Supraflex Cruz

Stainless Steel Cobalt Chromium Coronary Stent System

Instructions for use

STERILE EO

CE 2460

SMT

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1.0. Product Description

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

1.1. Device Component Description

The **SUPRAFLEX CRUZ™** Sirolimus eluting coronary stent system consists of a balloon expandable Sirolimus eluting stent, premounted on a stent delivery system. The physical characteristics of the device component are shown in Table 1.1.

Table 1.1: Device Component Description
SUPRAFLEX CRUZ™ Sirolimus-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)
Nominal Stent Foreshortening	< 3%
Recoil	< 4%
Drug	Sirolimus
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 1mm 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 : 0.67mm Distal : 0.89mm
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

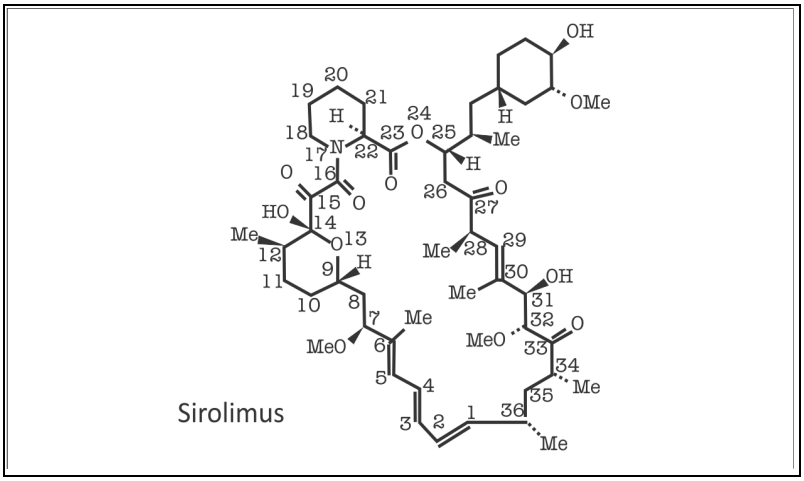
*Assure full deployment of the stent (See section 11.6 Deployment Procedure). Deployment pressures should be based on lesion characteristics.
Note: 1F is equivalent to 0.33mm.NP: Nominal Pressure, RBP: Rated Burst Pressure. 1 atm =1.01bar

1.2. Drug Component Description

The active pharmaceutical ingredient in the **SUPRAFLEX CRUZ™** Sirolimus eluting coronary stent is Sirolimus (also known as Rapamycin).

Sirolimus is a macrocyclic lactone produced by Streptomyces hygroscopicus. The chemical name (IUPAC) of Sirolimus (also known as Rapamycin) is [3S [3R* [S* (1R*, 3S*, 4S*)), 6S*, 7E, 9S*, 10S*, 12S*, 14R*, 15E, 17E, 19E, 21R*, 23R*, 26S*, 27S*, 34aR*]] - 9, 10, 12, 13, 14, 21, 22, 23, 24, 25, 26, 27, 32, 33, 34, 34a - Hexadecahydro –

9, 27-dihydroxy - 3 - [2 - (4 - hydroxy - 3 methoxycyclohexyl) -1 methylethyl] - 10, 21 - dimethoxy - 6, 8, 12, 14, 20, 26 - hexamethyl - 23, 27 - epoxy 3H pyrido [2, 1 - c] [1, 4] oxaazacyclohentriacontine - 1, 5, 11, 28, 29 (4H, 6H, 31H) - pentone. Its molecular formula is $C_{51}H_{79}NO_{13}$ and its molecular weight is 914.19 g/mol. The structural formula of Sirolimus is shown below:



Sirolimus is white or off-white powder and soluble in methanol, ethanol, acetone, ethyl acetate, dichloromethane and chloroform. It is sparingly soluble in ethyl ether, hexane and petroleum ether and insoluble in water.

The inactive ingredient in the **SUPRAFLEX CRUZ™** Sirolimus 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 (H_2O) which are excreted through urine.

The active ingredient, Sirolimus nominal content per stent ranges from 33 to 309µg as per stent length.

2.0. Indications

The **SUPRAFLEX CRUZ™** Sirolimus Eluting Coronary Stent System is indicated for improving coronary luminal diameter in patients with symptomatic Ischemic heart disease due to discrete de-novo stenotic lesions and in-stent restenotic lesions in native coronary arteries with a reference vessel diameter of 2.00 mm to 4.50 mm.

3.0. Contraindications

Use of the **SUPRAFLEX CRUZ™** Sirolimus eluting coronary stent system is contraindicated in the following patient types:

- Patients with contraindication for anti-platelet/anti-coagulant therapy.
- Patients judged to have lesion that prevents complete inflation of an angioplasty balloon.
- Known hypersensitivity to Sirolimus or its derivatives.
- 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 Sirolimus 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.

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 **SUPRAFLEX CRUZ™** 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.

5.1.2 Oral Antiplatelet Therapy

The optimal duration of dual antiplatelet therapy following DES implantation is unknown, and DES thrombosis may still occur despite continued therapy. Continuation of combination treatment with Acetyl Salicylic Acid (ASA) and clopidogrel after percutaneous coronary intervention (PCI) appears to reduce major adverse cardiac events. On the basis of current guideline Acetyl Salicylic Acid (ASA) 150-300mg (single shot), followed with 75-100 mg daily should be given indefinitely after PCI. Likewise, clopidogrel 75 mg daily should be given for at least 6 months in patients who are not at high risk of bleeding.
[Ref: Eur Heart J. 2014 Oct 1;35(37):2541-619.
http://dx.doi.org/10.1093/eurheartj/ehu278]

It is very important that the patient is compliant with the post-procedural antiplatelet recommendations. Premature discontinuation of prescribed antiplatelet medication could result in a higher risk of thrombosis, myocardial infarction or death. Prior to PCI, 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, 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. Use of more than two Sirolimus-Eluting Co-Cr Coronary Stent System has not been fully evaluated.

5.3. Brachytherapy

The safety and effectiveness of the **SUPRAFLEX CRUZ™** 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 an **SUPRAFLEX CRUZ™** Stent have not been established. Both vascular brachytherapy and the **SUPRAFLEX CRUZ™** Stent 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 **SUPRAFLEX CRUZ™** Stent implantation have not been established.

5.5. Use in Special Populations

5.5.1 Pregnancy

See Drug Information section 6.4. There are no adequate and well-controlled studies in pregnant women or men intending to father children. Systemic levels of Sirolimus have not been demonstrated in any pre-clinical or clinical trials with the **SUPRAFLEX CRUZ™** Stent. Effective contraception should be initiated before implanting an **SUPRAFLEX CRUZ™** Stent and for 12 weeks after implantation. The **SUPRAFLEX CRUZ™** Stent should be used during pregnancy only if the potential benefit outweighs the potential risk to the embryo or fetus.

5.5.2 Use during Lactation

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

5.5.3 Pediatric Use

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

5.5.4 Geriatric Use

Clinical studies of the Sirolimus-Eluting Co-Cr Coronary Stent System did not find that patients age 65 years and over differed with regard to safety and efficacy compared to younger patients.

5.6. Lesion/Vessel Characteristics

The safety and effectiveness of the **SUPRAFLEX CRUZ™** Sirolimus-eluting Coronary Stent have not been established in the following patient populations:

- Patients with unresolved vessel thrombus at the lesion site.
- Patients with coronary artery reference vessel diameter < 2.00mm or > 4.50mm
- Patients with lesions located in the left main coronary artery, ostial lesions, or lesions located at a bifurcation.
- Patients with diffuse disease or poor overflow distal to the identified lesions.
- Patients with tortuous vessels in the region of the obstruction or proximal to the lesion.
- Patients with a recent acute myocardial infarction where there is evidence of thrombus or poor flow.
- Patients with moderate or severe calcification in the lesion.
- Patients with multi-vessel disease.

5.7. Drug Interactions

Several drugs are known to affect the metabolism of Sirolimus, and other drug interactions may be inferred from known metabolic effects. Sirolimus is known to be a substrate for both cytochrome P450 IIIA4 (CYP3A4) and P-glycoprotein.

Consideration should be given to the potential for drug interaction when deciding to place a **SUPRAFLEX CRUZ™** Stent in a patient who is taking a drug that could interact with Sirolimus, or when deciding to initiate therapy with such a drug in a patient who had recently received a **SUPRAFLEX CRUZ™** Stent. The effect of drug interactions on the safety or efficacy of the **SUPRAFLEX CRUZ™** Stent has not been determined.

5.8. Magnetic Resonance Imaging (MRI) – Stent Migration

The **SUPRAFLEX CRUZ™** has been shown in non-clinical testing to be MRI safe immediately following implantation. MRI test conditions used to evaluate this stent were:

- Magnetic resonance environment of 3 Tesla.
- The response of overlapping stents or stents with fractured struts is unknown. Non-clinical testing has not been performed to rule out the possibility of stent migration at field strengths higher than 3 tesla.

5.9. Stent Handling Precautions

- For single use only. Do not resterilize 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 hemostatic 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 11.0. 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, 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 appropriate 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 11.8.) 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.
- When removing the entire Stent System and guide catheter as a single unit (NOTE: 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 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.
- Do not perform a Magnetic Resonance Imaging (MRI) scan on patient's post-stent implantation until the stent has completely endothelialized to minimize the potential for migration. The stent may cause artifacts in MRI scans due to distortion of the magnetic field.
- Prescribe an antiplatelet therapy for a period of 6 months to reduce the risk of stent thrombosis.

6.0. Drug Information

6.1. Mechanism of Action

The mechanism (or mechanisms) by which Sirolimus Eluting Cobalt Chromium Coronary Stent System affects neointima proliferation as seen in clinical studies has not been established. It is known that Sirolimus inhibits T-lymphocyte activation and smooth muscle and endothelial cell proliferation in response to cytokine and growth factor stimulation. In cells, Sirolimus binds to the immunophilin, FK Binding Protein-12 (FKBP-12). The Sirolimus-FKBP-12 complex binds and inhibits the activation of the

mammalian Target of Rapamycin (mTOR), leading to inhibition of cell cycle progression from G1 to S phase.

6.2. Drug Interactions Following Oral Administration of Sirolimus

Drug interaction studies have not been conducted with the Sirolimus Eluting Cobalt Chromium Coronary Stent System. Sirolimus is extensively metabolized by cytochrome P450 3A4 (CYP3A4) in the gut wall and liver and undergoes efflux from enterocytes of the small intestine by P-glycoprotein (P-gp). Therefore, absorption and the subsequent elimination of systemically absorbed Sirolimus may be influenced by drugs that affect these protein complexes. Inhibitors of CYP3A4 and P-gp may increase Sirolimus levels, while inducers of CYP3A4 and P-gp may decrease Sirolimus levels. The pharmacokinetic interaction between orally administered Sirolimus and concomitantly administered drugs is discussed below.

6.2.1 Ketoconazole

Multiple-dose Ketoconazole administration significantly affected the rate and extent of absorption and Sirolimus exposure after administration of a Sirolimus oral formulations, as reflected by increases in Sirolimus C_{max}, t_{max}, and AUC of 4.3-fold, 38%, and 10.9-fold, respectively. However, the terminal $t_{1/2}$ of Sirolimus was not changed. Single-dose Sirolimus did not affect steady-state 12-hour plasma Ketoconazole concentrations. It is recommended that Sirolimus oral solution and oral tablets should not be administered with Ketoconazole.

6.2.2 Rifampin

Pretreatment of 14 healthy volunteers with multiple doses of Rifampin, 600 mg daily for 14 days, followed by a single 20-mg dose of Sirolimus, greatly increased Sirolimus oral-dose clearance by 5.5-fold (range = 2.8 to 10), which represents mean decrease in AUC and C_{max} of about 82% and 71%, respectively. In patients where Rifampin is indicated, alternative therapeutic agents with less enzyme induction potential should be considered.

6.2.3 Diltiazem

The simultaneous oral administration of 10 mg of a Sirolimus oral solution and 120 mg of Diltiazem to 18 healthy volunteers significantly affected the bioavailability of Sirolimus. Sirolimus C_{max}, t_{max}, and AUC were increased 1.4-, 1.3-, and 1.6-fold, respectively. Sirolimus did not affect the pharmacokinetics of either Diltiazem or its metabolites desacetyldiltiazem and desmethyldiltiazem.

6.2.4 Cyclosporine

Single-dose pharmacokinetic interactions between Cyclosporine and Sirolimus were investigated for two Sirolimus oral formulations in studies using 24 healthy volunteers. Compared to results obtained when oral Sirolimus was administered alone, the oral administration of 10 mg Sirolimus 4 hours after a single dose of 300 mg Cyclosporine soft gelatin capsules increased mean Sirolimus AUC by 33% to 80% and increased mean Sirolimus C_{max} by 33% to 58%, depending on the Sirolimus formulation. The half-life of Sirolimus was not significantly affected. The Cyclosporine mean AUC and mean C_{max} were not significantly affected.

In a single dose cross-over drug-drug interaction study, 33 healthy volunteers received 5 mg Sirolimus alone, 2 hours before, and 2 hours after a 300 mg dose

of cyclosporine soft gelatin capsules. When given 2 hours before the cyclosporine administration, Sirolimus C_{max} and AUC were comparable to those with administration of Sirolimus alone. However, when given 2 hours after, the mean C_{max} and AUC of Sirolimus were increased by 126 % and 141 %, respectively, relative to administration of Sirolimus alone.

6.2.5 Erythromycin

The simultaneous oral administration of 2 mg daily of Sirolimus oral solution and 800 mg q 8 h of erythromycin as erythromycin ethylsuccinate tablets at steady state to 24 healthy volunteers significantly affected the bioavailability of Sirolimus and erythromycin. Sirolimus C_{max} and AUC were increased 4.4- and 4.2- fold, respectively, and t_{max} was increased by 0.4 hr. Erythromycin C_{max} and AUC were increased 1.6- and 1.7- fold, respectively, and t_{max} was increased by 0.3 hr.

6.2.6 Verapamil

The simultaneous oral administration of 2 mg daily of Sirolimus oral solution and 180 mg q 12 h of verapamil at steady state to 26 healthy volunteers significantly affected the bioavailability of Sirolimus and verapamil. Sirolimus C_{max} and AUC were increased 2.3- and 2.2- fold, respectively, without substantial change in t_{max}. The C_{max} and AUC of the pharmacologically active S (-) enantiomer of verapamil were both increased 1.5-fold and t_{max} was decreased by 1.2 hr.

6.2.7 Drugs which may be co administered without dose adjustment

Clinically significant pharmacokinetic drug-drug interactions were not observed in studies of drugs listed below in conjunction with orally administered Sirolimus. Sirolimus and these drugs may be co administered without dose adjustments.

- Acyclovir
- Digoxin
- Glyburide
- Nifedipine
- Norgestrel/ethinyl estradiol
- Prednisolone
- Sulfamethoxazole/Trimethoprim

6.2.8 Other drug interactions

Drugs that may increase Sirolimus blood concentrations include:

- **Calcium channel blockers:** nicardipine, verapamil
- **Antifungal agents:** clotrimazole, fluconazole, itraconazole
- **Macrolide antibiotics:** clarithromycin, erythromycin, troleandomycin
- **Gastrointestinal prokinetic agents:** cisapride, metoclopramide
- **Other drugs:** bromocriptine, cimetidine, danazol, HIV-protease inhibitors (e.g., ritonavir, indinavir)

Drugs that may decrease Sirolimus levels include:

- **Anticonvulsants:** carbamazepine, phenobarbital, phenytoin
- **Antibiotics:** rifabutin, rifapentine

Care should be exercised when drugs or other substances that are metabolized by CYP3A4 are administered concomitantly with Sirolimus-eluting Cobalt Chromium Coronary Stent System.

6.2.9 Grapefruit juice

Grapefruit juice reduces CYP3A4-mediated metabolism of Sirolimus.

6.2.10 Vaccination

Immunosuppressant may affect response to vaccination. Therefore, during treatment with Sirolimus, vaccination may be less effective. The use of live vaccines should be avoided; live vaccines may include, but are not limited to, measles, mumps, rubella, oral polio, BCG, yellow fever, varicella, and TY21a typhoid.

6.2.11 Drug-laboratory test interactions

There are no studies on the interactions of Sirolimus in commonly employed clinical laboratory tests.

6.3. Mutagenesis, Carcinogenicity and Reproductive Toxicology

The genotoxicity, carcinogenicity, and reproductive toxicity of Sirolimus Eluting Cobalt Chromium Coronary Stent System have not been evaluated. However, the genotoxicity, carcinogenicity, and reproductive toxicity of Sirolimus have been investigated in bacterial and mammalian cells *in vitro* and in laboratory animals *in vivo*.

Sirolimus was not genotoxic in the *in vitro* bacterial reverse mutation assay, Chinese hamster ovary cell chromosomal aberration assay, mouse lymphoma cell forward mutation assay, or *in vivo* mouse micronucleus assay.

Carcinogenicity studies in mouse showed hepatocellular adenoma and carcinoma at dosages of 1, 3 and 6 mg/kg/day orally. In the 104-week rat study at dosage of 0.2 mg/kg/day, there was a significant increase in the incidence of testicular adenoma.

There was no effect on fertility in female rats following the administration of Sirolimus at dosages up to 0.5 mg/kg/day. In male rats, there was no significant difference in fertility rate compared to controls at a dosage of 2 mg/kg/day. Reductions in testicular weights and/or histological lesions (e.g., tubular atrophy and tubular giant cells) were observed in rats following dosages of ≥0.65 mg/kg/day. These dosages are quiet higher than the amount of drug delivered by Sirolimus Eluting Cobalt Chromium Coronary Stent System.

6.4. Pregnancy

There are no adequate data from the use of Sirolimus in pregnant women. Sirolimus was embryo toxic in rats at dosages of ≥ 0.1 mg/kg/day. Embryo toxicity was manifested as mortality and reduced fetal weights (with associated delays in skeletal ossification). No teratogenic effect of Sirolimus was evident. There was no effect of Sirolimus on rabbit development at the maternally toxic dosage of 0.05 mg/kg/day. Effective contraception should be initiated before Sirolimus therapy, during Sirolimus therapy and for 12 weeks after Sirolimus therapy. The Sirolimus should be used during pregnancy only if the potential benefit outweighs the potential risk to the embryo or fetus.

6.5. Lactation

Sirolimus is excreted in trace amounts in milk of lactating rats. It is not known whether Sirolimus is excreted in human milk. The pharmacokinetic and safety profiles of Sirolimus in infants are not known. Because many drugs are excreted in human milk and because of the potential for adverse reactions in nursing infants from Sirolimus, a

decision should be made whether to discontinue nursing or to implant the stent, taking into account the importance of the stent to the mother.

7.0 Adverse Events

7.1. 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:

- 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
- Cardiac Tamponade
- Cardiogenic Shock
- Death
- Dissection
- Emboli, distal (air, tissue, thrombotic, Device materials or stent delivery System materials)
- Heart Failure
- Hematoma
- Hemorrhage, requiring transfusion
- Infection, local and/or systemic
- Myocardial Ischemia
- Pain at the access site
- Perforation or Rupture of one or more coronary arteries
- Pericardial effusion
- Pseudoaneurysm, femoral
- 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 Sirolimus drug coating:

- Abnormal liver function tests
- Anemia
- Arthralgias
- Diarrhea

- Hypercholesterolemia
- Hypersensitivity, including anaphylactic/anaphylactoid type reactions
- Hypertriglyceridemia (see section 5.10)
- Hypokalemia
- Infections
- Interstitial lung disease
- Leukopenia
- Lymphoma and other malignancies
- Thrombocytopenia

8.0. Individualization of Treatment

See also Precautions section 5.5. Use in Special Populations and Precautions section 5.6 Lesion/Vessel Characteristics.

The risks and benefits described above should be considered for each patient before use of the **SUPRAFLEX CRUZ™** Sirolimus-eluting 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 Contraindications).

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.

9.0. 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 Sirolimus-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.

10.0. 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 **SUPRAFLEX CRUZ™** Sirolimus-eluting Stent 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.

11.0. Operator's Manual / Clinical Use Information

11.1 Access to Package Holding Sterile Stent Delivery System

Tear open outer foil pouch to reveal second inner pouch. Note: DO NOT drop or hand inner pouch into sterile field using an aseptic technique. Remove inner pouch from outer foil pouch. Peel open inner pouch using aseptic technique to reveal sterile package.

11.2 Inspection Prior to Use

Before opening, carefully inspect the stent delivery system package, and check for damage to the sterile barrier. Prior to using the device, carefully remove the system from

the package and inspect it for bends, kinks, and other damage. Do not use the device if any damage to the packaging is noted.

11.3 Materials Required

Quantity	Material
N/A	Appropriate Guiding Catheter(s)
2-3	10-20 cc Syringes
1,000 u /500 cc	Sterile Heparinized Normal Saline (HepNS)
1	0.014 inch x 175 cm (minimum length) Guide Wire
1	Rotating hemostatic valve with 0.096 inch minimum inner diameter
N/A	Contrast diluted 1:1 with normal Saline
1	Inflation Device
1	Stopcock (3-way minimum)
1	Torque Device
1	Guide Wire Introducer
N/A	Appropriate anticoagulation and anti-platelet drugs

11.4 Preparation

11.4.1 Guidewire Lumen Flush

Step	Action
1	Remove the protective cover from tip.
2	Flush guidewire lumen with HepNS until fluid exits guidewire exit notch.

11.4.2 Delivery System Preparation

Step	Action
1	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 the inflation device/syringe with diluted contrast medium
3	Attach the inflation device/syringe to stopcock; attach it to the inflation port. Do not bend the hypotube when connecting to inflation Device/syringe.
4	With tip down, orient Delivery System vertically.
5	Open stopcock to Stent System; pull negative for 15 seconds; release to neutral for contrast fill
6	Close stopcock to Delivery System; purge inflation device/syringe of all air.
7	Repeat steps 4 through 6 until all air is expelled. If bubbles persist, do not use product.
8	If a syringe was used, attach a prepared inflation device to stopcock.
9	Open stopcock to Stent System.
10	Leave on neutral.

11.5. Delivery Procedure

Step	Action
1	Prepare the vascular access site according to standard practice.
2	Predilate the lesion with PTCA 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.

11.6.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).
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.

11.7. Removal Procedure

Step	Action
1	Ensure that the balloon is fully deflated.
2	Fully open rotating hemostatic 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.**

11.8. 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=1.01bar

12.0 Patient Information

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

- Evaluation Form that includes both patient and **SUPRAFLEX CRUZ™** Sirolimus -eluting Coronary Stent specific information. All patients will be expected to keep this card in their possession at all times for procedure/stent identification.

13.0 Disclaimer of Warranty and Limitation of Remedy

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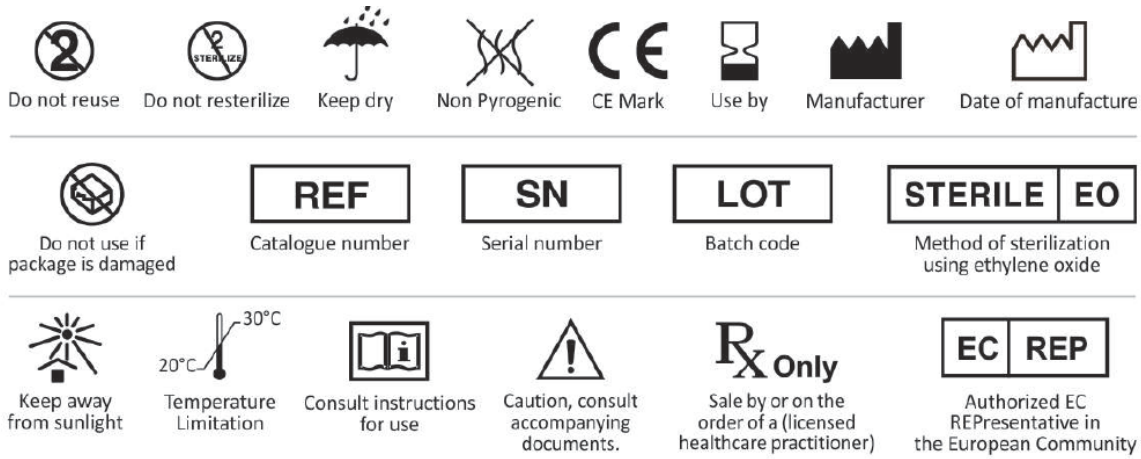
14.0 Explanation of symbols as per MDD 93/42/EEC & BS EN ISO 15223



SAHAJANAND MEDICAL TECHNOLOGIES PVT. LTD.

Registered Office / Corporate Office :
"Sahajanand Estate", Wakharia Wadi, Near Dabholi Char Rasta, Ved Road, Surat 395004,
Gujarat, INDIA Tel.: +91 261 3060606 Fax: +91 261 3060607

Factory :
Plot No: 33, 34, 35, 52, 53 & 54, Surat Special Economic Zone, Sachin,
Surat - 394230, Gujarat, INDIA. Tel: +91 261 3980800 Fax: +91 261 3980801
Email : contact@sahmed.com Visit us at : www.smtpl.com

Consumer Care Helpline +91 261 3060696 contact@sahmed.com
State Consumer Helpline 1800 233 0222
ISO 13485 Certified Company • GMP Certified Company

EC REP

Obelis s.a
Boulevard Général Wahis 53
1030 Brussels, BELGIUM
Tel: +(32) 2. 732.59.54
Fax: +(32) 2.732.60.03
E-Mail : mail@obelis.net