

SUMMARY OF SAFETY AND EFFECTIVENESS

I. GENERAL INFORMATION

Device Generic Name: Device, Fecal Incontinence, Implanted

Device Trade Name: Acticon™ Neosphincter

Applicant's Name and Address:

American Medical Systems
10700 Bren Road West
Minnetonka, MN 55343
952-930-4666

Humanitarian Device Exemption (HDE) Number: H990003

Date of Humanitarian Use Device Designation: December 22, 1998
HUD 98-0028

PMA Number: P010020

Date of Good Manufacturing Practices Inspection:

The last FDA QSP/GMP inspection was conducted October 11th-12th, 2000 at AMS facility in Minnetonka, MN. The inspection was performed in response to a 30-day Express PMAS for transferring manufacturing processes from one facility to another facility. No FDA 483 was issued as a result of this inspection.

II. INDICATIONS FOR USE

The AMS Acticon Neosphincter is an implantable device used to treat severe fecal incontinence in post-pubescent males and females who have failed, or are not candidates for, less invasive forms of restorative therapy. It is intended to mimic the natural process of bowel control and bowel movement.

III. DEVICE DESCRIPTION

The AMS Acticon Neosphincter is an implantable, fluid filled, solid silicone elastomer device. The prosthesis consists of three interconnected components an occlusive cuff, a pressure regulating balloon and a control pump with a septum. The three components are connected with kink-resistant tubing . The device simulates normal anal sphincter function by allowing the anal canal to open at the control of the patient. In both males and females, the cuff is implanted around a segment of the anal canal. The cuff encircles the anal canal and occludes it by applying pressure on the circumference of the canal. When the device is

active, the cuff remains filled. To evacuate the bowel, the patient squeezes and releases the pump mechanism, located in the labium or scrotum, several times to move fluid from the cuff to the pressure-regulating balloon implanted in the abdomen. This movement of fluid empties and deflates the cuff, resulting in release of the occlusive force around the anal canal. The patient voids and residual pressure within the balloon allows fluid to flow back into the cuff, automatically refilling the cuff within a few minutes.

IV. CONTRAINDICATIONS, WARNINGS, AND PRECAUTIONS

Contraindications

1. This device is contraindicated in patients whom the physician determines to be poor candidates for surgical procedures and/or anesthesia due to physical and mental conditions.
2. This device is contraindicated in patients with fecal incontinence complicated by an irreversibly obstructed proximal bowel segment.

Warnings

1. Patients with urinary tract or gastrointestinal infections, diabetes, spinal cord injuries, open sores, or skin infections in the region of the surgery have an increased risk of infection associated with a prosthesis. Appropriate measures should be taken to reduce the risk of infection.
2. Infection that fails to respond to antibiotic therapy may result in removal of the prosthesis. Infection followed by explantation of the device may result in scarring which may make subsequent reimplantation more difficult.
3. Erosion may be caused by infection, pressure on the tissue, improper cuff sizing, improper balloon selection, tissue damage, or component misplacement. Erosion may be caused by the introduction of medical instruments into the anal canal prior to deflating the cuff. The cuff may erode around the anal canal or the control pump may erode through the scrotal or labial skin. The pressure-regulating balloon can erode into the bladder. Failure to evaluate and promptly treat the erosion may result in a substantial worsening of the condition leading to infection and loss or scarring of tissue.
4. This device is composed of a number of materials, including solid silicone elastomers. This device does not contain silicone gel. Scientific literature has included reports of adverse events in patients with implantable silicone devices. These adverse events, as reported, indicate allergic-like reactions or autoimmune like symptoms. No causal relationship has been established between these events and solid silicone elastomer.
5. Surgical, physical, psychological, or mechanical complications, if they occur, may necessitate revision or removal of the prosthesis. Removal of the device without timely reimplantation of a new device may complicate subsequent reimplantation.

The timing of reimplantation should be determined by the treating physician based on the patient's medical condition and history.

6. Receptive anal intercourse may damage the occlusive cuff and is not recommend for patients implanted with this prosthesis.

Precautions

Patient Related

1. Patient selection requires thorough preoperative consultation and evaluation by the physician.
2. Patients should be counseled in order to have a realistic expectation of the physical, psychological, and functional outcome of the implantation of an Acticon Neosphincter. Although the prosthesis is designed to restore bowel control, some patients continue to have a degree of incontinence after this procedure.
3. Patients may experience pain when the device is activated in the postoperative period and during periods of initial use. Cases have been reported of chronic pain associated with device implantation. Pain with a severity or duration beyond that which is expected can be symptomatic of medical complications or mechanical device malfunction, which may lead to medical or surgical intervention. Patients should be counseled on expected postoperative course of pain including severity and duration.
4. Tissue fibrosis, previous surgery, or radiation therapy in the area of the implant may preclude implantation of the cuff at the bladder neck of bulbous urethra.
5. Acute pathological conditions of the bowel, e.g. diarrhea or constipation, can interfere with proper functioning of the device and may require the use of external pads or manipulations to assist defecation.
6. Any progressively degenerative disease, e.g. multiple sclerosis, may limit the future usefulness of the implanted prosthesis as a treatment of the patient's fecal incontinence.
7. Adequate manual dexterity, strength, and motivation are required for proper use of the device.
8. Trauma or injury to the pelvic, perineal or abdominal areas, such as impact injuries associated with sports, can result in damage to the implanted device and/or surrounding tissues. This damage may result in the malfunction of the device and may necessitate surgical correction including replacement of the prosthesis. The physician should advise patients of these possibilities and warn them to avoid trauma to these areas.
9. If radiopaque solution is used to fill the device, assure that the patient is not allergic to radiopaque solution.

10. Vaginal delivery of children may interfere with future proper functioning of the occlusive cuff.

Surgery Related

1. Improper cuff sizing, improper balloon selection, or other causes may result in tissue erosion, migration of components, or continued incontinence.
2. Component migration can occur if the cuff is sized improperly, if the pump or balloon are not positioned correctly, or if the tubing lengths are incorrect. Migration can result in pain, complications, device malfunction and surgical revision.
3. Unsuccessful outcomes may result from the implantation of this device. These may be due to improper surgical technique, anatomical misplacement of components, improper sizing and filling of components, failure of the device to function as intended, psychological problems, and/or simply be associated with patient dissatisfaction. Unsuccessful outcomes may necessitate removal or replacement of the device.
4. Although reinforced tubing has been designed to be more kink resistant, tubing kinks may still result from tailoring the connecting tubing to an improper length during the implant procedure.

Device Related

1. As with any biomedical prosthesis this device is subject to wear and eventual failure over time. It is not feasible to predict how long the implanted prosthesis will function in a particular patient.
2. If the deactivation valve is closed when the cuff is inflated, fluid cannot transfer from the cuff to the balloon and sustained fecal obstruction may occur.
 - a) In the event of large pressures within the bowel, automatic pressure relief that normally occurs with the device would be prevented. The fecal obstruction can be relieved by cycling the device.
 - b) Cycling the device may be difficult if deactivation occurs when the pump bulb is deflated. If unable to cycle the prosthesis, squeezing the sides adjacent to the deactivation button will allow fluid to fill the pump bulb and then the pump can be cycled normally.

- c) Release of the deactivation valve may require greater pressure than normally used to cycle the device.
- 3. Use caution when passing any instrument through the anal canal. For certain procedures, e.g., anal ultrasound or colonoscopy, first deflate the cuff then deactivate the device prior to passing any instrument through the anal canal.
- 4. System pressures may change over time.

V. ADVERSE EFFECTS OF THE DEVICE ON HEALTH

Adverse effects data have been collected during two clinical studies. Adverse events reported in the first clinical study conducted in the United States (Investigational Device Exemption No. G880037) are presented in Table 1.

Table 1: Adverse Events Reported for G880037 (n=21)

Adverse Events	# of Patients
Infection	5
Mechanical	5*
Pain	2
* Two patients experienced multiple mechanical complications	

Adverse events reported for the second clinical study conducted in the United States (Investigational Device Exemption No. G960116) are presented in Table 2.

Table 2: Adverse Events Reported for G960116 (n=115)

Adverse Events	# of Events ¹
Pain/Discomfort	44
Infection	41
Constipation	33
Fecal Incontinence	29
Erosion	28
Impaction	27
Mechanical Malfunction	15
Surgical Injury	15
Difficult Evacuation	13
Wound Problems	13
Edema	10
Erythema	10
Wound Separation	10
Device Migration	9
Rectal Bleeding	9
Anorectal Condition	8
Device Function	7
Diarrhea	7
Fever	7
Wound Drainage	7
Device Fit	6
Gastrointestinal Condition	6
Ecchymosis	4
Malposition	4
Device Operation Difficulty	3
Abscess	2
Difficult Activation	2
Hematoma	2
Intraoperative Bleeding	2
Seroma	1
Urinary Tract Infection	1
Other	20

¹ Patients may have had more than one event of the same type

Mechanical malfunctions include types of problems that are directly related to the device not functioning as intended. Examples of this type of adverse event include the following:

- Fluid loss can result in the cuff only partially filling or not filling at all if sufficient fluid is lost. Fluid loss has been associated with damage to one of the silicone components of the system, damage to the system such as perforation of the device by a surgical instrument, and wear to the cuff.
- Pump failure can result in the device not functioning. Balloon problems range from leaks to decrease in the pressure of the balloon which may result in incontinence.
- Cuff failure can result in the device not functioning. Cuff problems are primarily related to leaks caused by wear, fatigue, or intra-operative damage.

Patient/implant related failure includes the types of events that can be the result of the implantation surgery, or the patient's response to the presence of the device. The types of events that have been reported with use of the Acticon prosthesis include the following:

- Erosion and migration involve the movement of the prosthesis within the body or from the inside to the outside of the body.
- Implantation of the device involves the risk of infection. Infection has been the most serious of the adverse events reported to date.
- Pain is an expected occurrence; however, some patients experience an unacceptable amount of pain. Pain may be caused by the misplacement or missizing of the components, undiagnosed problems such as infection, erosion, migration, or factors not related to the implant.
- Patient dissatisfaction may be related to unrealistic expectation of the results, or to patient difficulty operating the device.
- Fibrous capsule formation of a silicone prosthesis is a normal physiologic response. This capsule is usually inconsequential to the functioning of the device. It is thought that the presence of the capsule will frequently support the prosthesis allowing it to function without migration or displacement.
- Iatrogenic complications result from poor surgical technique or lack of adequate care during surgery. These may include mechanical failure, perforation, or functional difficulties.
- Other complications associated with the use of the Acticon Neosphincter include evacuation difficulties such as impaction or incontinence.

Each of these adverse events, except for fibrous capsule formation has necessitated removal of the device in some patients, with or without reimplantation.

VI. ALTERNATIVE PRACTICES AND TREATMENTS

Fecal incontinence is the involuntary loss of flatus, liquid, or solid stool and presents in a range of severity. Severe fecal incontinence is a distressing and socially isolating condition that can have a devastating effect on a person's working life, social life, and emotional well-being. Individuals who suffer from the condition often alter their lifestyle to minimize the likelihood of bowel accidents in public places. Over time, this can result in progressive social isolation and work incapacity. The vast majority of cases are mild to moderate and can be managed or resolved with medical interventions such as pharmacological therapy, biofeedback training and dietary management. For some patients with a sphincter defect, surgical procedures such as sphincteroplasty, postanal repair, or total pelvic floor repair may be attempted.

For a limited number of individuals with severe fecal incontinence (the involuntary loss of solid stool or liquid stool on a weekly or more frequent basis) who have failed medical interventions and/or are not candidates for sphincter repair, the choices are limited.

An alternative surgical procedure, adynamic muscle transposition, may be used in patients where the anal sphincter is either denervated or anatomically absent. It involves the transposition of a muscle, usually the gracilis or gluteus maximus, to create a barrier to the passage of stool. The procedure, first introduced in the 1950s, has had limited success and is rarely used in current practice.

More recently, sacral nerve stimulation has been investigated to treat fecal incontinence in patients who demonstrate a functional deficit of the internal anal sphincter or the external anal sphincter muscles without any apparent structural defects. Electrodes are implanted in the sacral nerve roots at the sacral foramen (S2 or S3). The nerves are stimulated using a pulse generator, similar to one currently marketed for treating urinary incontinence. Preliminary results from studies with small numbers of patients appear promising. Anal resting pressures were increased and urgency decreased. Overall, continence was improved in patients implanted with the device. The treatment is still being investigated and the devices are not legally marketed for this use in the United States.

Finally, some patients are faced with a choice of permanent ostomy, a surgically created passage to allow bodily wastes to be expelled from the body through the abdominal wall, or life-long management of incontinence with pads or diapers. Neither of these alternatives provides the kind of normalcy with respect to bowel function and fecal continence that patients desire.

No devices comparable to the AMS Acticon Neosphincter have received marketing clearance or marketing approval for commercialization in the United States.

VII. MARKETING HISTORY

Foreign Market Introduction

A CE-mark for the Acticon was received in May of 1996. Limited marketing of the Acticon Neosphincter in select European countries and Australia began in July of 1996. During this launch, 62 patients were implanted with the Acticon prosthesis. Based on these results, in 1998 the Acticon was introduced in other markets. The Acticon Neosphincter currently is available in Australia, Brazil, Canada, China, Europe, Taiwan and many other countries. The Acticon Neosphincter has not been withdrawn from marketing for any reason related to lack of safety or effectiveness.

Domestic Market Introduction

Humanitarian Device Exemption approval was received in September of 1999. In accordance with HDE approval orders, including IRB approval, marketing of the Acticon Neosphincter at select centers in the United States began in October 1999.

VIII. SUMMARY OF PRECLINICAL TESTING

MECHANICAL TESTING

A risk analysis, including failure modes and effects analysis (FMEA), was used to identify safety and reliability attributes considered applicable to the Acticon Neosphincter or its components. Bench testing was performed to characterize the device attributes and functions. All bench testing was performed on finished, sterilized devices or components.

Performance Characteristic Testing

Performance characteristics of the device were evaluated by testing samples for the following performance characteristics:

- Squeeze force versus fluid displacement
- Fluid displacement per pump stroke
- Prevention of spontaneous deflation
- Pump output pressure produced by pump squeeze force
- Pump bulb refill time
- Pump deactivation force and activation pressure
- Pump valve leakage and maximum back pressure
- Tubing kink resistance
- Balloon capacity
- Cuff expansion and maximum pressure

Performance testing demonstrated acceptable prosthesis or component performance.

Reliability Testing

Device reliability attributes were evaluated in bench testing by subjecting samples to representative *in-vivo* conditions, where possible, and to a number of uses likely to exceed the number of uses over the estimated life of the device, for the following reliability attributes:

- Cuff deflation/inflation cycling
- Pump cycling
- Balloon inflation/deflation cycling
- Pump cycling and septum access
- Cuff fold wear resistance to life cycling
- Prosthesis adhesive bond reliability

Reliability testing demonstrated acceptable prosthesis or component performance.

Component Strength Testing

Device strength attributes were evaluated by subjecting test samples to representative *in vivo* conditions, where possible, and to a number of uses likely to exceed the number of uses over the estimated life of the prosthesis for the following strength attributes:

- Cuff maximum pressure and expansion
- Cuff leakage or unbuckling under pressure
- Connector strength

- Tubing burst/leak pressure
- Connector/component leak pressure
- Subassembly bond strength
- Prosthesis material strength

Component strength testing demonstrated acceptable prosthesis or component performance.

MATERIALS SAFETY AND TOXICOLOGY

The safety of materials used in AMS Acticon Neosphincter was established through a testing program which included chemical analysis of exhaustive extracts, infrared spectral analysis of surfaces having direct tissue contact, and a series of *in-vitro* and *in-vivo* biological studies. All biological nonclinical laboratory safety studies were conducted in compliance with FDA's Good Laboratory Practice Regulations (21 CFR Part 58).

Chemical Analysis of Extractives

Testing was conducted on the Acticon and the AMS Sphincter 800 Urinary Prosthesis (AUS) and AMS Dynaflex inflatable penile prosthesis because these devices use identical materials. The design of the AUS is almost identical to the Acticon Neosphincter. Extractives analysis identified compounds which may leach from the Acticon Neosphincter and quantified the potential total exposure to each extractive. These include polydimethylsiloxanes of varying molecular weights (296->150,000 daltons), water soluble silica (silicic acid), formaldehyde, and traces of platinum and tin catalysts. For each extractable compound known to produce some toxic or irritant effects(s) the total potential exposure from an Acticon Neosphincter was shown to be well below the exposures required to produce any observed effect based on published toxicity data for each extractive. Exposure to leachable components at the concentrations present in Acticon Neosphincter does not constitute a significant health risk for patients.

Infrared Spectra Surface Analysis

To document the principal chemistry of the outer surface of each device component having direct tissue contact, infrared spectra were collected using attenuated total reflectance Fourier transform infrared spectroscopy (ATR-FTIR). Test results showed only polydimethyl siloxane has direct tissue contact. No other materials or unusual spectral features were detected.

Biological Safety Tests

Finished products were subject to the complete spectrum of biological tests cited in the *Guidance for Manufacturers of Silicone Devices Affected by Withdrawal of Dow Corning Silastic Materials (July 6, 1993)*. This included tests for *in vitro* cytotoxicity, acute systemic toxicity, intracutaneous irritation, sensitization, direct tissue contact (intramuscular implantation), and three genetic toxicity tests.

Studies were also conducted in which substantial amounts of ground silicone elastomer were implanted subcutaneously in Sprague Dawley rats. These studies examined the fate of the implanted material and its effect on host systems. The program included an acute

pharmacokinetic study, tests for effects on the immunological system (immunomodulation and adjuvanticity), and studies for sub-chronic and chronic toxicity, reproductive effects, and oncogenicity. Test results indicate that the materials used in the Acticon Neosphincter do not produce localized or systemic toxic effects when implanted.

Shelf Life Testing

Shelf life was determined to be equivalent to the shelf life of AMS' inflatable penile prostheses products (700, Ultrex, CX, Ambicor) and the AMS Sphincter 800. The three product lines use very similar materials for device construction and use the same materials for packaging. An accelerated aging study was performed on the package configuration and showed the packaging would provide physical protection and a sterile barrier for a 5-year shelf life with a 2-year safety margin. The Acticon Neosphincter is labeled with a "use before date" which is 5 years from the date of manufacture.

IX. SUMMARY OF CLINICAL STUDIES

Two clinical studies were conducted in the United States on this device. The first study (IDE No. G880037) began in August 1988 and was closed in April of 1995. In the second study (IDE No. G960116) patient enrollment began in February 1997 and was closed in December 1999. In addition, the Acticon Neosphincter is currently available in Australia, Brazil, Canada, China, Europe, Taiwan and many other countries.

G880037 was a multi-center, prospective study of the Artificial Bowel Sphincter (ABS), an earlier version of the Acticon Neosphincter. Patients selected for the study demonstrated severe fecal incontinence unresponsive or unlikely to respond to accepted medical or surgical alternatives. Patients with ongoing inflammatory bowel disease or active pelvic sepsis were excluded.

A total of 21 patients were enrolled at 3 sites. Patient enrolled included 10 males and 11 females ranging from 15 to 68 years of age. The reported caused of incontinence are provided in Table 3.

Table 3: Etiology of Incontinence

Etiology of Incontinence	Total Number	Percent
Major Trauma	6	28.6
Birthing Injury	5	23.8
Imperforate Anus	3	14.2
Spinal Cord Tumor	2	9.5
Laminectomies	2	9.5
Spina Bifida	1	4.8
Myasthenia Gravis	1	4.8
Prolapse Intervertebral Disc	1	4.8
Total Patients	21	100

Seven (7) patients had a stoma at the time of enrollment and 5 patients had a temporary stoma created at the time of device implantation. It was believed a temporary stoma would decrease the risk of infection. Patients were followed for periods ranging from 6 to 76

months. Functional outcomes were determined based on water perfusion and manometry testing and continence diaries. The investigators reported that 65% of patients achieved complete continence to liquid and solid stool. An additional 18% of patients achieved continence to solid stool but experienced occasional leakage of liquid stool.

Complications included infection (5 patients), mechanical malfunctions (5 patients, with 2 patients having multiple problems), and pain (2 patients). Of the 5 patients who developed an infection, 3 underwent permanent explantation of the device, 1 had an explantation with replacement of the device, and in 1 patient the infection resolved with antibiotics. All 5 patients who experienced mechanical problems underwent revision procedures. Three (3) of these patients achieved an acceptable level of continence but the other 2 underwent device removal. The 2 patients with pain had resolution of their pain.

Of the 12 patients who experienced complications during the study, 7 were successfully treated but 5 patients (24%) required permanent device removal. For the remaining 16 patients, 13 (82%) demonstrated either improvement or resolution of their fecal incontinence.

Study Conclusion (G880037)

Based on the promising results of this study the sponsor conducted additional product development, which included modifications to the device, in preparation for an expanded and modified clinical trial. Differences between the first study device and the modified device, the Acticon Neosphincter, are (1) a reinforced longer cuff, (2) a larger (40cc) pressure regulating balloon used in the Acticon, and (3) a septum port added to the control pump for the Acticon.

G960116 was a multi-center, prospective, non-randomized, clinical trial which was on-going at the time of the HDE approval. Each patient was his or her own control utilizing defined primary and secondary endpoints. Post-pubescent patients who had severe fecal incontinence without regard to etiology are considered for implantation of the device. To enroll in the study, a patient must have had fecal incontinence for at least six months, have tried at least one non-surgical treatment prior to enrollment, and have an Incontinence Score of ≥ 88 according to the Fecal Incontinence Scoring System. In addition, patients with ongoing inflammatory bowel disease or active pelvic sepsis are excluded.

A total of 115 patients were enrolled in the study. One hundred twelve (112) patients were implanted with the device. In the United States and Canada, 104 patients were enrolled in the study and 101 patients were implanted with the device at 16 sites. The causes of the patients' incontinence are shown in Table 4.

Table 4: Etiology of Incontinence

Etiology of Incontinence	Total Number	Percent
Obstetric Trauma	34	29.57
Neurological	23	20.00
Congenital Abnormality	23	20.00
Anorectal Trauma	21	18.26
Other ¹	14	12.17
Total Patients	115	100

¹Other includes: rectal prolapse (3), idiopathic (3), radiation (1), surgical (3), scleroderma (1), traumatic defecation (1), musculoskeletal (1), and anal canal squamous cell carcinoma (1)

Safety

Adverse Events

No life-threatening conditions or unanticipated adverse device effects were reported in the study. No unanticipated adverse device effects were reported in the study.

A total of 456 adverse events were reported during the study. Three hundred ninety-five (395) device-related or potentially device-related events occurred during the study. Sixty-one (61) non device-related adverse events occurred during the study. Surgical interventions were required for 142 device-related events, including 81 revisions in 56 patients. More than one type of intervention may have been used for each event and patients may have had multiple events treated with the same intervention.

Table 5: Treatment for Adverse Events

Adverse Event Type	Number of Patients ¹	Number of Events ²	Methods of Intervention ³			
			None Required	Medication	Surgery	Other ⁴
Pain/Discomfort	37	44	15	15	8	14
Infection	36	41	0	16	33	3
Erosion	24	28	0	3	27	2
Fecal incontinence	22	29	2	3	13	11
Constipation	22	33	2	26	2	7
Impaction	21	27	2	7	3	17
Other	17	20	7	3	1	9
Surgical injury	15	15	2	0	11	1
Wound problems	12	13	7	2	1	3
Mechanical malfunction	12	15	1	0	13	1
Wound separation	10	10	4	4	1	2
Difficult evacuation	10	13	1	5	1	8
Rectal bleeding	9	9	5	1	2	1
Edema	9	10	3	3	4	2
Erythema	9	10	3	6	1	2
Fever	7	7	0	6	1	0
Anorectal condition	7	8	1	0	1	6
Device migration	7	9	1	0	7	0
Device Fit	6	6	2	1	3	1
Device Function	6	7	0	0	0	7
Wound drainage	6	7	1	2	1	3
Gastrointestinal condition	5	6	1	1	2	2
Diarrhea	5	7	2	1	0	4
Ecchymosis	4	4	3	0	0	1
Malposition	4	4	1	0	3	0
Device operation difficulty	3	3	0	0	0	3
Abscess	2	2	0	0	2	1
Difficult activation	2	2	0	0	0	2
Hematoma	2	2	1	0	0	1
Intraoperative bleeding	2	2	0	0	1	2
Seroma	1	1	0	0	0	1
Urinary tract infection	1	1	0	1	0	0
Totals		395	67	106	142	117

¹Patients may have had more than one type of event. ²Patients may have had more than one event of the same type.

³There may have been more than one type of intervention for each event, and patients may have multiple events that are treated with the same intervention.

⁴Other interventions reported were: fluid added to pump via septum (15), enemas (14), deactivation of device (13), patient education (11), hospitalization (9), disimpaction (5), observation (5), managed by HMO (4), offered a colostomy (4), wound care (3), time (3), catheterization (2), clear liquids (2), diagnostic x-rays (2), manipulation of pump (2), stopped antibiotics (2), suture (2), TPN (2), diagnostic testing (2), and one intervention each of aspiration, bowel regimen, change medication regimen, chemotherapy, consultation with other specialist, cuff sizer removed, diet change, digital vaginal pressure to assist evacuation, fiber, flexible sigmoidoscopy, ice packs, local therapy, nebulizer, offered a revision surgery, reassured, sitz baths, wound packing, and wound draining. There were 18 reports of an unspecified "other" intervention.

Out of 395 device related adverse events, 81 revisions were performed in 56 patients. Multiple reasons may have been reported for a single revision. A single patient may have experienced more than one revision. Table 6 lists reasons for revisions and their frequency.

Table 6: Reasons for Device Revisions

Reason for revision	Frequency	Patients (n=56)
Infection	30	28
Erosion	27	24
Malfunction	13	11
Recurring Incontinence	11	10
Migration	7	6
Pain	6	6
Patient Dissatisfaction	4	4
Malposition	3	3
Other	13	13

Infection and erosion were the most frequently reported reasons for revisions. In 13 patients, infection and erosion were both listed as reasons for revision. Twenty-eight (28) patients experienced 30 revisions due to infection. The rate of revisions due to infection was 25.0%. Cuff erosions occurred in 22 patients (rectum 12; perineum 10). Pump erosions occurred in four (4) patients and one (1) patient had a tubing erosion.

Peri-operative antibiotic prophylaxis is included in the protocol and has been used throughout the study. Initially, AMS did not offer any recommendations regarding specific antibiotic regimens. In 1999, AMS retained an infection control specialist to study the procedure and to make recommendations of antibiotic regimens for use with the Acticon. In September 1999, these recommendations were provided to all Investigators and all physicians implanting under the Humanitarian Device Exemption. Along with recommending specific antibiotics and doses, the specialist emphasized that antibiotic loading must be completed 0-60 minutes before the first incision. Many Acticon implanters also irrigate wounds with antibiotic solutions and stage the prepared components in antibiotic baths. Compliance with the recommended antibiotic regimen is voluntary. As of February 2001, results from the study showed that 16 of the 112 study patients implanted used the recommended antibiotic regimen. Two out of 16 patients had an infection. Of the 96 patients who did not use the regimen, 25 patients had an infection (27 patients had experienced infections at this point of the study). These results were not statistically significant due to the small number of patients using the regimen, however, the regimen appears to have some clinical significance.

AMS also analyzed study data in search of common factors leading to infection among study patients. The following results were obtained:

- Patients with a history of allergies or musculoskeletal abnormalities (major trauma patients) were at the greatest risk of developing infection ($p=0.0392$; $p=0.0003$).
- Five of the 27 patients with an infection were diabetic. While diabetics appear to have an increased risk of infection, the increase was not significant ($p = 0.0706$).
- Eight of the 27 patients with an infection had a history of psychiatric disorder. While patients with this type of pre-implant medical history appear to be at greater risk of developing infection, this was not found to be statistically significant ($p=0.0551$).

- It appears that the first patient implanted at a site is less likely to be revised due to infection than the next four patients. The Investigators speculated that this was likely due to careful patient selection, and proctorship by an experienced Action Neosphincter implanter.
- No significant differences between sites relative to device revision for infection.
- No significant differences in rates of infection relative to length of operative procedure. Patients revised due to infection tended to have lower overall operative procedure times.
- Rate of infection by gender corresponded to the rate of enrollment by gender.
- Days from implantation to first sign of infection ranged from 2 – 984, (mean 103) days. Of the infections that required device revision, approximately 50% occurred in the first 30 days post-implantation, and approximately 62% occurred within the first 60 days. Seventeen of the 29 infections that required device revision occurred prior to device activation. Of the twelve infections that occurred after activation, eight (67%) occurred in the first 30 days.

Results of AMS’ analysis and the most recent recommendations by the infection control specialist have been sent to all physicians who implant the Acticon Neosphincter. AMS’ training and labeling emphasize that several factors, not just antibiotics, are important in preventing infection, including:

- appropriate patient selection
- patient counseling
- adequate pre-implantation bowel preparation
- properly timed antibiotic administration
- limited traffic in the operating room
- meticulous post-operative wound care
- post-operative bowel management.

Effectiveness

Endpoints

The Fecal Incontinence Scoring System (FISS) is the primary endpoint used to assess the effectiveness of the Acticon Neosphincter. The FISS is based on responses to a self-administered questionnaire regarding the frequency of the patient’s symptoms. A clinically significant improvement is a reduction of ≥ 24 in scores from pre-implant to follow-up. Table 7 shows FI values and their definitions.

Table 7: Fecal Incontinence (FI) Score Definitions

FI Value	Definition
0-60	Continent to solid and liquids
61-72	Incontinent < monthly
73-84	Incontinent > monthly
85-96	Incontinent >weekly
97-108	Incontinent daily
109-120	Incontinent >daily

Secondary endpoints were also evaluated pre- and post-implantation to assess the safety, effectiveness and impact on patient quality of life with the Acticon Neosphincter . These

endpoints included anorectal manometry, two Quality of Life Questionnaires, and adverse device effects.

Results

Device implantation was attempted in 115 patients, but in 3 patients implantation was aborted (1 cuff sizer was left in place and later explanted, 1 rectal perforation, and 1 vaginal perforation). Discussion of the effectiveness of the device is based on the 112 implanted patients. Discussion of the safety of the device is based on 115 patients.

Table 8: Follow-up Compliance

	Activation	6 Months	1 Year
Follow-up performed	98	73	67
Due for follow-up	0	0	1
Missed follow-up	1	6	7
Not eligible for follow-up	0	0	0
Explanted, not to be reimplanted	11	24	27
Explanted, possibly to be reimplanted	2	7	7
Deceased	0	0	0
Lost to follow-up	0	2	3
Total Patients	112	112	112

- Pre-implant fecal incontinence scores were not attainable from 14 patients due to a pre-existing stoma. The mean pre-implant score for patients without a pre-existing stoma was 106 (n=100, range 71-120). The average patient enrolled in the study was incontinent, at least daily, prior to Acticon Neosphincter implantation.
- At the six-month follow-up, pre-implant and six-month FISS scores were collected from 67 patients. The mean pre-implant FISS score was 106 (range 71-120). The mean six-month score was 50 (range 0-108). This patient group showed a mean reduction of 55 points (range 16-120) in the FISS score. The 55-point drop demonstrates that patients, on average, were taken from complete incontinence to liquid or solid stool at least daily (pre-implant), to incontinence only to seepage daily at six-months. For the six-month cohort of patients, 54 of 67 patients (80.6%) had a successful outcome.
- At the 12-month follow-up, pre-implant and twelve-month FISS scores were collected from 61 patients. The mean pre-implant FISS score was 106 (range 71-120). The mean 12-month score was 49 (range 0-120). This patient group showed a mean reduction of 57 points (range 13-114) in the FISS score, more than two times the amount of drop (≥ 24) necessary to indicate significance. The 57-point drop demonstrates that patients, on average, were taken from complete incontinence to liquid or solid stool at least daily (pre-implant), to incontinence only to seepage daily at 12-months. For the 12-month cohort of patients, 52 of 61 patients (85.2%) had a successful outcome.
- Anorectal Manometry – Normal parameters for anorectal manometry resting pressures range from 40 to 80 mmHg. Average pre-implant resting pressures were 26 mmHg. At

activation, resting pressures were received on 73 patients with an average resting pressure increase to 47 mmHg. At six-months, resting pressures were received on 61 patients with an average resting pressure of 46 mmHg. At one year, resting pressures were received on 53 patients with an average resting pressure of 45 mmHg. The difference in resting pressures between pre-implant and 12 months was significant ($p < 0.0001$). In general, higher resting pressures indicate improved sphincteric function. A definitive correlation between resting pressures and clinical outcomes has not been established.

- Health Status Questionnaire – analyzes scores for eight scales of health status, function, limitations and perceptions. Change in each of the scales between pre-implantation and 12-month follow-up was compared. Data was available for 48 patients at 12-month follow-up. Six of the eight scales showed significant improvement in patient's health status.
- Fecal Incontinence Quality of Life – At baseline many patients reported altering their activities to avoid bowel accidents in public places. However, following implantation, patients reported marked improvements in their quality of life. Many patients reported less restriction on their activities and spent less time worrying about fecal incontinence.

Study Conclusions (G960116)

Results of the study showed improved or complete continence in at least 80% of patients who have completed 6-month or 12-month follow-up. While the adverse event rate is high, it is comparable to other colorectal procedures with or without an implant. Most adverse events can be resolved without invasive medical intervention. Device revisions can be performed without long-term adverse sequelae. The procedure is reversible. The Acticon Neosphincter shows effectiveness as an alternative for treatment of severe fecal incontinence. The potential risks from adverse events, including device revisions, are balanced by the effectiveness of complete or significantly improved continence.

Adverse Events Reported from AMS Post-market Surveillance

The Acticon Neosphincter has been marketed outside the United States since 1996. Since HDE approval in September 1999, the Acticon has been commercially distributed in the United States. Approximately 1,000 devices have been commercially distributed around the world, including about 150 in the U.S. Adverse events from commercially available devices may be reported to AMS as part of the post-market surveillance activities conducted by AMS' Quality System.

Table 9: Summary of Reasons for Revisions from Post Market Surveillance (n=460)

Reason for Revision	Frequency
Fluid loss	18
Erosion	16
Infection	15
Recurring incontinence	14
Pain	4
Patient dissatisfaction	1
Migration	0
Malposition	0
Other*	17
Total	85

* The 17 reasons captured under “Other” include: not specified (7); cuff resized (3); air in system (3); cuff does not fit properly (1); tubing problem (1); balloon resized (1); cuff inverted (1).

One hundred-nineteen (119) revisions were performed for 94 patients. Some revisions reported to AMS did not include a reason for the revision.

X. CONCLUSIONS DRAWN FROM STUDIES

Preclinical studies assessed the device design, mechanical properties, reliability, and materials biocompatibility. Results from this testing provide assurance that the device design is appropriate for the intended use.

Results from the clinical trial indicate that most (>80%) patients who retained the device had a successful outcome (reduction in the number of incontinent episodes) six months and one year after implantation.

The adverse events profile associated with use of the Acticon Neosphincter shows a high number of adverse events, most of which resolved without invasive medical intervention and permanent sequelae. Thirteen percent (13%) of the adverse events were non-device related and 21% of the device-related adverse events required revision surgery.

These rates of adverse events for the Acticon Neosphincter are comparable to other colorectal surgeries. In a study examining the overall mortality and morbidity for patients undergoing resection of the colon and rectum, 361 out of 971 patients (37%) undergoing elective surgery experience at least one postoperative complication¹. In another study examining the change in patterns in the morbidity and mortality following colorectal surgery, for 304 patient who underwent elective surgery for colorectal disease the overall complication rate ranged for 36%-39%². Additional studies examining colorectal surgical procedures also have reported rates of morbidity comparable and higher to those seen in the Acticon study, including 29%-56% for sphincter sparing resection, 23-68% for abdominoperineal resection, and 46% for the Hartmann operation^{3,4,5,6}. These studies examined colorectal surgeries that did not include implantation of a prosthetic device.

In 1999, results were reported from a multi-center study examining treatment of refractory fecal incontinence that included colorectal surgery and the implantation of a device⁷. One-hundred thirty-nine patients (139) were implanted with intramuscular leads and a neurostimulator to stimulate transposed muscle wraps. (The intramuscular leads and neurostimulator are not commercially available in the United States for this indication.) The muscle wrap surrounds either a non-functional native sphincter or a neoanus created during total anorectal reconstruction. The series documents a significant morbidity rate associated with dynamic muscle plasty. Overall, 151 adverse events were reported in the 139 patients in the study. The study reports that infection rates were high, reflecting a combination of the location of the procedure in the “inherently contaminated perianal area” and the addition of foreign material to the operative site. “Major wound complications” were observed in one-third of the patients and most involved infection with or without associated tissue necrosis. Another one-third of the patients had minor wound complications.

The overall rate of infection following implantation of the Acticon is 25%. Infection resulted in revisions for 28 patients. The infection rate seen in the study could be expected due to the presence of a prosthetic device that may impair local host defenses⁸ and the location of the surgery.

Results from the clinical studies (G880037 and G960116) provide reasonable assurance that the device is safe and effective as an alternative for the treatment of severe fecal incontinence, taking into account the risks and benefits of currently available alternative forms of treatment for this specific patient population.

Risks and Benefits

The information provided in the PMA, including preclinical studies, clinical studies, clinical results from the literature, and the approval of H990003 by FDA provide reasonable assurance that the AMS Acticon Neosphincter is safe and effective for treating severe fecal incontinence in carefully selected patients. Results from clinical studies and literature on the device show the treatment is reversible, if necessary, and no long-term sequelae have occurred due to treatment with the device. Results from the clinical study demonstrate the device improved continence and the quality of life for a majority of patients. The accumulated data in the PMA and the results from the clinical study demonstrate that the benefits to patients’ health from use of the device outweigh the risks of injury or illness, taking into account the alternative forms of treatment for this specific patient population.

XI. REFERENCES

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