Edwards

MITRIS RESILIA Mitral Valve, Model 11400M

Instructions for Use

CAUTION: Federal (USA) Law restricts this device to sale by or on the order of a physician.

Figure 1: MITRIS RESILIA Mitral Valve

1.0 Device and Accessories Description

1.1 Device Description

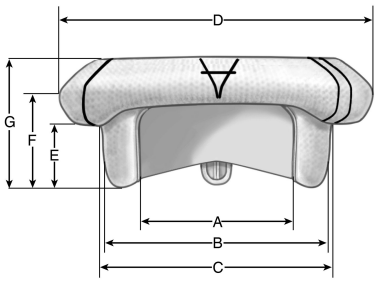
The MITRIS RESILIA mitral valve, model 11400M, is a stented tri-leaflet prosthetic heart valve comprised of RESILIA bovine pericardial tissue. This low-profile valve is based on the Edwards PERIMOUNT valve design with a nitinol wireform. The valve is mounted on a retainer with a holder system attached to the valve. The holder system has a dial that is turned prior to implantation to allow the posts to be folded inward during implantation.

The valve is stored under dry packaging conditions and does not require rinsing prior to implantation. The valve is available in sizes 25, 27, 29, 31 and 33 mm. See Table 1 for nominal dimensions.

The MITRIS RESILIA mitral valve can only be used with the handle model 1140M. The handle consists of a textured grip and a malleable nitinol shaft for ease of implantation.

The MITRIS RESILIA mitral valve is designed to be used with sizers model 1173B and 1173R.

Table 1: Nominal Dimensions for MITRIS RESILIA Mitral Valve, Model 11400M



Valve Size	25 mm	27 mm	29 mm	31 mm	33 mm
A: Stent Diameter (Wireform, mm)	25	27	29	31	31
B: External Stent Post Diameter (Tip, mm)	27	29	30	33	33
C: Tissue Annular Diameter (mm)	27.5	29.5	31.5	33.5	33.5
D: External Sewing Ring Diameter (mm)	36	38	40	42	44
E: Effective Profile Anterior (mm)	7	7.5	8	8.5	8.5
F: Effective Profile Posterior (mm)	10	10.5	11	11.5	11.5
G: Total Profile Height (mm)	15	16	17	18	18
Geometric Orifice Area (mm^2)	424	499	580	653	653
Note: For Sizing, Refer to Section 11.2					

RESILIA Tissue

RESILIA tissue is created with a novel technology called 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 replaces the traditional storage in liquid-based solutions such as glutaraldehyde. The storage method eliminates tissue exposure to the residual unbound aldehyde groups commonly found in glutaraldehyde storage solutions.

Valve Structure

The lightweight wireform is made of a corrosion-resistant nickel-titanium alloy (nitinol), chosen because of its superelastic characteristics, allowing it to fold inward during implantation, and is covered with a polyester fabric.

A cobalt-chromium alloy band and polyester band surround the base of the valve below the wireform frame providing structural support for the orifice. Similar to other Edwards bioprosthetic valves, the nickel-titanium alloy wireform and cobalt-chromium alloy band in the model 11400M can be identified on fluoroscopy. This allows for identification of the valve's inflow and outflow edges to facilitate identifying the landing zone

for potential future transcatheter interventions. A compliant silicone-rubber sewing ring that is covered with a porous, seamless polytetrafluoroethylene (PTFE) cloth is attached to the wireform frame and facilitates tissue ingrowth and encapsulation.

The sewing ring is scalloped along its anterior portion to conform to the natural irregularities of the mitral annulus.

The valve has a posteromedial commissure mark (single black line), an anterolateral commissure mark (double black line), and an anterior segment mark ("A" mark). The black commissure markers facilitate the orientation of the valve and help avoid obstruction of the left ventricular outflow tract by stent posts. In addition, the wide, saddle-shaped physiologic design of the sewing cuff mimics the native mitral annulus and the anterior portion of the valve positions the valve out of the ventricle, limiting protrusions of the valve into the LVOT allowing for unobstructed flow of blood through the aortic valve. This may contribute to lower LVOT obstruction risk if valve-in-valve therapy is required in the future.

1.2 Sizers and Tray

Use only sizers model 1173B or 1173R (Figure 2) with the model 11400M MITRIS RESILIA mitral valve.

CAUTION: Do not use other manufacturers' valve sizers, or sizers not listed above to size the model 11400M MITRIS RESILIA mitral valve.

Sizer model 1173B is used for sizing of the annulus while sizer model 1173R allows to assess the fit of the MITRIS RESILIA mitral valve within the annulus of the patient. The barrel of the sizer model 1173B indicates the external stent diameter at the base. The lip of the replica sizer model 1173R replicates the sewing ring of the valve, with its scalloped anterior portion and black markings.

The sizers model 1173B and 1173R are labeled with the valve size. The complete set of sizers is housed in a tray, model SET1173, which can be resterilized and reused.

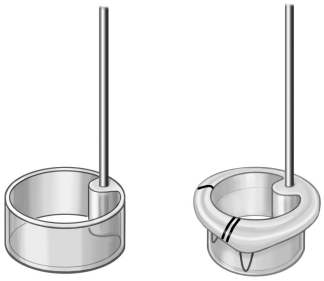


Figure 2: Model 1173B Barrel Sizer (left) and 1173R Replica Sizer (right)

1.3 Valve Holder System and Handle

A holder is attached to the valve by means of a blue polymer thread to facilitate handling and suturing the valve during implantation.

The holder/handle assembly consists of two components; the holder system (Figure 3 and Figure 4) that is mounted to the model 11400M MITRIS RESILIA mitral valve, and a handle (model 1140M) that is attached to the holder system at the time of surgery. The holder is detached by the surgeon. (Refer to **Section 11.4 Device Implantation**).

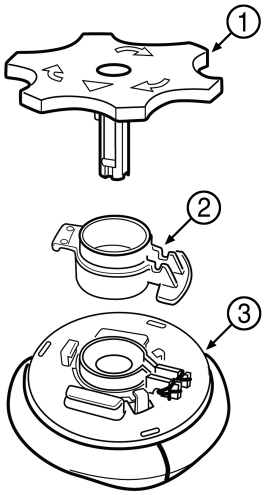


Figure 3: MITRIS Holder System

1. Dial
2. Adapter
3. Holder

Only the following handle (Table 2) may be used with the model 11400M MITRIS RESILIA mitral valve:

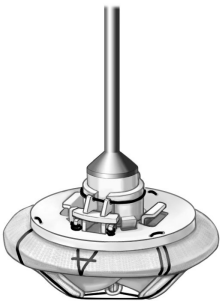


Figure 4: MITRIS RESILIA Valve attached to Holder and Handle

Table 2: Accessory Handles

Model	Shaft Material	Overall Length		Reusable
		in	cm	
1140M	Nitinol	11.3	28.6	Yes

The model 1140M handle has a malleable nitinol shaft. The handle is supplied by Edwards non-sterile and must be sterilized prior to use. After sterilization, the nitinol shaft returns to its original straight shape.

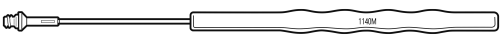


Figure 5: Model 1140M Accessory Handle

2.0 Intended Use and Indications for Use

The MITRIS RESILIA mitral valve, model 11400M, is intended for use as a heart valve replacement.

The MITRIS RESILIA mitral valve, model 11400M, is indicated for the replacement of native or prosthetic mitral heart valves.

3.0 Contraindications

There are no known contraindications with the use of the MITRIS RESILIA mitral valve, model 11400M.

4.0 Warnings

FOR SINGLE USE ONLY. This device is designed, intended, and distributed for single use only. Do not resterilize or reuse this device. There is no data to support the sterility, non-pyrogenicity, and functionality of the device after sterile reprocessing. Resterilization could lead to injury or infection, as the device may not function as intended.

DO NOT FREEZE OR EXPOSE THE VALVE TO EXTREME HEAT. Exposure of the valve to extreme temperatures will render the device unfit for use. (Refer to Section 10.2 Storage, for recommended storage conditions).

DO NOT USE the valve if:

- **The foil pouch, sealed trays or lids are opened, damaged, or stained**
- **The expiration date has elapsed, or**
- **It is dropped, damaged, or mishandled in any way. Should a valve be damaged during insertion, do not attempt repair.**

DO NOT EXPOSE the valve to any solutions, chemicals, antibiotics, etc., except for sterile physiological saline solution. Irreparable damage to the leaflet tissue, which may not be apparent under visual inspection, may result.

DO NOT GRASP the leaflet tissue of the valve with instruments or cause any damage to the valve. Even the most minor leaflet tissue perforation may enlarge in time to produce significant impairment of valve function.

DO NOT OVERSIZE. Oversizing may cause valve damage or localized mechanical stresses, which may in turn injure the heart or result in leaflet tissue failure, stent distortion and regurgitation.

DO NOT PASS CATHETERS, transvenous pacing leads, or any surgical instrument across the valve with the exception of a surgical mirror used to examine struts and suture placement. Other surgical devices may cause leaflet tissue damage.

As with any implanted medical device, there is a potential for the patient to develop an immunological response. Some components of the model 11400M are a metal alloy that contains nitinol (an alloy of nickel and titanium), cobalt, chromium, nickel, molybdenum, manganese, carbon, beryllium and iron. Care should be exercised in patients with hypersensitivities to these materials. This device was not made with natural rubber latex but may have been produced in a latex-containing environment. Prior to implantation, patients should be counseled on the materials contained in the device, as well as potential for allergy/hypersensitivity to these materials. Safety of the MITRIS valve has not been tested in patients with Nickel allergy.

5.0 Adverse Events

5.1 Observed Adverse Events

As with all prosthetic heart valves, serious adverse events, sometimes leading to death, may be associated with the use of tissue valves. In addition, adverse events due to individual patient reaction to an implanted device or to physical or chemical changes to the components, particularly those of biological origin, may occur at varying intervals (hours or days) necessitating reoperation and replacement of the prosthetic device.

The MITRIS RESILIA mitral valve, model 11400M, is similar in design to the Carpentier-Edwards PERIMOUNT Magna Mitral Ease pericardial bioprosthesis, model 7300TFX.

Adverse events associated with the use of Carpentier-Edwards PERIMOUNT pericardial bioprostheses compiled from the literature and from reports received through the product surveillance system in accordance with the United States regulations establishing Good Manufacturing Practices, section 820.198, include stenosis, regurgitation through an incompetent valve, perivalvular leak, endocarditis, hemolysis, thromboembolism, thrombotic obstruction, bleeding diatheses related to the use of anticoagulation therapy, and malfunctions of the valve due to distortion at implant, fracture of the wireform, or physical or chemical deterioration of valve components. Types of tissue deterioration include infection, calcification, thickening, perforation, degeneration, suture abrasion, instrument trauma, and leaflet detachment from the valve stent posts. These complications may present clinically as abnormal heart murmur, shortness of breath, exercise intolerance, dyspnea, orthopnea, anemia, fever, arrhythmia, hemorrhage, transient ischemic attack, stroke, paralysis, low cardiac output, pulmonary edema, congestive heart failure, cardiac failure, and myocardial infarction.

5.2 Potential Adverse Events

Adverse events potentially associated with the use of valves and the surgical procedure include:

- 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 (circumflex) injury
- 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
  - Patient Prosthesis Mismatch (PPM) (due to inappropriate sizing)
  - Distortion at implant
- Valve - Structural dysfunction/deterioration
- Valve - Thrombosis

Calcific and non-calcific (fibrotic) degeneration of bioprosthetic valves is reported with use of chemoradiotherapy to treat malignant conditions [Ref 2 and 3].

It is possible that these complications may lead to:

- Reoperation
- Explantation
- Permanent disability

- Death

6.0 Clinical Studies

The clinical safety and effectiveness of the MITRIS RESILIA mitral valve, model 11400M was established based on the outcome data of the COMMENCE trial, which assessed the safety and effectiveness of the model 11000A (aortic) and model 11000M (mitral) valves.

The COMMENCE trial is an open-label, prospective, non-randomized, multicenter trial without concurrent or matched controls. Following a pre-surgical assessment, subjects are followed for one year to assess primary safety and effectiveness. Subjects are followed annually thereafter for a minimum of five years post-surgical experience.

The trial population in the mitral arm consisted of adult subjects (18 years or older) diagnosed with mitral valve disease requiring a planned replacement of the native or prosthetic mitral valve. Concomitant coronary bypass surgery and ascending aorta resection and replacement from the sinotubular junction without the need for circulatory arrest are permitted.

Trial candidates with prior valve surgery which included the implant of a prosthetic valve or annuloplasty ring that will remain *in situ* are excluded. Concomitant valve repair or replacement are excluded. Surgical procedures outside the cardiac area are not permitted. Various clinical presentations and histories may cause exclusion from the trial.

The reporting period for the COMMENCE trial is January 2013 through August 2017. At the time of the database lock, 777 subjects were enrolled at thirty-four (34) investigational sites in the US and Europe. Of the enrolled population, 99.2% (771/777) of the subjects were successfully implanted with a trial valve. This includes 689 subjects treated with the model 11000A (aortic) at twenty-seven (27) sites and eighty-two (82) subjects treated with the model 11000M (mitral) at seventeen (17) sites.

Table 3 provides trial demographics, NYHA Classification and Risk Scores; Table 4 lists the combined observed adverse event rates during study; Table 5 lists the observed adverse event rates during study for the mitral cohort only; Table 6 gives the linearized late rates compared to the objective performance criteria (OPC); Table 7 lists linearized late rates for valve-related events compared to the OPC; Table 8 provides NYHA Classification data at baseline and 1-year follow-up; and Table 9 lists hemodynamic parameters at 1-year.

In the clinical study, the analysis of effectiveness is based on NYHA functional classification and echocardiography data at one (1) 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, 88.9% (64/72) of model 11000M patients have 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 are consistent with current literature regarding other stented aortic bioprostheses and indicate acceptable hemodynamic performance of the Edwards pericardial mitral bioprosthesis, model 11000M.

The results from the COMMENCE clinical trial demonstrate a 0.1% observed rate of structural valve deterioration (SVD), with a 95% upper confidence interval of 0.7%, which is statistically less than 1% after 1-year of follow-up. All objective performance criteria (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 3.3% and major bleeding was 1.8%. For the mitral cohort alone, the upper 95% confidence limit for the linearized rate for all bleeding was 10.1% and for major bleeding was 6.6% 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 showed no clear indication that the major bleeding events were directly related to model 11000A or model 11000M valves. The CEC adjudicated valve-related events are provided in Table 6.

Table 3: Demographics Combined Aortic and Mitral Cohorts

	COMMENCE Trial Study	Mitral Cohort Only
Age at Implant	**N: Mean ± SD (Min - Max)**	**N: Mean ± SD (Min - Max)**
Age (years)	771: 67.2 ± 11.4 (20.0, 90.0)	82: 68.9 ± 9.4 (47.0, 86.0)
Sex	**% (n/N)**	**% (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/IV	29.7% (229/771)	58.5% (48/82)
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)

N is the number of subjects with available data for the given parameter.
[1]STS scores only calculated for aortic arm subjects undergoing isolated AVR or AVR+CABG, and mitral arm subjects undergoing MVR or MVR+CABG.

Table 4: Observed Adverse Events - Combined Aortic and Mitral Cohort

Adverse Event or Outcome	Early[1] (N=771) n, m (%)	Late[2] (LPY[3] = 1671.84) n, m, (%/pt-yr)	Freedom-from Event at 1 Year (POD 390) (SE)[4]
All mortality	9, 9, (1.2%)	63, 63, (2.3%)	0.972 (0.006)
Valve-related mortality	4, 4, (0.5%)	12, 12, (0.4%)	0.989 (0.004)
Reoperation	1, 1, (0.1%)	10, 10, (0.4%)	0.996 (0.002)

Adverse Event or Outcome	Early[1] (N=771) n, m (%)	Late[2] (LPY[3] = 1671.84) n, m, (%/pt-yr)	Freedom-from Event at 1 Year (POD 390) (SE)[4]
Explant	0, 0, (0.0%)	8, 8, (0.3%)	0.997 (0.002)
Thromboembolism	18, 19, (2.3%)	41, 46, (1.7%)	0.962 (0.007)
Valve thrombosis	0, 0, (0.0%)	1, 1, (0.0%)	1.000 (0.000)
All bleeding	7, 7, (0.9%)	65, 74, (2.8%)	0.946 (0.008)
Major bleed	6, 6, (0.8%)	34, 37, (1.4%)	0.972 (0.006)
All Paravalvular Leak	2, 2, (0.3%)	3, 3, (0.1%)	0.996 (0.002)
Major PVL	1, 1, (0.1%)	2, 2, (0.1%)	0.997 (0.002)
Endocarditis	0, 0, (0.0%)	12, 13, (0.5%)	0.995 (0.003)
Hemolysis	0, 0, (0.0%)	1, 1, (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): For 'Early' 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 frst occurrence (early or late). Standard Error (SE) based on Greenwood's formula.

Table 5: Observed Adverse Events - Mitral Cohort Only

Adverse Event or Outcome	Early[1] (N=82) n, m (%)	Late[2] (LPY[3] = 114.65) n, m, (%/pt-yr)	Freedom-from Event at 1 Year(SE)[4]
All-cause mortality	1, 1 (1.2)	9, 9 (4.3%)	0.938 (0.027)
Valve-related mortality	1, 1 (1.2)	1, 1 (0.5%)	0.988 (0.012)
Reoperation	0, 0 (0.0)	3, 3 (1.4%)	0.986 (0.013)
Explant	0, 0 (0.0)	2, 2 (1.0%)	0.986 (0.013)
Thromboembolism	2, 3 (2.4)	4, 4 (1.9%)	0.963 (0.021)
Valve thrombosis	0, 0 (0.0)	1, 1 (0.5%)	1.000 (0.000)
All bleeding	1, 1 (1.2)	13, 14 (6.7%)	0.912 (0.032)
Major bleeding	1, 1 (1.2)	8, 8 (3.8%)	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 (0.5%)	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 (0.5%)	0.987 (0.013)

[1] For 'Early Events' (events occurring thru post-implant day 30): For 'Early' 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 frst occurrence (early or late). Standard Error (SE) based on Greenwood's formula.

Table 6: Linearized late rates compared to the OPC - Combined Aortic and Mitral Cohort

Adverse Event or Outcome	Late[1] (LPY[2] = 1671.84) n, m, (%/pt-yr)	95% UCL[3]	2X OPC[4]
Thromboembolism	41, 46, (1.7%)	2.2%	5.0

Adverse Event or Outcome	Late[1] (LPY[2] = 1671.84) n, m, (%/pt-yr)	95% UCL[3]	2X OPC[4]
Valve thrombosis	1, 1, (0.0%)	0.1%	0.4
All bleeding	65, 74, (2.8%)	3.3%	2.8
Major bleeding	34, 37, (1.4%)	1.8%	1.8
All paravalvular leak	3, 3, (0.1%)	0.3%	2.4
Major paravalvular leak	2, 2, (0.1%)	0.2%	1.2
Endocarditis	12, 13, (0.5%)	0.7%	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 Criteria for tissue valves as described in Table R.1 of EN ISO 5840:2009, Annex R.1.

Table 7: Linearized late rates for valve-related events compared to the OPC - Combined Aortic and Mitral Cohort

OPC Event	Late Events Late pt-yrs =1671.84 n, m (%/pt-yr)	Upper 95% CI	2X OPC
Thromboembolism	3, 3 (0.1)	0.3	5.0
Bleeding	0, 0 (0.0)	0.1	2.8
Major Bleeding	0, 0 (0.0)	0.1	1.8
Paravalvular Leak	3, 3 (0.1)	0.3	2.4
Major Paravalvular Leak	2, 2 (0.1)	0.2	1.2
Endocarditis	12, 13 (0.5)	0.7	2.4
Valve Thrombosis	1, 1 (0.0)	0.1	0.4
OPC Event	18, 20 (0.7)	1.1	-

'n' is the number of subjects with the event.
'm' is the number of events.
Major PV leaks are any PV Leak events resulting in surgical intervention or classified as an SAE.
Minor PV leaks are +3 or +4 on an echo core lab for a subject without a major PV leak. The first echo reading of +3/+4 is considered the onset of the minor PV leak. A +2 PV leak on a core lab echo is also considered a minor leak if associated with a hemolysis AE.

Table 8: NYHA Classification at Baseline and 1-Year

Cohort	NYHA Class	Baseline NYHA % (n / N[1])	1-Year NYHA[2] % (n / N[1])
Combined Aortic and Mitral	Class I	21.8% (155 / 712)	82.7% (589 / 712)
	Class II	49.2% (350 / 712)	15.7% (112 / 712)
	Class III	26.1% (186 / 712)	1.3% (9 / 712)
	Class IV	2.9% (21 / 712)	0.3% (2 / 712)
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.

Table 9: Hemodynamic Parameters at 1-Year - Mitral Cohort Only

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)	5.3 ± 1.4 (5)	4.1 ± 1.4 (26)	4.1 ± 1.5 (20)	3.8 ± 1.9 (13)	3.3 ± 1.4 (6)
EOA (cm^2)	1.2 ± 0.3 (5)	1.2 ± 0.3 (24)	1.5 ± 0.6 (20)	1.5 ± 0.5 (13)	1.5 ± 0.7 (6)

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])

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

7.0 Post-Operation Management

MITRIS RESILIA mitral valve recipients should be maintained on anticoagulation therapy, except where contraindicated, during the initial stages after implantation as determined by the physician on an individual basis and as per guidelines [Ref 1]. Long-term anticoagulation and/or antiplatelet therapy should be considered for patients with risk factors for thromboembolism.

8.0 Patient Selection

The ultimate judgment regarding care of a particular patient must be made by the healthcare provider and patient in light of all the circumstances presented by that patient. A bioprosthesis is recommended for MVR in patients of any age for whom anticoagulant therapy is contraindicated, cannot be managed appropriately, or is not desired. Patient preference is a reasonable consideration in the selection of mitral valve operation and valve prosthesis. A mechanical prosthesis is reasonable for MVR in patients under 50 years of age who do not have a contraindication to anticoagulation. For patients between 50 and 70 years of age, it is reasonable to individualize the choice of either a mechanical or bioprosthetic valve prosthesis on the basis of individual patient factors and preferences, after full discussion of the tradeoffs involved. A bioprosthesis is reasonable for patients who elect to receive this valve for lifestyle considerations after detailed discussions of the risks of anticoagulation versus the likelihood that a second MVR may be necessary [Ref 1 and 2].

8.1 Specific Patient Populations

The safety and effectiveness of the model 11400M valve has not been established for the following specific populations because it has not been studied in these populations:

- Patients who are pregnant;
- Nursing mothers;
- Patients with abnormal calcium metabolism (e.g., chronic renal failure, hyperparathyroidism);
- Patients with aneurysmal aortic degenerative conditions (e.g., cystic medial necrosis, Marfan's syndrome);
- Children, adolescents, and young adults;
- Patients with hypersensitivity to metal alloys that contain cobalt, chromium, nickel, molybdenum, manganese, carbon, beryllium and iron;
- Patients with hypersensitivity to latex.

9.0 Patient Counseling Information

Careful and continued medical follow up (at least by an annual visit to the physician) is advised so that valve-related complications, particularly those related to material failure, can be diagnosed and properly managed. Patients with valves are at risk from bacteremia (e.g., undergoing dental procedures) and should be advised about prophylactic antibiotic therapy. Patients should be encouraged to carry their Implant Data Card/Patient Identification Card at all times and to inform their healthcare providers that they have an implant when seeking care.

10.0 How Supplied

10.1 Packaging

The MITRIS RESILIA mitral valve, model 11400M, is provided sterile and nonpyrogenic, in a double barrier tray package. The valve is sterilized by ethylene oxide. The double tray package is in a foil pouch which is in a carton. Upon receipt of the carton, inspect the exterior for signs of damage.

Each valve is contained in a carton with a temperature indicator displayed through a window on the side panel. The temperature indicator is intended to identify products that were exposed to transient temperature extremes. Upon receipt of the valve, immediately inspect the indicator and refer to the carton label to confirm a "Use" condition. If the "Use" condition is not apparent, do not use the valve and contact the local supplier or Edwards Lifesciences representative to make arrangements for return authorization and replacement.

WARNING: Carefully inspect the valve before implantation for evidence of extreme temperature exposure or other damage. Exposure of the valve to extreme temperatures will render the device unfit for use.

10.2 Storage

The MITRIS RESILIA mitral valve, model 11400M, should be stored at 10 °C to 25 °C (50-77 °F), in the foil pouch and shelf carton.

11.0 Directions for Use

11.1 Physician Training

The techniques for implanting this valve are similar to those used for any stented mitral surgical valve. No specific training or special facilities beyond that required for cardiac surgical procedures are required to implant the model 11400M.

The primary intended users are cardiac surgeons who perform these valve replacements and the staff (operating room nurses and technicians) responsible for preparation and implant of aortic and mitral valves.

11.2 Sizing

WARNING: Valve holders and fragments of handles and sizers are not radiopaque and cannot be located by means of an external imaging device.

CAUTION: Do not use other manufacturers' valve sizers, or sizers not listed above, to size the MITRIS RESILIA mitral valve.

CAUTION: Examine sizers for signs of wear, such as dullness, cracking or crazing, prior to use. Replace sizer if any deterioration is observed.

Sizer model 1173B is used for sizing of the annulus while sizer model 1173R is used to assess the fit of the MITRIS RESILIA mitral valve within the annulus. The barrel of the sizer model 1173B indicates the external stent diameter at the base. The lip of the replica sizer model 1173R replicates the sewing ring of the valve.

Sizing with barrel sizer model 1173B:

To size with barrel sizer model 1173B, pass the barrel portion of the sizer through the mitral annulus. Ensure the barrel portion is directly in plane of the mitral annulus (Figure 6).

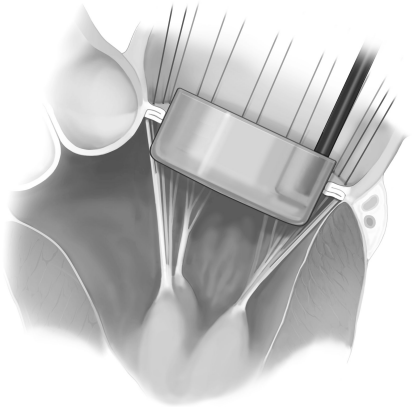


Figure 6

Assessing the fit with replica sizer model 1173R:

To assess the fit of the valve, pass the barrel portion of the replica sizer model 1173R through the mitral annulus so that the tip of the sizer, which simulates the sewing ring portion of the bioprosthesis, rests on the superior aspect of the annulus (Figure 7).

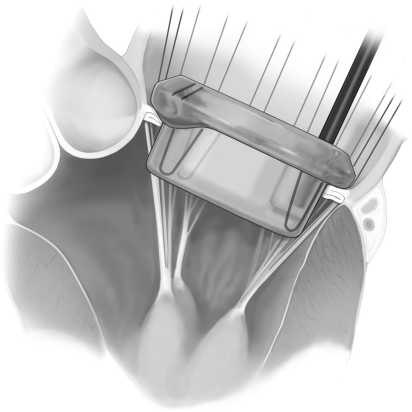


Figure 7

Some techniques such as use of pledgets, leaflet reefing, or mitral subvalvular apparatus preservation may further reduce the size of the mitral annulus which can result in the need for a smaller bioprosthesis to be implanted. When using these techniques, it is recommended to re-size the annulus to avoid oversizing of the bioprosthesis.

Sizers model 1173B and 1173R are made of a transparent material to allow visualization of the subvalvular apparatus during sizing. Ensure no chord will be in the way of the struts.

CAUTION: Exercise special care when using sub-valvular apparatus preservation techniques to avoid chordae entrapment by a strut.

WARNING: Avoid oversizing the bioprosthesis. Oversizing may cause bioprosthesis damage or localized mechanical stresses, which may in turn injure the heart or result in leaflet tissue failure, stent distortion and regurgitation.

11.3 Handling and Preparation Instructions

WARNING: Check expiration date on packaging before use. Do not use product if expiration date has passed.

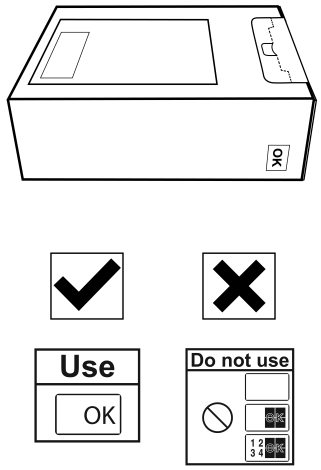
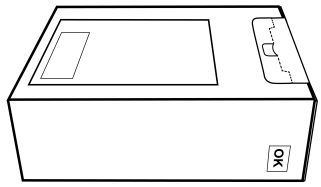
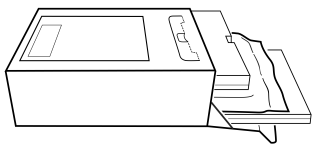
WARNING: Do not open foil pouch into sterile field, the foil pouch is a protective cover only. The innermost package tray may be introduced into the sterile field.

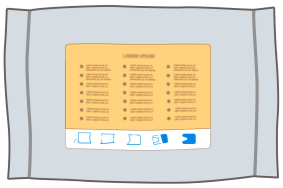
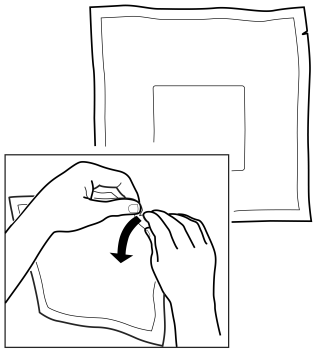
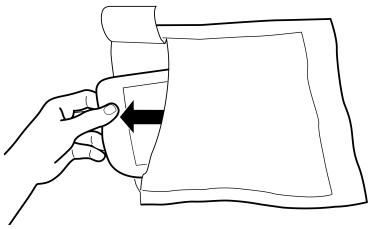
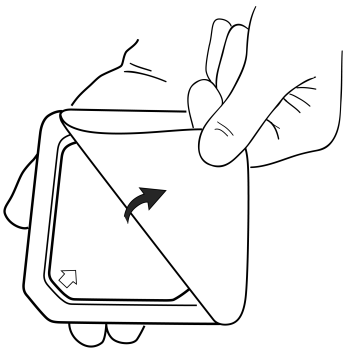
CAUTION: Do not open the MITRIS RESILIA mitral valve, model 11400M package until implantation is certain.

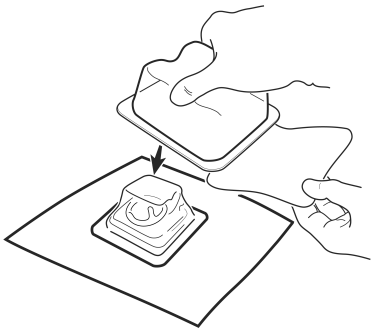
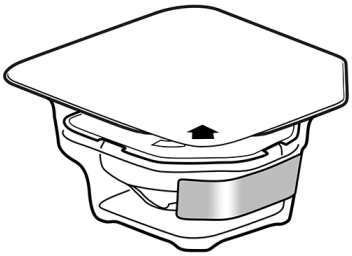
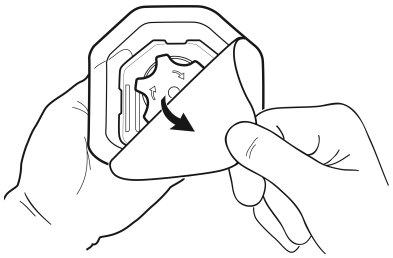
The model 11400M, DOES NOT REQUIRE RINSING prior to implantation.

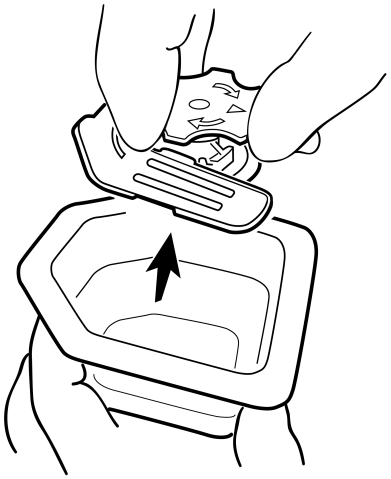
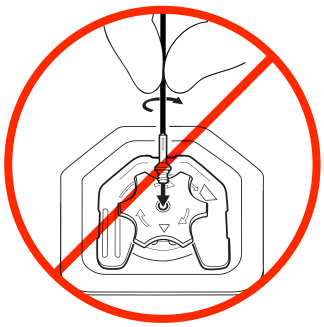
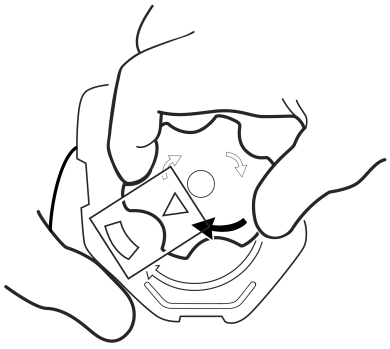
CAUTION: If the valve is rinsed prior to implantation, it must then be kept hydrated with sterile physiological saline irrigation on both sides of the leaflet tissue throughout the remainder of the surgical procedure. Rinsing every 1 - 2 minutes is recommended.

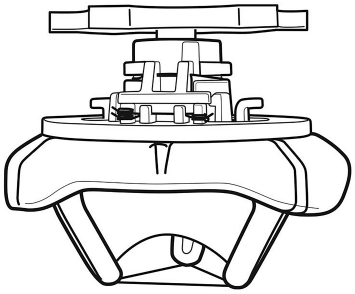
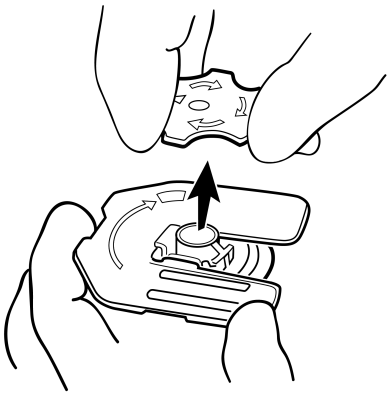
CAUTION: Avoid contact of the leaflet tissue with towels, linens, or other sources of particulate matter that may be transferred to the leaflet tissue.

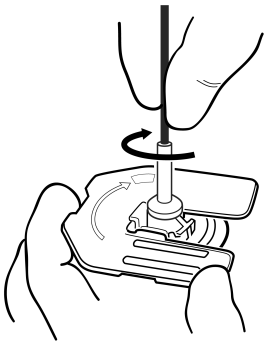
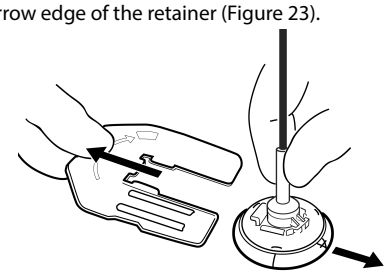
Step	Procedure
1	**Verify the TagAlert:** Verify that the TagAlert, visible through the shelf carton, indicates the valve is okay to use. Use the valve only if the TagAlert reads "OK" as shown in Figure 8.  **Figure 8**
2	**Examine the Shelf Carton Box:** Examine the package for evidence of damage and broken or missing seals (Figure 9).  **Figure 9**
3	**Open Carton Box and Remove Foil Pouch:** Once the appropriate size valve is chosen, open the carton and remove the foil pouch from the carton in the non-sterile field (Figure 10).  **Figure 10** Examine the foil pouch for evidence of damage and broken or missing seals. **Note: Review both sides of the foil pouch including the yellow label describing aseptic transfer steps for the valve (Figure 11).**

Step	Procedure
	 **Figure 11**
4	**Open Foil Pouch and Remove Outer Tray:** Open the foil pouch and remove the outer tray in non-sterile field. Examine the outer tray for evidence of damage and broken seals (Figure 12).   **Figure 12**
5	**Open the Outer Tray:** Near the sterile field, hold the base of the outer tray and peel the lid from the outer tray (Figure 13).  **Figure 13**
6	**Aseptic Transfer:** The inner tray and contents are sterile. Transfer the inner tray to the sterile field (Figure 14). The contents of the inner tray must be handled using a sterile surgical technique to prevent contamination.

Step	Procedure
	 **Figure 14**
7	**Silver Label Verification:** Verify that the serial number on the silver label matches with the shelf carton and Implant Data Card (Figure 15).  **Figure 15** **CAUTION: If any difference in serial number or size is noted, the valve should be returned unused.**
8	**Open the Inner Tray:** Before opening, examine the inner tray and lid for evidence of damage, stains, and broken or missing seals. Hold the base of the inner tray and peel the lid from the inner tray (Figure 16).  **Figure 16** **CAUTION: Do not open the inner package until implantation is certain and the surgeon is ready to place the valve.** **CAUTION: The valve is not secured to the inner tray. Care should be taken while peeling back the lid.** **CAUTION: The valve does not require soaking. If the valve is rinsed prior to implantation, it must then be kept hydrated with sterile physiological saline irrigation on both sides of the leaflet tissue throughout the remainder of the surgical procedure. Rinsing every 1 - 2 minutes is recommended.**

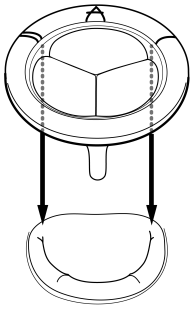
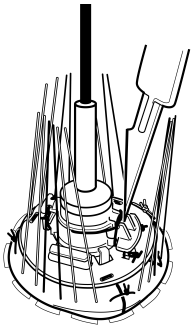
Step	Procedure
9	**Remove valve from the inner tray (Figure 17).**  **Figure 17** **CAUTION: Do not try to insert the handle into the Dial (Figure 18).**  **Figure 18**
10	**Fold the Commissure Posts:** While holding the retainer, turn the dial clockwise (Figure 19) to fold the stent posts (Figure 20). The dial should be turned until the triangle on the dial is at the landing zone on the retainer and a hard stop is felt. **Note: It is normal to hear a clicking noise and feel some resistance when turning the dial.**  **Figure 19**

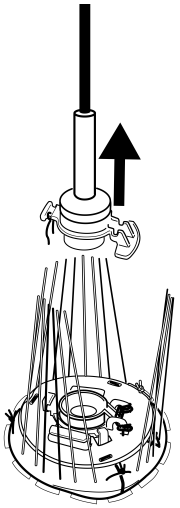
Step	Procedure
	 **Figure 20**
11	**Remove the Dial:** Remove the dial by pulling straight up on the dial (Figure 21). The dial will only be able to be removed when the triangle on the dial is within the landing zone on the retainer.  **Figure 21**

Step	Procedure
12	**Attach the Handle:** Attach the model 1140M handle. To attach, align the handle with the adapter on the valve holder and turn clockwise until resistance is felt (Figure 22).  **Figure 22** **CAUTION: Do not grasp the valve with hands or surgical instruments.** **CAUTION: Use only Edwards model 1140M handle.** **CAUTION: Examine the handle for signs of wear, such as dullness, cracking or crazing, prior to use. Replace handle if any deterioration is observed.** **CAUTION: The handle/holder assembly is required for implantation and should not be removed until the valve is sutured to the annulus.**
13	**Remove Retainer:** Hold the base of the model 1140M handle and pull the retainer away by grasping the ridge on the narrow edge of the retainer (Figure 23).  **Figure 23**

11.4 Device Implantation

Step	Procedure
1	The surgeon should be familiar with the recommendations for proper sizing and placement in the supra-annular position (Refer to Section 11.2 **Sizing**). Because of the complexity and variation of mitral valve replacement surgery, the choice of surgical technique, appropriately modified in accordance with the previously described **Warnings**, is left to the discretion of the individual surgeon. In general, the following steps should be employed: a) Surgically remove the diseased or damaged valve leaflets and all associated structures deemed necessary. Alternatively, techniques of chordal preservation can be performed. **CAUTION: Exercise special care when using sub-valvular apparatus preservation techniques to avoid chordae entrapment by a strut.** b) Surgically remove any calcium from the annulus to ensure proper seating of the sewing ring of the valve. c) Measure the annulus using only the mitral sizers, model 1173B and 1173R (See Figure 2). d) Place sutures through the sewing cuff. Ensure proper seating of the MITRIS RESILIA mitral valve. e) Tie sutures with the holder in place to minimize the potential for suture looping or chordal entrapment. f) Examine the bioprosthetic leaflets for distortion after removal of the holder. **CAUTION: When choosing a valve for a given patient, the size, age, and physical condition of the patient in relation to the size of the valve must be taken into consideration to minimize the possibility of obtaining a suboptimal hemodynamic result. The size selection of a valve, however, must ultimately be made by the physician on an individual basis after carefully weighing all of the risks and benefits to the patient.** **CAUTION: Adequate removal of calcium deposits from the patient's annulus must be performed before implantation to avoid damage to the delicate bioprosthesis leaflet tissue as a result of contact with calcium deposits. Insert the sizer into the mitral annulus. The barrel of the sizer should always fit comfortably in the annulus (See Sizing).** **CAUTION: Use only sizers model 1173B or 1173R during the selection of the valve size; other sizers may result in improper valve selection (Refer to Section 1.2 Sizers and Tray). Like other mitral bioprostheses, the MITRIS RESILIA mitral valve, model 11400M is usually implanted using pledgeted mattress sutures. It is recommended to size the annulus after the sutures have been placed, as sutures may decrease the size of the bioprosthesis that can be implanted.**
2	**Proper orientation of the MITRIS RESILIA mitral valve:** The wireform frame of the MITRIS RESILIA mitral valve, model 11400M is symmetrical, and the three (3) commissure stent posts are equally spaced. The black commissure markers on the sewing ring are intended to aid in proper orientation as the sewing ring is designed for a specific orientation of the valve. The scalloped part of the sewing ring, between the two protrusions, should be placed across the inter-commissural anterior portion of the annulus and straddle the left ventricular outflow tract. Prior to suturing the MITRIS RESILIA mitral valve, orient the valve such that the black "A" marking aligns with the anterior portion of the mitral annulus,

Step	Procedure
	the single commissure marker approximates the posteromedial commissure, and the double commissure marker approximates the anterolateral commissure. Using these orientation aids, the third post should naturally fall in place in or around the middle of the posterior leaflet.  **Figure 24** **Note: The intercommissural distance varies from patient to patient and the black commissure markers indicate approximate orientations.** **CAUTION: Special care must be exercised to avoid placing commissure posts in front of the left ventricular outflow tract, as it may impair long-term hemodynamic performance.**
3	Place sutures through the sewing cuff.
4	Use the handle to facilitate parachuting and positioning of the valve on the mitral annulus. Maintain tension on the sutures as the bioprosthesis is lowered onto the annulus; this minimizes the potential for the formation of suture loops that might entrap a leaflet.
5	Maintain the MITRIS RESILIA mitral valve placement on the annulus by gently placing forceps or gloved hands onto the holder. Cut the retaining blue polymer thread on the anterior side of the adapter with a scalpel (Figure 25). This enables removal of the handle and the adapter from the valve as one unit. Avoid cutting or damaging the stent or leaflet tissue when cutting the blue polymer thread.  **Figure 25**

Step	Procedure
6	Remove the handle and handle adapter by pulling handle away from the holder base (Figure 26).  **Figure 26** **CAUTION: The remaining part of the holder is required for implantation and should not be removed until the sutures are tied.**
7	Tie the suture knots to secure the valve onto the annulus and cut the sutures above the knots. **CAUTION: Avoid looping or catching a suture around the commissure stent posts of the MITRIS RESILIA mitral valve, which would interfere with proper valvular function. To minimize the potential for suture looping, it is essential to leave the deployed holder in place until all knots are tied.** **CAUTION: If the deployed holder attachment threads are cut before the sutures are tied down, the holder will no longer minimize the potential for suture looping around the commissure stent posts.** **CAUTION: When using interrupted sutures, it is important to cut the sutures close to the knots and to ensure that exposed suture tails will not come into contact with the leaflet tissue.** **CAUTION: Avoid placement of annular sutures deep into the adjacent tissue to avoid arrhythmias and conduction abnormalities or avoid damage to the conduction system.**

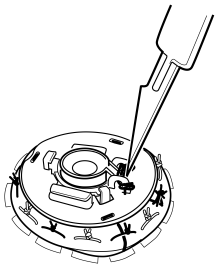
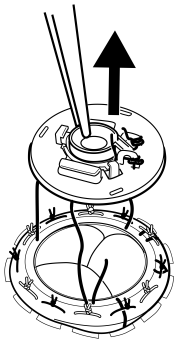
Step	Procedure
8	Cut the retaining blue polymer thread on the holder base at the single cut point at the anterior side of the base. This unfolds the commissure stent posts (Figure 27).  **Figure 27** **CAUTION: The single cut point contains three (3) blue polymer threads. Ensure all three (3) blue polymer threads are cut to allow the holder to be removed from the valve. Do not cut blue polymer threads at any other location.**
9	Use forceps to grasp the blue component of the holder to remove the holder and retaining blue polymer thread from the valve (Figure 28).  **Figure 28** After removing the holder, examine the leaflets for distortion and/or suture looped around a strut. It is recommended to place a surgical mirror through the leaflets after the holder removal in order to examine each strut and proper suture placement.

Figure 29 shows the MITRIS RESILIA valve implanted.

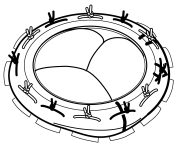


Figure 29

11.5 Accessory Cleaning and Sterilization

The accessories for the MITRIS RESILIA mitral valve, model 11400M, are reusable and packaged separately. Handle model 1140M and sizer model 1173B and 1173R are supplied nonsterile and must be cleaned, disinfected, and sterilized in the tray base and lid before each use. Refer to the Instructions for Use supplied with the reusable accessories for cleaning and sterilization instructions.

11.6 Return of Valves

Edwards Lifesciences is interested in obtaining recovered clinical specimens of the MITRIS RESILIA mitral valve, model 11400M, for analysis. Contact the local representative for return of recovered valves.

- Unopened Package with Sterile Barrier Intact: If the foil pouch or trays have not been opened, return the valve in its original packaging.
- Package Opened but Valve is Not Implanted: If the inner tray is opened, the valve is no longer sterile. If the valve is not implanted, it should be placed into a suitable histological fixative such as 10% formalin or 2% glutaraldehyde and returned to the manufacturer. Refrigeration is not necessary under these circumstances.
- Explanted Valve: The explanted valve should be placed into a suitable histological fixative such as 10% formalin or 2% glutaraldehyde and returned to the manufacturer. Refrigeration is not necessary under these circumstances.

11.7 Device Disposal

Used devices may be handled and disposed of in the same manner as hospital waste and biohazardous materials. There are no special risks related to the disposal of these devices.

12.0 MRI Safety Information

MR Conditional

Non-clinical testing demonstrated that the model 11400M valve is MR conditional. A patient with this device can be safely scanned in an MR system meeting the following conditions:

- Static magnetic field of 1.5T and 3.0T only
- Maximum spatial gradient field of 3000 gauss/cm (30 T/m) or less
- Maximum MR system-reported, whole-body-averaged specific absorption rate (SAR) of 2.0 W/kg per 15 minutes of scanning (i.e. per pulse sequence)
- Normal mode operation of the MR system for both SAR and gradients.

Under the scan conditions above, the model 11400M valve is expected to produce a maximum temperature rise of 2 °C after 15 minutes of continuous scanning.

In non-clinical testing, the image artifact caused by the device extends approximately 20 mm from the model 11400M valve when imaged with a gradient echo pulse sequence and a 3.0 tesla MRI system. Optimization of MR imaging parameters is recommended.

13.0 Patient Labeling

13.1 Patient Identification Card

A Patient Identification Card is provided to each patient implanted with the MITRIS RESILIA mitral valve, model 11400M.

13.2 Patient Information

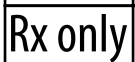
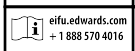
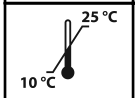
Patient information materials may be obtained from Edwards or an Edwards clinical sales specialist.

14.0 References

1. Nishimura, RA et al. 2017 AHA/ACC Focused update of the 2014 AHA/ACC Guideline for the management of patients with valvular heart disease, Journal of the American College of Cardiology (2017), doi: 10.1016/j.jacc.2017.03.011
2. Candice Baldeo et al. Does chemo-radiation predispose to structural valve deterioration? International Journal of Cardiology 211 (2016) 53–54
3. Syed Wamique Yusuf, et al., Radiation-induced heart disease: a clinical update, Cardiol. Res. Pract. (2011), 317659, 9 pages

Symbol Legend

	ISO Reg. No.[1]	English
	2493	Catalogue Number
	0434A	Caution
	N/A	MR Conditional
	1051	Do not re-use
	N/A	Quantity
	2607	Use-by date
	2497	Date of manufacture
	2498	Serial Number
	2724	Non-pyrogenic

	ISO Reg. No.[1]	English
	N/A	Size
	2501	Sterilized using ethylene oxide
	2606	Do not use if package is damaged
	N/A	Caution: Federal (USA) law restricts this device to sale by or on the order of a physician.
	1641	Consult instructions for use on the website
	3082	Manufacturer
	0632	Temperature limit
	N/A	Use product if indication is shown
	N/A	Do not use product if indication is shown

Note: The labeling of this product may not contain every symbol depicted in this legend.

[1] ISO 7000 *Graphical symbols for use on medical equipment - Registered symbols*

06/21
10048071001 A

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