



CIGNA MEDICAL COVERAGE POLICY

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Subject Endoscopic Anti-Reflux Procedures

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Hyperlink to Related Coverage Policies

Proton Pump Inhibitor Therapy
Wireless Esophageal pH Monitoring System (Bravo™)

INSTRUCTIONS FOR USE

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Coverage Policy

CIGNA does not cover endoscopic anti-reflux procedures for the treatment or management of gastroesophageal reflux disease (GERD) because they are considered experimental, investigational or unproven. Procedures that are considered experimental, investigational or unproven include, but are not limited to, the following:

- radiofrequency energy to the gastroesophageal junction (e.g., Stretta® System)
- endoluminal gastroplasty/gastrotomies (e.g., EndoCinch™ or Bard™ Endoscopic Suturing System [BESS], Endoscopic Plication™ System, Syntheon ARD Plicator, EsophyX™ System, StomaphyX™)
- injection/implantation of biocompatible material (e.g., plexiglas or polymethylmethacrylate [PMMA], Durasphere™, Gatekeeper™ Reflux Repair System)

General Background

Gastroesophageal reflux disease (GERD) is defined as symptoms or mucosa damage resulting from the reflux of gastric content into the esophagus. Mucosa damage can vary from none, to mild esophagitis, to more severe esophagitis, and, less commonly, Barrett's esophagus and esophageal carcinoma. The goal of therapy is to control both the symptoms and mucosal damage.

Treatment for GERD may include lifestyle changes (e.g., elevating the head of the bed, decreasing fat intake, quitting smoking, diet), pharmacological therapy (e.g., acid suppressants) or anti-reflux surgery. The majority of GERD patients have mucosal disease, and symptoms are controlled with medical therapy. Anti-reflux surgery may be an option for patients who have failed pharmacotherapy or for those who choose not to continue on medication therapy for the long term. An open or laparoscopic Nissen fundoplication may be considered for patients and is considered the standard surgical therapy.

Endoscopic Therapies

A variety of endoscopic therapies for the treatment of GERD have been developed and proposed as alternatives to pharmacological therapy or anti-reflux surgery. These techniques include the delivery of radiofrequency energy to the gastroesophageal junction, injection of bulking agents, or implantation of a bioprosthesis into the lower esophageal sphincter, and suture plication of the proximal gastric folds. These therapies are designed to alter structures at the gastroesophageal junction to prevent reflux of gastric contents (Richter, 2010).

Recent textbook literature reports most studies of endoscopic therapy have only limited follow-up information on a relatively small number of patients. The durability of these techniques beyond one to two years remains unclear and seems to gradually decrease over time. Most importantly, safety issues have resulted from these procedures, especially when used in the broader community of gastroenterologists. Chest pain, bleeding, esophageal perforations, mediastinitis, and at least eight deaths to date have been attributed to these endoscopic techniques (Richter, 2010). Currently, endoscopic therapies are not advocated in routine practice.

Radiofrequency Energy: Radiofrequency energy for the treatment of GERD requires a special single-use catheter and radiofrequency energy generator (Stretta[®] System, [currently manufactured by Mederi Therapeutics, Greenwich, CT]). The procedure is generally performed using standard conscious sedation but has required general anesthesia in some patients. The possible mechanisms of action that result from radiofrequency energy are scarring or neurolysis at, or near, the gastroesophageal junction. This procedure is commonly referred to as the Stretta procedure (Falk, et al., 2006a).

Gastroplasty/Gastroplication: There are two basic techniques designed to place sutures or staples at the cardia, including submucosal stitching devices and deep transmural plicating devices. Both techniques create pleats or plications of tissue just beneath the gastroesophageal junction. Sedation required for this technique varies as does procedure time. Examples of suturing/plication devices include the EndoCinch[™] or Bard Endoscopic Suturing System (BESS) (Bard Endoscopic Technologies, Billerica, MA); the full-thickness NDO Surgical Endoscopic Plication[™] System (NDO Surgical, Inc., Mansfield, MA); and the Syntheon ARD Plicator (Syntheon, Miami, FL).

The EsophyX[™] system (EndoGastric Solutions, Inc., Redmond, WA) creates a transoral incisionless fundoplication[®] (TIF). The EsophyX system deploys multiple full thickness serosa-to-serosa fasteners into the gastric wall to form an interrupted suture line at the base of the gastroesophageal junction, thus recreating the gastroesophageal valve mechanically. This is sometimes referred to as the endoluminal fundoplication (ELF) technique. The predicate device to the EsophyX system is the StomaphyX[™] (EndoGastric Solutions, Inc., Redmond, WA) (Demyttenaere, et al., 2010; ECRI, 2010).

Injection/Implantation of Biocompatible Material: Bulking agents are substances injected under endoscopic guidance into the esophageal wall at the level of the esophagastric junction to impede reflux (American Society for Gastrointestinal Endoscopy [ASGE]), 2007). In the 2006 American Gastroenterological Association (AGA) technical review on the use of endoscopic therapy for GERD, the authors reported that "there are no longer any devices that require injection of bulking agents or implantation of a bioprosthesis in the lower esophageal sphincter zone" (Falk, et al., 2006a). Implantable products/devices include:

- expandable hydrogel prosthesis (Gatekeeper[™] Reflux Repair System; Medtronic, Inc., Minneapolis, MN). It has been reported that the device was withdrawn in late 2005 before U.S. Food and Drug Administration (FDA) approval.
- ethylene vinyl alcohol copolymer with tantalum dissolved in dimethyl sulfoxide (Enteryx[™]; Boston Scientific Corp, Natick, MA).
- plexiglas polymethylmethacrylate microspheres (PMMA). This agent is not commercially available in the United States).

- pyrolytic carbon-coated graphite beads suspended in a water-based carrier gel suitable for suspending the carbon-coated beads (Durasphere™, Carbon Medical Technologies, St Paul, MN). Durasphere is an injectable bulking agent that is being proposed in the treatment of mild-moderate GERD. A small nonrandomized study (n=10) was conducted by Ganz et al (2009). This study is the first report of Durasphere for the treatment of GERD. On the basis of the findings and limitations of this study, further investigation of this agent is warranted including large controlled studies with long-term outcomes.

Adverse Events

Madan et al. (2006) summarized the adverse events of endoluminal therapies for the treatment of GERD. The FDA Manufacturer and User Facility Device Experience data base (MAUDE) was searched to examine all voluntary adverse events reported on emerging endoluminal therapies. The adverse events were divided into three categories: radiofrequency ablation, injection, and suture. A total of 50 adverse events were reported on four specific therapies. Half of the complications were a result of injection-based therapy, and 44% of the complications were found to result in radiofrequency ablation-based therapy. A total of eight deaths were reported (i.e., five in the injection group and three in the radiofrequency ablation group). Sixty-four percent of the adverse events resulted in hospitalizations, and 10% of the patients required surgery.

U.S. Food and Drug Administration (FDA)

The Stretta System (FDA, 2000a), EndoCinch or Bard Endoscopic Suturing System (FDA, 2000b), NDO Surgical Endoscopic Plication System (FDA, 2003), EsophyX System (FDA, 2007), EsophyX2™ System (FDA, 2009) and StomaphyX™ (FDA, 2007) have been approved through the 510(k) premarket notification process. The Syntheon ARD Plicator, Gatekeeper Reflux Repair System, and PMMA are not FDA-approved devices.

Although FDA approved for GERD in April 2003, the FDA issued Advice for Patients with Enteryx for Gastroesophageal Reflux Disease, stating Boston Scientific has recalled all Enteryx Procedure Kits and Enteryx Single Pack Injectors because of reports that improper injection procedures can lead to serious patient injury or death (FDA, 2009).

Durasphere™ received PMA-Premarket Approval in 1999. The FDA approval order statement states that, “this device is indicated for use in the treatment of adult women with stress urinary incontinence due to intrinsic sphincter deficiency” (FDA, 2008). There is no FDA indication for the treatment of GERD.

Literature Review

Radiofrequency Energy (Stretta Procedure): Aziz et al. (2010) conducted a 12-month randomized, double-blind, sham-controlled trial to assess the Stretta procedure. Thirty-six patients with antisecretory medication-dependent GERD for more than six months were randomized to receive a single-session radiofrequency (RF) procedure, a double-session RF procedure for patients who had < 75% improvement of GERD-HRQL at four months, or a sham procedure. Each patient in the active treatment groups received 56 RF lesions per session. With the double-session group, the authors examined whether 112 lesions created in two sessions several months apart were safer than 112 lesions created during a single session, which was the initial “dose” applied during development of the procedure and resulted in esophageal perforation in a few cases. Ten of 12 patients in the double-session group (83%) underwent both sessions. At 12 months, two of 12 patients (17%) in the single-session group, six of 12 patients (50%) in the double-session group, and zero of 12 patients in the sham group had discontinued antisecretory medication therapy. Within group comparisons showed statistically significant improvements in GERD-HRQL in all three treatment groups: In the single-session RF group, GERD-HRQL scores improved from a mean of 30 at baseline off meds to 14 post-treatment; in the double-session RF group, GERD-HRQL scores improved from 31 to 11; and in the sham group, GERD-HRQL scores improved from 30 to 25. Post-treatment values in the active treatment groups were significantly greater than the sham group ($p < 0.001$), but did not differ from each other ($p > 0.05$). Lower esophageal sphincter pressure increased in the active treatment groups to a statistically significant degree (from 12 mmHg to 16 mmHg in the single-session group, and from 12 mmHg to 20 mmHg in the double-session group; $p < 0.01$ for both groups) but not in the sham group (14 mmHg at baseline to 16 mmHg post-treatment, $p > 0.05$). The total time esophageal pH was less than 4.2 in a 24-hour period decreased to a statistically significant degree in the active treatment groups (from 9.4 minutes to 6.7 minutes in the single-session group ($p < 0.01$), and from 8.8 minutes to 5.2 minutes in the double-session group ($p < 0.01$) but not in the sham group (9.9 minutes at baseline to 8.2 minutes post-treatment ($p > 0.05$)). The clinical relevance of these changes is uncertain. Transient post-procedure adverse events (retrosternal discomfort requiring oral analgesics, mild fever, nausea/vomiting, and dysphagia) were experienced by more patients in the active treatment groups than in the sham groups. Serious adverse events

occurred in one patient in the single-session group who developed pneumonia and bilateral pleural. Two patients who received double sessions of RF treatment developed prolonged gastroparesis. During 12 months of follow-up evaluation, one of these two patients showed mild improvement, whereas the other showed no improvement despite high doses of prokinetic medication. The authors reported that “worsening gastroparesis may be due to vagal injury during Stretta treatment, especially with a greater number of RF lesions.”

Coron et al (2008) conducted an unblinded randomized trial of 43 PPI-dependent GERD patients who continued the effective dose of their PPI (n=20) or received the radiofrequency Stretta procedure (n=23). At six months, significantly more patients in the treatment group were able to discontinue or decrease their PPI use by at least 50% than in the control group, a difference that was not maintained at 12 months. The number of patients able to discontinue PPI medication did not differ between groups. Adverse events in the treatment group were described as “transient” and included epigastric discomfort or abdominal pain, odynophagia and fever. There were no adverse events in the control group. This study was interrupted prematurely because of the decision of Curon Ltd to stop the commercialization of Stretta devices. The authors report that at one year data are difficult to interpret because of the relatively small number of patients remaining in the trial.

In a prospective study, Noar et al. (2007) reported on data from a series of 109 consecutive drug-refractory GERD patients treated with the Stretta procedure who reached four-year follow-up assessment. Heartburn scores, total heartburn scores, and patient satisfaction improved (p<0.001). Medication usage decreased from 100% in patients who were on twice-daily PPI therapy at baseline to 75% of patients showing elimination of medications, or only as-needed use of antacids/over-the-counter PPIs, at 48 months (p<0.005). The authors reported no serious complications related to the procedure. The authors stated the limitations of this study are the lack of a comparative group and no long-term pH or motility studies. Similar findings were reported in a prospective study of 83 patients by Reymunde et al. (2007).

Lutfi et al. (2005) reported on data from their three-year experience with the Stretta procedure. GERD was documented by a positive 24-hour pH study. Patients were excluded from the study for the following: a hiatal hernia > 3 cm, a lower esophageal sphincter (LES) pressure < 8mm Hg, Barrett’s esophagus, active grade 3 or 4 esophagitis, American Society of Anesthesiologist 4, age < 18 years, and pregnancy. Patients were mailed SF-12 health status questionnaires and GERD-specific quality of life questionnaires, questions about satisfaction with Stretta and medication use. Seventy-seven patients with follow-up times > six months qualified for the study. Follow-up surveys were completed by 61 patients. Sixty-one percent of the patients were satisfied with the procedure. There were no long-term procedure-related complications. Twenty-six patients were completely off PPI at follow-up. There were 39 responder patients who were taking ≤ 50% of their original dosage or were completely taken off their medications. Twenty-two patients who remained on the same preoperative dosage or reduced their original dose by 50% were considered nonresponders, including eight patients who underwent Nissen fundoplication. The overall satisfaction rate was 73%. Ninety-five percent of the responders were satisfied, while only 41% of the nonresponders were satisfied and said they would have the procedure again. Twenty-four patients who completed the questionnaires agreed to undergo the 24-hour pH study, including 18 responders and six nonresponders. There was an improvement in distal acid exposure for those patients who had the 24-hour pH study ($7.8 \pm 2.6\%$ to 5.1 ± 3.3 ; p=0.001). The authors stated the limitations of this study are the small number of patients responding and the small number of patients who agreed to come back for the 24-hour pH study. Furthermore, the authors stated longer term studies with more complete follow-up are needed to fully assess the role of Stretta in the management of GERD.

In a randomized study, GERD patients received radiofrequency energy delivery to the gastroesophageal junction (n=35) or to a sham procedure (n=29). Principal outcomes were reflux symptoms and quality of life. Secondary outcomes were medication use and esophageal acid exposure. After six months, interested sham patients crossed over to active treatment. Results at six months indicate active treatment significantly and substantially improved patients' heartburn symptoms and quality of life. More active (61%) versus sham (33%) patients were without daily heartburn symptoms and more had a > 50% improvement in their GERD quality of life score (61% versus 30%). Symptom improvements persisted at 12 months after treatment. At six months, there were no differences in daily medication use after a medication withdrawal protocol or in esophageal acid exposure times. There were no perforations or deaths. The authors stated, “This procedure represents a new option for selected symptomatic GERD patients who are intolerant of, or desire an alternative to, traditional medical therapies” (Corley, et al., 2003).

In a multicenter study, researchers evaluated GERD symptoms, patient satisfaction, and antisecretory drug use in 558 patients treated with the Stretta procedure. Mean follow-up was eight months. After treatment, onset of GERD relief was less than two months (68.7%) or 2–6 months (14.6%). The median drug requirement improved from PPIs twice daily to antacids as needed. The percentage of patients with satisfactory GERD control, absent or mild, improved from 26.3% at baseline, on drugs, to 77.0% after Stretta. Median baseline symptom control on drugs was 50%, compared to 90% at follow-up. Baseline patient satisfaction on drugs was 23.2%, compared to 86.5% at follow-up. Authors contend these results support the use of the Stretta procedure for patients with GERD, particularly those with inadequate control of symptoms on medical therapy (Wolfsen, et al., 2002).

A prospective study of 94 patients evaluated the Stretta procedure. At 12 months follow-up, PPI requirement fell from 88.1% to 30% of patients. Also at 12 months, GERD symptom scores, patient satisfaction score, SF-36, and esophageal acid exposure by 24-hour pH improved significantly (Triadafilopoulos, et al., 2002).

A comparative study evaluated the short-term results of the radiofrequency treatment of the gastroesophageal junction known as the Stretta procedure versus laparoscopic fundoplication (LF) in patients with GERD. Patients were offered the Stretta procedure (n=65) if they had documented GERD and did not have a hiatal hernia larger than 2 cm, LES pressure less than 8 mmHg, or Barrett's esophagus. Patients with larger hiatal hernias, LES pressure less than 8 mmHg, or Barrett's were offered LF (n=75). Preoperative esophageal acid exposure time was higher in the LF group. Preoperative LES pressure was higher in the Stretta group. There was an equal magnitude of improvement between pre- and postoperative quality of life and SF-12 scores between Stretta and LF patients. Both groups were highly satisfied with their procedure. The authors reported that patients undergoing Stretta have improved GERD symptoms and quality of life comparable to LF and believe the Stretta procedure is an effective alternative to LF in well-selected patients (Richards, et al., 2003).

Gastroplasty/Gastroplication (EndoCinch Suturing System): In a randomized sham-controlled trial, Schwartz et al. (2007), reported on endoscopic gastroplication by the EndoCinch suturing system. A total of sixty patients with GERD were randomly assigned to three endoscopic gastroplications (n=20), a sham procedure (n=20) or observation (n=20). The primary outcome measures were PPI use and GERD symptoms. The secondary measure was 24-hour esophageal acid exposure. Follow-up assessments were performed at three, six, and 12 months. At three months, the percentage of patients who had reduced drug use by $\geq 50\%$ was greater in the active treatment group (65%) than in the sham (25%) or observation groups (0%) ($p < 0.02$). GERD symptoms improved more in the active group than in the sham group ($p < 0.01$). Esophageal acid exposure was modestly decreased after active treatment ($p < 0.02$) but was not significantly greater than after the sham procedure ($p = 0.61$). The active treatment effects on PPI use and symptoms persisted after six and 12 months of open-label follow-up (n=41), but 29% of patients were re-treated in this period. The authors stated, "Widespread use of the endoscopic suturing device should probably be avoided until the technique is improved and efficacy on objective end points has been proved in a sham-controlled fashion" (Schwartz, et al., 2007).

Montgomery et al. (2006) reported data from 46 patients enrolled in a single-center, randomized, sham-controlled trial of EndoCinch plications. There was no difference in the use of PPIs between the sham and the EndoCinch groups at six weeks or 12 months, whereas at three months, there was a significant reduction in the use of PPIs in the treatment group compared to controls ($p < 0.05$). Compared to baseline, there was a significant improvement in QOL as assessed by the gastrointestinal symptom rating scale (GSRS) at six weeks, as well as at three and 12 months post-procedure in both groups. At three months (but not at six weeks and 12 months), there was a significant difference in GSRS scores between the groups, favoring the treatment group versus the control group. Similarly to the sham group, the EndoCinch treatment group had no significant changes in esophageal acid exposure, as indicated by pH monitoring at three and 12 months, in any of the groups.

Chen et al. (2005) reported results of a prospective, multicenter trial with two-year follow-up of 85 patients who were treated with endoluminal gastroplication (ELGP) using the EndoCinch device for GERD. Inclusion criteria were three or more heartburn or regurgitation episodes per week, $> 4.2\%$ time in 24 hours with esophageal pH < 4 , and dependency on antisecretory medications. Exclusion criteria were the presence of varices, achalasia, aperistalsis, or previous gastric resection. Patients underwent manometry, 24-hour pH monitoring, and symptom severity scoring before and after the procedure. Patient diaries were used to assess medication use and to estimate annual medication cost. The authors reported that ELGP is safe and effective for the long-term control of GERD symptoms. The procedure also appears to reduce esophageal acid exposure substantially for at least six months. Antisecretory medications were significantly decreased after ELGP, resulting in a large reduction in annual drug costs. Seven patients experienced adverse events (i.e., oozing at suture site, melena,

bronchospasm, dysphagia, and hypoxemia from sedation). The authors stated patients with classic GERD symptoms who are responsive to antisecretory medications are good candidates for ELGP if an alternative to long-term medical therapy or surgery is being considered. Additional studies will be needed to evaluate whether the procedure should be routinely offered to patients who fail medical therapy or who have other unfavorable parameters.

Schiefke et al. (2005) prospectively evaluated the long-term outcome after EndoCinch. A total of 70 patients were interviewed using a standard questionnaire regarding their symptoms and medications prior to and 18 months after EndoCinch. Follow-up included endoscopy, 24-hour pH monitoring, and esophageal manometry. No major short- or long-term complications post-procedure were reported. At 18 months after procedure, 56/70 patients were considered treatment failures, as their heartburn symptoms did not improve, or PPI medication exceeded 50% of the initial dose. Endoscopy showed all sutures in situ in 12/70 patients, while no remaining sutures were detected in 18/70 patients. The authors summarized that EndoCinch was shown to be safe but not as effective as expected after 18 months of follow-up. The loss of plications was reported in the majority of patients which led to treatment failure.

A study of 87 consecutive patients compared transoral endoluminal gastroplasty (EG) by the Bard EndoCinch device and laparoscopic anti-reflux surgery (LAS) (Chadalavada, et al., 2004). Overall, 66% of patients were satisfied with EG as compared to 93% after LAS. Postoperative PPI/motility agent use was 32% for EG and 13% for LAS. Three EG patients subsequently had LAS within six months of the procedure. These researchers believe LAS offers a greater reduction in medication use than EG, as well as more durable patient satisfaction and that the benefits of EG may include short-term symptomatic improvement while considering definitive surgical management.

An evaluation was conducted to determine any benefit of the Endocinch technique in 22 patients seen up to 12 months post-procedure (Mahmood, et al., 2003). Heartburn symptom scores and regurgitation scores were reduced. Mean (standard error of mean) pH DeMeester acid score was reduced at three months post-procedure. Percentage upright acid exposure and number of reflux episodes were also reduced significantly. Use of PPIs was reduced by 64% at 12 months post-procedure. All quality of life assessments showed significant improvement.

A multicenter trial evaluated plication in 64 patients treated with a transoral, flexible endoscopic suturing (Filipi, et al., 2001). Eleven patients required repeat procedure for suboptimal results, and ten patients withdrew. In 47 patients with complete follow-up, gastroesophageal reflux symptoms improved. Twenty-four-hour pH monitoring at three and six months indicated improvement in 24 patients studied.

EsophX System: In a case series study, Testoni et al. (2010) assessed the effect of transoral incisionless fundoplication (TIF) using the new (2.0) version of the Esophyx device on symptoms, PPI use, esophageal motility, and pH impedance findings in a consecutive series of patients with symptomatic GERD. The EsophX 2.0 system deploys fasteners starting at the posterior and anterior sides of the gastroesophageal valve rather than at the middle of the valve. Eighteen patients, who had pathological GERD before the procedure, as measured by pH-impedance, were included in the outcomes analysis; two patients with normal 24-hour pH-impedance at baseline were excluded. At six months, 10 of the 18 patients (56%) had discontinued daily PPI therapy. GERD-HRQL scores improved from a mean of 45 at baseline off PPI to 16 post-treatment, a statistically significant improvement ($p < 0.001$). However, the post-treatment value did not appear to be different from the baseline score on PPI, 20. There were significantly fewer acid and non-acid refluxes. There was no significant difference in lower esophageal sphincter (LES) pressure or pH. Small hiatal hernias (< 3cm) were eliminated in eight of 13 patients (62%) who had hernias at baseline. No serious complications arose. All patients reported transient pharyngeal irritation and moderate epigastric pain not requiring analgesics at the time of the procedure. The limitations of this study are the small sample size, uncontrolled design and the short follow-up period.

In a case series study ($n=26$), Demyttenaere et al. (2010) evaluated patients undergoing Esophyx fundoplication for a one-year period between September 2007 and March 2009. Patients referred for surgical management of GERD were given the option of undergoing endolumenal fundoplication. Two complications of postoperative bleed occurred, requiring transfusion. The mean follow-up period was 10 months. Although 68% of the patients were still taking antireflux medications, 21% had reduced their dose by half. Three patients had persistent symptoms requiring Nissen fundoplication, and there was one late death unrelated to the procedure.

Both symptoms and health-related quality-of-life (HRQL) scores significantly improved after treatment. The authors reported that further study with pH testing and endoscopic evaluation of the neovalve are required. Increased experience will help to identify the patient population most likely to benefit from transoral incisionless fundoplication compared with other treatments. This study is limited by the lack of a control group and small sample size.

Cadière et al. (2009) reported on two-year follow-up results from a feasibility study of the Esophyx procedure. The study included 14 of 19 patients from the original case series (Cadière, et al., 2008a). Two patients were excluded from the original study due to gastric anomalies, two patients underwent surgical treatment or repeat endoscopic gastroplasty, and one patient was lost to follow-up. All patients had PPI-dependent GERD for more than six months. At two years, 10 patients (71%) had discontinued daily PPI therapy. GERD-Health-Related Quality of Life (HRQL) scores improved from a median of 17 at baseline on PPIs to seven post-treatment, a statistically significant improvement ($p=0.004$). GERD-HRQL scores <12 (indicative of heartburn elimination) were reported by 13 patients (93%). pH scores normalized in all patients, regardless of clinical response to treatment. Small hiatal hernias were eliminated in six of ten patients (60%) who had hernias at baseline. Although patients reported transient pharyngeal irritation, bloating, and mild epigastric pain at the time of the procedure, no adverse procedure-related events were reported at two-year follow-up. The authors reported that although the presented two-year results were encouraging, they had a limited value for generalization because of the small study population and the exclusion of patients who required retreatment. A multicenter study is currently underway to evaluate the long-term efficacy of TIF in eliminating symptoms and normalizing acid exposure.

In a case series study ($n=20$), Repici et al. (2010) evaluated the six and 12 month clinical results of endoluminal fundoplication (ELF) with EsophyX. All patients had PPI-dependent GERD for at least six months. Four patients with persistent GERD symptoms despite the use of standard PPI doses were scheduled for laparoscopic fundoplication at month six, and one patient was lost to follow-up. Seven patients (35%) had discontinued PPI therapy at 12 months. Eleven patients (55%) had an improved GERD-HRQL $>50\%$ (median baseline GERD-HRQL = 40). There was no significant change from baseline in mean LES pressure and acid or non-acid reflux. Two additional patients (for a total of six of 20 patients, 30%) were scheduled for laparoscopic surgery after the 12-month follow-up for persistence of symptoms. Serious adverse events occurred in two patients with hematemesis on the first and eighth postoperative day. Of note, in the four patients who underwent laparoscopic fundoplication at six months, fasteners were found partially extruded as if the stomach wall had disengaged from the H suture, which was still present on the esophageal side. The authors reported that based on their experience, ELF with EsophyX should still be considered an investigational procedure with no role in routine treatment of GERD.

In a prospective study, Cadière et al. (2008b) evaluated the safety and efficacy of transoral incisionless fundoplication (TIF) using the EsophyX system in the treatment of GERD. A total of 86 patients with chronic GERD treated with PPIs were enrolled. Exclusion criteria included an irreducible hiatal hernia > 2 cm. The TIF procedure ($n=84$) reduced all hiatal hernias ($n=49$) and constructed valves measuring 4 cm (2–6 cm) and 230 degrees (160–300 degrees). At 12 months, 73% of the study participants had 50% or greater improvement in GERD health-related quality life scores. A total of 85% of the study participants discontinued daily PPI use, and 81% had complete cessation of PPIs. Less than 37% had normalization of esophageal acid exposure. EsophyX-TIF cured GERD in 56% of patients based on their symptom reduction and PPI discontinuation. Serious adverse events consisted of two esophageal perforations upon device insertion and one case of postoperative intraluminal bleeding. Other adverse events were mild and transient.

Endoscopic Plication System: In a multicenter prospective, open-label, postmarket registry study, Birk et al. (2009) assessed full-thickness fundoplication using the Plicator for the treatment of GERD. The study included 131 patients variably responsive to PPI therapy. At 12 months, 50 patients (38%) were lost to follow-up or had not yet reached their 12-month follow-up visit. Sixty-six percent of the remaining 81 patients demonstrated a 50% reduction in their GERD-Health Related Quality of Life (GERD HRQoL) score compared to their pre-fundoplication (off meds) score. No serious adverse events were reported. The lack of a control or comparison group limits the use of these findings.

The safety and efficacy of the Plicator procedure was studied in a prospective multicenter trial and evaluated in four subsequent reports with follow-up of 6, 12, 36 and 60 months, respectively (Pleskow et al., 2004; Pleskow et al., 2005; Pleskow et al., 2007; Pleskow et al., 2008). Sixty-four patients initially underwent plication to assess

the safety and efficacy of endoscopic full-thickness plication. At six months after plication, PPI therapy had been eliminated in 74% of previously medication-dependent patients. Twenty-nine patients completed the 12-month and 36-month follow-up. All procedure-related adverse events occurred acutely, and no new events were observed during extended follow-up. At 36-months post-procedure, 57% of baseline PPI-dependent patients remained off daily PPI therapy. Treatment effect remained stable from 12–36 months, with 21/29 patients off daily PPI at 12 months compared to 17/29 patients at 36 months. Median GERD–Health Related Quality of Life (HRQL) scores remained significantly improved at 36 months versus baseline off meds scores (8 versus 19, $p < 0.001$). In addition, the proportion of patients achieving $\geq 50\%$ improvement in GERD-HRQL score was consistent from 12 months (59%) to 36 months (55%). No long-term procedural adverse effects were reported. The results of the prospective, uncontrolled studies suggested that endoscopic full-thickness plication was effective, reducing symptoms and medication use associated with GERD. Treatment effect was stable for at least five years postprocedure. The authors considered the procedure safe, despite a few complications (gastric perforation, dyspnea, and mucosal abrasion in the fundus). The studies were limited by small sample size and lack of a control group. In addition, due to termination of the initial 64-subject study and the challenge of retaining subject contact during the extended time period since initial Plicator treatment, only a subset of subjects who had originally undergone the Plicator procedure were enrolled in this 60-month follow-up study, therefore, the potential for a referral bias exists. Another limitation of this study design is its exclusion criteria. Potential GERD subjects excluded from this study are those frequently encountered in a practice setting. Their characteristics may include: presenting with a large hiatal hernia, advanced erosive esophagitis, and/or nonresponse to antisecretory therapy. A final limitation of this study is that evidence of long-term Plicator integrity was not assessed.

Studies of the Plicator procedure to date have been limited to placement of a single transmural suture to create the endoscopic gastroplication. In a prospective multicenter study, von Renteln et al. (2008) evaluated the safety and efficacy of placing multiple transmural sutures for the treatment of GERD. The study included patients with symptomatic GERD who require daily maintenance PPI therapy. Study exclusions were hiatal hernia >3 cm, grades III and IV esophagitis, Barrett's epithelium, and esophageal dysmotility. Forty-one patients received two or more transmural sutures placed linearly in the anterior gastric cardia approximately 1 cm below the GE junction. The data demonstrated that the Plicator improved overall patient outcomes when compared with the preprocedure baseline. GERD-HRQL improved 76%, heartburn symptoms measured by VAS were improved 80%, 74% of patients experienced a positive improvement in acid exposure, and 35% of patients with mild esophagitis improved at least one grade level. The authors reported that further studies and long-term data regarding the safety and efficacy of this procedure will be necessary to define the value of the Plicator compared with already-established GERD therapies. Other limitations of this study are the small sample size and lack of a comparison with a single implant group. At 12-months, 24 of 41 patients (59%) had discontinued daily PPI therapy. Twenty-six of 41 patients (63%) had an improved GERD-HRQL $>50\%$. GERD-HRQL scores improved from a median of 25 at baseline off PPI to eight post-treatment, a statistically significant improvement ($p < 0.001$), and from a median of 11 at baseline on PPI to eight post-treatment, a statistically significant improvement ($p = 0.015$). Acid exposure was not measured. All procedure-related adverse events occurred within the first post-procedure week. The authors stated that the long-term durability of the endoscopically restructured gastroesophageal junction and the long-term effects on esophagitis and pH-metry should be compared with surgical therapy. These data are necessary to define the value of the Plicator compared with established GERD therapies (von Renteln, 2009).

In a randomized, prospective multicenter trial, Rothstein et al. (2006) examined the effectiveness of endoscopic full-thickness plication for the treatment of GERD in comparison with a sham procedure. Patients with symptomatic GERD requiring maintenance PPI therapy were entered into the trial. A total of 78 patients were randomly assigned to undergo endoscopic full-thickness restructuring of the gastric cardia with transmural suture, while 81 patients underwent a sham procedure. Group assignments were revealed following the three-month evaluation. The primary end point was greater than or equal to 50% improvement in GERD HRQL score. Secondary end points included medication use and esophageal acid exposure. By intention-to-treat analysis, at three months, the proportion of patients achieving greater than or equal to 50% improvement in GERD-HRQL score was significantly greater in the active group (56%) compared to the sham group (18.5%; $p < 0.001$). Complete cessation of PPI therapy was higher among patients in the active group than in the sham group by intention-to-treat analysis (50% versus 24%; $p = 0.002$). The percent reduction in median percent time pH less than four was significantly improved within the active group versus baseline (7 versus 10, 18%, $p < 0.001$) but not in the sham group (10 versus 9, -3%, $p = 0.686$). Between-group analysis revealed the active therapy to be superior to the sham in improving median percent time pH less than 4 ($p = 0.010$). Twenty-four patients

randomized in the study were lost to follow-up or excluded from further study because they were ruled ineligible by entry criteria. The authors stated, "Further studies, including those with longer term follow-up, will help clarify the role of this promising procedure across a broader range of patients with GERD" (Rothstein, et al., 2006).

Technology Assessments/Reviews

Chen et al. (2009) conducted a systematic review of 33 studies examining seven endoscopic treatments for GERD. Literature databases were searched up to May 2006 without language restriction. A total of 33 studies examining seven endoscopic procedures (Stretta procedure, Bard EndoCinch, Wilson-Cook Endoscopic Suturing Device, NDO Plicator, Enteryx, Gatekeeper Reflux Repair System and Plexiglas) were included in the review. Of the three procedures that were tested against sham controls (Stretta procedure, Bard EndoCinch and Enteryx), patient outcomes in the treatment group were either as good as, or significantly better than, those of control patients in terms of heartburn symptoms, quality of life and medication usage. However, for the two procedures that were tested against laparoscopic fundoplication (Stretta) procedure and Bard EndoCinch), outcomes for patients in the endoscopic group were either as good as, or inferior to, those for the laparoscopic group. The authors concluded that, "Despite the potential benefits of these procedures, there is insufficient evidence at present to establish their safety and efficacy, particularly in the long-term."

In 2009, the National Institute for Clinical Excellence (NICE) an organization within the United Kingdom which provides healthcare guidance issued an interventional procedure guidance document titled Endoscopic Radiofrequency Ablation for GERD and concluded that the evidence on safety and efficacy of endoscopic radiofrequency ablation for GERD is inadequate and there are inconsistencies in the evidence on efficacy (NICE, 2009).

Fry et al. (2007) conducted a systematic review of the evidence on the effect of endoscopic therapies for GERD. Forty-three studies met their inclusion criteria including four randomized controlled trials. Many of the studies were small feasibility studies, with follow-ups of less than one year. No study comparing endoscopic techniques with other established treatment options such as PPIs existed. All endoscopic therapies were associated with a small percentage of mild to severe complications, which included perforation, abscess and death. The authors concluded that the data from most of the short-term follow-up and the few sham-controlled studies demonstrate that subgroups of patients experienced improvement or resolution of typical GERD symptoms and decreased PPI usage. The authors stated that there is limited data on safety, efficacy and durability to support the use of endoluminal therapies for GERD in routine clinical practice.

Torquati et al. (2007) conducted an evidence-based review of the literature of FDA-approved modalities of endoluminal treatment of GERD. Sixteen studies met the inclusion criteria, representing 787 patients. The studies were categorized according to the guidelines for levels of evidence and grades of recommendation supplied by the Oxford Centre for Evidence-Based Medicine. The authors concluded that, "The methodological quality of most of the included studies was average; four studies were grade 1b (individual randomized trial), 10 were grade 2b (individual cohort study), and two were grade 3b (individual case-control study). There is grade 1b and 2b evidence demonstrating the EndoCinch plication is effective in reducing GERD symptoms at short-term follow up. However, in the majority of the studies analyzed, the procedure does not significantly reduce the acid exposure in the distal esophagus. The majority of the studies with long-term outcome showed disappointing outcomes, probably due to suture loss in the majority of patients. There is grade 1b and 2b evidence demonstrating that the Stretta procedure is effective in reducing GERD symptoms at short- and mid-term follow-up. However, in the majority of the studies analyzed, the procedure did not reduce significantly the acid exposure in the distal esophagus. There is grade 1b and 2b evidence demonstrating that full-thickness plication is effective in reducing GERD symptoms, and acid exposure in the distal esophagus" (Torquati, et al., 2007).

In 2005, the Agency for Healthcare Research and Quality issued a report on the Comparative Effectiveness of Management Strategies for GERD. The authors concluded that, "The quality, quantity, and consistency of studies on the endoscopic approaches to treatment of GERD are inferior to those of medical or surgical therapy, which can be expected since endoscopic approaches are new developments and data are evolving. At present, their efficacy compared with continued (or intensified) medical therapy is unclear. Sham controlled trials have demonstrated that some of the benefits of these procedures observed in the uncontrolled trials may not be directly attributable to the interventions, thus underscoring the need for additional sham-controlled trials. Although these devices are already commercially available, their long term efficacy and safety have not yet been established" (Ip, et al., 2005).

In 2005, the NICE issued an interventional procedure guidance document titled Endoluminal Gastroplication for GERD and concluded that the current evidence suggests that there are no major safety concerns associated with endoluminal gastroplication for GERD. However, evidence of efficacy is not adequate for this procedure to be used without special arrangements for consent and for audit or research (NICE, 2005).

Professional Societies/Organizations

In 2009 the Society of American Gastrointestinal and Endoscopic Surgeons (SAGES) published a position statement addressing endolumenal therapies for gastrointestinal diseases. The authors discuss the current gastrointestinal applications for endolumenal surgery including endolumenal therapies for GERD. The authors state that “endolumenal techniques, either existing or still in development, may well represent the procedure of choice for selected patients with GERD in the future.” The authors state that, “to facilitate progress in endolumenal therapy, several key issues still need to be addressed beyond the needed technology development. These include defining criteria for patient selection, defining the requisite skill set needed by the treating physician, defining the setting for these procedures to be performed in, and addressing reimbursement/coding issues” (SAGES, 2009).

The American Gastroenterological Association (AGA) Medical Position Statement on the Management of Gastroesophageal Reflux Disease states that due to insufficient information they can make no recommendation for or against the use of currently commercially available endolumenal antireflux procedures in the management of patients with an esophageal syndrome (AGA, 2008).

The AGA Institute Position Statement on the Use of Endoscopic Therapy for GERD states, “Most studies of endoscopic therapy have only limited follow-up information of a relatively small number of patients. Thus, the durability of these technologies beyond 1–2 years remains unclear. Short-term and long-term safety issues are unresolved, but serious adverse events led to the voluntary withdrawal of Enteryx by the manufacturer in September 2005 and suspension of the clinical program in late 2005. The economics of all techniques for the patient, practitioner, and society are unknown. While newer devices and improvements in endoscopic anti-reflux techniques may yield better and more durable treatment outcomes, current data suggest that there are no definite indications for endoscopic therapy for GERD at this time. Both practitioners and patients need to be aware of the limitations in the evidence that exist with these devices at present” (Falk, et al., 2006b).

The American Society for Gastrointestinal Endoscopy (ASGE) Practice Guideline Role of Endoscopy in the Management of GERD states that “Most studies of endolumenal therapies for GERD have involved small numbers of PPI-dependent patients and have provided relatively limited follow-up information, so the durability of these therapies remains in question. Additionally, both short and long-term safety issues surrounding the endolumenal devices continue to be a concern, and the economics of their use are unknown. The new endoscopic antireflux techniques represent a rapidly evolving area of GI endoscopy, but additional research is needed before they can be widely recommended. Appropriate patient selection and endoscopist experience should be carefully considered before pursuing these therapies. It is important that patients and practitioners alike be aware of the limitations in the evidence that exist with these devices at the present time” (ASGE, 2007).

In 2005, the American College of Gastroenterology (ACG) updated their 1999 Practice Guidelines for GERD. The committee recommendations state endoscopic therapy controls symptoms in selected patients with well-documented GERD. The techniques seem to improve reflux symptoms, although significant changes in lower esophageal pressure have not been documented. Less than 35% of the patients have demonstrated normalization of their intraesophageal acid exposure, which is measured by ambulatory pH testing. The available published manuscripts and abstracts leave many issues unresolved, including long-term durability, safety and efficacy of endoscopic therapies performed outside of clinical trials with efficacy in atypical presentations of GERD, among others (DeVault, et al., 2005). There has been no update to this practice guideline since 2005.

Summary

There are several proposed modalities to treat gastroesophageal reflux disease (GERD) (i.e., medications, endoscopic therapies, surgery). For patients who have severe GERD, laparoscopic fundoplication remains the procedure of choice. Endoscopic therapy studies for the treatment of GERD have been prospective but generally not randomized or controlled. Patient selection criteria needs to be optimized. Comparative studies between the different endoscopic therapies are needed. Large, well-designed, controlled trials showing long-term safety and efficacy outcomes are lacking.

Coding/Billing Information

Note: This list of codes may not be all-inclusive.

Experimental/Investigational/Unproven/Not Covered:

CPT* Codes	Description
43201 [†]	Esophagoscopy, rigid or flexible; with directed submucosal injection(s), any substance
43236 [†]	Upper gastrointestinal endoscopy including esophagus, stomach, and either the duodenum and/or jejunum as appropriate; with directed submucosal injection(s), any substance
43257	Upper gastrointestinal endoscopy including esophagus, stomach, and either the duodenum and/or jejunum as appropriate; with delivery of thermal energy to the muscle of lower esophageal sphincter and/or gastric cardia, for treatment of gastroesophageal reflux disease
43499 [†]	Unlisted procedure, esophagus

[†]**Note:** Experimental, investigational or unproven and not covered when used to report endoscopic anti-reflux procedures performed for the treatment or management of gastroesophageal reflux disease (GERD)/esophageal reflux.

HCPCS Codes	Description
C9724	Endoscopic full-thickness placcation in the gastric cardia using endoscopic placcation system (EPS); includes endoscopy

ICD-9-CM Diagnosis Codes	Description
530.11	Reflux esophagitis
530.81	Esophageal reflux

*Current Procedural Terminology (CPT®) © 2010 American Medical Association: Chicago, IL.

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Policy History

Pre-Merger Organizations	Last Review Date	Policy Number	Title
CIGNA HealthCare	12/15/2007	0019	Endoscopic Anti-reflux procedures

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Connecticut General Life Insurance Company has acquired the business of Great-West Healthcare from Great-West Life & Annuity Insurance Company (GWLA). Certain products continue to be provided by GWLA (Life, Accident and Disability, and Excess Loss). GWLA is not licensed to do business in New York. In New York, these products are sold by GWLA's subsidiary, First Great-West Life & Annuity Insurance Company, White Plains, N.Y.