

SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

I. GENERAL INFORMATION

Device Generic Name: Replacement Heart Valve

Device Trade Name: Edwards Pericardial Mitral Bioprosthesis, Model 11000M

Device Product Code: LWR

Applicant's Name and Address: Edwards Lifesciences LLC
One Edwards Way
Irvine, California 92614

Date(s) of Panel Recommendation: None

Premarket Approval Application (PMA) Number: P150048/S012

Date of FDA Notice of Approval: August 9, 2018

The original PMA (P150048) was approved on June 29, 2017 and is indicated for the replacement of native or prosthetic aortic heart valves. The SSED to support the indication is available on the CDRH website (https://www.accessdata.fda.gov/cdrh_docs/pdf15/P150048B.pdf) and is incorporated by reference here. The current supplement was submitted to add the mitral position, the Edwards Pericardial Mitral Bioprosthesis, Model 11000M, to its bioprosthesis product line.

II. INDICATIONS FOR USE

The Edwards Pericardial Mitral Bioprosthesis, Model 11000M is indicated for the replacement of native or prosthetic mitral heart valves.

III. CONTRAINDICATIONS

There are no known contraindications.

IV. WARNINGS AND PRECAUTIONS

The warnings and precautions can be found in the Edwards Pericardial Mitral Bioprosthesis labeling.

V. DEVICE DESCRIPTION

The Edwards Pericardial Mitral Bioprosthesis, Model 11000M (**Figure 1**) is a stented trileaflet valve comprised of RESILIA bovine pericardial tissue. RESILIA tissue is

created by treating bovine pericardial tissue with Edwards Integrity Preservation. The technology incorporates a stable capping anticalcification process, which blocks residual aldehyde groups that are known to bind with calcium. The technology also incorporates tissue preservation with glycerol, which allows the valve to be stored without a traditional liquid-based solution, such as glutaraldehyde. The valve is stored under dry packaging conditions and consequently does not require rinsing prior to implantation. The Model 11000M valve is available in sizes 25, 27, 29, 31, and 33mm.

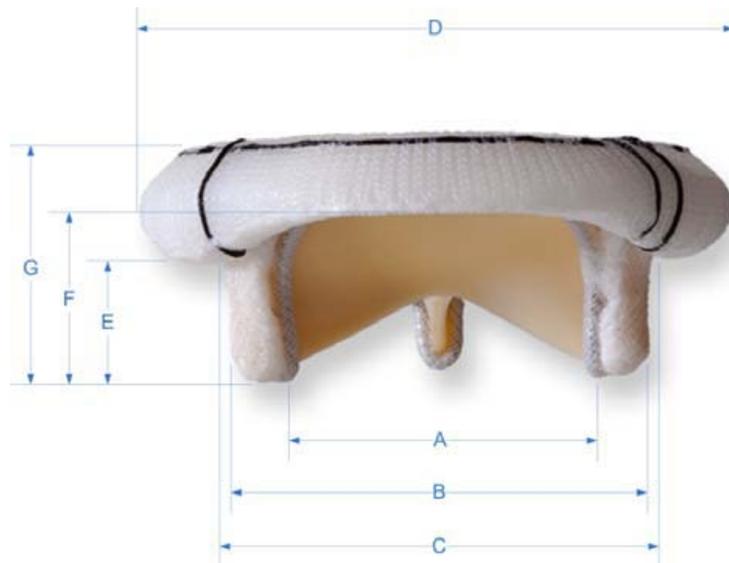


Figure 1: Edwards Pericardial Mitral Bioprosthesis, Model 11000M

The three (3) leaflets are mounted on a flexible cobalt-chromium alloy wireform. A thin cobalt-chromium alloy band and polyester support band surround the base of the valve below the wireform frame to provide structural support for the orifice. A silicone-rubber sewing ring that is covered with a porous, seamless polytetrafluoroethylene (PTFE) cloth is attached to the wireform frame and is scalloped to conform to the native mitral annulus. A holder is attached to the valve by means of sutures to facilitate handling and suturing the valve during the implant procedure. The Model 11000M is visible under fluoroscopy to allow for identification of the valve's inflow and outflow edges.

VI. ALTERNATIVE PRACTICES AND PROCEDURES

There are several other alternatives for the correction of diseased and malfunctioning heart valves. Alternative treatments include palliative medical therapy, mitral valve repair using an annuloplasty ring, or surgical replacement of the mitral valve with another commercially available mechanical or bioprosthetic valve. The choice of repair or replacement depends on an assessment of patient factors which include age, preoperative condition, anatomy and the patient's ability to tolerate long-term anticoagulant therapy. Each alternative has its own advantages and disadvantages. A patient should fully

discuss these alternatives with his/her physician to select the method that best meets expectations and lifestyle.

VII. MARKETING HISTORY

The Edwards Pericardial Mitral Bioprosthesis, Model 11000M received CE Mark approval for European commercial distribution in the following countries: Austria, Belgium, Bulgaria, Croatia, Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Iceland, Ireland, Italy, Latvia, Liechtenstein, Lithuania, Luxemburg, Malta, Netherlands, Norway, Poland, Portugal, Romania, Slovakia, Slovenia, Spain, Sweden, Switzerland, Turkey, and the United Kingdom. The device has not been withdrawn from marketing for any reason related to its safety or effectiveness.

VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

Below is a list of the potential adverse effects (e.g., complications) associated with the use of the device.

- Allergic reaction/immunological response
- Angina
- Annulus (damage, dissection, tear)
- Arterial dissection
- Asystole and/or cardiac arrest
- Bleeding
 - Peri- or post-procedural
 - Anticoagulant related
 - Pericardial tamponade
 - Hematoma
 - Hemorrhage
 - Cerebrovascular
- Blood – Coagulopathy
- Blood – Hemolysis/Hemolytic Anemia
- Blood – Anemia
- Blood Pressure alteration (hypotension, hypertension)
- Cardiac – Arrhythmias/Conduction Disturbances
- Cardiogenic shock
- Coronary artery ostia occlusion
- Deep vein thrombosis (DVT)
- Disseminated intravascular coagulation (DIC)
- Embolism
- Esophageal tear/rupture
- Endocarditis
- Hypoxemia
- Infection – local, wound or systemic
- Myocardial infarction

- Multi-system organ failure (MOF)
- Neurologic Events
 - Stroke (CVA)
 - Transient Ischemic Attack (TIA)
- Pericardial effusion
- Pleural effusion
- Pulmonary edema
- Pneumonia
- Prosthetic Insufficiency – Regurgitation/Stenosis
- Reduced exercise tolerance
- Renal failure, acute
- Renal insufficiency
- Respiratory failure
- Thrombocytopenia, (Non-HIT)
- Thrombocytopenia, heparin induced (HIT)
- Thromboembolism
 - Arterial, venous, peripheral, central
- Transvalvular or Valvular Leaking
- Valve dislodgement/instability
- Valve – Nonstructural dysfunction
 - Paravalvular Leak
 - Leaflet impingement
 - Leaflet tissue damage (instruments /sutures)
 - Pannus
 - Prosthesis Mismatch (PPM) (due to inappropriate sizing)
 - Distortion at implant
- Valve – Structural dysfunction/deterioration
- Valve – Thrombosis

- It is possible that these complications may lead to:
 - Reoperation
 - Explantation
 - Permanent disability
 - Death

For the specific adverse events that occurred in the clinical study, see **Section X** below.

IX. SUMMARY OF PRECLINICAL STUDIES

A summary of previously reported preclinical studies can be found in the SSED for the original PMA (https://www.accessdata.fda.gov/cdrh_docs/pdf15/P150048B.pdf).

Additional testing performed to support the specific conditions applicable to the mitral indication for Model 11000M is presented below.

A. Laboratory Studies

1. Hydrodynamic Performance

In vitro hydrodynamic testing was conducted on the Edwards Pericardial Mitral Bioprosthesis, Model 11000M. Studies were conducted in accordance with ISO 5840:2009 Cardiovascular Implants-Cardiac Valve Prostheses. The tests are summarized in **Table 1** below.

Table 1: Model 11000M Hydrodynamic Testing and Results

Test	Purpose/ Objective	Test and reference articles	Results
Flow Visualization	To qualitatively assess the flow characteristics of the valve.	Test: Model 11000M size: 25mm Reference: Carpentier-Edwards PERIMOUNT Magna Ease size 25mm	Model 11000M offers acceptable aortic flow patterns throughout the entire cardiac cycle. No retrograde jets or valvular incompetence were observed.
Bernoulli Coefficient	Use pressure drop testing to confirm the Bernoulli coefficient for Model 11000A is consistent with the theoretical coefficient.	Test: Model 11000M sizes: 25mm, 29mm, and 33mm Reference: PERIMOUNT Magna Ease sizes: 25mm, 29mm, and 33mm	Pressure drop testing for Model 11000M test valves show no statistically significant differences from the Carpentier-Edwards PERIMOUNT Magna Ease reference valves that previously demonstrated correlation with the Bernoulli relationship. These data justify using a Bernoulli coefficient of four with Model 11000M.
Steady Forward Flow Test	To determine pressure drop at various steady forward flow rates.	Test: Model 11000M sizes: 25-31mm Reference: PERIMOUNT Magna Ease sizes: 25-31mm	Model 11000M offers acceptable hydrodynamics with pressure gradients and effective orifice areas (EOA) that are comparable to the reference valves.
Steady Back Flow Test	To determine the leakage rate at various steady back flow pressures.	Test: Model 11000M sizes: 25-31mm	Model 11000M offers acceptable performance in terms of its competency to prevent significant transvalvular aortic backflow

Test	Purpose/ Objective	Test and reference articles	Results
		Reference: PERIMOUNT Magna Ease sizes: 25-31mm	during the diastolic phase, with results that are comparable to the reference valves.
Pulsatile Flow Pressure Drop	To determine pressure drop and effective orifice area performance under pulsatile flow conditions.	Test: Model 11000M sizes: 25- 31mm Reference: PERIMOUNT Magna Ease sizes: 25-31mm	Model 11000M offers acceptable hydrodynamics and meet the effective orifice area required by ISO 5840:2009/ISO 5840-2:2015, with results that are comparable to the reference valves.
Pulsatile Flow Regurgitation	To determine regurgitation performance under pulsatile flow conditions.	Test: Model 11000M sizes: 25- 31mm Reference: PERIMOUNT Magna Ease sizes: 25-31mm	Model 11000M offers acceptable hydrodynamics with regurgitant fractions that meet ISO 5840:2009/ISO 5840-2:2015, with results that are comparable to the reference valves.

2. Structural Performance

The structural performance of the Edwards Pericardial Mitral Bioprosthesis, Model 11000M, was evaluated per the testing listed in **Table 2**. Studies were conducted in accordance with ISO 5840:2009 Cardiovascular Implants-Cardiac Valve Prostheses.

Table 2: Model 11000A and 11500A Structural Performance Evaluation

Test	Purpose/ Objective	Test and reference articles	Results
Accelerated Wear Testing	To assess long-term performance of Model 11000M valve through accelerated wear.	Test: Model 11000M sizes: 25- 31mm Reference: PERIMOUNT Magna Ease sizes: 25-31mm	All valves survived durability testing to 200 million cycles in accelerated wear testers without functional impairment. After 200 million cycles all valves met the EOA and regurgitation fraction requirements of ISO 5840:2009.
Dynamic Failure Mode	To obtain information about the failure modes affecting the	Test Model 11000M sizes: 25- 31mm	All of the failures of the test valves occurred at pressures well beyond what would be expected <i>in vivo</i> .

Test	Purpose/ Objective	Test and reference articles	Results
	durability of the valve.	Reference: PERIMOUNT Magna Ease sizes: 25-31mm	
Stent Deflection	To determine the relationship between peak pressure difference and stent post deflection of the study valve.	Test: Model 11000M sizes: 25-31mm Reference: PERIMOUNT Magna Ease sizes: 25-31mm	Testing demonstrated no statistical difference between Model 11000M and PERIMOUNT Magna Ease which has previously shown acceptable stent fatigue results.
Sewing Ring Integrity	To determine the force required to separate the sewing ring from the stent subassembly of the study valve.	Test: Model 11000M size: 25mm	Test results demonstrated that the sewing ring integrity of Model 11000M is acceptable.
Suture Retention	To evaluate the sewing ring suture retention strength of the study valve.	Test: Model 11000M size: 25mm	Test results demonstrated that the sewing ring integrity of Model 11000A and Model 11500A is acceptable.
Corrosion Resistance	To characterize the corrosion resistance of metallic components in accordance with ASTM F2129.	Test: Model 11000M sizes: 25- 31mm Reference: PERIMOUNT Magna Ease sizes: 25-31mm	Test results show high corrosion resistance of the cobalt chromium stiffener band/wireform.
Tissue Ultimate Tensile Strength	To determine the tensile strength of processed tissue.	Test: RESILIA tissue leaflets Reference: Tissue processed with Edwards ThermaFix process	Test results demonstrate the ultimate tensile strength of the RESILIA tissue is not inferior to the reference tissue.
Tissue Stress Relaxation	To determine the relaxation properties of processed tissue.	Test: RESILIA tissue leaflets Reference: Tissue processed with Edwards	Test results demonstrate the stress relaxation of the RESILIA tissue is not inferior to the reference tissue.

Test	Purpose/ Objective	Test and reference articles	Results
		ThermaFix process	
Tissue Shrinkage Temperature	To determine the shrinkage temperature of the RESILIA tissue.	Test: RESILIA tissue leaflets Reference: Tissue processed with Edwards ThermaFix process	Test results demonstrate the shrink temperature of the RESILIA tissue is equivalent to the reference tissue.

3. Animal Studies

The performance of the Edwards Pericardial Mitral Bioprosthesis, Model 11000M, was evaluated in the mitral position in the young adult ovine model. A total of 10 test articles (Model 11000M) and eight (8) control articles (four (4) each of Carpentier-Edwards PERIMOUNT Magna Mitral Pericardial Bioprosthesis Models 7000TFX and Carpentier-Edwards PERIMOUNT Theon Mitral Pericardial Bioprosthesis 6900PTFX) were implanted in the mitral position for 20 weeks. The performance of the test and control valves was assessed by evaluating the general health of each animal, *in vivo* hemodynamics, and an examination of both the animal and valve at explant.

Study results demonstrated that the Model 11000M mitral valve was biocompatible in the ovine model, had normal healing, was durable, and had similar performance to the control valves, models 7300TFX and 6900PTFX, when implanted in adult sheep for 20 weeks. Implant characteristics, calcification, thrombus, and vegetations were similar among the three (3) groups. The valves were all hemocompatible, as there was no clinically significant hemolysis or valve related thromboemboli observed among the test and control groups.

B. Additional Studies

1. Magnetic Resonance Imaging (MRI) Compatibility

Non-clinical testing has demonstrated that the Edwards Pericardial Mitral Bioprosthesis, Model 11000M, is MR Conditional. A patient with the Edwards Pericardial Mitral Bioprosthesis, Model 11000M, can be scanned safely under the following conditions:

- Static magnetic field of 1.5 Tesla or 3 Tesla only.
- Maximum spatial gradient magnetic field of 3,000 gauss/cm (30 T/m) or less.

- Maximum MR system-reported, whole-body averaged specific absorption rate (SAR) of 2.0 W/kg in Normal Operating Mode.

Under the scan conditions defined above, the Edwards Pericardial Mitral Bioprosthesis, Model 11000M, is expected to produce a maximum *in vivo* temperature rise of 2.3°C after 15 minutes of continuous scanning.

In non-clinical testing, the image artifact extends approximately 11.5 mm from the Model 11000M valve when imaged with a spin echo pulse sequence and 36 mm from the device when imaged with a gradient echo pulse sequence and a 3 Tesla MRI system. The artifact obscures the device lumen.

2. Package Integrity and Shelf Life

The packaging for the Edwards Pericardial Mitral Bioprosthesis, Model 11000M, consists of a double barrier tray package sealed with a Tyvek lid. The double tray package is in a foil pouch which is in a carton that includes the Instructions for Use. A temperature indicator is displayed through a window on the side panel of the carton to identify products exposed to transient temperature extremes. The shelf life of the Edwards Pericardial Mitral Bioprosthesis is two (2) years as demonstrated by package and functional product integrity testing on aged valves and packaging.

X. SUMMARY OF PRIMARY CLINICAL STUDY

The applicant performed a clinical study to establish a reasonable assurance of safety and effectiveness of heart valve replacement with the Edwards Pericardial Mitral Bioprosthesis, Model 11000M, for patients who require replacement of their native or prosthetic mitral valve in the US and in the European Union under IDE # G120108. Data from this clinical study were the basis for the PMA approval decision. A summary of the clinical study is presented below.

The COMMENCE study is a two-arm clinical study to assess the safety and effectiveness of the Edwards Pericardial Aortic Bioprosthesis, Model 11000A, and the Edwards Pericardial Mitral Bioprosthesis, Model 11000M. The aortic valve, Model 11000A, was approved under P150048 on July 29, 2017. The Edwards Pericardial Mitral Bioprosthesis, Model 11000M, was assessed under the mitral arm of the COMMENCE study and has a similar valve design and identical tissue treatment to Model 11000A. Data from the aortic arm of the COMMENCE clinical study was used to supplement that of the mitral arm to support the safety and effectiveness of Model 11000M as a surgical replacement heart valve.

A. Study Design

Patients were treated between January 2013 and July 2016. The database for this PMA reflected data collected through July 20, 2016, and included 777 patients (694 aortic patients and 83 mitral patients). Of these patients, 771 were implanted with the trial valve (689 aortic patients and 82 mitral patients). There were 36 investigational sites (27 sites in the aortic arm and 17 sites in the mitral arm).

The study was an open-label, prospective, non-randomized, multicenter clinical study for the Edwards Pericardial Mitral Bioprosthesis, Model 11000M. Adverse Event (AE) rates as compared to a set of Objective Performance Criteria (OPC) and to literature-based control data were used for the design and analysis of this study. New York Heart Association (NYHA) functional classification status and hemodynamic performance of the valve by echocardiography were evaluated using a comparison to literature-based control data. All echocardiographic data were evaluated by an independent Echocardiographic Core Laboratory (ECL). The study also used an independent Data Monitoring Committee (DMC) that was instructed to notify Edwards Lifesciences of any safety or compliance issues and a Clinical Events Committee (CEC) that was responsible for adjudicating endpoint-related events reported during the trial per definitions established *a priori*.

1. Clinical Inclusion and Exclusion Criteria

Enrollment in the COMMENCE study was limited to patients who met the following inclusion criteria:

1. Is 18 years of age or older
2. Provides written informed consent prior to trial procedures
3. Agrees to attend follow-up assessments for up to 5 years and is willing to comply with specified follow-up evaluations at clinical investigational sites that are participating in the COMMENCE trial and/or obtain the protocol-specified diagnostic tests at centers that are under the same IRB or the same healthcare system
4. Diagnosed with aortic or mitral valve disease requiring valve replacement based on preoperative evaluation
5. Scheduled to undergo planned aortic or mitral valve replacement with or without concomitant bypass surgery
6. Scheduled to undergo planned aortic valve replacement with or without resection and replacement of the ascending aorta from the sinotubular junction and without the need for circulatory arrest for hemi arch or arch replacement

Patients were not permitted to enroll in the COMMENCE study if they met any of the following exclusion criteria:

1. Requires emergency surgery
2. Requires multiple valve replacement/repair (with the exception of mitral valve replacement with tricuspid valve repair)
3. Has prior valve surgery, which included implant of a bioprosthetic valve, mechanical valve, or annuloplasty ring that will remain *in situ*
4. Requires a surgical procedure outside of the cardiac area (e.g., vascular bypass)
5. Requires surgical replacement of the aortic root
6. Has active endocarditis/myocarditis or endocarditis/myocarditis within 3 months to the scheduled aortic or mitral valve replacement surgery
7. Has renal insufficiency as determined by creatinine (S-Cr) level ≥ 2.5 mg/dL or end-stage renal disease requiring chronic dialysis at screening visit
8. Has MRI or CT scan confirmed stroke, cerebrovascular accident (CVA) or transient ischemic attack (TIA) within 6 months (180 days) prior to planned valve surgery
9. Has acute myocardial infarction (MI) within 30 days prior to planned valve surgery
10. Has presence of non-cardiac disease limiting life expectancy to less than 12 months
11. Diagnosed with hypertrophic obstructive cardiomyopathy (HOCM)
12. Diagnosed with abnormal calcium metabolism and hyperparathyroidism
13. Exhibits left ventricular ejection fraction $\leq 20\%$ as validated by diagnostic procedure prior to planned valve surgery
14. Echocardiographic evidence of an intra-cardiac mass, thrombus, or vegetation
15. Hemodynamic or respiratory instability requiring inotropic support, mechanical circulatory support, or mechanical ventilation within 30 days prior to planned valve surgery
16. Documented leukopenia ($WBC < 3.5 \times 10^3/\mu L$), acute anemia ($Hgb < 10.0$ gm/dL or 6 mmol/L), thrombocytopenia (platelet count $< 50 \times 10^3/\mu L$) accompanied by history of bleeding diathesis or coagulopathy
17. Has prior organ transplant or is currently an organ transplant candidate
18. Current or recent participation (within 6 weeks prior to surgery) in another drug or device trial
19. Was previously implanted with the investigational device
20. Pregnant (female subject of childbearing potential only), lactating, or planning to become pregnant during the duration of participation in trial
21. Currently incarcerated or unable to give voluntary informed consent
22. Documented history of substance (drug or alcohol) abuse within the last 5 years prior to implant
23. Requires concomitant left ventricular assist device (LVAD) placement

2. Follow-Up Schedule

All patients were scheduled to return for follow-up examinations at discharge, 3 months, 1 year, and annually thereafter for a minimum of 5 years postoperatively.

Preoperatively, demographic and baseline data were collected. Postoperatively, the objective parameters measured during the study included echocardiographic data and NYHA functional classification. Adverse events and complications were recorded at all visits.

The key time-points are shown below in the tables summarizing safety and effectiveness.

3. Clinical Endpoints

With regards to safety, the following criteria were evaluated:

1. Rate of Structural Valve Deterioration (SVD) of the trial valve through the 1-year (post-operative discharge day 390) follow-up visit.
2. Adverse Event (AE) rates defined by the Objective Performance Criteria (OPC) reported in Table R.1 in EN ISO 5840:2009, Annex R.

With regards to effectiveness, the following criteria were evaluated:

1. New York Heart Association (NYHA) functional classification status
2. Hemodynamic performance evaluated by echocardiography

With regard to success/failure criteria, success was defined by comparing OPC category event rates with 2x the OPC values listed in ISO 5840:2009 as well as a comparison of literature controls from commercially available devices.

B. Accountability of PMA Cohort

At the time of database lock, of 771 patients enrolled and implanted in the aortic and mitral cohorts of the PMA study, 97.3% (716/736) patients were available for analysis of the primary endpoint (12 months), and 1734.8 patient-years were collected (1671.8 late patient-years) for the combined aortic and mitral cohorts. A total of 121.4 patient-years was collected (114.6 late patient-years) for the mitral only cohort. Of the 771 enrolled subjects, 99.3% (689/694) of aortic subjects were successfully implanted with the Model 11000A and 98.8% (82/83) of mitral subjects were successfully implanted with Model 11000M. Subject compliance is detailed in **Table 3**.

Table 3: Subject Compliance – Combined Aortic and Mitral Cohorts

Visit Interval	Eligible Subjects (N ₁)	Follow-up Compliance % ¹ (n)	Censored ² (N ₂)
Combined Aortic and Mitral Arms			
Pre-operative	771	100.0% (771)	0
Discharge	764	100.0% (764)	7
1 Month	762	99.6% (759)	9
3 Month	757	97.0% (734)	14
1 Year	736	97.3% (716)	35
2 Year	648	94.3% (611)	123
3 Year	302	92.4% (279)	469
Mitral Arm			
Pre-operative	82	100.0% (82)	0
Discharge	82	100.0% (82)	0
1 Month	81	100.0% (81)	1
3 Month	80	95.0% (76)	2
1 Year	75	97.3% (73)	7
2 Year	31	96.8% (30)	51
3 Year	3	100.0% (3)	79

¹ % compliance = 100*n/N₁

² Censoring due to pending visit, explant, study exit, death, or lost to follow-up

C. Study Population Demographics and Baseline Parameters

The demographics of the study population are typical for a mitral heart valve study performed in the US. Baseline demographics for the combined aortic and mitral cohorts and the mitral cohort alone are shown in **Table 4**.

Table 4: Preoperative Subject Demographics

	Combined Aortic and Mitral Cohorts	Mitral Cohort Only
Age at Implant	N: Mean ± SD (Min - Max)	N: Mean ± SD (Min - Max)
Age (years)	771: 67.2 ± 11.4	82: 68.9 ± 9.4
Sex	% (n/N)	
Female	31.4% (242/771)	58.5% (48/82)
Male	68.6% (529/771)	41.5% (34/82)
NYHA Classification	% (n/N)	% (n/N)
Class I	21.9% (169/771)	6.1% (5/82)
Class II	48.4% (373/771)	35.4% (29/82)
Class III	26.2% (202/771)	41.5% (34/82)
Class IV	3.5% (27/771)	17.1% (14/82)
Risk Scores	N: Mean ± SD (Min - Max)	N: Mean ± SD (Min - Max)
STS risk of mortality (%) ¹	578: 2.2±2.3 (0.3, 23.3)	40: 4.8±4.7 (0.6, 23.3)
EuroSCORE II (%)	771: 3.1±4.0 (0.5, 36.0)	82: 8.0±7.5 (0.7, 36.0)

¹ STS scores only calculated for the following:

- Aortic subjects undergoing isolated aortic valve replacement (AVR) or AVR and coronary artery bypass grafting.
- Mitral subjects undergoing isolated mitral valve replacement (MVR) or MVR and coronary artery bypass grafting.

D. Safety and Effectiveness Results

1. Safety Results

The analysis of safety was based on data from the 82 patients who received the Edwards Pericardial Mitral Bioprosthesis and the 689 patients who received the Edwards Pericardial Aortic Bioprosthesis over the course of a combined 1671.8 late patient-years. This data includes 1613.4 patient years (1557.2 LPY) from the aortic cohort and 121.4 patient years (114.6 LPY) from the mitral cohort.

The key safety outcomes and adverse events for this study are presented below in **Table 5** and **Table 6** for combined and mitral cohorts. Simple proportions are presented to describe early event rates, linearized rates (%/patient-year) are presented for late events, and “freedom from event” at 1 year based on Kaplan-Meier analysis are provided based on all reported events both “early” and “late.” Trial results demonstrated a 0.1% observed rate of SVD which is statistically less than 1% after 1 year of follow-up.

Table 5: Observed Adverse Event Rates – Combined Aortic and Mitral Cohort

Adverse Event or Outcome	Early¹ (N=771) n, m (%)	Late² (LPY³ = 1671.8) n, m, (%/pt-yr)	Freedom-from Event at 1 Year (SE)⁴
All-cause mortality	9, 9 (1.2)	39, 39, (2.3)	0.972 (0.006)
Valve-related mortality	4, 4 (0.5)	10, 10, (0.6)	0.989 (0.004)
Reoperation	1, 1 (0.1)	8, 8 (0.5)	0.996 (0.002)
Explant	0, 0 (0.0)	6, 6 (0.4)	0.997 (0.002)
Thromboembolism	18, 19 (2.3)	32, 35 (2.1)	0.962 (0.007)
Valve thrombosis	0, 0 (0.0)	0, 0 (0.0)	1.000 (0.000)
All bleeding	7, 7 (0.9)	48, 54 (3.2)	0.948 (0.008)
Major bleeding	6, 6 (0.8)	24, 26 (1.6)	0.972 (0.006)
All paravalvular leak	2, 2 (0.3)	2, 2 (0.1)	0.996 (0.002)
Major paravalvular leak	1, 1 (0.1) 0	0, 0 (0.0)	0.997 (0.002)
Endocarditis	0, 0 (0.0)	11, 11 (0.7)	0.995 (0.003)
Hemolysis	0, 0 (0.0)	0, 0 (0.0)	1.000 (0.000)
Structural Valve Deterioration	0, 0 (0.0)	1, 1 (0.1)	0.999 (0.001)

¹ For ‘Early Events’ (events occurring thru post-implant day 30): m is the number of events; n is the number of subjects experiencing an event; % = n/N.

² For ‘Late Events’ (events occurring after post-implant day 30): m is the number of events; n is the number of subjects experiencing an event; and % = m/LPY.

³ LPY: Late patient-years; LPY are calculated from post-implant day 31 until the last patient contact.

⁴ Based on Kaplan-Meier analysis of time to first occurrence (early or late). Standard Error (SE) based on Greenwood’s formula.

Table 6: Observed Adverse Event Rates – Mitral Only Cohort

Adverse Event or Outcome	Early¹ (N=82) n, m (%)	Late² (LPY³ = 114.65) n, m, (%/pt-yr)	Freedom-from Event at 1 Year (SE)⁴
All-cause mortality	1, 1 (1.2)	7, 7 (6.1)	0.938 (0.027)
Valve-related mortality	1, 1 (1.2)	1, 1 (0.9)	0.988 (0.012)
Reoperation	0, 0 (0.0)	3, 3 (2.6)	0.983 (0.017)
Explant	0, 0 (0.0)	2, 2 (1.7)	0.983 (0.017)
Thromboembolism	2, 3 (2.4)	2, 2 (1.7)	0.963 (0.021)
Valve thrombosis	0, 0 (0.0)	0, 0 (0.0)	1.000 (0.000)
All bleeding	1, 1 (1.2)	9, 10 (8.7)	0.912 (0.032)

Adverse Event or Outcome	Early¹ (N=82) n, m (%)	Late² (LPY³ = 114.65) n, m, (%/pt-yr)	Freedom-from Event at 1 Year (SE)⁴
Major bleeding	1, 1 (1.2)	6, 6 (5.2)	0.937 (0.027)
All paravalvular leak	0, 0 (0.0)	0, 0 (0.0)	1.000 (0.000)
Major paravalvular leak	0, 0 (0.0)	0, 0 (0.0)	1.000 (0.000)
Endocarditis	0, 0 (0.0)	1, 1 (0.9)	1.000 (0.000)
Hemolysis	0, 0 (0.0)	0, 0 (0.0)	1.000 (0.000)
Structural Valve Deterioration	0, 0 (0.0)	1, 1 (0.9)	0.986 (0.014)

¹ For ‘Early Events’ (events occurring thru post-implant day 30): m is the number of events; n is the number of subjects experiencing an event; % = n/N.

² For ‘Late Events’ (events occurring after post-implant day 30): m is the number of events; n is the number of subjects experiencing an event; and % = m/LPY.

³ LPY: Late patient-years; LPY are calculated from post-implant day 31 until the last patient contact.

⁴ Based on Kaplan-Meier analysis of time to first occurrence (early or late). Standard Error (SE) based on Greenwood’s formula.

The results of the COMMENCE mitral arm, combined with the aortic arm, were compared to the OPC as described in Table R.1 in EN ISO 5840:2009, Annex R.1. Thromboembolism, valve thrombosis, all and major paravalvular leak, and endocarditis met the statistical standard. In the COMMENCE combined aortic and mitral cohorts, the upper 95% confidence limit for the linearized rate for all bleeding was 4.0% and major bleeding was 2.1%. Separately, the upper 95% confidence limit for the linearized rate for all bleeding for the mitral cohort alone was 14.2% and major bleeding was 9.8%. None of the bleeding events in the aortic or mitral arms were CEC-adjudicated as device-related. Anti-coagulant intake was associated with the majority (92.3%; 24/26) of late, major bleeding events. The data for the combined aortic and mitral arms was statistically powered for comparison to the OPCs (Table 7). Linearized rates for the mitral arm alone are presented in **Table 8** for reference, but were not powered for a separate statistical analysis.

Table 7 : Linearized late rates compared to the OPC – Combined Aortic and Mitral Arms

Adverse Event or Outcome	Late¹ (LPY² = 1671.8) n, m, (%/pt-yr)	95% UCL³	2X OPC⁴
Thromboembolism	32, 35, (2.1)	2.7	5.0
Valve thrombosis	0, 0, (0.0)	0.1	0.4
All bleeding	48, 54, (3.2)	4.0	2.8
Major bleeding	24, 26, (1.6)	2.1	1.8
All paravalvular leak	2, 2, (0.1)	0.3	2.4

Adverse Event or Outcome	Late¹ (LPY² = 1671.8) n, m, (%/pt-yr)	95% UCL³	2X OPC⁴
Major paravalvular leak	2, 2, (0.1)	0.5	1.2
Endocarditis	11, 11, (0.7)	1.1	2.4

¹ For ‘Late Events’ (events occurring after post-implant day 30): m is the number of events; n is the number of subjects experiencing an event; and % = m/LPY.

² LPY: Late patient-years; LPY are calculated from post-implant day 31 until the last patient contact.

³ UCL is the one-sided 95% Upper Confidence Limit for the linearized rate.

⁴ FDA Objective Performance Criterion for tissue valves as described in Table R.1 of EN ISO 5840:2009, Annex R.1.

Table 8 : Linearized late rates Mitral Arm Only – For Reference

Adverse Event or Outcome	Late¹ (LPY² = 114.65) n, m, (%/pt-yr)	95% UCL³	2X OPC⁴
Thromboembolism	2, 2, (1.7)	4.8	5.0
Valve thrombosis	0, 0, (0.0)	1.7	0.4
All bleeding	9, 10, (8.7)	14.2	2.8
Major bleeding	6, 6, (5.2)	9.8	1.8
All paravalvular leak	0, 0, (0)	1.7	2.4
Major paravalvular leak	0, 0, (0)	1.7	1.2
Endocarditis	1, 1, (0.9)	3.4	2.4

¹ For ‘Late Events’ (events occurring after post-implant day 30): m is the number of events; n is the number of subjects experiencing an event; and % = m/LPY.

² LPY: Late patient-years; LPY are calculated from post-implant day 31 until the last patient contact.

³ UCL is the one-sided 95% Upper Confidence Limit for the linearized rate.

⁴ FDA Objective Performance Criterion for tissue valves as described in Table R.1 of EN ISO 5840:2009, Annex R.1.

2. Effectiveness Results

The analysis of effectiveness was based on the 73 evaluable patients that received the Edwards Pericardial Mitral Bioprosthesis over the course of 124.4 patient-years combined with the 638 evaluable patients that received the Edwards Pericardial Aortic Bioprosthesis. Effectiveness of the Edwards Pericardial Mitral Bioprosthesis was evaluated by NYHA functional class and echocardiographic assessment of the hemodynamic performance of the valve. NYHA functional classification at baseline and at 1 year for the combined aortic and mitral cohorts and the mitral cohort alone is shown in **Table 9**.

Table 9: NYHA Functional Classification

Cohort	NYHA Class	Baseline NYHA % (n / N ¹)	1-Year NYHA ² % (n / N ¹)
Combined Aortic and Mitral	Class I	21.8% (155 / 711)	82.8% (589 / 711)
	Class II	49.2% (350 / 711)	15.6% (111 / 711)
	Class III	26.0% (185 / 711)	1.3% (9 / 711)
	Class IV	3.0% (21 / 711)	0.3% (2 / 711)
Mitral Only	Class I	5.5% (4 / 73)	90.4% (66 / 73)
	Class II	38.4% (28 / 73)	9.6% (7 / 73)
	Class III	43.8% (32 / 73)	0.0% (0 / 73)
	Class IV	12.3% (9 / 73)	0.0% (0 / 73)

¹ N is the number of subjects who have both preoperative and 1-year NYHA data.

² Improvement in NYHA observed demonstrated by a *p*-value < 0.0001 based on the test for marginal homogeneity after converting NYHA Class to numeric values (Class I = 1, Class II = 2, Class III = 3, Class IV = 4). Values of 0 were replaced with 0.5 to avoid sparseness of data.

Effective orifice area (EOA) and mean gradient at 1-year follow-up are presented in **Table 10**, and total mitral regurgitation at one year is shown in **Table 11**.

Table 10: Hemodynamic Results at 1-Year – Mitral Cohort

Parameter	25 mm Mean ± SD (N ¹)	27 mm Mean ± SD (N ¹)	29 mm Mean ± SD (N ¹)	31 mm Mean ± SD (N ¹)	33 mm Mean ± SD (N ¹)
Mean Gradient (mmHg)	4.9 ± 1.2 (4)	4.1 ± 1.4 (25)	4.1 ± 1.5 (20)	3.9 ± 2.0 (12)	3.3 ± 1.4 (6)
EOA (cm ²)	1.1 ± 0.4 (4)	1.2 ± 0.3 (23)	1.5 ± 0.6 (20)	1.4 ± 0.5 (12)	1.5 ± 0.7 (6)

¹ N represents the number of subjects with evaluable data for the specified valve size.

Table 11: Total Mitral Regurgitation at 1-Year – Mitral Cohort

Total Regurgitation	19 mm % (n/N ¹)	21 mm % (n/N ¹)	23 mm % (n/N ¹)	25 mm % (n/N ¹)	27 mm % (n/N ¹)
None (0)/Trivial (+1)	100.0% (4/4)	80.0% (20/25)	95.2% (20/21)	92.3% (12/13)	83.3% (5/6)
Mild (+2)	0.0% (0/4)	16.0% (4/25)	0.0% (0/31)	0.0% (0/13)	16.7% (1/6)
Moderate (+3)	0.0% (0/4)	4.0% (1/25)	4.8% (1/21)	0.0% (0/13)	0.0% (0/6)
Severe (+4)	0.0% (0/4)	0.0% (0/25)	0.0% (0/21)	7.7% (1/13)	0.0% (0/6)

¹ N represents the number of subjects with evaluable data for the specified valve size.

A Quality of life assessment was also performed for the combined aortic and mitral cohort at 1 year. The assessment was not statistically powered. The SF-12v2 Health Survey is a standardized measure of health status developed by QualityMetric Inc. to provide a simple, generic assessment of physical and mental health. Patients complete 12 questions designed to measure functional health and well-being. Summary scores are then calculated based on a weighted algorithm which is standardized against the collected scores for the U.S. general population.

Table 12: SF-12v2 Health Assessment Results at 1-Year – Combined Aortic and Mitral Cohort

Score	Preoperative 1-Year Visit p-value n: mean ± SD median (min - max)	1-Year Visit p-value n: mean ± SD median (min - max)
Mental Health	672: 50.4 ± 10.1 52.3 (11.4 - 72.0)	672: 53.9 ± 8.6 56.9 (24.2 - 71.0)
Physical Health	672: 43.1 ± 9.7 42.8 (15.5 - 66.0)	672: 49.4 ± 8.9 51.9(11.6 - 66.3)

3. Subgroup Analysis

Gender was evaluated for potential association with outcomes. Among the 771 subjects enrolled for the combined aortic and mitral cohorts, 72% were male and 28% were female.

Analysis was performed on the 771 patients who were successfully implanted in order to assess potential differences between the sexes that may be relevant to the clinical evaluation of the Edwards Pericardial Mitral Bioprosthesis. The COMMENCE study was not designed nor powered to study safety and effectiveness differences between sexes, so this analysis is considered exploratory without definitive conclusions.

Freedom from structural valve deterioration, thromboembolism, bleeding, paravalvular leak, endocarditis, death, and reoperation at 1 year were comparable between populations based on log-rank testing comparing time to event (**Table 13**). No cases of valve thrombosis were observed for either cohort.

Table 13: Female vs. Male Freedom from Safety Outcomes at 1-Year

Adverse Event or Outcome	Probability Event Free at 1 Year ¹		<i>p</i> -value ²
	Female	Male	
Structural Valve Deterioration	99.6%	100.0%	0.140
Death	98.3%	96.7%	0.220
Reoperation	99.6%	99.6%	0.945
Thromboembolism	97.1%	95.8%	0.385
Valve Thrombosis	100.0%	100.0%	---
All Bleeding	95.8%	94.3%	0.427
Major Bleeding	98.7%	96.5%	0.088
OPC All PVL	99.6%	99.6%	0.943
OPC Major PVL	99.6%	99.8%	0.570
Endocarditis	100.0%	99.2%	0.174

¹ Probability event free based on Kaplan-Meier analysis; time to event truncated at 1 year (POD 365).

² *p*-values are based on log-rank test comparing time to event.

NYHA classification at 1 year was similar between males and females (**Table 14**) based on a Chi-Square test for categorical variables.

Table 14: Female vs. Male NYHA Classification at 1-Year

Post-operative NYHA	Female %(n/N ¹)	Male %(n/N ¹)	<i>p</i> -value ²
Class I/II	97.8% (219/224)	98.8% (481/487)	0.3155
Class III/IV	2.2% (5/224)	1.2% (6/487)	

¹ N is the number of subjects with available data at the 1-year visit.

² *p*-values are based on Chi-Square tests for categorical variables

EOA, mean gradient, and regurgitation severity at 1 year were also comparable between sexes based on mixed models for continuous variables and ordinal logistic regression for categorical variables with valve size and baseline Body Surface Area (BSA) as covariates (**Table 15**).

Table 15: Female vs. Male Hemodynamic Performance at 1-Year

Parameter		Female	Male	p-value ²
EOA (cm ²)		N ¹ : mean ± SD	N ¹ : mean ± SD	
Aortic		174: 1.38 ± 0.39	447: 1.81 ± 0.55	0.1338
Mitral		39: 1.21 ± 1.59	26: 1.61 ± 0.62	0.0451
Mean Gradient (mmHg)		N ¹ : mean ± SD	N ¹ : mean ± SD	0.9186
Aortic		176: 11.93 ± 5.74	452: 9.57 ± 3.90	0.8611
Mitral		41: 4.10 ± 1.59	26: 3.91 ± 1.47	0.9885
Total Regurgitation		% (n/N ¹)	% (n/N ¹)	
Aortic	0 None/+1 Trivial	93.2 (165/177)	96.2% (434/ 451)	0.3772
	+2 Mild	6.8% (12/177)	3.5% (16/451)	
	+3 Moderate	0.0% (0/177)	0.2% (2/451)	
	+4 Severe	0.0% (0/177)	0.0% (0/451)	
Mitral	0 None/+1 Trivial	88.1% (37/42)	88.9% (24/27)	0.4234
	+2 Mild	7.1% (3/42)	7.4% (2/27)	
	+3 Moderate	2.4% (1/42)	3.7% (1/27)	
	+4 Severe	2.4% (1/42)	0.0% (0/27)	

¹ N is the number of subjects with evaluable data at the 1-year visit.

² p-values are based on mixed models for continuous variables or ordinal logistic regression for categorical variables with valve size and baseline BSA as covariates.

The comparisons of safety and effectiveness data support the conclusion that the results of the overall study can be applied equally well to males and females.

4. Pediatric Extrapolation

In this premarket application, existing clinical data was not leveraged to support approval of a pediatric patient population.

E. Financial Disclosure

The Financial Disclosure by Clinical Investigators regulation (21 CFR 54) requires applicants who submit a marketing application to include certain information concerning the compensation to, and financial interests and arrangement of, any clinical investigator conducting clinical studies covered by the regulation. The pivotal clinical trial included 187 investigators (34 principal investigators) none of which were full-time or part-time employees of the sponsor and 11 had disclosable financial interests/arrangements as defined in 21 CFR 54.2(a), (b), (c) and (f) as described below:

- Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: None

- Significant payment of other sorts: 9 investigators
- Proprietary interest in the product tested held by the investigator: None
- Significant equity interest held by investigator in sponsor of covered study: 3 investigators

The applicant has adequately disclosed the financial interest/arrangements with clinical investigators. Statistical analyses were conducted by FDA to determine whether the financial interests/arrangements had any impact on the clinical outcome. The information provided does not raise any questions about the reliability of the data.

XI. PANEL MEETING RECOMMENDATION AND FDA'S POST-PANEL ACTION

In accordance with the provisions of section 515(c)(3) 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.

XII. CONCLUSIONS DRAWN FROM PRECLINICAL AND CLINICAL STUDIES

A. Effectiveness Conclusions

In the mitral arm of the COMMENCE clinical study, the analysis of effectiveness was based on NYHA functional classification and echocardiography data at one year. Improvement in NYHA classification from baseline to the one-year visit was observed based on subjects with available data at both time intervals.

Based on Echocardiographic Core Lab assessments of echocardiography data, 88.4% of patients had no detectable or trivial mitral regurgitation at one year. Based on core lab assessments of echocardiography data, mean effective orifice areas (EOA) and mean gradients were consistent with current literature regarding other stented mitral bioprostheses and indicate acceptable hemodynamic performance of the Edwards Pericardial Mitral Bioprosthesis, Model 11000M.

B. Safety Conclusions

The risks of the device are based on nonclinical laboratory and animal studies as well as data collected in a clinical study conducted to support PMA approval as described above. The results from the pre-clinical laboratory studies performed on the Edwards Pericardial Mitral Bioprosthesis, Model 11000M, for biocompatibility, hydrodynamic performance, and structural performance demonstrate that this device is suitable for long-term implant.

The results from the COMMENCE clinical trial demonstrate a 0.1% observed rate of Structural Valve Deterioration which is statistically less than 1% after one year of

follow-up. Furthermore, the rates for all OPC-defined adverse events are lower than the established standard of twice the FDA's Objective Performance Criteria for a bioprosthetic valve, with the exception of all bleeding and major bleeding. In the COMMENCE combined aortic and mitral cohorts, the upper 95% confidence limit for the linearized rate for all bleeding was 4.0% and major bleeding was 2.1%. The upper 95% confidence limit for the linearized rate for all bleeding for the mitral cohort alone was 14.2% and major bleeding was 9.8% which exceeds the FDA criterion of twice the OPC (all bleeding: 2.8% and major bleeding: 1.8%). However, detailed analysis of the major bleeding events by the Clinical Events Committee showed no clear indication that the major bleeding events were directly related to Model 11000A or Model 11000M valves.

C. Benefit-Risk Determination

Mitral valve disease is a progressive and potentially lethal condition. Diseased mitral valves can be treated by medication, surgical repair using an annuloplasty ring, or surgical replacement with a commercially available prosthetic heart valve. The probable benefits of the Edwards Pericardial Mitral Bioprosthesis, Model 11000M include improved mitral valve hemodynamic performance and improved NYHA functional classification compared to baseline values. The risks associated with the Edwards Pericardial Mitral Bioprosthesis, Model 11000M, include complications such as valvular thrombosis, thromboembolism, paravalvular leak, endocarditis, structural valve deterioration, nonstructural dysfunction, reoperation, explant, and death. However, the risks are the same as those for other alternative mitral bioprosthetic valves.

1. Patient Perspectives

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

In conclusion, given the available information above, the data support that, for the replacement of native or prosthetic mitral heart valves, the probable benefits of implanting the Edwards Pericardial Mitral Bioprosthesis, Model 11000M outweigh the probable risks.

D. Overall Conclusions

The data in this application support the reasonable assurance of safety and effectiveness of this device when used in accordance with the indications for use. Preclinical and clinical studies provided in the PMA application demonstrate reasonable assurance that the Edwards Pericardial Mitral Bioprosthesis, Model 11000M, is safe and effective for replacement of native or prosthetic mitral heart valves.

XIII. CDRH DECISION

CDRH issued an approval order on August 9, 2018. The final conditions of approval cited in the approval order are described below.

1. *ODE Lead Post-Approval Study - Edwards Pericardial Mitral Bioprosthesis, Model 11000M, Continued Follow-Up*: This study will consist of all IDE patients who are currently enrolled and alive. The study objective is to characterize the safety and effectiveness of the Edwards Pericardial Mitral Bioprosthesis, Model 11000M. All IDE patients who are currently enrolled and alive will be followed to 5 years. In addition, all mitral patients enrolled at three sites (n=25) will be followed annually through 10 years post-procedure. For continued follow-up of patients, the safety and effectiveness endpoints are listed in the protocol as follows: the primary effectiveness endpoints include clinically acceptable hemodynamic performance confirmed by echocardiography, change in NYHA functional classification, and improvement in quality of life.

The primary safety endpoint is the rate of implanted subjects that experience structural deterioration of the Model 11000M valve as determined by a Clinical Events Committee (CEC). Additional secondary safety endpoints include thromboembolism, valve thrombosis, all bleeding/major bleeding, endocarditis, all-cause mortality, valve-related mortality, valve-related reoperation, all paravalvular leak/major paravalvular leak, non-structural valve deterioration, explant, and hemolysis.

XIV. APPROVAL SPECIFICATIONS

Directions for use: See device labeling.

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

Post-approval Requirements and Restrictions: See approval order.