DE NOVO CLASSIFICATION REQUEST FOR DURAGRAFT VASCULAR CONDUIT SOLUTION

REGULATORY INFORMATION

FDA identifies this generic type of device as:

> **Flushing and storage solution for vascular autografts at room temperature**. A flushing and storage solution for vascular autografts at room temperature is a device that is used for flushing or short-term storage of vascular grafts. This generic type of device is intended to maintain cell viability and structural integrity of vascular grafts during short-term storage at room temperature during the surgical procedure.
>
> **NEW REGULATION NUMBER:** 21 CFR 876.4100
>
> **CLASSIFICATION:** Class II
>
> **PRODUCT CODE:** QEJ

BACKGROUND

> **DEVICE NAME:** DuraGraft Vascular Conduit Solution
>
> **SUBMISSION NUMBER:** DEN230002
>
> **DATE DE NOVO RECEIVED:** January 3, 2023
>
> **SPONSOR INFORMATION:**
>
> > Marizyme, Inc.
> > 555 Heritage Drive Suite 205
> > Jupiter, FL 33458-5290

INDICATIONS FOR USE

The DuraGraft is indicated as follows:

> DuraGraft Vascular Conduit Solution is a solution indicated for adult patients undergoing Coronary Artery Bypass Grafting Surgeries and is intended for flushing and storage of the saphenous vein grafts from harvesting through grafting for up to 4 hours.

LIMITATIONS

The sale, distribution, and use of the DuraGraft Vascular Conduit Solution are restricted to prescription use in accordance with 21 CFR 801.109.

DuraGraft Vascular Conduit Solution is not intended for direct injection or intravenous infusion.

DuraGraft Vascular Conduit Solution includes a component, L-arginine. L-arginine may cause an allergic reaction in certain patients.

PLEASE REFER TO THE LABELING FOR A COMPLETE LIST OF WARNINGS, PRECAUTIONS AND CONTRAINDICATIONS.

DEVICE DESCRIPTION

DuraGraft Vascular Conduit Solution is a clear, colorless to slightly yellow, aseptically processed, non-pyrogenic solution for room temperature flushing and storage of vascular conduits used during the harvesting and grafting interval in Coronary Artery Bypass Grafting (CABG) surgeries.

DuraGraft Vascular Conduit Solution is supplied in two separate containers composed of a Solution A (237.5mL) and a Solution B (12.5-13.5mL). Solution A is mixed with 12.5mL of Solution B prior to use.

DURAGRAFT Vascular Conduit Solution has an osmolality of about 305 mOsmol/kg, viscosity of 1.06 cST, a sodium concentration of 155-160 mEq/L, a potassium concentration of 5.8 mEq/L, and a pH of about 7.4 at room temperature. Composition and molar concentrations of DuraGraft (mixed solution) is given in Table 1 below.

Table 1: Composition of DuraGraft (Mixed Solution)

SOLUTIONS A + B (19:1 ratio)	
Ingredients	**Concentration in mM**
Calcium chloride	0.95
Potassium chloride	5.37
Potassium phosphate monobasic	0.44
Magnesium sulfate	0.41
Magnesium chloride	0.49
Sodium chloride	136.89
Sodium bicarbonate	4.29
Sodium phosphate dibasic	0.19
L-Glutathione	1.01
D-Glucose	5.55
L-Arginine	0.86
L-Ascorbic acid	0.51
pH	7.4
Water For Injection	

Please refer to the labeling for additional device description details.

SUMMARY OF NONCLINICAL/BENCH STUDIES

BIOCOMPATIBILITY/MATERIALS

DuraGraft is considered to have limited indirect contact with the blood (<24 hours) based on the nature of use and duration of exposure. The device was evaluated with respect to its intended use per FDA guidance, "Use of International Standard ISO 10993-1, 'Biological evaluation of medical devices--Part 1: Evaluation and testing within a risk management process.'" Testing was performed on the final mixed solution and heparin mixture as used clinically. The following tests were performed:

1. Cytotoxicity
2. Irritation
3. Guinea Pig Maximization Test (GPMT) sensitization
4. Acute systemic toxicity
5. Hemolysis
6. Material mediated pyrogen
7. Chemical leachable testing of container on aged solutions

The results supported the biocompatibility of the DuraGraft device.

SHELF LIFE/STERILITY

DuraGraft Vascular Conduit Solution is provided aseptically processed in two bottles using aseptic filling procedures. Sterilization validation testing was performed to validate the sterility of the solution containers with a sterility assurance level (SAL) of 10^{-6} prior to aseptic filling. The containers also underwent endotoxin testing using a 3-log reduction of endotoxin as an acceptable level of endotoxin reduction for the container. Aseptic filling is conducted in accordance with EN ISO 13408-2: 2011, Aseptic Processing of Health Care Products-Part: Filtration, and in compliance with the FDA guidance, "Sterile Drug Products Produced by Aseptic Processing – Current Good Manufacturing Practice", September 2004. Testing to support aseptic filling for both solutions included aseptic filling validation and filter validation testing. Testing was provided to support a 3 year shelf life using devices accelerated-aged at 40° C and simulated shipping testing after devices were real-time aged for 3 years per ASTM D4169 DC13 and Assurance level II. Container closure integrity (CCI) testing was provided for kits that were real-time aged 3 years and then simulated shipped. Sterility and endotoxin testing was provided following aging.

PERFORMANCE TESTING - BENCH

Solution A and Solution B of DuraGraft were evaluated for pH per USP <791>, osmolality per USP <785>, and particle count per USP <788>. Testing was also conducted to evaluate the stability of Solution B (arginine, glucose, ascorbic acid, and glutathione) at time points from 0 to 36 months to support the device stability and 3-year shelf-life.

The following preclinical studies support DuraGraft for use as a short-term flushing and storage solution for vascular conduits.

Table 2. Preclinical Studies Supporting DuraGraft

Publication	Experimental Conditions	Summary and Conclusions
Pachuk et al., 2019[1]	Human saphenous vein (HSV) segments collected from 9 patients undergoing CABG surgery stored for up to 5 hours in DuraGraft or normal saline solution (NSS)	Graft cell viability was maintained in human saphenous vein segments when the segments were flushed and stored in DuraGraft up to 5 hours. Loss of graft cell viability was observed within 15 minutes following flushing and storage in NSS.
	Pig mammary vein segments were flushed and stored with DuraGraft or NSS for 45 minutes and 24 hours.	H&E staining and Immunohistochemistry staining for CD31 and von Willibrand factor (vWF) showed normal morphology by H&E staining and strong immunostaining of endothelial surface markers CD31 and vWF that was continuous across the endothelium at both timepoints for veins stored in DuraGraft. NSS stored veins had normal morphology by H&E staining at 45 minutes but displayed multifocal aggregation of and missing patches of endothelium at 24 hours. CD31 and vWF staining was weaker for NSS stored grafts.
Korkmaz-Icoz et al., 2021[2]	Rat thoracic aortic rings undergoing cold ischemic storage in either DuraGraft or NSS at 4 °C for 24 hours were incubated in an organ bath culture containing 200μM sodium hypochlorite for 30 minutes to induce free radical formation as seen in reperfusion.	Vasoactive physiologic arterial dysfunction was observed when aortic rings were stored in saline.
Aschacher et al., 2021[3]	Radial Artery and HSV segments from 23 patients undergoing CABG surgery were flushed and stored in either DuraGraft or Ringers lactate solution (RL) at room temperature for 60 minutes or times up to 3 hours at room temperature.	DuraGraft treated grafts showed normal endothelial and sub-endothelial structure whereas RL-treated grafts showed damaged endothelial surface and beginning incongruence of intimal structure. DuraGraft treated grafts were associated with a lower level of reactive oxygen species that correlated with a reduction of hypoxic damage and significant increase in oxidation-reduction potential.

SUMMARY OF CLINICAL INFORMATION

DuraGraft Prospective Randomized Study

The sponsor conducted a prospective, multicenter, randomized controlled trial outside of the U.S. to evaluate the effects of DuraGraft on graft level anatomic parameters (Perrault 2019)[4]. The study employed a "within-patient control" design, in which patients received both a control saline-treated saphenous vein graft (SVG) and a DuraGraft-treated SVG, randomly assigned per graft. The initial trial included multidetector computed tomography (MDCT) evaluation at 1 and 3 months. Follow-up was extended to 1-year with an additional MDCT evaluation in the second protocol requiring re-consenting the patients. Safety was assessed in both protocols through the incidences of vein graft thrombosis/occlusion, composite safety events, adverse events and SAEs. The primary safety endpoint for both protocols was the incidence of graft thrombosis/occlusion. Secondary safety endpoints included a composite safety endpoint consisting of Major Adverse Cardiac Events (MACE) (deaths, myocardial infarction (MI) and repeat revascularization), increased angina, arrhythmia, shortness of breath, decreased lumen change, graft occlusion, significant stenosis based on Fitzgibbon's scale B and O, if determined to be related to a specific graft, and incidence of adverse events (AE) and serious adverse events (SAE).

A total of 125 patients were randomized and enrolled from September 2014 to December 2016 at seven investigational sites in Canada, Ireland, and Denmark. 125 grafts were treated with DuraGraft, and 125 grafts treated with saline. Mean Society of Thoracic Surgeons score for mortality was 0.9 ± 0.6 and mean European System for Cardiac Operative Risk Evaluation II score was 1.1 ± 0.6. Grafts were assessed using serial MDCT at 1 month (n=116), 3 months (n=118), and 12 months (n=97), respectively.

Inclusion & Exclusion Criteria:

Inclusion Criteria:

1. Subject to undergo primary, multi-vessel CABG with at least two SVGs
2. Subject ≥18 years and ≤80 years of age
3. Subject with no contraindications to cardiopulmonary bypass
4. Subject who were willing and able to provide consent and shows commitment to participate in a follow-up evaluation, including a clinical visit between 4-6 weeks and 3 months (±1 Week) post CABG
5. If female, subject surgically sterile or postmenopausal
6. Subject has had no previous CABG surgery
7. Subject who was hemodynamically stable

Exclusion Criteria:

1. Subject with in-situ internal mammary artery (IMA) graft(s) only (no SVG or free arterial grafts)
2. Subject with prior CABG or planned concomitant valve surgery or aortic aneurysm repair
3. Subject that was pregnant or lactating woman
4. Subject had left ventricular ejection fraction (LVEF) <40%
5. Subject was known to be HIV positive, is receiving anti-retroviral drugs, or is immunosuppressed
6. Subject had an acute infection at screening
7. Subject had active chronic bacterial, parasitic or viral infection within 3 months prior to CABG surgery
8. Subject had a malignancy diagnosed within the previous 5 years (except successfully resected basal cell cancer)
9. Subject unable to provide consent or undergoing emergency cardiac surgery for an immediately life-threatening condition
10. Subject is participating in a device study or received active drug product in an investigational drug study within1 month prior to screening
11. Subject has a history of transient ischemic attack or stroke within the 12 weeks prior to the CABG procedure
12. Subject who had significant renal impairment (Glomerular Filtration Rate <50 mL/min)
13. Subject who had liver impairment as demonstrated by hepatic transaminases (AST and/or ALT) >2.5x upper limit of normal (ULN) or conjugated bilirubin >1.5x ULN
14. Subject had any condition or disease detected prior to study start that would render the subject unsuitable for the study, place the subject at undue risk or interfere with the ability of the subject to complete the study in the opinion of the investigator (e.g., drug dependence, mental illness)

15. Subject had uncontrolled diabetes mellitus (HbA1C >10%)
16. Subject had any confirmed significant allergic reactions against any drug or multiple allergies (non-active hay fever is accepted)
17. Subject who required uninterrupted use of systemic steroids or immunosuppressive agents
18. Subject had platelet count <100,000/mm3, hematocrit >62% (Hb >18 g/dL) or <30% (Hb<10 g/L)
19. Subject had varicose veins or veins <2 mm in diameter
20. Subject had target coronary artery <1.5 mm in internal diameter
21. Subject had diffuse coronary disease
22. Subject had severe uncontrolled systemic hypertension (i.e., systolic pressure >160 mmHg)
23. Subject with prior severe reaction to contrast dye

Results:

The results of the safety endpoint analysis is exhibited below (Table 3). Vein graft occlusions were observed in 7.2% of the DuraGraft treated grafts and 8.8% of the saline treated grafts. According to the Fitzgibbon classification, a stenosis type B (flow limited) or type O (occlusion) was observed in 1.6% of the grafts in the DuraGraft group and 2.4% of the saline group. No MACE events were observed in the DuraGraft group compared to 1 in the saline group and in particular no deaths were observed in either group. The composite event rate was 8.8% for DuraGraft treated grafts and 11.2% for saline treated grafts.

Table 3. Adjudicated safety outcomes after graft treatment by either DuraGraft or saline after a follow-up duration of 110.3 patient-years (1 year follow-up timepoint)

Outcome	DuraGraft (n = 125)	Saline (n = 125)
Major adverse cardiac events†	0	1 (0.8) [0.009]
Composite end point‡	11 (8.8) [0.100]	14 (11.2) [0.127]
Death	0	0
Myocardial infarction	0	1 (0.8) [0.009]
Repeat revascularization	0	0
Increased angina	0	1 (0.8) [0.009]
Increased arrhythmia	0	0
Increased shortness of breath	0	0
Vein graft thrombosis/ occlusion	9 (7.2) [0.082]	11 (8.8) [0.100]
Fitzgibbon class B and O	2 (1.6) [0.018]	3 (2.4) [0.027]

Values are n (%) [number of events per patient-year]
†Death, myocardial infarction, or repeat revascularization.
‡Composite of all adverse events
*Perrault et al., JTCVS 2019

MDCT analysis revealed that there was no significant difference between the DuraGraft group and the saline group in terms of change in mean wall thickness between 1 and 3 months in the analysis of whole grafts. However, at 12 months, DuraGraft treated SVGs had smaller mean wall thickness versus their saline-treated counterparts 0.12±0.06 mm vs 0.20±0.31 mm (Figure 1) and the change in maximal focal narrowing 0.2 ± 3.8 mm versus 4.7 ± 12.7 mm (Figure 2).

Figure 1: Wall thickness analysis by MDCT for whole graft

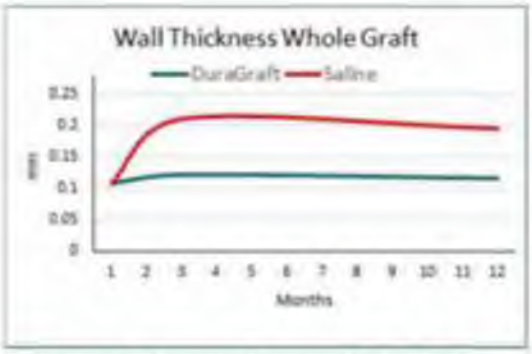

Figure 2: Maximum Focal Narrowing analysis by MDCT for whole graft

DuraGraft EU Registry

The DuraGraft EU Registry[5] is an ongoing European post-market study designed to support an international CABG registry database used to assess patients receiving DuraGraft during CABG surgery and whose free vascular grafts (4,454 venous grafts and 586 arterial conduits) have been treated with DuraGraft. A total of 2,964 patients were enrolled in the Registry, which enrolled patients between December 2016 and August 2019. There were 45 enrolling centers in eight countries: Austria, Germany, Ireland, Italy, Spain, Switzerland, Turkey and United Kingdom. Follow-up data has been completed out to one (1) year and will continue for up to five (5) years.

The subjects have an average age of 67.8 ±9.2 years (range 33 - 90 years). The majority of subjects were males (82.3%, 2438/2964) and were Caucasian (88.3%, n=2610/2956). The majority of subjects had a history of hypertension 84.4% (2486/2946), dyslipidemia 76.9% (2251/2929), and diabetes was present in 43.7% (1294/2962). The overall mean EuroSCORE II (ESII) for all patients is 2.6 ± 3.7 (n=2964). For CABG only patients (n=2532), the mean score is 2.3 ± 3.4 and for CABG +valve patients (n=432) is 4.3 ± 5.0.

Results:

In the total study population, 120 (4.1%) patients experienced a MACE at 30 days and 7.4% at 1 year. The 30-day incidence of death, myocardial infarction and repeat revascularization was 2.7%, 1.6% and 1.1%, respectively for all patients, isolated CABG and CABG + valve cohorts and at 1 year was 5.2%, 2.2% and 2.1%, respectively. In the total population, 2.3% of the patients experienced a stroke at 1 year. The 1-year all-cause death rate was 5.2% (148/2964). 30-day and 1-year Kaplan Meir rates for MACE are given in Table 4.

In the isolated CABG group, the 30-day MACE rate was 3.5% with all-cause death (2.3%), myocardial infarction (1.3%), and repeat revascularization (1.0%). The 1-year MACE rate was 6.6% with all-cause death (4.4%), myocardial infarction (2.0%), and repeat revascularization (2.2%).

The 30-day MACE rate for the combined CABG + valve groups was 7.5% with rates of death 5.4%, myocardial infarction 3.1% and repeat revascularization 0.7%. The 1-year MACE rate was 12.0% with rates of death 9.9%, myocardial infarction 3.3% and repeat revascularization 1.3% Cumulative incidence of primary endpoints and incidents are shown in Figure 3.

Table 4. 30-Day and 1-Year Kaplan Meier rates for MACE

	All patients (n=2964)		**Isolated CABG (n=2532)**		**CABG and valve (n=432)**	
	% (No. of events)		*% (No. of events)*		*% (No. of events)*	
	30 days	1 year	30 days	1 year	30 days	1 year
MACE	4.1% (120)	7.4% (210)	3.5% (88)	6.6% (160)	7.5% (32)	12.0% (50)
MACCE	5.2% (153)	8.6% (247)	4.6% (115)	7.8% (190)	8.9% (38)	13.6% (57)
All-Cause Death	2.7% (80)	5.2% (148)	2.3% (57)	4.4% (107)	5.4% (23)	9.9% (41)
Cardiovascular Death	2.7% (80)	4.5% (130)	2.3% (57)	3.8% (92)	5.4% (23)	9.1% (38)
Myocardial Infarction	1.6% (46)	2.2% (63)	1.3% (33)	2.0% (49)	3.1% (13)	3.3% (14)
All Repeat Revascularization	1.1% (31)	2.1% (58)	1.1% (28)	2.2% (53)	0.7% (3)	1.3% (5)
PCI	0.8% (22)	1.8% (48)	0.8% (21)	1.9% (45)	0.2% (1)	0.8% (3)
Re-CABG	0.3% (9)	0.3% (10)	0.3% (7)	0.3% (8)	0.5% (2)	0.5% (2)
Stroke	1.7% (50)	2.3% (65)	1.5% (37)	1.9% (46)	3.1% (13)	4.6% (19)

*Percentages indicate cumulative event rates by Kaplan Meier estimates.

**MACE: major adverse cardiac events; MACCE: major adverse cardiac and cerebrovascular events; PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting.

Figure 3: Cumulative incidence of Primary endpoints and components

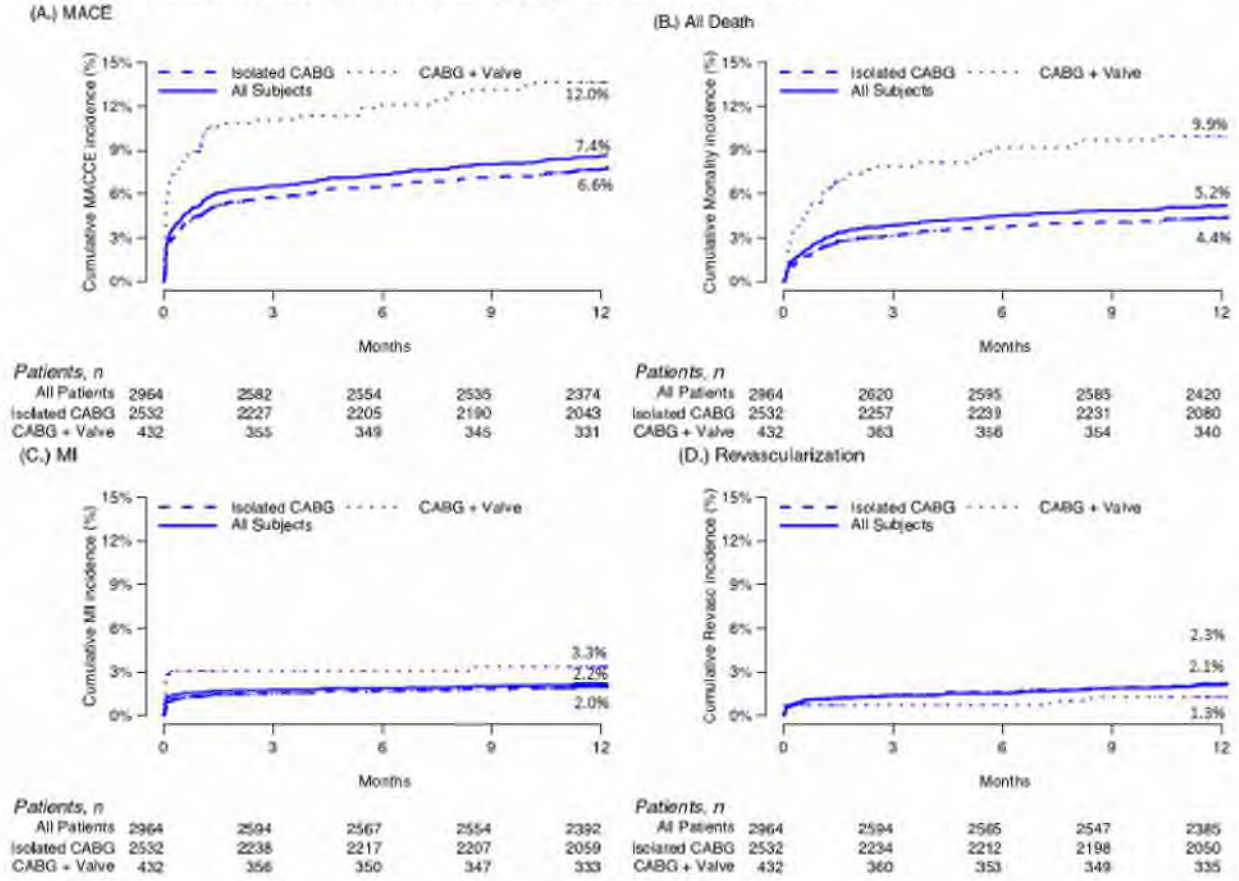

Figure 3: Cumulative incidence of (A) the primary outcome; Major Adverse Cardiac Events (MACE); and the individual components of the primary outcome (B) all-cause death; (C) myocardial infarction; (D) repeat revascularization, at 1 year.

Propensity Matched Comparison of DuraGraft EU Registry to STS Registry

To compare mortality of patients in the single arm DuraGraft Registry, the Society of Thoracic Surgery (STS) Database was identified and determined suitable for use as a contemporaneous control. 2532 patients underwent isolated CABG surgery in the DuraGraft Registry between December 2016 and August 2019. 294,725 isolated CABG patients were identified in the STS Registry who were operated on between 2016 and 2018 and had at least 1 year mortality data available from linkage to the US National Death Index (NDI), a database maintained by the National Center for Health Statistics (NCHS), which captures all death records for the US and US territories. An analysis was conducted comparing Isolated CABG patients from the DuraGraft Registry to a propensity matched control group from the STS Registry Adult Cardiac Surgery Database. 2400/2532 patients were matched from the DuraGraft cohort to 2400 patients in the STS Database, matching on the following 35 prespecified variables, selected to be predictive of mortality risk in the operative, peri-operative, and follow-up periods.

Demographics

1. Age
2. Male sex
3. Black race

Cardiac Risk Factors

4. BMI < 20 kg/m^2
5. Previous or current smoker
6. Diabetes on insulin
7. Diabetes not on insulin
8. CRF (Cr > 2.0 mg/dl)
9. Renal dialysis
10. Peripheral vascular disease
11. Pulmonary hypertension
12. History of pulmonary disease
13. History of CVA

Pre-Operative Cardiac Status

14. MI ≤ 24h
15. MI > 24h
16. Unstable angina
17. Congestive heart failure
18. Cardiogenic shock
19. Pre-operative atrial fibrillation
20. Re-operation
21. Left ventricular function (EF<30%)
22. Status urgent
23. Status emergent

Coronary Anatomy

24. Left main stem coronary artery stenosis ≥ 50%
25. Three (3) vessel disease
26. Previous CABG
27. Previous PCI

Surgical Technique

28. Number of distal anastomoses
29. On pump status
30. Presence of LIMA graft
31. Number of arterial grafts
32. Number of venous grafts
33. All arterial grafts
34. All venous grafts
35. Harvesting technique - endoscopic

Results:

The cumulative incidence of mortality through 36 months of follow up in the 2,400 propensity matched DuraGraft and STS registry subjects is presented as Kaplan Meier estimates in Figure 4 And Table 5. At 30 days and 12 months the mortality estimate in DuraGraft was 2.38% [95% CI, 1.84% - 3.07%] and 4.32% [CI, 3.58% - 5.22%] compared to the STS Registry patients 1.96% [95% CI 1.47% - 2.60%] and 4.79% [95% CI 4.01% - 5.72%], respectively. At 36 months the

mortality estimate in DuraGraft patients was reduced compared to the STS Registry patients (7.37% [95% CI, 6.36% - 8.53%] vs. 9.65% [95% CI 8.37% - 11.10%]).

Figure 4. Kaplan Meier estimates of all-cause mortality through 36 months in 2400 DuraGraft patients and Kaplan Meier estimates of all-cause mortality through 36 months in 2400 Propensity Matched STS patients

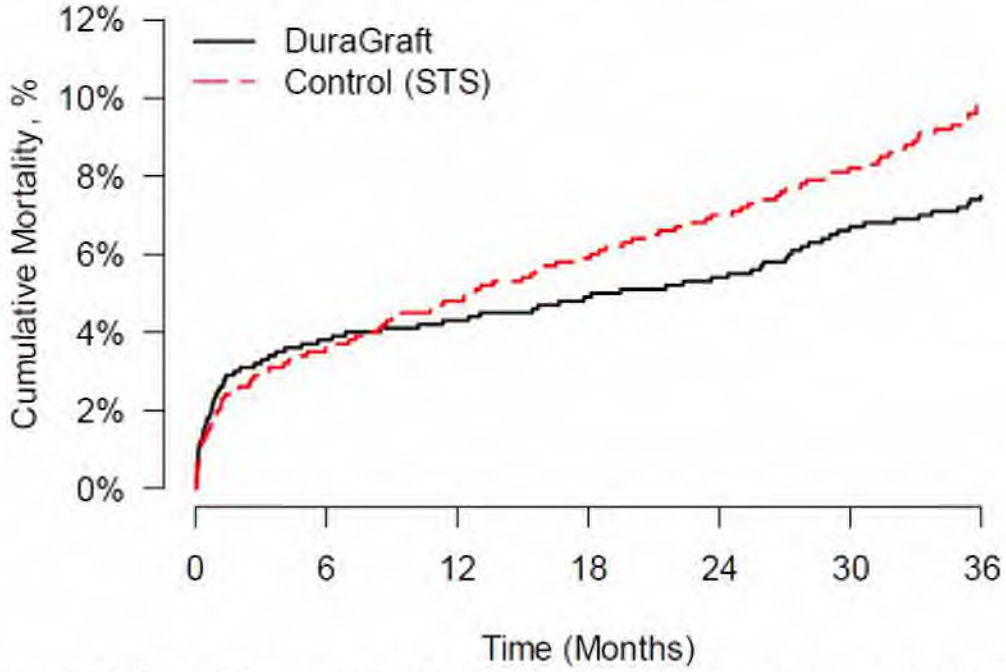

Table 5. Kaplan Meier estimates of all-cause mortality through 36 months in 2400 DuraGraft patients that were Propensity Matched to STS patients. Product Limit (PL) Estimates.

	DuraGraft				STS Registry			
Time Points (days)	*Number at Risk*	*Number Failed*	*Survival Estimate*	*Standard Error*	*Number at Risk*	*Number Failed*	*Survival Estimate*	*Standard Error*
0	2400	1	99.96%	0.04%	2400	1	99.96%	0.04%
30	2341	57	97.62%	0.31%	2353	47	98.04%	0.28%
180	2264	90	96.23%	0.39%	2316	84	96.50%	0.38%
365	2209	103	95.68%	0.42%	2285	115	95.21%	0.44%
725	2024	126	94.63%	0.47%	1552	160	93.04%	0.53%
1085	1729	166	92.63%	0.55%	798	194	90.35%	0.69%

Clinical Outcomes for DuraGraft Registry vs Published Literature

The sponsor conducted a literature review of published registries to gain further perspective on the observed outcomes in the single-arm DuraGraft Registry. Outcomes evaluated at 30 days and 1 year included all-cause mortality and the components of MACE versus the published literature using EuroSCORE II values for comparison. Values are presented in the table when reported in each study.

Mortality data for the DuraGraft Registry is comparable to contemporary registry studies, which reported 30-day and/or in-hospital mortality for patients undergoing isolated CABG surgery as seen in Table 6. The 30-day death rate was 2.3% in the DuraGraft Registry and ranged from 1.1% in Bangalore et al[6] to 3.2% in Adelborg et al[7]. It is notable that the comparative registries mostly reported in-hospital mortality. One-year mortality in real world registry studies ranged from 4.8% in the MAIN COMPARE[8] registry to 10.5% in Biancari et al[9], compared to 4.5% in the DuraGraft Registry.

Table 6. 30-Day and 1-Year Comparative MACE Event Rates in Patients Receiving Isolated CABG Surgery – Registry Studies

	European Registries						Non-European Registries		
Study	**DuraGraft Registry**	**Paparella (2014)[10]**	**Biancari (2012)[9]**	**Kieser (2016)[11]**	**Adelborg (2017)[7]**	**Beckman (2019)[12]**	**Bangalore (2015)[6]**	**MAIN-COMPARE (2008)[8]**	**Puskas (2012)[13]**
Number of CABG patients	2,544	2,605	1,027	1,125	47,415	34,224	9,223	542	20,014
EuroSCORE (II)	2.3% ± 3.4		4.5% ± 6.7	1.5%					
Syntax score									
30 days or In-Hospital	**30 days**	**In-hospital**	**30 days**	**In-hospital**	**30 days**	**In hospital**	**30 days + in-hospital**		**30 days**
Death	2.3%	3%	3.7%	3.2%	3.2%	2.7% (3% OPCAB)	1.1%		2.1%
Cardiac death	2.3%				1.4%				
Non cardiovascular	0.0%								
MI	1.3%						0.4%		
Revascularizations	1.3%								
Stroke	1.5%		2.4%				1.2%		
1 year	**1 year**		**1 year**		**1 year**			**1 year**	**1 year**
Death	4.5%		10.5%		6.0%			4.8%	5.4%
MI	2.1%								
Revascularizations	2.5%							1.5%	
Stroke	2.1%								

Pediatric Extrapolation

In this De Novo request, existing clinical data were not leveraged to support the use of the device in a pediatric patient population.

References

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[11] Kieser, Teresa M., M. Sarah Rose, and Stuart J. Head. "Comparison of logistic EuroSCORE and EuroSCORE II in predicting operative mortality of 1125 total arterial operations." European Journal of Cardio-Thoracic Surgery 50.3 (2016): 509-518.
[12] Beckmann, Andreas, et al. "German heart surgery report 2018: the annual updated registry of the German Society for Thoracic and Cardiovascular Surgery." The Thoracic and cardiovascular surgeon 67.05 (2019): 331-344.
[13] Puskas, John D., et al. "The society of thoracic surgeons 30-day predicted risk of mortality score also predicts long-term survival." The Annals of thoracic surgery 93.1 (2012): 26-35.

LABELING

The sponsor provided labeling that included the instructions for use and package labels. The labeling includes instructions intended to minimize the risk of improper use of the DuraGraft device. The labeling also includes a summary of the non-clinical and clinical performance testing that supports use of the device as a flushing and storage solution for vascular autografts.

Important components of the labeling include:

A description of the intended patient population, age, and condition. DuraGraft is indicated for adult patients undergoing Coronary Artery Bypass Grafting Surgeries and is intended for flushing and storage of the saphenous vein grafts.

Saphenous vein grafts may be stored in DuraGraft for up to 4 hours.

DuraGraft Vascular Conduit Solution includes a component, L-arginine. L-arginine may cause an allergic reaction in certain patients.

DuraGraft is not intended for direct injection or intravenous infusion.

Prior to use, each container should be checked for leaks and particulate matter. If a leak, particulate matter, precipitates, or contamination are evident in the solution, the product should be discarded.

The re-use of this product is hazardous to patient safety and may cause serious infections from contamination of opened product, leading to serious injury or death.

RISKS TO HEALTH

The table below identifies the risks to health that may be associated with use of the flushing and storage solution for vascular autografts at room temperature and the measures necessary to mitigate these risks.

Risks to Health	Mitigation Measures
Adverse tissue reaction	Biocompatibility evaluation
Damage to vascular grafts leading to major adverse cardiac events or vascular injury	Clinical performance data Non-clinical performance testing Shelf life testing Labeling
Particulate matter contamination leading to vascular occlusion, coronary artery embolization and occlusion, phlebitis, infarction, and death	Clinical performance data Non-clinical performance testing Shelf life testing Labeling
Infection	Sterilization validation

SPECIAL CONTROLS

In combination with the general controls of the FD&C Act, the flushing and storage solution for vascular autografts at room temperature is subject to the following special controls:

(1) Clinical data must evaluate adverse events associated with clinical use of the device. Devices indicated for vascular grafts for coronary artery bypass graft surgeries must include an evaluation of the incidence of major adverse cardiac events, vein graft occlusion, and mortality.
(2) Non-clinical performance testing must demonstrate that the device performs as intended under anticipated conditions of use. The following performance characteristics must be tested:
    (i) Maintenance of cell viability and structural integrity of vascular conduits during storage at the labeled temperature and storage duration; and
    (ii) Evaluation of visible and non-visible particulates in the final mixed solution.
(3) Shelf life testing must demonstrate the stability of the device's chemical components over the identified shelf life.
(4) The device must be demonstrated to be biocompatible.
(5) Performance data must demonstrate the sterility of the device.
(6) Labeling must include:
    (i) The maximum storage duration for vascular autografts in the solution;
    (ii) A description of all additives or supplements that are added at the point of care;
    (iii) The need for visual inspection of the solution for particulate matter prior to use;

(iv) A statement regarding the duration of stability of the final solution after preparation;
(v) A summary of the non-clinical performance testing that supports use of the device as a flushing and storage solution for vascular autografts; and
(vi) A summary of the clinical data that supports use of the device as a flushing and storage solution for vascular autografts.

BENEFIT-RISK DETERMINATION

The risks to health of a flushing and storage solution for vascular autografts can generally include adverse tissue reaction, damage to the vascular graft leading to major adverse cardiac events or vascular injury, and clinical risk of particulate matter contamination including vascular occlusion, coronary artery embolization and occlusion, phlebitis, infarction, and death. However, there is no evidence from the preclinical and clinical studies of any adverse events related to the DuraGraft Vascular Conduit Solution. The preclinical and clinical testing for the DuraGraft Vascular Conduit Solution demonstrated that these risks are adequately mitigated by biocompatibility testing, non-clinical performance testing, and clinical performance testing. The device safety is supported by data collected in the clinical studies described above. The sponsor provided short-term and follow-up data up to 1 year from an ongoing all-comers European prospective registry of patients who received DuraGraft-treated vascular grafts as a post-approval study for CE Mark in Europe. A total of 2,964 patients were enrolled in the Registry, between December 2016 and August 2019, at 45 centers in eight countries. Following a comprehensive review of the literature, the sponsor compared Major Adverse Cardiac Events (MACE) and the individual components that make up MACE (e.g., death, myocardial infarction and repeat MI) from the registry to contemporary literature derived from trials of CABG surgery. The 30-day death rate was 2.3% in the DuraGraft Registry and ranged from 1.1% to 3.2% in the cited references. The observed mortality of 4.5% at one year is comparable to rates reported in multiple clinical trials, which range from 2.7% to 7.5%. In the isolated CABG registry, the 30 day and 1-year all-cause mortality are within the range of what has been reported in the literature for comparable patient populations. The incidence for myocardial infarction and revascularization were also within the same range. The DuraGraft Registry includes 2,522 patients who underwent Isolated CABG surgery. An additional comparison was made to select propensity matched cohorts of patients from the STS database and evaluate all-cause mortality between the matched cohorts at 30 days, 1 year, and 3 years of follow-up.

The review of these clinical studies is supportive of the device safety; however, there is no clear clinical evidence that the device is more effective compared to the standard of care. In a prospective randomized self-control study, the sponsor demonstrated favorable effects related to the use of DuraGraft on saphenous vein wall thickness compared to standard of care. A radiographic assessment of the saphenous vein grafts at 12 months by multidetector computed tomography (MDCT) evaluation showed reduced wall thickness in DuraGraft-treated saphenous vein grafts compared to standard of care treated saphenous vein grafts. However, there is no evidence that this biomarker can serve as a surrogate for long term vein graft patency.

The probable benefits of the device are based on nonclinical laboratory studies described above to support the device use as a flushing and storage solution for saphenous vein grafts at room

temperature for up to 4 hours. Non-clinical performance testing demonstrated that human saphenous vein segments and pig mammary vein segments that were flushed and stored in DuraGraft for time points ranging from 15 minutes to 24 hours exhibited increased graft cell viability and improved maintenance of graft endothelial morphology compared to vein segments that were stored in normal saline solution.
Additionally, as there is no alternative legally marketed solution for the short-term flushing and storage of saphenous vein grafts during CABG surgery, the device addresses an unmet need.

Patient Perspectives

This submission did not include specific information on patient perspectives for this device.

Benefit/Risk Conclusion

In conclusion, given the available information above, for the following indication statement:

> DuraGraft Vascular Conduit Solution is a solution indicated for adult patients undergoing Coronary Artery Bypass Grafting Surgeries and is intended for flushing and storage of the saphenous vein grafts from harvesting through grafting for up to 4 hours.

The probable benefits outweigh the probable risks for the DuraGraft Vascular Conduit Solution device. The device provides benefits and the risks can be mitigated by the use of general controls and the identified special controls.

CONCLUSION

The De Novo request for DuraGraft Vascular Conduit Solution is granted and the device is classified as follows:

> Product Code: QEJ
> Device Type: Flushing and storage solution for vascular autografts at room temperature
> Regulation Number: 21 CFR 876.4100
> Class: II