

SUMMARY OF SAFETY AND EFFECTIVENESS DATA

I. GENERAL INFORMATION

Device Generic Name: Intravascular Stent with Delivery System

Device Trade Name: Rithron-XR Coronary Stent System

Applicant's Name and Address: Biotronik GmbH
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**Premarket Approval
Application (PMA) Number:** P030037

Date of Panel Recommendation: None

**Date of Notice of Approval
To Applicant:** April 29, 2005

II. INDICATIONS FOR USE

The Rithron-XR Coronary Stent System is intended for use in patients eligible for balloon angioplasty with symptomatic ischemic heart disease characterized by discrete de novo coronary artery lesions with reference vessel diameter from ≥ 3.0 mm or ≤ 4.0 mm, the target lesion length is ≤ 20.0 mm.

III. CONTRAINDICATIONS

The use of the Rithron-XR premounted Coronary stent system, and stent implantation in general, is contraindicated for use in:

- patients in whom antithrombogenic and anticoagulant therapy is contraindicated;
- patients who exhibit stenoses that inhibit the complete inflation of an angioplasty balloon;
- patients who are allergic to stainless steel, gold, or silicon carbide, or exhibit incompatibility with the coating material (amorphous silicon carbide).

IV. WARNINGS AND PRECAUTIONS

Please refer to the device labeling for a list of warnings and precautions.

V. Device Description

The Rithron-XR Coronary Stent System consists of the following:

- ✦ The Tenax-XR stent features a tubular slotted design, laser-cut from a single tube of 316L stainless steel. Two gold markers at the proximal and distal end of the stent increase the radiopacity. The stent is completely coated with amorphous silicon carbide.
- ✦ A Fast Exchange PTCA catheter, on which the Tenax-XR stent is pre-mounted. These types of catheters primarily consist of a balloon and a distal and proximal shaft. The distal shaft is manufactured of a synthetic outer and inner tube. The proximal shaft uses an inner steel tube and an outer synthetic tube. The Rithron-XR catheter is constructed coaxially in the distal part. The inner tube receives the guide wire, which is extended out of the catheter 28 cm from the distal end. There are two platinum/iridium marker bands on the inner tube adjacent to the proximal and distal ends of the stent, designed to ensure visibility and facilitate a controlled placement of the stent within the lesion of the treated vessel. Characteristics of the CSS appear in Table 1.

Table 1. Stent Delivery System Specifications

Stent Diameter	Nominal Pressure	Rated Burst Pressure	Guide Compatibility
3.00 mm	6 Atm	14 Atm	5 F (.055")
3.50 mm	6 Atm	14 Atm	(.055")
4.00 mm	6 Atm	12 Atm	5 F (.055")

The Rithron-XR CSS is available in nine device models with stent diameters of 3.0, 3.5, and 4.0 mm and stent lengths of 10, 15 and 20 mm, as shown in Table 2.

Table 2. Rithron-XR System Product Matrix

Stent Diameter	Stent Length		
	10 mm	15 mm	20 mm
3.00 mm	X	X	X
3.50 mm	X	X	X
4.00 mm	X	X	X

VI. ALTERNATIVE PRACTICE AND PROCEDURES

Alternative treatments of coronary atherosclerotic disease include diet, medication (e.g. thrombolysis), atherectomy, balloon angioplasty, coronary bypass (CABG) surgery or stenting with commercially available stents.

VII. MARKETING HISTORY

The Rithron-XR Coronary Stent System began distribution outside the United States in April 2001 and has been commercially distributed in the following countries (in alphabetical order): Argentina, Australia, Austria, Belgium, Brazil, Canada, China, Colombia, Croatia, Cyprus, Czech Republic, Egypt, France, Germany, Great Britain,

Hungary, Iceland, India, Israel, Italy, Latvia, Lebanon, Macedonia, Malaysia, Malta, Mexico, Netherlands, Norway, Pakistan, Poland, Romania, Russia, Slovenia, South Africa, Spain, Sweden, Switzerland, Turkey, Uruguay, and Venezuela.

Biotronik's Rithron-XR Coronary Stent System has not been withdrawn from any of these markets for any reason.

VIII. SUMMARY OF NON-CLINICAL STUDIES

A. Biocompatibility

Biocompatibility testing of all tissue-contacting materials used in BIOTRONIK's Rithron-XR Coronary Stent System has been successfully completed. The following list summarizes the system components of the Rithron-XR Coronary Stent System that are in contact with human tissue.

<ul style="list-style-type: none"> • Stent Coating • Balloon • Outer tube, proximal part • Outer tube, distal part • Guide Wire Lumen Tip 	<ul style="list-style-type: none"> • Shaft and Tip Coating: • Proximal Shaft and Distal Tip: • Distal Shaft: • Hydrophilic Coating
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The Rithron-XR Coronary Stent System successfully completed all biocompatibility validation tests required by the manufacturer's validation plan. The tests performed to substantiate the biocompatibility of the Rithron-XR Coronary Stent System are described below:

a. Sensitization in accordance with ISO 10993:1:1997 "Biological evaluation of medical devices" - PTCA catheter & Stent

Ten samples were tested per ISO 10993-10: 1994, ISO 10993-12: 1996, and the methods specified by Magnusson and Kligman to determine the sensitizing or irritative effects. To obtain extracts from the object under test, physiological saline solution was used as a polar medium and cottonseed oil as a non-polar medium. There were no sensitization effects.

b. Irritation Test – PTCA Catheter and Stent

Intracutaneous activity testing was carried out on three samples by injecting a polar and a non-polar extract of the test object under the skins of rabbits. The injection sites were examined after 24, 48 and 72 hours, and all observed effects were recorded. There was no reddening of the skin or edemas on the skin as specified.

c. Cytotoxicity – PTCA Catheter & Stent

Three samples were tested per ISO 10993-5: 1992. In order to determine the cytotoxicity of the test object, the effect of material extracts on the cytogenesis of L-929 mouse fibroblasts was analyzed. The fibroblasts were incubated together with material extracts and control extracts for a period of 72 hours. The protein content of the cells was measured in order to determine the effect on the cell proliferation behavior. There were no cytotoxic reactions or effects.

d. Acute Systemic Toxicity in accordance with ISO 10993:1 “Biological evaluation of medical devices” - PTCA Catheter & Stent

Six samples were tested per ISO 10993-11: 1993 and ISO 10993-12: 1996. Acute systemic toxicity tests were carried out according to the "Acute Toxicity Limit Test" method. Two groups, each consisting of 3 male and 3 female rats were treated once with four different extracts of the test object. After 2 weeks of clinical observation, the animals were euthanized and their organs were inspected for noticeable pathological changes. There were no adverse results during the observation period and pathological examinations.

e. Hemocompatibility in accordance with ISO 10993:1: 1997 “Biological evaluation of medical devices“ – PTCA Catheter & Stent

Three samples were tested per ISO 10993:1: 1997, ISO 10993-4: 1993 and ISO 10993-12: 1996. Hemocompatibility was tested in a dynamic whole-blood model in which the test categories specified in ISO 10993-4 were evaluated: thrombosis, coagulation, platelets, hematology and immunology. Standard heparin in a concentration of 1 I.U./ml was used as an anticoagulation agent during the 30 min incubation time with human whole blood. There were no damaging effect on leukocytes and erythrocytes.

f. Test for Pyrogens in accordance with ISO 10993:1: 1997, “Biological evaluation of medical devices” – PTCA Catheter & Stent

Three samples were tested per ISO 10993:1: 1997. The Pyrogen test was used to determine chemically or bacterially induced pyrogenic effects of the medicinal product. Rabbits were given a simple intravenous injection of the test object extract at a dosage of 10ml/kg body weight. The test animals' body temperatures were observed for a three-hour period after the extract was injected. Body temperature increase was less than 0.5° C as specified.

g. Implantation according to ISO 10993-1: 1997 – Stent

Three samples were tested per ISO 10993-6:1994 and ISO 10993-12: 1996. Test specimens 10 mm x 1mm in size were implanted in the paravertebral muscle of rabbits. For evaluation of the reaction, USP negative controls of the same size were injected in the muscle on the opposite side. After periods of 1, 4 and 12 weeks, a macroscopic and a histological evaluation of the test item effects were performed. The biological effects of the test item corresponded to the negative control.

h. Ames test according to ISO 10993-1: 1997 – Stent

Six samples were tested per ISO 10993-3:1992 and ISO 10993-12: 1996. The Ames test determined the mutagenic potential of the test item. Polar and non-polar test item extracts were examined for their effects on Salmonella. To avoid false negative concentrations, 6 concentrates with 10, 20, 40, 60, 80 and 100% of the original extract were used. No mutagenic changes in the Salmonella typhimurium test strains employed occurred.

i. Chromosome Aberration according to ISO 10993-1: 1997 – Stent

100 metaphases were tested per ISO 10993-3:1992 and ISO 10993-12: 1996. Extracts of the test specimen were applied on a cell culture of Chinese hamster cells. Chromosomal alterations were examined after and without metabolic activation. 100 metaphases of each culture were examined for structural or chromosomal alterations. Compared to the control group, the test specimen extracts showed no relevant increase in chromosomal alterations.

B. Physical Testing

In vitro bench testing to support the Rithron-XR Coronary Stent System was conducted, as applicable, in accordance with the FDA Guidance for the Submission of Research and Marketing Applications for Interventional Cardiology Devices, May 1995.

STENT TESTING

The *in vitro* stent testing conducted on the stent used in the Rithron-XR Coronary Stent System is summarized below. The stent has passed all validation tests.

1) Stent Material Specification Conformance Testing

a) Material Analysis 316L VM Tube for Coronary Stent "Tenax"

The 316LVM raw material was analyzed and certified to meet the requirements of the standards ISO 5832-1: 1987, ASTM F138-92; DIN 17443: 1986.

b) Material Analysis of the a-SiC Coating: Determination of the Coating Thickness, Band Gap, Electrical Conductivity

A Menzel glass pane and a stent were coated with a-SiC. The coating thickness and the band gap were determined using a spectroscopic method. The electrical conductivity was measured in a high-vacuum. Coating Thickness was between 50 – 200nm; Band Gap: 2.00 ± 0.15 eV; Conductivity: $> 5 \text{ E-}5$ (1/(Ohm cm)) as specified.

c) Material Analysis: Inspection of the Coating Thickness of the Gold Marker

Cross-sections of nine embedded stents were prepared. Visual measurements were taken of the coating thickness under a light microscope using a magnification of 1,000X; measurements were taken of the outer and inner face of the cross-sectioned stents at 8 different struts. Mean calculation and standard deviation were determined. Thickness values met internal specifications.

d) Material Analysis: Tenax X-ray Markers - Identification of Coating Materials Used

All materials and process materials used for galvanization were identified and in accordance with the information from the product specification requirement - purchase specification for the coating material.

e) **Mechanical Properties: Determination of Tensile Strength after Heat Treatment of Gold Plated Samples**

The mechanical properties of tube sections were determined after:

- 1) Recrystallization annealing
- 2) Recrystallization annealing and soft annealing of gold plating
- 3) Recrystallization annealing, gold plating and soft-annealing of gold plating.

Five samples were tested per condition.

For all conditions, the following mechanical characteristics were achieved:

- ReH (upper yield point) ≥ 270 MPa
- Rm (tensile strength) ≥ 580 MPa
- A (maximum elongation) ≥ 35 %
- F ≥ 3 N

f) **Corrosion: Stability Against Corrosion and Degradation under Implantation Conditions**

The test was performed according to DIN 50900 – 50928. The following tests were performed to check for stability against corrosion:

- Equilibrium rest potential measurement
- Cyclical volt meter for ascertaining of the breakdown of Up and repassivation potential
- REM examination before and after voltammogram
- ICP analysis of electrolyte after aging experiments

Two samples were tested per condition. No component of the stent was diffused in the body during application. The stent was resistant to corrosion after implantation. The gold marker did not cause corrosion of the stent under implant conditions. The position of the balloon was visible in the x-ray image as specified.

2) **Stent Integrity Testing**

a) **Relative Material Proportion in Relation to Stent Diameter**

The relative material proportion in relation to stent diameter was calculated using 3D CAD. Relative material proportion of stent in total surface area did not exceed 30% as specified.

b) Stent Uniformity Testing: Change in Length of the Dilated Coronary Stent as a Function of Outer Stent Diameter

12 stents were tested using a non-contact laser device specifically designed for measurements in a water bath. The stents were expanded by means of a balloon catheter. The stent length after expansion was measured with a vernier caliper. The change in length of the stents was less than 3% at a nominal pressure of 6 bar and less than 10% up to 10 bar as specified.

c) Stent Uniformity Testing: Outer Diameter of Stent as a Function of the Inflation Pressure of the Balloon Catheter

12 stents were tested per EN 12006-3, using a non-contact laser device specifically designed for measurements in a water bath. The stents were expanded by means of a balloon catheter. The following were measured:

- Outside diameter of the stents after expansion, profile of the stent outer diameter
- Inner diameter of the stents after expansion
- Length of the stents after expansion
- Elastic recoil
- Radial strength
- Visual surface examination after expansion

The outer diameter of the stents was greater than the nominal pressure of the balloon catheter and linear to the diameter change of the balloon.

d) Stent Uniformity Testing: Determination of the Dimensional Uniformity over the Entire Dilation Area

12 stents were tested per EN 12006-3, using a non-contact laser device specifically designed for measurements in a water bath. The stents were expanded by means of a balloon catheter. Diameter change was measured using a cylindrical step gauge in increments of 0.1mm. The outer diameter of the dilated stents was determined over the entire expansion range as a function of degree of dilation. The difference between the maximum and minimum diameters was less than 0.5mm.

e) Radial Strength: Diameter Change of the Dilated Stent as a Function of External Pressure

12 stents were tested per EN 12006-3, using a non-contact laser device specifically designed for measurements in a water bath. The stent was expanded by means of a balloon catheter. Diameter change was measured using a cylindrical step gauge in increments of 0.1 mm. The stent exhibited no plastic deformation for external pressures less than 0.5 bar.

f) Fatigue Testing: Finite Element Method (FEM)

Tension analysis on a net element of the stent was conducted to determine tension distribution and deformation. Non-linear material behavior (plastic deformation) and large deformations of the component were evaluated. The

objective was to ascertain the stress on the material when crimped and when expanded > 200%, after release (elastic recoil) as well as determine residual tension in the component. There was a correlation of the deformation FEM figure with the experiment as well as no failure of the material.

g) Fatigue Testing: Life Time Simulation (10 years applied under implantation conditions)

9 samples were tested per EN 12006-3. In-vitro fatigue testing of stents equivalent to 10 years of life (at a rate of 80 bpm) was performed (420.5 million loading cycles). Accelerated testing was at 100 Hz for 49 days. The pressure chamber simulated physiological conditions by applying a dynamic loading (+/- 25 mmHg) and static pressure (50 mmHg) simultaneously. After a simulated implantation time of 10 years, the stent showed no signs of damage to the main body or coating.

h) Stent Recoil: Determination of Elastic Recoil

12 stents were tested. The guidewire was inserted into the balloon catheter and was connected to a linear actuator. The stent was moved forward in increments of 0.5 mm and its diameter was measured over the stent length at each of the specified pressure intervals. After attaining the final pressure (full stent expansion), the balloon was deflated and subsequently the stent profile was determined again. The elastic recoil was determined over the entire expansion range as a function of dilation. The difference between the inflated and deflated diameters was less than 10% of the outer stent diameter as specified.

i) Magnetic Resonance Imaging: Interaction between the Stent and Electromagnetic Fields

Measurements were taken of the magnetic moment of a stent depending on the magnetic field set-up externally (hysteresis curve) by a vibration magnetometer. The coronary stent did not display signs of magnetic moment.

j) Stent Expansion: Examination of the Surface at Maximum Expansion Levels

The stent was examined in the following cases using Reflection Electron Microscopy (REM) images:

1. Uncrimped
2. Manually and machine crimped
3. Manually and machine crimped and dilated to 4.5 mm

There was no surface peeling. Microscopically detectable cracking was allowed.

k) Stent Expansion: Determination of the Minimum Pressure for the Plastic Deformation during Dilation

12 stents were tested for radial strength. The test chamber was filled with temperature controlled water connected to a pressure controller. The balloon

in the catheter was expanded to 6 bars and then collapsed. The pressure in the test chamber was increased in increments, applying a radial force over the entire stent. A pressure-diameter characteristic curve was generated. The minimum pressure allowed for plastic deformation was 1 – 3 bars as specified.

l) Stent Expansion: REM Examination System / Inspection of the Coronary Stent and the Coating (machine crimping)

REM Examination of ten stents was performed under the following conditions:

1. Initial State (uncrimped and undilated)
2. After Machine Crimping
3. After Machine Crimping and Dilation to a Diameter of 4.0 mm

No fractures in the main body, no large microparticles released from the coating, and no peeling or separation on the edges occurred.

m) Stent Expansion: Dimensional and Visual Inspection of the Coronary Stent, coated

Nine stents were tested per EN 12006-3:1999, Section 7.1.5

1. Dimensional inspection was conducted and compared to internal design drawings (width and coating thickness were measured)
2. The stent was visually inspected, noting coating irregularities, characteristics of the edges, geometry of the coating (x-ray markers, coating depth)
3. Inspection of the Coating Thickness

All widths, coating thicknesses wall strengths, and coating depth of the gold marker were within specifications. The coating showed no irregularities.

CATHETER TESTING

The delivery catheter of the Rithron-XR Coronary Stent System is a Fast Exchange PTCA catheter. This catheter consists of a balloon and a distal and a proximal shaft. The distal shaft is manufactured of a synthetic outer and inner tube. The proximal shaft utilizes an inner steel tube and an outer synthetic tube. The sizes differ for the various balloon diameters and balloon lengths. The Fast Exchange PTCA Catheter successfully completed all validation tests required by the manufacturer's validation plan. The tests performed to validate the performance of the Fast Exchange PTCA catheter are detailed below.

1) Balloon Minimum Burst Strength, Compliance, Inflation/Deflation Performance: Deflation Period, Expansion Reaction and Burst Pressure Test

The deflation time of six catheters was measured in a water medium, using models with a distal shaft of 2.5 F and 2.7 F. The deflation time was ≤ 7 sec and ≤ 10 sec for the 2.5 F distal shaft and 2.7 F distal shaft, respectively. The compliance test was performed to determine the balloon diameter as defined by the applied pressure. Compliance was 8 – 12% as specified. (The difference between the maximum and minimum diameters was below 0.5 mm) Burst

pressure was determined by evaluating the maximum pressure at which the balloon bursts. The burst pressure was at least 18 bar for balloons ≤ 2.5 F, 16 bar for balloons > 2.5 F and ≤ 3.5 F; 14 bar > 3.5 F and ≤ 4.0 F as specified.

2) Balloon Fatigue: Balloon Durability with Remaining Deformation and Catheter Main Body Test

20 samples were tested. During the interval test, the balloon and the connection points of the entire catheter were tested for durability by applying an alternating stress. A pressure of 12 bars was applied. There was no outflow of fluid from the catheter.

3) Bond Strength: Tensile Strength of the Entire Catheter

10 samples were tested per EN ISO 10555-1:1996, Section 4.5. Measurements were taken of the tensile strength between the balloon and the hypotube for 2.5 F and 2.7 F shaft catheter. The tensile strength was greater than 5 N as specified.

4) Catheter Diameter and Balloon Profile: Dimensional and Visual Inspection of the Stent System

10 samples were tested per EN ISO 10555-1:1996, Sections 5 and 4.3 and EN ISO 10555-4:1997, Sections 4.3; 4.4.1 and 4.4.3. A dimensional inspection was conducted to verify conformance to the drawing as well as the position of the x-ray marker. There were no surface defects, sharp edges, deformation, or contamination. Inscriptions were legible and positioned according to the drawing.

5) Catheter Diameter and Balloon Profile; Stenosis Passability and Crossing Profile

10 samples were tested. The diameter of the folded, deflated balloon was measured. The stenosis crossability was defined as the maximum diameter in the area between the distal tip and proximal ring. The diameter was less than or equal to 1.25 mm as specified.

6) Tip Pull Strength: Tensile Strength of the Joint Tip on Distal Inner Tube

10 samples were tested. Tensile testing of the welding of the inner tube (Pebax 3533/HDPE) and balloon consisted of application of a pre-force 0.5 N/mm^2 with a free clamping length of 25 mm and test speed of 500 mm/min. The extraction force of the inner tube from the weld joint of the distal tip was evaluated. The allowable force was at least 3N as specified.

7) Balloon Preparation: Evaluation of the Balloon Preparation

Preparation of the balloon conducted according to the technical manual was evaluated. The following were evaluated: removal from the packaging ring, connection to an inflation syringe, removal of the folding guide, use of the hypotube clip, and the flex radius of the hypotube. When handling the catheter, the flex radius did not fall below 5 mm, in order to prevent the risk of kinking.

8) Balloon Preparation: Stability against Wiping and Adhesive Strength of the Inscription

Test was performed according to EN 45502-1: 1997, Section 13.1. The inscription for Hypotube flex-guard (anti-kink) and proximal hub were inspected. The wipe test consisted of wiping across the labeling with a cloth soaked in ethanol for 15 seconds. For the adhesive strength test, a film strip adhered to the inscription was perpendicularly ripped off. The inscription was not wiped off (ethanol resistant) or removed (adhesive strength).

9) Adhesiveness / Evenness of the Hydrophilic coating (exemplary)

Seven samples were tested. After application of a defined mechanical load, the test objects were examined to check the evenness of the hydrophilic coating and whether the coating peeled off. This was done by applying an adhesive tape to a 50 mm section of the catheters in a dry state and in a moist state and pulling the tape off after 30 seconds. The path of the wire across the adhesive tape was examined. Under a microscope, at a magnification of 20X, there were no visible signs of corrosion or peeling. The surface roughness was less than 20% of the coating thickness as specified.

10) Resistance of the Hydrophilic Coating of Catheters to Tactile Contact (exemplary)

The 30 cm long coatings of 10 catheters were handled, both in the dry and in the wet state. Following this, an optical microscope was used to inspect the catheters for damage to the coating. The coating was not significantly affected by handling during normal use.

11) Examination of UV Absorption of Aqueous Extract

14 samples were tested per ISO/CD 10993-18: January 2000 and DIN 13273. The samples to be inspected were extracted 72h at 50°C in a sodium chloride solution. The UV absorption of the extracts was ascertained with a photometer in the wave length range between 230 and 360 nm. The extracts showed UV absorption of less than 0.2 as specified.

STENT/CATHETER TESTING

The Rithron-XR Coronary Stent System consists of the following:

- the coronary stent, Tenax-XR;
- the corresponding Fast Exchange PTCA catheter on which the Tenax-XR stent is pre-mounted and mechanically and thermally fixed.

The Rithron-XR Coronary Stent System successfully completed all validation tests required by the manufacturer's validation plan. The tests performed to validate the performance of the Tenax-XR stent with the PTCA catheter are described below.

1) Maximum Pressure: Deflation Period, Expansion Reaction and Burst Pressure Test

58 samples were tested. The deflation period was measured in a water medium with models with a distal shaft of 2.5 F and 2.7 F. The deflation period was ≤ 7 seconds and ≤ 10 seconds for distal shafts of 2.5 F and 2.7 F, respectively. The compliance test determined the balloon diameter as defined by the applied pressure. Compliance was 8-12% as specified. Burst pressure was determined by evaluating the maximum pressure at which the balloon bursts. The burst pressure was 18 bar for balloons ≤ 2.5 F; 16 bar for balloons > 2.5 F and ≤ 3.5 F; 14 bar > 3.5 F and ≤ 4.0 F.

2) Stent Crimping: Determination of the Retention Forces

Eight samples were tested. A stent was crimped on the catheter. The wire diameter 0.36 mm lies in the inner tube under the stent. The catheter had a vacuum applied. The tensile strength of the stent on the catheter was determined by a tension test in which the maximum force for the movement and removal of the stent from the catheter was measured. The retention force was at least 0.7 N as specified.

3) Diameter and Profile: Dimensional and Visual Inspection of the Stent System

40 stents were tested per EN ISO 10555-1: 1996, Sections 5 and 4.3 and EN ISO 10555-4:1997, Sections 4.3, 4.4.1 and 4.4.3. A dimensional inspection was conducted to verify conformance to the drawing as well as the position of the x-ray marker. There were no surface defects, sharp edges, deformation, or contamination. Inscriptions were legible and positioned according to the drawing.

4) Diameter and Profile: Stenosis Passability and Crossing Profile

Ten samples were tested. The diameter of the folded deflated balloon was measured. The catheter in a folded state was connected to an inflation syringe containing 5 ml water and a vacuum was created by pulling back the syringe. The catheter, from the distal tip to the proximal ring, was passed through the drilled holes in the screen beginning with the largest diameter. The smallest hole through which the catheter can be passed was documented. The diameter of the folded, deflated balloon was measured. The stenosis crossability is defined as the maximal diameter in the area between the distal tip and proximal of the ring. The diameter did not exceed 1.25 mm as specified.

5) Transmission of the Torsion Motion, Torsion Strength

The transmission of the torsional motion was determined with a straight catheter and a catheter in a pushability test set-up. The catheter was rotated and the number of rotations until the distal end rotated around the guidewire was recorded. During the torsional test, the distal end was fixed and the number of rotations until the catheter breaks was recorded. There was no mechanical damage to the shaft after 50 rotations.

C. Animal Testing

A randomized blinded comparative paired study in the rabbit bi-iliac artery was conducted to evaluate the coronary stent design of the Rithron-XR Coronary Stent System with silicon carbide coating (utilized in the current Rithron-XR Coronary Stent System) and without silicon carbide coating.

The stents were systematically implanted in 13 New Zealand White rabbits (26 stents). In order to reduce inter-animal variation effects, a coated and an uncoated stent were implanted in the same rabbit. The animal study showed that the silicon carbide coated stents did not play a pivotal role in neointimal hyperplasia.

Further animal studies were conducted in the course of the biocompatibility testing with silicon carbide coated pins to investigate the biological response (see Biocompatibility Validation Testing, "Implantation Test").

IX. POTENTIAL ADVERSE EFFECTS

A. Potential Adverse Events

Possible complications include, but are not limited to:

- Death
- Acute myocardial infarction
- Cardiac dysrhythmia (ventricular fibrillation)
- Injury to the coronary artery wall, Intimal tear
- Arteriovenous fistula
- Pseudoaneurysm formation
- Hypo/hypertension
- Angina
- Dissection
- Stroke / CVA
- Myocardial ischemia
- Incomplete stent apposition
- Coronary artery spasm
- Restenosis of the dilated artery
- Total occlusion of the coronary artery
- Emergency CABG
- Infection
- Hemorrhage or hematoma
- Embolism
- Thrombosis
- Allergic reactions
- Cardiac tamponade
- Stent embolization
- Fever
- Stent migration

B. Observed Adverse Events

A total of 250 patients were enrolled in the Rithron-XR Stent System US Registry, a prospective, multi-center, consecutive, non-randomized registry study. The control group from the European TRUST Randomized Trial served as the control group.

Table 3: Reported Adverse Events

MACE	#	% (N)
TVR Free at 180 days	237	94.6% (251)
TVF Free at 180 days	232	92.6% (251)
In-Hospital Complications		
MACE (Death, MI, Emergent CABG, TLR)	4	1.6% (250)
Death	0	0.0% (250)
Q-wave MI	0	0.0% (250)
Non-Q-wave MI	4	1.6% (250)
Emergent CABG	0	0.0% (250)
Target Lesion Revascularization (TLR)	0	0.0% (250)
Target Vessel Revascularization, non TLR	0	0.0% (250)
Bleeding Complication	0	0.0% (250)
Cerebrovascular Accident (CVA)	0	0.0% (250)
Vascular Complication	3	1.2% (250)

Out-of-Hospital Complications (up to 180 days)		
MACE (Death, MI, Emergent CABG, TLR)	14	5.8% (241)
Death	3	1.2% (241)
Q-wave MI	0	0.0% (241)
Non-Q-wave MI	0	0.0% (241)
Emergent CABG	0	0.0% (241)
Target Lesion Revascularization (TLR)	1	0.4% (241)
Target Vessel Revascularization, non TLR	3	1.3% (240)
Bleeding Complication	0	0.0% (240)
Cerebrovascular Accident (CVA)	0	0.0% (240)
Vascular Complication	1	0.4% (240)
Out-of-Hospital Complications (up to 360 days)		
MACE (Death, MI, Emergent CABG, TLR)	29	12.7% (229)
Death	4	1.7% (229)
Q-wave MI	0	0.0% (229)
Non-Q-wave MI	0	0.0% (229)
Emergent CABG	0	0.0% (229)
Target Lesion Revascularization (TLR)	3	1.3% (229)
Target Vessel Revascularization, non TLR	6	2.7% (226)
Bleeding Complication	0	0.0% (226)
Cerebrovascular Accident (CVA)	0	0.0% (226)
Vascular Complication	1	0.4% (226)

MACE – Death, MI, emergent CABG, or target lesion revascularization.

Cerebrovascular Accident (CVA) – Sudden onset of vertigo, numbness, aphasia, or dysarthria due to vascular lesions of the brain such as hemorrhage, embolism, thrombosis, or rupturing aneurysm, that persisted >24 hours.

X. SUMMARY OF CLINICAL STUDIES

Purpose

The Rithron-XR Stent System US Registry (#G000119) was a prospective, multi-center, consecutive, non-randomized registry study designed to assess the safety and effectiveness of the Rithron-XR Coronary Stent System in the treatment of single *de novo* lesions in native coronary arteries.

Conclusions

The data received and analyzed from the Rithron-XR Stent System US Registry study demonstrate the safety and effectiveness of the Rithron-XR Coronary Stent System when analyzed individually and when compared to the control arm of the TRUST randomized study. The clinical data, therefore, provides assurance that the Rithron-XR Coronary Stent System is safe and effective in the treatment of single *de novo* lesions in native coronary arteries as specified in the Indications for Use.

Study Design

The Rithron-XR Stent System US Registry was a prospective, multi-center, consecutive, non-randomized registry. The study enrolled 250 patients from 17 clinical sites in the US and Canada. Enrollment in the Rithron-XR Stent System US Registry was completed in March 2002.

Patients enrolled in the study met the following criteria:

- Planned single lesion/single stent treatment in a *de novo* native coronary artery, with the target vessel reference site between 3.0 mm and 4.0 mm in diameter and a target lesion length ≤ 20 mm by visual estimates
- Target lesion in a native coronary artery with greater than or equal to 50% and less than 100% stenosis
- The patient or guardian provided written informed consent using a form that was reviewed and approved by the Human Investigational Review Board of the respective clinical site.

Patients were excluded if any of the following criteria were met:

- The patient was not an acceptable candidate for emergent coronary artery bypass surgery
- The patient had a known hypersensitivity or contraindication to aspirin, heparin, ticlopidine, clopidogrel, stainless steel or a sensitivity to contrast media, which could not be adequately pre medicated
- The patient had left ventricular ejection fraction of $< 30\%$
- The patient had a myocardial infarction within the last 48 hours, or in the investigators' opinion, the patient was currently experiencing a myocardial infarction
- The patient suffered a stroke or transient ischemic neurological attack (TIA) within the past 12 months
- The patient suffered an episode of ventricular tachycardia resulting in syncope within the last 6 months.

The control arm from the European TRUST Randomized Trial acts as the control group for the US IDE registry. The TRUST Randomized Trial was designed as a randomized, prospective, multi-center study to evaluate the safety and efficacy of the Tenax-XR silicon carbide coated stent (the same stent used in the Rithron-XR Coronary Stent System) in comparison with commercially available “bare metal stents”. The study enrolled 485 patients (238 study devices and 247 control devices) at 38 study sites in Europe and Canada. Data from the control arm of the TRUST Randomized Trial was compared and adjudicated to the endpoints, hypothesis, definitions, and procedures of the Rithron-XR Stent System US Registry. Statistical comparisons of the endpoints were made once the differences between the Rithron XR Stent System US Registry and the TRUST Randomized Trial were adjusted.

The TRUST control arm represents contemporary stenting outcomes and is statistically more flexible than a historical control (referred to as an OPC, Objective Performance Criterion). This flexibility is derived from using the entire dataset of the TRUST control arm for case-mix adjustment of unique patient characteristics of the Rithron-XR Stent System US Registry that may affect the estimates of safety and efficacy endpoints. Moreover, all stents used in the TRUST trial control arm are balloon expandable stainless steel stents that were legally marketed in the U.S., Canada, or European Union.

PRIMARY ENDPOINT

The primary endpoint for which this trial was powered was Target Vessel Failure (defined as the combined clinical endpoint of cardiac death, recurrent myocardial infarction or clinical driven repeat revascularization of the target vessel) at 6 months after the index procedure as compared to the control group from the European TRUST Randomized Trial.

SECONDARY SAFETY ENDPOINTS

The secondary safety endpoints investigated in this trial included:

Major Adverse Cardiac Events (MACE), defined as a combined clinical endpoint which includes death, Q wave or non Q wave MI, emergent bypass surgery, or repeat target lesion revascularization, 30 days and 6 months after stent placement, and in the incidence of vascular and bleeding complications

SECONDARY EFFICACY ENDPOINTS

The secondary efficacy endpoints that were investigated in this trial included rates of device success, lesion success, procedure success. Additionally, the minimal lumen diameter (in stent and in lesion) post-procedure and 180 days after the index procedure, and angiographic binary restenosis ($\geq 50\%$ diameter stenosis) 180 days after the index procedure were also included.

GENDER BIAS

Gender selection during the Rithron-XR IDE Stent Registry was completely random and based solely on inclusion / exclusion criteria. No selection bias on the basis of gender

was identified during the review. The ratio of men (75.2%) versus women (24.8%) in this trial is reflective of the underlying distribution of the disease for the given age groups, ethnic groups, and stages of disease. Additionally, there were no differences in the safety and effectiveness of the device based on gender.

Clinical Study Conclusions

STATISTICAL ADJUSTMENTS FOR BASELINE AND DEMOGRAPHIC CHARACTERISTICS

Prior to comparing the results of the Rithron-XR Stent System US Registry to the TRUST Control group on the incidence of MACE and TVF, baseline and demographic characteristics were compared between the two groups to assess comparability. The prevalence of smokers was significantly lower in Rithron-XR than in TRUST Control (19.0% vs. 30.0%; $p=0.006$). Other than this risk factor, the Rithron-XR patients generally had significantly more co-morbidities than did the TRUST Control patients. Specifically, the Rithron-XR patients were older, though not significantly, by an average of 1.2 years ($p=0.201$). Rithron-XR patients had a significantly higher prevalence of history of diabetes, history of hypertension requiring medication, history of dyslipidemia requiring medication, ($p<0.001$ for all), and history of CABG ($p=0.025$). In addition, Rithron-XR patients had significantly more major native coronaries >50% stenosed ($p=0.011$) and a significantly lower ejection fraction ($p<0.001$) than did the TRUST Control patients.

With regard to baseline lesion characteristics, the Rithron-XR patients had significantly lower mean percent diameter stenosis (67.70% versus 74.85%; $p<0.001$) and significantly larger mean minimal lumen diameter (0.92 mm vs. 0.74 mm; $p<0.001$) than did TRUST Control patients. Rithron-XR patients had significantly less prevalence of LAD as the target lesion vessel than did the TRUST Control group (38.2% vs. 49.4%; $p=0.014$).

All baseline demographic and lesion characteristics that were found to be significantly different between the two groups were included as covariates in the analysis comparing the groups using multivariate regression techniques.

PRIMARY ENDPOINT ANALYSES

Safety and effectiveness was measured as the combined clinical endpoint of target vessel failure (TVF, defined as the combined clinical endpoint of cardiac death, recurrent myocardial infarction or clinically driven repeat revascularization of the target vessel) 6 months after the index procedure. The observed TVF rate in this registry was compared to the control arm of the TRUST Randomized Trial.

The primary analysis was based on a case-mix analysis as discussed in the protocol, which yielded similar results as the direct comparison of Rithron-XR and TRUST. The focus of the case-mix analysis was to compare Rithron-XR Stent System US Registry vs. TRUST (all patients) on 180-day TVF by first determining an objective performance criterion (OPC), or an expected 180-day TVF rate for Rithron-XR patients, using TRUST data. As stated in the protocol, this was to be performed by first relating TRUST baseline demographic and lesion characteristics to 180-day TVF in TRUST by a multivariate regression model (Cox Proportional Hazards regression was used in order to account for censoring) and then plugging in baseline characteristics of Rithron-XR patients into this TRUST-based model to determine the OPC. Once an OPC was determined, a non-inferiority analysis of the true Rithron-XR 180-day TVF rate was to be statistically compared to this OPC. The resulting model led to an OPC of 7.5% at 180 days. A delta of 4% was applied for the analysis of non-inferiority.

From the Rithron-XR Stent System US Registry report, the observed 180-day TVR rate was 7.4% with a two-sided 95% CI of 4.1% to 10.7%. Since the upper bound of this two-sided 95% confidence interval is less than 11.5% (the non-inferiority limit), non-inferiority to the OPC is met.

The Kaplan-Meier estimates of freedom from TVF and freedom from MACE at 180 days were 92.5% and 93.1%, respectively for the Rithron-XR Stent System US Registry patients. The device success rate in these patients was 97.2% (244/251). The lesion success rate was 100% (251/251). The overall procedure success rate was 98.4% (246/250).

Comparisons of safety and effectiveness outcomes through 180 days between Rithron-XR Stent System US Registry patients and TRUST Control patients are presented in Table 4, Table 5, and Table 6.

Table 4: Safety and Effectiveness Results (up to 180 days)

	Rithron-XR (N=250 Pts N=251 Lesions)	TRUST (Control Group) (N=247 Patients N=247 Lesions)	Difference [95% CI]	P- value
Effectiveness Measures				
Lesion Success	100% (251/251)	100.0% (247/247)	0.0% [--, --]	N/A
Device Success	97.2% (244/251)	100.0% (247/247)	-2.8% [-4.8%, -0.8%]	0.015
Procedure Success	98.0% (245/250)	98.8% (244/247)	-0.4% [-2.5%, 1.7%]	1.000
TLR-Free at 180d	95.4%	93.8%	1.6% [-2.4%, 5.6%]	0.422
TVR-Free at 180d	94.6%	93.9%	0.8% [-3.4%, 4.9%]	0.694
TVF-Free at 180d	92.6%	93.5%	-0.8% [-5.4%, 3.7%]	0.744
MACE-Free at 180d	93.1%	93.5%	-0.4% [-4.9%, 4.1%]	0.879
Safety Measures and Other Clinical Events				
In-Hospital MACE	1.6% (4/250)	1.2% (3/247)	0.4% [-1.7%, 2.5%]	1.000
Out-of-Hospital MACE	5.8% (14/241)	5.3% (13/243)	0.5% [-3.6%, 4.5%]	0.846
MACE	7.1% (17/241)	6.6% (16/243)	0.5% [-4.0%, 5.0%]	0.859
Target Vessel Failure (TVF)	7.5% (18/241)	6.6% (16/243)	0.9% [-3.7%, 5.4%]	0.726
Bleeding Complication	0.0% (0/240)	0.0% (0/242)	0.0% [--, --]	N/A
Vascular Complication	1.7% (4/240)	0.0% (0/242)	1.7% [0.0%, 3.3%]	0.061
Cerebrovascular Accident (CVA)	0.0% (0/240)	0.0% (0/242)	0.0% [--, --]	N/A

Table 5 provides an analysis of Minimal Luminal Diameter (MLD) for both the in-stent and in-lesion target vessels. MLD is defined as the mean minimum lumen diameter derived from two orthogonal views by quantitative coronary angiography laboratory.

Table 5: Minimal Luminal Diameter Analysis

	RESULTS
Post-Procedure In-Stent Minimal Lumen Diameter (MLD, in mm) Mean \pm SD (N) Range (min,max)	2.80 \pm 0.40 (248) (1.71, 4.34)
Post-Procedure In-Lesion Minimal Lumen Diameter (MLD, in mm) Mean \pm SD (N) Range (min,max)	2.53 \pm 0.47 (249) (1.12, 4.35)
6-month Follow-up In-Stent Minimal Lumen Diameter (MLD, in mm) Mean \pm SD (N) Range (min,max)	2.02 \pm 0.66 (198) (0.00, 3.56)
6-month Follow-up In-Lesion Minimal Lumen Diameter (MLD, in mm) Mean \pm SD (N) Range (min,max)	1.90 \pm 0.62 (198) (0.00, 3.47)

Table 6 provides an analysis of in-stent binary restenosis ($\geq 50\%$ diameter stenosis) at 6 months after the index procedure for the Rithron-XR stent. If an in-stent measurement was not available, the in-lesion diameter was used in this analysis. The results of the binary restenosis are within the clinically acceptable ranges for stents.

Table 6: Binary Restenosis Analysis

	RESULTS
Post-Procedure In-Stent Percent Diameter Stenosis (% DS) Mean \pm SD (N) Range (min,max)	6.75 \pm 7.63 (248) (-14.72, 35.78)
Post-Procedure In-Lesion Percent Diameter Stenosis (% DS) Mean \pm SD (N) Range (min,max)	16.07 \pm 8.51 (249)

	RESULTS
	(4.07, 53.72)
6-month Follow-up In-Stent Percent Diameter Stenosis (% DS)	
Mean ± SD (N)	26.79 ± 19.99
Range (min,max)	(198) (-16.89, 100.00)
6-month Follow-up In-Stent Binary Restenosis	14.6% (29 / 198)

XI. CONCLUSIONS FROM CLINICAL AND NON-CLINICAL STUDIES

The multi-center clinical investigation was designed to validate the safety and effectiveness of BIOTRONIK's Rithron-XR Coronary Stent System when used in accordance with the indications for use. The Rithron-XR Coronary Stent System was extensively studied in the 250 enrolled patients. The Primary Endpoint was analysis of the Target Vessel Failure rate at 6 months compared to the control arm. The TVF rate was 7.4% in Rithron-XR Coronary Stent System vs. 6.5% in the control group with the upper limit of the two-sided 95% confidence interval of the study device minus control difference of 4.9%, well below the delta of 7.0%. The specific predefined objectives of the investigation have been met and statistically proved to meet or exceed predefined minimum results as determined by the control group selected prior to study initiation.

The pre-clinical in-vitro testing presented in this summary included testing of the individual components of the stent system. This testing was designed to demonstrate the safety and effectiveness of BIOTRONIK's Rithron-XR Coronary Stent System, including the following devices:

- the coronary stent, Tenax-XR
- the corresponding Fast Exchange PTCA catheter on which the Tenax-XR stent is pre-mounted and mechanically and thermally fixed.

This information demonstrates that the stent system is in compliance with the system performance specifications. This testing provides reasonable assurance that the Rithron-XR Coronary Stent System is safe and effective, when used as indicated in the labeling.

XII. PANEL RECOMMENDATION

In accordance with the provisions of section 515(c)(2) of the act as amended by the Safe Medical Devices Act of 1990, this PMA was not referred to the Circulatory Systems Panel, and FDA advisory committee, for review and recommendation because the information in the PMA substantially duplicates information previously reviewed by this panel.

XIII. CDRH DECISION

FDA issued an approval order on April 29, 2005. The applicant's manufacturing facility was inspected and was found to be in compliance with the Quality System Regulation (21 CFR 820).

XIV. APPROVAL SPECIFICATIONS

Directions for use: See the labeling.

Hazards to Health from Use of the Device: See Indications, Contraindications, Warnings, precautions and Adverse Events in the labeling.

Postapproval Requirements and Restrictions: See approval order.