the back so it can be attached to an I.V. pole.

The Flow Regulator is preset for the appropriate output conditions and may not be manipulated by the user. No manual adjustments are necessary. There are no electronics. The Flow Regulator works for inlet pressure ranges of 3.44-13.79 bars (50-200 psi) of compressed air or compressed nitrogen gas.

The Flow Regulator is not an electrical device.

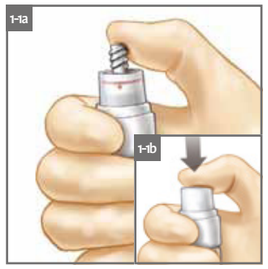
Flow Regulator (ref. FR-6065)

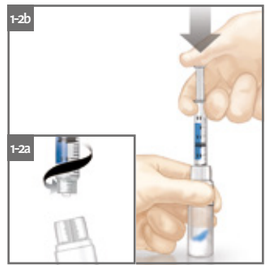
2.4 Product Assembly

Preparing the Assembly of DuraSeal® Dural Sealant System

1-1 Depress threaded fitting of vial cap (Figure 1-1a). Ensure red line is no longer visible (Figure 1-1b).

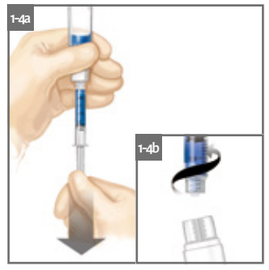
1-2 Remove syringe cap from blue precursor syringe. Screw blue precursor syringe onto powder vial (Figure 1-2a), then inject syringe contents into vial (Figure 1-2b).



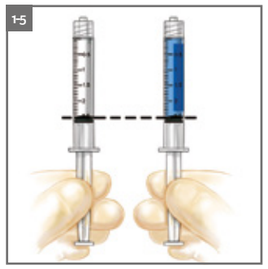


1-3 Gently shake vial/syringe assembly until powder is completely dissolved. The solution will turn blue (Figure 1-3).

1-4 Invert vial/syringe assembly, then draw vial contents back into syringe (Figure 1-4a). Unscrew syringe from vial and discard vial (Figure 1-4b).



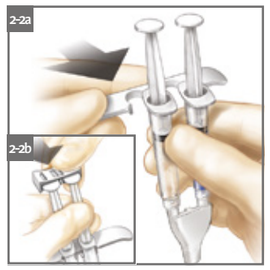
1-5 Remove syringe cap from clear precursor syringe. Prior to applicator assembly, eliminate bubbles from both syringes and ensure precursor volume in two syringes is equal (Figure 1-5).



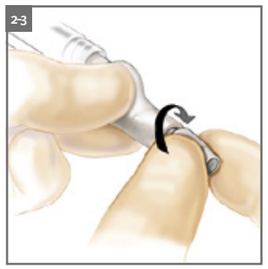
Assembly of DuraSeal® System with **Dual Liquid Applicator**

2-1 Screw clear and blue precursor syringes onto applicator (Figure 2-1).

2-2 Slide syringe holder (Figure 2-2a) along syringe barrels until it fits snugly against syringe flanges. Attach plunger cap (Figure 2-2b) to syringe plungers.



2-3 Attach a spray tip to the Dual Liquid Applicator (Figure 2-3).



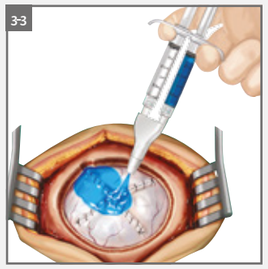
Application

3-1 Prepare application site by removing all blood clots and fluid.

3-2 Do not prime Dual Liquid Applicator prior to use, as plugging may result.

3-3 Position Dual Liquid Applicator tip (Figure 3-3) approximately 2 cm from target site. Rapidly depress syringes to ensure precursor mixing and spray-like application of gel.

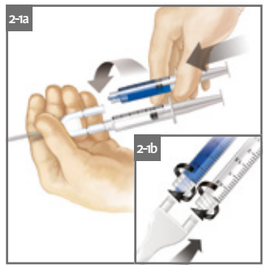
3-4 Apply sealant to create 1-2 mm maximum thickness.

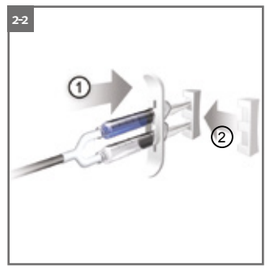


Assembly of DuraSeal® System with **Extended Tip Applicator**

2-1 Screw clear and blue precursor syringes onto applicator (Figure 2-1a).

2-2 Slide syringe holder (Figure 2-2 ①) along syringe barrels until it fits snugly against syringe flanges. Attach plunger cap (Figure 2-2 ②) to syringe plungers.





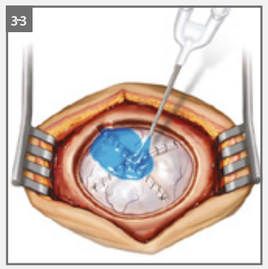
2-3 Adjust malleable applicator shaft to improve access or visualization (Figure 2-3).

Application

3-1 Prepare application site by removing all blood clots and fluid.

3-2 While in surgical field, whenever anatomically possible, briefly spray sealant on gauze and without interrupting flow move to the target site (Figure 3-2).

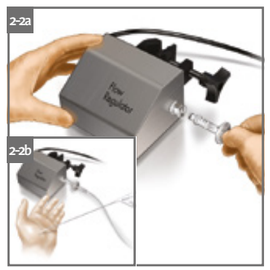
3-3 Position applicator tip 2-4 cm from the target site, depress syringes using strong, even pressure (Figures 3-3). Using a continuous motion, apply an even, approximately 1-2 mm thin coating of hydrogel.



Assembly of DuraSeal® System with MicroMyst® Applicator

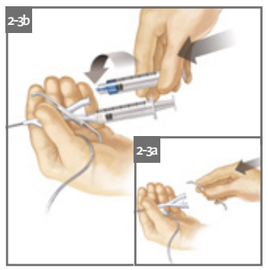
2-1 Ensure the Flow Regulator is connected to a compressed air or Nitrogen source (Figure 2-1). Confirm the nitrogen source is set to 50 - 200psi (3.45 - 13.8 Bar).

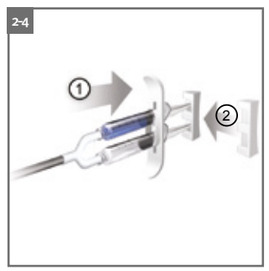
2-2 Connect MicroMyst® applicator line to Flow Regulator (Figure 2-2a). Ensure air is flowing through MicroMyst® applicator (Figure 2-2b).



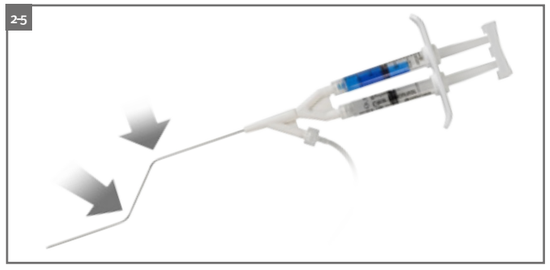
2-3 Position syringe holder over applicator fittings (Figure 2-3a). Screw clear and blue precursor syringes onto applicator (Figure 2-3b).

2-4 Slide syringe holder (Figure 2-4 ①) along syringe barrels until it fits snugly against syringe flanges. Attach plunger cap (Figure 2-4 ②) to syringe plungers.





2-5 Adjust malleable applicator shaft to improve access or visualization (Figure 2-5).

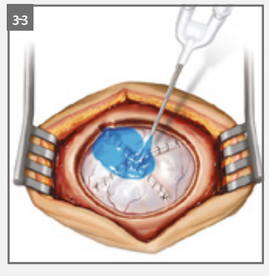


Application

3-1 Prepare application site by removing all blood clots and fluid.

3-2 While in surgical field, whenever anatomically possible, briefly spray sealant on gauze and without interrupting flow move to the target site (Figures 3-2).

3-3 Position applicator tip 1-4 cm from the target site, depress syringes using strong, even pressure (Figures 3-3). Using a continuous motion, apply an even, approximately 1-2 mm thin coating of hydrogel.



Application Tips

General Recommendations

1. Do not prime any applicator prior to use as plugging may result.
2. Prepare application site by removing all blood clots and fluid.
3. While in the surgical field, spray on gauze briefly prior to moving to the target site.

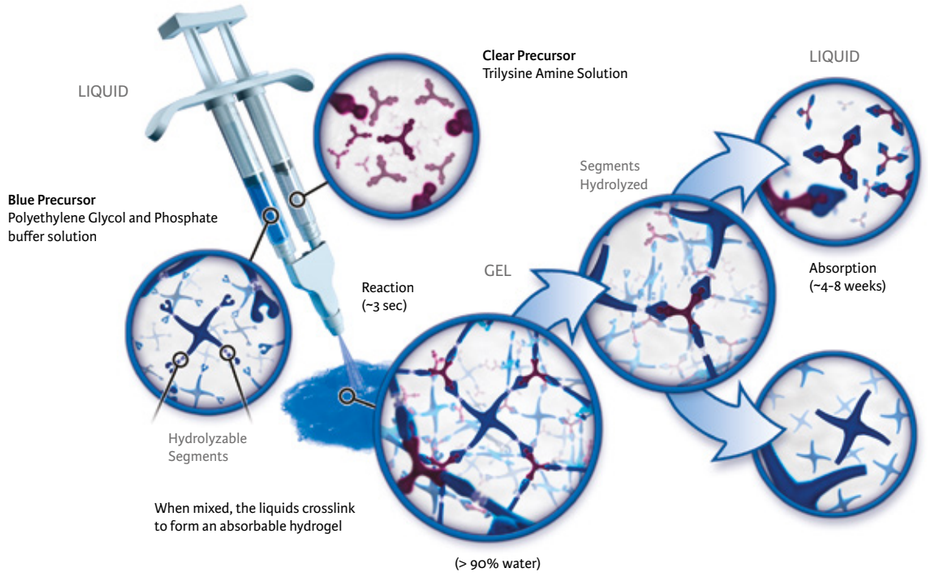
Dual Liquid Applicator:
When using the Dual Liquid Applicator, these one should be positioned approximately 2-4cm from the target site.
Extended Tip Applicator:
When attaching a spray tip to the Extended Tip Applicator, gently twist the spray tip onto the applicator so that the treads engage cleanly. Use strong even pressure with non air-assisted applicators. The Extended Tip Applicator should be positioned approximately 2-4cm from the target site.

MicroMyst® Applicator:
When using the MicroMyst® Applicator move tip back and forth during application to improve mixing of solutions. The MicroMyst® Applicator should be positioned approximately 1-4cm from the target site.

Flow Regulator:
The Flow Regulator provides air flow to facilitate a consistent and even spray. Only use the MicroMyst® Applicator with the Flow Regulator.
NOTE: Supplied pressure from N2 or compressed air source should be set between 50-200 psi (3.44 - 13.79 Bar) solutions. improve mixing of solutions.

3. Mode of Action

Polymerization: the mechanics behind the formation of the hydrogel



The polymerization is carried out rapidly at the application site without heat. The resulting surgical sealant hydrogel contains more than 90% water, the active components (PEG ester and trilysine amine) representing 0.5 grams of the hydrogel. The blue precursor contains PEG ester. The clear solution contains the trilysine amine precursor. When the 2 precursors mix, the trilysine amine locate on the terminations of the PEG molecules and allow crosslinking to occur, resulting in a flexible, biocompatible hydrogel. The PEG ester-trilysine amine combination was selected for its safety, adherence and 4 to 8 weeks resorption profile. Hydrolysis releases the soluble PEG molecules and trilysine molecules into the water. PEG is a water-soluble polymer, non-toxic, nonimmunogenic. Its pharmaco-kinetics have been well established.

3.1 Main Features

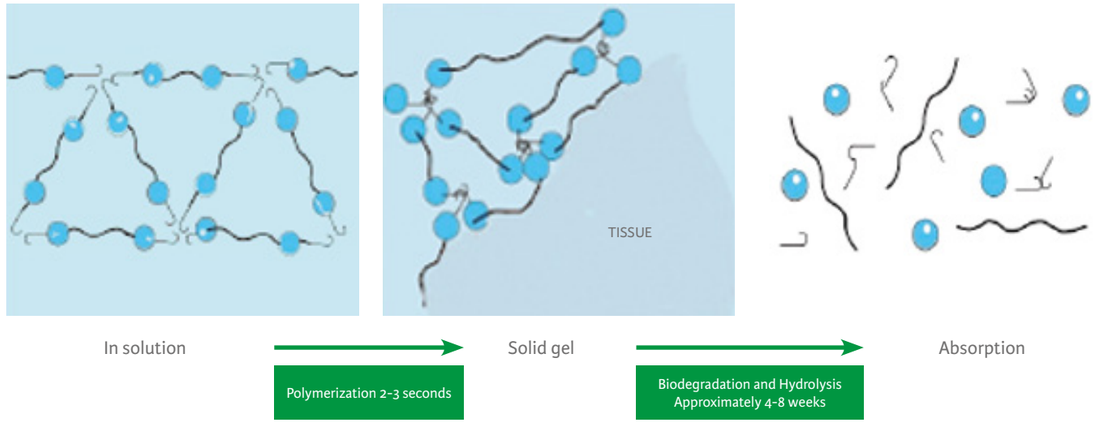
- STRENGTH[1]: Tissue adherence and cohesive strength to withstand critical pressures.
- BIOCOMPATIBILITY[2,3]: Biocompatible PEG (polyethylene glycol) hydrogel.
- VISIBILITY: Distinctive blue colorant provides visualization to assess sealant coverage and thickness.
- SPEED[2,4]: Prepared in less than 2 min. When applied, forms a watertight seal in seconds.
- CONVENIENCE: Single kit, stored at room temperature (at or below 25°C).

3.2 Resorption Profile

DuraSeal® dural sealant system is totally resorbed in 4-8 weeks by hydrolysis and renal elimination.

1. In-vitro Product Comparison Study of Wound Healing Sealants. Report no: R090417B (Cyanta Report)
2. Cosgrove GR et al. "Safety and efficacy of a novel polyethylene glycol hydrogel sealant for watertight dural repair". J Neurosurg 106: 52-58, 2007
3. Safety Testing for 4420kSG-trilysine sealant with BHT. Report no: ER1105, page 2-9
4. Delashaw JB. et al. "Reconstruction After Posterior Cranial Fossa Surgery: Application of a Synthetic Tissue Sealant to Augment Dural Closure." Case Report 2009

Life cycle of hydrogel



3.3 Composition

Composition of the DuraSeal® sealant system

Water, PEG ester, trilysine amine, decahydrated sodium borate, sodium phosphate, FD&C Blue #1 dye (colorant also called "brilliant blue") and butylhydroxytoluene, or BHT. The formulation permits sealing efficacy and a total resorption in approximately 4 to 8 weeks.

Detail of individual doses by component:

Component	Concentration %	Tolerance %	Quantity mg	Tolerance mg
Water for Injection	89.6	± 1.5%	64.0	± 1.0
PEG Ester	8.87	± 1.33%	6.34	± 0.95
Trilysine amine	0.211	± 0.026%	0.151	± 0.018
Sodium Borate Decahydrate	1.28	± 0.18%	0.914	± 0.127
Sodium Phosphate	0.0533	± 0.0084%	0.0381	± 0.0058
FD&C Blue #1	0.010	± 0.009%	0.0071	± 0.0056
BHT	0.00177	± 0.00050%	0.0013	± 0.0002

Assuming the use of one polymer kit (5ml, representing a layer of 2mm thickness over a surface of 25cm²), the mass of sealant used on a patient is 5 g, or a dose of 71.4mg/kg for a 70kg patient.
The safety of the materials was demonstrated through biocompatibility tests, pre-clinical and clinical studies. The results of these studies show that DuraSeal® sealant is inert and that there are no negative effects associated with the hydrolysis and absorption of the components.

3.4 Biocompatibility and Pre-Clinical Testing

Biocompatibility Testing

A series of in-vitro and in-vivo tests were carried out on the polymer. These tests were intended to verify the functionality, performance, and the safety of the product. The tests were conducted in accordance with the recommendations of ISO-10993 (as detailed in the following table) and showed that DuraSeal® dural sealant system conforms to the established specifications.

Table: ISO 10993 tests required for surgical sealants and list of tests carried out.

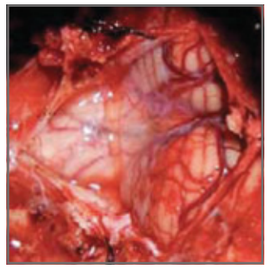
Tests required according to ISO 10993	Tests carried out
Cytotoxicity	Cytotoxicity Agarose Overlay Method
Sensitization	ISO Maximization Sensitization Study
Irritation (or Intracutaneous Reaction)	ISO Modified Intracutaneous Study
Systematic Acute Toxicity	USP and ISO Modified Systemic Toxicity Study
	Material Mediated Pyrogenicity
Sub-Chronic Toxicity	Rat Subchronic Toxicity Following Subcutaneous Implantation (6 weeks)
Genotoxicity	In Vitro Mammalian Cell Gene Mutation Tests
	Micronucleus Cytogenetic Assay in Mice
	In Vitro Mammalian Chromosome Aberration Test
	Bacterial Reverse Mutation Study
Implantation	ISO Muscle Implantation Study (2 weeks)
	ISO Subcutaneous Implantation Study in the Rat (10 days)
Hemocompatibility	In Vitro Hemolysis
Chronic toxicity	**Not performed, justification provided below.
Carcinogenicity	**Not performed, justification provided below.
Other Test*	In Vitro Proliferative Effects of DuraSeal® in Various Human Cancer Cell Lines

*Test not specifically required per ISO 10993
**Carcinogenicity and chronic toxicity testing were not deemed necessary for the following reasons:
- There was no evidence of mutagenic or proliferative effects based on the series of mutagenicity and in vitro proliferative testing performed,
- Exposure to the product is limited as the product is absorbed/degraded within 4-8 weeks of implant,
- The well-known metabolic pathway and rapid clearance of the PEG component material,
- The trilysine amine component is a by-product of a natural occurring amino acid (lysine),
- PEG, FD&C Blue Dye #1 and BHT preservative all have a well-established history of use in the production of foods and pharmaceuticals, and the levels to which the patient will be exposed during absorption of the hydrogel are well below levels used in other food/medical applications.

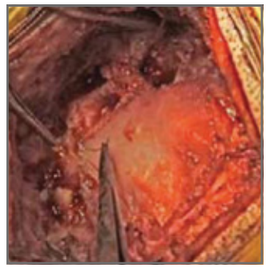
3.5 Clinical Results

DuraSeal® dural sealant system has been studied in two separate, prospective, non-randomized clinical investigations.[1,2]

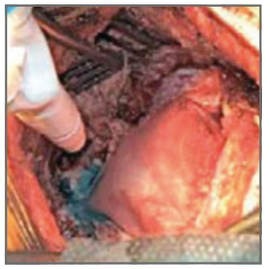
In 111 patients treate, the dural sealant demonstrated a total of 100%[1] intraoperative success rate in holding a watertight seal with no overt CSF leakage upon a subsequent Valsalva maneuver.



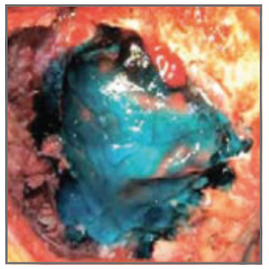
Midline suboccipital craniectomy with dural opening for Chiari Malformation. Cerebellar tonsils below foramen magnum.



Dura closed with bovine pericardial graft using 6-O Prolene™* suture for duroplasty for treatment of symptomatic Chiari malformation.



Application of DuraSeal® sealant to augment dural closure.



Completion of Duraseal® dural sealant application of duraplasty for decompression of Chiari malformation.

Watertight closure success rate

	Patients	Follow-up	Rate of success (no overt CSF leak)
Cosgrove[1]	111	3 months	100%
Boogaarts[5]	47	1 month	95.3%

Images: **Delashaw J, Coppa N.** *"Closure Techniques for Common Craniotomies in the Posterior Fossa"* (White Paper)
1. **Cosgrove GR et al.** *"Safety and efficacy of a novel polytheylene glycol hydrogel sealant for watertight dural repair"*. J Neurosurg 106: 52-58, 2007t
2. **Boogaarts JD et al.** *"Use of a novel absorbable hydrogel for augmentation of dural repair: results of a preliminary clinical study"*.Neurosurgery. 57:146-151, 2005
*Trademarks of their respective owners.

3.6 Standard

DuraSeal® dural sealant system is manufactured by Confluent Surgical (COVIDIEN) in accordance with the ISO 13485: requirements, in locations appropriate to the manufacture of such implantable surgical devices.

4. Appendix

EC Design Examination Certificate

ZERTIFIKAT ◆ CERTIFICATE ◆ 認証書 ◆ СЕРТИФИКАТ ◆ CERTIFICADO ◆ CERTIFICAT

Product Service

EC Certificate

EC Design-Examination Certificate

Directive 93/42/EEC on Medical Devices (MDD), Annex II (4)
(Devices in Class III)

No. G7 13 05 77937 004

Manufacturer: **Covidien llc**
15 Hampshire Street
Mansfield MA 02048
USA

EC-Representative: **Covidien Ireland Limited**
IDA Business and Technology Park
Tullamore
IRELAND

Product: **Wound Care Products**
DuraSeal Sealant System

The Certification Body of TÜV SÜD Product Service GmbH declares that a design examination has been carried out on the respective devices in accordance with MDD Annex II (4). The design of the devices conforms to the requirements of this Directive. For marketing of these devices an additional Annex II certificate is mandatory. See also notes overleaf.

Report no.: 713021854

Valid from: 2013-06-13
Valid until: 2018-06-12

Date, 2013-06-12

Hans-Heiner Junker

582593

TÜV SÜD Product Service GmbH is Notified Body with identification no. 0123

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TÜV SÜD Product Service GmbH · Zertifizierstelle · Ridlerstraße 65 · 80339 München · Germany

ZERTIFIKAT ◆ CERTIFICATE ◆ 認証書 ◆ СЕРТИФИКАТ ◆ CERTIFICADO ◆ CERTIFICAT

Product Service

EC Certificate
EC Design-Examination Certificate
Directive 93/42/EEC on Medical Devices (MDD), Annex II (4)
(Devices in Class III)
No. G7 13 05 77937 004

Model(s): DuraSeal Sealant System:
- DS-D-5005
- DSD5001

Parameters: -/-

Facility(ies): Covidien
15 Crosby Drive, Bedford, MA 01730, USA

Covidien
60 Middletown Avenue, North Haven CT 06473, USA

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A1 / 04.11

TÜV SÜD Product Service GmbH · Zertifizierstelle · Ridlerstraße 65 · 80339 München · Germany

Declaration of Conformity for DuraSeal® (Class III)

Declaration of Conformity
BIO-1006

Legal Manufacturer Covidien llc 15 Hampshire Street Mansfield, MA 02048, USA	**European Representative** Covidien Ireland Limited IDA Business and Technology Park Tullamore Ireland
Product	Wound Care Products DuraSeal Sealant System
Classification (MDD)	Class III
Reorder Codes/GMDN Codes	See Attached
Conformity Assessment Route (Annex Applied)	European Medical Device Directive 93/42/EEC and its amendments, Annex II, Section 4

We herewith declare that the above mentioned products meet the provisions of the Council Directive 93/42/EEC and its amendments and the Essential Principles and classification rules according to Clause 1.8 Schedule 3 of the Australian Therapeutic Goods Regulations 2002. All supporting documentation is retained under the premises of the manufacturer.

Notified Body	TÜV SÜD Product Services GmbH Ridlerstrasse 65 D-80339 Munich Germany 0123	
Design Examination Certificate (if applicable)	G7 13 05 77937 004	
EC Certificate	G1 11 10 77937 007	
Standards to which Conformity is Declared	EN ISO 13485:2003/AC: 2012 EN 20594-1:1994 ISO 15223-1: 2012 EN ISO 14630:2009 EN ISO 14971:2012 EN ISO 14155-1/-2, 2011 EN ISO 11607-1:2009 EN ISO 11607-2:2006 EN 540:1993	EN ISO 10993-1:2009 EN 556-1: 2001/AC: 2006 EN 1041:2008 EP 2.6.14 v. 6.6 ISO 14644: 2004 EN ISO 11137-1:2006 EN ISO 11137-2: 2012 EN ISO 11737-1, 2006/AC: 2009
Original Date of Issue	June 13, 2008	
Place, Date of Issue	North Haven, CT USA June 12, 2013	
Signature		

Print Name: Eileen Martinez

Position: Manager, Regulatory Affairs

Page 1 of 2

Declaration of Conformity for the MicroMyst® Applicator (Class IIa)

Declaration of Conformity
BIO-1009

COVIDIEN

Legal Manufacturer Covidien llc 15 Hampshire Street Mansfield, MA 02048, USA	**European Representative** Covidien Ireland Limited IDA Business and Technology Park Tullamore Ireland
Product	MicroMyst Applicator
Classification (MDD)	Class IIa
Reorder Codes/GMDN Codes	See Attached
Conformity Assessment Route (Annex Applied)	European Medical Device Directive 93/42/EEC and its amendments, Annex II, Section 3

We herewith declare that the above mentioned products meet the provisions of the Council Directive 93/42/EEC and its amendments and the Essential Principles and classification rules according to Clause 1.8 Schedule 3 of the Australian Therapeutic Goods Regulations 2002. All supporting documentation is retained under the premises of the manufacturer.

Notified Body	TÜV SÜD Product Services GmbH Ridlerstrasse 65 D-80339 Munich Germany 0123		
Design Examination Certificate (if applicable)	N/A		
EC Certificate	G1 11 10 77937 007		
Standards to which Conformity is Declared	ISO 13485:2003 BS/EN 20594-1:1994 EN 1041:2008	ISO 10993-1:2009 EN/ISO 11607-1:2009 EN 14971:2007	BS/EN/ISO 11135-1:2007 EN 980:2008 EP 2.6.14 v. 6.6
Original Date of Issue	May 7, 2009		
Place, Date of Issue	Bedford, MA USA, November 28, 2011		
Signature			

Print Name: Melanie Archer

Position: Manager, Regulatory Affairs

15 Crosby Drive
Bedford, MA
01801

Page 1 of 2

Declaration of Conformity for the Extended Tip Applicator (Class IIa)

Confluent Surgical

Declaration of Conformity

Manufacturer	Confluent Surgical, Inc 101A First Avenue Waltham, MA 02451 USA
European Representative	Tyco Healthcare UK Limited 154 Fareham Road Gosport Hampshire PO13 OAS United Kingdom
Product	Extended Tip Applicator 20-5010
Classification (MDD)	Class IIA
Conformity Assessment Route (Annex Applied)	European Medical Device Directive 93/42/EEC Annex II, Section 3

We herewith declare that the above mentioned products meet the provisions of the Council Directive 93/42/EEC for medical devices. All supporting documentation is retained under the premises of the manufacturer.

Notified Body	TÜV Product Services GMBH Riddlerstrasse 65 D-80339 Munich Germany
Notified Body Identification No.	0123
EC Certificate	G1 09 03 45423 029
Start of CE Marking	March 19, 2008
Place, Date of Issue	Waltham, MA, USA, May 7, 2009
Reference ERC	ERC 1012
Signature	Heather V. Nigro
Name:	Heather Nigro
Position:	Manager, Regulatory Affairs

Form 2101-2 Rev. H

Declaration of Conformity for the Flow Regulator (Class IIa)

Declaration of Conformity
BIO-1008

COVIDIEN

Legal Manufacturer Covidien llc 15 Hampshire Street Mansfield, MA 02048, USA	**European Representative** Covidien Ireland Limited IDA Business and Technology Park Tullamore Ireland
Product	Flow Regulator
Classification (MDD)	Class IIa
Reorder Codes/GMDN Codes	See Attached
Conformity Assessment Route (Annex Applied)	European Medical Device Directive 93/42/EEC and its amendments, Annex II, Section 3

We herewith declare that the above mentioned products meet the provisions of the Council Directive 93/42/EEC and its amendments and the Essential Principles and classification rules according to Clause 1.8 Schedule 3 of the Australian Therapeutic Goods Regulations 2002. All supporting documentation is retained under the premises of the manufacturer.

Notified Body	TÜV SÜD Product Services GmbH Ridlerstrasse 65 D-80339 Munich Germany		
	0123		
Design Examination Certificate (if applicable)	N/A		
EC Certificate	G1 11 10 77937 007		
Standards to which Conformity is Declared	ISO 13485:2003 EN 14971:2007	980:2008	EN 1041:2008

Original Date of Issue	November 17, 2006
Place, Date of Issue	Bedford, MA USA, November 28, 2011
Signature	Melanie Archer

Print Name: Melanie Archer
Position: Manager, Regulatory Affairs

15 Crosby Drive
Bedford, MA
01801

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Data Sheet		
1. Administrative information		
1.1	Name: Integra	
1.2	**Europe, Middle-East and Africa** Integra LifeSciences Services (France) SAS Immeuble Séquoia 2 97 allée Alexandre Borodine - Parc technologique de la Porte des Alpes 69800 Saint Priest FRANCE **Latin America, Pacific Asia and Canada** Integra LifeSciences Corporation 311 Enterprise Drive Plainsboro, New Jersey 08536 USA	**Europe, Middle-East and Africa** Phone: +33 (0)4 37 47 59 00 Fax: +33 (0)4 37 47 59 99 Email: emea.info@integralife.com Website: integralife.eu **Latin America, Pacific Asia and Canada** Phone: +1 609 936 5400 Fax: +1 609 750 4259 Email: lapac_cs@integralife.com Website: integralife.com
1.3	Contact information of the medical device vigilance dept.: TBD	E-mail: emeacomplaint@integralife.com
2. Information pertaining to the device or equipment		
2.1	Generic name: dural sealant system	
2.2	Trade name: DuraSeal® dural sealant system	
2.3	LPPR code (ex-TIPS if applicable): n/a	
2.4	Medical device class: III Applicable eu directive: 93/42/EC Number of organization notified: 0123 Date first marketed in the EU: 2003 Manufacturer of medical device: Covidien	
2.5	Description of device  The DuraSeal® dural sealant system consists of components for preparation and delivery of a synthetic absorbable surgical sealant. DuraSeal® sealant is composed of two solutions: a polyethylene glycol (PEG) ester solution and a trilysine amine solution (referred to as the blue and the clear precursors, respectively). When mixed together, the precursors link to form an absorbable hydrogel. The mixing of the precursors is accomplished as the materials exit the tip of the applicator. The DuraSeal® dural sealant system is absorbed in a timeframe of 4 to 8 weeks, sufficient to allow for normal wound healing. The DuraSeal® system is fully synthetic and has no human or animal derived products. All components are provided sterile.	

2.6	Ordering Information:			
	For EUROPE, MIDDLE-EAST and AFRICA			
	DSD5001	DuraSeal® dural sealant system - 5mL	1kit/box	All EUROPE, MIDDLE-EAST and AFRICA countries
	DS-D-5005	DuraSeal® dural sealant system - 5mL	5kits/box	
	205108	Extended Tip Applicator - 8cm length	5kits/box	
	205115	Extended Tip Applicator - 15cm length	5kits/box	
	20-5000**	MicroMyst® Applicator - 14cm length	5kits/box	
	FR-6065	Flow Regulator	1 unit/box	
	For LATIN AMERICA, ASIA PACIFIC and CANADA			
	DSD5001	DuraSeal® dural sealant system - 5mL	1kit/box	LATIN AMERICA and ASIA PACIFIC countries*
	DS-D-5005	DuraSeal® dural sealant system - 5mL	5kits/box	LATIN AMERICA and ASIA PACIFIC countries*
	20-2010	DuraSeal® dural sealant system - 5mL - NOT CE MARKED	1kit/box	LATIN AMERICA and ASIA PACIFIC countries*
	20-2050	DuraSeal® dural sealant system - 5mL - NOT CE MARKED	5kits/box	LATIN AMERICA and ASIA PACIFIC countries*
	209001	DuraSeal® dural sealant system - 5mL - NOT CE MARKED	1kit/box	Canada ONLY
	20-9005	DuraSeal® dural sealant system - 5mL - NOT CE MARKED	5kits/box	Canada ONLY
	JDSD5001	DuraSeal® dural sealant system - 5mL - NOT CE MARKED	1kit/box	Japan ONLY
	JDSD5001	DuraSeal® dural sealant system - 5mL - NOT CE MARKED	5kits/box	Japan ONLY
	205108	Extended Tip Applicator - 8cm length	5kits/box	LATIN AMERICA, ASIA PACIFIC countries* and CANADA
	205115	Extended Tip Applicator - 15cm length	5kits/box	LATIN AMERICA, ASIA PACIFIC countries* and CANADA
	20-5000**	MicroMyst® Applicator - 14cm length	5kits/box	LATIN AMERICA, ASIA PACIFIC countries* and CANADA
	FR-6065	Flow Regulator	1 unit/box	LATIN AMERICA, ASIA PACIFIC countries* and CANADA

* Not all products are available in all regions. Please check the specific reorder number to determine which product is available in your region.
For all the medical devices specially identified as "NOT CE MARKED", please refer to the appropriate Instruction for use: the indications and contraindications of the product may be different as the ones mentioned on this document for CE MARKED medical devices.
** MicroMyst® Applicator requires an air source to operate – used in conjunction with the Flow Regulator.

2.7	Composition of device and accessories Ingredients: Polyethylene glycol ester solution and trilysine amine solution. Materials: No latex or dehp
2.8	Scope - Indications & Contraindications: Scope of use: Neurosurgery **Indications: The DuraSeal® dural sealant system** is intended for use as an adjunct to standard methods of dural repair, such as sutures, to provide watertight closure. **The Extended Tip Applicator** is intended for use in the simultaneous delivery of two non-homogenous solutions onto a surgical site. **The MicroMyst® Applicator** is intended for use in the delivery of two non-homogenous solutions onto a surgical site. **The Flow Regulator** is intended to provide pressurized gas (air or nitrogen) to gas-assisted applicators. **Contraindications:** Do not apply the **DuraSeal® Dural Sealant** in abdominopelvic surgical procedures for use as a sealant or adhesion barrier. Do not use **Extended Tip Applicator, MicroMyst® Applicator and Flow Regulator** for other indications than ones provided in the instructions for use.
3. Sterilization Procedure	
3.1	Medical device sterile: yes
3.2	Sterilization method of device: radiation / irradiation
4. Storage Conditions	
4.1	Storage conditions: at room temperature - 25 °c max.
4.1	Shelf life: 18 months for DuraSeal® dural seamant system, 36 months for MicroMyst® Applicator and 60 months for Extended Tip Applicators
5. Safety	
5.2	Technical safety: please read carefully the instructions for use
6. Biological safety (if applicable)	
6.1	Usage guidelines: please read carefully the instructions for use
6.1	Operating instruction: please read carefully the instructions for use
6.1	Indications: please read carefully the instructions for use
6.1	Precautions: please read carefully the instructions for use
6.1	Contraindications: please read carefully the instructions for use

5. Bibliography

5.1. Boogaarts JD, et al. 2005
Use of a novel absorbable hydrogel for augmentation of dural repair: results of a preliminary study.

SUMMARY:
This prospective, nonrandomized, single center clinical trial evaluates the safety and performance of a synthetic dural sealant (DuraSeal® system) as an adjunct to standard surgical dural repair techniques to prevent cerebrospinal fluid (CSF) leakage. 46 evaluable discharged patients were scheduled for elective cranial (44 patients - 95.6%) and intradural spinal (2 patients - 4.3%) surgeries. Cranial approaches included basal approach (23 patients - 50%) and convexity approach (21 patients - 45.7%). A wide variety of diseases treated included:

- Astrocytoma (23.9%)
- Vestibular Schwannoma (15.2%)
- Metastatic disease (13%)
- Meningioma (8.7%).

The primary end point was defined as no leak with the Valsalva maneuver after dural sealant application. The patients were followed-up for 3 months after surgery.

RESULTS:

- DuraSeal® Efficacy:
  - Intraoperative CSF leaks: after the application of DuraSeal® dural sealant system, there was no spontaneous CSF leak and no leak after the Valsalva maneuver in all treated patients. At the 3 months follow-up, 2 patients (4.9%) had a CSF leak.
- DuraSeal® Safety:
  - **Wound Healing:** wound healing was excellent in most patients (2 infections reported).
  - **Adverse Events:** there was no relation between the hydrogel and the adverse events. Neurological adverse events that occurred were related to the disease or the operation.

Boogaarts JD, Grotenhuis JA, Bartels RH, Beems T.
Neurosurgery 57(1 Suppl):146-51, 2005

5.2. Grotenhuis JA, et al. 2005
Costs of postoperative cerebrospinal fluid leakage: 1-year, retrospective analysis of 412 consecutive nontrauma cases.

SUMMARY:
This single-center retrospective study evaluates the direct cost associated with cerebrospinal fluid (CSF) leaks across multiple neurosurgical procedures, comparing the costs of using a synthetic agent (DuraSeal® dural sealant system) to prevent such leaks with the costs attributed to CSF leaks. 412 consecutive, nontrauma, elective procedures were examined, including:

- Supratentorial craniotomies (269 patients - 65%)
- Extensive skull base procedures (52 patients - 13%)
- Infratentorial craniotomies (47 patients - 11%)
- Endoscopic transsphenoïdal procedures (44 patients - 11%)

The factors used to calculate the direct medical costs were days of hospital and intensive care unit stay, surgeon's fee including costs of extra CSF drainage and/or surgical reexploration, costs of diagnostic procedures and costs of antibiotic therapy.

RESULTS:

- **Postoperative CSF Leaks incidence:** procedures involving postoperative CSF leaks accounted for 10.7% of all procedures (44 patients): 34.6% CSF leaks occurred during Extensive skull base procedures, 12.8% during Infratentorial procedures, 6.8% during Transsphenoïdal procedures and 6.3% during Supratentorial procedures.
- **Cost impact:** There are significant differences in the incidence and cost impact of CSF leaks across procedures. Procedures involving CSF leaks cost, on average, 141% more than procedures that do not result in a postoperative CSF leak. Procedures involving CSF leaks accounted for 21.7% of the total costs. The total extra cost attributed to CSF leaks for all 412 patients was 621.198€ which represents an average of 1.508€ per patient (10.3%).
- **Impact of the use of a synthetic agent:** If a synthetic sealant would have been used in all cases, the saving cost would be 226.600€ during 1-year period with 412 procedures, that being so 550€ saved per patient.

Grotenhuis JA.
Surg Neurol. 64(6):490-3, 2005

5.3. Cosgrove GR, et al. 2007
Safety and efficacy of a novel polyethylene glycol hydrogel sealant for watertight dural repair.

SUMMARY:

This multicenter, prospective, single-arm clinical investigation evaluates the safety and efficacy of a novel polyethylene glycol (PEG) hydrogel sealant (DuraSeal® dural sealant system) in 111 patients undergoing cranial surgery with documented cerebrospinal fluid (CSF) leakage after sutured dural repair. The most common indications include: Resection of malignant or benign tumors (46%), Microvascular decompression (18.9%), Aneurysms (10.8%), Epilepsy (9%), Arteriovenous malformations (6.3%), Chiari Malformation (5.4%). The location of the neurological procedure was Infratentorial in 53 patients (48%) and Supratentorial in 58 patients (52%).

RESULTS:

- DuraSeal® Efficacy:
  - Intraperative CSF leaks: All patients enrolled in this study demonstrated a spontaneous CSF leak or a Valsalva maneuver-induced leak after primary suture closure. After a maximum of 2 sealant application no intraoperative CSF leaks were apparent during subsequent Valsalva maneuvers. The PEG hydrogel sealant was 100% effective in creating watertight closure where none existed previously.
  - Postoperative CSF leaks: There were no signs of CSF leaks in 106 patients (95.5%). For the 5 patients with CSF leakage (incisional or pseudomeningocele), the time to first leakage ranged from 7 to 29 days.
  - Wound Healing: at 6-week examination the swelling had resolved in 81% of the patients. At the 3-month examination, the wounds of all 107 patients remaining (100%) were healed.
- DuraSeal® Safety:
  - Adverse Events: At no time during the study did unanticipated adverse event related to DuraSeal® dural sealant system occur.
- DuraSeal® Application:
  - Rate of success: A single PEG hydrogel sealant application was effective in obtaining a watertight closure in 105 patients (95%). Persistent leakage was present in 6 patients (5%) and was treated successfully with a second hydrogel application.
  - Ease of use: At the time of sealant application, 95% of the surgeons rated the DuraSeal® system as "easy" or "very easy" to use.

Cosgrove GR, Delashaw JB Jr, Grotenhuis JA, Tew JM, Van Loveren H, Spetzler RF, Payner T, Rosseau G, Shaffrey ME, Hopkins LN, Byrne R, Norbash A.
J Neurosurg 106: 52-58, 2007

5.4. Preul MC, et al. 2007
Application of a hydrogel sealant improves watertight closures of duraplasty onlay grafts in a canine craniotomy model.

SUMMARY:

This pre-clinical animal study (12 canine models) evaluates whether a polyethylene glycol-based (PEG) hydrogel sealant (DuraSeal® system) improved dural closures with collagen-based duraplasty onlay grafts. Two different commercially available collagen duraplasty onlay grafts were evaluated in conjunction with application of DuraSeal® dural sealant system: DuraGen® matrix (bovine Achilles tendon, Integra) and Durepair® (fetal bovine skin, Medtronic). In 6 canines, hydrogel was applied onto the dural onlays. The other 6 canines underwent duraplasty only. After treatment, intraoperative CSF leakage was assessed in each animal using a Valsalva maneuver to achieve a mean pressure of 20 cm H_2O. Then, the bone flap was replaced.

RESULTS:

- DuraSeal® Efficacy:
  - Intraoperative CSF leaks: the 6 duraplasty-only dogs (100%) had spontaneous CSF leakage that was visible without performing a Valsalva maneuver. Canines that received DuraSeal® dural sealant system over the duraplasty onlay had no spontaneous CSF leaks, and all 6 withstood the Valsalva maneuver without CSF leakage.
  - Postoperative CSF leaks: no overt CSF leakage through the incision was noted. In many canines subcutaneous CSF accumulations were obvious within 1 week of surgery. These leaks were evident in the 6 duraplasty-only canines (100%), but in only one of the 6 canines (16.7%) receiving DuraSeal® dural sealant system (p=0.0152).
  - Dura mater-Bone Flap Adhesions: In the canines receiving DuraSeal® dural sealant system, there was less scarring to the bone flaps. The adhesion score of the hydrogel-treated canines was significantly lower (82.6% in average) than that of the duraplasty-only dogs (p=0.0043).
- DuraSeal® Safety:
  - Adverse Events: DuraSeal® dural sealant system over the collagen duraplasty materials was not associated with neurotoxicity, delayed healing, degenerative changes, increased dural brain adhesions, or impaired neodura formation.

Preul MC, Campbell PK., Bichard WD. And Spetzler RF.
J Neurosurg 107: 642-650, 2007

5.5. Than KD, et al. 2008
Polyethylene glycol hydrogel dural sealant may reduce incisional cerebrospinal fluid leak after posterior fossa surgery.

SUMMARY:

This retrospective study evaluates the safety of PEG hydrogel dural sealant (DuraSeal® dural sealant system), as an adjunct to sutured dural closure, in reducing the incidence of postoperative incisional CSF leak after posterior fossa surgery in 100 patients. The results were compared with a retrospective cohort of 100 patients with fibrin glue augmented dural closure. The pathology of the posterior fossa lesions of the 2 groups was similar: mainly Vestibular Schwannomas (29 and 38% respectively), Meningiomas (15 and 16% respectively), Metastatic lesions (5 and 8% respectively). Different dural closure techniques have been used in both groups, including:

- Primary dural closure (48 and 54% respectively),
- Fascia/muscle (13 and 20% respectively),
- Sutured dural patch (30 and 16% respectively),
- DuraGen® matrix (20 and 28% respectively).

Total dural closures techniques are greater than 100% because DuraGen® matrix was used in both primary and fascia or patch closure.

RESULTS:

- DuraSeal® Efficacy:
  - **Incisional CSF leaks:** An incisional CSF leak has been developed in 2 patients (2%) in the DuraSeal® dural sealant system group, compared with 10 patients (10%) in the fibrin glue group (p=0.03). The odds ratio for developing an incisional CSF leak in the fibrin glue group was 5.4 compared with the PEG group (0.18 odds ratio).
  - **Hospital Length of Stay:** Patients in whom DuraSeal® dural sealant system was used had a mean length of stay (LOS) of 5.4 days, compared with 6.4 days in the fibrin glue group (p=0.09).
  - **Hospital Readmission:** Notably, hospital readmission for CSF leak management required 47 additional hospital days for the 10 patients in the fibrin glue group, whereas 10 days were required for the 2 patients readmitted in the DuraSeal® dural sealant system group.

Than KD, Baird CJ, Olivi A.
Neurosurgery 63[ONS Suppl 1]: ONS184-ONS189, 2008

5.6. Weinstein JS, et al. 2010
The safety and effectiveness of a dural sealant system for use with nonautologous duraplasty materials.

SUMMARY:

This multicenter, retrospective, nonrandomized study demonstrates the safety and efficacy of a dural sealant system (DuraSeal®) in 66 patients when used for watertight dural closure in conjunction with nonautologous duraplasty materials. This cohort was compared with 50 well-matched patients from a Pivotal Trial group (treated with DuraSeal® dural sealant system and autologous duraplasty material).

- **Retrospective population** (66 patients): 46 patients (71%) of the patients received DuraGen® matrix (bovine Achilles tendon, Integra), 9 patients (14%) received Dura-Guard™ matrix (bovine pericardium, Synovis), 5 patients (8%) received Durepair® (fetal bovine skin, Medtronic), 4 patients (6%) received DuraGen® matrix + Durepair™ and 1 patient (1%) received Gore-Tex (synthetic graft, W.L. Gore & Associates, INC.)
- **Pivotal Trial population** (50 well-matched patients): 16 patients (32%) received fascia, 12 patients (24%) received pericranium and 3 patients (6%) received fat muscle (48%).

RESULTS:

- DuraSeal® Efficacy:
  - **Postoperative CSF leaks:** postoperative CSF leaks occurred in 5 patients (7.6%) in the retrospective population and in 3 patients (6%) in the Pivotal Trial population. All CSF leaks in the Retrospective population were treated and resolved with no residual effects.
- DuraSeal® Safety:
  - **Surgical Site Infections:** there were no surgical site infections in the retrospective population. In the Pivotal Trial population, the overall incidence of surgical site infection was 8% (4 patients).
  - **Meningitis:** There were no reported cases of meningitis in the retrospective population. In the Pivotal Trial population, bacterial meningitis was confirmed in 1 patient (2%), and aseptic meningitis was documented in 2 patients (4%).
- **Surgery Duration:** The mean duration of surgery was comparable for both populations: 252.6 minutes for the retrospective population versus 242.9 minutes for the Pivotal Trial population.

Weinstein JS, Liu KC, Delashaw JB, Burchiel KJ, Van Loveren HR, Vale FL., Agazzi S, Greenberg MS, Smith DA., Tew J.
J Neurosurg 112: 428-433, 2010

5.7. Osbun JW, et al. 2012
A multicenter, single-blind, prospective randomized trial to evaluate the safety of a polyethylene glycol hydrogel (Duraseal Dural Sealant System) as a dural sealant in cranial surgery.

SUMMARY:

This multicenter, single-blind, prospective randomized trial to evaluate the safety of a polyethylene glycol hydrogel (DuraSeal® Dural Sealant System) as a dural sealant in cranial surgery on a total of 237 patients. Dural closures were augmented with the PEG hydrogel (120 patients) or a control "standard of care" (117 patients) dural sealing technique after Valsalva maneuver, demonstrating an intraoperative non-watertight dural closure. The standard of care materials used in the control group was: Adhesive/glue (57 patients - 48.7%), Absorbable gelatin sponge (41 patients - 35%), Hemostatic agent (31 patients - 26.5%), Suture only (25 patients - 21.4%), Dural graft matrix (23 patients - 19.7%), Dura substitute (8 patients - 6.8%) and Soft tissue patch/vascular graft (8 patients - 6.8%).

RESULTS:

- DuraSeal® Efficacy: The incidences of CSF leaks were similar between treatment and control groups, with no statistically significant difference between the measures:
  - **Postoperative CSF leaks (within 30 days):** 1 patient (0.8%) in the DuraSeal® dural sealant system group versus 2 patients (1.7%) in the control group (P=0.619).
- DuraSeal® Safety: The incidences of neurosurgical complications and surgical site infections were similar between treatment and control groups, with no statistically significant difference between the measures:
  - **Neurosurgical complications:** 7 patients (5.8%) in the DuraSeal® dural sealant system group versus 9 patients (7.7%) in the control group.
  - **Surgical site infection:** 2 patients (1.7%) in the DuraSeal® dural sealant system group versus 3 patients (2.6%) in the control group.
- DuraSeal® Preparation and Application:
  - **Preparation Time:** the preparation time was less than 5 minutes in 96.6% of the DuraSeal® dural sealant system group compared with 66.4% of controls (P < 0.001).
  - **Application:** The dural augmentation was applied in less than 1 minute in 85.7% of the DuraSeal® dural sealant system group compared with 66.4% of the control group (P < 0.001).

Osbun JW, Ellenbogen RG, Chesnut RM, Chin LS, Connolly PJ, Cosgrove GR, Delashaw JB Jr, Golfinos JG, Greenlee JD, Haines SJ, Jallo J, Muizelaar JP, Nanda A, Shaffrey M, Shah MV, Tew JM Jr, van Loveren HR, Weinand ME, White JA, Wilberger JE.
World Neurosurg 78(5):498-504, 2012

Notes

Notes

Integra®

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integralife.eu/duraseal-order/

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Availability of these products might vary from a given country or region to another, as a result of specific local regulatory approval or clearance requirements for sale in such country or region.

- Please read carefully the instructions for use.
- Non contractual document. Integra reserves the right, without prior notice, to modify the products in order to improve their quality.
- Warning: Applicable laws restrict these products to sale by or on the order of a physician.

Additional information for EMEA Customers only:

Products mentioned in this document are CE class II a and III devices. Please contact Integra customer service should you need any additional information on devices classification. All the medical devices mentioned on this document are CE marked according to European council directive 93/42/EEC on medical devices and its relatives, unless specifically identified as "NOT CE MARKED".