Enteryx™ Procedure Kit for GERD
INSTRUCTIONS FOR USE

CAUTION: Federal (USA) law restricts this device to sale, distribution, and use 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

DESCRIPTION

Enteryx Procedure Kit is comprised of the following components:

Enteryx Procedure Kit		900-100137
Enteryx solution (1)	10 ml	800-100180
Primer solution (1)	10 ml	800-100181
Enteryx Injector (1)	2.4 mmx165 cm	900-100000
Syringes (2)	1ml	900-100129
Needles (2)	18G x1	800-100186

INDICATIONS FOR USE

The Enteryx procedure kit is indicated for endoscopic injection into the lower esophageal sphincter (LES) for the treatment for gastroesophageal reflux disease (GERD).

CONTRAINDICATIONS

The Enteryx procedure is contraindicated in patients with portal hypertension.

PRECAUTIONS

The safety and effectiveness have not been established in patients with Barrett's epithelium, scleroderma, esophageal motility disorders, esophageal or gastric cancer, large hiatal hernias (? 3cm by endoscopic evaluation), prior gastric or GERD surgery, persistent high grade esophagitis, esophageal or gastric varices, gross obesity (BMI ? 35), or immune suppressant therapy. The safety and effectiveness have not been established in pregnant or lactating women.

DIRECTIONS FOR USE

Patient Preparation

Prep patient as required for upper GI endoscopy. It is recommended that patients be administered prophylactic antibiotics before and after procedure.

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. Deploy the injector needle, puncture the mucosa in an antegrade direction, and advance the needle into the muscle.
4. 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. Otherwise use multiple discrete injections 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.
5. The injection rate should be no faster than 1.0 ml/minute. Slow injection speeds allow for consistent placement of the Enteryx solution within and along the muscle layer of the lower esophageal sphincter.
6. Allow the needle to remain in place for at least 20 seconds to allow for stabilization of the Enteryx material.

Instructions to Patients

1. The majority of patients experience mild to moderate retrosternal pain following the procedure. It is recommended that patients take pain medication prophylactically.
2. Patients may notice a garlic-type smell or taste after the procedure. This is normal and typically lasts no more than several days.
3. It is recommended that patients eat only bland, non-spicy and soft foods for 5 days following the procedure.
4. Patients should continue administration of their current anti-secretory medication(s) for approximately 10 days following treatment with Enteryx.

CLINICAL STUDIES

Use of GERD Medications

A successful outcome was defined as elimination of all PPI use or a reduction in use of PPIs of at least 50% 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.

At twelve months, 80.3% of all study subjects (C.I. 69.9% to 88.3%) were able to completely eliminate (70.4%) or reduce their use of PPIs by =50% (9.9%). 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. Therefore it can be concluded that treatment with Enteryx is highly effective in the management of GERD, as evidenced by the ability of GERD patients with a history of use of PPIs and other GERD medication to eliminate or significantly reduce use of these medications.

PPI USE 12 MONTHS POST-PROCEDURE

	N	% (CI) [1]
Medication Improved	65/81	80.3% (69.9 to 88.3%)
Off all PPIs	57	70.4%
Dose reduced ? 50%	8	9.9%
Medication Not Improved	16/81	19.7%
Dose reduced < 50%	1	1.2%
Dose maintained	12	14.8%
Dose increased	3	3.7%

OTHER EFFICACY 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 questions related to regurgitation scores (sum of questions 10-13).

Sum of Questions 1-9 (Heartburn Score)

The mean severity score for the sum of questions 1-9 was significantly worse at baseline with patients off PPI therapy as compared to baseline on PPI medications (26.4 vs 5.4, p<0.001). 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). Consistent with the findings for each of the individual questions that are comprised in the summary score, scores following Enteryx treatment were comparable to those observed for patients on PPI therapy at baseline, further confirming that treatment with Enteryx is an effective alternative to chronic use of PPI therapy.

Sum of Questions 10-13 (Regurgitation Score)

The mean regurgitation severity score for the sum of questions 10-13 was significantly worse at baseline with patients off PPI therapy as compared to baseline PPI medications (11.1 vs 2.8, p<0.001). Mean severity scores following Enteryx treatment were significantly improved compared to baseline scores for patients off PPI treatment (p<0.001). Also consistent with the scores for the individual questions, scores for the sum of questions 10-13 were comparable for patients at baseline while on PPIs and following treatment with Enteryx.

In conclusion, the GERD-HRQL data indicate that at 12 months following Enteryx treatment, study subjects felt significantly better compared to baseline symptoms off PPIs and had comparable symptom control to baseline scores on PPIs. These data illustrate that the Enteryx procedure can relieve heartburn and regurgitation symptoms and provide an effective alternative to chronic PPI use.

	Baseline (on PPIs)		Baseline (off PPIs)		
	N	Mean (SD)	N	Mean (SD)	p value
Symptom score					
GERD-HRQL (Q1-9)	85	5.4 (3.74)	85	26.4 (6.62)	<0.001
GERD-HRQL (Q10-13)	85	2.8 (3.33)	85	11.1 (5.31)	<0.001

	Baseline (off PPIs)		12 Months post-Treatment		
	N	Mean (SD)	N	Mean (SD)	p value
Symptom score					
GERD-HRQL (Q1-9)	77	26.2 (6.67)	77	8.9 (9.70)	<0.001
GERD-HRQL (Q10-13)	77	10.9 (5.40)	77	3.1 (4.22)	<0.001

1 Clopper-Pearson 95% Confidence Interval

SF-36 Health Survey

The SF-36 Health Survey questionnaire, another secondary efficacy 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). Since the change from baseline for SF-36 MCS was not statistically significant by the Wilcoxon signed ranks test, the results were examined for the patients who were improved at 12 months (i.e., PPI use eliminated or reduced = 50%) using the sign test. While a less powerful statistical tool, patients whose medication use improved following Enteryx treatment continued to have statistical significance (p=.026), suggesting a favorable trend in treatment responders.

Together, these findings suggest that Enteryx is capable of replacing PPIs with no change in SF-36 scores.

	Baseline (on PPIs)		Baseline (off PPIs)		
	N	Mean (SD)	N	Mean (SD)	p value
Quality of life score					
SF-36 MCS	81	51.2 (9.44)	81	48.5 (11.49)	0.077
SF-36 PCS	81	47.8 (9.43)	81	43.1 (10.13)	<0.001

	Baseline (off PPIs)		12 Months post-Treatment		
	N	Mean (SD)	N	Mean (SD)	p value
Quality of life score					
SF-36 MCS	74	50.2 (9.71)	74	50.5 (10.76)	0.160
SF-36 PCS	74	43.4 (10.16)	74	49.4 (9.32)	<0.001

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 six and twelve months following Enteryx treatment. The following data were recorded:

- % total time pH $\leq$ 4
- % upright time pH $\leq$ 4
- % supine time pH $\leq$ 4
- total number of episodes
- longest episode duration (minutes)

Percentage of Total Time pH < 4

For all subjects with paired data at Month 12, 26/67 (39%) of subjects normalized their pH measurement, as compared to baseline. Further, 43.1% (25/58) of patients who experienced an improvement in PPI use at 12 months also had normalized pH. In contrast, among patients who did not experience an improvement in PPI use at 12 months, only 11.1% (1/9) had normalized pH.

At baseline for the cohort of patients who had baseline and 12 month pH metry performed, the mean percentage of time during testing that pH was < 4 was 14.34% (SD 14.68%). At twelve months following Enteryx treatment, the mean percentage of time at pH < 4 was 9.21% (SD 9%). The mean overall percentage of time at pH < 4 was significantly reduced (improved) at twelve months following Enteryx treatment (p = 0.002) compared to baseline off PPIs. These statistically significant reductions in overall time at pH < 4 are indicative of a significant improvement in pH-metry at six and twelve months post-treatment with Enteryx.

Percentage of Upright Time pH < 4

At baseline for the cohort of patients who had baseline and 12 month pH metry performed, the mean percentage of upright time during testing that pH was < 4 was 14.27% (SD 15.35%). At twelve months following Enteryx treatment, the mean percentage of upright time at pH < 4 was 9.92% (SD 10.72%). The mean percentage upright time at pH < 4 was significantly reduced (improved) at twelve months following Enteryx treatment (p = 0.026) compared to baseline off PPIs. These statistically significant reductions in upright time at pH<4 are indicative of a significant improvement in pH-metry at six and twelve months post-treatment with Enteryx.

Percentage of Supine Time pH < 4

At baseline for the cohort of patients who had baseline and 12 month pH metry performed, the mean percentage of supine time during testing that pH was < 4 was 12.01% (SD 18.57%). At twelve months following Enteryx treatment, the mean percentage supine time at pH < 4 was 6.97% (SD 12.08%). The mean percentage supine time at pH < 4 was significantly reduced (improved) at twelve months following Enteryx treatment (p = 0.032) compared to baseline off PPIs. These statistically significant reductions in supine time at pH<4 are indicative of a significant improvement in pH-metry at six and twelve months post-treatment with Enteryx.

Total Number of Episodes

At baseline for the cohort of patients who had baseline and 12 month pH-metry performed, the mean total number of episodes with pH was < 4 w as 162.04 (SD 112.12). At twelve months following Enteryx treatment, the mean total number of episodes with pH < 4 was 114.82 (SD 77.21). The mean total number of episodes with pH < 4 was significantly reduced (improved) at twelve months following Enteryx treatment (p = 0.002) compared to baseline off PPIs. These statistically significant reductions in the mean total number of episodes with pH<4 are indicative of a significant improvement in pH-metry at six and twelve months post-treatment with Enteryx.

Longest Episode Duration

The longest recorded episode duration of pH < 4 in study subjects at baseline for the patients with baseline and 12 month data was 33.5 minutes (SD 45.89), while the longest recorded episode duration at 12 months follow-up after treatment with Enteryx, was 21.4 min. (SD 25.54). These results indicate that there was a reduction in the maximum episode duration at the twelve month visit following Enteryx treatment as compared to baseline off PPI treatment, although this difference did not reach statistical significance (p=0.209).

	Baseline (off PPIs)		12 Months		
	N	Mean (SD)	N	Mean (SD)	p value
24-hr pH monitoring					
pH ? 4 (%) total	67	14.34 (14.68)	67	9.21 (9.00)	0.002
pH ? 4 (%) upright	58	14.27 (15.35)	58	9.92 (10.72)	0.026
pH ? 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

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 and length were recorded, as was peristaltic amplitude and residual LES pressure during relaxation.

There were no significant changes or findings following treatment with Enteryx, with the exception of LES length. Mean LES length increased at six months. While this increase was significant at six months as compared to baseline, the LES length at 12 months was not statistically different compared to baseline (2.8 vs. 2.6, p=0.258). Since the change from baseline was not statistically significant by the Wilcoxon signed ranks test, the results were examined for the patients who were improved at 12 months (i.e., PPI use eliminated or reduced = 50%) using the sign test. While a less powerful statistical tool, patients whose medication use improved following Enteryx treatment continued to have significantly longer LES length (p = 0.012), suggesting a favorable trend in treatment responders.

Physiologic Method		Baseline	Month 12

LES pressure (mm Hg)	N	69	69
	Mean	14.27	13.10
	Standard deviation	7.03	7.75
	p-value[2]		0.651
LES length (cm)	N	59	59
	Mean	2.6	2.8
	Standard deviation	1.04	1.28
	p-value		0.258
Peristaltic amplitude (mm Hg)	N	68	68
	Mean	74.7	79.2
	Standard deviation	30.75	36.82
	p-value		0.502
Residual LESP during relaxation (mm Hg)	N	65	65
	Mean	2.90	2.53
	Standard deviation	5.39	3.84
	p-value		0.577

SAFETY RESULTS

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.

This definition of "severe" adverse events was in contrast with the description used in the majority of clinical trials. Customarily, "severe" is used to describe adverse events that may be reportable under 21 CFR 812.150 if they are serious and device related, i.e., lead to death, are potentially life threatening, cause disability or require or prolong hospitalization. In this trial, due to the general good health of the study participants, more conservative definitions were applied. On this basis, "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 serious adverse device related events reported during the course of this trial, i.e., 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).

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%

[2] Wilcoxon Signed-Rank

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.

PROCEDURAL PRECAUTIONS

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 manufactured by Olympus® before 2001 have been found to be DMSO compatible. The user should verify the chemical compatibility of other gastroscopes.

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.

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

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

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.

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

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.

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.

Manufacturer
Enteric Medical Technologies, Inc.
551 Foster City Blvd., Suite G
Foster City, CA 94404, USA

Authorized Representative in EU
OPUS MEDICAL bvba.
Spoorwegstraat 76
B-3500 Hasselt Belgium

International Distributor
Boston Scientific Corporation
One Boston Scientific Place
Natick, MA 01760