Tetrilimus™

Everolimus Eluting Cobalt Chromium Coronary Stent System

Instructions for use

SAHAJANAND MEDICAL
TECHNOLOGIES LIMITED

Registered Office / Corporate Office :
"Sahajanand Estate", Wakharia Wadi, Near Dabholi Char Rasta, Ved Road, Surat 395004, Gujarat, INDIA Tel.: +91 261 6112800 Fax: +91 261 6112801

Factory :
Plot No: 33, 34, 35, 52, 53 & 54, Surat Special Economic Zone, Sachin, Surat - 394230, Gujarat, INDIA. Tel: +91 261 6112999 Fax: +91 261 6112801
Email : contact@smtpl.com Visit us at : www.smtpl.com

Consumer Care Helpline +91 261 6112820 contact@smtpl.com
State Consumer Helpline 1800 233 0222

ISO 13485 Certified Company

STERILE EO

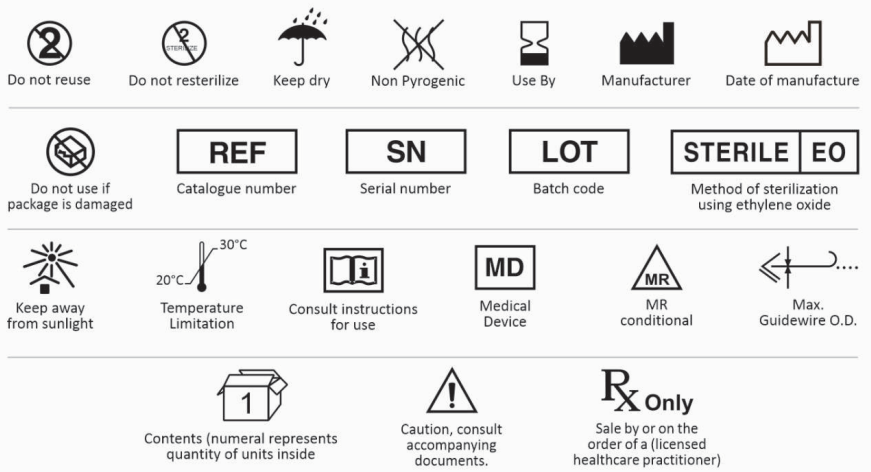
TLIFUWEN REV 09
01JUL2022

Table of Contents

authority to bind Sahajanand Medical Technologies Limited to any representation or warranty except as specifically set forth herein.

Descriptions or specifications in Sahajanand Medical Technologies Limited printed matter, including this publication, are meant solely to generally describe the product at the time of manufacture and do not constitute any express warranties.

15.0 Explanation of Symbols as per MDR(EU) 2017/745 & BS EN ISO 15223



5	If stent sizing/apposition requires optimization, readvance the Stent System balloon, or another high-pressure, non- compliant balloon catheter of the appropriate size, to the stented area using standard angioplasty techniques.

12.6. Removal Procedure

Step	Action
1.	Ensure that the balloon is fully deflated.
2.	Fully open rotating haemostatic valve.
3.	While maintaining guide wire position and negative pressure on inflation device, withdraw delivery system. NOTE. Should **unusual resistance** be felt at any time during either lesion access or removal of delivery system post-stent implantation, the entire system should be **removed as a single unit**. See Precautions 5.11 Stent/System Removal Precautions for specific delivery system removal instructions.
4.	Tighten the rotating hemostatic valve.
5.	Repeat angiography to assess stented area. If necessary, post-dilate within stent. Balloon inflations should utilize balloon of size closely matching vessel.
6.	Final stent diameter should match reference vessel. **ASSURE THAT THE STENT IS NOT UNDERDILATED.**

12.7. *In-Vitro* Information

Pressure [atm]	2.00 mm	2.25 mm	2.50 mm	2.75 mm	3.00 mm	3.50 mm	4.00 mm	4.50 mm
8	2.02	2.23	2.46	2.69	2.92	3.27	3.86	4.28
9	2.06	2.27	2.48	2.73	2.97	3.32	3.92	4.34
10	2.10	2.30	2.50	2.76	3.02	3.37	3.97	4.41
11	2.13	2.33	2.52	2.78	3.05	3.50	4.01	4.50
12	2.16	2.35	2.53	2.81	3.09	3.56	4.05	4.56
13	2.18	2.37	2.55	2.83	3.13	3.61	4.08	4.62
14	2.20	2.39	2.57	2.86	3.16	3.65	4.12	4.68
15	2.23	2.43	2.60	2.89	3.19	3.69	4.16	4.72
16	2.26	2.45	2.63	2.93	3.22	3.72	4.18	4.75

Nominal= 8 atm, for 2.00 mm to 2.25 mm, 10 atm for 2.50 mm to 3.00 mm,
11 atm for 3.50 to 4.50 mm
RBP=16 atm for all sizes

1 atm = 1.01 bar=101.33kpa

13.0 Patient Information

In addition to these instructions for Use booklet, the following patient specific information regarding the **TETRILIMUS™** Everolimus-eluting Coronary Stent is available:

- Stent Implant Card that includes both patient and **TETRILIMUS™** Everolimus-eluting Coronary Stent specific information. All patients will be expected to keep this card in their possession at all times for procedure/stent identification.

14.0 Disclaimer of Warranty and Limitation of Remedy

There is no express or implied warranty, including without limitation any implied warranty of merchantability or fitness for a particular purpose, on the Sahajanand Medical Technologies Limited's product(s) described in this publication. Under no circumstances shall Sahajanand Medical Technologies Limited be liable for any direct, indirect, incidental or consequential damages resulting from reuse of the product and other than as expressly provided by specific law. No person has the

1.0. Product Description

The **TETRILIMUS™** Everolimus eluting coronary stent system is a combination product comprised of two regulated components: a device (Tetrinium coronary stent system as a platform) and a drug product (a formulation of Everolimus drug with the blend of biodegradable polymers).

1.1. Device Component Description

The **TETRILIMUS™** Everolimus eluting coronary stent system consists of a balloon expandable Everolimus eluting stent, premounted on a stent delivery system. The physical characteristics of the device component are shown in Table 1.

Table 1-1: Device Component Description

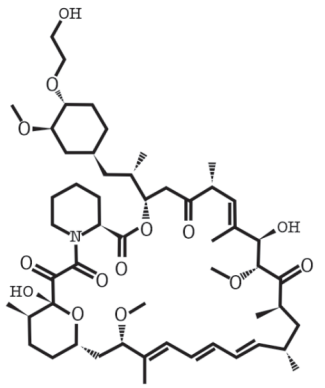
TETRILIMUS™ Everolimus eluting coronary stent System	
Available Stent Lengths, (mm)	8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48
Available Stent Diameters (mm)	2.00, 2.25, 2.50, 2.75, 3.00, 3.50, 4.00, 4.50
Stent Material	L-605 Co-Cr Alloy
Stent Design	Laser cut from seamless tubing in a serpentine pattern
Stent Platform	Tetrinium
Stent Strut Dimension	Thickness: 0.06 mm (60 µ)
Drug	Everolimus
Polymers Type	Biodegradable Polymers
Delivery System Usable Length	1400mm (140 cm)
Delivery System Y - Adapter Ports	Single access port to inflation/deflation lumen. A guidewire exit port is located 25cm away from the tip. Designed for guidewire of Ø0.014inch.
Stent Delivery Balloon	Polyamide balloon, nominally 1 mm longer than the stent. Mounted stent length and location is defined by two radio opaque markers at proximal and distal ends of the stent.
Catheter Shaft Outer Diameter	Proximal : 0.72mm Distal : 0.95mm
Balloon Inflation Pressure	*NP: 8 atm for 2.00 & 2.25 mm,10 atm for 2.50 to 3.00 mm, 11 atm for 3.50 to 4.50 mm RBP: 16 atm
Guiding Catheter	5 F compatible (min.)
Guidewire Diameter	0.014 inch (0.36 mm)

*Assure full deployment of the stent (See section 12.5 Deployment Procedure). Deployment pressures should be based on lesion characteristics.
Note: 1F is equivalent to 0.33mm.NP: Nominal Pressure, RBP: Rated Burst Pressure.
1 atm =1.01bar =101.33kpa

1.2. Drug Component Description

The active pharmaceutical ingredient in the **TETRILIMUS™** Everolimus eluting coronary stent is Everolimus. It is a derivative of the natural macrocyclic lactone Sirolimus with immunosuppressant properties.

Everolimus is a 40-O-(2-Hydroxyethyl)-Rapamycin. It is Sirolimus analogue with a single minimal alteration in its molecular structure (position 40) without a chemical modification of the mTOR binding domain. Therefore works similarly to Sirolimus as an inhibitor of mammalian target of rapamycin (mTOR). The IUPAC name of Everolimus is dihydroxy-12-[(2R)-1-[(1S,3R,4R)-4-(2-hydroxyethoxy)-3-methoxycyclohexyl]propan-2-yl]-19,30-dimethoxy 15, 17, 21, 23, 29, 35–hexamethyl-11, 36-dioxa-4-azatricyclo[30.3.1.$0^{4,9}$] hexatriaconta-16, 24, 26, 28-tetraene- 2, 3, 10, 14, 20-pentone. Its molecular formula is $C_{53}H_{83}NO_{14}$ and its molecular weight is 958.22 g/mol. The structural formula of Everolimus is shown below:



Chemical Structure of Everolimus

Everolimus is white or off-white powder and soluble in methanol, ethanol and chloroform. It is very poorly soluble in water.

The inactive ingredient in the **TETRILIMUS™** Everolimus eluting coronary stent is a combination of biocompatible, biodegradable polymers formulated to provide programmed release of the drug. The polymeric chains are cleaved by hydrolysis to form monomeric acids and are eliminated from the body through Kreb's cycle, primarily as carbon dioxide (CO_2) and water (H2O) which are excreted through urine.

The active ingredient, Everolimus nominal content per stent ranges from 23 to 221µg as per stent length.

2.0. Indications

The **TETRILIMUS™** Everolimus Eluting Coronary Stent System is indicated for improving coronary luminal diameter in patients with symptomatic coronary artery disease due to artery lesions with a reference vessel diameter from 2.00 mm to 4.50 mm.

3.0. Contraindications

Use of the **TETRILIMUS™** Everolimus Eluting coronary stent system is contraindicated in the following patient types:

7. If a syringe was used, attach a prepared inflation device to stopcock.
8. Open the stopcock to the delivery system.
9. Leave on neutral.

Do not wipe with gauze sponges as fibers may disrupt the stent.

Note: Do not pull negative pressure on inflation device before beginning the preparation step.

Note: Do not apply positive pressure to the balloon during the delivery system preparation.

Note: Do not apply negative pressure on inflation device after balloon preparation and prior to delivering the stent. This may cause dislodgement of the stent from the balloon.

Note: If air is seen in the shaft, repeat Section 12.3.3 Delivery System Preparation, steps 3 through 5, to prevent uneven stent expansion.

12.4. Delivery Procedure

Step	Action
1.	Prepare the vascular access site according to standard practice.
2	Predilate the lesion with PTCA (Percutaneous Transluminal Coronary Angioplasty) catheter.
3	Maintain neutral pressure on the inflation device. Open the rotating hemostatic valve as widely as possible.
4	Backload the Delivery System onto the proximal portion of guide wire while maintaining the guide wire position across target lesion.
5	Advance the stent delivery system over the guidewire to the target lesion. Use the radiopaque balloon markers to position the stent across lesion; perform angiography to confirm the position of the stent. NOTE: If during the process of moving the delivery system into position you notice the stent has moved on the balloon, do not deploy the stent. The entire system should be removed as a single unit. See 5.11 Stent/System Removal Precautions section for specific Delivery System removal instructions.
6	Tighten rotating hemostatic valve. Stent is now ready to be deployed.

12.5.Deployment Procedure

Step	Action
1.	Inflate the delivery System expanding the stent to a nominal pressure. Higher pressure may be necessary to optimize stent apposition to the arterial wall. Balloon pressure must not exceed RBP.
2	Maintain inflation pressure for 15-30 seconds for full expansion of the stent
3	Deflate balloon by pulling negative pressure on inflation device until balloon is fully deflated.
4	Confirm stent position and deployment using standard angiographic techniques. For optimal results, the entire stenosed arterial segment should be covered by the stent. Fluoroscopic visualization during stent expansion should be used in order to properly judge the optimum expanded stent diameter as compared to the proximal and distal coronary artery diameter(s). Optimal expansion requires that the stent be in full contact with the artery wall. Stent wall contact should be verified through routine angiography or intravascular ultrasound (IVUS).

12.3. Preparation

12.3.1 Packaging Removal

Note: The foil pouch is not a sterile barrier. The inner Tyvek Pouch within the foil pouch is the sterile barrier. Only the contents of the inner pouch should be considered sterile. The outside surface of the inner pouch is NOT sterile.

1. Carefully remove the delivery system from its protective tubing for preparation of the delivery system. When using a rapid exchange (RX) system, do not bend or kink the hypotube during removal.
2. Remove the product mandrel by grasping the catheter just proximal to the stent (at the proximal balloon bond site), and with the other hand, grasp the stent protector and gently remove distally. If unusual resistance is felt during product mandrel removal, do not use this product and replace with another. Follow product returns procedure for the unused device.
3. Examine the device for any damage. If it is suspected that the sterility or performance of the device has been compromised, the device should not be used.

12.3.2 Guide Wire Lumen Flush

1. Connect a syringe containing heparinized normal saline to an appropriately sized flushing needle. Carefully apply the needle to the distal tip of the delivery system and flush the guidewire lumen until fluid exits the guidewire exit port.

Note: Use caution while flushing guidewire lumen with flushing needle to avoid damage to catheter tip.

Note: Avoid manipulation of the stent while flushing the guide wire lumen, as this may disrupt the placement of the stent on the balloon.

Note: Stent contact with any fluid is not recommended as there is a possibility of initiating drug release. However, if it is absolutely necessary to flush the stent with saline, contact time should be limited (1 minute maximum).

2. Prepare balloon lumen with 50/50 contrast-saline mixture as follows:

a) Using a 20 cc syringe containing 5 cc of contrast-saline mixture, apply negative pressure for 20-30 seconds, allowing air removal from the balloon. An excessive amount of air released into the syringe or no air released from the balloon may indicate damage to the stent delivery system.

Should there be an indication of damage to the stent delivery system, do not use.

b) Release pressure slowly allowing negative pressure to draw mixture into balloon lumen. Do not apply negative pressure on inflation device after balloon preparation and prior to delivering the stent.

c) Detach syringe, leaving a meniscus of mixture on the hub of the balloon lumen.

12.3.3 Delivery System Preparation

- Do not attempt pre-inflation technique to purge balloon lumen.
- Do not use air or any gaseous medium to inflate the balloon.

1. Prepare an inflation device/syringe with diluted contrast medium.
2. Attach an inflation device/ syringe to the stopcock; attach it to the inflation port of the product. Do not bend the product hypotube when connecting to the inflation device/syringe.
3. With the tip down, orient the delivery system vertically.
4. Open the stopcock to delivery system; pull negative for 30 seconds, release to neutral for contrast fill.
5. Close the stopcock to the delivery system; purge the inflation device/syringe of all air. Attach inflation device to balloon lumen directly. Apply the "meniscus to meniscus" technique to ensure that no air bubbles remain at connection.
6. Repeat steps 3 through 5 until all air is expelled. If bubbles persist, do not use the product.

- Patients with a contraindication for anti-platelet/anti-coagulant therapy.
- Patients judged to have lesion that prevents complete inflation of an angioplasty balloon.
- Known hypersensitivity to Everolimus
- Known allergy to Cobalt Chromium.
- Known allergy to biodegradable polymers
- Polymers might enhance inflammatory reactions and Prothrombotic response.

4.0. Warnings

- Please ensure that the inner package has not been opened or damaged as this may indicate the sterile barrier has been breached.
- The use of this product carries the risks associated with coronary artery stenting, including subacute thrombosis, vascular complications, and/or bleeding events.
- Persons allergic to L-605 cobalt chromium alloy or Everolimus or the polymers may suffer an allergic reaction to this implant.
- For single patient use only. Do not reuse, reprocess or resterilize. Reuse, reprocessing or resterilization may compromise the structural integrity of the device and/or lead to device failure which, in turn, may result in patient injury, illness or death. Reuse, reprocessing or resterilization may also create a risk of contamination of the device and/or cause patient infection or cross-infection, including, but not limited to, the transmission of infectious disease(s) from one patient to another. Contamination of the device may lead to injury, illness or death of the patient.
- Discard all disposable device used during this procedure per local requirements for medical device waste disposal

5.0. Precautions

5.1. General Precautions

5.1.1 General Precautions

- Only physicians who have received adequate training should perform implantation of the stent.
- Stent placement should only be performed at hospitals where emergency coronary artery bypass graft surgery can be readily performed
- Subsequent stent blockage may require repeat dilatation of the arterial segment containing the stent. The long-term outcome following repeat dilatation of endothelialized stents is not well characterized.
- Consideration should be given to the risks and benefit of use in patients with history of severe reaction to contrast agents.
- Do not expose the delivery System to organic solvents such as alcohol or detergents.
- Care should be taken to control the position of the guide catheter tip during stent delivery, deployment and balloon withdrawal.
- The use of **TETRILIMUS™** Stents in patients and lesions like more tortuous anatomy may have an increased risk of adverse event including stent thrombosis, stent embolization, myocardial infarction, or death.

Overexpansion -Post-Deployment Dilatation

The stents should not be expanded to a diameter beyond the maximum labelled diameter listed on the label per IFU. Do not dilate the stent beyond the following limits:

Nominal Stent Diameter	Dilation Limit
2.00-2.25 mm	3.25 mm.
2.50-3.50 mm	4.25 mm,
4.00-4.50 mm	5.50 mm

5.1.2 Oral Antiplatelet Therapy

Antiplatelet drugs should be used in combination with the **TETRILIMUS™** Everolimus eluting coronary stent system, per the latest guidelines [the American College of Cardiology, and American Heart Association (ACC/AHA) or the European Society of Cardiology (ESC)].

It is very important that the patient is compliant with the post-procedural antiplatelet recommendations given by their physician. Premature discontinuation of prescribed antiplatelet medication could result in a higher risk of thrombosis, myocardial infarction or death. Prior to PCI (Percutaneous Coronary Intervention), if a surgical or dental procedure is anticipated that requires early discontinuation of antiplatelet therapy, the interventional cardiologist and patient should carefully consider whether a drug- eluting stent and its associated recommended antiplatelet therapy is the appropriate PCI choice. Following PCI (Percutaneous Coronary Intervention) should a surgical or dental procedure be recommended that requires suspension of antiplatelet therapy, the risks and benefits of the procedure should be weighed against the possible risk associated with premature discontinuation of antiplatelet therapy.

Patients who require premature discontinuation of antiplatelet therapy secondary to significant active bleeding should be monitored carefully for cardiac events and, once stabilized, have their antiplatelet therapy restarted as soon as possible per the discretion of their treating physicians.

5.2. USE of Multiple Stents

A patient's exposure to drug and polymer is proportional to the number and total length of implanted stents. When multiple stents are required, resulting in stent-to-stent contact, stents should be of similar composition. Placing multiple stents of different materials in contact with each other may increase potential for corrosion. Potential interactions of the **TETRILIMUS™** Everolimus eluting coronary stent with other drug-eluting or coated stents have been has not been fully evaluated and should be avoided whenever possible.

5.3. Brachytherapy

The safety and effectiveness of the Stent in patients with prior brachytherapy of the target lesion have not been established. The safety and effectiveness of use of brachytherapy to treat in-stent restenosis in a **TETRILIMUS™** Stent have not been established. Both vascular brachytherapy and the Stent **TETRILIMUS™** alter arterial remodeling, the synergy between these two treatments has not been determined.

5.4. Use in Conjunction with Other Procedures

The safety and effectiveness of using mechanical atherectomy devices (directional atherectomy catheters, rotational atherectomy catheters) or laser angioplasty catheters in conjunction with **TETRILIMUS™** Stent implantation have not been established.

5.5. Use in Special Populations

5.5.1 Pregnancy

See Drug Information - section 6.4. The **TETRILIMUS™** stent has not been tested in pregnant women or men intending to father children. Effects on the developing fetus have not been studied. Effective contraception should be initiated before implanting an **TETRILIMUS™** stent and continued for one year after implantation. While there is no contraindication, the risks and reproductive effects are unknown at this time.

5.5.2 Lactation

See Drug Information-section 6.5. A decision should be made whether to discontinue nursing prior to stent implantation, taking into account the importance of the stent to the mother.

5.5.3 Pediatric Use

The safety and efficacy of the **TETRILIMUS™** Stent in pediatric patients have not been established.

11.0. How Supplied

Sterile : This product is sterilized with ethylene oxide gas. It is intended for single use only. Do not resterilize. Non-pyrogenic. Do not use if package is opened or damaged.

Contents : One (1) The **TETRILIMUS™** Everolimus-Eluting Coronary Stent mounted on a rapid exchange stent delivery system.

Storage : Storage temperature: 20° to 30° C

- Avoid exposure to direct sunlight or heaters.
- Keep the product in a cool, dark and dry place.

12.0. Operator's Manual / Clinical Use Information

12.1 Inspection Prior to Use

1. Carefully inspect the sterile package before opening and check for damage to the sterile barrier. Do not use if the integrity of the sterile package has been compromised.
2. Check foil pouch for "Use By" date. Do not use after the "Use by" date.
3. Tear open the foil pouch and remove the inner pouch.
   Note: The outside of the inner pouch is NOT sterile. Open the inner pouch and pass or drop the product into the sterile field using an aseptic technique.
   Note: Special care must be taken not to handle the stent or in any way disrupt its placement on the balloon. This is most important during catheter removal from packaging, placement over guidewire, and advancement through the rotating haemostatic valve and guiding catheter hub.
   Note: Excessive manipulation, e.g., rolling the mounted stent, may cause dislodgement of the stent from the delivery balloon.
4. If sterile package is intact, carefully remove the system from the package and inspect for bends, kinks, and other damage. Do not use if any defects are noted. However, do not manipulate touch, or handle the stent which may cause coating damage, contamination, or stent dislodgement from the delivery balloon.
   Note: At any time during use of device, if the stainless-steel proximal shaft has been bent or kinked, do not continue to use the catheter.
5. If the integrity of the foil pouch or the sterile package has been compromised prior to the product "Use By date" (e.g., damage of the package), contact your local **SMT (Sahajanand Medical Technologies Limited)** representative for return information.

12.2 Materials Required (not included in stent system package)

Quantity	Material
N/A	Guiding catheter(s) ≥ 5F (1.42 mm, 0.056 inch) inner diameter]
2-3	20 cc syringes
1,000 u /500 cc	Heparinized normal saline (HepNS)
1	<0.014 in (0.36 mm) guidewire
1	Rotating haemostatic valve with 0.096 inch (2.44 mm) minimum
inner diameter	
N/A	Contrast diluted 1:1 with heparinized normal saline
1	Inflation Device (with luer fitting)
1	Three-way stopcock
1	Torque device (Optional)
1	Guide wire introducer
1	Pre-deployment dilatation catheter
N/A	Appropriate arterial sheath
N/A	Appropriate sized pre-dilatation angioplasty balloon
N/A	Appropriate sized post-dilatation noncompliant angioplasty balloon
N/A	Appropriate anticoagulation and antiplatelet drugs

- Pulmonary edema
- Renal Failure
- Respiratory Failure
- Restenosis of stented segment
- Shock
- Stent embolization
- Stent migration
- Stent thrombosis/occlusion
- Stroke/cerebrovascular accident/Transient Ischemic Attack (TIA)
- Total occlusion of coronary artery
- Vessel Spasm
- Vessel trauma (dissection, perforation, rupture or injury, including coronary) requiring surgical repair or reintervention

Potential adverse events not captured above, that may be unique to the Everolimus drug coating:

- Abnormal liver function tests
- Anemia
- Arthralgias
- Diarrhea
- Hypercholesterolemia
- Hypersensitivity, including anaphylactic/anaphylactoid type reactions
- Hypertriglyceridemia
- Hypokalemia
- Infections
- Interstitial lung disease
- Leukopenia
- Lymphoma and other malignancies
- Thrombocytopenia

9.0. Individualization of Treatment

The risks and benefits described above should be considered for each patient before use of the **TETRILIMUS™** Everolimus eluting coronary stent. Patient selection factors to be assessed should include a judgment regarding risk of anti-platelet therapy. Stenting is generally avoided in those patients at heightened risk of bleeding (e.g., those patients with recently active gastritis or peptic ulcer disease, see section 3.

Premorbid conditions that increase the risk of a poor initial result and the risks of emergency referral for bypass surgery (diabetes mellitus, renal failure, and severe obesity) should be reviewed.

10.0. Patient Counseling Information

Physicians should consider the following in counseling patient about this product:

- Discuss the risks associated with stent placement
- Discuss the risks associated with a Everolimus-eluting implant
- Discuss the risks/benefits issues for this particular patient
- Discuss alteration to current lifestyle immediately following the procedure and over the long terms.

5.5.4 Geriatric Use

Clinical studies of the Everolimus eluting stent did not find that patients age 65 years and over differed with regard to safety and effectiveness compared to younger patients.

5.6. Lesion/Vessel Characteristics

The safety and effectiveness of the **TETRILIMUS™** Everolimus-eluting coronary stent have not been established in patients with coronary artery reference vessel diameter < 2.00 mm and > 4.50 mm.

5.7. Drug Interactions

See Drug Information-section 6.2 Several drugs are known to affect the metabolism of Everolimus, and other drug interactions may also occur. Everolimus is known to be a substrate for both cytochrome P450 IIIA4 (CYP3A4) and P-glycoprotein (PgP). Everolimus absorption and subsequent elimination may be influenced by drugs that affect these pathways. Everolimus has also been shown to reduce the clearance of some prescription medications when administered orally along with cyclosporine (CsA). Formal drug interaction studies have not been performed with the Everolimus Eluting Stent because of limited systemic exposure to everolimus eluted from stent. Therefore, consideration should be given to the potential for both systemic and local drug interactions in the vessel wall when deciding to implant an Everolimus Eluting Stent in a patient taking a drug with a known interaction with everolimus, or when deciding to initiate therapy with such a drug in a patient who has recently received an Everolimus Eluting Stent.

5.8. Magnetic Resonance Imaging (MRI) - Safety Information

Non-clinical testing and MRI simulations were performed to evaluate the entire family, including single and two-overlapped versions of the **TETRILIMUS™** Everolimus-eluting Coronary Stent. Non-Clinical testing demonstrated that the entire family of this product (i.e., including all single and two or more overlapped versions up to 120 mm in length) is MR Conditional. The **TETRILIMUS™** Everolimus-eluting Coronary Stent has been shown in non-clinical testing to be MRI safe immediately following implantation. A patient with an implant from this family can be scanned safely in an MR system under the following conditions:

- Static magnetic field of 1.5-Tesla or 3-Tesla
- Maximum spatial gradient magnetic field of 1,500-gauss/cm (15-T/m)
- Maximum MR System reported, whole body averaged specific absorption rate (SAR) of 2-W/kg for 15 minutes of scanning (i.e. per pulse sequence) in normal operating Mode

Under the scan condition defined, an implant from the **TETRILIMUS™** Everolimus-eluting Coronary Stent is expected to produce a maximum temperature rise of 3.5°C after 15 minutes of continuous scanning (i.e. per pulse sequence).

In-non-clinical testing, the image artifact caused by and implant from the **TETRILIMUS™** Everolimus-eluting Coronary Stent extends approximately 4 mm from this device when imaged with a gradient echo pules sequence and a 3-Tesla MR system.

5.9. Stent Handling – Precautions

- For single use only. Do not re-sterilize or reuse this device. Note the “Use By” date on the product label.
- Do not remove the stent from the delivery balloon – removal may damage the stent and/or lead to stent embolization. The stent system is intended to perform as a system
- Do not induce a vacuum on the delivery system prior to reaching the target lesion.
- Special care must be taken not to handle or in any way disrupt the stent on the balloon. This is most important while removing the catheter from the packaging, placing it over the guidewire, and advancing it through the large-bore rotating haemostatic valve and guiding catheter hub.
- Stent manipulation (e.g., rolling the mounted stent with your fingers) may loosen the stent from the delivery system balloon and cause dislodgment as well it may damage the coating.
- Use only the appropriate balloon inflation media. Do not use air or any gaseous medium to inflate the balloon as this may cause uneven expansion and difficulty in deployment of the stent.

5.10. Stent Placement Precautions

- Do not prepare or pre-inflate balloon prior to stent deployment other than as directed. Use balloon purging technique described in Section 12.0. Operator's Manual.
- When treating multiple lesions, the distal lesion should be initially stented, followed by stenting of the proximal lesion. Stenting in this order obviates the need to cross the proximal stent in placement of the distal stent and reduces the chances for dislodging the proximal stent.
- Implanting a stent may lead to dissection of the vessel distal and/or proximal to the stent and may cause acute closure of the vessel requiring additional intervention (CABG-Coronary artery bypass graft, further dilatation, placement of additional stents, or other).
- Do not expand the stent if it is not properly positioned in the vessel. (See Precautions –5.11 Stent/System Removal Precautions.)
- Placement of a stent has the potential to compromise side branch patency.
- The vessel should be pre-dilated with an appropriately sized balloon.
- Balloon pressures should be monitored during inflation. Do not exceed rated burst pressure as indicated on the product label. (See Inflation Pressure Recommendations in 12.7) Use of pressures higher than those specified on the product label may result in a ruptured balloon with possible intimal damage and dissection.
- Do not attempt to pull an unexpanded stent back through the guiding catheter, as dislodgement of the stent from the balloon may occur. Remove as a single unit as per instructions in Precautions 5.11 Stent/System Removal Precautions.
- If an unexpanded stent is to be retracted back into the guiding catheter, it is recommended to be done extremely carefully with no or minimal forward movement of the stent delivery system. Once the unexpanded stent is retrieved in the guiding catheter, then the entire system along with the guiding catheter should be withdrawn as a single unit. No attempts should be made to remove the unexpanded stent from the guiding system or the body by itself.
- Stent retrieval methods (use of additional wires, snares and/or forceps) may result in additional trauma to the coronary vasculature and/or the vascular access site. Complications may include bleeding, hematoma or Pseudoaneurysm.
- Do not induce a negative pressure on the delivery catheter prior to placement of the stent across the lesion. This may cause premature dislodgment of the stent from the balloon.
- Although the stent delivery balloon catheter is strong enough to expand the stent without rupture, a circumferential tear of the carrier balloon distal to the stent and prior to complete expansion of the stent could cause the balloon to become tethered to the stent, requiring surgical removal. In case of rupture of the balloon, it should be withdrawn and, if necessary, a new balloon catheter exchanged over the guidewire to complete the expansion of the stent.
- Ensure full coverage of the entire lesion/dissection site so that there are no gaps between stents.

5.11. Stent/System Removal – Precautions

- If unusual resistance is felt at any time during lesion access before stent implantation, the Stent System and the guide catheter should be removed as a single unit.
- Do not attempt to pull an unexpanded stent back into the guide catheter, as stent or coating damage or stent dislodgment from the balloon may occur.
- Stent retrieval methods (use of additional wires, snares and/or forceps) may result in additional trauma to the vascular site. Complications can include bleeding, hematoma or pseudoaneurysm.
- Note: When removing the entire Stent System and guide catheter as a single unit the following steps should be executed under direct visualization using fluoroscopy
- Following stent placement, confirm complete balloon deflation. If greater than usual resistance is felt during delivery System balloon withdrawal, pay particular attention to guide catheter position. In some cases, it may be necessary to pull back slightly on the

Table 5 – Optical Coherence Tomography Outcomes

	3 months cohort1	6 months cohort1
Number of analyzed lesions	13	31
Total number of analyzed struts	5,526	15,354
Analyzed struts per lesion	425.08 ± 187.99	495.29±158.4
Analyzed strut per cross-section	9.61 ± 3.32	10.13 ± 3.17
Covered struts per lesion, %	95.48 ± 5.99	99.77 ± 0.45
Uncovered struts per lesion, %	4.52 ± 5.99	0.23 ± 0.45
Malapposed struts per lesion, %	0.33 ± 0.53	0 ± 0
NIH thickness overlying covered struts, mm	0.11 ± 0.06	0.21 ± 0.07

Neointimal hyperplasia (NIH)

Reference: [1]Kaul U et al. Catheter Cardiovasc Interv. 2021 Jun 1. [2]Abhyankar A et al. Indian Heart J. 2019 Mar-Apr;71(2):149-154. [3]Kasturi S et al. Abstract presented at EuroPCR-2018 and published on 15 May 2018 (Euro18A-POS134). [4]Shravan R et al. Abstracts of EuroPCR 2021, Scientific Abstract e-book (Euro21A-POS012). [5]Bolinera SV et al. Minerva Med. 2020 Aug;111(4):315-323.

8.0 Adverse Events

8.1 Potential Adverse Events

Potential adverse events (in alphabetical order) which may be associated with the use of a Coronary Stent in native coronary arteries include but are not limited to:

- Potential adverse events (in alphabetical order) which may be associated with the use of a Coronary Stent in native coronary arteries include but are not limited to:
- Abrupt Stent Closure
- Acute myocardial infarction
- Allergic reaction to anticoagulants or antithrombotic therapy or contrast medium or stent Materials including stent scaffold
- Aneurysm (Coronary)
- Angina
- Arrhythmias, including ventricular fibrillation (VF) and ventricular tachycardia (VT)
- Arteriovenous Fistula
- Bleeding Complications
- Cardiac Tamponade
- Cardiogenic Shock
- Death
- Dissection
- Emboli, distal (air, tissue, thrombotic, Device materials or stent delivery System materials)
- Emergent or non- emergent coronary artery bypass graft surgery
- Fever
- Heart Failure
- Hematoma
- Hemorrhage, requiring transfusion
- Hypotension/Hypertension
- Infection, local and/or systemic
- Myocardial Ischemia
- Nausea
- Pain at the access site
- Palpitations
- Perforation or Rupture of one or more coronary arteries
- Pericardial effusion
- Pseudoaneurysm, femoral

Stent details						
Total no. of stents	61	275	254	815	766	155
No. of stents deployed per patient, mean ± SD	-	1.29±0.53	1.25±0.48	1.4±0.5	1.3±0.5	1.1±0.3
Stent length (mm), mean ± SD	24.0 ± 8.1	30.68±10.12	23.66±8.90	27.6±9.7	33.5±10.7	46.3±2.0
Stent diameter (mm), mean ± SD	3.0 ± 0.4	2.86±0.36	2.99±0.43	3.0±0.3	2.8±0.3	2.8±0.3

Left Main (LM), Left Anterior Descending (LAD), Left Circumflex (LCX), Right Coronary Artery (RCA), Saphenous Vein Graft (SVG)

Table 4 - Clinical Outcomes

Parameter	TETRILIMUS™ vs. XIENCE Comparative Study[2]		PERFORM-EVER Registry[3,4]		TETRILIMUS™ Single-center Registry[5]			
	TETRILIMUS™	XIENCE			Overall population		Long lesion sub-group	
Follow-up	1-year		1-year	3-year	1-year	3-year#	1-year	3-year#
No. of patients at follow-up	213	204	594	545	558	518	143	134
Death from any cause, n (%)	2 (0.9%)	4 (2.0%)	11 (1.8%)	21 (3.9%)	5 (0.9%)	14 (2.7%)	1 (0.7%)	4 (2.9%)
Cardiac death, n (%)	1 (0.5%)	2 (1.0%)	9 (1.5%)	14 (2.6%)	4 (0.7%)	9 (1.7%)	1 (0.7%)	3 (2.2%)
Non-cardiac death, n (%)	1 (0.5%)	2 (1.0%)	2 (0.3%)	7 (1.3%)	1 (0.2%)	5 (1.0%)	0 (0%)	1 (0.7%)
Target vessel MI, n (%)	3 (1.4%)	4 (2.0%)	8 (1.4%)	19 (3.5%)	8 (1.4%)	23 (4.4%)	2 (1.4%)	6 (4.5%)
TLR, n (%)	5 (2.3%)	4 (2.0%)	5 (0.8%)	14 (2.6%)	2 (0.4%)	15 (2.9%)	1 (0.7%)	5 (3.7%)
ST, n (%)	2 (0.9%)	1 (0.5%)	9 (1.5%)	10 (1.8%)	4 (0.7%)	5 (1.0%)	1 (0.7%)	2 (1.5%)
Major Adverse Cardiac Events (MACE), n (%)	9 (4.2%)	10 (4.9%)	22 (3.7%)*	47 (8.6%)*	14 (2.5%)	47 (9.1%)	4 (2.8%)	14 (10.4%)

* Target lesion failure, # Data on file
Myocardial Infarction (MI), Target Lesion Revascularization (TLR), Target Vessel Revascularization (TVR), Stent Thrombosis (ST)

The "evaluation of **TETRILIMUS™** everolimus-eluting coronary stent by OCT" (EverOCT) study evaluated the healing response at strut-level and cross-section level after implantation of **TETRILIMUS™** stent using optical coherence tomography at 3 and 6 months. EverOCT study revealed rapid early healing of ultra-thin **TETRILIMUS™** with a high percentage of covered struts per lesion within 3 months and at 6 months accompanied with low accumulation and uniform distribution of neointimal hyperplasia. Detailed optical coherence tomography outcome from EverOCT study depicted in the following Table 5.

guide catheter in order to prevent deep seating (unplanned advancement) of the guide catheter and subsequent vessel damage. In cases where unplanned guide catheter movement has occurred, angiographic assessment of the coronary tree should be undertaken to ensure that there is no damage to the coronary vasculature.

- Maintain guidewire placement across the lesion during the entire removal process. Carefully pull back the Stent System until the proximal balloon marker of the Stent System is just distal to the guide catheter distal tip.
- The Stent System and the guide catheter should be pulled back until the tip of the guide catheter is just distal to the arterial sheath, allowing the guide catheter to straighten.
- Carefully retract the Stent System into the guide catheter and remove the Stent System and the guide catheter from the patient as a single unit while leaving the guidewire across the lesion. Failure to follow these steps, and/or applying excessive force to the Stent System, can potentially result in stent or coating damage, stent dislodgment from the balloon, and/or damage to the delivery System.

5.12. Post Implantation – Precautions

- Great care must be exercised when crossing a newly deployed stent with an intravascular ultrasound (IVUS) catheter, a coronary guidewire or balloon catheter to avoid disrupting the stent geometry and stent coating.
- If patient requires MR imaging, refer to Section 5.8 - Magnetic Resonance Imaging (MRI) Safety Information above

6.0. Drug Information

6.1. Mechanism of Action

The mechanism by which Everolimus Eluting Cobalt Chromium Coronary Stent System affects neointima proliferation as seen in clinical studies has not been established. It is known that Everolimus inhibits smooth muscle cell proliferation and growth factor. Everolimus forms a complex with the cytoplasmic protein FKBP12. Thereafter the complex FKBP12-Everolimus binds to and thus interferes with the function of FKBP12-rapamycin associated protein (FRAP) also known as mammalian Target of Rapamycin (mTOR). FRAP is a key regulatory protein which governs cell metabolism, growth, and proliferation. Disabling FRAP function explains the cell cycle arrest at the late G1 stage caused by Everolimus.

6.2. Interaction with Drugs or Other Substances

Everolimus is extensively metabolized by CYP3A4 in the liver and to some extent in the intestinal wall, and is a substrate for the multidrug efflux pump PgP. Concurrent treatment with strong 3A4-inhibitors and inducers is not recommended. Inhibitors of PgP may decrease the efflux of Everolimus from intestinal cells and increase everolimus blood concentrations. In vitro, Everolimus was a competitive inhibitor of CYP3A4 and CYP2D6, potentially increasing the concentrations of medicinal products eliminated by these enzymes. Thus, caution should be exercised when co-administering Everolimus with 3A4- and 2D6 substrates with a narrow therapeutic index.

- CYP3A4 isozyme inhibitors (ketoconazole, itraconazole, voriconazole, ritonavir, erythromycin, clarithromycin, fluconazole, calcium channel blockers [verapamil and diltiazem], aprepitant, atazanavir, nefazodone, amprenavir, indinavir, nelfinavir, delavirdine, fosamprenavir, saquinavir and telithromycin)
- Inducers of CYP3A4 isozyme (St. John's Wort, rifampin, rifabutin, carbamazepine, efavirenz, nevirapine, phenobarbital, phenytoin, dexamethasone)
- Antibiotics (ciprofloxacin, ofloxacin)
- Glucocorticoids
- HMGCoA reductase inhibitors (simvastatin, lovastatin)
- PgP inhibitors (Digoxin, cyclosporine)
- Cisapride (theoretical potential interaction)
- Sildenafil (Viagra®) (theoretical potential interaction)

- Antihistaminics (terfenadine, astemizole)
- Grapefruit/grape fruit juice

Everolimus is approved in the United States under the name of Zortress® for the prophylaxis of organ rejection in adult kidney transplant recipients at low-moderate immunologic risk, at the dose of 1.5 mg/day when taken by mouth. In India, everolimus is approved under the name of Advacan manufactured by Biocon for same use. Everolimus is used for the treatment of patients with advanced renal cell carcinoma (cancer) after failure of treatment with sunitinib or sorafenib, at doses of 5 to 20 mg/day when taken by mouth. The amount of drug that circulates in the bloodstream following implantation of **TETRILIMUS™** stent will be several folds lower than that obtained with oral doses (1.5 mg to 20 mg/day).

6.3. Carcinogenicity, Genotoxicity, and Reproductive Toxicity

The carcinogenicity, genotoxicity, and reproductive toxicity of the **TETRILIMUS™** stent have not been evaluated; however, long term carcinogenicity and teratology studies performed on the, stent with same drug entity, are discussed below.

In 26-week carcinogenicity study conducted to evaluate the carcinogenic potential of Everolimus Eluting Stent (EES) following subcutaneous implantation in transgenic mice, there were no abnormal clinical observations that suggested a carcinogenic effect of EES. The test group did not demonstrate an increased incidence of neoplastic lesions when compared to the negative control group. The positive control and the experimental positive control groups demonstrated notable increases in the incidence of neoplastic lesions compared to either the test or the negative control group. The EES did not appear to be carcinogenic when implanted in transgenic mice for 26 weeks.

Genotoxicity studies conducted on the EES in mammalian cells and bacteria included gene mutations in bacteria (Ames test), gene mutations in mammalian cells (chromosomal aberration), test for clastogenicity in mammalian cells, and mammalian erythrocyte micronucleus test. The EES was found to be non genotoxic.

A reproductive toxicity (teratology) study was conducted in female Sprague-Dawley rats. The EES did not affect the fertility or reproductive capability of female Sprague-Dawley rats. There was no statistical difference between the test article and the control system. The test article had no effect on litter size and caused no increase of in utero mortality. Additionally, the EES did not cause any reproductive toxicity in the offspring in the study.

6.4. Pregnancy

There are no adequate Everolimus or **TETRILIMUS™** stent related studies in pregnant women. When administered at oral doses of 0.1 mg/kg or above, everolimus showed effects on prenatal and postnatal rat development limited to slight body weight changes and fetal survival without any specific toxic potential. Effective contraception should be initiated before implanting **TETRILIMUS™** stent and continued for one-year post-implantation. The **TETRILIMUS™** stent should be used in pregnant women only if potential benefits outweigh potential risks. The safety of the **TETRILIMUS™** stent has not been evaluated in males intending to father children.

6.5. Lactation

It is unknown whether Everolimus is distributed in human milk. Also, everolimus pharmacokinetic and safety profiles have not been determined in infants. Consequently, mothers should be advised of potential serious adverse reactions to everolimus in nursing infants. Prior to **TETRILIMUS™** stent implantation, decisions should be made regarding whether to discontinue nursing or conduct an alternate percutaneous coronary intervention procedure.

7.0 Overview of Clinical Experience

The primary clinical safety and performance of **TETRILIMUS™** Everolimus eluting coronary stent system has been established by comprehensive clinical studies.1-4 These studies have evaluated clinical outcomes of **TETRILIMUS™** stent in broad patient populations. The details of baseline patient characteristics, lesion characteristics, and clinical outcome are summarized in the following table 2, 3, and 4, respectively.

Table 2 - Baseline Patient Characteristics

Parameter	EverOCT Study[1]	TETRILIMUS™ vs. XIENCE Comparative Study[2]		PERFORM-EVER Registry[3,4]	TETRILIMUS™ Single-center Registry[5]	
		TETRILIMUS™	XIENCE		Overall population	Long lesion sub-group
No. of patients	57	213	204	594	558	143
Age (years), mean ± SD	55.0±12.7	55.1±11.5	53.0±10.8	55.6±12.1	57.0±10.2	58.9±9.5
Male, n (%)	47 (82.5%)	142 (66.7%)	130 (63.7%)	453 (76.3%)	393 (70.4%)	65 (45.5%)
Cardiovascular Risk						
Diabetes mellitus, n (%)	26 (45.6%)	85 (39.9%)	62 (30.4%)	138 (23.2%)	215 (38.5%)	58 (40.6%)
Hypertension, n (%)	32 (56.1%)	103 (48.4%)	93 (45.6%)	192 (32.3%)	273 (48.9%)	77 (53.8%)
Smoking, n (%)	6 (10.5%)	48 (22.5%)	50 (24.5%)	141 (23.7%)	101 (18.1%)	29 (20.3%)
Hypercholesterolemia, n (%)	16 (28.1%)	83 (39.0%)	70 (34.3%)	-	67 (12.0%)	31 (21.7%)
Family history of CAD, n (%)	-	-	-	53 (8.9%)	12 (2.2%)	5 (3.5%)
Previous MI, n (%)	-	8 (3.8%)	7 (3.4%)	37 (6.2%)	36 (6.5%)	6 (4.2%)
Previous CABG, n (%)	-	3 (1.4%)	9 (4.4%)	7 (1.2%)	-	-
Previous PCI, n (%)	-	15 (7.0%)	24 (11.8%)	39 (6.6%)	42 (7.5%)	13 (9.1%)
Previous stroke, n (%)	-	0 (0.0%)	2 (1.0%)	2 (0.3%)	1 (0.2%)	-

Coronary Artery Disease (CAD), Myocardial Infarction (MI), Coronary Artery Bypass Graft (CABG), Percutaneous Coronary Intervention (PCI)

Table 3 - Lesion and Procedural Characteristics

Parameter	EverOCT Study[1]	TETRILIMUS™ vs. XIENCE Comparative Study[2]		PERFORM-EVER Registry[3,4]	TETRILIMUS™ Single-center Registry[5]	
		TETRILIMUS™	XIENCE		Overall population	Long lesion sub-group
No. of patients	57	213	204	594	558	143
No. of lesions	59	258	239	735	695	155
Target-vessel location						
LM, n (%)	-	1 (0.4%)	2 (0.8%)	1 (0.1%)	1 (0.1%)	-
LAD, n (%)	32 (54.2%)	117 (45.3%)	114 (47.7%)	381 (51.8%)	313 (45.0%)	63 (40.6%)
LCX, n (%)	17 (28.8%)	50 (19.4%)	52 (21.8%)	139 (18.9%)	243 (35.0%)	18 (11.6%)
RCA, n (%)	10 (16.9%)	89 (34.5%)	69 (28.9%)	214 (29.1%)	138 (19.9%)	74 (47.7%)
SVG, n (%)	-	1 (0.4%)	2 (0.8%)	-	-	-