

# DRAFT - Questions for Discussion

## Circulatory System Devices Panel

### TAXUS™ Paclitaxel-Eluting Coronary Stent System P030025

November 20, 2003

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#### Evaluation of Safety and Effectiveness

The sponsor has conducted a multi-center, double-blinded, randomized, clinical investigation, referred to as the TAXUS IV Trial (N = 1326 at 76 sites; 12 subjects “deregistered”) with the TAXUS™ Express<sup>2</sup>™ Paclitaxel-Eluting Coronary Stent System (CSS) in the following patient population:

patients with *de novo* native coronary artery lesions  $\geq 10$  mm and  $\leq 28$ mm in length and  $\leq 2.5$ mm and  $\leq 3.75$ mm in diameter (by visual estimate).

The stent sizes available for implantation in the TAXUS IV [slow release (SR) formulation] study were the 2.5mm, 3.0mm and 3.5mm diameter stents in lengths of 16 mm, 24 mm, and 32 mm, which meant that the nominal drug dosage per stent ranged from 108 $\mu$ g to 209 $\mu$ g. The average vessel diameter in the study was 3.05 mm  $\pm$  0.35 mm (for the TAXUS™ stent arm) and the average stented lesion length was 21.79 mm  $\pm$  7.79 mm (for the TAXUS™ stent arm). The control (uncoated Express™ stent) device is approved for use in *de novo* lesions with diameters  $\leq 3.0$ mm to  $\leq 5.0$ mm.

For this PMA application, the sponsor is requesting approval for use in the following patient population with the stent sizes designated in Table 1:

patients with *de novo* native coronary artery lesions (length  $\leq 28$ mm) and reference vessel diameters ranging from 2.5mm to 3.75mm.

**Table 1: Proposed TAXUS™ Express<sup>2</sup> Paclitaxel-Eluting CSS Product Matrix & Nominal Drug Dosages**

Stent Diameter	Stent Length						
	8mm	12mm	16mm	20mm	24mm	28mm	32mm
2.50mm	50 $\mu$ g	79 $\mu$ g	108 $\mu$ g	137 $\mu$ g	151 $\mu$ g		
2.75mm	50 $\mu$ g	79 $\mu$ g	108 $\mu$ g	137 $\mu$ g	151 $\mu$ g	180 $\mu$ g	209 $\mu$ g
3.00mm	50 $\mu$ g	79 $\mu$ g	108 $\mu$ g	137 $\mu$ g	151 $\mu$ g	180 $\mu$ g	209 $\mu$ g
3.50mm	50 $\mu$ g	79 $\mu$ g	108 $\mu$ g	137 $\mu$ g	151 $\mu$ g	180 $\mu$ g	209 $\mu$ g

NOTE: The 2.50-3.50mm diameter stents use one design. The same stent is crimped on various size delivery catheter balloons, which are sized from 2.50 to 3.50mm. Because the identical stent component is used for the entire 2.50-3.50mm diameter range, the total drug per stent is a function of stent length, irrespective of stent diameter.

## **Evaluation of Safety**

The pathology findings from the animal studies submitted in the application noted endothelial coverage of the stent, no structural deterioration of the coronary artery wall, and an absence of thrombus, which correspond with the clinical findings from TAXUS I, II and IV. However, the animal studies also revealed marked histologic changes in the media (i.e., smooth muscle cell loss, ingrowth of fibrous tissue, neovascularization, dystrophic calcification) in the vessel wall. In addition, parastrut amorphous material or “PAM” (also identified as “drug effect,” strut fibrin, and thrombus within the study reports) was noted. These findings were more pronounced in the MR formulation versus the SR formulation that is proposed for commercialization. The degree of response appeared to correlate with increasing dose, with the least response occurring in the animals implanted with the SR formulation.

These findings were present at all time points, including 180 and 360 days, but appeared to be resolving over time, and did not result in structural deterioration of the coronary wall.

Although FDA generally recommends that long-term animal studies include follow up to 180 days, it is unknown how findings present at this time point would correlate with the human clinical experience because healing progresses at a faster rate in the nonatherosclerotic swine model.

- 1. Does the combination of 9 month clinical data from the pivotal TAXUS IV (SR formulation) study and the adjunctive data from TAXUS I (SR formulation) and TAXUS II (SR and MR formulations) adequately address the potential concerns raised by the animal studies?**

The potential for interactions with several drugs has been described in the Taxol® Directions for Use. Interactions with other drugs might be expected based on known drug metabolism.

- 2a. Are the clinical studies presented adequate to address concerns about possible adverse effects from interactions with drugs typically administered to the target patient population?**
- 2b. Please comment on whether the clinical studies adequately address other drug interactions that are likely to be important or of interest. If not, what other information or studies should be provided? Specifically, please consider the potential for the following types of interactions:**
  - i. with anti-neoplastic agents**  
(E.g., cardiac toxicities have been noted when doxorubicin HCl is combined with paclitaxel; however, from the literature, FDA is unaware of any reports to date of paclitaxel-eluting stents enhancing doxorubicin HCl cardiac toxicity.)
  - ii. with chemotherapeutic agents, where a hypersensitivity reaction could be induced**

The safety endpoints evaluated in the TAXUS IV (SR formulation) study included:

Safety endpoint*	TAXUS™ Stent	Express™ Stent	p-value
MACE to 270 days	8.5% (56/662)	15.0% (98/652)	0.0002**
Stent thrombosis to 30 days	0.3% (2/662)	0.6% (4/652)	0.4487
Stent thrombosis to 270 days	0.6% (4/662)	0.8% (5/652)	0.7513

\* Rates presented as number of patients with events per number of patients in analysis.

\*\*statistically significant

Incomplete Apposition*	TAXUS™ Stent	Express™ Stent	p-value
Post procedure	11.6% (13/112)	6.4% (7/109)	0.2415
To 270 days	4.0% (4/99)	3.0% (3/100)	0.7209
Paired Data			
Resolved	6.4% (6/94)	5.4% (5/93)	1.0000
Persistent	3.2% (3/94)	1.1% (1/93)	0.6210
Late Acquired	1.1% (1/94)	2.2% (2/93)	0.6210

\*Rates are presented as number of patients with incomplete apposition per number of patients with IVUS at the relevant timepoint.

Safety information available from TAXUS I (SR formulation), and TAXUS II (SR and MR formulations) included:

Safety Endpoint*	TAXUS I SR formulation (n=31)	TAXUS II SR Cohort (n=131)	TAXUS II MR Cohort (n=135)
<b>Time point of analysis</b>	<b>2 years</b>	<b>12 months</b>	<b>12 months</b>
MACE	3.0% (1/31)	10.9% (14/129)	9.9% (13/131)
Stent Thrombosis to 30 days	0% (0/31)	0.8% (1/131)	0.0% (0/135)
Stent Thrombosis (through time-point of analysis)	0% (0/31)	1.5% (2/131)	0.7% (1/135)

\* "Rates" presented as number of events per number of patients in analysis.

- Do the clinical data submitted from the pivotal TAXUS IV (SR formulation) study, plus the data from the adjunctive TAXUS I (SR formulation), and TAXUS II (SR and MR formulations) studies, provide reasonable assurance of safety?**

### Evaluation of Effectiveness

The primary effective endpoint for the TAXUS IV (SR formulation) study was target vessel revascularization (TVR) at 9 months (270 days). Rates of TVR at 270 days were 4.7% (31/662) for the TAXUS™ group and 12.0% (78/652) for the Express™ control group.

- Does the clinical data at 270 days presented on the TAXUS™ stent from the pivotal TAXUS IV study provide reasonable assurance of effectiveness?**

## **Labeling**

One aspect of the pre-market evaluation of a new product is the review of its labeling. The labeling must indicate which patients are appropriate for treatment, identify potential adverse events with the use of the product, and explain how the product should be used to maximize benefits and minimize adverse effects.

The proposed labeling currently states in Section 2, Indications:

The TAXUS™ Express<sup>2</sup>™ Paclitaxel-Eluting Coronary Stent System is indicated for improving luminal diameter and reducing restenosis for the treatment of *de novo* lesions  $\leq 28$ mm in length in native coronary arteries  $\geq 2.5$  to  $= 3.75$ mm in diameter.

The proposed indication represents a change from the bare Express<sup>2</sup>™ Coronary Stent System indication because it includes the phrase “reducing restenosis.”

### **5a. Does the evidence presented on the TAXUS™ product support the proposed labeling indication?**

The TAXUS IV (SR formulation) clinical trial was designed to investigate use of a single stent, with bailout stenting allowed. Out of the 652 patients treated with the TAXUS™ stent (SR formulation), only 44 patients had two stents placed, and 1 patient had 3 stents placed. All patients receiving overlapping stents were included in the IVUS subset, and no clinical concerns were noted for these patients.

The proposed labeling currently states in Section 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 TAXUS™ Express<sup>2</sup>™ stents has not been fully evaluated. 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.

### **5b. Please comment on whether the labeling should specify that multiple stents should only be used for bailout purposes (e.g., dissection, insufficient lesion coverage) and whether in these cases the shortest stent available (i.e., 8 mm) should be used.**

### **5c. Please comment on whether the labeling should address the potential combination of the TAXUS™ stent with an additional drug-eluting stent in the same vessel.**

The labeling currently states in Section 5.1, General Precautions:

Antiplatelet therapy is recommended for a period of 6 months post-procedure.

The labeling does not recommend any specific pre-procedural or procedural anticoagulation regimens. The TAXUS IV (SR formulation) study was designed to include mandatory aspirin ( $\geq 325$ mg p.o. QD) at least 1 hour pre-procedure; clopidogrel (300mg p.o.) or ticlopidine (500mg

p.o.) pre-procedure (within 24 hours) or within 2 hours after the procedure; heparin or other procedural antithrombotics (Abciximab, eptifibatid, and tirofiban were allowed); and clopidogrel (75mg p.o. QD) or ticlopidine (250mg p.o. BID), and aspirin ( $\geq$  325mg p.o. QD) for at least 6 months post-procedure. Recent publications have addressed the risks and benefits of various pre-procedural and procedural anticoagulation regimens and post-procedural anti-platelet regimens.

**5d. Please comment on whether the labeled recommendation for post-procedural antiplatelet regimen is appropriate, and whether additional recommendations on procedural anticoagulation regimens are warranted.**

**5e. Please comment on any other aspects of the product labeling, such as:**

- i. Contraindications**
- ii. Warnings/Precautions (such as use with brachytherapy, conjunction with other procedures, etc.)**
- iii. Drug pharmacology, pharmacokinetics or specific drug safety information (e.g., use in special populations, warnings, precautions)**

### **Postmarket Study Design**

The panel package included the available 9-month data for the TAXUS™ Express2™ product (SR formulation) in the TAXUS IV study. In addition, the available data were provided for the TAXUS I (SR formulation - 2 year) and TAXUS II (SR & MR formulations - 1 year), and safety updates were provided for all patients currently enrolled in the TAXUS series of studies.

The applicant has proposed continued follow-up (to 5 years) on subjects from the TAXUS series of studies. The applicant has also proposed to collect data through two years on approximately 2000 patients implanted with the marketed product, using an electronic database. This study will consist of two phases. Phase 1 will consist of a pre-market continued access study with up to 500 consecutive patients enrolled at 10 U.S. sites. Phase 2 will be a post-market registry with 1500 consecutive patients enrolled at 40 U.S. sites. Geographically diverse U.S. community-based facilities representing a variety of annual implant volumes will participate.

**6. Please discuss long-term adverse effects that may be associated with TAXUS™ stents, and whether the proposed 5–year follow-up on the clinical trial cohorts and the proposed pre/post-marketing study are appropriate to evaluate the chronic effects of the implantation of the TAXUS™ stent. If not, what additional information should be collected? Specifically, discuss how long patients should be followed, and what endpoints and adverse events should be measured.**