Product: Infinnium® Paclitaxel Eluting Coronary Stent System

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1. Product Description

The **INFINNIUM®** Paclitaxel–eluting Coronary Stent **(INFINNIUM® Stent)** is a combination product comprised of two regulated components: a device (a coronary stent system) and a drug product (a formulation of Paclitaxel contained in a polymer coating).

1.1 Device Component Description

The **INFINNIUM®** Paclitaxel–eluting Coronary Stent System consists of a Paclitaxel eluting balloon expandable 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

INFINNIUM® Paclitaxel-Eluting Coronary Stent System	
Available Stent Lengths, Unexpanded (mm)	8 to 39mm
Available Stent Diameters (mm)	2.25, 2.50, 2.75, 3.00, 3.50, 4.00mm
Stent Material	Surgical grade 316L Stainless Steel (SS) the **Millennium Matrix®** Laser cut from seamless tubing in a serpentine pattern coated with a biodegradable polymers and Paclitaxel blend in multiple layers.
Stent Strut thickness	0.08mm (80µ)
Stent Foreshortening	< 1%
Recoil	< 5%

Note: Please refer balloon code on Product Label to follow one of the tables mention below.

Table 1.1A: Information of BG Delivery System

Delivery System Usable Length	1400mm (140cm)
Delivery System Y – Adapter Ports	Single access port to inflation/deflation lumen. A guidewire exit port is located at 25cm from the tip. Designed for guidewire 0.356mm (0.014inch)
Stent Delivery Balloon	Polyamide balloon, nominally 1 mm longer than stent. Mounted stent length and location is defined by radio opaque marker at proximal and distal to stent.
Catheter Shaft Outer Diameter	Proximal: 1.95F
	Distal: 2.7F
Balloon Inflation Pressure	*Nominal Pressure: 8 bar
	Rated Burst Pressure: 16 bar (**14 bar)
Guiding Catheter	5 Fr compatible
Guidewire Diameter	0.014 inch

Table 1.1B: Information of BH Delivery System

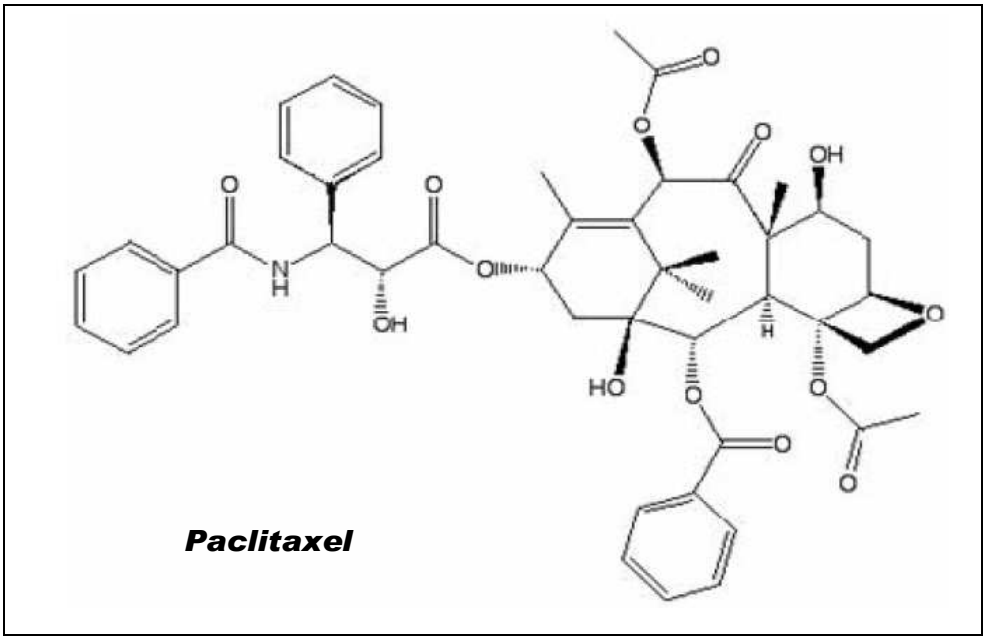
Delivery System Usable Length	1350 mm (135 cm)
Delivery System Y – Adapter Ports	Single access port to inflation/deflation lumen. A guidewire exit port is located at 25cm from the tip. Designed for guidewire 0.355 mm (0.014 inch)
Stent Delivery Balloon	Pebax/Nylon balloon, nominally 1 mm longer than stent.

	Mounted stent length and location is defined by radio opaque marker at proximal and distal to stent.
Catheter Shaft Outer Diameter	Proximal: 2.0 F
	Distal: 2.7F (2.25 - 3.0 mm) and 2.8 F (3.50 - 4.0 mm)
Balloon Inflation Pressure	*Nominal Pressure: 6 atm
	Rated Burst Pressure: 16 atm
Guiding Catheter	5 F
Guidewire Diameter	0.014 inch

Note: * Assure full deployment of the stent (See section 12.6 Deployment Procedure). Deployment pressures should be based on lesion characteristics.
** 14bar for 4mm diameter with length higher than 30mm
1F is equivalent to 0.33mm.

1.2 Drug Component Description

The active pharmaceutical ingredient in the **INFINNIUM®** Stent System is Paclitaxel. Paclitaxel is a natural diterpenoid antitumoral drug compound extracted from the bark of *Taxus brevifolia*, the Western Yew tree. The chemical name (IUPAC) of Paclitaxel is Benzenepropanoic acid, β-(benzoyalamino)-α-hydroxy, 6,12b-bis(acetyloxy)-12(benzoyloxy)-2a,3,4,4a,5,6,9,10,11,12,12a, 12b-dodecahydro-4,11dihydroxy-4a,8,13,13-tetramethyl-5-oxo-7,11-methano-[H-cyclodeca[3,4] benz[1,2-b]oxet-9-ylester,[2aR-[2aα,4β,4aβ,6β,9α(αR*,βS*), 11α,12α,12aα,12bα]], (2aR,4S, 6R, 11S,12S,12bS)-1,2a,3,4,4a,6,-9,10,11,12,12a,12b-dodecahydro-4,6,9,11,12,12b-hexahydroxy-4a,8,13,13-tetramethyl-7,11-methano-5Hcyclodeca[3,4]benz[1,2-b]oxet-5-one 6,12bdiacetate,12-benzoate, 9-ester with (2R,3S)-Nbenzoyl-3-phenylisoserine. Its molecular formula is $C_{47}H_{51}NO_{14}$ and its molecular weight is 853.93 a.m.u. The structural formula of Paclitaxel is shown below:



Paclitaxel is off-white crystalline powder, highly lipophilic, insoluble in water, sparingly soluble in Methanol, highly soluble in dichloromethane and has a melting temperature of approximately 218°C to 220°C (capillary tube). The inactive ingredients in the **INFINNIUM®** Paclitaxel-

eluting Coronary Stent is a combination of biocompatible biodegradable polymers (Poly L-Lactide, Poly DL-Lactide-co-Glycolide, Poly L-Lactide-co-Caprolactone, Polyvinyl Pyrrolidone) formulated in to multiple layers to provide programmed release of the drug. The polymers are converted to monomers and enter into Crab's Cycle and are finally reduced to Carbon Dioxide (CO_2) and water (H_2O) which are excreted through urine.
The active ingredient, Paclitaxel loading per stent ranges from 50 to 500 µg as per stent length.

2 Indications

The **INFINNIUM®** Paclitaxel-eluting coronary stent system is indicated for improving luminal diameter and reducing restenosis for treatment of coronary artery lesions with a reference vessel diameter ranging from 2.25mm to 4.0mm.

3 Contraindications

Use of the **INFINNIUM®** Paclitaxel-eluting coronary stent system is contraindicated in the following patient types:

- 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 Paclitaxel or its derivatives.
- Known allergy to stainless steel.
- Polymers might enhance inflammatory reactions and Prothrombotic response.

4 Warnings

- Please ensure that the inner package has not been opened or damaged as this may indicate the sterile barrier has been breached.
- Since the use of this device carries the associated risk of subacute thrombosis, vascular complications and/or bleeding events, judicious selection of patients is necessary.
- Persons allergic to 316L stainless steel or Paclitaxel may suffer an allergic reaction to this implant.

5 Precautions

5.1 General Precautions

- The **INFINNIUM®** Paclitaxel-eluting stent should not be exposed to any direct handling or contact with liquids prior to preparation and delivery as the coating may be susceptible to damage or premature drug elution.
- 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.

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 **INFINNIUM®** Stents has not been fully evaluated. Use of more than two **INFINNIUM®** Stents will result in the patient receiving larger amounts of

drug and polymer than the experience reflected in the clinical studies. When multiple stents are required, resulting in stent-to-stent contact, stent materials should be of similar composition to avoid the possibility of dissimilar metal corrosion.

5.3 Brachytherapy
The safety and effectiveness of the **INFINNIUM®** 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 **INFINNIUM®** Stent have not been established. Both vascular brachytherapy and the **INFINNIUM®** 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 **INFINNIUM®** Stent implantation have not been established.
5.5 Use in Special Populations
5.5.1 Pregnancy: See Drug Information 6.6.
There are no adequate and well-controlled studies in pregnant women or men intending to father children. Systemic levels of Paclitaxel have not been demonstrated in any pre-clinical or clinical trials with the **INFINNIUM®** Stent. Effective contraception should be initiated before implanting an **INFINNIUM®** Stent and for 12 weeks after implantation. The **INFINNIUM®** 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 **INFINNIUM®** Stent in pediatric patients have not been established.
5.5.4 Geriatric Use: Clinical studies of the **INFINNIUM®** 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 **INFINNIUM®** Paclitaxel-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 < 2.25mm or > 4.0mm.
- 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
Consideration should be given to the potential for drug interaction when deciding to place the **INFINNIUM®** Stent in a patient who is taking a drug that could interact with Paclitaxel, or when

deciding to initiate therapy with such a drug in a patient who had recently received the **INFINNIUM®** Stent. The drug interactions are unlikely to be detectable.

5.8 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 **INFINNIUM®** Stent, the period of vulnerability may be longer, but there is currently insufficient information to provide a specific recommendation.

5.9 Stent Handling Precautions

- For single use only. Do not resterilize or reuse this device. Note the "Use Before" date on the product label.
- Do not remove the stent from the delivery balloon as 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 during stent system removal from packaging, placement over guide wire, and advancement through rotating hemostatic valve adaptor and guiding catheter hub.
- Do not "roll" the mounted stent with your fingers as this action may loosen the stent from the delivery balloon and 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.
- In the event the **INFINNIUM®** Stent is not deployed, follow product return procedures and avoid handling of the stent with hands.
- Stent contact with any fluid prior to placement is not recommended as there is a possibility of drug release. However, if it is absolutely necessary to flush the stent with sterile/isotonic saline, contact time should be limited (1 minute maximum).

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, 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 12.9) 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 per instructions in Precautions 5.11 Stent/System Removal Precautions.
- An unexpanded stent should be introduced into the coronary arteries one time only. An unexpanded stent should not be subsequently moved in and out through the distal end of the guiding catheter as stent damage or stent dislodgement 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.

5.11 Stent/System Removal Precautions

- Should unusual resistance be felt at any time during either lesion access or removal of the Delivery System post-stent implantation, the entire system should be removed as a single unit.
- Do not attempt to pull an unexpanded stent back through the guiding catheter while engaged in the coronary arteries, as stent damage or stent dislodgement from the balloon may occur.

When removing the Delivery System as a single unit:

- DO NOT retract the Delivery System into the guiding catheter.
- Position the proximal balloon marker just distal to the tip of the guiding catheter.
- Advance the guide wire into the coronary anatomy as far distally as safely possible.
- Tighten the rotating hemostatic valve to secure the Delivery System to the guiding catheter; then remove the guiding catheter, guiding wire and Delivery System as a single unit.

Failure to follow these steps and/or applying excessive force to the Delivery System can potentially result in loss or damage to the stent and/or Delivery System components.

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

5.12 Post Implantation Precautions

- Great care must be exercised when crossing a newly deployed stent with a coronary guide wire 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 Drug Information

6.1 Mechanism of Action

The mechanism of action by which the **INFINNIUM®** Paclitaxel-eluting Coronary Stent reduces or reverses neointima formation and proliferation, leading to restenosis, as demonstrated in clinical studies has not been established. It is known that Paclitaxel is an antiproliferative agent that block the mitotic cycle at the metaphase/anaphase transition. Paclitaxel is microtubule-

stabilizing compound that inhibits microtubule by inhibiting their depolymerization resulting in an inhibition of cellular replication at the G0/G1 and G1/M phases. Paclitaxel inhibits smooth muscle cell proliferation and migration in a dose-dependent manner in monocultures and co-cultures even in the presence of mitogens.

6.2 Pharmacokinetics of the INFINNIUM® Paclitaxel-eluting Coronary Stent

With local drug delivery using the **INFINNIUM®** Paclitaxel Eluting stent system, systematic paclitaxel levels have not been above the limit of detection (10 nanogram/ mL) using high sensitivity assays in the clinical studies. Similarly in the pre-clinical studies also the systematic paclitaxel levels have not been above the limit of detection. However for the estimation of amount of paclitaxel into various tissues such as stented vessel, heart, kidney, liver etc at various time periods, the tissue extracts were subjected to chromatographic analysis. Except for the stented vessel tissue, the paclitaxel level was below the lower limit of quantitation < LLOQ 10 nanogram/ mL in all other tissue assays. On the first day, a moderate amount of paclitaxel (0.312 ng/ mg) was present in the stented vessel. After 3 days, a fall in the level of the drug (0.106 ng/mg) was noted. This level climbed to 0.443 ng/ mg in seven days. The level of the drug sharply declined to an average value of 0.073ng/md in fifteen days and to0.034 ng/mg after thirty days. Hence a correlation was seen between the quantity of the released drug and its level in the stented vessel. During the period of seven days nearly 40 % of the drug was released and only an additional 15 % of the drug was released between seven to thirty days period indicating a trend towards the attainment of plateau phase. A proportional reduction of the level of the drug in the stented vessel can be seen during this period. Hence a T ½ was estimated to be 24 days in the preclinical studies.

6.3 Pharmacokinetics Following Oral Administration of Paclitaxel

The pharmacokinetics of paclitaxel have been evaluated over a wide range doses, up to 300 mg/m^2, and infusion schedules, ranging from 3 to 24 hours.

Following intravenous administration, paclitaxel exhibits a biphasic decline in plasma concentrations. The initial rapid decline represents distribution to the peripheral compartment and elimination; the later phase is due, in part, to a relatively slow efflux of paclitaxel from the peripheral compartment. Maximum plasma concentrations are related to dose. In patients treated with doses of 135 and 175 mg/m^2 given as 3 and 24 hour infusions, mean terminal half-life has ranged from 3.0 to 52.7 hours, and total body clearance has ranged from 11.6 to 24.0 $L/h/m^2$. Mean steady state volume of distribution following single dose infusion of 135 and 175 mg/m^2 has ranged from 198 to 688 L/m^2, indicating extensive extravascular distribution and/or tissue binding. The volume of distribution is reduced in female subjects. Following 3 hour infusions of 175 mg/m^2 mean terminal half-life was estimated to be 9.9 hours; mean total body clearance was 12.4 $L/h/m^2$.

Variability in systemic paclitaxel exposure, as measured by AUC (0-∞) for successive treatment courses was minimal; there was no evidence of accumulation of paclitaxel with multiple treatment courses.

Some studies indicate that the pharmacokinetics of paclitaxel may be non-linear. There is evidence of a disproportionately large increase in C_{max} and AUC with increasing dose, and total body clearance appears to decrease with higher plasma concentrations of paclitaxel. These findings were most readily observed in patients in whom high plasma concentrations of

paclitaxel were achieved. Saturable processes in elimination/metabolism may account for these findings.
On average, 89% of drug is bound to serum proteins; the presence of cimetidine, ranitidine, dexamethasone, or diphenhydramine does not affect protein binding of paclitaxel. Premedication with this combination of drugs reduces the total body clearance from 14.2 L/hr/m^2 to 8.6 L/hr/m^2. Preliminary animal/*ex vivo* data indicate that ketoconazole may inhibit the metabolism of paclitaxel. Likewise, preliminary reports suggest that plasma levels of doxorubicin (and its active metabolite doxorubicinol) may be increased when paclitaxel and doxorubicin are used in combination. The mechanism for this interaction is unknown. The pharmacodynamic consequences of this interaction are unclear. The disposition of paclitaxel has not been fully elucidated in humans. Mean values for cumulative urinary recovery of unchanged drug have ranged from 1.8 to 12.6% of the dose, indicating extensive non-renal clearance. Hepatic metabolism has been demonstrated in animals. Hydroxylated metabolites isolated in bile have been demonstrated to be the principal metabolites. Hepatic metabolism and biliary clearance may be the principal mechanism for disposition of paclitaxel. The effect of renal or hepatic dysfunction on the disposition of paclitaxel has not been investigated.

6.4 Drug Interactions Following Oral Administration of Paclitaxel
Drug interaction studies have not been conducted with the **INFINNIUM®** Paclitaxel-eluting stent system. Systemic levels of Paclitaxel following implantation of **INFINNIUM®** Paclitaxel-eluting stent system have not been detected, therefore drug interactions are unlikely.
The following is the summary of drug interaction following oral administration of Paclitaxel.
The metabolism of Taxol is catalyzed by cytochrome P450 isoenzymes CYP2C8 and CYP3A4. Recent studies in humans and mice have demonstrated that intestinal P-glycoprotein plays a causative role in the limited absorption of orally administered paclitaxel.
Thus, absorption and the subsequent elimination of systematically absorbed Paclitaxel (Taxol) may be influenced by the drugs that affect these proteins. Multidrug resistance (MDR)-reversing agents, such as cyclosporin A and PSC 833, are known to increase the systemic exposure to orally administered Paclitaxel by enhancing absorption in the intestinal tract and decreasing elimination via the biliary tract. In this study, it was demonstrated that coadministration of the MDR-reversing agent MS-209, which is known to inhibit P-glycoprotein function by direct interaction, improved the bioavailability of orally administered Paclitaxel and consequently enhanced its antitumor activity.
6.4.1 Ketoconazole: Preliminary animal/*ex vivo* data indicate that ketoconazole may inhibit the metabolism of paclitaxel; caution should be exercised when treating patients with Taxol if they are receiving ketoconazole.
6.4.2 Cisplatin: In a dose-finding trial in which Taxol was administered as a 24-hour infusion and cisplatin was administered as a 1 mg/min infusion, myelosuppression was more profound when Taxol was given after cisplatin than when Taxol was given before cisplatin. Pharmacokinetic data demonstrated a reduction in paclitaxel clearance of approximately 33% when Taxol was administered following cisplatin.
6.4.3 Doxorubicin: Sequence effects characterized by more profound neutropenic and stomatitis episodes have been observed with combination use of Taxol and doxorubicin when Taxol was administered before doxorubicin and using longer than recommended infusion times (Taxol administered over 24 hours; doxorubicin over 48 hours). Plasma levels of doxorubicin (and its active metabolite doxorubicinol) may be increased when paclitaxel and doxorubicin are used in

combination. However, data from a trial using bolus doxorubicin and 3-hour Taxol infusion found no sequence effects on the pattern of toxicity.

6.4.4 Medications concomitantly administered with Taxol are as follows and they did not appear to interact adversely.

- corticosteroids
- antihistamines,
- H_2 antagonists

6.4.5 Other drug interactions

Drug that may increase Paclitaxel blood concentrations include:

Ritonavir may increase the paclitaxel levels in blood.

Drug that may decrease Paclitaxel level include:

Grapefruit juice: Paclitaxel may exhibit increased serum concentration based on this interaction.

6.5 Carcinogenicity, Genotoxicity and Reproductive Toxicology

Carcinogenicity, genotoxicity and reproductive toxicology are not expected with the low Paclitaxel concentrations of the **Infinnium®** Stent. Histopathological evaluation of **Infinnium®** Stent implant sites from animals at one year showed no evidence of any pre-neoplastic or neoplastic cells.

Genotoxicity studies were conducted across a broad range (0.03 to 0.45 ng/mg) of Paclitaxel concentrations bracketing those found in animal tissues following stenting with the **Infinnium®** Paclitaxel-Eluting Coronary Stent System. Paclitaxel was non-mutagenic in the in vitro bacterial reverse mutation assay (Ames test). Based on the in vitro and in vivo testing, paclitaxel has been shown to be aneugenic at concentrations similar to maximum local drug concentrations after application of a single **Infinnium®** stent due to its pharmacodynamic action, which is interference with microtubule disassembly. The relevance of this specific mechanism of genotoxicity for human carcinogenity risk is currently not known.

There are no preclinical reproductive toxicity studies on the proposed paclitaxel-eluting stent system. In rats, paclitaxel impaired the male and female fertility at doses equal to or greater than 1 mg/kg/day. In developmental toxicity studies at doses up to 0.6 mg/kg, there were no effects on maternal parameters and no changes in the offspring, other than delayed hair growth at 0.6 mg/kg. The developmental NOEL was 0.3 mg/kg and 60µg/kg after application of a safety factor of 5 to extrapolate to human metabolism. Patients receive 1.67 – 8.12 µg/kg paclitaxel after a single stent implantation. From these data a safety margin larger than 7 can be calculated. As such, there is no concern for human reproduction. In addition, the intended use of the proposed stent system during pregnancy is probably low. For caution see the parts 6.6 Pregnancy and 6.7 Lactation of this booklet.

6.6 Pregnancy

Paclitaxel may cause fetal harm when administered to pregnant women. Administration of paclitaxel during the period of organogenesis to rabbits at doses of 3 mg/kg/day (about 0.2 the daily maximum recommended human dose on a mg/m^2 basis) caused embryo- and fetotoxicity, as indicated by intrauterine mortality, increased resorptions and increased fetal deaths. Maternal toxicity was also observed at this dose. No teratogenic effects were observed at 1 mg/kg/day (about 1/15 the daily maximum recommended human dose on a mg/m^2 basis); teratogenic potential could not be assessed at higher doses due to extensive fetal mortality.

There are no adequate and well-controlled studies in pregnant women. If paclitaxel is used during pregnancy, or if the patient becomes pregnant while receiving this drug, the patient should be apprised of the potential hazard to the fetus. Women of childbearing potential should be advised to avoid becoming pregnant.

6.7 Lactation

It is not known whether the drug is excreted in human milk. Following intravenous administration of carbon-14 labeled paclitaxel to rats on days 9 to 10 postpartum, milk concentrations of radioactivity exceeded and declined in parallel with the plasma concentrations. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants, it is recommended that nursing be discontinued when receiving paclitaxel therapy.

7 Adverse Events

7.1 Observed Adverse Events

Observed adverse event experience comes from the clinical study, the SIMPLE I, trial. Refer Section- 8.0. Clinical Studies for more complete descriptions of the study designs and results.

7.1.1 Safety and Efficacy study of INFINNIUM® - Paclitaxel eluting stent (SIMPLE I) in real world coronary artery lesions: 3 yrs Follow Up

Prof. D.S. Gambhir

Objective

To evaluate the safety and efficacy of **INFINNIUM®** Paclitaxel- Eluting Coronary Stent System in real world coronary artery lesions.

Study Design

SIMPLE I is a non-randomized, open label study in 282 real world CAD patients.

Result

SIMPLE I study reveals an outcome comparable with the other commercially available drug eluting stent in the European market. At mean follow up of 3 years the cardiac death observed was 3.9%. The TLR was reported to be 6.7%. In SIMPLE I study the late loss and percentage of restenosis at 6 months was found to be 0.2 ±0.66 mm and 5.9% respectively. The overall event-free survival at 3 yrs. was reported to be 87.80% In spite of the complex patient and lesion characteristics in SIMPLE I study (i.e.,33.3% diabetics, 25.2% chronic total occlusion, 10.6% Multi-vessel Disease, 62.3 % LAD treatment and 1.1% Left Main Stenting) the safety and efficacy outcome was comparable to other approved drug eluting stents. The 3yrs outcome results for SIMPLE I supports long term safety of **INFINNIUM®** as incidences of aneurysms, incomplete opposition were not reported and stent thrombosis was statistically non-significant when compared with other clinical outcome of the studies with other approved stent.

7.2 Potential Adverse Events

Potential adverse events which may be associated with the use of a coronary stent include but are not limited to:

- Abrupt stent closure
- Acute myocardial infarction
- Allergic reaction to anti-coagulant and/or antithrombotic therapy or contrast medium
- Angina
- Aneurysm

- Arrhythmias, including ventricular fibrillation (VF) and ventricular tachycardia (VT)
- Arterial perforation
- Arterial rupture
- Arteriovenous fistula
- Bleeding complications
- Bradycardia
- Cardio Tamponade
- Cardiogenic Shock
- Coronary spasm
- Coronary or stent embolism
- Coronary or stent thrombosis
- Death
- Dissection of the coronary artery
- Drug reactions to antiplatelet agents / anticoagulation agents / contrast medium
- Emboli, distal (air, tissue or thrombotic emboli)
- Emergency or non-emergent Coronary Artery Bypass Graft Surgery
- Entry site complications
- Heart Failure
- Hematoma
- Hemorrhage, requiring transfusion
- Hypotension / Hypertension
- Infection
- Infection and/or pain at the access site
- Injury to the coronary artery
- Ischemia
- Nausea and vomiting
- Palpitations
- Perforation or rupture
- Pericardial effusion
- Pseudoaneurysm, femoral
- Renal Failure
- Respiratory Failure
- Restenosis of the stented segment
- Rhythmical disturbances
- Shock/Pulmonary edema
- Spasm
- Stroke/cerebrovascular accident/TIA
- Total occlusion of the coronary artery
- Unstable angina pectoris
- Vascular complications, which may require vessel repair
- Ventricular fibrillation

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

- Allergic/immunologic reaction to drug or stent coating
- Allopecia

- Anemia
- Blood product transfusion
- Gastrointestinal symptoms
- Hematologic dyscrasia (including leukopenia, neutropenia, thrombocytopenia)
- Hepatic enzyme changes
- Histologic changes in vessel wall, including inflammation, cellular damage or necrosis
- Myalgia/Arthralgia
- Peripheral neuropathy

8 Clinical Studies

8.1 Overview of Clinical Studies

Observed Adverse Events

Observed Adverse event experience comes from the clinical study, the SIMPLE I trials, refer Section-8.0.Clinical Studies for more complete descriptions of the study designs and results.

8.2 SIMPLE I Study

Safety and Efficacy study of **INFINNIUM®** - Paclitaxel eluting stent (SIMPLE I) in real world coronary artery lesions: 3 yrs Follow Up.

Prof. D.S. Gambhir

Objective

To evaluate the safety and efficacy of **INFINNIUM®** Paclitaxel- Eluting Coronary Stent System in real world coronary artery lesions.

Method

The SIMPLE I study included 282 non-randomized patients from forty eight centers in India, with a total of 318 **INFINNIUM®** stents implanted (1.13 **INFINNIUM®**/ patient). The population of the study was with complexities like 33.3% diabetes, 25.2% chronic total occlusion, 10.6% Multivessel Disease, 62.3 % LAD treatment and 1.1% left main stenting. We have reported 36-month outcome of the 282 patients of SIMPLE I study.

Study Design

SIMPLE I is a non-randomized, open label study in 282 real world CAD patients.

Result

SIMPLE I study reveals an outcome comparable with the other commercially available drug eluting stent in the European market. At mean follow up of 3 years the cardiac death observed was 3.9%. The TLR was reported to be 6.7%. In SIMPLE I study the late loss and percentage of restenosis at 6 months was found to be 0.2 ±0.66 mm and 5.9% respectively. The overall event-free survival at 3 yrs. was reported to be 87.80% In spite of the complex patient and lesion characteristics in SIMPLE I study (i.e.,33.3% diabetics, 25.2% chronic total occlusion, 10.6% Multi-vessel Disease, 62.3 % LAD treatment and 1.1% Left Main Stenting) the safety and efficacy outcome was comparable to other approved drug eluting stents. The 3yrs outcome results for SIMPLE I supports long term safety of **INFINNIUM®** as incidences of aneurysms, incomplete opposition were not reported and stent thrombosis was statistically non-significant when compared with other clinical outcome of the studies with other approved stent.

Conclusion

The **INFINNIUM®** Paclitaxel Eluting Coronary Stent System is a safe and effective device in a broad range of clinical conditions and lesions morphologies represented in this study.

9 Individualization of Treatment

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

The risks and benefits described above should be considered for each patient before use of the **INFINNIUM®** Paclitaxel-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 3.0. 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.

Thrombosis following stent implantation is affected by several baseline angiographic and procedural factors. These include vessel diameter less than 3.0 mm, intra-procedural thrombus, or poor distal runoff and/or dissection following stent implantation. In-patients, who have undergone coronary stenting, the persistence of a thrombus or dissection should be considered a maker for subsequent thrombotic occlusion. These patients should be monitored very carefully during the first month after stent implantation.

10 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 Paclitaxel-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.

11 How Supplied

Sterile : This device is sterilized with ETO, Non-pyrogenic.
Do not use if the package is opened or damaged.

Contents : One (1) The **INFINNIUM®** Paclitaxel-eluting Stent.

Storage : Storage temperature: 2°C-25°C

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

12 Operator's Manual

12.1 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.
- Remove inner pouch from outer foil pouch.
- Peel open inner pouch using aseptic technique to reveal sterile package.

12.2 Inspection Prior to Use

Prior to using the **INFINNIUM®** Paclitaxel Eluting Stent, carefully remove the system from the package and inspect for bends, kinks, and other damage. Verify that the stent is located between the radiopaque balloon markers. Do not use if there is any damage to the packaging.

12.3 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	Torque device
1	Guidewire Introducer

12.4 Preparation

12.4.1 Guidewire Lumen Flush

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

12.4.2 Delivery System Preparation

Step	Action
1	Prepare the inflation device or syringe with diluted contrast medium.
2	Attach the inflation device/syringe to the stopcock; attach to inflation port.
3	With tip down, orient Delivery System vertically.
4	Open stopcock to Delivery System; pull negative for 30 seconds; release to neutral for contrast fill.
5	Close stopcock to Delivery System; purge inflation device/syringe of all air.
6	Repeat steps 3 to 5 until all air is expelled.
Note: If air is seen in shaft, repeat Balloon Preparation steps 3 to 5 to prevent uneven stent expansion.	
7	If a syringe was used, attach a prepared inflation device to stopcock.
8	Open stopcock to Delivery System.
9	Leave inflation device on neutral.

12.5 Delivery Procedure

Step	Action
1	Prepare the vascular access site according to standard practice.
2	Predilate the lesion with a 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 the guidewire while maintaining the guidewire position across the 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 the 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 Precautions – 5.11 Stent/System Removal Precautions for specific Delivery System removal instructions. 6 Tighten rotating hemostatic valve. Stent is now ready to be deployed.

12.6 Deployment Procedure

Step	Action
1	CAUTION. Refer to product label for in vitro stent diameter, deployment pressure, and RBP. Deploy the stent by slowly pressurizing the system in 2 bar/atm increments, every 5 seconds, until the stent is completely expanded. Maintain pressure for 30 seconds. If necessary, the balloon can be repressurized or further pressurized to assure complete apposition of the stent to artery wall. Do not exceed RBP or expand the stent beyond 4.5 mm.
2	Deflate balloon by pulling negative on inflation device for 30 seconds.

12.7 Removal Procedure

Step	Action
1	Ensure that the balloon is fully deflated.
2	Fully open rotating hemostatic valve
3	While maintaining guidewire position and negative pressure on inflation device, withdraw Delivery System.
4	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.
5	Tighten rotating hemostatic valve.
6	Repeat angiography to assess stented area. If necessary, post dilates within stent. Balloon inflations should incorporate balloon size closely matching vessel.
7	Final stent diameter should match reference vessel. ASSURE STENT IS NOT UNDERDILATED

12.8 Antiplatelet Regimen

Patients receiving the **INFINNIUM®** Paclitaxel-eluting coronary stent should prescribe an antiplatelet therapy like clopidogrel or ticlopidogrel or ticlopidine for a period of 6 months post procedure and aspirin indefinitely to reduce the risk of stent thrombosis.

12.9 In-vitro Information

Note: Please refer balloon code on Product Label to follow one of the tables mention below.

- **For BG Catheter**

Pressure [bar]	2.25 mm	2.5 mm	2.75 mm	3.0 mm	3.5 mm	4.0 mm
2	1.96	2.21	2.46	2.71	3.21	3.71
4	2.06	2.31	2.56	2.81	3.31	3.81
6	2.16	2.41	2.66	2.91	3.41	3.91
8	**2.25**	**2.50**	**2.75**	**3.00**	**3.50**	**4.00**
10	2.31	2.56	2.81	3.06	3.56	4.08
12	2.37	2.62	2.87	3.12	3.62	4.16

14	2.43	2.68	2.93	3.18	3.68	4.24
16	**2.49**	**2.74**	**2.99**	**3.24**	**3.74**	**4.30**
18	2.52	2.78	3.03	3.29	3.80	4.36

***** 14 bar for 4 mm diameter with length higher than 30 mm

- **For BH Catheter**

Inflation Pressure (atm)	2.25 (mm)	2.5 (mm)	2.75 (mm)	3.0 (mm)	3.5 (mm)	4.0 (mm)
4	2.20	2.46	2.71	2.94	3.42	3.91
5	2.23	2.48	2.73	2.97	3.46	3.96
6	**2.25**	**2.50**	**2.75**	**3.00**	**3.50**	**4.00**
7	2.28	2.52	2.77	3.03	3.54	4.04
8	2.31	2.54	2.79	3.05	3.58	4.08
9	2.33	2.56	2.81	3.08	3.61	4.11
10	2.34	2.57	2.83	3.10	3.65	4.15
11	2.36	2.58	2.85	3.13	3.68	4.18
12	2.38	2.60	2.86	3.15	3.71	4.22
13	2.40	2.61	2.88	3.17	3.74	4.24
14	2.41	2.62	2.89	3.19	3.77	4.26
15	2.43	2.64	2.91	3.21	3.80	4.29
16	**2.44**	**2.65**	**2.92**	**3.24**	**3.83**	**4.32**
17	2.46	2.67	2.94	3.26	3.86	4.35
18	2.47	2.68	2.95	3.28	3.89	4.37
19	2.49	2.70	2.97	3.30	3.92	4.40
20	2.50	2.71	2.98	3.32	3.95	4.42
21	2.52	2.73	3.00	3.34	3.98	4.45
22	2.53	2.74	3.01	3.36	4.01	4.47

Gray background: Nominal pressure**, Black background:** RBP (Rated Burst Pressure)

13 Patient Information

In addition to these Instructions for Use booklet, the following patient specific information regarding the **INFINNIUM**® Paclitaxel -eluting Coronary Stent is available:

- A Patient Implant Card that includes both patient and **INFINNIUM**® Paclitaxel-eluting Coronary Stent specific information. All patients will be expected to keep this card in their possession at all times for procedure / stent identification.
- A Patient Information Guide, which includes information on the implant procedure, and the **INFINNIUM**® Paclitaxel-eluting Coronary Stent System.

14 Disclaimer of Warranty and Limitation of Remedy

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15 Explanation of symbols as per MDD 93/42/EEC & EN 980

	Do not reuse
	Use by
	Batch code
	Serial number
	Date of manufacture
	Method of sterilization using ethylene oxide
	Catalogue number
	Caution, consult accompanying documents
	Manufacturer
	Authorized EC REPresentative in the European Community
	Consult instructions for use
	CE mark
	Temperature limitation for storage
	Keep away from sunlight
	Keep dry
	Do not use if package is damaged

Manufacturing License No. : DD/537

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