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10056733-3

Instructions for Use

CYPHER™ Sirolimus-eluting Coronary Stent on RAPTOR™ Over-the-Wire Delivery System

and

CYPHER™ Sirolimus-eluting Coronary Stent on RAPTORRAIL® Rapid Exchange Delivery System

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

1. Product Description

The **CYPHER™** Sirolimus-eluting Coronary Stent (**CYPHER** Stent) is a combination product comprised of two regulated components: a device (a stent system) and a drug product (a formulation of sirolimus in a polymer coating).

1.1. Device Component Description

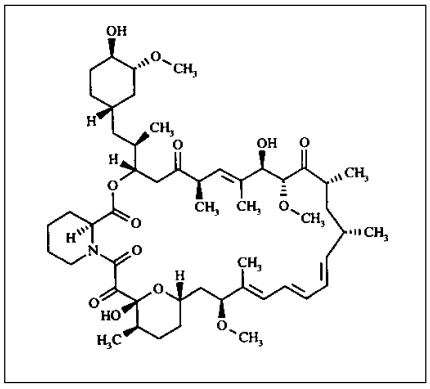
The device component consists of a stent mounted onto a stent delivery system (SDS). The physical characteristics of the device component are shown in Table 1-1.

Table 1-1: Device Component Description

	CYPHER™ Sirolimus-eluting Coronary Stent on RAPTOR™ Over-the-Wire (OTW) Stent Delivery System	**CYPHER™ Sirolimus-eluting Coronary Stent on RAPTORRAIL® Rapid Exchange (RX) Stent Delivery System**
Available Stent Lengths, unexpanded (mm):	8, 13, 18, 23, 28, 33	8, 13, 18, 23, 28, 33
Available Stent Diameters (mm):	2.50, 2.75, 3.00, 3.50	2.50, 2.75, 3.00, 3.50
Stent Material:	Electropolished stainless steel (316L), laser-cut from seamless tubing in a sinusoidal pattern coated with a polymer and sirolimus mixture.	
Stent Geometry:	Six circumferential cells (2.50 – 3.00 mm stents) or Seven circumferential cells (3.50 mm stents)	
Nominal Stent Foreshortening:	≤ 1 mm	
Delivery System Usable Length:	145 cm	137 cm
Delivery System Y-Adapter Ports:	Y-Connector (Side arm for access to balloon inflation/deflation lumen. Straight arm is continuous with shaft inner lumen – designed for guidewire ≤ 0.014" (0.36 mm).)	Single access port to the inflation lumen. A guidewire exit port is located at 28 cm from the tip. Designed for guidewire ≤ 0.014" (0.36 mm).
Stent Delivery Balloon:	Single-layer nylon, nominally 2 mm longer than stent. Mounted stent length and location is defined by 2 platinum-iridium radiopaque marker bands.	
Balloon Inflation Pressure:	Nominal pressure: 11 atm (1115 kPa) Rated burst pressure: 16 atm (1621 kPa)	
Guiding Catheter Inner Diameter:	≥ 0.067" (1.7 mm)	≥ 0.056" (1.4 mm) for 2.50 – 3.00 mm ≥ 0.067" (1.7 mm) for 3.50 mm
Catheter Shaft Outer Diameter:	3.3F (1.10 mm) proximally, 2.7F (0.90 mm) distally.	2.3F (0.75 mm) proximally; 2.6F (0.85 mm) distally (Ø up to 3.00 mm); 2.9F (0.95 mm) distally (Ø > 3.00 mm).

1.2. Drug Component Description

The active ingredient in the **CYPHER** Sirolimus-eluting Coronary Stent is sirolimus (also known as rapamycin). Sirolimus is a macrocyclic lactone produced by *Streptomyces hygroscopicus*. The chemical name of sirolimus (also known as rapamycin) is (3*S*,6*R*,7*E*,9*R*,10*R*,12*R*,14*S*,15*E*,17*E*,19*E*,21*S*,23*S*,26*R*,27*R*,34a*S*)-9,10,12,13,14,21,22,23,24,25,26,27,32,33,34,34a-hexadecahydro-9,27-dihydroxy-3-[(1*R*)-2-[(1*S*,3*R*,4*R*)-4-hydroxy-3-methoxycyclohexyl]-1-methylethyl]-10,21-dimethoxy-6,8,12,14,20,26-hexamethyl-23,27-epoxy-3*H*-pyrido[2,1-*c*][1,4] oxaazacyclohentriacontine-1,5,11,28,29 (4*H*,6*H*,31*H*)-pentone. Its molecular formula is $C_{51}H_{79}NO_{13}$ and its molecular weight is 914.2. The structural formula of sirolimus is shown below:



Sirolimus is a white to off-white powder and is insoluble in water, but freely soluble in benzyl alcohol, chloroform, acetone, and acetonitrile. Please refer to Table 1-2 for the nominal dosages of sirolimus on the **CYPHER** Sirolimus-eluting Coronary Stents.

The inactive ingredients in the **CYPHER** Sirolimus-eluting Coronary Stent contain parylene C and the following two non-erodible polymers: polyethylene-co-vinyl acetate (PEVA) and poly n-butyl methacrylate (PBMA). A combination of the two polymers mixed with sirolimus (67%/33%) makes up the basecoat formulation which is applied to a parylene C treated stent. A drug-free topcoat of PBMA polymer is applied to the stent surface to control the release kinetics of sirolimus. The drug/polymer coating is adhered to the entire surface (i.e., luminal and abluminal) of the stent. The structural formulae of the polymer subunits are shown below:

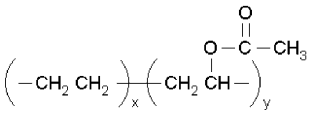
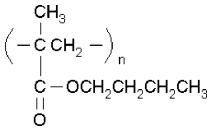
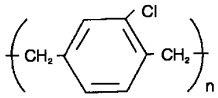
PEVA	PBMA	Parylene C
		

Table 1-2: CYPHER Sirolimus-eluting Coronary Stent System
Product Matrix & Nominal Sirolimus Dosages

Product Code		Nominal Expanded Stent ID (mm)	Nominal Unexpanded Stent Length (mm)	Nominal Sirolimus Content (µg)	Product Code		Nominal Expanded Stent ID (mm)	Nominal Unexpanded Stent Length (mm)	Nominal Sirolimus Content (µg)
OTW	RX				OTW	RX			
CWS08250	CXS08250	2.50	8	71	CWS23250	CXS23250	2.50	23	190
CWS08275	CXS08275	2.75	8	71	CWS23275	CXS23275	2.75	23	190
CWS08300	CXS08300	3.00	8	71	CWS23300	CXS23300	3.00	23	190
CWS08350	CXS08350	3.50	8	83	CWS23350	CXS23350	3.50	23	221
CWS13250	CXS13250	2.50	13	111	CWS28250	CXS28250	2.50	28	229
CWS13275	CXS13275	2.75	13	111	CWS28275	CXS28275	2.75	28	229
CWS13300	CXS13300	3.00	13	111	CWS28300	CXS28300	3.00	28	229
CWS13350	CXS13350	3.50	13	129	CWS28350	CXS28350	3.50	28	268
CWS18250	CXS18250	2.50	18	150	CWS33250	CXS33250	2.50	33	268
CWS18275	CXS18275	2.75	18	150	CWS33275	CXS33275	2.75	33	268
CWS18300	CXS18300	3.00	18	150	CWS33300	CXS33300	3.00	33	268
CWS18350	CXS18350	3.50	18	175	CWS33350	CXS33350	3.50	33	314

2. Indications

The **CYPHER** Sirolimus-eluting Coronary Stent is indicated for improving coronary luminal diameter in patients with symptomatic ischemic disease due to discrete *de novo* lesions of length ≤ 30 mm in native coronary arteries with a reference vessel diameter of ≥ 2.5 to ≤ 3.5 mm.

Long-term outcome (beyond 12 months) for this permanent implant is unknown at present.

3. Contraindications

Use of the **CYPHER** Sirolimus-eluting Coronary Stent is contraindicated in the following patient types:

- Patients with a hypersensitivity to sirolimus or its derivatives.
- Patients with a known hypersensitivity to polymethacrylates or polyolefin copolymers.

Coronary artery stenting is contraindicated for use in:

- Patients in whom antiplatelet and/or anticoagulation therapy is contraindicated.
- Patients judged to have a lesion that prevents complete inflation of an angioplasty balloon.

4. 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 device carries the risks associated with coronary artery stenting, including subacute thrombosis, vascular complications, and/or bleeding events.
- Patients with a known hypersensitivity to 316L stainless steel may suffer an allergic reaction to this implant.

5. Precautions

5.1. 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.
- To avoid the possibility of dissimilar metal corrosion, do not implant stents of different materials in tandem where overlap or contact is possible.
- Do not use Ethiodol or Lipiodol contrast media.[1]
- Do not expose the delivery system to organic solvents, such as alcohol, or detergents.

5.2. Use of Multiple Stents

The extent of the patient's exposure to drug and polymer is directly related to the number of stents implanted. Use of more than two **CYPHER** Stents has not received adequate clinical evaluation. Use of more than two **CYPHER** Stents will result in the patient receiving larger amounts of drug and polymer than the experience reflected in the clinical studies.

5.3. Brachytherapy

The safety and effectiveness of the **CYPHER** 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 **CYPHER** Stent have not been established. Both vascular brachytherapy and the **CYPHER** Stent alter arterial remodeling. The synergy between these two treatments has not been determined.

[1] Ethiodol and Lipiodol are trademarks of Guerbet, S.A.

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 **CYPHER** Stent implantation have not been established.

5.5. Use in Special Populations

5.5.1. **Pregnancy:** Pregnancy Category C. See **Drug Information – 6.6 Pregnancy**.
There are no adequate and well controlled studies in pregnant women. Effective contraception should be initiated before implanting a **CYPHER** Stent and for 12 weeks after implantation. The **CYPHER** 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 – 6.7 Lactation**. 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 **CYPHER** Stent in pediatric patients below the age of 18 years have not been established.

5.5.4. **Geriatric use:** Clinical studies of the **CYPHER** Stent 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 **CYPHER** 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 < 2.5 mm or > 3.5 mm.
- 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.

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. See **Drug Information – 6.4 Drug Interactions Following Oral Administration of Sirolimus** for more specific information.

Consideration should be given to the potential for drug interaction when deciding to place a **CYPHER** 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 **CYPHER** Stent. The effect of drug interactions on the safety or efficacy of the **CYPHER** Stent has not been determined.

5.8. Coronary Artery Surgery – Effect on Anastomoses

There have been rare reports of bronchial anastomotic dehiscence of transplant anastomoses in lung transplant patients who were receiving oral sirolimus therapy. In a vessel that has recently been implanted with a **CYPHER** Stent, the sirolimus concentrations are expected to be several fold higher than systemic sirolimus concentrations. Therefore, consideration should be given to the possibility that the presence of a **CYPHER** Stent may compromise the healing of coronary artery vascular anastomoses. No such event was observed in the very limited experience from clinical trials.

5.9. Immune Suppression Potential

Sirolimus, the active ingredient of the **CYPHER** Stent, is an immunosuppressive agent that is also available in oral formulations. The mean peak systemic blood concentration of sirolimus following placement of up to two **CYPHER** Stents (1.05 ng/ml) is substantially lower than the therapeutic concentrations usually obtained when sirolimus oral formulations are used as prophylaxis for renal transplant rejection (see **Drug Information – Pharmacokinetics** (6.2)). In clinical studies of **CYPHER** Stents when used according to its intended use, there were no reports of immune suppression. However, for patients who receive several **CYPHER** Stents simultaneously, it may be possible for systemic concentrations of sirolimus to approach immunosuppressive levels temporarily, especially in patients who also have hepatic insufficiently or who are taking drugs that inhibit CYP3A4 or P-glycoprotein. This possibility should be considered for such patients, particularly if they are also taking oral sirolimus (or rapamycin), other immunosuppressive agents, or are otherwise at risk for immune suppression.

5.10. Lipid Elevation Potential

The use of oral sirolimus in renal transplant patients was associated with increased serum cholesterol and triglycerides that in some cases required treatment. The effect was seen with both low and high dose prolonged oral therapy in a dose related manner. When used according to the indications for use, the systemic sirolimus concentrations from the **CYPHER** Stent are expected to be lower than the concentrations usually obtained in transplant patients, but the magnitude and duration of any effect of those concentrations on lipids is not known.

5.11. Magnetic Resonance Imaging (MRI) – Stent Migration

An MRI scan should not be performed on a patient after stent implantation until there is adequate neointimal investment of the stent because of a potential for stent migration. For a conventional uncoated 316L stainless steel stent this period is usually considered to be eight weeks. Because of the reduced neointimal formation associated with the **CYPHER** Stent, the period of vulnerability may be longer, but there is currently insufficient information to provide a specific recommendation.

5.12. 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.
- 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.

5.13. Stent Placement Precautions

- **Do not prepare or pre-inflate the balloon prior to stent deployment other than as directed. Use the balloon purging technique described in Section 12 – Operator's Manual.**
- Guiding catheters used must have lumen sizes that are suitable to accommodate the stent delivery system (see **Product Description – 1.1 Device Component Description**).
- 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.

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