1. Summary Of Safety And Effectiveness Data

1.1 General Information

1.1.1 Device Generic Name

Totally Implanted Spinal Cord Stimulator for Pain Relief

1.1.2 Device Trade Name

Genesis Neurostimulation (IPG) System

1.1.3 Applicant's Name and Address

Advanced Neuromodulation Systems (ANS), Inc.
6501 Windcrest Drive, Suite 100
Plano, Texas 75024

1.1.4 PMA Number

P010032

1.1.5 Date of Notice of Approval to the Applicant

November 21, 2001

1.2 Indications for Use

ANS Genesis Neurostimulation (IPG) System is indicated as an aid in the management of chronic intractable pain of the trunk and/or limbs, including unilateral or bilateral pain associated with the following: failed back surgery syndrome, intractable low back and leg pain.

1.3 Device Description

1.3.1 Genesis Neurostimulation System

The Genesis Neurostimulation (IPG) System consists of the following components: Model 3608 Implanted Pulse Generator (IPG), Model 3850 Patient Programmer, Model 1232 Programming Wand, and Model 1210 Patient Magnet.

The Genesis Neurostimulation (IPG) System is intended to be used with the following ANS' legally marketed components:

- percutaneous lead models 3143, 3146, 3153, 3156, 3183 and 3186
- surgical lead models 3222, 3240, 3244 and 3280
- extension models 3382, 3383, 3341, 3342 and 3343
- ANS TS8 test stimulation system.

The IPG is connected to a lead with four or eight electrodes, either directly or with a lead extension. The electrodes contact the patient along the spinal cord. The IPG is implanted in a subcutaneous pocket, and receives radio frequency (RF) programming signals from an external Patient

Programmer. The IPG decodes the RF signals and delivers stimulation pulses to the patient via a selected combination of output electrodes. The IPG is powered by a hermetically sealed battery enclosed within a hermetically sealed titanium case and uses an integrated circuit to generate electrical stimulation.

1.3.1.1 Implantable Pulse Generator (IPG)

The Model 3608 IPG is designed to produce a monophasic capacitively coupled rectangular output pulse. The IPG is current regulated and is capable of producing output stimulus in the following ranges: amplitude 0 to 25.5 mA, pulse width 52 to 507 µs, and frequency 2 to 200 Hz. The IPG is powered by an internal 3.7 volt lithium thionyl chloride battery. The IPG has the following specifications:

Dimensions: 50mm (1.96") X 54mm (2.11") X 14mm (0.54")
Weight: 53 grams (1.8 oz.)
Volume: 29 cm^3 (1.75 in^3)

1.3.1.2 Patient Programmer and Wand

The Model 3850 IPG Patient Programmer is a battery-operated device that is connected to the Model 1232 wand, which allows for two-way communication with the IPG for the purpose of programming the stimulation output parameters and receiving feedback from the IPG. The programmer communicates with the IPG by sending RF signals from the programmer wand to the implanted IPG. The stimulation RF output signals are programmed using a combination of amplitude, frequency pulse width and electrode polarity.. The programmer allows clinicians to set the output stimulation parameters that best provide pain relief for individual patients. It also allows the user to select individual pre-set stimulation parameters within clinician prescribed ranges. The Patient Programmer has the following specifications:

Dimensions: 6.8 cm (2.7") X 10.77 cm (4.2 ") X 2.6 cm (1.0")
Weight: 128 grams (4.6 oz)
Power: 3 AAA Alkaline Batteries

1.3.1.3 Magnet

The Genesis Model 1210 magnet allows the user to turn the IPG on and off at any time.

1.4 Contraindications, Warnings, and Precautions

1.4.1 Contraindications

The system is contraindicated in patients with demand type cardiac pacemakers.

Patients that are unable to operate the system or fail to receive effective pain relief during trial stimulation should not be implanted with a SCS.

1.4.2 Warnings

Spinal cord stimulation (SCS) should not be used on patients that are poor surgical risks, those with multiple illnesses or active general infections.

Diathermy Therapy – Do not use short-wave diathermy, microwave diathermy or therapeutic ultrasound diathermy (all now referred to as diathermy) on patients implanted with a neurostimulation system. Energy from diathermy can be transferred through the implanted system and cause tissue damage at the location of the implanted electrodes, resulting in severe injury or death.

Diathermy is further prohibited because it may also damage the neurostimulation system components resulting in loss of therapy, requiring additional surgery for system implantation and replacement. Injury or damage can occur during diathermy treatment whether the neurostimulation system is turned “On” or “Off”. All patients are advised to inform their health care professional that they should not be exposed to diathermy treatment.

Cardioverter Defibrillators – Neurostimulation systems may adversely affect the programming of implanted cardioverter defibrillators.

Magnetic Resonance Imaging (MRI) – Patients with implanted neurostimulation systems should not be subjected to MRI. The electromagnetic field generated by a MRI may dislodge implanted components, damage the device electronics and induce voltage through the lead that could jolt or shock the patient.

Explosive or Flammable Gases – Do not use the patient programmer in an environment where explosive or flammable gas fumes or vapors are present. The operation of the patient programmer could cause them to ignite, causing severe burns, injury or death.

Theft Detectors and Metal Screening Devices – Certain types of antitheft devices such as those used at entrances/exits of department stores, libraries, and other public establishments, and/or airport security screening devices may interfere with the operation of the device. It is possible that patients who are implanted with non-adjacent multiple leads and/or patients that are sensitive to low stimulation thresholds may experience a momentary increase in their perceived stimulation, which has been described by some patients as uncomfortable or jolting. It is recommended that patients use caution when approaching such a device and request assistance to bypass the device. If they must proceed through the device the patient should turn off the stimulator and proceed with caution, ensuring to move through the detector quickly.

Lead Movement – Patients should be instructed to avoid bending, twisting, stretching, or lifting objects over five pounds, for six to eight weeks post-implantation. Extension of the upper torso or neck may cause lead movement and alter the stimulation field (especially with leads in the cervical area), resulting in overstimulation or ineffective stimulation.

Operation of Machinery and Equipment – Patients should not operate potentially dangerous machinery, power tools, vehicles, climb ladders, etc., when the IPG is operating. Postural changes or abrupt movement could alter the perception of stimulation intensity and cause patients to fall or

lose control of equipment or vehicles, injure others, or bring injury upon themselves.

Postural Changes – Changes in posture or abrupt movements may result in a decrease or increase in the perceived level of stimulation. Perception of higher levels of stimulation has been described by some patients as uncomfortable, painful, or jolting. Patients should be advised to turn down the amplitude or turn off the IPG before making extreme posture changes or abrupt movements such as stretching, lifting of arms over head, or exercising. If unpleasant sensations occur, the IPG should be turned off immediately.

Pediatric Use – Safety and effectiveness of spinal cord stimulation has not been established for pediatric use.

Pregnancy – Safety for use during pregnancy has not been established.

Device Components – The use of non-ANS components with this system may result in damage to the system and increased risk to the patient.

Case Damage – If the IPG case is pierced or ruptured, severe burns could result from exposure to the battery chemicals.

1.4.3 Precautions

GENERAL PRECAUTIONS

Physician Training – Implanting physicians should be experienced in the diagnosis and treatment of chronic pain syndromes and have undergone sufficient surgical and device implantation training.

Patient Selection – It is extremely important to appropriately select patients for spinal cord stimulation. Thorough psychiatric screening should be performed. Patients should not be dependent on drugs and should be able to operate the stimulator.

Infection – It is important to follow proper infection control procedures. Infections related to system implantation might require that the device be explanted.

Implantation of Two Systems – If two systems are implanted, ensure that at least 8 in. (20 cm) separates the implanted IPGs to minimize the possibility of interference during programming.

Implantation of Multiple Leads – If multiple leads are implanted, the leads should be routed to the IPG in adjacent tunnels. Nonadjacent leads have the possibility of creating a conduit for stray electromagnetic energy that could cause unwanted stimulation in the patient.

High Stimulation Outputs – Stimulation at high outputs may cause unpleasant sensations or motor disturbances, or render the patient incapable of controlling the patient programmer. If unpleasant sensations occur, the device should be turned off immediately.

Stimulation Parameters – Patients should be cautioned that stimulation parameters must be determined under the supervision of a physician and that they should not adjust stimulation parameters within prescribed programs except under direct orders from their physician.

Cellular Phones – The effect of cellular phones on spinal cord stimulators is unknown and patients should avoid placing cellular phones directly over the device.

FCC Statement – **FCC ID: PX2001** – This device (Patient Programmer) complies with part 15 of the FCC Rules. Operation is subject to the following conditions: (1) This device may cause interference, and (2) this device must accept any interference received, including interference that may cause undesirable operation.

STERILIZATION AND STORAGE

Single-Use Device – The implanted components of the ANS Genesis IPG System are intended for a single-use only. Do not resterilize or reimplant an explanted system for any reason because of risk of infection and device malfunction.

Storage Temperature – Store system components between -10°C (14°F) and 55°C (131°F) because temperatures outside this range can damage components.

Storage Humidity – Store components between 10% and 90% humidity.

HANDLING, IMPLEMENTATION, AND EXPLANTATION

Expiration Date – Do not implant a device if the use-before date has expired.

Care and Handling of Components – Use extreme care when handling system components prior to implantation. Excessive heat, excessive traction, excessive bending, excessive twisting or the use of sharp instruments may damage and cause failure of the component.

Package and Component Damage – Do not implant a device if the sterile package or components show signs of damage, the sterile seal is ruptured, or if contamination is suspected for any reason. Return to ANS for evaluation.

Exposure to Body Fluids or Saline – Exposure of the internal metal (i.e., contacts on the lead, the IPG or extension) to body fluids or saline can cause corrosion and affect stimulation. If this occurs, clean with sterile, de-ionized or distilled water and dry completely prior to lead connection and subsequent implantation.

System Testing – The operation of the system should always be tested after implantation and before the patient leaves the surgery suite to assure correct operation.

Component Disposal – Return all explanted components to ANS for safe disposal.

HOSPITAL AND MEDICAL ENVIRONMENTS

High Output Ultrasonics and Lithotripsy – The use of high output devices such as an electrohydraulic lithotriptor may cause damage to the electronic circuitry of an implanted IPG. If lithotripsy must be used, do not focus the energy near the IPG.

Ultrasonic Scanning Equipment – The use of ultrasonic scanning equipment may cause mechanical damage to an implanted neurostimulation system if used directly over the implanted device.

External Defibrillators – The safety of discharge of an external defibrillator on patients with implanted neurostimulation systems has not been established.

Therapeutic Radiation – Therapeutic radiation may damage the electronic circuitry of an implanted neurostimulation system, although no testing has been done and no definite information on radiation effects is available. Sources of therapeutic radiation include therapeutic x-rays, cobalt machines, and linear accelerators. If radiation therapy is required the area over the implanted IPG should be shielded with lead.

Electrosurgery Devices – Electrosurgery devices should not be used in close proximity to an implanted neurostimulation IPG or lead(s). Contact between an active electrode and an implanted IPG, lead or extension can cause direct stimulation of the spinal cord and cause severe injury to the patient. If use of electrocautery is necessary turn the IPG off.

HOME AND OCCUPATIONAL ENVIRONMENTS

Electromagnetic Interference (EMI) – Certain commercial electrical equipment (arc welders, induction furnaces, resistance welders), communication equipment (microwave transmitters, linear power amplifiers, high power amateur transmitters), and high voltage power lines may generate sufficient EMI to interfere with the neurostimulation system operation if approached too closely.

1.5 Alternative Practices and Procedures

Alternative practices to the use of totally implanted IPG for spinal cord stimulation to treat chronic pain of trunk and limbs include:

1. Non-surgical treatment options for chronic pain patients include:
    a. Oral medication
    b. Rehabilitative therapy
    c. Transcutaneous electrical nerve stimulation (TENS);
    d. Behavior modification
    e. Neurolysis (i.e.,Therapeutic nerve block, Cryoanalgesia RF Lesioning)
2. Surgical treatment options for chronic pain patients include:
    a. Sympathectomy- severing the nerve pathway
    b. Partially Implanted spinal cord stimulation (SCS) Systems – RF implantable spinal cord stimulators (the power source in this system is external).

c. Commercially available fully implanted SCS Systems.

1.6 Marketing History

The Genesis Neurostimulation (IPG) System for the treatment of chronic pain of trunk and limbs is currently approved for commercial distribution in Europe. The CE mark was received in 2000. No Genesis Neurostimulation (IPG) System has been withdrawn from marketing for reasons related to safety and effectiveness of the device.

1.7 Potential Adverse Effects of the Device on Health

1.7.1 Adverse Events

The implantation of a neurostimulation system involves risk. In addition to those risks commonly associated with surgery, the following risks are also associated with implantation, and/or use of a neurostimulation system:

- Undesirable changes in stimulation may occur over time. These changes in stimulation are possibly related to cellular changes in tissue around the electrodes, changes in the electrode position, loose electrical connections and/or lead failure.
- Placement of a lead in the epidural space is a surgical procedure that may expose the patient to risks of epidural hemorrhage, hematoma, infection, spinal cord compression, and/or paralysis.
- Battery failure and/or battery leakage may occur.
- Radicular chest wall stimulation.
- CSF leakage.
- Persistent pain at the electrode or IPG site.
- Seroma at the implant site.
- Lead migration, which can result in changes in stimulation and subsequent reduction in pain relief.
- Allergic or rejection response to implant materials.
- Implant migration and/or local skin erosion.
- Paralysis, weakness, clumsiness, numbness or pain below the level of implantation.
- Device Failure

1.8 Summary of Nonclinical Studies

Qualification testing was conducted to provide adequate data to support the intended use of the device system. Testing was largely based on commonly recognized test methods and standards, such as International Standards Organization (ISO), European Standards (EN), American Society and Materials (ASTM) and military standards.

1.8.1 IPG

1.8.1.1 Environmental Testing

The following testing was performed to simulate the environmental conditions the device may encounter during normal usage: operating pressure, operating temperature, ultrasonic energy, drop testing, vibration resistance and exposure to defibrillation. IPG function was verified after exposing the device to the following environmental conditions: a pressure

of 70 and 150 kPa for five minutes respectively per EN 45502-1 Section 25.1; operating temperatures of 29°C, 37°C, and 45°C while the IPG is submerged in a 0.9% saline solution; exposure of the IPG for one hour to ultrasonic energy per EN 45502-1 Section 22.1; dropping onto a stainless steel tray resting on a 2 inch thick hard maple wooden bench top from a distance of 8 inch in each of six axes; random vibration per EN 45502-1 Section 23 and exposure to a defibrillation source per EN 45502-1 Section 20.2. Testing demonstrated that the IPG operated according to specification after exposure to the above environmental conditions. Additionally the device was subjected to storage temperature extremes (-20°C to +55°C) and was tested for proper operation. Testing demonstrated that the device operates as expected and within specification over the operating temperature range of the device and after exposure to storage temperature extremes.

Environmental testing for the Genesis IPG was performed to demonstrate compliance to Environmental Storage, Shipping Sterilization, and Shelf Life Requirements. Testing was performed in accordance with the standard: ASTM D 4169 – 98 – "Standard Practice for Performance Testing of Shipping Containers and Systems". The test results met the standards requirements.

1.8.1.2 Surface Temperature Testing

Testing was performed per EN 45502-1 to ensure the surface temperature of the IPG would not be greater than 2°C above normal surrounding body temperature (37°C) when implanted and functioning under normal operation, or in any single-fault condition. The test results met the requirement.

1.8.1.3 Hermeticity

The IPG was tested for hermeticity as defined in MILSTD 883E. Results demonstrated that the welds for the battery, titanium can and feedthroughs did not leak when exposed to helium leak testing in accordance with MILSTD 883E.

1.8.1.4 Electrical Characterization

Characterization of the electrical design of the IPG was performed. The testing included variations in temperature, supply voltage, load resistance, output current, pulse width, and frequency. Characterization of the device's output along the Impedance /Current curve under loads from 300 to 2000 ohms was performed. Results verified that the IPG system performed in accordance with design specifications.

1.8.1.5 Header Adhesion Testing

Bonding of the IPG header to its titanium can and the bonding of the dip coating material to the titanium case were characterized. The test was designed to ensure the material bonds do not delaminate due to shear stresses between the materials caused by a force applied to one of the two materials. Header bonding was performed using titanium strip samples overlapped with header material strip samples. In addition to the strip samples, three sample IPG devices were assembled and tested to ensure there was no shorting path between the feed through leads and the IPG case. Results of the header bonding test exceeded the anticipated 44.2 PSI shear stress. Results of the dip-coating test demonstrate the shear

strength of the dip coating and the titanium is higher than the strength of the header bonding by a factor of 2 to 1. Results of the overall testing for the header demonstrate the method for bonding a header to the IPG can and dip coating the titanium case meet acceptance criteria and are adequate for its intended use.

1.8.2 Battery Testing

Design verification testing was divided into segments of non-destructive and destructive testing and was designed to simulate the conditions of usage, handling, shipping and storage.

Each battery sample was subjected to visual, dimensional, radiographic, electrical, and hermeticity evaluation before and after environmental testing to assure the acceptability of the battery. Other non-destructive tests included high pressure (90 psi), low pressure (equivalent to atmospheric pressure at 30,000 ft), mechanical shock and vibration, temperature cycling (-40 °C to 70 °C twice in 48 hours), high temperature storage at 60 degrees C, low temperature storage at -40 °C, and short circuit testing for four hours at 37 °C.

Destructive testing included slow dent/puncture, crush and battery capacity testing. Battery capacity testing included discharging the batteries at a constant rate to determine any changes due to battery chemistry and to determine the battery capacity. The batteries showed no evidence of loss of hermeticity or sudden electrical failure that was attributable to the design.

Non-destructive and destructive testing for the battery demonstrates that the battery is suitable and can reliably perform within the IPG.

Electrical characterization for the Elective Replacement Indicator (ERI) and the End of Service (EOS) was performed. Characterization testing included ERI voltage, minimum communication voltage and minimum operating voltage measured under minimum, nominal and maximum operating conditions as well as for 0, 100, and 200 Ohm source impedances. The device met acceptance criteria.

Testing demonstrating that the battery source impedance at which a false ERI could occur was performed. The worst case battery source impedance at which a false low battery indication occurred was 160 ohms, which is greater than the typical source impedance expected during normal operation of a lithium thionyl chloride battery of 10–50 ohms.

1.8.3 Programmer and Wand Testing

Software for the Genesis Neurostimulation (IPG) System was developed and meets the recommendations provided in the Food and Drug Administration (FDA) guidance document, entitled, “Guidance for the Content of Premarket Submissions for Software Contained in Medical Devices.” Mechanical verification of the Patient Programmer/Wand design included size and weight measurements, operational environment testing for temperature/humidity, pressure, heat generation, vibration, and drop testing. The devices were tested in accordance with EN 45502-1 and IEC 60601-1. Test results demonstrated that the device meets functional requirements when operated in a worse case fault condition.

In addition to mechanical and software verification tests, testing of the ability of the packaging to protect the device during shipping and handling was performed. The packages were tested in accordance with ASTM shipping test D4169-98. Results of the testing show that all acceptance criteria were met. Testing of the programmer's capability to reliably communicate with the IPG device from specified distances and orientations was performed. Testing demonstrated the device operates as expected and exceeds all communication distance/alignment requirements. Temperature testing for the AAA battery pack and the wand was performed. The testing demonstrated that the temperature of these devices does not rise to unsafe levels.

1.8.4 Electromagnetic Compatibility (EMC) Testing

The Genesis Neurostimulation (IPG) System has been evaluated for effects on its functioning and /or programming by external sources of interference in accordance with all applicable sections of IEC 60601-1-2 "Medical Electrical Equipment - Part 1: General Requirements for Safety: Electromagnetic Compatibility- Requirements and Tests". Testing included radiated emissions, RF immunity, magnetic immunity, and electrostatic discharge.

The test results met the requirements of the applicable sections of the standard.

1.8.5 Hazard Analysis

A risk analysis was performed using the failure modes and effects analysis (FMEA) on the complete device and the critical components. A risk assessment was performed in accordance with EN1441. The hazard analysis was incorporated into the design and development processes to ensure that critical failure mode or potentially hazard situations have been identified and adequately eliminated or mitigated. The software risk assessment was conducted as part of the system risk assessment.

All potential faults were identified in the FMEA/Failure Analysis and in the Fault/Failure Tree. The full analysis consisting of the Risk Assessment, the Software Risk Assessment, the Unacceptable Risks Analysis, and the FMEA all conclude that through the appropriate design, as well as testing, the hazards or unacceptable risks have been mitigated to an acceptable level.

1.8.6 Reliability Testing

The Genesis Neurostimulation (IPG) System was tested and analyzed for reliability. The testing included accelerated life testing that estimated the expected real time longevity performance and failure rate of the device.

Results of the reliability prediction analysis document that the failure rate for the nominal mode 0.076% per month and the failure rate for worst case mode was 0.103% per month. The failure rates are lower than the design goal of 0.15% failures per month.

1.8.7 Sterilization and Shelf Life

The devices are EtO sterilized with a sterility assurance level (SAL) of 10^{-6}. Validation for the sterilization cycle was performed in accordance with ISO

11135. Validation of the Shelf Life Study for sterile package supports a 2 year shelf life for the Genesis Neurostimulation (IPG) System.

1.8.8 Biocompatibility

All the tissue contacting raw materials for the implantable components of the Genesis Neurostimulation (IPG) System have been tested with the exception of titanium that houses the IPG. Titanium has been historically used in implanted medical devices. The titanium material used in the manufacture of the IPG is in compliance with ASTM F67, " Standard Specification for Unalloyed Titanium for Surgical Implant Applications". Biocompatibility testing was performed in compliance with ISO-10993, "Biological Evaluation of Medical Devices, Part 1: Evaluation and Testing".

The following testing has been conducted on the tissue contacting raw materials:

- Cytotoxicity (ISO elution method), Hemolysis (Extraction method)
- Systemic Toxicity (USP method, rat model), Acute Intracutaneous Reactivity (rabbit model)
- Muscle Implantation (7 day and 90 day)
- Ames Salmonella/ Mammalian Microsome Mutagenicity Assay
- Rabbit Pyrogen Study
- Delayed Contact Sensitization Study (Saline Extract)

The results of these tests showed that the raw materials used in the Genesis Neurostimulation (IPG) System are biocompatible and therefore, suitable for the intended use.

ANS performed biocompatibility tests on the finished device in accordance with ISO 10993 to determine the potential for *in vitro* cytotoxicity. The results from testing on the sterilized finished IPG product found the device to be non-toxic.

1.8.9 Packaging Qualification

Qualification testing for the packaged product consisted of environmental stress tests including extreme temperature/humidity conditions, extreme vibration, stacking and drop testing. Visual inspection and functional testing of sterile package seals, package materials and contents were performed. Functionality of each device was verified at the completion of the tests. The packaging met the test requirements

1.9 Summary of Clinical Studies

The clinical data summarized below consisted of available peer reviewed published literature for similar implantable spinal cord stimulation (SCS) systems. The Genesis Neurostimulation (IPG) System device is similar to the SCS systems reported in the published literature in intended use, target patient population, technology, device design and output characteristics. Three key studies which met specific inclusion and exclusion criteria were included in the effectiveness analysis. A total of 16 studies which met safety specific inclusion and exclusion criteria were included in the safety analysis. The effectiveness data represents a total of 116 patients that were implanted with SCS systems, while the safety data represents a total of 1253 patients that received SCS systems.

1.9.1 Objectives of Studies

Based on nonclinical studies that demonstrated the Genesis Neurostimulation (IPG) System has comparable output characteristics to the commercially available SCS systems reported in the literature, the primary objective was to provide clinical evidence of the effectiveness of the Genesis Neurostimulation (IPG) System, using literature articles, for the relief of failed back surgery syndrome, intractable low back, and limb pain.

Effectiveness was demonstrated by 1) a reduction of pain as demonstrated by a significant reduction in the Visual Analog Scale (VAS) score, 2) a 50% reduction in pain using either a 3 or 4 point scale in at least 30% of patients included in that study, 3) a significant difference in pain reduction as measured by a VAS score when compared to a control group, and/or 4) a significant reduction in pain medication.

Safety of the Genesis Neurostimulation (IPG) System was established using literature articles, for the relief of failed back surgery syndrome, intractable low back, and limb pain. This was accomplished by examining the incidence of complications of the SCS systems used in the published literature.

1.9.2 Effectiveness

Three (3) clinical literature studies were used to assess the effectiveness of the Genesis Neurostimulation (IPG) System (Ohnmeiss et al. 1996, Villavicencio et al. 2000 and Hassenbusch SJ et al. 1995). The studies included a total of 116 patients that were implanted with an SCS system. A total of approximately 3166 device months of experience was considered in the retrospective clinical evaluation. All three studies examined the effectiveness of SCS on patients with chronic pain of the trunk and/or limbs including unilateral or bilateral pain associated with the following: failed back surgery syndrome or intractable low back and leg pain. In all studies, an identified totally implantable spinal cord stimulator was used in association with a quadripolar percutaneous epidural lead or a quadripolar lead. These studies provide the same diagnostic or therapeutic intervention for the same disease/conditions and patient population as the Genesis Neurostimulation (IPG) System.

- The prospective study by Ohnmeiss et al. 1996 examined the long-term effectiveness of SCS in patients with intractable leg pain. A total of 40 patients were implanted with SCS systems and evaluated at 6 weeks, 12 months, and 24 months follow-up. Outcome measures included the VAS, pain drawings, medication use, SIP, isometric lower extremity testing, and patient questionnaires. An intent to treat analysis was also performed. After patients had SCS for 24 months, leg pain, pain when walking, standing pain, pain's effect on overall lifestyle, and the total analog scale scores were significantly improved from baseline. In this study, SCS was effective in improving intractable leg pain.

  In addition, 3 patients from this study had their stimulators repositioned due to pain at the original location. Also, 3 patients had reoperations to adjust lead position; 1 patient required 2 reoperations, 1 had the device removed due to infection and later to have a new device implanted. A diabetic patient had skin problems which required device removal; a new device was later implanted. Two patients had the device removed due to unsatisfactory pain relief.

- The prospective study by Villavicencio et al. 2000 included 41 patients with pain of various etiologies. The majority of the patients, 24 (59%), had Failed Back Surgery Syndrome (FBSS), 7 (17%) had Complex Regional Pain Syndrome) CRPS I and II, 4 (10%) had neuropathic pain syndrome, and 6 (15%) were diagnosed as stroke or other. Patients underwent an initial trial period for SCS with temporary leads. If the trial resulted in greater than 50% reduction in the patient's pain, as measured by the VAS, the patient was implanted with a SCS system. In the study, 27/41 (66%) patients had permanent implants. All patients were examined after 6 weeks. Pain measurements were assessed at 3-6 month intervals for the first year and annually thereafter. The median long-term follow-up was 34 months. A total of 24/27 (89%) patients reported greater than 50% reduction in pain. Since the majority of the patients were treated for FBSS, this article supports the use of SCS for the treatment of FBSS.

  In this study, 1 patient required a revision because of electrode fracture. One patient required removal of the system due to local infection. One patient required replacement of the IPG due to mechanical failure. Overall, 16 of 27 (59%) patients required a total of 36 repositioning procedures.

- A retrospective analysis by Hassenbusch SJ et al. 1995 included patients with chronic lower body pain, predominately neuropathic pain and pain either midline lower back and/or unilateral or bilateral leg pain treated over a 5 year period. The study was a comparison of SCS to spinal infusion of opioids. For patients with radicular pain involving one leg with or without unilateral buttock pain, a trial of SCS was recommended first. For patients with midline back pain and /or bilateral leg pain, a trial of long-term spinal infusion was recommended first. If the patients failed screening with either of these modalities, the other was then tested. If the treatment reduced the pain by 50%, the systems were internalized. A retrospective analysis of patients with unilateral leg and/or buttock pain treated initially with SCS and bilateral leg or mainly low back pain treated initially with spinal infusions of opioids was then done.

  In this study, 42 patients were screened; 26 (62%) patients received spinal stimulation; 16 (38%) received opioids via a spinal infusion pump. A total of 5 patients did not receive adequate pain relief with SCS; 3 (7%) of these patients underwent trial spinal infusions and had effective pain relief. There were of 4 (10%) patients that underwent a trial of spinal infusion of opioid but did not receive adequate pain relief; these patients were not tested with SCS. Pain severity was rated using a verbal digital pain scale: "On a scale of 0 to 10 where 0 is no pain and 10 is the worst pain you could ever imagine, what is your pain now?" (Hassenbusch SJ et al. 1995) 16/26 patients (62%) had greater than 50% pain relief with SCS. A total of 2/16 (13%) patients had greater than 50% pain relief with opioids. Mean follow-up was 2.1 $\pm$ 0.3 years. This analysis supports the use of SCS for intractable low back and leg pain.

  In the Hassenbusch study, 7 (17%) patients suffered complications after implantation of the device; 5 (12%) patients required repositioning of catheter type electrodes and 2 patients required revision of the stimulator generator.

The output of the Genesis Neurostimulation (IPG) System when used with percutaneous lead models 3143, 3146, 3153, 3156, 3183, and 3186, surgical lead models 3222, 3240, 3244 and 3280 and extension models 3382, 3383, 3341, 3342 and 3343 is within the range of the output parameters of the SCSs and associated leads reported in the retrospective literature evaluation. The Genesis

Neurostimulation (IPG) System and the associated leads may produce a greater output when compared with the devices reported in the literature. Instructions for use will ensure that energy output is adeqaute to achieve optimum effectiveness.

1.9.3 Safety

Sixteen (16) studies, as listed in the references, were identified based on the detailed inclusion/exclusion criteria to demonstrate the safety of the Genesis (IPG) Neurostimulation System. The studies included a total of 1253 patients. The following complications were seen in the retrospective clinical evaluation: lead migration, infection, hematoma, paralysis, cerebral spinal fluid (CSF) leak, over/under stimulation, pain over the implant, allergic reaction, skin erosion, lead breakage, hardware malfunction, loose connection, other biologic reaction specific to an IPG, and battery failure.

Table 2 -Summary of Risks Identified In the Literature Review

Risks	# of Patients	# of Events	% of Patients
Lead Migration	1059	144	13.6
Infection	1253	37	3.0
Epidural Hemorrhage	1253	0	0
Seroma	1253	0	0
Hematoma	1253	5	0.4
Paralysis	1253	1	0.1
CSF Leak	1253	6	0.5
Over/Under Stim	1059	27	2.6
Intermittent Stim	1059	0	0
Pain over Implant	1059	12	1.1
Allergic Reaction	1059	2	0.2
Skin Erosion	1059	1	0.1
Lead Breakage	1059	182	17.2
Hardware Malfunction	1059	32	3.0
Loose Connection	1059	10	1.0
Battery Failure	911	17	1.9
Other	1059	24	2.3

The above table depicts the number of patients, the number of events observed, and the percentage of occurrences of each event compared to the total number of patients. It should be noted that several studies include both IPG and RF Systems. FDA believes that the clinical experience reported in the literature on RF systems is relevant to determining the safety of totally implantable IPG systems.

1.10 Conclusion Drawn from the Studies

The nonclinical laboratory testing performed on the IPG, battery, programmer and programming wand demonstrate that the individual components, as well as the combined system, are reliable and that the probable benefits to health from the use of the device outweigh any probable injury or illness from such use. Further, the nonclinical laboratory studies conducted by the applicant, when considered with the clinical experience reported in the public literature on similar SCS systems, provides reasonable assurance that the Genesis Neurostimulation (IPG) System is safe and effective when used to treat chronic intractable pain of the

trunk and/or limbs, including unilateral or bilateral pain associated with failed back surgery syndrome or intractable low back and leg pain.

1.11 CDRH Decision

Prior to the ANS, Inc. submission of PMA number P010032, the Genesis Neurostimulation (IPG) System was the subject of a reclassification petition submitted by ANS, Inc. on June 16, 1999. Although the request to reclassify this device type from class III (premarket approval) to class II (special controls) was subsequently denied by the Agency, much of the data and information submitted in this PMA had been carefully evaluated by FDA during the review of the reclassification petition. In fact, on September 17, 1999, FDA consulted with the Neurological Devices Panel (the Panel) during which time the Panel reviewed many of the nonclinical studies, as well as the clinical literature, that ANS, Inc. included in PMA number P010032 as evidence of their device's safety and effectiveness. While FDA disagreed with the Panel's recommendation that the device be reclassified from class III to class II, FDA acknowledged that considerable valid scientific evidence existed in the public domain that the applicant could use to streamline the PMA process and support approval of a PMA.

Upon completion of the evaluation of the information submitted in this PMA, FDA has concluded that the Genesis Neurostimulation (IPG) System is sufficiently similar to the SCS systems reported in literature in regard to intended use, targeted patient population, technology, device design, and electrical output characteristics, that the literature can provide a basis upon which the performance of the Genesis Neurostimulation (IPG) System can be judged. FDA has also concluded that the available published clinical studies constitute valid scientific evidence for the purposes of determining safety and effectiveness. FDA has determined that this evidence, when combined with the nonclinical data included in the PMA, provides reasonable assurance of the safety and effectiveness of the Genesis Neurostimulation (IPG) System for treating chronic intractable pain of the trunk and/or limbs, including unilateral or bilateral pain associated with failed back surgery syndrome or intractable low back and leg pain. Furthermore, FDA inspections of the manufacturing facilities demonstrated that all sites involved in the manufacture of the Genesis Neurostimulation (IPG) System are in compliance with the Quality System Regulation.

In arriving at this conclusion, FDA has taken into consideration, as required under section 205 of the Food and Drug Administration Modernization Act of 1997, the least burdensome means to market, while maintaining the statutory threshold for approval of a PMA, i.e., reasonable assurance of safety and effectiveness.

1.12 Approval Specifications (To be completed by FDA)

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.

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