

Summary of Safety and Effectiveness

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CardioSEAL? STARFlex? Septal Occlusion System with Qwik Load?

SUMMARY OF SAFETY AND EFFECTIVENESS

1. GENERAL INFORMATION

Device Generic Name: Transcatheter Cardiac Occlusion Device

Device Trade Name: CardioSEAL? STARFlex? Septal Occlusion System with Qwik Load

Applicant's Name and Address: NMT Medical, Inc.
27 Wormwood Street
Boston, Mass. 02210

PMA Application Number: P000049/S3

Date of Panel Recommendation: [FDA to complete]

Date of Good Manufacturing Practices Inspection: March 27-28, 2001

Date of Notice to the applicant: [FDA to complete]

2. INDICATIONS FOR USE

The CardioSEAL STARFlex Septal Occlusion System with QwikLoad is indicated for closure of patent foramen ovale (PFO) in patients at risk for a recurrent cryptogenic stroke or transient ischemic attack (TIA) due to presumed paradoxical embolism through a PFO and, who are poor candidates for surgery or conventional drug therapy.

3. DEVICE DESCRIPTION

The CardioSEAL STARFlex Septal Occlusion System with Qwik Load consists of a permanent implant, referred to as STARFlex, and a delivery catheter. The STARFlex is constructed of a metal (MP35N) "double-umbrella" configured framework to which polyester fabric is attached. The Delivery Catheter is a coaxial polyurethane catheter designed specifically to facilitate attachment, loading, delivery and deployment of the STARFlex. The implant is available in sizes 23mm, 28mm and 33mm. A single delivery catheter is compatible with all implant sizes.

4. CONTRAINDICATIONS

Patients with thrombus at or near the intended site of implant, or documented evidence of venous thrombus in the vessels through which access to the defect is gained unless the patient is protected with other embolic protection devices such as a vena cava filter.

Active endocarditis, or other infections producing a bacteremia.

Patients whose vasculature, through which access to the defect is gained, is inadequate to accommodate a 10F delivery sheath.

Patients whose defect is too small to allow the 10 F sheath to cross the defect.

Anatomy in which the STARFlex size or position required would interfere with other intracardiac or intravascular structures, such as valves or pulmonary veins.

Patients who are unable to take Aspirin, Heparin, Coumadin, or other anticoagulants.

Patients with an intra-cardiac mass or vegetation.

5. WARNINGS AND PRECAUTIONS:

See Warnings and Precautions in the final labeling (Information for Use).

6. ADVERSE EVENTS

Adverse events that were categorized as serious or moderately serious and were definitely, probably or possibly related to the device, implantation or catheterization procedure are summarized in Table 1.

Table 1 – Serious and Moderately Serious Adverse Events¹

	<i>Percent [95% Confidence Interval]</i>	<i>Number of Patients</i>
Device -Related		
Atrial Fibrillation	6.1% [1.3%, 16.9%]	3
Thrombus w/ Transient Neurological Symptoms	2.0% [0.1%, 10.9%]	1
Palpitations	4.1% [0.5%, 14.0%]	2
SVT	2.0% [0.1%, 10.9%]	1
Implantation-Related		
Air embolism	2.0% [0.1%, 10.9%]	1
Catheterization-Related		
Catheter induced arrhythmia	4.1% [0.5%, 14.0%]	2
Retroperitoneal hematoma	2.0% [0.1%, 10.9%]	1
Vomiting	4.1% [0.5%, 14.0%]	2

1. Table includes all serious and moderately serious adverse events that were definitely, probably or possibly related to the device, implantation or catheterization procedure

Device arm fractures were observed in 7 of the 49 devices (14%). No fracture related adverse events occurred.

6.2 Potential Adverse Events:

Placement of the STARFlex involves using standard interventional cardiac catheterization techniques. Complications commonly associated with these procedures include, but are not limited to:

- Air Embolus
- Allergic dye reaction
- Anesthesia reactions
- Apnea
- Arrhythmia
- Death
- Fever
- Headache / Migraines

Hematoma and/or Pseudoaneurysm including blood loss requiring transfusion
 Hypertension; Hypotension
 Infection including Endocarditis
 Perforation of Vessel or Myocardium
 Stroke / Transient Ischemic Attack
 Thromboembolic events
 Valvular regurgitation.

6.3 Observed Device Malfunctions:

One device was discarded after it was collapsed into the loader (but prior to insertion in delivery catheter) when it was observed that one of the device arms was bent. Loading technique is the suspected cause.

7. ALTERNATIVE PRACTICES AND PROCEDURES

Alternative treatments for symptomatic PFO in high risk patients include surgical closure and long term anticoagulation and/or antiplatelet therapy.

8. MARKETING HISTORY

The CardioSEAL STARFlex Septal Occlusion System has received the CE Mark for marketing in Europe. It has not been withdrawn from marketing for any reason related to the safety or effectiveness of the device.

9. SUMMARY OF PRECLINICAL STUDIES

The primary difference between the STARFlex and CardioSEAL is the addition of the nitinol centering spring to STARFlex. Preclinical studies that were conducted to support this change are summarized below.

Biocompatibility Testing

Biocompatibility tests of the STARFlex centering spring were conducted in accordance with ISO 10993-1. Test results indicate that the STARFlex is biocompatible. Tests conducted are listed in Table 1 below.

Table 1: Biocompatibility Testing

TESTS CONDUCTED	IMPLANT
cytotoxicity	✓
sensitization	✓
systemic toxicity	✓
intracutaneous reactivity	✓
pyrogenicity, material mediated	✓
genotoxicity	✓
hemolysis	✓
hemocompatibility	✓
thromboresistance	✓
mutagenicity	✓
muscle implantation	✓

Toxicity Analysis

Toxicity and galvanic corrosion analyses of the STARFlex implant were conducted. The results indicate that the STARFlex has an acceptable toxicological safety profile.

Animal Testing

An acute study was conducted to evaluate STARFlex device performance. STARFlex loading, deployment, retrievability, positioning and seating within a created ASD were evaluated and compared to the predecessor CardioSEAL device. Thirteen STARFlex devices were deployed in 10 atrial septal defects that were created in 6 sheep. STARFlex device performance was acceptable.

A second study in the sheep model was conducted to compare the product performance and biological response of the STARFlex as compared to CardioSEAL. STARFlex devices were implanted in 8 sheep which were then explanted at 1 (n=4) and 3 (n=4) months. STARFlex device performance was acceptable, and there were no significant differences in the biological response between the two devices at 1 and 3 months.

Sterility Testing

The STARFlex implant is sterilized using the same method and cycle as CardioSEAL, a 100% ETO cycle that has been validated to achieve an SAL of 10^{-6} in accordance with ANSI/AAMI/ISO 11135-1994. Sterilization residual limits meet the requirements of ANSI/AAMI/ISO 10993-9:1995. Bacteriostasis, Fungistasis and Product Immersion Sterility Testing met USP requirements. It was determined that the minor difference between the implants did not warrant repeat testing. Therefore, sterility testing provided in the original PMA is applicable to STARFlex.

Package Integrity

The STARFlex implant is packaged and shipped using the same materials and methods as CardioSEAL. It was determined that the minor difference between the implants did not warrant repeat testing. Therefore, package integrity information provided in the original PMA is applicable to STARFlex.

MRI Compatibility

MRI testing conducted on CardioSEAL is applicable to STARFlex since the only difference between the two implants is the addition of a non-ferromagnetic centering spring.

Product Performance Testing

Product performance tests conducted to support the addition of the centering spring are listed in Table 2. A brief summary of each test follows the table.

STARFLEX IMPLANT	STARFLEX IMPLANT + QL DELIVERY SYSTEM
?? Self Centering Capability ?? Centering Spring Attachment Joint Integrity ?? Centering Spring to Occluder Suture Attachment Tensile Test to Failure	?? Simulated Use Load & Deployment

Table 2: Product Performance Testing

STARFlex Implant

Self-Centering Capability

Testing was conducted to confirm the self-centering capabilities of the STARFlex implant (sizes 23-40mm) using an in-vitro defect model. All samples tested (n=28) met test requirements.

Centering Spring Attachment Joint Integrity

Testing was conducted to confirm the integrity of the spring attachment joint following simulated load and deployment. All samples tested (n=28) met test requirements.

Centering Spring to Occluder Suture Attachment Tensile Test to Failure

Testing was conducted per FDA request to evaluate tensile load to failure. Fourteen samples were tested. The mean maximum load (lb) =0.18, and the mean maximum deflection (in) = 5.21.

See Table 4.1.4, "Pre-Clinical Testing-STARFlex Implant Performance for a summary of the implant performance testing.

STARFlex Implant + QL Delivery System

Simulated Use Load and Deployment

Testing was conducted under conditions that simulate the use of the system in the clinical environment. Implant minimum side lengths, forces into and out of the loader and springback gap measurements were collected. All samples tested met performance requirements.

Shelf Life

With the exception of the centering spring, the STARFlex and the CardioSEAL are equivalent with respect to materials, processing methods, packaging methods and materials, and sterilization cycle and methods. Therefore, it was determined that the minor difference between the implants did not warrant repeat testing. Shelf life testing provided in the original PMA is applicable to STARFlex.

10. CLINICAL STUDIES:

Study Design/Objective: The multi-center clinical trial conducted by Children's Hospital, Boston, Massachusetts, is a prospective, non-randomized trial studying the use of the STARFlex Septal Occlusion system to close a variety of hemodynamically significant defects. The risks of surgical closure for the patients enrolled in this trial were considered sufficient to justify the known and potentially unknown risks of transcatheter closure with the STARFlex device. The study (referred to as the High-risk study) is ongoing and is summarized below. Data from patients undergoing PFO closure were extracted from this study.

Patient Entry: Patients were eligible for enrollment in the High risk study if they had a defect(s) of sufficient size to require closure, but were considered to be at high risk for surgical closure, due to either complex medical or cardiac disease. An independent peer review group determined whether a patient should be enrolled into the trial based on the following criteria:

- the patient had a type of defect that was technically difficult or impossible to close surgically, such that the surgical risks were sufficient to justify the known and potential unknown risks of the device, or

- the patient's overall medical condition was such that the surgical risks were sufficient to justify the known and potential unknown risks of the device.

Methods: After enrollment, patients underwent cardiac catheterization. Position and size of the defect were confirmed by angiography. A hemodynamic assessment was performed pre-implant, and after test occlusion of the defect with a balloon. When these data suggested that the defect contributed to unfavorable hemodynamics and was feasible for transcatheter closure, device placement proceeded. Patients received aspirin, 1mg/kg/day, rounded to the nearest half tablet of 80 mg size, for at least six months following the procedure. Patients were seen for follow up assessments at 1, 6, 12 and 24 months. Additionally, an assessment of the echocardiographic closure status was made at each time point both at the evaluating facility, and by an unaffiliated core laboratory. Residual flow was assessed using Doppler color flow mapping.

Results: At the time the PFO data was analyzed, 49 patients were enrolled in the study for closure of a PFO with a STARFlex device. Enrollment occurred at four investigational sites. All but one patient had a prior neurological event as their indication for device closure (98%).

Device placement was successful, using a single device at a single procedure, in all 49 patients (100%).

The cohort included patients with significant comorbid illness, including significant pre-procedure arrhythmias (16%), elevated pulmonary vascular resistance (16%) and significant non-cardiac medical illness (43%). Twenty-four (49%) of the patients were males and 25 (51%) were females. The age of the patients ranged from 2.0 years to 72.6 years, with a median age of 39.1 years.

The primary efficacy outcome was defined as a reduction of embolic risk as demonstrated by complete PFO closure by echocardiography at most recent follow-up. The secondary efficacy outcomes were the occurrence of potential embolic neurological events after device implantation, and, an improvement in oxygen saturation in those patients with fixed right-to-left shunt prior to implant.

During the follow-up period (median 6.5 months, range 1 day to 21.2 months), 43 of 44 patients (98%, 95% C.I. [88%, 100%]) with echocardiographic assessment of residual flow had reduction of their risk of embolic events, as evidenced by documented complete closure of their PFO. The remaining patient had trivial residual flow.

There were no patient deaths, device embolizations or strokes during the follow-up period.

Four patients experienced transient neurological symptoms during the follow-up period, only one of which was consistent with TIA. Resultant device explant occurred in 1 of the 4. The device was explanted surgically approximately one month after implant in a patient with a history of CVA and atrial ectopy, who experienced episodes of atrial fibrillation and transient left sided weakness. At explant, clot was found to be adherent to the device and also to the atrial myocardium, remote from the device.

Ten of the 49 patients had documented fixed right-to-left shunt prior to implant. In these 10 patients, median oxygen saturation improved from 88% prior to implantation to 98.5% at most recent follow-up (p=0.02). No patient experienced a decrease in oxygen saturation.

Baseline demographics, principal effectiveness measures and principal safety measures are summarized in Table 4.

Table 4 - Baseline Demographics, Principal Effectiveness Measures, & Principal Safety Measures

Patient Demographics			
Age (years)	median [range]	39.1 [2.0, 72.6]	
Gender			
Female		25 (51%)	
Male		24 (49%)	
Patient Enrollment (number of patients)			
Enrolled		49	
Occluder Implanted		49 (100%)	
Single Procedure		49 (100%)	
Principal Effectiveness Measures (n=49)			
	Percent [95% C.I.]		Number of Patients
Technical Success ¹	100% [92.7%, 100%]		49
Procedural Success ²	97.7% [88.0%, 99.9%]		43
Secondary Efficacy Outcomes ³			
-Stroke	0% [0.0%, 7.3%		0
-TIA	2.0% [0.1%, 10.9%]		1
-Other Transient Neurological Symptoms	6.1% [1.3%, 16.9%]		3
	Median O ₂ Saturation	p-value	
Pre-implant oxygen saturation	88%		9
Post-implant oxygen saturation ⁴	98.5%	0.02	8
Principal Safety Measures (n=49)			
	Percent [95% C.I.]	Number of Patients	
Serious & Moderately Serious Adverse Events ⁵			
Device Related	14.3% [5.9%, 27.2%]	7	
Procedure Related ⁶	12.2% [4.6%, 24.8%]	6	
Device Fractures ⁷	14.3% [5.9%, 27.2%]	7	

1. Technical success- successful deployment of the STARFlex implant.

2. Procedural success- primary efficacy outcome defined as reduction of embolic risk as demonstrated by complete closure by echocardiography at most recent follow -up. Among the 49 patients, follow -up echocardiography was available on 44 patients.

3. Secondary efficacy outcome defined as the occurrence of potential embolic neurological event after device implantation.

4. Secondary efficacy outcome defined as an improvement in oxygen saturation at most recent follow-up in patients with fixed right-to-left shunt prior to implant. Ten of the 49 patients fall under this category. One of the 10 did not have a baseline oxygen saturation value recorded, but this patient was on oxygen prior to device implant. Follow-up oxygen saturation rates were available on 8 patients.
5. Includes all serious and moderately serious adverse events that were definitely, probably or possibly related to the device, implantation or catheterization procedure.
6. Includes implantation and catheterization procedure related adverse events.
7. Device arm fractures were observed in 7 of 49 implants. No fracture related adverse events occurred.

11. **Conclusions Drawn from Studies**

The preclinical studies indicate that the CardioSEAL STARFlex Septal Occlusion System with Qwik Load is biocompatible and meets performance specification requirements.

The clinical studies support that the device is safe and effective for use in the intended patient population. In a high risk patient population with significant comorbid illness in which all but one patient had a prior neurological event as their indication for PFO closure (98%), the device was easily implanted and highly efficacious for PFO closure, with 98% of the patients achieving complete closure. Patients with fixed right-to-left shunting showed a significant improvement in oxygen saturation. There were no deaths, device embolizations or strokes. Four patients experienced transient neurological symptoms, only one of which was consistent with TIA.

12. **Panel Recommendations**

[To be completed by FDA]

13. **FDA DECISION**

[To be completed by FDA]

14. **APPROVAL SPECIFICATIONS**

Indications for Use: See the Instructions for Use (Attachment 1)

Hazards to Health from use of the Device: See CONTRAINDICATIONS, WARNINGS and PRECAUTIONS, and ADVERSE EVENTS in the Instructions for Use (Attachment 1).

Postapproval requirements and restrictions: See approval order.

The Approval Order, Summary of Safety and Effectiveness Data, and labeling can be found on the Internet at address _____ [To be completed by FDA]