Summary of Safety and Effectiveness Data
Edwards Prima Plus Stentless Bioprosthesis Model 2500P
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1. GENERAL INFORMATION

Device Generic Name:	Replacement Heart Valve
Device Trade Name:	Edwards Prima Plus Stentless Bioprosthesis Model 2500P
Applicant's Name and Address:	Edwards Lifesciences LLC One Edwards Way Irvine, CA 92614
PMA Application Number:	P000007
Date of Panel Recommendation:	
Date of Notice of Approval to the Applicant:	FEB 27 2001

2. INDICATIONS FOR USE

The Edwards Prima Plus Stentless Bioprosthesis Model 2500P is indicated for patients who require replacement of their native or prosthetic aortic valve using the subcoronary implantation technique.

3. DEVICE DESCRIPTION

The Edwards Prima Plus Stentless Bioprosthesis Model 2500P is a porcine valve aortic root cylinder that has been preserved in a buffered glutaraldehyde solution. The bioprosthesis is treated according to the Edwards XenoLogiX process, which uses ethanol and polysorbate-80 (a surfactant), and is packaged and terminally sterilized in glutaraldehyde. Glutaraldehyde is shown to both reduce the antigenicity of tissue xenograft valves and increase tissue stability; however, glutaraldehyde has not been shown to affect or reduce the calcification rate of the valve.

The Edwards Prima Plus Stentless Bioprosthesis Model 2500P is designed for the aortic position and is available in the following implantation diameters: 21, 23, 25, and 27mm.

Woven polyester cloth is sewn with green suture around the inflow annulus to give additional support to the first suture line. Green marking sutures midway around the intercommissural periphery aid in the placement of stitches around the annulus. Black marking sutures at the mid-commissural positions on the inflow rim aid in proper alignment with the patient's anatomy. A green trim guide placed externally on the valve wall indicates the recommended limit for trimming the valve for subcoronary implantation while maintaining adequate tissue for placement of the second suture line.

4. CONTRAINDICATIONS

None known.

5. WARNINGS AND PRECAUTIONS

Please refer to device labeling for a list of the warnings and precautions.

6. ALTERNATIVE PRACTICES AND PROCEDURES

The alternative to the Edwards Prima Plus Stentless Bioprosthesis Model 2500P is surgical replacement of the malfunctioning aortic valve with an allograft or another prosthetic replacement heart valve for which there is an approved premarket approval application (PMA). When a replacement heart valve is chosen as the appropriate therapy, the option of choosing between a mechanical or biological valve prosthesis exists. The choice of replacement heart valve depends on an assessment of patient factors that include age, preoperative condition, anatomy, and the patient's ability to tolerate long-term anticoagulant therapy.

Other forms of treatment may include the use of cardiac drug therapy or other types of surgical treatment, such as native valve reconstruction or modification.

7. MARKETING HISTORY

Currently the Edwards Prima Plus Stentless Bioprosthesis Model 2500P is distributed in Australia, Austria, Belgium, Canada, Chile, China, Denmark, Egypt, Finland, France, Germany, Greece, Hong Kong, India, Ireland, Israel, Italy, South Korea, Luxembourg, Malaysia, Netherlands, New Zealand, Norway, Pakistan, Portugal, Singapore, South Africa, Spain, Sweden, Switzerland, Thailand, Turkey, the United Kingdom, and Uruguay.

The Edwards Prima Plus Stentless Bioprosthesis Model 2500P has not been withdrawn from marketing in any country for any reason relating to the safety and/or the effectiveness of the device.

8. ADVERSE EVENTS

Two multi-center, non-randomized, prospective clinical studies were conducted. The first study was a long-term evaluation of 160 patients implanted with the Edwards Prima Stentless Bioprosthesis Model 2500 in the subcoronary configuration and was conducted between 1991 and 1999. The second study was a short-term evaluation of 206 patients implanted with the Edwards Prima Plus Stentless Bioprosthesis Model 2500P in the subcoronary configuration and was conducted between 1998 and 2000. In the long-term study, patients were evaluated preoperatively, intraoperatively/at discharge, at 3 to 6 months, at 1 year, and annually thereafter. In the short-term study, patients were evaluated preoperatively, intraoperatively/at discharge, at 3 to 6 months, and at 1 year.

Table 1 presents the observed rates for early adverse events (≤30 days for valve-related adverse events), the linearized rates for late adverse events (>30 days postoperatively), and the cumulative freedom from adverse event rates at 1, 5, and 8 years postoperatively. The adverse event rates were based on 366 patients at 13 centers, with one center participating in both the long-term and short-term studies. The cumulative follow-up was 1074.2 patient-years with a mean follow-up of 2.9 years (SD=2.9 years, range=0 to 8.2 years).

Table 1: Observed Adverse Event Rates
(Subcoronary Implant Technique)
All patients analyzed: N= 366 Cumulative follow-up: 1074.2 patient-years

Complication	Early Events		Late Events[1]		Freedom from Event (%) ± 95% CI[2]		
	n[3]	%	n	%/pt.-yr.	1 year (n = 366)	5 years (n = 134)	8 years (n = 56)
Mortality (all)	12	3.3	42	4.0	94.6 ± 2.9	81.3 ± 6.3	66.6 ± 37.7
Valve-related events							
Valve-related mortality	2	0.5	18	1.7	98.3 ± 1.7	93.1 ± 4.4	87.0 ± 30.7
Explant	0	0.0	6	0.6	99.6 ± 0.8	96.9 ± 3.0	95.1 ± 20.6
Reoperation[4]	0	0.0	0	0.0	100 ± 0.0	100 ± 0.0	100 ± 0.0
Bleeding	7	1.9	9	0.9	95.2 ± 2.8	95.2 ± 2.8	93.5 ± 27.1
Endocarditis	0	0.0	9	0.9	99.2 ± 1.2	94.5 ± 4.0	94.5 ± 21.7
Hemolysis	0	0.0	0	0.0	100 ± 0.0	100 ± 0.0	100 ± 0.0
Nonstructural dysfunction[5]	5	1.4	9	0.9	96.1 ± 2.6	96.1 ± 3.6	96.1 ± 26.4
Perivalvular leak	5	1.4	8	0.8	96.5 ± 2.5	96.5 ± 3.4	96.5 ± 25.1
Structural valve deterioration	0	0.0	11	1.1	100 ± 0.0	96.0 ± 3.4	86.8 ± 30.9
Thromboembolism	12	3.3	28	2.7	95.8 ± 2.7	84.8 ± 6.2	82.7 ± 38.9
Valve thrombosis	0	0.0	0	0.0	100 ± 0.0	100 ± 0.0	100 ± 0.0

Notes:
1. Late event rates were calculated as linearized rates (%/pt-yr) based on 1044.3 late patient-years (>30 days postoperatively).
2. Freedom from event rates were calculated using the Kaplan-Meier method. Greenwood's formula was used for calculation of the 95% confidence intervals.
3. n = number of patients
4. Includes reoperation without valve explant.
5. Nonstructural dysfunction includes perivalvular leak. All operative nonstructural dysfunction events were perivalvular leaks.

9. SUMMARY OF NONCLINICAL STUDIES

9.1. Bench Testing

In vitro studies were performed for the Edwards Prima Plus Stentless Bioprosthesis Model 2500P as recommended in the FDA's *Draft Replacement Heart Valve Guidance* (1994). Although tested in the nonclinical studies, the clinical study (Section 10) did not generate sufficient data to support the safety and effectiveness of sizes 19 and 29 aortic valves. The data from the preclinical testing of these sizes are included in the summaries below since the results were used in the overall evaluation of the approved devices.

9.1.1. Biocompatibility Studies

Biocompatibility tests were performed in accordance with the requirements of ISO 10993-1, with the exception of carcinogenicity and hemocompatibility testing. Carcinogenicity testing was determined to be unnecessary because the test articles demonstrated no mutagenic potential at levels at or above those intended for the clinical application. Device hemocompatibility was evaluated and found to be acceptable in animal implantation studies (refer to Section 9.2.1). All studies were performed by Edwards Lifesciences LLC, Irvine, CA in accordance with the FDA GLP Regulations (21 CFR 58). A matrix of the tests performed and the corresponding results are provided in Table 2.

Table 2: Biocompatibility Tests and Results

Test Performed	Test Objective	Samples: Control	Samples: Prima Plus	Results
In vitro inhibition of cell growth	Assess the effect of the aqueous extract of a material on the normal growth of cells in culture. The sample is considered non-inhibitory to cell growth if the percent of inhibition is equal to or less than 29%	Negative control only: Water	Polyethylene terephthalate (PET) cloth Polytetrafluoroethylene (PTFE) thread PTFE impregnated PET thread Black silk suture thread	Non-inhibitory to cell growth. 0% inhibition. Non-inhibitory to cell growth. 0% inhibition. Non-inhibitory to cell growth. 0% inhibition. Non-inhibitory to cell growth at a concentration representative of that used in the device. Inhibitory to cell growth at elevated sample concentrations.
In vitro cytotoxicity (Medium eluate method)	Evaluate the cytotoxic effects of a material growth medium extract on a human fibroblast monolayer. A sample is judged non-cytotoxic if lysis is not greater than the negative control.	Negative Control: Cell growth medium Positive Control: Approximately 5% Ethanol in water	PET cloth PTFE thread PTFE impregnated PET thread Black silk suture thread	Non-cytotoxic to cells. 0% cell lysis. Non-cytotoxic to cells. 0% cell lysis. Non-cytotoxic to cells. 0% cell lysis. Non-cytotoxic at concentrations representative of that used in the device. Cytotoxic at concentrations above those used on the device.
In vitro cytotoxicity (Agar overlay assay)	Evaluate the cytotoxicity of diffusible components of a material through an agar overlay assay. A sample is judged non-cytotoxic if lysis is not greater than the negative control.	Negative control: Polypropylene solid sample Positive control: Polyvinyl chloride (PVC) with Organotin	PET cloth PTFE thread PTFE impregnated PET thread Black silk suture thread	Non-cytotoxic to cells. 0% cell lysis. Non-cytotoxic to cells. 0% cell lysis. Non-cytotoxic to cells. 0% cell lysis. Moderate to severe cytotoxicity (20 to 60% cell lysis) due to glutaraldehyde and formaldehyde residuals present in these exaggerated sample sizes and under the static environments imposed in this *in vitro* test.
In vitro mutagenicity (Sister chromatid exchange assay)	Detect the presence of mutagenic moieties in biomaterials using activated and non-activated systems.	Negative control: Distilled water or the corresponding medium used for the test article extraction. Positive control (non-activated system): Distilled water with mitomycin C @ 0.005 µg/mL). Positive control (activated system): Distilled water with cyclophosphamide @ 1.0 µg/mL)	PET cloth PTFE thread PTFE impregnated PET thread Black silk suture thread	Non-mutagenic using activated and non-activated systems. Non-mutagenic using activated and non-activated systems. Non-mutagenic using activated and non-activated systems. Non-mutagenic at all concentrations using the activated system and at concentrations representative of the final device using the non-activated system
USP mouse systemic injection	Evaluate the systemic effect of a material extract in mice. The sample is considered systemically non-toxic if all the mice treated with the sample extract survive at the end of 72 hours and none shows an outward symptom of greater reaction or weight change than mice treated with the negative control.	Negative control: Normal saline and vegetable oil or the corresponding medium used for the test article extraction	PET cloth PTFE thread PTFE impregnated PET thread Black silk suture thread	All mice normal. Non-toxic. All mice normal. Non-toxic. All mice normal. Non-toxic. All mice normal. Non-toxic.
USP rabbit intracutaneous irritation	Evaluate the effects of a material extract in contact with the dermis of rabbits. The sample is considered non-irritating if the average erythema/edema rating for any given time is not remarkably greater than that for the negative control.	Negative control: Normal saline and vegetable oil or the corresponding medium used for the test article extraction	PET cloth PTFE thread PTFE impregnated PET thread Black silk suture thread	All rabbits normal. Non-irritating. All rabbits normal. Non-irritating. All rabbits normal. Non-irritating. All rabbits normal. Non-irritating.

Table 2: Biocompatibility Tests and Results (continued)

Test Performed	Test Objective	Samples: Control	Samples: Prima Plus	Results
USP rabbit intramuscular implantation test (subchronic and chronic)	Evaluate the effect of direct exposure of the test material when implanted into the paravertebral muscle of rabbits for 7, 30, 60, or 90 days. A material is biocompatible if there is no gross visible evidence of tissue damage and if histopathological examination shows no signs of chemical-induced cytotoxicity	Negative control: Polyethylene 306	PET cloth	Material is biocompatible (sub-chronic and chronic evaluations) with no signs of chemical-induced cytotoxicity.
			PTFE thread	Material is biocompatible (sub-chronic and chronic evaluations) with no signs of chemical-induced cytotoxicity.
			PTFE impregnated PET thread	Material is biocompatible (sub-chronic and chronic evaluations) with no signs of chemical-induced cytotoxicity.
			Black silk suture thread	Material is biocompatible (sub-chronic and chronic evaluations) with no signs of chemical-induced cytotoxicity.
Guinea pig maximization test	Evaluate the potential of a material to produce sensitization when the material saline extract is repeatedly exposed to guinea pigs. A material is considered to possess no apparent sensitizing properties if the erythema and edema score is not remarkably greater than the negative control.	Negative control: Normal saline and vegetable oil or the corresponding medium used for the test article extraction	PET cloth	All guinea pigs normal. Non-sensitizing.
			PTFE thread	All guinea pigs normal. Non-sensitizing.
			PTFE impregnated PET thread	All guinea pigs normal. Non-sensitizing.
			Black silk suture thread	All guinea pigs normal. Non-sensitizing.

9.1.2. Hydrodynamic Performance

In vitro hydrodynamic performance studies of the Edwards Prima Plus Stentless Bioprosthesis Model 2500P (sizes 19, 25, and 29mm in the subcoronary configuration) were performed in accordance with a tailored protocol reviewed and approved by FDA. Sizes 19, 25, and 31mm Carpentier-Edwards Bioprosthesis (CEBP) Aortic Model 2625 porcine valves were used as a reference in studies requiring concurrent testing of a tissue valve marketed in the U.S. A matrix of the hydrodynamic tests and results is provided in Table 3.

Table 3: Hydrodynamic Testing and Results

Test	Sample Size: Prima Plus Stentless	Sample Size: Reference Valve (CEBP)	Results
Steady Forward Flow Pressure Drop	3 of each	1 of each	Pressure drop < reference valve
Steady Backflow Leakage Testing .	3 of each	1 of each	Leakage rates > reference valve
Pulsatile Flow Pressure Drop	3 of each	1 of each	Relatively low and comparable pressure drops
Pulsatile Flow Regurgitation	3 of each	1 of each	Relatively low and comparable leakage rates
Flow Visualization	1 - 19 mm	N/A[1]	Acceptable flow patterns
Verification of the Bernoulli Relationship	3 of each	N/A	Good correlation in transvalvular pressure drop obtained by Doppler ultrasonography and transducer

Note:
1. N/A = not applicable

In vitro hydrodynamic pulsatile flow performance studies of the Edwards Prima Stentless Bioprosthesis Model 2500 (sizes 19, 25, and 29mm in the subcoronary configuration) were also performed in accordance with the tailored protocol reviewed and approved by FDA. Results

from these studies, when statistically compared with the corresponding results from the studies above, indicate that no clinically significant differences exist in valve performance.

9.1.3. Structural Performance

In vitro structural performance (accelerated wear) studies of the Edwards Prima Plus Stentless Bioprosthesis Model 2500P (sizes 19, 25, and 29mm in the subcoronary configuration) were performed in accordance with testing recommendations outlined in the FDA's *Draft Replacement Heart Valve Guidance* (1994), ISO 5840:1996 *Cardiovascular Implants - Cardiac Valve Prostheses*, and CEN/TC 285 *Non-Active Surgical Implants - Part 1. Heart Valve Substitutes*. A 31mm Carpentier-Edwards Bioprosthesis (CEBP) Aortic Model 2625 porcine valve was used as a reference in studies requiring concurrent testing of a tissue valve marketed in the U.S. All test and reference valves were final production samples. A matrix of the structural performance tests performed on the device are provided in Table 4.

Table 4: Structural Performance Testing and Results

Test	Sample Size: Prima Plus Stentless	Sample Size: Reference Valve	Results
Accelerated Wear Testing	3 of each	1-31 mm	None of the Prima Plus stentless valves or the reference valves showed any failure during durability testing out to 5 equivalent years. Valves displayed good opening throughout durability testing. The visual inspection observations were supported by the valve regurgitation results, which did not increase with durability testing time. The mean pressure drop in Prima Plus stentless and in the control valves decreased after 5 equivalent years durability testing

9.2. Animal Studies

9.2.1. Valve Implantation Studies

Two chronic *in vivo* animal implantation studies were conducted using Edwards Prima Stentless Bioprosthesis Model 2500 valves implanted in a healthy juvenile sheep model. A total of nine valves were implanted in the aortic position using the subcoronary implant technique for a total of five months. All nine animals remained healthy throughout the in-life period. The animals demonstrated no clinical signs indicative of valve-related abnormalities over the five-month (20-week) evaluation period.

Parameters evaluated during the study included physical observations, surgical implant observations, hematology and blood chemistry measurements (prior to implant and at explant), cardiac output and peak transvalvular gradients (at explant only), explant valve analysis for calcium and phosphate content, necropsy observations, and histopathological evaluation of selected organs and of the explanted valve and host tissue.

Clinical Chemistry and Hematology

Hematology and blood chemistry measurements were within normal limits for the age and size of sheep evaluated.

Hemodynamic Performance

Cardiac outputs and peak transvalvular gradient measurements conducted at explant were as follows: cardiac output: 4.1 ± 0.2 L/min, and peak gradient: 27 ± 12 mmHg. Left ventricular catheterization and angiography performed at explant on four sheep showed no detectable

regurgitation in two sheep; mild perivalvular regurgitant jets (1+) in one sheep; and mild regurgitant jets at the valvular coaptation (1+) in one sheep.

Histopathology

All surviving animals were sacrificed at approximately 20 weeks post-implant. Selected systemic organs were grossly examined and microscopically evaluated; no untoward effects were noted. The bioprosthetic valve and sheep host tissue were explanted and x-rayed for appearance prior to being microscopically examined. Histopathologically, there was evidence of calcification in one of the nine sheep. Histologically, this series of explants demonstrated consistent findings with those previously observed in porcine aortic valve bioprostheses. There was evidence of cuspal calcification in one of the nine explanted bioprosthetic valves. The studies also demonstrate that the calcification of the aortic wall tissue is expected to occur at a more rapid rate than that of the cuspal tissue.

Anticalcification Treatment Effectiveness

Samples of the explanted bioprosthetic valve leaflets and the sheep native tissue were evaluated for calcification by measuring calcium (Ca) and phosphate (PO_4) content. The measured values were not considered significant unless they were 1% or greater over the background measurement. All results were under this threshold except for leaflet samples from one sheep and wall samples from one sheep. Of the nine valves, two valves (20%) had elevated quantitative calcium content in the leaflet or wall tissue versus the remaining seven valves after 20 weeks of implantation. The measured levels (mean ± std. dev.) of calcium and phosphate in the explanted leaflet tissue and wall tissue were 6.3 ± 18 mg calcium/g dry tissue weight and 4.4 ± 1.8 mg PO_4/g dry tissue weight, and 4.2 ± 9.7 mg calcium/g dry tissue weight and 8.2 ± 13 mg PO_4/g dry tissue weight, respectively.

Handling Characteristics

All valves were sewn in with relative ease and observed to have good coaptation and fit within each annulus.

9.2.2. Subcutaneous Implantation Studies

Two *in vivo* subcutaneous implantation studies in rats and rabbits were performed. Porcine valve leaflet tissue exposed to the Edwards Lifesciences XenoLogiX process (fixation in glutaraldehyde, processing in a solution containing ethanol and polysorbate 80 [a surfactant], and packaging in glutaraldehyde) was tested against tissue exposed to glutaraldehyde only. Samples were implanted into subcutaneous pockets created in weanling rats approximately 24 to 28 days of age and into juvenile rabbits approximately 8 weeks of age. Implant duration ranged from approximately 30 days to 90 days from the date of implantation. After explant, samples were evaluated for x-ray evaluation, histological evaluation, and quantitative elemental results. The results indicate that porcine leaflet tissues exposed to the Edwards Lifesciences process show a statistically significant reduction in calcification potential when compared to samples that are exposed to the glutaraldehyde fixation process alone ($p<0.05$). The clinical significance of these study results is unknown. A matrix of the subcutaneous implant studies performed is provided in Table 5.

Table 5: Subcutaneous Implant Study Results

Study and Test Parameter	Results: Prima Porcine Leaflet Tissue (n=3)	Results: Glutaraldehyde Porcine Leaflet Tissue (n=3)	Statistical Analysis Results
90-Day Rat Subcutaneous Implant Study			
X-ray evaluation[1]	1.1 ± 1.2	3.0 ± 0.0	$p<0.05$
Histological evaluation[2]	1.4 ± 1.4	3.7 ± 0.5	$p<0.05$
Elemental analyses[3]	Calcium: 56 ± 69 Phosphate: 74 ± 89	Calcium: 218 ± 38 Phosphate: 324 ± 38	$p<0.05$ $p<0.05$
90-Day Rabbit Subcutaneous Implant Study			
X-ray evaluation[1]	1.9 ± 1.2	3.0 ± 0.0	$p<0.05$
Histological evaluation[2]	1.4 ± 1.4	3.3 ± 0.5	$p<0.05$
Elemental analyses[3]	Calcium: 102 ± 77 Phosphate: 126 ± 94	Calcium: 250 ± 25 Phosphate: 360 ± 23	$p<0.05$ $p<0.05$

[1] Explanted tissue is examined by x-ray and graded for degree of calcification: 0=none; 1=mild; 2=moderate; 3=severe. Statistical analyses between groups performed using the Wilcoxon rank sum test.

[2] Explanted tissue is Von Kassa stained and examined histologically for the presence of calcium phosphate: 0=negative; 1=minimal; 2=mild; 3=moderate; 4=marked; 5=severe. Statistical analyses between groups performed using the Wilcoxon rank sum test.

[3] Explanted tissue is analyzed for calcium and phosphate content. Results are reported as mg calcium (or phosphate) per g dry tissue weight. Statistical analyses between groups performed using a two-sided t-test.

9.3. Sterilization

The Edwards Prima Plus Stentless Bioprosthesis Model 2500P is terminally sterilized in buffered glutaraldehyde solution. After terminal sterilization, the product is held in quarantine until sterility is verified per process specifications. Requalification of the process is performed quarterly.

9.4. Shelf Life

Both packaging and product integrity studies were conducted to ensure that the shelf life for the package and product is maintained for a minimum of four (4) years. Packaging integrity studies consisted of real-time and accelerated aging, whereas product integrity samples underwent real-time aging.

9.4.1. Package Integrity

The integrity of the valve packaging components was evaluated after exposure to the maximum steam sterilization cycles and terminal liquid sterilization process. Package integrity testing consisted of physical (leak and glutaraldehyde packaging solution concentration) and sterility testing before and after exposure to glutaraldehyde in an elevated temperature condition, and after a simulated shipping process. Accelerated aging results simulating 0, 1, and 4 years real-time demonstrated package integrity throughout the 4-year shelf life period. Packaging validation studies conducted after maximum exposure to the terminal liquid sterilization process demonstrated that this sterilization method does not adversely affect package integrity.

9.4.2. Product Integrity

Non-biological Component Shelf Life

Thread and cloth components were evaluated by functional testing of the individual non-biological materials after 4 years of real-time storage in glutaraldehyde. Results demonstrate that storage in glutaraldehyde for up to 4 years has minimal effect on the properties and functions of the individual non-biological materials used in the valve.

Tissue Shelf Life

Porcine valve tissue stability and storage solution adequacy were evaluated using three parameters: shrinkage temperature, moisture content, and glutaraldehyde concentration. Tissue samples subjected to real-time aging were evaluated at designated intervals for shrinkage temperature and moisture content. Glutaraldehyde content of the storage solution was determined by glutaraldehyde assay.

The results demonstrated that the tissue shrinkage temperature is stable over time at the recommended storage temperature of 4° to 25°C for a duration exceeding the 4-year shelf life. The effects of storage time on the moisture content were monitored because chemical changes in the tissue could affect the hydration level of the tissue. A gradual decrease in moisture content with time was seen, with a more rapid decline at higher temperatures. Glutaraldehyde assays showed the expected trend of a gradual increase in concentration over time, with a more rapid increase at higher storage temperatures. Acceptable levels of glutaraldehyde concentration were maintained for the 4-year shelf life period in the recommended storage temperature range of 4° to 25°C. These results demonstrate product integrity to 4 years.

10. SUMMARY OF CLINICAL STUDIES

The safety endpoints captured in the prospective studies were adverse events; blood analyses were used to confirm the absence or presence of hemolysis, hemolytic anemia, and endocarditis. The safety results are provided above in Table 1. Effectiveness endpoints were New York Heart Association (NYHA) functional classification and echocardiographic assessments. Preoperative and operative patient demographics are presented below, followed by the effectiveness results. There were insufficient clinical data to support the safety and effectiveness of this device for root inclusion or full root implantation.

Table 6: Preoperative Patient Demographics

Variable	Category	Study Results (N=366; 1074.2 total pt-yrs.)	
		n	% (n/N)[1]
Age at implant	Mean ± SD	366	70.2± 7.1
Gender	Male	217	59.3%
	Female	149	40.7 %
NYHA Classification	I	23	6.3%
	II	138	37.7%
	III	177	48.4%
	IV	25	6.8%
	Not reported	3	0.8%
Diagnosis	Stenosis	243	66.4%
	Regurgitation	27	7.4%
	Mixed Disease	94	25.7%
	Malfunctioning prosthesis	2	0.5%

Note:

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

Table 7: Operative Patient Demographics

Variable	Category	Study Results (N=366; 1074.2 total pt-yrs.)	
		n	% (n/N)[1]
Etiology[2]	Calcification/degeneration	297	81.1%
	Rheumatic heart disease	33	9.0%
	Congenital abnormalities	31	8.5%
	Other[3]	6	1.6%
Concomitant Procedures[2]	None	230	62.8%
	CABG[4]	122	33.3%
	AAA[5] repair	5	1.4%
	Mitral valve repair	3	0.8%
	Mitral valve replacement	1	0.3%
	Other[6]	8	2.2%
Pre-existing Conditions[2]	None	143	39.1%
	TIA/CVA[7]	26	7.1%
	Congestive Heart Failure	36	9.8%
	Arrhythmias	37	10.1%
	Systemic Hypertension	88	24.0%
	CAD[8]/CABG	133	36.3%
Valve Size (mm)	19	7	1.9%
	21	47	12.8%
	23	85	23.2%
	25	123	33.6%
	27	81	22.1%
	29	23	6.3%

Notes:

1. n = number of patients in each category; N = total number of study patients
2. May be more than one per patient
3. Includes previously failed prosthesis, root dilatation, and ischemic disease
4. CABG = Coronary Artery Bypass Graft
5. AAA=Abdominal Aortic Aneurysm
6. Includes carotid endarterectomy, fistula exploration, ventricular septal defect repair, aortotomy, intra-aortic balloon pump, tumorectomy, and interatrial septum exploration
7. TIA = Transient ischemic attack. CVA = Cerebrovascular accident.
8. CAD = Coronary Artery Disease

Table 8: Effectiveness Outcomes, Functional NYHA

NYHA Functional Class	Preoperative Assessment		Postoperative Assessments			
			1 Year		4 to 5 Years	
	n/N[1]	%	n/N	%	n/N	%
I	17/313	5.4%	184/250	73.6%	58/160	36.3%
II	119/313	38.0%	23/250	9.2%	37/160	23.1%
III	156/313	49.8%	3/250	1.2%	8/160	5.0%
IV	21/313	6.7%	0/250	0.0%	1/160	0.6%
Not Available	0/313	0.0%	40/250	16.0%	56/160	35.0%

Notes:

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

Table 9: Effectiveness Outcomes, Hemodynamic Results[1]

Hemodynamic Parameter	Results By Valve Size					
	19mm	21mm	23mm	25mm	27mm	29mm
Discharge (n=312)						
Mean gradient[2]	n = 7	n = 41	n = 68	n = 95	n = 69	n = 20
• mean ± sd	15.4 ± 7.4	15.9 ± 7.5	13.5 ± 5.6	10.7 ± 5.4	9.5 ± 5.3	7.0 ± 5.2
• min, max	6.0, 24.0	4.0, 37.0	2.0, 28.0	1.0, 34.0	1.0, 30.0	1.0, 21.0
EOA[3]	n = 6	n = 37	n = 62	n = 80	n = 55	n = 16
• mean ± sd	1.05 ± 0.32	1.17 ± 0.33	1.35 ± 0.37	1.68 ± 0.60	1.87 ± 0.54	2.71 ± 1.64
• min, max	0.70, 1.45	0.50, 1.96	0.64, 2.26	0.89, 4.61	1.15, 3.60	1.20, 8.19
Regurgitation[4]	n = 7	n = 43	n = 70	n = 98	n = 72	n = 21
0	7 (100%)	33 (76.7%)	45 (64.3%)	66 (67.3%)	50 (69.4%)	18 (85.7%)
1+	0 (0.0%)	9 (20.9%)	17 (24.3%)	25 (25.5%)	13 (18.1%)	1 (4.8%)
2+	0 (0.0%)	1 (2.3%)	8 (11.4%)	6 (6.1%)	7 (9.7%)	2 (9.5%)
3+	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.0%)	0 (0.0%)	0 (0.0%)
4+	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Not available	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (2.8%)	0 (0.0%)
1 year (n=208)						
Mean gradient[2]	n = 7	n = 24	n = 46	n = 72	n = 45	n = 5
• mean ± sd	17.8 ± 9.0	14.5 ± 6.4	11.5 ± 8.7	9.5 ± 5.8	6.7 ± 3.0	4.4 ± 2.7
• min, max	6.3, 31.0	5.0, 29.0	2.0, 55.9	1.9, 29.0	2.0, 17.0	1.5, 8.0
EOA[3]	n = 7	n = 21	n = 44	n = 61	n = 37	n = 4
• mean ± sd	0.88 ± 0.20	1.20 ± 0.48	1.43 ± 0.43	1.74 ± 0.53	2.04 ± 0.62	2.64 ± 0.56
• min, max	0.68, 1.30	0.76, 2.50	0.60, 2.64	0.80, 3.70	0.76, 3.42	2.12, 3.22
Regurgitation[4]	n = 7	n = 26	n = 48	n = 74	n = 45	n = 5
0	5 (71.4%)	16 (61.5%)	29 (60.4%)	45 (60.8%)	28 (62.2%)	3 (60.0%)
1+	2 (28.6%)	9 (34.6%)	11 (22.9%)	17 (23.0%)	15 (33.3%)	1 (20.0%)
2+	0 (0.0%)	0 (0.0%)	8 (16.7%)	11 (14.9%)	2 (4.4%)	1 (20.0%)
3+	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.4%)	0 (0.0%)	0 (0.0%)
4+	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Not available	0 (0.0%)	1 (3.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
1 to 5 Years (n=112)						
Mean gradient[2]	n = 2	n = 13	n = 26	n = 38	n = 21	n = 1
• mean ± sd	27.9 ± 5.8	15.9 ± 7.0	9.9 ± 5.7	8.8 ± 4.9	6.5 ± 3.9	4.2
• min, max	23.8, 32.0	5.5, 32.2	3.0, 23.2	1.3, 23.0	1.0, 14.0	4.2, 4.2
EOA[3]	n = 1	n = 12	n = 23	n = 30	n = 16	n = 0
• mean ± sd	1.00	1.10 ± 0.36	1.60 ± 0.51	1.91 ± 0.36	2.06 ± 0.58	--
• min, max	1.00, 1.00	0.20, 1.68	0.47, 2.60	0.93, 4.06	1.20, 3.20	--
Regurgitation[4]	n = 5	n = 17	n = 31	n = 41	n = 21	n = 1
0	4 (80.0%)	11 (64.7%)	17 (54.8%)	24 (58.5%)	17 (81.0%)	0 (0.0%)
1+	0 (0.0%)	6 (35.3%)	9 (29.0%)	12 (29.3%)	2 (9.5%)	0 (0.0%)
2+	0 (0.0%)	0 (0.0%)	4 (12.9%)	1 (2.4%)	1 (4.8%)	1 (100%)
3+	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (4.8%)	0 (0.0%)
4+	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Not available	1 (20.0%)	0 (0.0%)	1 (3.2%)	4 (9.8%)	0 (0.0%)	0 (0.0%)

Notes:
1. Hemodynamic evaluations were performed using transthoracic echocardiography (TTE).
2. Mean gradient in mm Hg.
3. EOA: Effective Orifice Area, cm^2
4. Regurgitation: 0 = none; 1+ = trivial; 2+ = mild; 3+ = moderate; 4+ = severe

10.1. Description of Patients and Analysis for Gender Bias

A gender bias was not found in the Edwards Lifesciences clinical studies.

Of the 366 patients followed in the clinical studies, 59% were male and 41% were female. This gender distribution is consistent with the incidence of patients presenting for aortic valve replacement in the U.S. The log-rank test was used to compare all adverse event outcomes by gender. No significant difference in outcomes between males and females were noted for any valve-related adverse event. Therefore, the results for valve-related adverse events following aortic valve replacement in this study are representative for both men and women.

11. RISK-BENEFIT ANALYSIS

Laboratory and clinical data provide reasonable assurance that the Edwards Prima Plus Stentless Bioprosthesis Model 2500P is safe and effective when used according to the approved labeling.

12. CONCLUSIONS DRAWN FROM THE STUDIES

The results from pre-clinical laboratory studies performed on the Edwards Prima Plus Stentless Bioprosthesis Model 2500P for biocompatibility testing, hydrodynamic performance testing (steady forward flow pressure drop, steady backflow leakage testing, pulsatile flow pressure drop, pulsatile flow regurgitation, flow visualization, and verification of the Bernoulli Relationship), and structural performance testing (accelerated wear testing) demonstrate that this device is suitable for long-term implant.

The animal studies show that the Edwards Prima Plus Stentless Bioprosthesis Model 2500P is safe for valve replacement.

The clinical studies submitted in the PMA provide sound scientific evidence that the Edwards Prima Plus Stentless Bioprosthesis Model 2500P is safe and effective for the replacement of native or prosthetic aortic valves using the subcoronary implantation technique.

13. 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, a FDA advisory committee, for review and recommendation because the information in the PMA substantially duplicates information previously reviewed by this panel.

14. FDA DECISION

The applicant's manufacturing and control facilities were inspected and the facilities were found to be in compliance with the Quality System Regulation (QSR)(21 CFR Part 820).

FDA issued an approval on February 27, 2001.

15. APPROVAL SPECIFICATIONS

Directions for use: See Final Approved Labeling (Instructions for Use).

Hazards to Health from Use of the Device: See Indications, Contraindications, Warnings, Precautions, and Adverse Events in the Final Draft Labeling (Instructions for Use).

Post-approval Requirements and Restrictions: See Approval Order.