Enteryx™ Procedure Kit for GERD
INSTRUCTIONS FOR USE

CAUTION: Federal (USA) law restricts this device to sale by or on the order of a physician.

This device should be used only by physicians with a thorough understanding and training in the use of endoscopic injection of materials for treatment of esophageal disorders.

ENGLISH

SYMBOLS

	It is important to read the instructions for use with careful attention to cautions, notes and warnings prior to using this product.
	STERILE: This device is provided sterile. Syringes, needles and Enteryx™ injectors sterilized using ethylene oxide gas.
	STERILE: This device is provided sterile. Enteryx™ and Primer solutions sterilized using dry heat.
	DO NOT REUSE OR RESTERILIZE
	Keep dry
	Keep away from heat
REF	Catalog Number
	Use by
	Batch code
	Not Labeled for Individual Sale

Contents supplied STERILE. Do not use if sterile barrier is damaged. If damage is found call your Boston Scientific representative.

For single use only. Do not reuse, reprocess or resterilize. Reuse, reprocessing or resterilization may compromise the structural integrity of the device and/or lead to device failure which, in turn, may result in patient injury, illness or death. Reuse, reprocessing or resterilization may also create a risk of contamination of the device and/or cause patient infection or cross-infection, including, but not limited to, the transmission of infectious disease(s) from one patient to another. Contamination of the device may lead to injury, illness or death of the patient.

DESCRIPTION

Enteryx is a biocompatible polymer (EVOH) with radiopaque marker (tantalum) in a liquid solvent (DMSO). This low viscosity solution precipitates as a spongy mass forming a permanent implant. Enteryx Procedure Kit is comprised of the following components:

Enteryx Procedure Kit	
Enteryx solution (1)	10 ml
Primer solution (1)	10 ml
Enteryx Injector (1)	2.4 mm x 165 cm
Syringes (2)	1ml
Needles (2)	18G x1½"

INDICATIONS FOR USE

The Enteryx™ procedure kit is indicated for endoscopic injection into the region of the lower esophageal sphincter (LES) for the treatment of gastroesophageal reflux disease (GERD) symptoms in patients responding to and requiring daily pharmacological therapy with proton pump inhibitors.

CONTRAINDICATIONS

1. The Enteryx procedure is contraindicated in patients with esophageal varices particularly related to portal hypertension.

2. The Enteryx™ procedure is contraindicated in patients whom the physician determines to be a poor candidate for endoscopic procedures and/or anesthesia.

PRECAUTIONS

1. The safety and effectiveness of Enteryx™ have not been established in patients with the following conditions:
   - Barrett's epithelium
   - Persistent high-grade esophagitis
   - Esophageal strictures
   - GERD symptoms refractory to pharmacological therapy
   - Scleroderma
   - Esophageal motility disorders
   - Esophageal or gastric cancers
   - Hiatal hernia $\geq$ 3cm
   - Prior esophageal or gastric surgery
   - Morbid obesity (BMI > 35)
   - Pregnant or lactating women
   - Age <18

2. The long-term effects beyond one year of treatment with Enteryx™ have not been established.

3. The safety and effectiveness of multiple treatment procedures with Enteryx have not been evaluated and established.

4. The Enteryx material cannot be removed from the esophagus after injection.

5. To use Enteryx, physicians must have a thorough understanding of the technical principles, clinical applications and risks associated with endoscopic gastrointestinal injection therapy.

6. Patient selection requires thorough consultation and evaluation by the physician.

7. Patients should be counseled in order to have a realistic expectation of the functional outcome of the implantation of Enteryx. Although the device is intended to reduce the requirements for pharmacological therapy of GERD, some patients may continue to have symptoms after the procedure and require medical therapy.

8. Use only the supplied syringe, needle and Enteryx injector to inject the DMSO based Primer and Enteryx solutions. Other syringes, needles and injectors may not be compatible. All gastroscopes that have a working channel lined with polytetrafluoroethylene (PTFE), polyethylene or polypropylene are compatible with DMSO. Check with the original manufacturer of the gastroscope or the gastroscope reconditioner if your scope has been reconditioned, to determine compatibility.

9. Failure to continuously mix Enteryx solution for the required time may result in inadequate suspension of the tantalum contrast agent, resulting in reduced fluoroscopic visualization.

10. Premature precipitation of the Enteryx solution may occur if the liquid comes in contact with saline, blood, or mucosal fluid.

11. Inspect all vials and pouches for damage prior to use. If damage is suspected, discard item and replace.

12. If flow through the injector becomes restricted, do not attempt to clear the injector by high-pressure infusion. Use of excessive pressure may result in injector rupture. Remove the injector and replace it with a new one. Flush with the Primer solution prior to use.

13. Failure to uncoil the Enteryx injector prior to deploying and retracting the needle may cause injector damage. If injector is damaged, discard and replace.

14. Inject the Enteryx and Primer solutions at a slow, steady rate but not greater than 1ml/minute as described in step 5 of the injection procedure. Faster injection speeds may result in inconsistent placement of the Enteryx solution.

15. Use the Enteryx and Primer solutions at or above 65°F (19°C). If product freezes due to exposure to colder temperatures, thaw at room temperature before use.

ADVERSE EVENTS

Eighty-five (85) patients were enrolled in a single arm controlled study and followed for 12 months. Adverse events were classified as device related, procedure related, and unrelated to the device or procedure. The severity of adverse events was defined as follows:

- Mild: causing no limitation of usual activities
- Moderate: causing some limitation of usual activities
- Severe: causing inability to carry out usual activities.

Severe events were defined in terms of disruption of the patient's daily life. The classification of mild, moderate, or severe was not related to whether medical intervention was necessary.

There were no events that were potentially life threatening or required surgical intervention.

A total of 122 device-related adverse events were reported for the study population. These adverse events included retrosternal chest pain (78/85 or 91.8%), dysphagia (17/85, or 20.0%), fever (10/85, or 11.8%), belching/burping (6/85, or 7.1%), bloating/flatulence (5/85, or 5.9%), body odor/bad taste (4/85, or 4.7%), and one case each of rib pain and flu syndrome. Of these adverse events, only five (4%) events were rated as severe at onset, which as noted above, indicated interference with the subject's daily life. The "severe" device-related adverse events consisted of retrosternal chest pain (n=4) and bloating (n=1).

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DEVICE-RELATED ADVERSE EVENTS
(85 Patients)

Event	Mild	Moderate	Severe	#	%
Retrosternal Chest Pain	39	35	4	78	91.8%
Dysphagia	10	7	0	17	20.0%
Fever	7	3	0	10	11.8%
Belching/Burping	3	3	0	6	7.1%
Bloating/Flatulence	1	3	1	5	5.9%
Other					
Body Odor/Bad Taste	2	2	0	4	4.7%
Rib Pain	0	1	0	1	1.2%
Flu Syndrome	1	0	0	1	1.2%

A total of 29 (34.1%) adverse events related to the procedure were reported during the course of this study. None of these events were considered to be severe. The events consisted of pharyngitis (n=9), nausea and vomiting (n=7), nausea (n=5), shoulder pain (n=3), dry mouth (n=2), anxiety (n=2), and breast pain (n=1).

SEVERITY OF PROCEDURE-RELATED ADVERSE EVENTS
(85 patients)

Event	Mild	Moderate	Severe	#	%
Sore Throat (Pharyngitis)	8	1	0	9	10.6%
Nausea / Vomiting	3	4	0	7	8.2%
Nausea	3	2	0	5	5.9%
Other					
Shoulder Pain	1	2	0	3	3.5%
Dry mouth	1	1	0	2	2.4%
Anxiety	1	1	0	2	2.4%
Breast Pain	0	1	0	1	1.2%

The procedure-related adverse events were anticipated and consistent with what is generally expected during the course of therapeutic endoscopy procedure.

For the 19 patients who received retreatment, adverse events occurring after the second treatment session included retrosternal pain (68.4%), dysphagia (10.5%), bloating (5.3%), and pharyngitis (5.3%).

DIRECTIONS FOR USE

Patient Counseling

Prior to scheduling Enteryx therapy, the patient must be given the Enteryx Patient Information Brochure. The patient should be fully apprised of the Enteryx implant indications, contraindications, precautions, treatment responses, adverse events, and method of administration.

Patient Preparation

Prep patient as required for upper GI endoscopy. Sedation and prophylactic antibiotics should be administered per the SOP of the institution. Endoscopy suite must have access to fluoroscopy (C-arm).

Enteryx Procedure Preparation

1. Resuspend the Enteryx solution by shaking for at least 10 minutes prior to use.
2. Remove the Enteryx injector from the pouch and carefully straighten by uncoiling. Confirm that the needle fully deploys and retracts from the distal end of the injector.
3. Remove Primer solution from the vial with the syringe and needle supplied in the kit. Attach syringe to the Enteryx injector. With the needle fully deployed on the Enteryx injector, flush and prime the injector.
4. Draw the Enteryx solution into the second syringe and needle, attach the syringe to the Enteryx injector and pre-load the system, completely filling the injector lumen removing all of the Primer solution and air.
5. Refill the syringe with the Enteryx solution and attach to the Enteryx injector. The Enteryx injector is then ready to be passed into the working channel of the gastroscope.

Enteryx Injection Procedure

1. Introduce gastroscope and visualize the lower esophageal sphincter (LES), the squamo-columnar junction and the cardia of the stomach.
2. Pass the Enteryx injector down the working channel of the gastroscope until the tip is visualized at the distal end.
3. Place the tip of the Enteryx injector at the desired location at or just below the squamocolumnar junction (Figure 1a). Deploy the injector needle, puncture the mucosa in an antegrade direction, and advance the needle into the muscle. It is recommended that the needle not be introduced perpendicularly as this may increase the likelihood of a transmural injection. Injecting from a retroflex position is not recommended.
4. Use endoscopic and fluoroscopic guidance to confirm intramural implant location. Place at least 6ml of Enteryx solution circumferentially into and along the muscle layer of the lower esophageal sphincter. If the material forms an arc or ring,

continue to use multiple syringes to add material at the same injection position (Figure 1b). Otherwise use multiple discrete injections (Figure 1c) of 1-2 ml each for a total of at least 6ml of Enteryx solution circumferentially into and along the muscle layer of the lower esophageal sphincter. Note, residual volumes of >12 ml have not been adequately investigated.

a. Optimally placed implants are within or along the muscle layer. Endoscopically they appear as a light gray region below the mucosa, with no bulging of the mucosa. On fluoroscopy these implants appear as fuzzy blebs which often have distinct arcuate extensions and may even coalesce to form a complete ring.
b. Enteryx material placed superficially in the submucosa generally appears as a dark gray bulge endoscopically. Since superficial injections slough into the GI tract, discontinue such injections immediately, and choose a new injection site.
c. Transmural injections are often identified as sharp thin vertical lines on fluoroscopy or as radiographically very dense material, since the Enteryx material is not incorporated into the lower esophageal sphincter. In the case of transmural implantation, stop the injection immediately and choose a new injection site.

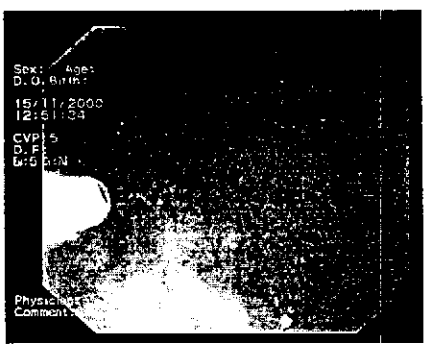

Figure 1a

Figure 1b

Figure 1c

5. The injection rate should be no faster than 1.0 ml/minute. It is suggested that the nurse count 6 seconds for each **0.1** ml administered. Slow injection speeds allow for consistent placement of the Enteryx solution within and along the muscle layer of the lower esophageal sphincter. It is recommended that the exchange of one syringe to another be smooth and quick to optimize procedure efficiency.
6. Once the injection is complete, the nurse should remove his or her thumb from the plunger of the syringe to release the positive pressure in the syringe. Allow the needle to remain in place for at least 20 seconds to allow for stabilization of the Enteryx material.
7. PA/lateral chest x-rays should be taken post-surgery with standard patient positioning for assessing the appearance of the implant at later time points.

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Instructions to Patients

1. Patients may notice a garlic-type smell or taste after the procedure. This is normal and typically lasts no more than several days.
2. Patients should continue administration of their current anti-secretory medication(s) for approximately 10 days following treatment with Enteryx.
3. Patients should be instructed to begin eating with a mechanically soft diet following the procedure and advance as tolerated.
4. Patients should be instructed to contact their physician for any severe or prolonged adverse events including chest pain, dysphagia, fever, and bloating.

CLINICAL STUDIES

Study Design

Eighty-five (85) patients were enrolled in a single arm controlled study and followed for 12 months. Patients were diagnosed with GERD whose symptoms responded to and required pharmacological therapy with daily proton pump inhibitors (PPIs). Nineteen (19) of these patients received a second treatment session of Enteryx between 1 and 3 months of the first treatment session. The mean volume of Enteryx injected into these 85 patients during the course of the study was 12.7 ml (range 6.6 to 16.2 ml).

Treatment Responses

A successful outcome was defined as elimination of all PPI use or a reduction in use of PPIs of at least 50% at 12 months as compared to baseline usage. Patients who experienced a smaller reduction in use of PPIs, i.e., <50%, who continued to use PPIs at the baseline levels, or who required an increase in PPI usage were considered not improved.

PPI USE 12 MONTHS POST-PROCEDURE

	Per Protocol		Intent to Treat	
	N	%	N	%
Medication Improved	65/81	80.3 (69.9 to 88.3%)[1]	65/85	76.5 (66.0 to 85.0%)
Off all PPIs	57	70.4%	57	67.1%
Dose reduced ≥ 50%	8	9.9%	8	9.4%
Medication Not Improved	16/81	19.7%	20/85	23.5%
Dose reduced < 50%	1	1.2%	1	1.2%
Dose maintained	12	14.8%	12	14.1%
Dose increased	3	3.7%	3	3.5%
Lost to follow-up			4	4.7%

At twelve months, 80.3% of all study patients were able to completely eliminate (70.4%) or reduce their use of PPIs by ≥50% (9.9%). In a secondary intent-to-treat analysis, in which the 4 study patients lost to follow-up were classified as treatment failures, 76.5% of all study patients were able to completely eliminate (67.1%) or reduce their use of PPIs by ≥50% (9.4%). This intent- to-treat analysis verifies that the study hypothesis was satisfied under the worst case assumption that all patients lost to follow-up were treatment failures.

The low level utilization of supplementary non-PPI GERD medications at 12 months was comparable to baseline use of these medications while on PPIs, demonstrating that PPI therapy was not simply being replaced with non-PPI treatment. About 1 of 4 patients (26%) who were able to reduce or eliminate their PPI use were taking over-the-counter antacids or H_2 blockers intermittently at 12 months. This is about the same number of patients who were taking supplementary over-the-counter antacids or H_2 blockers before the Enteryx procedure (22%).

Other Effectiveness Outcomes:

GERD-Health Related Quality of Life (HRQL)

Results of administering the GERD-HRQL instrument to each study subject were reported as the sum of questions related to heartburn scores (sum of questions 1-9) and as the sum of four (4) Sponsor added questions related to regurgitation scores (sum of questions 10-13).

Sum of Questions 1-9 (Heartburn Score)

Mean severity score improved significantly following treatment with Enteryx as compared to baseline scores while off PPIs at each follow-up interval ($p<0.001$). Mean scores were reduced 66% from 26.2 at baseline (off PPIs) to 8.9 at 12 months. Over 70% of the subjects were able to reduce their score by at least 50% at 12 months. This improvement was consistent for each of the individual 9 questions that are comprised in the summary score. Scores following Enteryx treatment were comparable to those observed for patients on PPI therapy

Sum of Questions 10-13 (Regurgitation Score)

Mean severity scores following Enteryx treatment were significantly improved compared to baseline scores for patients off PPI treatment ($p<0.001$). This improvement was consistent with the scores for each of the individual 4 questions that are comprised in the summary score. Scores for the sum of questions 10-13 were comparable for patients at baseline while on PPIs and following treatment with Enteryx.

[1] Clopper-Pearson 95% Confidence Interval

SF-36 Health Survey

The SF-36 Health Survey questionnaire, another secondary effectiveness measurement, was completed by each study subject at baseline while on PPI treatment, at baseline following withdrawal of PPI treatment for 10-14 days, and at 1, 3, 6 and 12 months following treatment with Enteryx. The questionnaire consists of a mental component score (MCS) and a physical component score (PCS).

SF-36 PCS mean scores at baseline were better for subjects while on PPI therapy than off PPIs. At 12 months following treatment with Enteryx, mean physical component scores were also significantly improved over the mean score at baseline for subjects off PPI therapy (49.4 vs 43.4, $p<0.001$) and were comparable to scores reported at baseline for subjects while on PPIs.

SF-36 MCS mean scores were *not* significantly better for subjects while on PPI therapy than off PPIs at baseline. At 12 months following treatment with Enteryx, mean scores were not significantly different than subjects either on PPI therapy at baseline (50.0 vs. 51.4, $p=0.444$) or off PPIs at baseline (50.5 vs. 50.2, $p=0.160$).

pH-Metry

Subjects underwent prolonged (> 12 hour) pH probe monitoring at baseline after at least 10 days off PPI therapy. The study was repeated again at twelve months following Enteryx treatment.

For subjects with paired data at 12 months, statistical analysis revealed significant improvement ($p \leq 0.05$) in mean percent total time, mean percent upright time, mean supine time, total number of episodes. No statistically significant improvement was detected for longest episode duration.

At month 12, 26/67 (39%) of the subjects with paired data normalized their pH measurement, while 19/67 (28%) improved but did not normalize when compared to baseline (while off medications). The remaining 22/67 (33%) had higher percent total times with pH $\leq$4 at 12 months when compared to baseline.

	Baseline (off PPIs)		12 Months		
	N	Mean (SD)	N	Mean (SD)	p value
24-hr pH monitoring					
pH $\leq$ 4 (%) total	67	14.34 (14.68)	67	9.21 (9.00)	0.002
pH $\leq$ 4 (%) upright	58	14.27 (15.35)	58	9.92 (10.72)	0.026
pH $\leq$ 4 (%) supine	59	12.01 (18.57)	59	6.97 (12.08)	0.032
Number of episodes (Normalized to 24 hrs)	67	162.04 (112.12)	67	114.82 (77.21)	0.002
Longest episode (min)	65	33.5 (45.89)	65	21.4 (25.54)	0.209

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Manometry

Subjects underwent manometry before treatment with Enteryx (i.e., within the three months prior to enrollment), six months, and twelve months following Enteryx treatment. Lower esophageal sphincter (LES) pressure, length, peristaltic amplitude, and residual LES pressure during relaxation were recorded. There were no statistically significant ($p \leq 0.05$) changes between baseline and 12 months.

Endoscopy

Of 30 subjects with esophagitis on baseline endoscopy, 23 had upper endoscopy results for comparison at 12 months. Seventeen (17) of these 23 subjects had Grade I esophagitis and 6 Grade II at baseline. Esophagitis healed (Grade 0) in 43% (10/23) of the subjects with baseline esophagitis and improved or remained stable in another 26% (6/23). In 31% (7/23) of the cases the esophagitis grade was higher at 12 months than at baseline (Grade II versus Grade I). In addition, 27% (12/45) of the subjects who did not have esophagitis at baseline were noted to have developed esophagitis at 12-month endoscopy. Altogether, 37% (25/68) of the evaluable subjects had esophagitis at 12 months, including 22% (15/68) with Grade II esophagitis. Note that of the patients who had Grade II esophagitis, approximately half (7/15) had resumed PPI use and, in particular, 70% of the patients with a 2 grade change had resumed PPI medication. No subjects developed Grade III/IV esophagitis or evidence of stricture during the 12 months of follow-up.

DEVICE RETENTION

Subjects enrolled in the clinical study underwent periodic chest x-rays to assess the residual amount of Enteryx™. Physicians estimated the percentage of remaining material in quartiles (0-25%, 26-50%, 51-75%, and 76-100%) when compared to the 1 month x-ray for subjects singly treated and the 3 month x-ray for those subjects who underwent retreatment.

For the singly treated subjects, 55% were estimated to have retained 76-100% of the injected Enteryx™ at 12 months while 28% retained $\leq$ 50%. Of the retreated subjects, 59% were estimated to have retained 76-100% while 18% retained $\leq$50%. The material that was not visualized was presumed to have sloughed into and out of the gastrointestinal tract.

WARRANTY

Boston Scientific Corporation (BSC) warrants that reasonable care has been used in the design and manufacture of this instrument. ***This warranty is in lieu of and excludes all other warranties not expressly set forth herein, whether express or implied by operation of law or otherwise, including, but not limited to, any implied warranties of merchantability or fitness for a particular purpose.*** *Handling, storage, cleaning and sterilization of this instrument as well as other factors relating to the patient, diagnosis, treatment, surgical procedures, and other matters beyond BSC's control directly affect the instrument and the results obtained from its use. BSC's obligation under this warranty is limited to the repair or replacement of this instrument and BSC shall not be liable for any incidental or consequential loss, damage, or expense directly or indirectly arising from the use of this instrument. BSC neither assumes, nor authorizes any other person to assume for it, any other or additional liability or responsibility in connection with this instrument.* ***BSC assumes no liability with respect to instruments reused, reprocessed or resterilized and makes no warranties, express or implied, including but not limited to merchantability or fitness for a particular purpose, with respect to such instrument.***

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