Proposed Package Insert (10-21-07)

Caution: Federal law restricts this device to sale by or on the order of a physician (or properly licensed practitioner (Rx ONLY)

PRODUCT DESCRIPTION

REPEL-CV®Bioresorbable Adhesion Barrier is a sterile, single use, synthetic, bioresorbable polymeric clear film designed to act as a barrier for reducing the severity of post-operative cardiac adhesions. REPEL-CV is composed of poly-lactic acid (PLA) and polyethylene glycol (PEG), components used extensively in implantable, absorbable medical devices. REPEL-CV has a faint caramel-like aroma.

INDICATIONS

REPEL-CV Bioresorbable Adhesion Barrier (hereinafter called REPEL-CV) is indicated for reducing the severity of post-operative cardiac adhesions in pediatric patients who are likely to require reoperation via sternotomy.

PRECAUTIONS

1. As with other surgically implanted foreign material, REPEL-CV should not be used where contamination or infection of the operative field is suspected.
2. The safety and effectiveness of REPEL-CV has not been established for coverage of large prosthetic surfaces such as ventricular assist devices and vascular replacement grafts.
3. Do not use if pouch is damaged or opened prior to use.
4. Single use only.
5. Do not resterilize.

ADVERSE EVENTS

In a multi-center, randomized, evaluator-masked, parallel comparative study to evaluate the safety and effectiveness of REPEL-CV, safety was evaluated in 142 pediatric cardiovascular surgery patients requiring staged median sternotomy procedures for surgical corrections of congenital heart malformations. The primary inclusion criterion was patients requiring two staged cardiovascular sternotomy procedures. Table 1 lists the Adverse Events for the REPEL-CV treated and Control groups where the frequency of occurrence was ≥ 2%. The results are similar between the two treatment groups and representative of adverse events expected for this high-risk patient population.

Table 1. Adverse Events ≥ 2% by Descending Frequency*

		REPEL-CV (N=73)	Control (N=69)
MedDRA Preferred Term		N (%)	N (%)
	Cardio-Respiratory Arrest	4 (5.5%)	2 (2.9%)
	Pleural Effusion	4 (5.5%)	3 (4.3%)
	Wound Dehiscence (superficial)	4 (5.5%)	3 (4.3%)

		REPEL-CV (N=73)	Control (N=69)
MedDRA Preferred Term		N (%)	N (%)
	Wound Infection (superficial)	4 (5.5%)	3 (4.3%)
	Ascites	3 (4.1%)	0
	Cardiac Arrest	3 (4.1%)	4 (5.8%)
	Bronchiolitis	3 (4.1%)	0
	Cardiac Output Decreased	3 (4.1%)	1 (1.4%)
	Hypoxia	3 (4.1%)	2 (2.9%)
	Pulmonary Artery Stenosis	3 (4.1%)	1 (1.4%)
	Mediastinitis(prior to 2nd sternotomy)	2 (2.7%)	1 (1.4%)
	Mediastinitis (after 2nd sternotomy)	2 (3.6%)	0
	Cyanosis	2 (2.7%)	1 (1.4%)
	Coarctation of the Aorta	2 (2.7%)	3 (4.3%)
	Necrotising Colitis	2 (2.7%)	3 (4.3%)
	Bacteraemia	2 (2.7%)	2 (2.9%)
	Respiratory Syncytial Virus Infection	2 (2.7%)	0
	Convulsion	2 (2.7%)	7 (10.1%)
	Atelectasis	2 (2.7%)	0
	Diaphragmatic Paralysis	2 (2.7%)	1 (1.4%)
	Respiratory Distress	2 (2.7%)	3 (4.3%)
	Haemodynamic Instability	2 (2.7%)	0
	Hypotension	2 (2.7%)	0
	Pyrexia	1 (1.4%)	2 (2.9%)
	Gastroenteritis	1 (1.4%)	2 (2.9%)
	Oxygen Saturation Decreased	1 (1.4%)	7 (10.1%)
	Chylothorax	1 (1.4%)	2 (2.9%)

*For AEs with frequency ≥ 2% and for which frequency of REPEL-CV's AE was not 0%

In considering all adverse events, the average number of adverse events on a per patient basis was similar between the treatment groups.

CLINICAL STUDY

U.S. Multi-Center Study

SyntheMed sponsored three feasibility/pilot clinical studies and one pivotal clinical study to evaluate the safety and effectiveness of REPEL-CV. Three studies were conducted in the United States under IDE G980030 and one study was performed in Europe to support the CE Mark. Table 2 includes a list of the clinical studies.

Table 2. Summary of Clinical Trials

Name	N	Description
Study 1. A Comparative, Evaluator-Blinded, Randomized, Parallel Study to Determine the Safety of REPEL-CV™ for Reducing Post-Operative Adhesions Following Adult Cardiothoracic Surgery (Protocol # LMS9802RCV)	15 REPEL-CV 12 Control	Safety study in adult patients undergoing CABG, Valvular and LVAD procedures
Study 2. A Comparative, Evaluator-Blinded, Randomized, Parallel Study to Determine the Safety and Effectiveness of REPEL-CV™ for Reducing Post-Operative Adhesions Following Pediatric Cardiothoracic Surgery (Protocol # LMS0001RCVP)	7 REPEL-CV 6 Control	Safety and effectiveness study in pediatric patients undergoing staged cardiac surgical procedures to correct congenital cardiac malformations
Study 3. Open Label, Multicenter Study to Determine the Effectiveness of REPEL-CV™ for Reducing Post-Operative Adhesions Following Pediatric Cardiothoracic Surgery (Protocol # LMS0104RCV)	19 REPEL-CV	Open safety and effectiveness study in pediatric patients undergoing staged cardiac surgical procedures to correct congenital cardiac malformations
Study 4. A Comparative, Evaluator-Masked, Randomized, Parallel, Multicenter Study to Determine the Safety and Effectiveness of REPEL-CV™ for Reducing Post-Operative Adhesions Following Pediatric Cardiothoracic Surgery (Protocol # LMS0103RCV)	73 REPEL-CV 71 Control	Safety and effectiveness pivotal study in pediatric patients undergoing staged cardiac surgical procedures to correct congenital cardiac malformations

Feasibility Studies

Study 1

This study was conducted in 1998 as a randomized trial and included adult patients. Although designed as a feasibility study for safety, assessment of adhesion extent at the time of re-explorative cardiac surgery was also conducted by a masked evaluator. Twenty-seven (27) patients were randomized who underwent a coronary artery bypass graft (CABG) operation (9 REPEL-CV, 11 Control), valve operations (4 REPEL-CV, 1 Control), and 2 cases (REPEL-CV) of left ventricular assist devices (LVADs) implanted for bridging to transplant. One of the patients with an LVAD suffered from coagulopathy, noted as possibly related to the device.

Study 2

This randomized study focused on the determination of safety and effectiveness of REPEL-CV for reducing post-operative adhesions in pediatric patients with an age range of 3-7 days. There were seven patients that received REPEL-CV and six were in the Control group. Of the seven patients who completed the study, three received the REPEL-CV. While the differences between the adhesion results for the patients were not significant for the sample size, there was a suggestion of effectiveness that prompted the sponsor to conduct a pivotal and European study.

Study 3

This study was an Open Label, European, single arm study that enrolled 19 REPEL-CV patients undergoing staged congenital cardiac procedures in a multi-center trial. The effectiveness endpoints were the percent of patients with any Grade 3 (severe) adhesions and the patient-specific percentage of the study-defined surface area of the investigational surgical site with Grade 3 adhesions at the time of the 2nd sternotomy.

Of the 19 patients enrolled, 15 completed the study and all were treated with REPEL-CV.

The mean age for these patients was 12.9 days, with a range of 4-54 days. A mean of 10% of the investigational surgical sites in 15 patients had Grade 0 adhesions, 60% had grade 1, 20% had grade 2, and 11% had grade 3 adhesions at re-exploration.

Pivotal Study – Study 4

Objectives. The objectives of this pivotal study were to evaluate the safety and effectiveness of REPEL-CV in its ability to reduce the severity and extent of post-operative adhesions following pediatric cardiovascular surgery. These objectives were based on feasibility experiences which demonstrated preliminary safety and effectiveness.

Study Design

This was a multi-center, randomized, evaluator-masked, parallel, comparative study to evaluate the safety and effectiveness of REPEL-CV in its ability to reduce the severity and extent of post-operative adhesions following pediatric cardiovascular surgery. Pediatric patients from 15 United States study sites, fulfilling the inclusion criteria and having none of the exclusion criteria, were enrolled into the study after their legal representative (guardian) had signed the informed consent form. Upon enrollment, but prior to surgery, patients underwent the required screening evaluations including clinical laboratory tests (hematology and chemistry).

Primary Safety Endpoint

Safety was assessed by comparing the type, severity, relationship, and timing of adverse experiences (including death) for each REPEL-CV group in the safety population.

Primary Effectiveness Endpoint

The primary effectiveness endpoint was the percent of the study-defined investigational surgical site (ISS) with severe (Grade 3) adhesions at the second sternotomy procedure. The same scale used in Study 3 was used for the pivotal study:

Grade 0 = **No** adhesions

Grade 1 = **Mild** Adhesions (filmy, non-cohesive adhesions requiring blunt dissection to separate the space between the epicardium and sternum)

Grade 2 = **Moderate** adhesions (filmy, non-cohesive adhesions requiring a combination of blunt and selective sharp dissection to separate the space between the epicardium and the sternum)

Grade 3 = **Severe** adhesions (dense, cohesive adhesions requiring extensive sharp dissection to separate the space between the epicardium and the sternum)

Demographic Data

Patients were randomized at 15 study sites. Table 3 summarizes the patient disposition by treatment group and includes the reasons for withdrawal. Standardized reasons for withdrawal were used to impose consistency across investigator sites. The control treatment group had two protocol violations and these subjects were discontinued from the study. These two patients were randomized but not treated as per the protocol.

Table 3. Patient Disposition

	REPEL-CV	Non-Treatment Control
Randomized	73	71
Safety Population***	73 (100%)	69 (97.2%)
Evaluable Population*	56 (76.7%)	54 (76.1%)
Did not undergo the planned second sternotomy	17 (23.3%)	17 (23.9%)
PP Population**	54 (74.0%)	49 (69.0%)
Second sternotomy within 2 months of randomization	2 (2.7%)	5 (7.0%)
Discontinued (withdrawn) Reclassified[a]	20	18
Adverse events	19	16
Protocol Violation	0	2
Withdrew Consent	1	1
Other	0	0

* Evaluable population includes patients who underwent the adhesion evaluations at the time of the planned second sternotomy.

** PP population includes patients who had the 2nd sternotomy at least 2 months after randomization, underwent the adhesion evaluations, and had no major protocol violations.

*** Safety population includes all randomized and treated patients

[a] Investigator reasons for early study withdrawal were reclassified to establish consistency across responses. The study investigator indicated that patient who received study control, completed the study because the second sternotomy was performed and efficacy evaluations were completed. The investigator also indicated a reason for early withdrawal (adverse event) due to the patient's death following the procedure.

The demographic variables for the evaluable population are summarized in Table 4. The evaluable patients are the population used to conduct the data analysis of the primary and secondary endpoints. The safety population is used for the safety endpoint. The majority of the patients were Caucasian or African American. Patients in the REPEL-CV treatment group were slightly smaller than those in the control group, although the difference was not clinically relevant. In addition, fewer patients in the REPEL-CV group experienced use of Heart-Lung Bypass.

Table 4. Demographics – Study 4

	REPEL-CV	Non-Treatment Control
	N=56	N=54
Age (days)		
Mean ± SD	13.6 ± 15.8	11.4 ± 9.0
Median	9.0	9.0
Range	2.0 - 93.0	2.0 -63.0
Gender		
Male	31 (55.4%)	38 (70.4%)
Female	25 (44.6%)	16 (29.6%)
Race		
Caucasian	34 (60.7%)	33 (61.0%)
African American	15 (26.8%)	9 (16.7%)
Hispanic	6 (10.7%)	6 (11.1%)
Asian	0 (0.0%)	3 (5.6%)
Other	1(1.8%)	3 (5.6%)
Height (cm)		
Mean ± SD	46.6 ± 7.7	49.9 ± 2.5
Median	48.0	50.0
Range	18.0 – 55.0	44.0 – 57.0
Weight (kg)		
Mean ± SD	3.0 ± 0.5	3.3 ± 0.5
Median	3.0	3.4
Range	2.1 – 4.5	2.5 – 4.6
Procedure Type		
Norwood	38 (67.9%)	43 (79.6%)
Non-Norwood	18 (32.1%)	11 (20.4%)
Use of Heart-Lung Bypass Machine		
Yes	45 (80.4%)	51 (94.4%)
No	11 (19.6%)	3 (5.6%)
Chest Closure Delay		
Delay	40 (71.4%)	43 (79.6%)
No Delay	16 (28.6%)	11 (20.4%)

*These data represent the evaluable patients.

Data Analysis and Results for Safety

In addition to the adverse event data presented earlier, Table 5 summarizes the adverse events and death. No differences in adverse events occurring post-randomization between the REPEL-CV and the non-treatment control group were detected.

Table 5. Summary of Adverse Events and Death – Safety Population

	REPEL-CV (n=73)		Control (n=69)	
	Patients	Events	Patients	Events
Number of Patients (percent) With at Least One Adverse Event	51 (69.9%)	135	49 (71.0%)	123
Possibly, Probably or Definitely Treatment Related Adverse Events	6 (8.2%)	6	1 (1.4%)	1
Number of Patients (percent) With at Least One Serious Adverse Events	37 (50.7%)	63	32 (46.4%)	53
Number of Possibly, Probably or Definitely Treatment Related Serious Adverse Events	4 (5.5%)	4	0	0
Number (percent) of Deaths (following the 1st and 2nd sternotomies)	12 (16.4%)	-	9 (13.0%)	-

Deaths and Other Serious Adverse Events

Table 6 summarizes the overall death rate. The death rate following the first sternotomy was 12.3% (9/73) for REPEL-CV vs. 10.1% (7/69) for Control. The overall death rate was 16.4% (12/73) for REPEL-CV vs. 13.0% (9/69) for Control with the inclusion of three REPEL-CV deaths and two Control deaths following the second sternotomy.

Table 6. Death Rates for Each Treatment Group*

	REPEL-CV	**Control**
Overall	16.4% (12/73)	13.0% (9/69)
95% CI (REPEL-CV - Control)	(-8.7%, 15.4%)	

*These data represent the evaluable patient population.

The distribution of adverse events and death between the REPEL-CV and control groups was similar. The adverse event profiles and death in both treatment groups were expected and consistent with the surgical procedures and clinical condition of this study population.

Data Analysis and Results for Primary Effectiveness Endpoint

The results presented are for the primary clinical endpoint: mean percent of the investigational surgical site (area) with Grade 3 (severe) adhesions. These data are shown in Table 7 for the evaluable population.

Table 7. Investigational Surgical Site Adhesion Assessments at Visit 3*

Extent of Severity (% Area)		REPEL-CV (N=56)	Control (N=54)	p-value**
% Area with Grade 3 (Severe) Adhesion	**Mean ± SD**	**21.3 ± 36.5**	**47.3 ± 42.7**	**0.0008**
	Median	**0.0**	**35.0**	**0.0001**
% Area with Grade 2 (Moderate) Adhesion	Mean ± SD	44.8 ± 36.3	35.5 ± 35.4	
	Median	45.0	25.0	
% Area with Grade 1(Mild) Adhesion	Mean ± SD	31.0 ± 35.8	16.2 ± 26.8	
	Median	20.0	0.0	
% Area with Grade 0 (No) Adhesion	Mean ± SD	2.9 ± 13.8	0.9	
	Median	0.0	0.0	

*These data represent the evaluable patient population.
**A t-test was used to compare treatment means and the Wilcoxon rank sum test for the medians

The mean percent of the study-defined surface area with severe (Grade 3) adhesions at the time of the second surgery was 21.3% for REPEL-CV (n= 56) and 47.3% for Control (n= 54; p=0.0008 for the mean and p=0.0001 for the median).

HOW SUPPLIED

REPEL-CV is supplied as a sterile, single use only.
The 18 cm x 13.5 cm x 137 microns film is packaged in a sterile foil pouch.

STORAGE CONDITIONS

REPEL-CV is to be refrigerated between 2-8 degrees Centigrade.

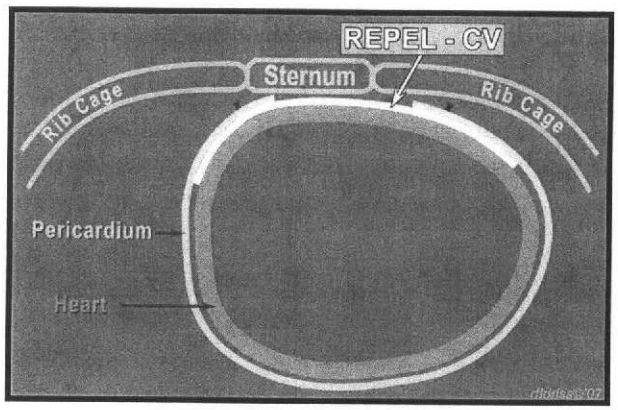
DIRECTIONS FOR USE - Preparation and Application of REPEL-CV

1. Trim REPEL-CV to the desired size. The material should extend at least 1.5 cm laterally beyond the pericardial edges between the pericardium and the heart to facilitate suturing to the pericardium. If desired, the material should extend further to cover the surface where intrapericardial adhesion protection is desired

2. Soak REPEL-CV for approximately two (2) minutes but no longer than five (5) minutes in Ringer's lactate or saline solution prior to placement

3. Remove all irrigation fluids and instillates from the pericardial cavity

4. Just prior to chest closure, apply REPEL-CV to fit between the pericardial edges and between the pericardium and the heart, and suture it to the pericardium using 4-0 or larger suture with a tapered needle, 2 to 3 tack sutures per edge (see diagram below).



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