

THE LAP-BAND[®] ADJUSTABLE GASTRIC BANDING SYSTEM
SUMMARY OF SAFETY AND EFFECTIVENESS DATA

I GENERAL INFORMATION

Device Generic Name:	Adjustable Silicone Gastric Band, Implanted
Device Trade Name:	LAP-BAND [®] Adjustable Gastric Banding (LAGB [®]) System
Applicant's Name and Address:	BioEnterics Corporation 1035 Cindy Lane Carpinteria, California 93013
PMA Number:	P000008
Date of Panel Recommendation:	June 19, 2000
Date of Notice of Approval to the Applicant:	June 5, 2001

II INDICATIONS FOR USE

The **LAP-BAND System** is indicated for use in weight reduction for severely obese patients with a Body Mass Index (BMI) of at least 40 or a BMI of at least 35 with one or more severe comorbid conditions, or those who are 100 lbs. or more over their estimated ideal weight according to the 1983 Metropolitan Life Insurance Tables (use the midpoint for medium frame). It is indicated for use only in severely obese adult patients who have failed more conservative weight-reduction alternatives, such as supervised diet, exercise and behavior modification programs. Patients who elect to have this surgery must make the commitment to accept significant changes in their eating habits for the rest of their lives.

III CONTRAINDICATIONS

The **LAP-BAND System** is contraindicated in:

1. Patients with inflammatory diseases of the gastrointestinal tract, including severe intractable esophagitis, gastric ulceration, duodenal ulceration, or specific inflammation such as Crohn's disease.
2. Patients with severe cardiopulmonary diseases or other serious organic disease which may make them poor surgical candidates.
3. Patients with potential upper gastrointestinal bleeding conditions such as esophageal or gastric varices or congenital or acquired intestinal telangiectases.

4. Patients with portal hypertension.
5. Patients with congenital or acquired anomalies of the GI tract such as atresias or stenoses.
6. Patients who have/experience an intra-operative gastric injury during the implantation procedure, such as a gastric perforation at or near the location of the intended band placement.
7. Patients with cirrhosis.
8. Patients with chronic pancreatitis.
9. Patients who are addicted to alcohol and/or drugs.
10. Non-adult patients (patients under 18 years of age).
11. Patients who have an infection anywhere in their body or where the possibility of contamination prior to or during the surgery exists.
12. Patients on chronic, long-term steroid treatment.
13. Patients who are unable or unwilling to comply with dietary restrictions, which are required by this procedure.
14. Patients who are known to have, or suspected to have, an allergic reaction to materials contained in the system or who have exhibited a pain intolerance to implanted devices.
15. Patients or family members with a known diagnosis or pre-existing symptoms of autoimmune connective tissue disease such as systemic lupus erythematosus or scleroderma.
16. Pregnancy: Placement of the LAP-BAND System is contraindicated for patients who currently are or may be pregnant. Patients who become pregnant after band placement may require deflation of their bands.

IV WARNINGS, AND PRECAUTIONS

Warnings

WARNING: Laparoscopic or laparotomic placement of the LAP-BAND System is major surgery and **death can occur**

WARNING: Failure to secure the band properly may result in its subsequent displacement and necessitate reoperation.

WARNING: A large hiatal hernia may prevent accurate positioning of the device. Placement of the band should be considered on a case-by-case basis depending on the severity of the hernia.

WARNING: The band should not be sutured to the stomach. Suturing the band directly to the stomach may result in erosion.

WARNING: Patients' emotional and psychological stability should be evaluated prior to surgery. Gastric banding may be determined to be inappropriate, in the opinion of the surgeon, for select patients.

WARNING: Patients should be advised that the LAP-BAND System is a long-term implant. Explant and replacement surgery may be indicated at any time. Medical management of adverse reactions may include explantation. Revision surgery for explantation and replacement may also be indicated to achieve patient satisfaction.

WARNING: Esophageal distension or dilatation has been reported to result from stoma obstruction due to over-restriction, due to excessive band inflation. Patients should not expect to lose weight as fast as gastric bypass patients, and band inflation should proceed in small increments. Deflation of the band is recommended if esophageal dilatation develops.

WARNING: Some types of esophageal dysmotility may result in inadequate weight loss or may result in esophageal dilatation when the band is inflated and require removal of the band. On the basis of each patient's medical history and symptoms, surgeons should determine whether esophageal motility function studies are necessary. If these studies indicate that the patient has esophageal dysmotility, the increased risks associated with band placement must be considered.

WARNING: Patients with Barrett's esophagus may have problems associated with their esophageal pathology that could compromise their post-surgical course. Use of the band in these patients should be considered on the basis of each patient's medical history and severity of symptoms.

WARNING: Patient self-adjustment of superficially placed access ports has been reported. This can result in inappropriate band tightness, infection and other complications.

Precautions

CAUTION: Laparoscopic band placement is an advanced laparoscopic procedure. Surgeons planning laparoscopic placement must:

1. Have extensive advanced laparoscopic experience, i.e., funduplications.
2. Have previous experience in treating obese patients and have the staff and commitment to comply with the long-term follow-up requirements of obesity procedures.
3. Participate in a training program for the LAP-BAND System authorized by BioEnterics Corporation or an authorized BioEnterics distributor (this is a requirement for use).

4. Be observed by qualified personnel during their first band placements.
5. Have the equipment and experience necessary to complete the procedure via laparotomy, if required.
6. Be willing to report the results of their experience to further improve the surgical treatment of severe obesity.

CAUTION: It is the responsibility of the surgeon to advise the patient of the known risks and complications associated with the surgical procedure and implant.

CAUTION: As with other gastroplasty surgeries, particular care must be taken during dissection and during implantation of the device to avoid damage to the gastrointestinal tract. Any damage to the stomach during the procedure may result in erosion of the device into the GI tract.

CAUTION: During insertion of the calibration tube, care must be taken to prevent perforation of the esophagus or stomach.

CAUTION: In revision procedures the existing staple line may need to be partially disrupted to avoid having a second point of obstruction below the band. As with any revision procedure, the possibility of complications such as erosion and infection is increased. Any damage to the stomach during the procedure may result in peritonitis and death, or in late erosion of the device into the GI tract.

CAUTION: Care must be taken to place the access port in a stable position away from areas that may be affected by significant weight loss, physical activity, or subsequent surgery. Failure to do so may result in the inability to perform percutaneous band adjustments.

CAUTION: Care must be taken during band adjustment to avoid puncturing the tubing which connects the access port and band, as this will cause leakage and deflation of the inflatable section.

CAUTION: The LAP-BAND System is for single use only. Do not use a band, access port, needle or calibration tube which appears damaged (cut, torn, etc.) in any way. Do not use one of them if the package has been opened or damaged, or if there is any evidence of tampering. If packaging has been damaged, the product may not be sterile and may cause an infection.

Do not attempt to clean, re-sterilize or re-use any part of the LAP-BAND Adjustable Gastric Banding System. The product may be damaged or distorted if re-sterilized.

CAUTION: It is important that special care be used when handling the device because contaminants such as lint, fingerprints and talc may lead to a foreign body reaction.

CAUTION: Care must be taken to avoid damaging the band, its inflatable section or tubing, the access port or the calibration tube. Use only rubber-shod clamps to clamp tubing.

CAUTION: The band, access port and calibration tube may be damaged by sharp objects and manipulation with instruments. A damaged device must not be implanted. For this reason, a stand-by device should be available at the time of surgery.

CAUTION: Failure to use the tubing end plug during placement of the band may result in damage to the band tubing during band placement.

CAUTION: Do not push the tip of any instrument against the stomach wall or use excessive electrocautery. Stomach perforation or damage may result. Stomach perforation may result in peritonitis and death.

CAUTION: Over-dissection of the stomach during placement may result in slippage or erosion of the band and require reoperation.

CAUTION: Failure to use an appropriate atraumatic instrument such as the LAP-BAND Closure Tool to lock the band may result in damage to the band or injury to surrounding tissues.

CAUTION: The band is not intended to be opened laparoscopically with surgical instruments. Unrecognized damage to the band may result in subsequent breakage or failure of the device.

CAUTION: When adjusting band volume take care to ensure that the radiographic screen is perpendicular to the needle shaft (the needle will appear as a dot on the screen). This will facilitate adjustment of needle position as needed while moving through the tissue to the port.

CAUTION: When adjusting band volume use of an inappropriate needle may cause access port leakage and require re-operation to replace the port. Use only LAP-BAND System Access Port Needles. Do not use standard hypodermic needles, as these may cause leaks.

CAUTION: When adjusting band volume never enter the access port with a “syringeless ” needle. The fluid in the device is under pressure and will be released through the needle.

CAUTION: When adjusting band volume once the septum is punctured, do not tilt or rock the needle, as this may cause fluid leakage or damage to the septum.

CAUTION: When adjusting band volume if fluid has been added to decrease the stoma size, it is important to establish, before discharge, that the stoma is not too small. Care must be taken during band adjustments not to add too much saline, thereby closing the gastric stoma. Check the adjustment by having the patient drink water. If the patient is unable to swallow, remove some fluid from the port, then recheck. A physician familiar with the adjustment procedure must be available for several days post-adjustment to deflate the band in case of an obstruction.

CAUTION: It is the responsibility of the surgeon to advise the patient of the dietary restrictions which follow this procedure and to provide diet and behavior modification support. Failure to adhere to the dietary restrictions may result in obstruction and/or failure to lose weight.

CAUTION: Patients must be carefully counseled on the need for proper dietary habits. They should be evaluated for nutritional (including caloric) needs and advised on the proper diet selection. If necessary to avoid any nutritional deficiencies, the physician may choose to prescribe appropriate dietary supplements. The appropriate physical monitoring and dietary counseling should take place regularly.

CAUTION: Patients must be cautioned to chew their food thoroughly. Patients with dentures must be cautioned to be particularly careful to cut their food into small pieces. Failure to follow these precautions may result in vomiting, stomal irritation and edema, possibly even obstruction.

CAUTION: Patients must be seen regularly during periods of rapid weight loss for signs of malnutrition, anemia or other related complications.

CAUTION: Anti-inflammatory agents, which may irritate the stomach, such as aspirin and non-steroidal anti-inflammatory drugs, should be used with caution. The use of such medications may be associated with an increased risk of erosion.

CAUTION: Patients who become pregnant or severely ill, or who require more extensive nutrition, may require deflation of their bands.

CAUTION: All patients should have their reproductive areas shielded during radiography.

CAUTION: Insufficient weight loss may be caused by pouch enlargement or more infrequently band erosion, in which case further inflation of the band would not be appropriate.

CAUTION: Elevated homocysteine levels have been found in patients actively losing weight after obesity surgery. Supplemental folate and vitamin B12 may be necessary to maintain normal homocysteine levels. Elevated homocysteine levels may increase cardiovascular risk and the risk of neural tube abnormalities.

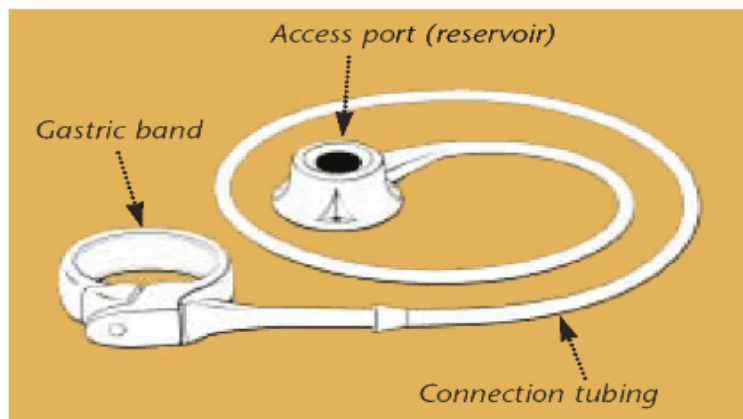
CAUTION: Although there have been no reports of autoimmune disease with the use of the LAP-BAND System autoimmune diseases, connective tissue disorders (i.e., systemic lupus erythematosus, scleroderma) have been reported following long-term implantation of other silicone devices. These conditions have primarily been hypothesized to be associated with silicone breast implants. There is currently no conclusive clinical evidence to substantiate a relationship between connective-tissue disorders and silicone implants. Definitive long-term epidemiological studies to further evaluate this possible association are currently underway. However, the surgeon should be aware that if autoimmune symptoms develop following

implantation, definitive treatment and/or band removal may be indicated. Likewise, patients who exhibit preexisting autoimmune symptoms should be carefully evaluated prior to implantation of the LAP-BAND System and may not be appropriate candidates (see Contraindications).

V DEVICE DESCRIPTION

The LAP-BAND System is a long-term implantable device intended to induce weight loss in morbidly obese patients by limiting food consumption (restrictive rather than malabsorption). The device is surgically implanted, using either a laparoscopic or open procedure, to create a restricted opening (stoma) and a small gastric pouch to limit food consumption and induce early satiety. The main components (Figure 1) of the device are the silicone elastomer band, the access port and kink-resistant tubing used to connect the other two components. The inner surface of the silicone band, which is placed around the stomach, is inflatable and connected by the tubing to the access port (a remote injection site). The access port is placed in or on the rectus muscle to permit non-surgical, percutaneous adjustments to the band and thus, the stoma diameter, using sterile saline.

Figure 1: LAP-BAND SYSTEM



The LAP-BAND Adjustable Gastric Banding System

The implantable components of the LAP-BAND System:

Adjustable Gastric Band – a 13mm-wide, sterile, band which, when fastened, forms a circular ring. Two sizes are available: 9.75cm and 10.00cm inner circumference. Each size transitions to a length of kink-resistant tubing which is 50cm in length. The band's slip-through buckle facilitates laparoscopic placement around the stomach resulting in the formation of a small gastric pouch and stoma.

Access Port – a stainless steel component with a self-sealing injection site. This sterile port is designed to allow for post-operative percutaneous adjustment in the stoma diameter. The port is attached to the inner surface of the gastric band by the kink-resistant tubing. Saline can be injected into the access port causing the inner surface of the band to inflate and thus decreasing the size of the stoma. Saline can also be removed from the LAP-BAND causing the band to deflate and increasing the size of the stoma. The access port is available in two

sizes (1.2” and 0.98” diameter). The larger diameter port is a component of the LAP-BAND System while the smaller port is available as a replacement component.

Kink-Resistant Tubing – a 50cm silicone tube (I.D. 0.5”, O.D. 0.13”) which connects the inner surface of the gastric band to the access port.

Other components used during the implantation procedure of the LAP-BAND System include:

Calibration Tube Assembly – a 157cm dual lumen, translucent, silicone tube with a 13mm-diameter sensor tip and an inflatable balloon attached to its distal end. The device is inserted into the patient’s esophagus intraoperatively and used to position and size the stoma of the gastric pouch. The calibration tube is supplied with the system and is provided clean, non-sterile, and for single use. The balloon is inflated via an inflation port, which is connected to the calibration tube’s smaller lumen and remains external during the procedure.

Silicone End Plug with Stainless Steel Connector – used to temporarily seal the System while the band is being positioned around the stomach. The end plugs are then removed and the other components of the system connected.

LAP-BAND Closure Tool (non-sterile, multiple use) – reusable laparoscopic surgical instrument measuring 50cm in length and with a diameter of 10mm. It is designed specifically for use when placing the LAP-BAND. The closure tool is used for “locking” the LAP-BAND in place around the patient’s stomach. It is designed for autoclave re-sterilization.

Blunt tip flushing needles – provided to facilitate preparation of the System by operating room personnel prior to surgery. The 16 gauge band priming needle is used to flush and prime the band tubing and inflatable shell with sterile saline. The 22 gauge access port flushing needle is used to flush and prime the access port with sterile saline.

Access Port Needle – a 20-gauge, 89mm long, non-coring, deflected-tip needle designed to penetrate the access port during postoperative adjustment of the band. Access port needles are provided sterile and are also available separately.

VI ALTERNATIVE PRACTICES AND PROCEDURES

Alternative practices and procedures available for the treatment of severe obesity (body mass index of greater than 35 kg/m²) can be divided into two categories, non-surgical treatments and obesity surgery.

Non-Surgical Treatments (Medical Therapy)

Non-surgical treatments of obesity include

- diet, exercise, and behavior modification programs;
- prescription weight loss medications; and

- other procedures and practices, such as jaw-wiring, hypnosis, counseling, psychotherapy, nutritional supplements, etc.

Several reports have suggested a rather high incidence of failure for severely obese patients to sustain long-term weight loss with any form of non-surgical treatment.^{1, 2}

Obesity Surgery

Numerous surgical techniques have been developed for the treatment of severe obesity. The most common obesity surgery procedures performed in the United States are the Roux-en-Y Gastric Bypass and the Vertical Banded Gastroplasty.

Roux-en-Y Gastric Bypass (GBP)

GBP is the most common of the restrictive-malabsorptive procedures. These procedures are considered to be restrictive (a small gastric pouch restricting the amount of food consumed) as well as having a malabsorptive component (bypassing some part of the intestines). In the GBP, the surgeon constructs a proximal gastric pouch, and then creates an outlet from the pouch to a limb of the small bowel. This results in a bypass of most of the stomach and duodenum.

Vertical Banded Gastroplasty (VBG)

VBG is one of a group of restrictive obesity procedures which decrease the amount of solid food a patient is able to ingest. Rows of staples are used to create a small stomach pouch along the lesser curvature of the stomach. The pouch outlet (stoma) is reinforced with a copolymer band or silicone ring placed through a hole in the stomach.

VII MARKETING HISTORY

The LAP-BAND® System has been in use in Europe since 1993. In 1997, the BioEnterics Corporation LAP-BAND® System was CE-marked. Regulatory approval has also been obtained in Australia (1994), Canada (1998), Israel (1997), Mexico (1996) and other countries. No regulatory approvals have been withdrawn.

Over 50,000 LAP-BAND® Systems have been distributed internationally and it has been widely reported on in the medical literature.

VIII POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

Adverse events that may result from use of the LAP-BAND System are both those commonly associated with obesity surgical procedures and others associated with the device specifically. Potential adverse events include perforation of the stomach and complications associated with laparoscopic surgery (e.g., spleen or liver damage, thrombosis and rupture of the wound, infection, and death). Other risks reported after gastric restriction procedures include ulceration, gastritis, gastroesophageal reflux, gas bloat, dysphagia, dehydration, constipation, nausea and vomiting, and weight regain. Elevated homocysteine levels have been found in patients actively losing weight after obesity surgery and may increase cardiovascular risk. In addition, the developing fetus of pregnant women with elevated homocysteine may be at risk for neural tube defects. During periods of rapid weight loss

patients may experience malnutrition, anemia or other related complications, such as the development of cholelithiasis.

Risks associated specifically with the LAP-BAND System are the possibility of intolerance to the components (foreign body reaction), mechanical malfunction (leakage and deflation of the inflatable section), access port site pain and access port displacement, band slippage/pouch dilatation, band erosion, gastric or esophageal perforation, stoma obstruction, and esophageal dilatation/dysmotility. Peritonitis and death can occur either as a consequence of a gastrointestinal perforation during implantation of the device or as a result of erosion of the gastric band. The LAP-BAND System is a long-term implant and the System or a component may need to be either explanted or replaced. In addition, medical management of adverse events may necessitate reoperation to revise or explant the device. As with any revision procedure, the possibility of complications such as erosion and infection are increased.

In the LAP-BAND System U.S. clinical trial, 266 of 299 (89%) subjects reported at least one adverse event. Peri-operative adverse events were reported in 44% of the study subjects. The most commonly reported peri-operative adverse events were abdominal pain and nausea and/or vomiting. Eighty-two percent (82%) of subjects reported having one or more adverse events during the post-operative period. The most commonly reported adverse events in the post-operative period were nausea and/or vomiting, gastroesophageal reflux, and band slippage/pouch dilatation.

The most frequently reported adverse events (occurring with a frequency of $\geq 5\%$) are shown in Table 6. Many adverse events were mild and required no intervention. Serious and severe adverse events were most commonly addressed either by band adjustment or by reoperation to revise, replace or remove either a component or the entire LAP-BAND System.

IX SUMMARY OF PRE-CLINICAL STUDIES

Testing of product samples was performed on the various components of the LAP-BAND® System to ensure the product performed according to product specifications. Testing was performed to evaluate all levels of the manufacturing process (i.e., raw materials used to fabricate the device, components from which the device is assembled, the finished device, the device's packaging, sterilization process of the device, and product shelf life performance). Laparoscopic placement of the LAP-BAND® System was evaluated and demonstrated as feasible in a series of procedures in pigs in 1993.

Physical Testing

LAP-BAND® System component mechanical testing was performed for all components. This data demonstrated that the components met design specifications and intended use. These components were subjected to dimensional and visual inspection as well as to break force and tensile strength testing. The finished assemblies were packaged and subjected to dry heat sterilization prior to testing. Testing included the following:

- Fill Tube Patency and Shell Inflation
- Laparoscopic Device Insertion

- Belt Head Insertion Force
- Shell Crease Fill Volume
- Shell Burst Volume
- Locked Buckle and Belt Head Tensile Strength
- Tear Strength of Punched Buckle Tab Hole
- Tensile Strength of Adhesive Bond of the Buckle
- Tensile Strength of Adhesive Bond of the Belt
- Tubing/Belt Bond Pull Test
- Tubing Kink Resistance
- End-Plug Pullout force
- Access Port Multiple Puncture and Over-Pressurization
- Access Port Assembly Fatigue Testing

Data from these tests demonstrated that finished devices meet the requirements and specifications for functionality as established in the LAP-BAND® System product specification.

Biocompatibility Testing

The materials and components of the LAP-BAND® System (including the Access Port, Tubing Connector, the Calibration Tube, Access Port Needle, and End Plug) that contact the patient are fabricated primarily from silicone elastomers and polymers. All patient-contacting materials have been evaluated and tested for biocompatibility and toxicity.

The materials used to fabricate the components in contact with the body were tested and evaluated for biocompatibility per ISO 10993-1, “Biological Evaluation of Medical Devices, Part 1: Guidance on Selection of Tests.” The tests were carried out in compliance with 21 CFR Part 58 Good Laboratory Practice Regulations. Materials used in the LAP-BAND® System included silicone elastomers, polysulfone, titanium and stainless steel. These materials have also been used in other medical device applications. Biocompatibility test results demonstrated that sterilized finished devices met the acceptance criteria for each of the tests.

Packaging and Sterilization

Dry heat sterilization was validated to provide a sterility assurance level (SAL) of 10^{-6} . Studies demonstrated that the packaging system maintains the sterile barrier and the devices remain sterile after being stored on the shelf for up to two years.

Real-time shelf life testing has been conducted; the LAP-BAND System has a two-year shelf life. Package qualification testing consists of three phases of evaluation: physical testing of the heat seals, functionality testing of the LAP-BAND assembly and calibration tube, and sterility testing of the device.

The LAP-BAND® Closure Tool, a reusable surgical instrument, is provided non-sterile and designed to be used in the surgical procedure for band closure. The procedures for cleaning and sterilizing this instrument have been validated and met acceptance criteria.

X SUMMARY OF CLINICAL STUDIES

Objectives:

A clinical study was conducted within the United States under a significant risk Investigational Device Exemption (IDE) to assess the safety and effectiveness of the LAP-BAND System in the treatment of severe obesity.

Study design:

The clinical study was a prospective, multi-center, single-arm trial in which each subject served as his or her own control.

Subjects were implanted with the LAP-BAND System at 8 clinical sites within the United States beginning in April 1995. The last subject was implanted in June 1998. A total of 299 subjects were enrolled in the study and 292 were implanted with the device. Seven subjects had previously been implanted with an earlier version of the device, the Adjustable Silicone Gastric Band (ASGB), and were not included in the study except for safety analyses of adverse events. Follow-up evaluations were conducted at 3 weeks, and 3, 6, 9, 12, 18, 24, 30 and 36 months post-implantation.

Evaluation of the safety and effectiveness of the LAP-BAND System was based on 36-month evaluation of the following clinical endpoints:

Effectiveness:

1. percent excess weight loss (%EWL) defined as weight loss divided by baseline excess weight. Excess weight was determined from ideal body weights based on sex and height-adjusted weight for a medium frame according to 1983 Metropolitan Life tables.
2. absolute weight loss
3. change in excess weight
4. change in BMI
5. change in quality of life (based on Beck Depression Index, the Multi-Dimensional Body-Self Relations Questionnaire (MBSR) questionnaire, and the RAND SF-36 questionnaire)

Safety:

Incidence and severity of complications (device and non-device related)

Patient Selection:

The inclusion criteria for study enrollment included:

1. age 18-55
2. male or female
3. BMI ≥ 40 or at least 100 pounds above ideal weight according to the 1983 Metropolitan Life Insurance Tables (medium frame)
4. willingness to comply with the substantial lifelong dietary restrictions required by the procedure
5. history of obesity for at least 5 years
6. history of failure with non-surgical weight loss methods
7. willingness to follow protocol requirements, including signed informed consent, routine follow-up schedule, completing quality of life questionnaires, completing

- laboratory tests, completing diet and behavior modification counseling
8. residing within a reasonable distance from the investigator's office and able to travel to the investigator to complete all routine follow-up visits

The exclusion criteria were:

1. surgery or treatment represents an unreasonable risk to the subject
2. family or patient history of inflammatory disease of the gastrointestinal tract (including ulceration, duodenal ulceration, Grade 2-4 esophagitis, or specific inflammation such as Crohn's disease or ulcerative colitis)
3. severe cardiopulmonary disease or other serious organic disease
4. severe coagulopathy, upper gastro-intestinal bleeding conditions such as esophageal or gastric varices, congenital or acquired intestinal telangiectasia
5. congenital or acquired anomalies of the GI tract such as atresias or stenoses
6. severe hiatal hernia
7. pregnant or has the intention of becoming pregnant in the next 12 months
8. alcohol or drug addiction
9. mentally retarded or emotionally unstable, or exhibits psychological characteristics which, in the opinion of the investigator, makes the subject a poor candidate for gastric band surgery
10. previous bariatric surgery (except Adjustable Silicone Gastric Band), intestinal obstruction or adhesive peritonitis
11. infection anywhere in the body at the time of surgery
12. family or patient history of a known diagnosis or pre-existing symptoms of systemic lupus erythematosus, scleroderma, or other autoimmune connective tissue disorder
13. participating in another ongoing clinical trial in which concomitant diagnosis or therapeutic intervention would adversely affect the integrity of the LAGB clinical trial

Only those patients satisfying the inclusion and exclusion criteria were allowed to participate. All patients signed an informed consent prior to being enrolled in the clinical trial.

Demographic Data:

A total of 247 women (85%) and 45 men (15%) met the inclusion criteria and were implanted with the LAP-BAND device. The majority of patients enrolled were Caucasian (81%), while African-Americans comprised 15% of the study population and Hispanics 4%. Almost half the patients enrolled had hypertension as a comorbidity (43%). Other comorbidities included gallbladder disease (26%), gastrointestinal diseases (24%), asthma (16%), and diabetes mellitus (16%).

The average age at time of surgery was 38.8 years (range of 18-56). The average weight at baseline was 293 pounds (range of 193-475) and the average BMI at baseline was 47.4 (range of 36.6-74.3). Thirty subjects had a BMI over 50 at entry. Patients had gained an average of 54 pounds in the 5 years prior to enrollment.

Device Implantation:

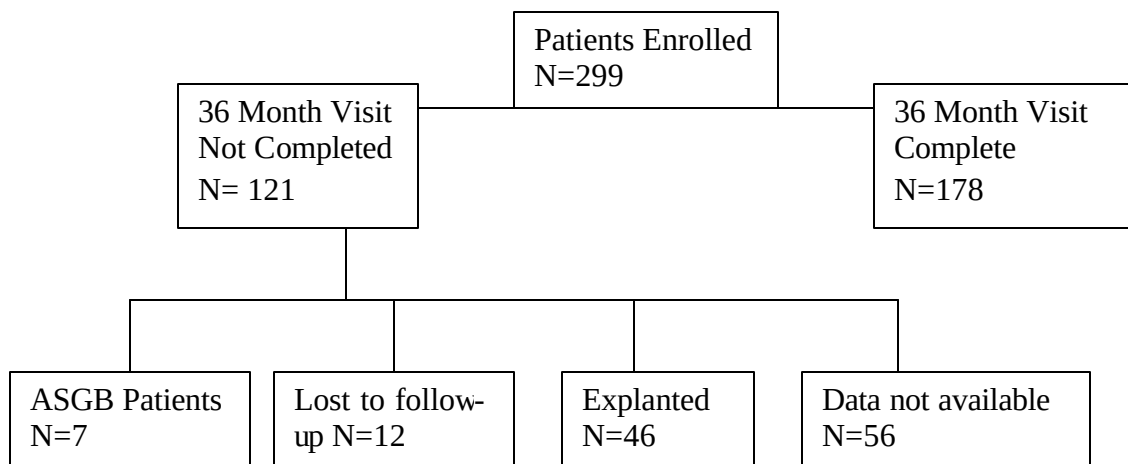
Patients enrolled in the study underwent implantation of the LAP-BAND System. The band was left empty or minimally inflated at the completion of the surgery. The first post-operative band adjustment occurred no sooner than 4-6 weeks, allowing a fibrous capsule to form around the band (helping to avoid slippage). At the initial adjustment, 1-2cc of normal saline was added.

The majority of subjects had the device placed laparoscopically (259 patients or 89%). Thirty-three subjects had the device implanted using an open procedure. Twenty of these 33 subjects were scheduled for the open procedure while the remaining 13 patients (5%) were converted from a laparoscopic attempt to open surgery during implantation. The reason for conversions included difficult anatomy, concomitant surgery, bleeding, and technical problems. The average hospital length-of-stay for patients was 1.6 days if performed laparoscopically and 4.4 days if done by open surgery. Mean surgery time was 178 minutes for laparoscopically placed devices and 166 minutes for open procedures.

Study Results:**Patient Accountability**

Two hundred and ninety-nine subjects were enrolled into the study. The last subject was enrolled in June 1998. Thirty-six month follow-up data were available for 178 subjects. The remaining 121 subjects were subdivided into 4 groups as shown in Figure 2 below. Seven (7) subjects had been previously implanted with the Adjustable Silicone Gastric Band (ASGB) and were included only in the safety analysis, 46 subjects had the device explanted, 12 subjects were lost to follow-up and 56 subjects either missed or had not yet reached the 36 month follow-up visit.

Figure 2: Patient Accountability – 36 months



Primary Effectiveness Endpoint:

The primary endpoint for the U.S. clinical trial was percent excess weight loss (defined as [baseline wt – measured wt at the given timepoint]/[baseline wt – ideal body wt]). Data representing %EWL is presented in Table 1 below:

Table 1: %EWL by Visit

Visit	N	Mean	SD	Median	Range	95% Confidence Interval
3 Weeks	184	9.9	5.0	9.8	-8.1 – 30.3	9.2 – 10.6
3 Months	245	18.4	10.0	17.6	-13.5 – 49.0	17.2 – 19.7
6 Months	233	26.5	13.8	25.9	-10.3 – 70.0	24.7 – 28.2
9 Months	185	30.8	17.1	29.1	-14.9 – 72.5	28.4 – 33.3
12 Months	233	34.5	19.0	32.0	-9.0 – 89.3	32.1 – 37.0
18 Months	190	36.4	20.4	33.7	-14.4 – 93.1	33.5 – 39.3
24 Months	189	37.8	22.5	34.7	-16.8 – 102.7	34.6 – 41.0
30 Months	148	37.9	22.9	34.8	-15.5 – 99.3	34.2 – 41.6
36 Months	178	36.2	24.6	34.0	-9.8 – 113.0	32.6 – 39.8

The %EWL increased between 3 weeks and 18 months and then remained relatively stable between 18 and 36 months. Patients who reached 36 months of follow-up were able to lose, on average, 36% of their excess body weight.

It should be noted that by 3 weeks after implantation, before the first post-operative band adjustment, patients had lost an average of 10% of their excess body weight. The reason for this is not known. Although not shown in Table 1, there were no significant differences in %EWL noted based on age, gender, or race.

Table 2 depicts the number and percentage of patients who were able to achieve certain benchmark changes in %EWL:

Table 2: Percentage of Subjects with Subsets of %EWL

Excess weight loss at 3 years	%	# patients
Gained more than 5% EWL	2%	4
No change 5% EWL	5%	9
Lost at least 25% EWL	62%	110
Lost at least 33% EWL	52%	93
Lost at least 50% EWL	22%	39
Lost at least 75% EWL	10%	18

Table 2 shows that for those patients successfully completing 36 months of follow-up (178 patients), 22% were able to lose ≥50% of their excess body weight and an additional 40% lost at least 25% of their excess body weight. Five percent of patients had minimal or no (±5%EWL) change in excess body weight and 2% gained more than 5% of their original excess body weight. Ten percent of patients lost at least 75% of their excess body weight.

Secondary Effectiveness Endpoints:

Other study endpoints included absolute weight loss and change in BMI. These results are depicted respectively in Tables 3 and 4 below:

Table 3: Mean Weight by Visit (in pounds)

Visit	N	Mean	SD	Median	Range	95% Confidence Intervals
Baseline	288	293.5	53.8	282.8	193.0 – 475.0	287.3 – 299.7
3 Weeks	184	278.8	52.2	267.2	185.4 – 446.0	271.3 – 286.3
3 Months	245	266.2	49.6	257.5	169.3 – 437.0	260.0 – 272.4
6 Months	233	254.5	51.5	244.5	161.8 – 435.0	247.9 – 261.1
9 Months	185	250.6	54.5	240.3	152.0 – 411.5	242.8 – 258.4
12 Months	233	241.8	53.1	240.0	138.0 – 412.0	235.0 – 248.6
18 Months	190	240.5	51.4	236.0	139.0 – 396.5	233.2 – 247.9
24 Months	189	234.5	52.2	230.0	125.0 – 400.0	227.1 – 241.9
30 Months	148	235.4	52.5	233.9	120.0 – 395.1	226.9 – 243.8
36 Months	178	240.6	55.1	239.5	113.0 – 405.6	232.5 – 248.7

Table 3 shows that for those patients completing 36 months of follow-up, the mean body weight decreased by 53 pounds, or 18% (293.5 to 240.6 pounds). Maximum mean weight loss (59 pounds), however, occurred at the 24 month point with a subsequent slight gain in weight between 24 and 36 months.

Table 4: Mean BMI by Visit

Visit	N	Mean	SD	Median	Range	95% Confidence Intervals
Baseline	288	47.5	7.0	45.8	36.6 – 74.3	46.7 – 48.3
3 Weeks	184	45.1	6.9	43.8	33.5 – 70.6	44.1 – 46.1
3 Months	245	43.2	7.1	41.6	30.9 – 68.1	42.3 – 44.1
6 Months	233	41.2	7.3	40.0	26.5 – 67.8	40.3 – 42.1
9 Months	185	40.4	7.6	39.7	27.6 – 68.8	39.3 – 41.5
12 Months	233	39.0	7.3	38.3	24.6 – 67.9	38.1 – 40.0
18 Months	190	38.7	7.1	38.7	23.3 – 65.4	37.7 – 39.7
24 Months	189	38.1	7.5	37.9	21.4 – 67.3	37.0 – 39.2
30 Months	148	38.1	7.1	38.7	23.3 – 60.7	37.0 – 39.3
36 Months	178	38.7	7.9	39.0	19.3 – 63.6	37.5 – 39.8

Patients enrolled in the study were required to have a BMI of ≥ 40 for implantation. The mean BMI at baseline was 47.5. As Table 4 above shows, the mean BMI decreased to 38.1 at 24 months and 38.7 at 36 months for those completing follow-up. This represents a 19% reduction in BMI for those patients by study's end.

Changes in quality of life as measured by the Beck Depression Index, Multi-Dimensional Body-Self Relations Questionnaire (MBSR) and the RAND SF-36 scales are depicted in Table 5 below:

Table 5: Quality of Life by Visit

Scale	Baseline (n=282)		36 months (n=145)	
	Mean	SD	Mean	SD
Beck Depression Index	13.5	8.5	7.0	8.3
MBSR Appearance Evaluation	1.9	0.6	2.7	0.9
RAND SF-36				
Physical function	49.1	24.5	76.1	25.9
Role Limit: Physical	39.1	40.6	78.8	35.9
Role Limit: Emotional	60.6	40.3	78.2	34.6
Energy/Fatigue	37.1	21.0	58.1	21.6
Emotional Well-Being	65.2	18.6	71.9	20.2
Social Function	57.4	27.3	81.2	24.3
Pain	58.2	25.4	78.6	24.7
General Health	52.4	23.0	71.6	19.7
Mental Health Composite	44.5	11.0	48.6	10.1
Physical Health Composite	23.6	8.5	31.4	7.6

Table 5 shows that for patients completing Quality of Life questionnaires at 36 months, there was an improvement in mean scores for all categories measured.

Safety and Adverse Events:

During the course of the US clinical study, 266 (89%) of the subjects enrolled reported at least one adverse event with 34% reported as being severe. Although signs and symptoms were recorded separately as individual adverse events, many of the events were associated with a “syndrome.” For example, patients with band slippage/pouch dilatation may also have reported nausea, vomiting, and stoma obstruction.

Adverse events were reported for the peri-operative period, 21 days post LAP-BAND implantation, or the post-operative period. The severity of each event was rated as mild, moderate or severe and then further rated as serious or not serious (Figure 3). These were defined as:

Mild – symptom barely noticeable to the patient; does not affect performance or functioning. Prescription drugs not ordinarily needed for relief of symptom.

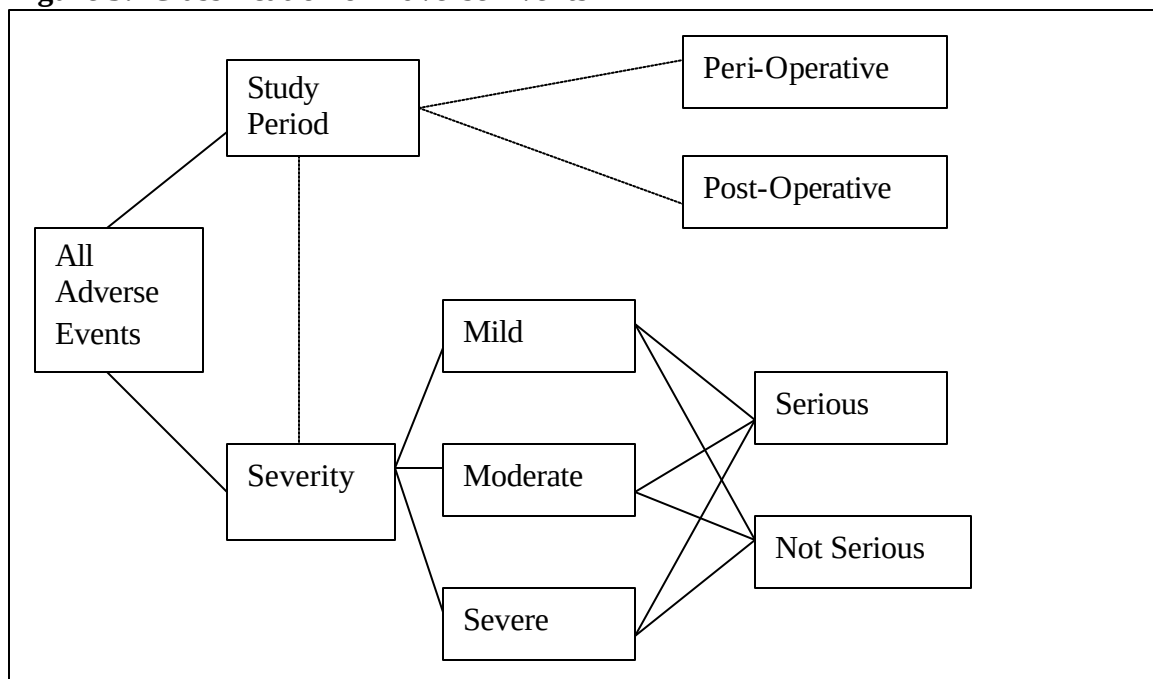
Moderate – symptom of sufficient severity to make patient uncomfortable; performance of daily activities affected; patient is able to continue in study; treatment of symptoms is needed.

Severe – symptom causes severe discomfort and may be of such severity that patient cannot perform daily activities. Severity may result in cessation of treatment or require removal of the device, or treatment of symptom may be given and/or patient hospitalized.

Adverse events were reported as *serious* if considered to be life threatening, permanently disabling, unexpected, fatal, requiring hospitalization, or prolonged hospitalization. All

events categorized as serious in the US clinical study were associated with intervention that required hospitalization or prolonged hospitalization.

Figure 3: Classification of Adverse Events



Adverse events occurring during the study with a frequency of greater than or equal to 5% are shown in the following table:

Table 6: All Adverse Events in the US Clinical Trial Occurring with Frequency $\geq 5\%$

All Adverse Events (Mild, Moderate, Severe)		(N=299) ($\geq 5\%$)
Digestive	N	%
Nausea and/or Vomiting	152	51
Gastroesophageal Reflux	103	34
Stoma Obstruction	41	14
Constipation	27	9
Dysphagia	26	9
Diarrhea	26	9
Abnormal Stools	18	6
Body as a Whole		
Abdominal Pain	80	27
Asthenia	25	8
Incisional Infection	21	7
Infection	20	7
Fever	18	6
Hernia	16	5
Pain	16	5
Chest Pain	15	5
Pain Incision	14	5
Band-Specific		
Band Slippage/Pouch Dilation	72	24
Esophageal dilatation/dysmotility	29	10
Metabolic and Nutritional		
Healing Abnormal	23	8
Port-Specific		
Port Site Pain	26	9
Port Displacement	18	6
Skin and Appendages		
Alopecia	23	8

Peri-operative adverse events were reported in 44% of the study subjects. The most commonly reported peri-operative adverse events were abdominal pain (10%), nausea and/or vomiting (9%), asthenia (5%), and incisional infection (5%). Other peri-operative adverse events occurred in <5% of the subjects.

Eighty-two percent of subjects reported having one or more adverse events during the post-operative period. The most commonly reported adverse events in the post-operative period were: nausea and/or vomiting (42%), gastroesophageal reflux (32%), band slippage/pouch dilatation (24%), abdominal pain (18%), stoma obstruction (14%), dysphagia (8%), alopecia (7%), esophageal dilatation (7%), diarrhea (6%), port site pain (6%), constipation (5%), port displacement (5%), infection (5%), hernia (5%), and constipation (5%). Other post-operative adverse events occurred in less than 5% of the subjects.

The severity of common adverse events (>5%) was also reported, (see Table 7 below). The last two columns in the table represent the total number and percentage of subjects who experienced at least one of the specified events. The severity scale represents the total number of events reported; one subject may have experienced a specific event more than once, and the percentage of all events were rated as mild, moderate, or severe.

Table 7: Common Adverse Events (>5%) in the US Clinical Trial by Severity

	Severity Scale							
Adverse e Event	Mild (n*=299)		Moderate (n=299)		Severe (n=299)		Total subjects with at least one event (n=299)	
	N**	%	N	%	N	%	n	%
Nausea/Vomiting	128	77.6	32	19.4	5	3.0	152	51
GE Reflux	72	60.5	39	32.8	8	6.7	103	34
Abdominal pain	55	64.7	23	27.1	7	8.2	80 ¹	27
Slippage/pouch dilatation	19	24.4	34	43.6	25	32.1	72	24
Stoma obstruction	6	14.6	18	43.9	17	41.5	41 ²	14
Dysphagia	14	50.0	11	39.3	3	10.7	27	9
Diarrhea	23	85.2	3	11.1	1	3.7	26	9
Constipation	20	76.9	6	23.1	0	0	27 ³	9
Alopecia	20	95.2	1	4.8	0	0	23 ⁴	8
Abnormal stool	18	100	0	0	0	0	18	6
Esophageal dilatation/dysmotility	7	30.4	8	34.8	8	34.8	29 ⁵	9.7
Port displacement	5	31.25	9	56.25	2	12.5	18 ⁶	6
Port site pain	19	73.1	6	23.1	1	3.8	26	9
Incision infection	11	50.0	7	31.8	4	18.2	21	7
Infection	9	40.9	10	45.5	3	13.6	20	7

* n=number of subjects

¹ severity not reported for 17 events

³ 1 Subject with no severity

⁵ Severity not reported for 9 events

**N=number of events

² Severity not reported for 11 events

⁴ 2 subjects with no severity

⁶ 2 Subjects with no severity

Some of the commonly reported events associated with the device necessitated revision in some subjects. Surgery may have been required to revise, replace or remove any or all components of the device. The most commonly reported events included:

Band slippage and/or pouch dilatation (BS/PD) – 72 subjects (24%) reported 78 events of band slippage/pouch dilatation. Band slippage refers to slippage of the stomach up through the band rather than slippage of the band down lower on the stomach. This results in an increase in the proximal pouch and a difference in the relative position of the band from where it was implanted. Slippage most commonly involves the posterior gastric wall, but can include any portion of the stomach.

Slippage and pouch dilatation are reported together due to the fact that pouch dilatation can result from band slippage or it may develop independently, and there is no standard for distinguishing between the two events.

The consequences of band slippage varied from subject to subject. In some cases, slippage was documented after radiological inspection of the band position. If subjects showed no symptoms of slippage, often no intervention was deemed necessary or the adjustment of the stoma was sufficient to resolve these asymptomatic findings.

Signs and symptoms reported in association with band slippage included abdominal pain, nausea and/or vomiting, gastroesophageal reflux, dysphagia, and gastric obstruction. For the 56 events reported as “resolved,” 52% of the subjects recovered after stoma adjustment or no intervention, while 48% underwent reoperation, either revision, replacement, or explantation of the device.

Stoma obstruction – Forty-one subjects (14%) in the US clinical trial experienced 52 events of stoma obstruction. Ten patients reported multiple episodes. Signs and symptoms associated with stoma obstruction included band slippage, asthenia, epigastric pain, nausea and vomiting, gastroesophageal reflux, dehydration and hypokalemia (secondary to vomiting). Fifty-six percent (23/41) of the subjects recovered after stoma adjustment or no intervention; 39% (16/41) of the events required surgery (7% revision or replacement and 32% band removal), and in 5% (2/41), the method of resolution was not reported.

Stoma obstruction and the band slippage/pouch dilatation that may be associated with it were the most common causes of LAP-BAND System reoperations.

Abdominal pain – Eighty subjects (27%) reported 102 events of abdominal pain. Abdominal pain often accompanied other events such as dysphagia, gastroesophageal reflux, or nausea and vomiting.

Dysphagia – was reported in 26 (9%) of subjects. It was most commonly associated with, or related to, stomach/band slippage, stoma obstruction, or nausea and/or vomiting.

Esophageal dilatation/dysmotility – Twenty nine subjects (10%) reported 32 events of either esophageal dilation (21), dysmotility (8) or both (3). Esophageal dilatation may be a consequence of incorrect band placement, over-restriction, stoma obstruction, or excess vomiting. Twenty of the events occurred at one site and were believed to be related to band over-inflation. Although most events appeared to resolve with deflation of the band, the long term consequences of this event are not known.

Port site pain – Twenty-six subjects (9%) reported port site pain. Seven were reported in the peri-operative period, 18 in the post-operative period, and one in both

the peri- and post-operative periods.

Port displacement – was reported in 18 subjects (6%). In several of the events the port was suspected on x-ray of being displaced but was found not to have been displaced on further examination.

Serious adverse events reported with a frequency of less than 5% are presented below. Except for the 2 reported deaths, these events always required surgery to remove, replace or revise the device.

Deaths – Two deaths occurred during the course of the study. One subject died from “mixed drug intoxication” one week after explantation. A second patient died one day after explantation of the LAP-BAND and conversion to a Roux-en-Y. Death was due to multiple pulmonary emboli. Neither death is believed to have been device-related.

Erosions – Four subjects (1%) experienced an erosion of the band into the gastric lumen. Two of the erosions were considered to have been secondary to intra-operative gastric perforations. All erosions resolved with explantation of the device.

Mechanical malfunctions – Eight subjects (3%) reported port leakage. The leakage was associated with either cracking of the kink-resistant tubing or disruption of the tubing connection from the port to the band. All of the events resolved after replacement of the port and/or port tubing. In addition, two subjects (0.7%) reported band leakage. One was reported to be due to a leak from a puncture through the thickness of the shell and the other was noted to have resulted from two small holes through the shell.

In addition, there were two reports of malfunction (irregular inflation) of the calibration tube and one report of breakage of the luer-lock connector end of the calibration tube.

Reoperations – Revisions, Replacements, and Explants

Twenty-six subjects (9%) underwent 27 surgical revisions involving the gastric band; one subject had two separate procedures. In 9 of the 27 procedures the band was removed and replaced during a single surgical procedure. Two subjects were reimplanted with a new band during a separate surgical procedure. In 16 of the 27 revision procedures the gastric band was not removed. Most revisions were to correct band slippage/pouch dilatation. Thirteen of the procedures (48%) were completed laparoscopically.

There were twenty-six revisions involving the access port. Thirteen access ports were removed and replaced due to tubing leaks at or near the tubing connections to the port (8/13), port displacement (1/13), or infection (4/13). Nine of these were replaced during the same surgical procedure. The four access ports explanted due to infection were reimplanted at a later time. An additional 13 access ports required revision but did not require removal of the port. The port was repositioned and/or re-sutured in place to correct either misalignment or

movement which resulted in an inability to access the port (9/13), pain associated with movement (3/13), or associated infection (1/13).

A total of 46 subjects (15%) underwent 48 device explantations within 3 years of implantation. An additional twenty-seven subjects (9%) had the band explanted after the 3 year study period. Fifty-one of the 75 explants (68%) were due to complications, primarily band slippage/pouch dilatation and/or obstruction 32% (24/75). Other adverse events cited for explantation of the band included erosion 5% (4/75), infection 4% (3/75), gastroesophageal reflux and/or dysphagia 11% (8/75), system leaks 4% (3/75), and esophageal dilatation or dysmotility 7% (5/75). In the other 24 subjects (32%), insufficient weight loss was cited as the reason for explantation.

In 45 subjects (60%) the explant procedure was performed laparoscopically. Approximately one-half of the explanted patients (37) were converted to a gastric bypass, 3 subjects were converted to a vertical banded gastrosplasty, and 35 subjects had the system removed with no other obesity surgery. Nineteen of the subjects had their obesity surgical procedure (e.g., gastric bypass) performed at the same time that the study device was removed.

Adhesions – Forty-two percent (42%) of those patients undergoing a revision procedure were reported to have developed adhesions involving the stomach. The exact incidence of adhesions is not known, as many of the implanted patients did not undergo re-operation.

XI CONCLUSIONS DRAWN FROM THE STUDIES

The pre-clinical and clinical data provide reasonable assurance of the safety and effectiveness of the LAP-BAND® System for use in weight reduction for severely obese patients, when the system is used in accordance with its labeling.

Results from the pivotal U.S. clinical trial indicate that, for those subjects who were able to complete 36 months of follow-up, a mean excess weight loss (EWL) of 36% and mean overall weight loss of 18% were achieved. Over half of these subjects (62%) lost more than 25% of their excess weight and 22% were able to lose more than 50% of their excess weight. Mean BMI decreased by 19% over the same period of time for these subjects. In addition, quality of life measures showed general improvement for subjects at 3 years.

A majority of the subjects implanted (89%) experienced at least one device-related adverse event. The most common events were nausea/vomiting (51%), gastroesophageal reflux symptoms (34%), abdominal pain (27%), and band slippage/pouch dilatation (24%). Twenty-six (26) of the 292 subjects originally implanted (9%) required surgical device revision and 46 (16%) required device explantation within 3 years of implantation. The indications for these re-operations included band slippage/pouch dilatation, GERD/dysphagia, esophageal dilatation, band erosion and component leakage.

Site-to-Site Variation

Some site-to-site variations in effectiveness and especially in safety were observed in the U.S. Clinical Study. Experience with advanced laparoscopic procedures, attitudes regarding restrictive bariatric procedures, and patient management and support practices were factors. For example, one site reported the majority of esophageal dilatations, which upon review

appeared to be related to a difference in postoperative management. No centers performed more than an average of two to three procedures a month. This limited and infrequent experience would be expected to cause and did cause a protracted learning curve in both laparoscopic placement and patient management, resulting in a higher incidence of adverse events and reoperations than reported in the published literature by surgeons with more experience.

XII PANEL RECOMMENDATION

The Gastroenterology and Urology Devices Panel met on June 19, 2000, to consider the safety and effectiveness of the BioEnterics Corporation LAP-BAND Adjustable Gastric Banding (LAGB) System. The Panel voted six to four to recommend that the Center for Devices and Radiological Health (CDRH) not approve the PMA for the LAP-BAND System. They believed that 2 years of follow-up data was not adequate and they recommended at least 3 years of follow-up prior to approval. The study protocol for the U.S. clinical study called for 3 years of patient follow-up.

XIII CDRH DECISION

CDRH agreed with the advisory panel recommendation and sent a major deficiency letter on August 7, 2000, detailing the data and information that was still needed. In addition to the 3 years of patient follow-up, recommendations concerned the labeling and a post-approval study.

The applicant continued its clinical study and on December 26, 2000, amended the PMA. After review of the additional information, CDRH determined that there is sufficient safety and effectiveness data to approve the LAP-BAND Adjustable Gastric Banding System. The sponsor submitted revised labeling and an outline for the post-approval study via email and fax. In the post approval study the subjects enrolled in the U.S. clinical trial will continue to be followed for a total of five years post implantation. The purpose of the post-approval study is to obtain additional information on excess weight loss, and adverse events, primarily esophageal dilatation and band erosion. Subjects will have continued follow-up for 5 years post-implantation.

XIV APPROVAL SPECIFICATIONS

Directions for Use: See attached Physician Labeling

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

Patient Information: A Surgical Aid in the Treatment of Morbid Obesity – LAP-BAND Adjustable Gastric Banding System Information for Patients

Post-approval Requirements and Restrictions: See approval order.

Training Program

Surgeon participation in a training program authorized by BioEnterics or by an authorized BioEnterics distributor is required prior to use of the LAP-BAND System.

XV REFERENCES

1. National Institutes of Health Technology Assessment Conference Panel. Methods for Voluntary Weight Loss and Control. *Ann Intern Med.* 1993; 119(7):764-770.
2. National Task Force on the Prevention and Treatment of Obesity. Long-term Pharmacotherapy in the Management of Obesity. *JAMA* 1996; 276(23):1907-1915.