SUMMARY OF SAFETY AND PROBABLE BENEFIT

1. General Information

Device Generic Name:	Intravascular Stent
Device Trade Name:	JOSTENT® Coronary Stent Graft
Applicant's Name and Address:	JOMED AB Drottninggatan 94 S-25 221 Helsingborg Sweden
Humanitarian Device Exemption (HDE) Number:	H000001
Date of Humanitarian Use Device Designation:	October 26, 1999
Date of Panel Recommendation:	Not Applicable (Refer to Section 12)
Date of Good Manufacturing Practices Inspection:	August 24, 2000
Date of Notice to the Applicant:	JAN 10 2001

2. Indications for Use

The JOSTENT® Coronary Stent Graft is indicated for the treatment of free perforations, defined as free contrast extravasation into the pericardium, in native coronary vessels or saphenous vein bypass grafts ≥ 2.75 mm in diameter.

3. Device Description

The JOSTENT® Coronary Stent Graft combines two flexible stents with an expandable PTFE (ePTFE) graft material. The stents are made of implantable, high-grade surgical steel (316L) and are manufactured from a solid tube using precision laser technology. The PTFE material is sandwiched between the two stents. The stent grafts will be available in lengths of 9, 12, 16, 19, and 26 mm. The stent grafts can be expanded to diameters from 2.75 to 5.0 mm by hand-crimping the stent on a currently marketed high-pressure, non-compliant balloon catheter approved for percutaneous transluminal coronary angioplasty (PTCA).

4. Contraindications

The JOSTENT® Coronary Stent Graft is contraindicated for use in:

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

5. Warnings and Precautions

See Warnings and Precautions in the final labeling (Instructions for Use).

6. Adverse Events

6.1 Observed Adverse Events

Data were collected from a total of 41 patients in a multi-center, retrospective analysis of use of the JOSTENT® Coronary Stent Graft to treat perforations. These patients form the basis of the observed events reported (See Clinical Studies).

A total of 14 of 41 patients (34.1%) receiving the JOSTENT® Coronary Stent Graft experienced one or more adverse events during the procedure. Only one patient (1/41, 2.4%) experienced events post-JOSTENT® implantation, due to an incompletely sealed perforation. All other adverse events can be attributed to the perforation since they occurred prior to stent implantation.

No patients who received the JOSTENT® Coronary Stent Graft died, experienced a Q-wave MI, or necessitated emergent CABG during the procedure or in-hospital stay. All stents were successfully delivered.

Table 1 Observed Adverse Events

	N occurrences
Patients experiencing any complication	14 (34.1%)
Procedural Complications[1]	
Pericardial effusion	9 (22.0%)
Tamponade	5 (12.2%)
Pericardiocentesis	6 (14.6%)
Cardiac arrest	1 (2.4%)
Hypotension	5 (12.2%)
Cardiogenic shock	4 (9.8%)
Bradycardia	4 (9.8%)
In-hospital MACE	
Death	0
Emergent CABG	0
Q-wave MI	0

[1] All complications occurred in the cardiac catheterization laboratory *prior to* JOSTENT® implantation, except for a single out of lab effusion that progressed to tamponade and required emergent re-PTCA with placement of a second JOSTENT® that sealed the perforation.

6.2 Potential Adverse Events

Potential adverse events include, but are not limited to:

- Acute myocardial infarction
- Arrhythmia's (including VF and VT)
- Coronary artery bypass surgery
- Death
- Dissection
- Drug reactions to antiplatelet agents/contrast medium
- Emboli, distal (air, tissue or thrombotic emboli)
- Emergent coronary artery bypass surgery
- Hemorrhage, requiring transfusion
- Hypotension / Hypertension

- Infection and pain at insertion site
- Ischemia, myocardial
- Perforation
- Pseudoaneurysm, femoral
- Restenosis of stented segment
- Spasm
- Stent embolization
- Stent thrombosis/occlusion
- Stroke/cerebrovascular accidents
- Total occlusion of coronary artery

6.3 Observed Device Malfunctions

No device malfunctions were noted during clinical use of the JOSTENT® Coronary Stent Graft.

7. Alternative Practices and Procedures

Alternative procedures include reversal of anticoagulation, subsequent balloon inflations, or operative intervention, including emergency CABG or pericardiocentesis (drainage to reduce cardiac tamponade).

8. Marketing History

The JOSTENT® Coronary Stent Graft has been marketed outside the U.S. since January 1998, in over 22 countries. The JOSTENT® Coronary Stent Graft has not been withdrawn from marketing for any reason related to the safety or effectiveness of the device in any of these countries. All complaints, oral or written, have been documented. In the past two years, nine complaints have been received, none of which resulted in a major adverse cardiac event.

9. Summary of Preclinical Studies

9.1 Biocompatibility Testing

Biocompatibility of the implant was shown to be acceptable by the following tests which were performed in accordance with the provisions of the ISO 10993-1 and Good Laboratory Practice (GLP) Regulations, 21 CFR 58:

- Cytotoxicity
- Sensitization
- Acute intracutaneous reactivity
- Acute systemic toxicity
- Genotoxicity (Ames mutagenicity (saline and DSMO extracts), bacterial reverse mutation study (saline and DSMO extracts), *in vitro* chromosomal aberration study, and mouse bone marrow micronucleus test)
- Hemolysis
- Material-mediated pyrogenicity

Additional testing of the JOSTENT® Coronary Stent Graft included plasma recalcification time coagulation, white blood cell morphology, and C3a complement activation.

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9.2 Bench Testing

The following testing was performed on finished, sterile products:

Visual and Dimensional Inspection

Visual inspection included inspection of the label, the packaging, the stent handle, the stent material, and the PTFE foil for particles and damage. Dimensional inspection included measurements of the stent length and the gap between the end of the stent and the PTFE foil. The stent length must meet the following specifications: 9.3, 12.3, 15.8, 18.8, and 25.6±0.5 mm. The PTFE foil must sit 0.043 to 0.52 mm from the edge of the stent. All devices met the visual and dimensional specifications.

Crimping the stent graft

The stent graft was crimped following the directions as presented in the Instructions for Use (IFU) on PTCA catheters with balloons ranging from 2.5 to 4.0 mm in diameter. The stent graft was then gently pushed to check the security of attachment.

Two of 159 stent grafts were not successfully crimped on the balloons. In these cases, the stent graft could be moved after crimping on the catheter. During clinical use, the IFU instruct the physician to perform the same test on each stent graft after crimping. If the stent graft can be moved, then the product should not be used.

Dimensions of crimped stent

The stent graft length and profile were measured after the crimping process. The stent graft length must be within ±1.6 mm of the nominal stent length. The crimped profile must be acceptable for use with the labeled guiding catheter compatibility. All devices met the length and profile specifications for the crimped stent graft.

Guiding Catheter Compatibility

All stent grafts were checked for guiding catheter compatibility after being crimped on balloon catheters. All stent grafts mounted on balloons ≤3.5 mm must be able to pass through a 6 F guiding catheter. All stent grafts mounted on larger balloons must be able to pass through a 7 F guiding catheter. All devices met the guide catheter compatibility specifications.

Expansion of the stent graft

The stent grafts were expanded in a 37°C water bath. The pressure for full expansion was recorded. All balloons must be fully expanded to the labeled diameter with a pressure <14 bar. All devices met the expansion pressure specification.

Recoil

The recoil of the stent graft was measured by recording the diameter of the stent graft with the balloon inflated and without the balloon inflated. In no case should the maximum recoil result in the stent graft being undersized by more than 10%. All devices met the recoil specification.

Foreshortening

Foreshortening was measured by comparing the original stent length to the stent length post-expansion. As the diameter of expansion increases, significant foreshortening occurs. The average foreshortening ranged from 4% to 24%. The results of this testing are summarized in the IFU so the physician can make an educated decision when choosing the stent length used to cover the perforation site.

Visual and Dimensional Inspection Post-expansion

Visual inspection included inspection of the stent material and the PTFE foil. The gap between the end of the stent and the PTFE foil was measured. In addition, the width of cells around the circumference of the stent was measured to check the uniformity of expansion.

After expansion, the PTFE foil was a maximum of 1.6 mm from the edge of the stent. This result is considered acceptable, and the information is included in the IFU. Expansion was considered relatively uniform around the circumference of the stent graft and acceptable for clinical use. All devices met the visual and dimensional post-expansion specifications.

Radial Force

The force was measured to compress an expanded stent to ½ of the expanded diameter. The radial force of the stent must exceed worst-case physiological pressures. All devices met the radial force specification.

Fatigue

Fatigue testing, simulating 10-year equivalent real time, was performed on 33 coronary stent grafts using a standard EnduraTEC stent tester with temperature control. Scanning electron microscopy review of 19 of the stent grafts indicated the appearance of a corrosion and contact stress process. This process is associated with contact between the stent and the latex tubing during cyclic loading.

One device experienced fractures on two helical structures. One fracture occurred on the inner stent, and one fracture occurred on the outer stent. An investigation concluded that the two failures had no effect on the radial force of the stent and no damage to the PTFE occurred.

Finite Element Analysis

An FEA was performed, modeling the device under a bending load, a radial pressure load, a torsional load, and a point load. All calculations were done using a complete elastic/elastic-plastic formulation of the material behavior using a true stress-true strain relation of the stent material (316L). The PTFE was assumed a low-tension elastic material. The analysis was performed with a simulated inflation diameter of 5.0 mm. All calculated maximum stresses must be below the tensile strength of the 316L material. The device design meets the specification for FEA, and the factor of safety is considered acceptable for all types of loading.

Testing with FDA-approved PTCA Catheters

The JOSTENT® Coronary Stent Graft has been tested with several non-compliant balloons, including: the Cordis Titan (RBP=16atm), the Scimed NC Ranger (RBP=18atm in a stent), and the Scimed Maxxum (RBP=20atm). A random sample of these catheters was used for compliance and burst testing. Twenty-two 9mm and 26 mm stents were mounted on the PTCA catheter balloons following the crimping directions presented in the IFU.

One balloon developed a pinhole leak before beginning to expand the stent. This stent system was retrieved through the guide catheter following the steps in the IFU. All other balloons burst well above their rated burst pressure.

Compliance of the balloons was also noted. Delivery of the JOSTENT® Coronary Stent Graft did not significantly affect balloon compliance.

9.3 Sterility and Shelf Life Qualification Studies

Finished JOSTENT® Coronary Stent Grafts are sterilized with EO sterilization. The sterilization procedure has been validated using the half-cycle method for a sterility assurance level of 10^{-6}.

A one-year shelf life for the JOSTENT® Coronary Stent Graft has been validated. The device packaging is durable and will maintain sterility for a period up to one year, and device functionality after aging has been confirmed.

9.4 Animal Testing

An animal study was designed to test the JOSTENT® Coronary and Peripheral Stent Grafts in a balloon-injury model in porcine peripheral arteries. JOSTENT® Coronary Stent Grafts were compared to bare metal stents after implantation in porcine renal arteries. In addition, JOSTENT® Peripheral Stent Grafts were implanted in iliac arteries and descending abdominal aorta for acute and long-term characterization assessment. Animals were sacrificed at different time points as follows: Group 1 – 1 day, n=2; Group 2 – 15 days, n=4; Group 3 – three months, n=4; and Group 4 – six months, n=4).

Histopathologic study by morphologic and morphometric analysis and by scanning electron microscopy were used to assess the following: incorporation characteristics of this type of stent in terms of inflammatory reaction and development of acute and/or subacute thrombosis; the re-endothelization extent and its time course up to six months after deployment; and the possibility to attenuate the neointimal response and reduce the severity of neointimal hyperplasia at the long-term follow-up in comparison with bare metal stenting.

This study demonstrated that the JOSTENT® Coronary Stent Graft can be implanted safely in porcine peripheral arteries. Acute and subacute thrombosis of the stents was minimal, despite the fact that a large number of stents were implanted in the same animal and that the animals

sustained a significant arterial injury, as demonstrated by the mean values of injury score (>1.2 in all cases). Furthermore, the midterm to late data demonstrated no significant luminal obstruction or mortality up to six months after stenting. An inflammatory reaction, although present in all stented segments, was, in the majority of cases, of mild degree and did not represent a major finding. Foreign body-type giant cell infiltration was occasional and mostly confined near the PTFE polymer. The JOSTENT® Coronary Stent Graft did not inhibit neointimal thickening compared with that for the bare metal stents. Re-endothelialization of the JOSTENT® Coronary Stent Graft started as soon as 15 days after implantation and was almost complete at six months.

10. Summary of Clinical Study

10.1 Objective

The objective of this study was to evaluate the technical success and safety of the JOSTENT® Coronary Stent Graft as a life-saving treatment in cases of coronary artery perforation.

10.2 Design

This study was multicenter, retrospective, and non-randomized. Demographic, clinical, and angiographic data were collected on the target population, including in-hospital and limited follow-up data from November 1998 through December 1999.

JOMED is aware of a total of 46 perforations treated worldwide with the JOSTENT® Coronary Stent Graft. Full procedural case report forms have been received for 41 of the 46 subjects. Follow-up forms were received for 27 of the 41 evaluable subjects. The follow-up time ranged from one week to one year. All subjects were enrolled after undergoing urgent or emergent use of the JOSTENT® Coronary Stent Graft to treat a native coronary artery or saphenous vein graft perforation.

10.3 Results

Demographics were collected for the 41 subjects. Sixty-five percent of the subjects were male. The subjects had a high incidence of previous MI (59.0%), previous CABG (27.5%), previous PTCA (30.8%), and CCS Class III/IV angina (83.3%). For this population, the in-hospital major adverse cardiac event (MACE) rate was 0%. There were no in-hospital incidents of death, Q-wave MI, or emergent CABG. In all cases, the JOSTENT® Coronary Stent Graft was deployed successfully. No device malfunctions were noted. In all cases, the perforation was sealed.

Study Population:

Table 2 Patient Demographics

N=41 subjects[1]	Occurrences (%)	Not reported
Average Age, years	65.2	1
Male	26 (65.0%)	1
Hx of MI	23 (59.0%)	2
Hx of CAD	30 (75.0%)	1
Hx of CABG	11 (27.5%)	1
Hx of PTCA	12 (30.8%)	2
Hx of CHF	2 (6.4%)	10
Hx of HTN	11 (36.7%)	11
Angina	41 (100%)	
CCS Class I/II	6 (16.7%)	5
CCS Class III/IV	30 (83.3%)	5
Diabetes	6 (23.1%)	15

[1] Procedural forms were never received for five of the total 46 cases reported to JOMED. No information has been received regarding these cases.

Safety and Effectiveness Data:

Table 3 Procedural Information

	N occurrences
Index procedure elective	38/40 (95.0%)
Index procedure emergent	2/40 (5.0%)
JOSTENT® indication	
Perforation	37 (90.2%)
Others: Aneurysm	1
Fistula	2
Rescue after embolized stent	1
Native vessel	33 (80.5%)
SVG	8 (19.5%)
Average number of stents used	1.3 (range: 1-3)
Number of stents used:	52
9 mm	2
12 mm	3
16 mm	13
19 mm	23
26 mm	8
JOSTENT® deployed successfully	52 (100%)
Perforation closed/vessel sealed	41 (100%)

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Adverse Reactions and Complications:

Table 4 Procedural Complications

	N occurrences
Patients experiencing any complication	14 (34.1%)
Procedural Complications[1]	
Pericardial effusion	9 (22.0%)
Tamponade	5 (12.2%)
Pericardiocentesis	6 (14.6%)
Cardiac arrest	1 (2.4%)
Hypotension	5 (12.2%)
Cardiogenic shock	4 (9.8%)
Bradycardia	4 (9.8%)
In-hospital MACE	
Death	0
Emergent CABG	0
Q-wave MI	0

[1] All complications occurred in the cardiac catheterization laboratory *prior to* JOSTENT implantation, except for a single out of lab effusion that progressed to tamponade and required emergent re-PTCA with placement of a second JOSTENT that sealed the perforation.

Table 5 In-hospital Adverse Events

	N occurrences	Historical Data[1]	
In-hospital MACE		Free Perforations	All Perforations
Death	0	20%	9%
Emergent CABG	0	60%	37%
Q-wave MI	0	10%	6%

[1] Ajluni SC, Glazier S, Blankenship L, O'Neill WW, Safian RD. Perforations after percutaneous coronary interventions: clinical, angiographic, and therapeutic observations. *Cathet Cardiovasc Diagn*. 1994;32:206-12.

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Table 6 Complications at Follow-up

Patient	Time Point	Complication
17JV	1 month	TVR/TLR on waiting list for CABG CCS class III angina
30MP	1 month	TVR/TLR Non-QMI Rehospitalization CCS class III angina
24AN	2 months	Occlusion of target lesion Recurrent angina
28RL	2 months	Non-QMI Rehospitalization (managed medically)
46RL	2 months	MI TVR/TLR Rehospitalization
5MK	6 months	TVR/TLR CCS class III angina (no restenosis at 1 year)
29PM	6 months	Occlusion of target lesion Rehospitalization
39OR	6 months	TVR (not TLR)
33MS	9 months	Revascularization[1]

[1] No further information was provided.

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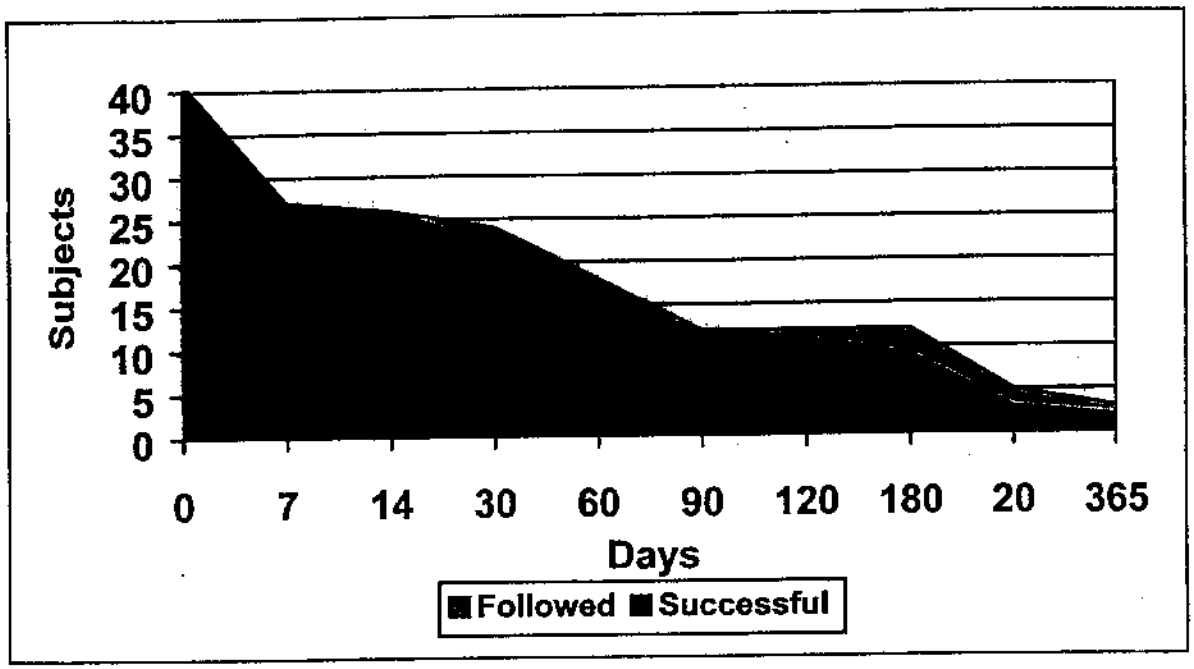
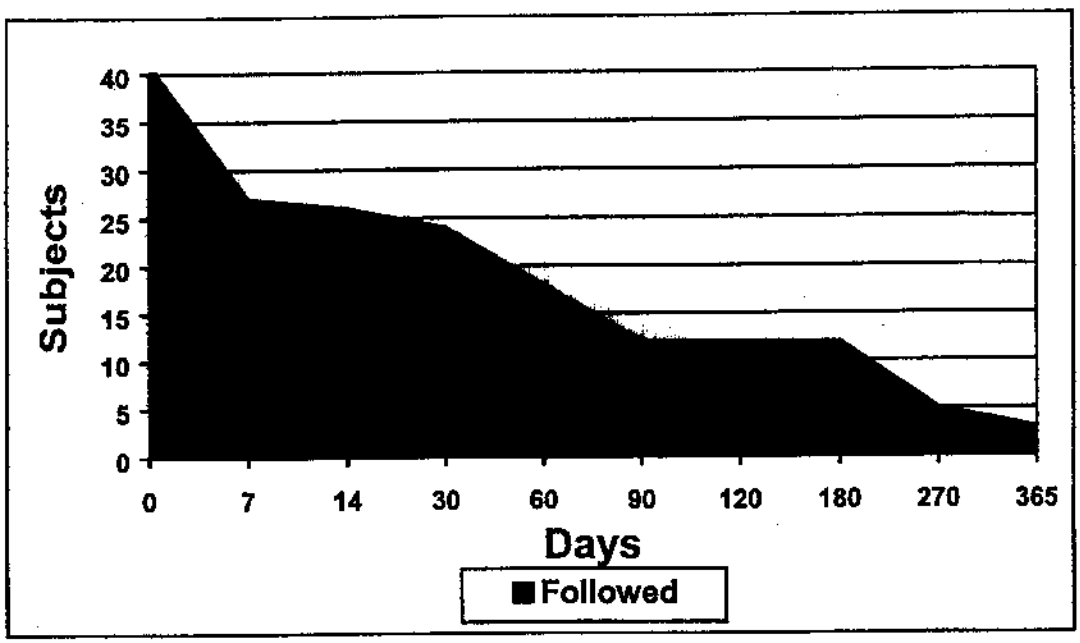
Graph 1 **Outcome at Follow-up**



Patient Discontinuation:

Follow-up forms were received for 27 of the 41 evaluable subjects. Every effort was made to obtain these patient follow-up forms. The follow-up time ranged from one week to one year.

Graph 2 **Loss to Follow-up**



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Patient Complaints:

No patient complaints were received.

Device Failures and Replacements:

No device failures were noted during implantation of the stent grafts.

11. Conclusions Drawn from the Studies

The pre-clinical studies indicate that the JOSTENT® Coronary Stent Graft is biocompatible and has the appropriate physical and performance characteristics for its intended use, as stated in the labeling. The bench studies demonstrate that hand-crimping of the stent did not notably alter the performance of the balloon catheters or introduce new failure modes to the balloon. The mounting and delivery procedures in the Instructions for Use were verified as adequate. The animal study provides reasonable assurance that the JOSTENT® Coronary Stent Graft can be implanted safely, and the midterm to late data demonstrated no significant luminal obstruction or mortality up to six months after stenting.

The clinical data from a small retrospective study suggest that the JOSTENT® Coronary Stent Graft can safely be deployed in coronary arteries to seal free perforations. Use of the JOSTENT® Coronary Stent Graft is not associated with increased risks compared to conventional treatment of perforations.

The pre-clinical studies and clinical experience with the device provide reasonable assurance of the safety and probable benefit of the JOMED JOSTENT® Coronary Stent Graft when used in accordance with its labeling.

12. Panel Recommendation

This HDE was not reviewed by an FDA Advisory Panel. The panel has previously reviewed similar implants such as three coronary stents and two endovascular grafts. This HDE does not raise any unanticipated safety issues. Therefore, it was determined that this application need not be submitted to the advisory panel.

13. CDRH Decision

CDRH has determined that, based on the data submitted in this HDE application, the JOMED JOSTENT® Coronary Stent Graft will not expose patients to an unreasonable or significant risk of illness or injury and the probable benefit to health from using the device outweighs the risk of illness or injury, and issued an approval order on January 10, 2001. All facilities involved in the manufacture of this device have been inspected and found to be in compliance with the Quality System Regulation.

14. Approval Specifications

Indications for Use: See Instructions for Use (attached).

Hazards to health from use of device: See contraindications, warnings, precautions, and adverse events in the instructions for use (attached).