

**Device Component Description:**

The CYPHER® Sirolimus-eluting Coronary Stent (CYPHER® Stent) is a device/drug combination product comprised of two regulated components: a device (BX VELOCITY® Coronary Stent System) and a drug product (a formulation of sirolimus in a polymer coating). The device component consists of the BX VELOCITY® Stent pre-mounted onto a stent delivery system (SDS), either the RAPTOR® PTCA Dilatation Catheter (Over-the-Wire (OTW)) or the RAPTORRRAL® PTCA Dilatation Catheter (Rapid Exchange (RX)). The range of stent diameters is made possible by varying the number of circumferential "cells" on the stent. The 2.50, 2.75 and 3.00 mm diameter 316L stainless steel stents have six circumferential cells, whereas, the 3.50 mm diameter 316L stainless steel stents have seven circumferential cells. The stent is crimped on various size delivery catheter balloons, which are sized from 2.50 to 3.50 mm.

**Drug Component Description:**

The active pharmaceutical ingredient in the CYPHER® Stent is sirolimus (also known as Rapamycin). Sirolimus is a macrocyclic lactone produced by *Streptomyces hygroscopicus*. The chemical name of sirolimus is (3S,6R,7E,9R,10,12R,14S,15E,17E,19E,21S,23S,26R,27R,34aS,9,10,12,13,14,15,17,23,24,25,26,27,32,33,34,34a-hexadeca-hydro-9,7-dihydroxy-3,11(R)-2-(11S,3R,4R)-4-hydroxy-3-methoxyloxy[hexyl]-1-methyl[ethyl]-10,21-dimethoxy-6,8,12,14,20,26-hexaazabicyclo[2,2,7]-epoxy-3-4H-pyrido[2,1-c][1,4]oxazolo[4,5-g]quinoline-1,5,11,28,29-(4H,6H,31H)-pentone. Its molecular formula is C<sub>51</sub>H<sub>79</sub>NO<sub>13</sub> and its molecular weight is 914.2.

The inactive ingredients in the CYPHER® Stent contain polyethylene (PE) 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 polymer C treated stent. A drug-free topcoat solution of PBMA polymer is applied to the stent surface. The topcoat polymer is adhered to the entire surface (i.e., luminal and abutment) of the stent.

**Indications:**

The CYPHER® 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 ≥ 2.50 to ≤ 3.50 mm.

**Contraindications:**

- Use of the CYPHER® Stent is contraindicated in the following patient types:
  - Patients with a hypersensitivity to sirolimus or its structurally related compounds.
  - Patients with a known hypersensitivity to polymethacrylates or polyethylene copolymers.
- Coronary artery stenting is contraindicated for use in:
  - Patients who cannot receive recommended antiplatelet and/or anticoagulation therapy.
  - Patients judged to have a lesion that prevents complete inflation of an angioplasty balloon or proper placement of the stent or delivery catheter.

**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 the product 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.
- Patients who are unlikely to comply with recommended antiplatelet therapy should not receive this product.

**Precautions – 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.
- Do not use Ethiodol or iodinated contrast media.
- Do not expose the delivery system to organic solvents, such as alcohol, or detergents.
- Stent thrombosis is a low frequency event that current drug-eluting stent (DES) clinical trials are not adequately powered to fully characterize. Signs of thrombotic events frequently associated with MI or death. Data from CYPHER® Stent randomized clinical trials (RAVEL and SIRIUS) have been prospectively evaluated and adjudicated using both the protocol definition of stent thrombosis and the definition developed by the Academic Research Consortium (ARC), and demonstrate specific patterns of stent thrombosis that vary depending on the definition used. In the CYPHER® Stent clinical trials analyzed to date, differences in the incidence of stent thrombosis observed with the CYPHER® Stent when compared to bare-metal stents have not been associated with an increased risk of cardiac death, myocardial infarction, or all-cause mortality. Additional data from longer-term follow-up in the randomized clinical trials on the CYPHER® Stent and analyses of DES-related stent thrombosis are expected and should be considered in making treatment decisions as data become available.
- When drug-eluting stents are used outside the specified indications for use, clinical outcomes may differ from the results observed in the pivotal trials.
- Compared to use within the specified Indications for Use, the use of drug-eluting stents in patients and lesions outside the labeled indications may have an increased risk of adverse events, including stent thrombosis, stent embolization, myocardial infarction, or death.

**Precautions – Pre- and Post-Procedure Antiplatelet Regimen**

In the pivotal clinical trial of the CYPHER® Stent, dipyridol or ticlopidine was administered pre-procedure and for a period of three months post-procedure. Aspirin was administered concomitantly with dipyridol or ticlopidine and then continued indefinitely to reduce risk of thrombosis. The use of aspirin together with dipyridol or ticlopidine is referred to as "dual antiplatelet therapy". The optimal duration of dual antiplatelet therapy, specifically dipyridol, is unknown and DES thrombosis may still occur despite continued therapy. Data from several studies suggest that a longer duration of dipyridol than was recommended post procedurally in drug-eluting stent pivotal trials (including SIRIUS) may be beneficial. Based upon consensus opinion practice guidelines recommend that patients receive aspirin indefinitely plus a minimum of 3 months of dipyridol, with dipyridol therapy extended to 12 months in patients at low risk of bleeding (ref: ACC/AHA/SCAI PCI Practice Guidelines<sup>1,2,3</sup>).

It is very important that the patient is compliant with the post-procedural antiplatelet recommendations. Early discontinuation of prescribed antiplatelet medication could result in a higher risk of thrombosis, myocardial infarction or death. Prior to Percutaneous Coronary Intervention (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 option. Following PCI, if a surgical or dental procedure is anticipated that requires suspension of antiplatelet therapy, the risks and benefits of the procedure should be weighed against the possible risk associated with early discontinuation of antiplatelet therapy.

Patients who require early discontinuation of antiplatelet therapy (e.g., secondary to active bleeding) should be monitored carefully for cardiac events. At the discretion of the patient's treating physicians, the antiplatelet therapy should be restarted as soon as possible.

**Precautions – 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 with any other drug-eluting stent will result in the patient receiving larger amounts of drug and polymer than the experience reflected in the clinical studies. To avoid the possibility of dissimilar metal corrosion, do not implant stents of different materials in tandem where overlap or contact is possible. Potential interactions of the CYPHER® Stent with other drug-eluting or coated stents have not been evaluated and should be avoided whenever possible.

In the SIRIUS trial, 30.7% (158/515) of patients in the CYPHER® Stent arm had overlapping stents to treat lesions < 30 mm in length.

**Precautions – 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 restenosis in a CYPHER® Stent have not been established. Both vascular brachytherapy and the CYPHER® Stent alter arterial biology, and the combined vascular responses of these two treatments have not been determined.

**Precautions – 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.

**Precautions – Use in Special Populations:**

- Pregnancy:** Pregnancy Category C. There are no adequate and well-controlled studies in pregnant women or men intending to father children. Effective contraception should be initiated before implanting a CYPHER® Stent and for 12 weeks after implantation of the CYPHER® Stent should be used during pregnancy only if the potential benefit outweighs the potential risk to the embryo or fetus.
- Use during 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.

Not all clinical studies of the CYPHER® Stent did not find any significant differences in safety and effectiveness for male and female patients.

**Ethnicity:** Clinical studies of the CYPHER® Stent did not include sufficient numbers of patients to assess for differences in safety and effectiveness due to ethnicity, either by individual category or when grouped by Caucasian and non-Caucasian.

**Pediatric use:** The safety and efficacy of the CYPHER® Stent in pediatric patients below the age of 18 years have not been established.

**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.

**Non-Coronary use:** The safety and effectiveness of this product have not been established in the cerebral, carotid, or peripheral vasculature.

**Precautions – Lesion/Vessel Characteristics:**

- The safety and effectiveness of the CYPHER® Stent have not been established in these noted patient groups:
  - 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 saphenous vein graft, in the unprotected 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 multi-vessel disease.
  - Patients with tortuous vessels in the region of the obstruction or proximal to the lesion.
  - Patients with a recent acute myocardial infarction.
  - Patients with lesions longer than 30 mm and requiring more than one CYPHER® Stent.
  - Patients with chronic total occlusions.
  - Patients with in-stent restenotic lesions.
- The safety and effectiveness of the CYPHER® Stent have not been established in the cerebral, carotid, or peripheral vasculature.

While not observed in pivotal clinical trials (First-in-Man, RAVEL and SIRIUS) that supported the CYPHER® Stent PMMA stent fractures are uncommon events but have been observed in long stented segments including those in which overlapping stents have been used. They have been observed in coronary segments that undergo significant motion, particularly in areas with severe angulation, tortuosity, and calcification. In the SIRIUS trial, there have been reports most often in certain lesion subgroups in which safety and effectiveness have not been established. The clinical implications of stent fracture are not well characterized.

**Precautions – 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 of cytochrome P450 3A4 (CYP3A4) and P-glycoprotein. 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 extent of drug interactions on the safety or efficacy of the CYPHER® Stent has not been determined.

**Precautions – 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.

**Precautions – 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 the scheduled 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. 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 insufficiency or who are taking drugs that in some cases require 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 attained in transplant patients, but the magnitude and duration of any effect of those concentrations on lipids is not known.

**Precautions – 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 attained in transplant patients, but the magnitude and duration of any effect of those concentrations on lipids is not known.

**Precautions – Magnetic Resonance Imaging (MRI):**

Non-clinical testing has demonstrated that single and two overlapping CYPHER® Stents are MR-compatible. They can be scanned safely, immediately post implantation, under the following conditions:

- Static magnetic field of 3 Tesla.
  - Maximum whole-body SAR of 300 Gauss/cm.
  - Maximum whole-body-averaged specific absorption rate (SAR) of 4.0 W/kg for 15 minutes of scanning.
- In non-clinical testing, a single CYPHER® Stent up to 33 mm in length produced a temperature rise of less than 1°C and two overlapping CYPHER® Stents up to 33 mm in length produced a net temperature rise of less than 2°C at a maximum whole body averaged SAR of 4.0 W/kg for 15 minutes of MR scanning in a 3 Tesla Siemens Whole Body MR Scanner serial 20514, Software NUMARIS/4, version Syngo MR D0301 DHHS, VX22A. The maximum whole body averaged SAR was determined by calorimetry following ASTM F1782-02.
- The image artifact extends approximately 1 mm from the device, both inside and outside of the device lumen when scanned in non-clinical testing using a pulse sequence generating a whole body SAR of 4.0 W/kg in a Siemens Whole Body MR Scanner, serial 20514, Software NUMARIS/4, version Syngo MR D0301 DHHS, VX22A with 3 Tesla coil.

**Precautions – Preparation:**

- AVOID manipulation of the stent during flushing of the guiding catheter. This may disrupt the placement of the stent on the balloon.
- Do NOT apply negative or positive pressure to the balloon during the delivery system preparation.

**Precautions – Stent Handling:**

- For single use only.** Do not sterilize or reuse this product. Note the "Use By" date on the product label.
- Do not remove the stent from the delivery balloon – removal may damage the stent and coating 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.**
  - The vessel should not be handled 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 cause coating damage, contamination, or dislodgement of the stent from the delivery system balloon.
- 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.

**Precautions – Stent Placement:**

- The vessel should be pre-dilated with an appropriate sized balloon.
- Do not prepare or pre-inflate the balloon prior to stent deployment other than as directed.
- Guiding catheters used must have lumen sizes that are suitable to accommodate the stent delivery system.
- Do not induce a negative pressure on the delivery catheter prior to placement of the stent across the lesion. This may cause premature dislodgement 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.
- Implanting a stent may lead to a dissection of the vessel distal and proximal to the stent, which may cause acute closure of the vessel requiring additional intervention (CABG, further dilatation, placement of additional stents, or other intervention).
- Do not expand the stent if it is not properly positioned in the vessel.
- Placement of the stent has the potential to compromise side branch patency.
- When treating multiple lesions, the distal lesion should be initially stented, followed by stenting of the more proximal lesion(s). Stenting in this order minimizes the need to cross the proximal stent in the placement of the distal stent and may reduce the chances of dislodging the proximal stent, or disrupting stent coating.
- Balloon pressures should be monitored during inflation. **Do not exceed rated burst pressure as indicated on the product label.** 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.

- 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.
- Ensure full coverage of the lesion/dissection site so that there are no gaps between stents.

**Precautions – Stent/System Removal:**

**SHOULD** unusual resistance be felt at any time during either lesion access or removal of the stent delivery system before stent implantation, the entire system **should be removed as a single unit.**

**When removing the delivery system as a single unit:**

- Do not retract the delivery system into the guiding catheter.
  - Advance the guidewire into the coronary anatomy as far distally as safely possible.
  - Tighten the rotating hemostatic valve to secure the stent delivery system to the guiding catheter; then remove the guiding catheter and stent delivery system as a single unit.
- Failure to follow these steps or applying excessive force to the stent delivery system can potentially result in loss or damage to the stent or stent delivery system.

If it is necessary to retain the guidewire in position for subsequent artery/lesion access, leave the guidewire in place and remove all other system components.

**Precautions – Post-Procedure:**

- 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 placement, apposition, geometry, and/or coating.
- Through non-clinical testing, single and two overlapping CYPHER® Stents have been shown to be MRI safe at field strengths of 3 Tesla or less. MR imaging quality may be compromised if the area of interest is in the exact same area or relatively close to the position of the stent.
- In the pivotal clinical trial of the CYPHER® Stent, dipyridol or ticlopidine was administered pre-procedure and for a period of three months post-procedure. Aspirin was administered concomitantly with dipyridol or ticlopidine and then continued indefinitely to reduce the risk of thrombosis.
- Patients who require early discontinuation of antiplatelet therapy (e.g., secondary to active bleeding) should be monitored carefully for cardiac events. At the discretion of the patient's treating physician, the antiplatelet therapy should be restarted as soon as possible.

**Drug Information**

**Mechanism of Action:**

The mechanism (or mechanisms) by which a CYPHER® Stent affects neointima production as seen in clinical studies has not been established. 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 to and inhibits the activation of the mammalian Target of Rapamycin (mTOR), leading to inhibition of cell cycle progression from the G<sub>1</sub> to the S phase.

**Pharmacokinetics of the CYPHER® Stent:**

The pharmacokinetics of sirolimus as delivered by the CYPHER® Stent has been determined in patients with coronary artery disease after implantation of one (n=10) or two (n=9) CYPHER® Stents. The results show that C<sub>max</sub> and AUC were closely dose-proportional over a 2-fold range in doses. The blood levels after stent implantation were 10 to 20 fold lower than what was observed after oral administration of sirolimus in either healthy volunteers or transplanted patients. The mean ± SD sirolimus terminal half-life (t<sub>1/2</sub>) was stent implantation for the combined groups (n = 19) was 213 ± 97 h. By comparison, the mean ± SD sirolimus t<sub>1/2</sub> values after single dose administration of sirolimus by oral solution in healthy subjects (n = 305) and renal transplant patients (n = 81) were 72.9 ± 19.3 h and 58.2 ± 19.2 h, respectively. The apparent discrepancy in half-lives after stent implantation and oral administration is due to the fact that the decrease in terminal sirolimus concentrations reflects the release of sirolimus from the stent and not elimination of sirolimus from the body.

For additional information regarding sirolimus, please see the CYPHER® Stent Instructions for Use.

**Potential Adverse Events:**

Adverse events (in alphabetical order) which may be associated with the implantation of a coronary stent in coronary arteries: Allergic reaction, Aneurysm, Arrhythmias, Cardiac tamponade, Death, Dissection, Drug reactions to antiplatelet agents/anticoagulation agents/contrast media, Embol, distal (tissue, air, or thrombotic emboli), Embolization, Stent, Emergency CABG, Failure to deliver the stent to the intended site, Fever, Festination, Hemorrhage, Hypotension/Hypertension, Incomplete stent apposition, Infection and pain at the intended site, Myocardial infarction, Myocardial ischemia, Occlusion, Prolonged angina, Pseudoaneurysm, Renal failure, Restenosis of stented segment (greater than 50% obstruction), Rupture of native and bypass graft, Stent migration, Stroke, Thrombosis (acute, subacute, late, or very late), Ventricular fibrillation, Vessel spasm, and Vessel perforations.

Potential adverse events (in alphabetical order) related to sirolimus (following oral administration): Abnormal liver function tests, Anemia, Arthralgias, Diarrhea, Hypercholesterolemia, Hypersensitivity, including anaphylactoid/anaphylactoid type reactions, Hypertrophy/dilatation, Hypokalemia, Infections, Interstitial lung disease, Leukopenia, Lymphoma and other malignancies, Thrombocytopenia.

The third-party trademarks used herein are the trademarks of their respective owners.

<sup>1</sup> Grines CL, Bonow RO, Casey DE, Gardner TJ, Lockhart PB, Moliterno DJ, O'Gara P, Whitlow P. Prevention of Premature Discontinuation of Dual Antiplatelet Therapy in Patients with Coronary Artery Stents. *Circulation*. 2007; 115:1-6.

<sup>2</sup> www.cardioscience.org/guidelines/clinicalareas/thienopyridines.pdf

<sup>3</sup> J. Am. Coll. Cardiol. 2006;47:126-135.