# Summary of Safety and Effectiveness Data
# Mitroflow Aortic Pericardial Heart Valve

## 1. General Information

| | |
|---|---|
| Device Generic Name: | Replacement Heart Valve |
| Device Trade Name: | Mitroflow Aortic Pericardial Heart Valve<br>Sizes 19, 21, 23, 25, and 27 mm |
| Applicant's Name and Address: | CarboMedics Inc., A Sorin Group Company<br>1300 East Anderson Lane<br>Austin, Texas 78752 |
| Premarket Approval (PMA) Application Number: | P060038 |
| Date of Notice of Approval to the Applicant: | October 23, 2007 |

## 2. Indications for Use

The Mitroflow Aortic Pericardial Heart Valve is intended for the replacement of diseased, damaged, or malfunctioning native or prosthetic aortic valves.

## 3. Contraindications

There are no known contraindications for the use of the Mitroflow valve.

## 4. Warnings and Precautions

The warnings and precautions for the Mitroflow Aortic Pericardial Heart Valve can be found in the Instructions for Use.

## 5. Device Description

### 5.1 Mitroflow Aortic Pericardial Heart Valve

The Mitroflow valve consists of a single piece of bovine pericardium that is preserved with glutaraldehyde and sewn onto a polyester covered polymer stent. A radiopaque, silicone sewing ring is attached to the outer perimeter of the inflow side of the valve.

The valves are sterilized using glutaraldehyde/formaldehyde based liquid chemical sterilant and are packaged in a sealed jar containing sterile 4% formaldehyde storage solution.

The Mitroflow valve is available in aortic sizes 19, 21, 23, 25, and 27 mm diameters.

### 5.2 Class I Accessories

The Mitroflow Aortic Pericardial Heart Valve instruments are non-sterile, Class I, reusable accessory devices for use with Mitroflow Aortic Pericardial Heart Valves. Mitroflow's non-sterile instrumentation includes Aortic Obturators and a Handle for use with the obturator and valve

holder. The obturators are packaged in a set of five individual sizers ranging from 19 to 27 mm. The handle is provided separately. A complete instrument set may also be provided with a non-sterile, Class I, reusable instrument tray.

The reusable instruments are intended to be used as accessory devices in the implantation of Mitroflow pericardial heart valves. The obturators are intended for use in aiding the surgeon in determining the optimum valve size, based on measurement of the patient's annulus. The handle is intended for use in assuring a firm grasp of the valve holder or obturator, and in facilitating exposure of the valve for suture placement.

The handles have minimal, if any, direct contact with the patient, while the obturators are intended to have transient contact. The instruments are constructed of materials that have a well-established history of use in medical devices.

## 6. Alternative Practices and Procedures

Alternative treatment to the Mitroflow Aortic Pericardial Heart Valve includes drug therapy or surgical treatments such as annuloplasty or valvuloplasty. If a patient requires surgical replacement of either his or her native aortic valve or a previously implanted aortic prosthetic valve, the alternatives include replacement of the malfunctioning aortic valve with a commercially available homograft, mechanical prosthetic valve, or bioprosthetic valve. The choice of replacement valve depends on an assessment of patient factors which include age, preoperative condition, anatomy, and the patient's ability to tolerate long-term anticoagulant therapy.

## 7. Marketing History

Commercial distribution of the Mitroflow Aortic Pericardial Heart Valve (Model 12) outside the United States began in 1992. The valve has been available in the following countries: Algeria, Australia, Austria, Bangladesh, Belgium, Belize, Bolivia, Canada, Chile, Colombia, Costa Rica, Cuba, Cyprus, Czech Republic, Denmark, El Salvador, Estonia, Finland, France, Germany, Greece, Guatemala, Honduras, Hong Kong, India, Indonesia, Ireland, Israel, Italy, Kenya, Lebanon, Macedonia, Malaysia, Malta, Morocco, Netherlands, New Zealand, Nicaragua, Nigeria, Norway, Oman, Pakistan, Panama, Paraguay, Peru, Philippines, Portugal, Saudi Arabia, Singapore, South Africa, Spain, Sri Lanka, Sweden, Switzerland, Syria, Trinidad/Tobago, Tunisia, Turkey, United Arab Emirates, United Kingdom, Uruguay, Venezuela, and Yemen. The Mitroflow Aortic Pericardial Heart Valve has never been withdrawn from commercial distribution for any reason relating to the safety or effectiveness of the device.

## 8. Potential Adverse Effects of the Device on Health

### 8.1 Observed Adverse Events

A prospective, nonrandomized, multi-center clinical study was conducted to assess the safety and performance of the Mitroflow Aortic Pericardial Heart Halve. Patients were evaluated preoperatively, within 30 days postoperative, 3-6 months postoperative, at one year (11-13 months) postoperative, and annually thereafter. Patients were monitored throughout the postoperative period for possible adverse events. Six hundred and ninety-nine (699) patients received isolated aortic valve replacement (AVR) in the study. Mortality and valve-related morbidity rates after implantation with the Mitroflow Aortic Pericardial Heart Valve are summarized in Table 1. There were an insufficient number of patients receiving the size 29 mm to evaluate effectiveness; however, the data from the 4 patients of this size have been included in the follow-up for safety data. The adverse event rates were based on 699 bioprostheses

implanted in 699 patients at 25 sites (28 hospitals). The cumulative follow-up was 835.9 patient-years with a mean follow-up of 14.4 months and a maximum follow-up of 28.5 months.

**Table 1. Observed Adverse Event Rates for AVR**

**Total patients analyzed: N = 699 Cumulative follow-up: 835.9 patient-years**

| Adverse event | Early Events[1] | | Late Events[2] | | Percent Freedom From Event [SE][3] | |
|---|---|---|---|---|---|---|
| | n | % of Patients | n | %/Pt-Yr | 1 Year | 2 Years |
| All mortality | 31 | 4.4 | 80 | 10.24 | 85.0 [1.4] | 81.4 [1.8] |
| Valve-related death (includes sudden death) | 2 | 0.3 | 18 | 2.30 | 96.7 [0.7] | 96.7 [0.7] |
| Structural valve deterioration | 0 | 0 | 2 | 0.26 | 99.8 [0.2] | 99.4 [0.4] |
| All Anticoagulant–related bleeding | 12 | 1.7 | 14 | 1.79 | 96.4 [0.7] | 95.5 [1.0] |
| Major Anticoagulant-related bleeding | 6 | 0.9 | 7 | 0.90 | 98.3 [0.5] | 97.4 [0.8] |
| Thromboembolism | 17 | 2.4 | 15 | 1.92 | 95.1 [0.9] | 94.7 [0.9] |
| Major thromboembolic event | 6 | 0.9 | 6 | 0.77 | 98.2 [0.6] | 97.8 [0.7] |
| Valve Thrombosis | 0 | 0 | 0 | 0 | 100 [0] | 100 [0] |
| Endocarditis | 1 | 0.1 | 19 | 2.43 | 96.8 [0.7] | 96.4 [0.8] |
| Non-structural valve dysfunction[4] | 4 | 0.6 | 6 | 0.77 | 98.6 [0.5] | 98.2 [0.6] |
| Perivalvular Leak | 4 | 0.6 | 4 | 0.51 | 98.7 [0.4] | 98.7 [0.4] |
| Hemolysis | 0 | 0 | 0 | 0 | 100 [0] | 100 [0] |
| Reoperation (including explant) | 0 | 0 | 9 | 1.15 | 98.5 [0.5] | 98.5 [0.5] |
| Explant | 0 | 0 | 8 | 1.02 | 98.7 [0.5] | 98.7 [0.5] |

[1] Early death occurred within 30 days of implant, and includes intraoperative deaths. Early valve-related events include postoperative events occurring 1-30 days post implant. Early event rates calculated as the percentage of patients with an event.
[2] Late postoperative events (>30 days post implant). Late event rates calculated as linearized hazard rates (%/patient-year). Calculations for linearized rates were based on 781.1 late patient-years.
[3] Freedom from first event (early or late) rates were calculated using the Kaplan-Meier method. SE = Standard error.
[4] Includes perivalvular leaks (8), and residual aortic stenosis (1) or insufficiency (1).

## 8.2 Potential Adverse Events

Adverse events potentially associated with the use of bioprosthetic heart valves (in alphabetical order) include (but may not be limited to):

- Angina
- Cardiac arrhythmias
- Endocarditis
- Heart failure
- Hemolysis
- Hemolytic anemia
- Hemorrhage
- Leak, transvalvular or perivalvular

- Myocardial infarction
- Non-structural dysfunction
  - Inappropriate sizing
  - Leaflet entrapment by tissue in-growth
  - Prosthesis regurgitation
  - Prosthesis stenosis
  - Suture entrapment on commissures
- Stroke
- Structural valve deterioration
  - Intrinsic and extrinsic mineralization (calcification)
  - Leaflet perforation or tear
  - Leaflet rupture
- Thromboembolism
- Valve thrombosis

It is possible that these complications could lead to:

- Reoperation
- Explant
- Permanent disability
- Death

## 9. Summaries of Non-Clinical Studies

### 9.1 In-Vitro Pre-Clinical Bench Testing

Mitroflow Aortic Pericardial Heart Valve sizes 19, 21, 23, 25, 27 and 29 mm were evaluated in pre-clinical bench tests. Although the 29mm size was withdrawn, some preclinical studies included testing on this size and these data are considered supportive of the sizes being approved.

#### 9.1.1 Biocompatibility

**Non-Biological Components**

Materials utilized in the Mitroflow Aortic Pericardial Heart Valve were subjected to a comprehensive screen for chemical stability, biological stability, and tissue/cell toxicity. The materials used in the construction of the valve were subjected to complete processing as per normal manufacturing conditions. The tests performed, test objectives and methods, controls, and test results are summarized in Table 2.

**Table 2. Biocompatibility Test Results: Non-Biological Components**

| Test Performed | Objective and Method | Controls | Test Articles | Results |
|---|---|---|---|---|
| Systemic Toxicity (USP [United States Pharmacopeia] Mouse Systemic Injection) | Evaluation of acute systemic toxicity of leachables extracted from the test article following a single intravenous or intraperitoneal injection in mice | Control animals dosed with extracts of USP negative control | Polyester fabric<br>Stent<br>Silicone sewing ring with 40% tungsten | Passed<br>No significant signs of systemic toxicity |
| Intracutaneous Reactivity (Rabbit Intracutaneous Reactivity Test) | Evaluation of local dermal irritation or toxic effects of leachables extracted from the test article following intracutaneous injection in rabbits | Reagent control per animal | Polyester fabric<br>Stent<br>Silicone sewing ring with 40% tungsten | Passed<br>Samples showed no signs of irritation |
| Implantation (Rabbit Intramuscular Implantation Test - 7 day) | Evaluation of a test article to local pathological effects on living tissue in rabbits (macro and microscopic examination of implant muscle sites) | USP negative control plastic | Polyester fabric<br>Stent<br>Silicone sewing ring with 40% tungsten | Passed<br>No significant inflammation noted |
| Cytotoxicity (Minimal Essential Medium [MEM] elution) | Evaluation of the biocompatibility of test article extract to determine the potential for cytotoxicity | High density polyethylene negative control, reagent control, and tin stabilized polyvinylchloride as a positive control | Stent | Passed<br>Non-cytotoxic |
| Pyrogenicity | Evaluation of test extract for material mediated pyrogenicity | Not applicable | Stent | Passed<br>Non-pyrogenic |
| Hemocompatibility | Determine whether the presence of any leachable chemicals from the test article would cause in-vitro red blood hemolysis | High density polyethylene negative control, SWFI (Sterile Water for Injection) as positive control | Stent | Passed<br>Non-hemolytic |

**Biological Components**

The use of glutaraldehyde-fixed bovine pericardium is well established in bioprosthetic heart valves and has an acceptable biocompatibility profile for this indication. The tissue in the Mitroflow Aortic Pericardial Heart Valve is liquid chemically processed in a manner that is similar to other commercially available heart valves incorporating animal tissue. A thorough assessment of potential leachables from the valve has been completed, including a study of extractable residuals during rinsing. The results confirm that the extractable chemical residues from the Mitroflow Aortic Pericardial Heart Valve are below acceptable limits published in the literature.

### 9.1.2 Hydrodynamic Performance

Hydrodynamic performance studies were conducted on the Mitroflow Aortic Pericardial Heart Valve in accordance with the FDA Draft Replacement Heart Valve Guidance Document (1994) and International Organization for Standardization (ISO) 5840, Cardiovascular Implants – Cardiac Valve Prostheses. Testing included: steady flow pressure drop, pulsatile flow pressure drop, dynamic regurgitation, static leakage, flow visualization, and confirmation of the Bernoulli relationship. Commercially available bioprosthetic heart valves were used as controls.

The hydrodynamic test results summarized in Table 3 support the safe performance of the Mitroflow Aortic Pericardial Heart Valve.

**Table 3. Summary of Hydrodynamic Performance Testing**

| Test Type | Sample Size | Control Size | Results |
|---|---|---|---|
| Steady Flow Pressure Drop | 3 of each size<br>18 total samples | 1 of each size<br>6 total controls | Steady flow pressure drop is directly correlated to and consistent with pulsatile flow pressure drop results. |
| Pulsatile Flow Pressure Drop/EOA (Effective Orifice Area) | 3 of each size<br>18 total samples | 1 of each size<br>6 total controls | Met requirements in ISO 5840:2005, Cardiovascular implants – Cardiac valve prostheses. |
| Dynamic Regurgitation | 3 of each size<br>18 total samples | 1 of each size<br>6 total controls | Valve maintains complete coaptation and meets requirements in ISO 5840:2005, Cardiovascular implants – Cardiac valve prostheses. |
| Static Leakage | 3 of each size<br>18 total samples | 1 of each size<br>6 total controls | Valve closes completely and maintains complete coaptation under a backpressure of 190 mmHg. |
| Flow Visualization | 1 size 19 and 1 size 23<br>2 total samples | Not applicable | The flow field was typical of stented tissue valves. Results indicate that the valve opens efficiently and symmetrically. No areas of stasis or regurgitant jets were observed during diastole. |
| Verification of Bernoulli Relationship | 1 each: size 19, 23, and 29<br>3 total samples | Not applicable | The Bernoulli relationship accurately projects the mean pressure gradient for the valve. |

### 9.1.3 Structural Performance

Structural performance studies of the Mitroflow Aortic Pericardial Heart Valve were completed in accordance with the FDA Draft Replacement Heart Valve Guidance Document (1994). Testing included accelerated wear/durability, dynamic failure mode, fatigue, stent creep, and sewing cuff integrity. The summary of structural performance testing provided in Table 4 demonstrates acceptable performance of the Mitroflow Aortic Pericardial Heart Valve.

**Table 4. Summary of Structural Performance Testing**

| Test Type | Sample Size | Control Size | Results |
|---|---|---|---|
| Accelerated Wear/ Durability | 5 each: size 19, 23, 29<br><br>3 each; size 21, 25, 27<br><br>24 total samples | 1 each: size 19, 21, 23, 25, 27, 29<br><br>6 total controls | All Mitroflow valves functioned normally exhibiting proper opening and closing while maintaining back pressure throughout the test. No failures were observed at 200 million cycles.<br><br>One control valve exhibited more than 20% regurgitation at 187 million cycles. |
| Dynamic Failure Mode | 5 each: size 19, 23, 29<br><br>3 each: size 21, 25, 27<br><br>24 total samples | 1 each: size 21, 23, 25, 27, 29<br><br>5 total controls | The failure mode observed was excessive regurgitation due to leaflet holes, tears and coaptation zone distortion. This is consistent with typical failure modes for tissue valves in this in-vitro test. Failures occurred between 360 million and 1 billion cycles at higher cycle counts than for the control valve. |
| Fatigue: Finite Element Analysis | Worst case dimensions: size 19 and 25 | Not applicable | Highest stress calculated was 2129 psi for the minimum thickness size 25 stent. |
| Fatigue Lifetime Analysis | Engineering analysis supplemented with testing of size 25 stents<br><br>30 total samples | Not applicable | Engineering analysis calculated probability of failure in 15 years to be $1.2 \times 10^{-13}$ based on Finite Element Analysis and coupon fatigue data. There were no failures of the 30 stent test articles through 600 million cycles at 2400 psi maximum stress. |
| Stent Creep | Size 25 stents<br><br>8 total samples | Not applicable | After 15 equivalent years, all stent creep was acceptable. |
| Sewing Cuff Integrity | 3 of each size<br><br>18 total samples | Not applicable | All test samples exhibited cuff retention in excess of the minimum device specification and a safety factor of at least 35. |

## 9.2 Pre-Clinical Animal Studies

Long-term animal studies with the Mitroflow valve were performed in the canine model after initial evaluation of the valve in a primate (baboon) model. The primate model utilized thirteen (13) young baboons implanted with size 21 Mitroflow or size 19 Ionescu-Shiley valves in the mitral position, with the exception of 1 of each valve implanted in the tricuspid position. In the canine model, twenty-two (22) mongrel dogs weighing between 50 and 70 pounds were implanted with size 21 Mitroflow valves in the mitral position. Size 21 Ionescu-Shiley valves were also implanted in the mitral position as controls.

The studies included evaluation of handling and implant characteristics, animal survival, hemodynamic performance including ventriculograms, valve pathology and mineralization. The implantation of the valve in a position other than indicated was not unusual and was done to

expose the valve to worst case conditions. The animal study results supported the determination to begin the study of the Mitroflow valve in humans. Results of these studies are summarized in more detail below.

**Handling and Implant Characteristics**
Handling and implant characteristics were considered unremarkable by the implanting surgeons in both studies.

**Animal Survival**
All of the 13 baboons survived to the scheduled sacrifice dates. Four of the 22 dogs died prior to scheduled sacrifice; two because of pulmonary edema, one because of dehiscence, and one due to valvular stenosis. These deaths were considered typical for this type of valve study. One six month animal was sacrificed seven days before the scheduled sacrifice date due to failing health; autopsy revealed thrombus and dehiscence. All other animals were sacrificed as scheduled.

**Hemodynamic Performance**
At the time of scheduled sacrifice, all animals were subjected to catheterization to obtain hemodynamic data and ventriculograms were recorded in the canines to observe valve function. All animals exhibited competent valves at scheduled sacrifice.

**Valve Pathology**
Valve pathology included photographic analysis and histology of the explanted valves. The canine studies demonstrated that all valves exhibited good healing, flexible leaflets, and good coaptation although some valves were occluded with mild to moderate thrombus; as were some of the baboon valves. The rate of thrombus incidence in the Mitroflow valve was comparable to that of the control valve in the canine study. Mitroflow valves exhibited minor calcification.

### 9.3 Sterilization

The Mitroflow Aortic Pericardial Heart Valve is sterilized with a multi-component liquid chemical sterilant. After sterilization, the product is held in quarantine until sterility is verified in accordance with process specifications.

The sterilization process has been validated to demonstrate a $10^{-6}$ sterility assurance level for the device. The validation was conducted in accordance with Association for the Advancement of Medical Instrumentation (AAMI)/ISO 14160-1998 Sterilization of single-use medical devices incorporating materials of animal origin – Validation and routine control of sterilization by liquid chemical sterilants. Annual revalidation of the sterilization process is conducted under worst case challenge conditions.

### 9.4 Magnetic Resonance Imaging (MRI) Compatibility

Non-clinical testing has demonstrated that the Mitroflow Aortic Pericardial Heart Valve is MR Conditional. It can be scanned safely under the following conditions:

- Static magnetic field of 3.0 Tesla or less
- Spatial gradient field of 525 Gauss/cm or less
- Maximum whole-body-averaged specific absorption rate (SAR) of 1.5 W/kg for 20 minutes of scanning.

In non-clinical testing, the Mitroflow Aortic Pericardial Heart Valve produced a temperature rise of less than 0.8°C at a maximum whole body averaged specific absorption rate (SAR) of 1.5 W/kg for 20 minutes of MR scanning in a 1.5 Tesla, Model Signa MR, GE Medical System, Milwaukee, WI, MR scanner.

MR image quality may be compromised if the area of interest is in the exact same area or relatively close to the position of the Mitroflow Aortic Pericardial Heart Valve. Therefore, it may be necessary to optimize MR imaging parameters to compensate for the presence of this implant.

### 9.5 Shelf Life

The shelf life for the Mitroflow Aortic Pericardial Heart Valve was validated to ensure that both the package integrity and product integrity are maintained for a minimum of 60 months.

#### 9.5.1 Package Integrity

The packaging used for the Mitroflow Aortic Pericardial Heart Valve has been shown to maintain sterility for five years. Structural integrity of the package and sterility of the packaging solution were evaluated after real-time aging to five years. The results demonstrate the package integrity is acceptable for a five-year shelf life.

#### 9.5.2 Product Integrity

The integrity of the finished device was evaluated after real-time aging to five years. The evaluation consisted of multiple tests to confirm device functionality through the examination of several aspects of valve performance. The testing included: visual inspection of the covered stent, functional testing including leaflet opening, coaptation height, leaflet-to-leaflet variation, depth of coaptation, leaflet response, tissue creases and stress lines, commisure post flexibility, tensile testing of the tissue, and tissue histopathology. The results demonstrate that the product integrity of the Mitroflow Aortic Pericardial Heart Valve is acceptable for a five-year shelf life.

## 10. Summary of Clinical Study

### 10.1 Study Design

A prospective, nonrandomized, multi-center clinical study was conducted at 25 sites (28 hospitals) in Canada (5 sites) and the United States (20 sites) to assess the safety and effectiveness of the Mitroflow Aortic Pericardial Heart Valve. All sites in the study followed a common protocol including patient selection, inclusion and exclusion criteria, and obtaining an informed consent. All sizes of the Mitroflow Aortic Pericardial Heart Valve (19, 21, 23, 25, 27 and 29mm) were evaluated in the clinical study but the size 29mm valve was withdrawn due to an insufficient amount of clinical data available at the time of evaluation. Evaluation of safety was based on analysis of adverse event rates and presence of hemolysis. Adverse events were analyzed in relation to the Objective Performance Criteria (OPC) established by the FDA. Effectiveness of the study was assessed on postoperative functional improvements as determined by the New York Heart Association (NYHA) functional classification and hemodynamic performance as determined by Doppler echocardiography.

### 10.2 Description of Patients

Six hundred and ninety-nine patients underwent isolated aortic valve replacement between November 2003 and December 31, 2005. Demographic and baseline data were collected preoperatively. The demographic profile of the study cohort is shown in Table 5.

**Table 5. Preoperative Patient Demographics**

| Patient Characteristics | | Isolated AVR (N = 699) | |
|---|---|---|---|
| | | n | % (n/N)[1] |
| Age at Implant | Mean (range) | 699 | 74.3 (27-93) |
| Age at Implant | 20-29 | 1 | 0.1 |
| | 30-39 | 3 | 0.4 |
| | 40-49 | 5 | 0.7 |
| | 50-59 | 29 | 4.1 |
| | 60-69 | 117 | 16.7 |
| | 70-79 | 359 | 51.4 |
| | 80-89 | 180 | 25.8 |
| | 90-99 | 5 | 0.7 |
| Gender | Female | 302 | 43.2 |
| | Male | 397 | 56.8 |
| NYHA Functional Classification | I | 62 | 8.9 |
| | II | 264 | 37.8 |
| | III | 300 | 42.9 |
| | IV | 66 | 9.4 |
| | Not reported | 7 | 1.0 |
| Aortic valve lesion | Regurgitation | 57 | 8.2 |
| | Stenosis | 417 | 59.7 |
| | Mixed Lesion | 215 | 30.8 |
| | Previous Prosthetic valve | 10 | 1.4 |

[1] n = number of patients in each category. N = total number of study patients.

## 10.3 Results

The effectiveness endpoints in this study were NYHA functional classification and hemodynamic assessments obtained by echocardiography. Table 6 presents patient NYHA functional classification outcomes. Table 7 presents patient Hemodynamic results at one year follow-up.

**Table 6. Effectiveness Outcomes, NYHA Functional Classifications**

| NYHA Class | Preoperative (N=692)[1] | | Postoperative Assessments | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | 3-6 months (N=571) | | 1 year (N=544) | | 2 years (N=245) | |
| | n[2] | % | n | % | n | % | n | % |
| I | 62 | 9.0 | 431 | 75.1 | 427 | 78.5 | 188 | 76.7 |
| II | 264 | 38.2 | 129 | 22.5 | 109 | 20.0 | 51 | 20.8 |
| III | 300 | 43.4 | 11 | 1.9 | 6 | 1.1 | 6 | 2.4 |
| IV | 66 | 9.5 | 3 | 0.5 | 2 | 0.4 | 0 | 0.0 |

[1] N = total number of patients with NYHA evaluation at each postoperative assessment.
[2] n = number of patients in each NYHA category.

**Table 7. Effectiveness outcomes, Hemodynamic results[1] at 1 year: Isolated AVR (N = 544)**

| Hemodynamic Data | Valve Size[2] | | | | |
|---|---|---|---|---|---|
| | 19 (N[3] =34) | 21 (N=143) | 23 (N-193) | 25 (N=128) | 27 (N=42) |
| Mean gradient (mmHg) | n[4] =33 | n=136 | n=189 | n=122 | n=39 |
| Mean ± SD | 13.4 ± 5.0 | 11.4 ± 4.4 | 10.5 ± 4.2 | 8.7 ± 3.3 | 7.4 ± 2.7 |
| Effective orifice area ($cm^2$) | n=30 | n=131 | n=185 | n=121 | n=37 |
| Mean ± SD | 1.1 ± 0.2 | 1.2 ± 0.3 | 1.4 ± 0.3 | 1.6 ± 0.3 | 1.8 ± 0.3 |
| Regurgitation | n=34 | n=143 | n=193 | n=128 | n=42 |
| None | 21 (61.8%) | 103 (72.0%) | 145 (75.1%) | 98 (76.6%) | 33 (78.6%) |
| Trace | 8 (23.5%) | 18 (12.6%) | 35 (18.1%) | 22 (17.2%) | 4 (9.5%) |
| Mild | 4 (11.8%) | 20 (14.0%) | 13 (6.7%) | 6 (4.7%) | 5 (11.9%) |
| Moderate | 1 (2.9%) | 1 (0.7%) | 0 (0.0%) | 2 (1.6%) | 0 (0.0%) |
| Severe | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Not Reported | 0 (0.0%) | 1 (0.7%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |

[1] Hemodynamic evaluation performed using transthoracic echocardiography.
[2] Size 29mm valves were studied but data for this size are not included in this table because of the limited clinical data available at the time of PMA evaluation.
[3] N = total patients with echo evaluation in each valve size.
[4] n = patients in each valve size with valid measurement of hemodynamic parameter.

### 10.4 Analysis for Gender Bias

There were 397 males (56.8%) and 302 females (43.2%) in the Mitroflow PMA cohort. The ratio of males to females in the study is consistent with the distribution of male and female patients presenting with aortic valve replacement in the United States and Canada.

The log-rank test was used to compare valve-related adverse events and outcomes by gender. There were no statistically significant differences between males and females for any of the safety endpoints compared. Therefore the results of the analysis of valve-related adverse events in the study are representative for both men and women.

Effectiveness endpoints were compared for both males and females. Male and female patients exhibited a significant improvement in NYHA classification at 12 months ($p<0.001$). Based on the evaluation of echocardiography endpoints, the hemodynamic performance of the Mitroflow valve was equivalent in men and women. Therefore the hemodynamic results presented in this study are representative for men and women.

## 11. Conclusions Drawn from the Studies

The results from the in-vitro pre-clinical studies conducted on the Mitroflow Aortic Pericardial Heart Valve for biocompatibility, hydrodynamic performance, and structural performance suggest that the device is non-toxic and performs acceptably.

The in vivo animal studies in primate and canine models demonstrate that the Mitroflow Aortic Pericardial Heart Valve performs acceptably.

The preclinical and clinical studies submitted in the PMA application provide reasonable assurance that the Mitroflow Aortic Pericardial Heart Valve, available in sizes 19, 21, 23, 25, and 27 mm, is safe and effective for the replacement of native or prosthetic aortic valves when used in accordance with the approved labeling.

Note that the size 29mm Mitroflow Aortic Pericardial Heart Valves were included in the in vitro preclinical studies and the clinical studies; however, at the time of PMA application submission, the number of patients implanted with the size 29mm valve, as well as length of follow-up, were insufficient to support approval for the size 29mm valve.

## 12. Panel Recommendations

In accordance with the provisions of section 515(c)(2) of the Act as amended by the Safe Medical Devices Act of 1990, this PMA was not referred to the Circulatory Systems Device panel, an FDA advisory committee, for review and recommendation because the information in the PMA substantially duplicates information previously reviewed by this panel.

## 13. FDA Decision

The FDA issued an approval order on October 23, 2007. The applicant's manufacturing facility was inspected and was found to be in compliance with the Quality System Regulation (21 CFR 820).

## 14. Approval Specifications

Instructions for Use: See labeling

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

Post-approval Requirements: See approval order.