

## **SWEET TIP<sup>®</sup> Rx Endocardial Steroid Eluting Pacing Leads**

### **SUMMARY of SAFETY and EFFECTIVENESS DATA**

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***SUMMARY of SAFETY and EFFECTIVENESS DATA***  
***SWEET TIP® Rx Endocardial Steroid Eluting Pacing Leads***

**1. GENERAL INFORMATION**

Device Generic Name: Transvenous Unipolar/Bipolar Pacing Lead

Device Trade Names: SWEET TIP® Rx  
Models 4143, 4144, 4145, 4243, 4244, 4245  
Steroid Eluting, Positive Fixation Endocardial Pacing Lead

Applicant's Name and Address: GUIDANT Corporation / Cardiac Pacemakers (CPI)  
4100 Hamline Ave. North  
St. Paul, MN 55112-5798

PMA Number: P960006

Date of Notice of Approval to Applicant: October 2, 1998

**2. INDICATIONS FOR USE**

The SWEET TIP Rx Steroid-Eluting, Positive Fixation Lead, unipolar Models 4143/4144/4145 and bipolar Models 4243/4244/4245, are intended for chronic pacing and sensing of the atrium and/or ventricle when used with a compatible pulse generator.

### 3. CONTRAINDICATIONS

- Use of this lead is contraindicated in patients with a hypersensitivity to a single dose of 1.0 mg of dexamethasone acetate.
- Use of this lead is contraindicated in patients with an allergy to mannitol.
- Use of this lead is contraindicated in patients with tricuspid valvular disease.
- Use of this lead is contraindicated in patients with mechanical tricuspid heart valves.

### 4. WARNINGS and PRECAUTIONS

*Same as final product labeling*

### 5. DEVICE DESCRIPTION

The Sweet Tip Rx steroid eluting, positive fixation, endocardial leads, unipolar Models 4143/4144/4145 and bipolar Models 4243/4244/4245, are atrial and ventricular transvenous pace/sense leads designed for use as an integral part of a pulse generator system with IS-1 ports. The lead uses a platinum-iridium porous-tip electrode with a fixation helix that provides a pacing and sensing surface by promoting fibrotic tissue ingrowth and physically stabilizing the tissue interface. The electrically active platinum-iridium helix anchors the pace/sense electrode to the endocardial surface without support of trabecular structures.

The tip electrode contains a nominal dose of 1.0 mg dexamethasone acetate contained in a silicone rubber collar.

The dissolvable mannitol capsule is designed to facilitate passage of the helix through the heart and blood vessels and to protect the helix from damage. When the electrode tip is inserted into the vein, dissolution begins. The lead body consists of a corrosion resistant multistrand conductor coil that provides a conductive pathway. The conductor is sheathed in a thin-walled tube of silicone rubber insulation, and is biocompatible and chemically stable for permanent implantation. The IS-1 connector provides a pulse generator connection.

## 6. ALTERNATIVE PRACTICES and PROCEDURES

Electrical pacing of the heart with a cardiac pulse generator and transvenous steroid eluting leads is the standard and accepted treatment modality for the indications described above in Section 2.

Other commercially available leads may meet the needs of the patients with the symptoms described above in Section 2.

## 7. MARKETING HISTORY

As of February 28, 1998, over 3200 SWEET TIP Rx Model 4143/4144/4145/ 4243/4244/4245 leads have been sold worldwide including the following countries: Japan, Brazil, Australia, Germany, United Kingdom, France, Belgium, and Canada.

## 8. ADVERSE EVENTS

Table 1 and Table 2 report the complications and observations for the Sweet Tip Rx lead.

### 8.1 OBSERVED ADVERSE EVENTS

**Table 1. SWEET TIP Rx Complications and Observations in the Atrium**

Event	Number of Patients	Percentage (95% CI)	Number of Leads	Adverse Event Rate (95% CI)
<b>Complications<sup>1</sup> (total)</b>	<b>2</b>	<b>3.0%</b> <b>[0.5, 10.5]</b>	<b>2</b>	<b>0.071</b>
Brady capture – none or loss of capture	1	1.5% [0.1, 0.81]	1	0.036
Dislodgment	1	1.5% [0.1, 0.81]	1	0.036
<b>Observations<sup>2</sup> (total)</b>	<b>4</b>	<b>6.0%</b> <b>[1.9, 14.7]</b>	<b>4</b>	<b>0.142</b>
Oversensing	1	1.5% [0.1, 0.81]	1	0.036
Placement Difficulty	1	1.5% [0.1, 0.81]	1	0.036
Threshold difficulty	2	3.0% [0.5, 10.5]	2	0.071

**Table 2. SWEET TIP Rx Complications and Observations in the Ventricle**

	# of pts (n = 67)	% of pts (95% CI)	# of leads (n = 67)	Adverse Events post-implantation
<b>Complications<sup>1</sup> (total)</b>	<b>3</b>	<b>4.5%</b> [1.2, 12.7]	<b>3</b>	<b>0.071</b>
Impedance related, pacing lead, less than 200 ohms	1	1.5% [0.1, 8.1]	1	0.036
Pericardial effusion (Chest pain)	2	3.0% [0.5, 10.5]	2	0.071
<b>Observations<sup>2</sup> (total)</b>	<b>6*</b>	<b>9.0%</b> [3.7, 18.6]	<b>7</b>	<b>0.249</b>
Intermittent loss of capture	1	1.5% [0.1, 8.1]	1	0.036
Mesh, fracture or tear suspected	1	1.5% [0.1, 8.1]	1	0.036
Placement Difficulty	4*	6.0% [1.9, 14.7]	5	0.178

1. Complications are defined as adverse events requiring invasive measures to correct (e.g., surgical intervention).
  2. Observations are defined as adverse events which are correctable by noninvasive measures (e.g., reprogramming).
- \* Patients and leads may have multiple AEs.

## 8.2 POTENTIAL ADVERSE EVENTS

Historically reported potential physical effects from implantation of a lead are contained in the Physicians Manual and are listed below in alphabetical order:

- Air embolism
- Allergic reaction
- Bleeding
- Cardiac perforation
- Chronic nerve damage
- Displacement/dislodgment
- Erosion/extrusion
- Fibrotic tissue formation
- Hematoma
- Inappropriate therapy
- Incomplete connection with pulse generator
- Infection
- Keloid formation
- Lead abrasion
- Lead fracture, insulation break
- Lead tip deformation and/or breakage
- Local tissue reaction
- Low amplitude VF signals

- Myocardial injury
- Myocardial irritability
- Pneumothorax
- Post-shock rhythm disturbances
- Random component failures
- Shunting or insulation of current during defibrillation with internal or external paddles
- Transvenous lead-related thrombosis
- Threshold elevation
- Venous occlusion
- Venous perforation

## 9. SUMMARY OF PRE-CLINICAL STUDIES

Nonclinical laboratory (bench) tests were performed to evaluate the mechanical and electrical integrity of the SWEET TIP Rx lead. These tests revealed that the leads met the requirements of the device specifications.

### 9.1. COMPONENT TESTS

SWEET TIP Rx lead subassembly tests included the electrode portion of the lead, lead body, and connector. The electrode portion is different from other CPI bradycardia leads because of the steroid carrier (drug collar) proximal to the tip electrode. Mechanical pull tests and drug collar analyses were conducted on eight (8) samples. The lead body and connector are comparable to other CPI commercially available pacing leads. All parts tested passed the test acceptance criteria.

Testing performed on full lead assemblies (6 to 18 samples) examined visual appearance, mechanical integrity, electrical integrity, and appropriate dimensions (length). Samples were tested to verify that the leads met product specifications. All samples met the test acceptance criteria.

Fatigue resistance of the conductor coils was evaluated through *in vitro* flex testing in a dry environment. Two (2) mid-sections and a distal section of each lead were evaluated to verify that they could withstand flex stress. In accordance with the test protocol and acceptance criteria, all

lead segments withstood flex cycling without failure of the conduction path. All lead segments were tested post flex cycling and met the resistance requirements of the device specification.

Connector performance testing was conducted on sixteen (16) samples. The tests included dimensional analysis, insertion and withdrawal force testing, set screw deformation testing and lead connector electrical isolation testing. All connectors passed the dimensional and functional requirements.

## **9.2. IN-VITRO (BENCH) TESTS**

Bench tests were performed to evaluate the mechanical and electrical integrity of the SWEET TIP Rx Lead. Bench tests included Design Verification Testing, Finished Device Qualification Testing, Bond/Crimp/Weld Strength Testing, Flex Fatigue Testing, IS-1 Connector Testing, Thermal/Humidity Resistance Testing, Lead Stiffness Testing, and Stylet Performance Testing. These tests revealed that the leads met the requirements of the device specifications.

### **9.2.1. Design Verification Testing**

Design Verification Testing was performed to evaluate the mechanical and electrical integrity of the SWEET TIP Rx Lead.

*Lead Visual Inspection:* Visual inspection of eight (8) finished leads for surface imperfections and proper assembly demonstrated that all leads met the requirements of the device specification. No discrepancies were noted.

*Resistance Test:* The direct current resistance was measured on eight (8) completed leads to assess continuity of the crimp and weld joints, and to measure the overall resistance of the lead. All leads met the acceptance criteria of 115 ohms maximum for the bipolar lead cathode circuit path (tip to connector pin), 55 ohms maximum for the bipolar lead anode circuit path (ring to connector ring) and 115 ohms maximum for the unipolar model cathode circuit path.

*Insulation Integrity:* Insulation dielectric strength for the sensing/pacing cathode conduction path and the sensing/pacing anode conduction path was assessed on the eight (8) leads that were subjected to the axial pull test. All assemblies passed the acceptance criterion of no current above 0.6 milliamps when 1500 volts alternating current (VAC) were applied between adjacent conductors.

*Stylet Insertion/Withdrawal Performance:* Forces required to insert and withdraw stylets into and out of fully assembled leads were measured. A 0.014" diameter tapered stylet was inserted and withdrawn from each lead while the lead was straight. All eight (8) leads passed the acceptance criterion of not requiring more than 4.0 oz. of force for insertion or withdrawal.

*Axial Pull Test:* Lead length was measured before and after axial pull testing. Eight (8) leads were suspended, each with a 1.1 lb weight attached to one end. After five minutes, the weight was removed and the lead was left to recover for one hour and measured again for length. All specimens passed the acceptance criterion of no permanent deformation in excess of 5%.

*Drug Collar Analysis:* The quantity of dexamethasone acetate (DXA) was measured in eight (8) steroid collars via high performance liquid chromatography (HPLC). This measurement was made to verify appropriate steroid quantity. The steroid collars yielded an average of 0.94 mg with a range of 0.88 mg to 0.96 mg of DXA. All samples tested within the design acceptance criteria of 0.7 to 1.3 mg of DXA.

All leads that underwent Design Verification Testing passed the test acceptance criteria.

### **9.2.2. Finished Device Qualification Testing**

The purpose of the qualification testing was to verify that fully assembled SWEET TIP Rx Leads met device specifications. Each test conducted is described below:

*Packaging Visual:* Eighteen (18) sample packages were visually inspected. Packages were required to have proper labeling, correct literature, proper assembly and no external damage. All samples passed the acceptance criteria.

*ASTM Shipping Test:* The ASTM shipping test D-4169-92 was performed six (6) final packaged leads by an outside testing facility. Following testing, the packages were required to be sealed, although slight damage to the corners and edges were acceptable. Leads were to retain their proper orientation with no damage. All samples passed the shipping test with no discrepancies noted.

*Lead Visual:* Visual inspection of eighteen (18) finished leads under 10x magnification verified that no leads showed any tears, nicks, breaks, voids, or discoloration. All leads met the visual requirements set forth in this test.

*Stylet Insertion/Withdrawal Performance:* Forces required to insert and withdraw stylets into and out of eighteen (18) fully assembled leads were measured. A 0.016" diameter tapered stylet was inserted and withdrawn from each lead while the lead was straight. All 18 leads passed the acceptance criterion of not requiring more than 4.0 oz of force for insertion or withdrawal.

*Mannitol Dissolution:* The purpose of the mannitol dissolution test was to verify the complete dissolution of the mannitol within 3-5 minutes as required by the device specification. Six (6) leads showed appropriate mannitol dissolution times with a range of 3.2 minutes to 4.2 minutes.

*Dimensional:* Six (6) leads were measured for appropriate overall length, mannitol capsule length, mannitol capsule width and drug collar width per the device specifications. All leads met these dimensional requirements.

*Axial Pull Test:* Lead length was measured before and after axial pull testing. Six (6) leads were suspended, each with a 1.1 lb weight attached to one end. After five minutes, the weight

was removed and the lead was left to recover for one hour and measured again for length. All specimens passed the acceptance criterion of no permanent deformation in excess of 5%.

*Steroid Collar:* A total of six (6) leads were analyzed by HPLC to determine the amount of dexamethasone acetate (DXA) in the steroid collars. All collars passed the test and yielded a range of 1.12 mg - 1.15 mg of DXA. These were within the design acceptance criteria of 0.7 mg to 1.3 mg of DXA

All leads that underwent Qualification Testing passed the test acceptance criteria.

### **9.2.3. Bond/Crimp/Weld Strength Testing**

Pull testing performed on lead subassemblies examined the bond/crimp/weld strengths of various joints. Samples of each subassembly type were clamped in a test fixture and pulled or pushed using a tensile tester until separation occurred.

*Outer Coil to Electrode Ring Weld:* The weld strength between the outer coil and the electrode ring was tested on eighteen (18) subassemblies. All samples passed the acceptance criterion of not less than 4.40 lbs.

*Inner Coil to Terminal Connector Weld:* The weld strength between the inner coil and the terminal connector was tested on fifteen (15) subassemblies. All samples passed the acceptance criterion of not less than 4.40 lbs.

*Outer Coil to Terminal Ring Weld:* The weld strength between the outer coil and the terminal ring was tested on eighteen (18) subassemblies. All samples passed the acceptance criterion of not less than 4.40 lbs.

*Tubing to Electrode Ring Bond:* The bond strength between the silicone rubber tubing

and the electrode ring was tested on eighteen (18) subassemblies. All samples passed the acceptance criterion of not less than 1.10 lbs.

*Inner Tubing to Terminal Connector Bond:* The bond strength between the inner silicone rubber tubing and the terminal connector was tested on eighteen (18) subassemblies. All samples passed the acceptance criterion of not less than 1.10 lbs.

*Terminal Ring to Terminal Connector Bond:* The bond strength between the terminal ring and terminal connector was tested on eighteen (18) subassemblies. All samples passed the acceptance criterion of not less than 1.10 lbs.

*Neck to Inner Tubing Bond:* The bond strength between the molded rubber neck and the silicone rubber inner tubing was tested on eighteen (18) subassemblies. All samples passed the acceptance criterion of not less than 1.10 lbs.

*Neck to Electrode Ring Bond:* The bond strength between the molded rubber neck and the electrode ring was tested on eighteen (18) subassemblies. All samples passed the acceptance criterion of not less than 1.10 lbs.

*Electrode Tip to Tubing/Steroid Collar Bond:* The bond strength between the electrode tip and the tubing/steroid collar bond tested on thirty-one (31) subassemblies. All samples passed the acceptance criterion of not less than 1.10 lbs.

*Electrode Tip to Neck/Steroid Collar Bond:* The bond strength between the molded rubber neck and the tip subassembly tested on thirty (30) subassemblies. All samples passed the acceptance criterion of not less than 1.10 lbs.

*Electrode Tip to Subassembly Crimp:* The crimp strength of the electrode tip subassembly to the inner coil tested on fifteen (15) subassemblies. All samples passed the acceptance criterion of not less than 2.20 lb.

*Electrode Screen to Electrode Platinum/Iridium Collar Bond:* The bond strength of the sintered electrode screen to the electrode collar was tested via a push test on fifteen (15) subassemblies. All samples passed the acceptance criterion of not less than 2.20 lbs.

#### **9.2.4. Flex Fatigue Testing**

Flex fatigue resistance testing consisted of mounting lead conductor coils in a flex test fixture. Mid- and distal sections of the lead were flexed to verify that they could withstand the stresses imparted by an equivalent of ten years of flexing. Twenty-four (24) conductor coils were flexed under ambient room conditions at specified radii and number of cycles. All lead conductors were required to withstand flex testing without fatigue failure. Fatigue failure was defined as a physical break in the conduction path verified by visual criteria. Resistance measurements were made using an ohmmeter. In accordance with the test acceptance criteria, all lead segments withstood flex cycling without failure of the conduction path.

#### **9.2.5. IS-1 Connector Testing**

The IS-1 connector dimensional and performance testing were conducted on sixteen (16) SWEET TIP Rx terminal connectors in accordance with the IS-1 Standard ISO 5841.3:1992.

*Dimensional Analysis:* Visual inspection demonstrated dimensional conformance of the lead connector to the IS-1 Standard.

*Terminal connector insertion and Withdrawal Force Testing:* The objective of this test was to determine the forces required to insert and withdraw the lead connector from the lead connector go-gauge. The insertion and withdrawal force measurements could not exceed 3.15 lbf, as specified in the IS-1 Standard. All units passed the test with the maximum force recorded at 2.3 lbf.

*Electrical Impedance Test:* The objective of this test was to verify that the IS-1 lead connector seal design would provide adequate sealing in the connector cavity as defined by the IS-1 Standard. The minimum electrical resistance between conductive elements intended to be

electrically insulated by the sealing rings was to be 50 Kohms following a ten day soak. All samples passed the acceptance criteria of 50 Kohms maximum.

*Set screw Deformation Test:* The objective of this test was to determine if setscrew forces could deform the lead connector to the extent that insertion and withdrawal forces become excessive. The insertion/withdrawal force measurements could not exceed 3.15 lbf as specified by the IS-1 Standard. Lead connectors were inserted into a test cavity conforming to IS-1 dimensions. Setscrews were torqued to a minimum of 22 in-oz and then retracted. The highest insertion value after test was 1.1 lbs. The highest withdrawal value was 1.7 lbs. The lead connectors passed the acceptance criteria.

*Dielectric test:* The objective of this test was to verify that the preceding setscrew deformation test did not adversely affect the electrical function of the leads. After the setscrew deformation test, each lead had  $1500 \pm 50$  VAC applied pin to ring for 5-10 seconds. The leads must withstand this voltage without allowing more than 0.6 milliamps of current flow between the conductors. All leads met the acceptance criteria.

All connectors tested passed the dimensional and functional requirements of the IS-1 Standard ISO 5841.3:1992.

#### **9.2.6. Thermal Cycling Testing**

Since devices may experience temperature and humidity fluctuations during shipping, testing was conducted to demonstrate that the SWEET TIP Rx Leads are resistant to thermal shock and humidity variations. Eight (8) packaged SWEET TIP Rx leads were subjected to ten temperature cycles fluctuating between  $-55^{\circ}\text{C}$  and  $+75^{\circ}\text{C}$ . Testing conducted post-cycling included a visual inspection, final electrical testing, mechanical testing and steroid collar analysis. There were no visual defects on the leads evaluated. Resistance measurements on the leads were within device specifications. Dielectric strength test results showed that current measured between conducting paths on the bipolar leads did not exceed 0.6 mA. Stylet insertion and withdrawal measurements were made to verify the force required to insert a stylet into the lead or withdraw a stylet from the

lead. All leads met the acceptance criteria of not exceeding an insertion or withdrawal force of 4.0 ounces. Axial pull testing demonstrated that all of the leads withstood a minimum axial tensile load of 1.1 lbf (0.50 kgf) and exhibited no permanent deformation in excess of 5% of total lead length. The amount of dexamethasone acetate in a steroid collar from each lead was determined by High Performance Liquid Chromatography (HPLC) analysis. All steroid collars met the specification requirements of 0.7 to 1.3 mg.

These test results verified the resistance of these leads to thermal stress. The SWEET TIP Rx Lead was unaffected by exposure to extreme fluctuations in environmental conditions.

#### **9.2.7. Lead Stiffness Testing**

Stiffness of the SWEET TIP Rx Lead was characterized by testing the flexural stiffness of lead/stylet assemblies. Three (3) bipolar Model 4244 leads were tested against three (3) commercially available non-steroid SWEET TIP Model 4269 leads. The two stylet wires tested with the leads were 0.014" (soft) and 0.016" (firm) inches in diameter. Test results showed that the stiffness of the SWEET TIP Rx Leads was not significantly different from the control leads.

#### **9.2.8. Stylet Performance Testing**

Stylet insertion and withdrawal testing was discussed previously in the Device Verification Testing and the Finished Device Qualification Testing.

*Stylet Torqueability/Lead Fixation:* Testing was conducted on twelve (12) fixation helices (80/20 platinum/iridium) used in SWEET TIP Rx. This was the same helix used in the commercially available SWEET TIP Lead. Evaluations included torsional force required for electrode fixation, simulation of lead implant fixation, compressive deformation of the electrode helix, axial loading of the helix and a torsional overload test. The fixation helix passed all test requirements.

#### **9.2.9. Assessment of Drug Collar Dimensional Stability**

*In-vitro* and *in-vivo* tests were conducted on steroid/silicone rubber collars to measure for dimensional changes after exposure to saline or water, or after implantation in canines. For the

*in-vitro* testing, three (3) collars prepared with 30% dexamethasone acetate were soaked in normal saline at 37 degrees C. After 468 days, the collar diameters were measured and compared against non-soaked dry retention samples. The dexamethasone steroid collars showed no detectable dimensional change when compared to the dry control.

For the *in-vivo* testing, three (3) positive fixation leads with dexamethasone acetate steroid collars were implanted in dogs. At 35 days post-implant, the leads were explanted and the steroid collar diameters were measured and compared against non-implanted, control leads. No detectable difference in collar diameter was observed between the explanted collars and the non-implanted control collars.

### **9.3. BIOCOMPATIBILITY**

Biocompatibility testing of processed components used in the SWEET TIP Rx Lead was conducted in accordance with the ISO Standard 10993-1, Biological Evaluation of Medical Devices, Part 1: Guidance on Selection of Tests. The tests conducted included Intracutaneous Toxicity, Sensitization, Cytotoxicity, Systemic Toxicity, Hemolysis, Pyrogenicity, Muscle Implant, Ames Mutagenicity, Subchronic Toxicity and Chronic Toxicity. The results of these tests showed that the leads are biocompatible and acceptable for human use.

### **9.4. IN-VIVO (ANIMAL) TESTS**

Thirty canines were implanted with a SWEET TIP Rx lead placed in the ventricle (fifteen unipolar/fifteen bipolar) and the atrium (fourteen unipolar/twelve bipolar) to verify the electrophysiologic performance of the SWEET TIP Rx Lead with respect to pacing and sensing characteristics. Ventricular data was compared to the electrical performance of the CPI commercially available Model 4160/4260 passive fix lead, which served as the non-steroid control group in the ventricle. Atrial data was compared to the commercially available SWEET TIP Model 4169/4269 positive fix lead, which served as the non-steroid control group in the atrium. Electrical data were taken at implant and at days 3, 7, 10, 14, 21, and 28 post-implant. Information recorded included capacitive coupled voltage thresholds, constant current thresholds, slew rate, R-wave and P-wave amplitudes, and sensing and pacing impedance.

The unipolar and bipolar SWEET TIP Rx Leads demonstrated acceptable handling characteristics and acceptable acute and chronic canine implant performance with respect to their pacing and sensing characteristics. The study leads met the original design objectives. The pacing thresholds were reduced over the entire post implant time compared to control leads. The data shows that peak pacing thresholds were noticeably reduced at day 7 - 21 post implant in the atrium and ventricle. Both the unipolar and bipolar atrial SWEET TIP Rx lead met the primary study objective as voltage thresholds were significantly reduced in the study lead when compared to the control leads, particularly over the maturation phase, from 7 - 14 days. Bipolar ventricular data that SWEET TIP Rx has a lower voltage threshold compared to the control leads. SWEET TIP Rx peaks at day 7 with a threshold of 1.16 Volts. In contrast, the passive fixation control lead peaks at day 21 with a threshold of 1.88 Volts.

All canines in the study were survived for 49 days before being sacrificed for histopathology data. Of these, ten dogs from the 28-day study were maintained in order to gather longer term (120 day) follow-up performance data. Pacing and sensing data were collected on these leads at 35, 42, 49, 77, 105, and 120 days post-implant. Results were compared to historical non-steroid control leads from dogs at 120 days post-implant (Model 4169 and 4269). On average, stimulation thresholds for the steroid leads were lower than those for the non-steroid group. As demonstrated in the 28-day results, other pacing parameters such as R-wave amplitudes, slew rates and sensing impedance remained unchanged as compared to the controls. These animals were sacrificed at 120 days and the histology report revealed no abnormal tissue reactions.

Necropsy and histology examination of all the animals in this study revealed typical observations and no abnormal tissue reactions.

#### **9.5. SHELF-LIFE TESTS (BENCH AND ANIMAL)**

Testing of leads subjected to accelerated aging was conducted to support the SWEET TIP Rx lead 24-month shelf life. Testing included 1) package testing to verify sterility, 2) electrical

performance testing in animals to verify steroid efficacy in threshold reduction and appropriate lead function, 3) mechanical testing to verify maintenance of lead integrity, and 4) infrared spectroscopy and high performance liquid chromatography to verify drug stability after aging.

#### *Package Testing for Sterility*

A total of 100 packages were involved in an accelerated aging study to evaluate the sterility barrier characteristics of the lead tray-in-tray packaging system. Twenty-five packages for the control group were initially sent out for ASTM shipping tests and these packages were then peel tested using an Instron tensile tester to determine the pull strength of the adhesive bond. Seventy-five lead packages were subjected to eight weeks of accelerated aging (equivalent to 48 months shelf-life). Fifty of these aged packages were then sent out for ASTM shipping tests, twenty-five of which were subsequently peel tested and 25 of which were dye penetrant tested. The remaining 25 aged packages were shipped to a contract testing site and subjected to a microbial challenge after which sterility was verified. These studies confirm that the shipping tests do not produce any visible damage to the package, the aging process does not adversely affect the peel strength, and the integrity of the microbial seal is not adversely affected by the aging process.

#### *Electrical Performance in Animals*

Testing was conducted to demonstrate that the SWEET TIP Rx lead reduces acute pacing thresholds even after longer term shelf storage prior to implantation. CPI obtained six year shelf-life data by exposing leads to accelerated aging conditions and subsequently implanting these leads in dogs. The purpose of the GLP dog study was to establish the acute electrophysiologic performance, pacing and sensing characteristics, and general implant suitability of SWEET TIP Rx Leads after aging. The SWEET TIP Rx test leads were manufactured, sterilized and packaged according to standard processing procedures. To accomplish accelerated aging, these packaged leads were subsequently exposed to 40° C (104° F) and 60% relative humidity (RH) for ten weeks. The ten-week accelerated aging is equivalent to six years of ambient real-time aging.

A total of 47 leads (16 study and 31 control) were implanted in this study. The aged SWEET TIP Rx leads were implanted in the right atrial appendage and ventricular apex of dogs, two leads per animal. Voltage thresholds, current thresholds, pacing impedances, sensing impedances, R-wave and P-wave amplitudes, and slew rate were measured at implant, 7, 14, 21 and 28 days post-implant.

The data collected was tabulated, graphed and compared with atrial data generated from the CPI positive fix non-steroid SWEET TIP lead Models 4169/4269. Ventricular data was compared to the CPI passive fix non-steroid Models 4160/4260. The study included forty-two (42) total animals (test & controls).

In summary, the aged unipolar and bipolar SWEET TIP Rx Leads demonstrated acceptable handling characteristics and acceptable acute and chronic canine implant performance with respect to their pacing and sensing characteristics. Results for the aged SWEET TIP Rx leads are consistent with those observed in the GLP study for the non-aged SWEET TIP Rx leads. Aging the SWEET TIP Rx leads to six years worth of shelf-life did not affect the electrical performance of these leads.

#### *Mechanical and Electrical Bench Tests for Lead Integrity*

The purpose of this testing was to directly measure basic lead mechanical and electrical properties through bench testing. These tests were conducted on four-year aged SWEET TIP Rx Leads. The aged leads were required to meet the same test acceptance criteria as the non-aged leads in the original design verification testing to examine whether any degradation had occurred. Results were as follows:

*Lead Visual:* Eight (8) leads were visually inspected for surface imperfections and proper assembly using a microscope. All of the aged and non-aged leads met the visual requirements of the device specification.

*Resistance Test:* Eight (8) leads were tested to measure the direct current resistance to assess continuity of the crimp and weld joints, and to measure the overall resistance of the lead. All leads, aged and non-aged, met the acceptance criteria of 115 ohms maximum for the bipolar lead cathode circuit path (Tip), 55 ohms maximum for the bipolar lead anode circuit path (anode) and 115 ohms maximum for the unipolar model cathode circuit path.

*Insulation Integrity:* Eight (8) leads were subjected to insulation dielectric strength testing to assess the sensing/pacing cathode conduction path and the sensing/pacing anode conduction path on the leads that were subjected to the axial pull test. All assemblies passed the acceptance criterion of no current above 0.6 milliamps when 1500 VAC were applied between adjacent conductors.

*Stylet Insertion/Withdrawal Performance:* A total of eight (8) unipolar and bipolar leads were tested for the force required to insert and withdraw stylets into and out of fully assembled leads. A 0.014" diameter tapered stylet was inserted and withdrawn from each lead while the lead was straight. All leads, aged and non-aged, passed the acceptance criterion of not requiring more than 4.0 oz of force for insertion or withdrawal.

*Axial Pull Test:* Eight (8) leads were subjected to an axial pull test to measure elongation where a 1.1 lb weight was applied for 5 minutes, at which time the lead length was measured. After 60 minutes, the lead length was measured again. All specimens passed the acceptance criterion of no permanent deformation in excess of 5%.

#### *Drug Stability After Accelerated Aging*

The steroid from ten (10) sterilized and acceleration-aged lead subassemblies (representing 5 years, 10 months shelf life) built with two steroid collar lots were analyzed through Fourier Transform Infrared Spectroscopy (FTIR) and compared to a reference sample of non-aged steroid collars. The analysis showed comparable spectra for the aged and non-aged dexamethasone acetate (DXA), thus supporting no discernible change in the DXA composition over the aging period.

Ten steroid collars from sterilized and acceleration-aged lead subassemblies (representing 5 years shelf life) were analyzed through High Performance Liquid Chromatography (HPLC) and compared to the non-aged steroid collars of the same lot for dexamethasone acetate content. All aged steroid collars met the specification requirements of 0.7 to 1.3 mg dexamethasone acetate, and the results were found to be statistically no different from the non-aged collars using the student's t-test.

Results from the package sterility testing, the electrical performance testing in animals, the mechanical and electrical bench testing, and the drug stability testing, demonstrated that the aged SWEET TIP Rx leads showed no signs of degradation and continued to meet original design specifications. These results support a two-year shelf life for the SWEET TIP Rx lead.

## **10. Summary of Clinical Studies**

The Sweet Tip Rx Steroid Eluting Lead was clinically evaluated to validate the safe and effective performance of the lead when used for cardiac pacing and sensing.

### **10.1. OBJECTIVES**

The objective of the Sweet Tip Rx clinical study was to evaluate the safety and effectiveness of the Sweet Tip Rx lead. Specifically, to validate that the Sweet Tip Rx lead had significantly lower pacing thresholds than the non-steroid control lead at all follow-ups out to 3 months and to validate that complication rate of the Sweet Tip Rx lead was equivalent to the control group.

### **10.2. PATIENT POPULATION**

One hundred thirty patients were implanted in the Sweet Tip Rx study. Patients were randomized at the time of implant in a 1:1 ratio between the SWEET TIP Rx lead and the non-steroid control lead. A total of 63 patients received the SWEET TIP Rx lead and 67 patients received the Control lead. A mean implant duration of the entire population was 5.4 months. A total of 15 clinical centers participated in the evaluation. The number of implants ranged from 2 leads to 40 leads per center, with the median number of lead implants of sixteen. No statistical differences were found in the baseline variables between the patients groups with respect to demographic profiles. Additional demographic information is presented in Table 3 below.

**Table 3. Patient Population Characteristics (n = 130 patients)**

Demographics	SWEET TIP Rx	Control
Number of Patients	63	67
Gender		
Male	34 (54.0%)	35 (52.2%)
Female	29 (46.0%)	32 (47.8%)
Age at Implant		
Range	27.9-85.7	43.0-91.0
Mean $\pm$ Standard Deviation	69.5 $\pm$ 12.5	72.3 $\pm$ 11.4

The predominant pacing indications for the study population were third degree heart block 32%, sinus bradycardia (atrial) 23%, brady-tachy syndrome 16%, and sinus arrest/block 11%.

#### Gender Bias Analysis

Sixty-nine males (53.1%) and sixty-one females (46.9%) were implanted in the SWEET TIP Rx clinical investigation. Patients implanted with SWEET TIP Rx leads had a mean age of 69. Patients implanted with control leads had a mean age of 72. There were no significant differences in age ( $p = 0.18$ ) or gender ( $p = 0.84$ ) between the SWEET TIP Rx and Control lead groups. All patients met indications for pacemaker implant that are consistent with accepted ACC/AHA guidelines (Dreifus, 1991).

### 10.3. RESULTS

Effectiveness of the Sweet Tip Rx lead was demonstrated by comparing the acute (0-3 months) pacing thresholds for the Sweet Tip Rx lead to the commercially available, non-steroid control lead. Results found in Table 4 and Table 5 below indicate that the Sweet Tip Rx lead was effective in reducing the typical post-implant threshold rise normally associated with non-steroid leads.

**Table 4. Mean Atrial Voltage Threshold (V) at 0.5 ms by Follow-up Period (n=130)**

Follow-up	Sweet Tip Rx		Control		p-value
	Mean (SD)	n	Mean (SD)	n	
Post Implant	0.72 (0.27)	48	0.77 (0.53)	53	0.40
2 weeks	0.80 (0.46)	47	1.25 (0.59)	57	< 0.01*
6 weeks	0.76 (0.36)	52	1.48 (1.14)	54	< 0.01*
3 months	0.74 (0.35)	44	1.29 (0.82)	51	< 0.01*

\*Statistically significantly different ( $p \leq 0.05$ )

**Table 5. Mean Ventricular Voltage Threshold (V) at 0.5 ms by Follow-up Period (n=130)**

Follow-up	Sweet Tip Rx		Control		p-value
	Mean (SD)	n	Mean (SD)	n	
Post Implant	0.56 (0.18)	44	0.59 (0.24)	54	0.47
2 weeks	0.70 (0.28)	53	1.69 (0.86)	63	< 0.01*
6 weeks	0.77 (0.28)	59	1.68 (0.74)	61	< 0.01*
3 months	0.76 (0.30)	49	1.52 (0.52)	54	< 0.01*

\*Statistically significantly different ( $p \leq 0.05$ )

In the atrium, for a pulse width of 0.5 ms, mean voltage thresholds for the Sweet Tip Rx lead were 35% lower at 2 weeks post implant, 49% lower at 6 weeks post implant, and 43% lower at 3 months post implant compared to the control lead. In the ventricle, for a pulse width of 0.5 ms, mean voltage thresholds for the Sweet Tip Rx lead were 59% lower at 2 weeks post implant, 54% lower at 6 weeks post implant, and 50% lower at 3 months post implant compared to the control lead.

Sweet Tip Rx lead impedance values in both chambers were obtained using a Pacing System Analyzer (PSA) at time of implant and telemetered pacing diagnostics for subsequent follow-up. The mean Sweet Tip Rx lead impedance remained above the nominal industry standard of 500 ohms at all follow-ups.

Sweet Tip Rx P- and R-wave amplitude measurements were obtained using telemetered pacemaker diagnostics during follow-up. The P- and R-wave amplitude measurements were used to demonstrate appropriate electrical compatibility of the Sweet Tip Rx lead with the pulse generator compared to the control lead. At each follow-up, the amplitude measured for the

Sweet Tip Rx was equivalent to the measurements obtained with the Control lead as verified by equivalence tests (Blackwelder, 1982). The results are given below in Table 6 and Table 7 .

**Table 6 . Mean P-wave Amplitudes by Follow-up Period (n=130)**

Follow-up	Sweet Tip RX			Control			Test for Equivalence	
	Mean (mV)	Std. Dev.	n	Mean (mV)	Std. Dev.	n	t-statistic	p-value
Post Implant	2.63	1.33	57	2.66	1.27	63	-1.97	0.03*
2 weeks	3.15	1.54	50	2.69	1.68	61	-3.85	< 0.01*
6 weeks	3.25	1.73	52	2.78	1.55	57	-3.99	< 0.01*
3 months	2.94	1.47	50	2.59	1.42	54	-2.97	< 0.01*

\*Statistically significant  $p \leq 0.05$ , t-test for equivalent, minimum clinical difference,  $\Delta=0.5$  mV

**Table 7. Mean R-wave Amplitudes by Follow-up Period (n=130)**

Follow-up	Sweet Tip RX			Control			Test for Equivalence	
	Mean (mV)	Std. Dev.	n	Mean (mV)	Std. Dev.	n	t-statistic	p-value
Post Implant	8.03	2.50	56	7.89	2.99	60	-3.98	< 0.01*
2 weeks	8.36	1.96	50	8.28	2.33	56	-4.03	< 0.01*
6 weeks	8.52	2.02	53	7.94	2.74	54	-4.94	< 0.01*
3 months	8.17	2.19	50	8.13	2.51	52	-3.56	< 0.01*

\*Statistically significant  $p \leq 0.05$ , t-test for equivalent, minimum clinical difference,  $\Delta=1.6$  mV

Thirty-five leads were removed from service for patients deaths, difficulty during implants, and difficulty during positioning during the clinical study. Eleven leads were returned to CPI for analysis (7 SWEET TIP Rx, 4 Control leads). All returned leads were analyzed and found to meet performance specifications. Table 8 provides a list of the Out-of-Service Leads.

**Table 8. Out-of-Service Leads**

Reason for removal from Service	SWEET TIP Rx	Control	Total
Difficulty Positioning	6	3	9
Dislodgment	1	1	2
Helix Elongation/break	5	1	6
Insulation Break	1	1	2
Patient Death	8	8	16
<b>TOTAL</b>	<b>21</b>	<b>14</b>	<b>35</b>

There was one failure of the SWEET TIP Rx lead reported in the clinical study due to an insulation break due to entrapment in the clavicle/first-rib region. This represents the only known failure and as a result the worldwide performance of the SWEET TIP Rx lead, based on data as of 7/30/97, represents a failure rate of 0.045% per month. This compares favorably to the failure rate of CPI's currently commercially available leads.

## 11. CONCLUSIONS DRAWN FROM THE STUDIES

The *in vitro* electrical and mechanical bench test results provide reasonable assurance that the SWEET TIP Rx Lead, Models 4143, 4144, 4145, 4243, 4244, 4245, meet design specifications and are reliable.

The results of the clinical studies provide reasonable assurance that the SWEET TIP Rx lead is safe and effective when it is used as indicated in the labeling.

## 12. PANEL RECOMMENDATION

Pursuant to section 515(f)(2) of the act as amended by the Safe Medical Devices Act of 1990, the PMA was not referred to the Circulatory System Devices Panel, as an FDA advisory panel, for review and recommendation because the information in the PMA substantially duplicated information previously reviewed by this panel.

### **13. FDA DECISION**

FDA issued an approval order on October 2, 1998. FDA performed an inspection and found the applicant in compliance with the Quality System Regulation (21 CFR part 820).

### **14. APPROVAL SPECIFICATION**

**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

**Post-approval Requirements and Restrictions:** See approval order