

Presentation to the Pediatric Advisory Committee
September 14, 2016

Enterra[®] Therapy System

Humanitarian Device Exemption (HDE) H990014

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Presentation Outline

- Device description & distribution numbers
- Medical device report review-focusing on pediatric reports
- Literature review
- Conclusions and recommendation
- Question to the PAC

Device Description

- Enterra is a surgically-implanted gastric electrical stimulator (GES) that consists of the following:
 1. A neurostimulator placed in a subcutaneous pocket in the abdomen, which functions like a pacemaker in delivering electrical pulses to the stimulation leads.
 2. Two intramuscular leads that connect to the neurostimulator, implanted into the muscularis propria on the greater curvature at the limit of the corpus-antrum. The leads deliver electrical pulses to the stomach muscle.
 3. An external clinician programmer.

Indications for Use

- Enterra is indicated for the treatment of patients with chronic, intractable (drug-refractory) nausea and vomiting secondary to gastroparesis of diabetic or idiopathic etiology in patients aged 18 to 70 years.

Distribution Numbers

- **The HDE Annual Distribution Number (ADN) is defined as the number of devices reasonably needed to treat, diagnose, or cure a population of 4,000 individuals in the United States**
 - The ADN for Enterra is 4,000
- **During this reporting period (May 1, 2015 and April 30, 2016), the following implantable Enterra components were sold in the U.S.**
 - 1,819 neurostimulators
 - 2,151 intramuscular leads
- **103 neurostimulators were implanted in pediatric (<22 year old) patients**
 - 39 were implanted in patients 18 to 21 years old
 - 32 were implanted in patients <18 years old
 - 32 previously implanted pediatric patients received a replacement device

Medical Device Report Review

Methods

Medical Device Report (MDR) Database

MDR Search Criteria:

- Product Code: LNQ (Intestinal Stimulator)
- Date Report Entered: between May 1, 2015 and April 30, 2016

Search Result: **351 total MDRs**
17 were pediatric (range 9 to <22 years)
112 were of indeterminate age



Overall Event Type Distribution by Patient Age

Event Type	Total MDR Count 5/1/15 – 04/30/16	MDR Count by Patient Age (years)			
		Pediatric (<18)	Pediatric (18 to <22)	Adult (≥22)	Indeterminate (No Reported Age)
Death	0	0	0	0	0
Injury*	203	6	7	117	73
Malfunction**	112	0	4	69	39
Total MDR Count	315	17		186	112

* Injury per regulatory definition (CFR 803.3) includes an event that is life-threatening or results in permanent impairment of a body function or permanent damage to a body structure or necessitates medical or surgical intervention(s) to preclude permanent impairment of a body function or permanent damage to a body structure.

** Malfunction per regulatory definition (CFR 803.3) means the failure of a device to meet its performance specifications or otherwise perform as intended ; it is reportable when it is likely to cause or contribute to a death or serious injury if the malfunction were to recur.

Time to Event Occurrence (TTEO)

Time to Event Occurrence (TTEO)	MDR Count by Patient Age (years)			
	Pediatric (<18)	Pediatric (18 - <22)	Adult (≥22)	Indeterminate (No Reported Age)
≤30 days	0	3	25	1
31 days – 364 days	3	4	14	8
1 – 5 years	0	0	45	10
>5 years	0	0	15	1
Totals (N=129)	3	7	99	20

Clinical events identified with pediatric patients, year-to-year comparison

Clinical Events 4/2014 – 4/2015	Occurrences in MDRs*
Inappropriate Electric Shock	5
Nausea/Vomiting [Complaint ill-defined]	6
Pain/Discomfort/ Abdominal Pain	5
Return of Symptoms [Therapeutic Response, Decreased]	3

Clinical Events 4/2015 – 5/2016	Occurrences in MDRs*
Electric Shock/Nerve Stimulation, Undesired/ [Inappropriate Electric Shock]	6
Nausea/Vomiting [Complaint ill-defined]	4
Pain/Discomfort/ Abdominal Pain	2
Infection/Erosion	2

*Note: Only the most observed patient problems and issues contained in the narratives of the pediatric MDRs are included. Because a single MDR can contain multiple clinical events, the total number of occurrences in MDRs does not equal the total number of pediatric MDRs.

Conclusions from MDR Review

- Overall, patient problems and device problems observed for pediatric patients, were similar to those observed for adult patients and for reports with indeterminate age.
- While these issues are known inherent risks for the device and do not represent any new or previously unknown concerns regarding patient safety, more reported impedance issues noted in this year's analysis.
- Those issues directly related to impedance often had to do with battery issues and/or lead placement of which the evaluation of these device was hindered due to not being returned in 284 of the 315 MDRs

Literature Review

An Updated Systematic Literature Review on the Safety and Probable Benefits of Enterra in the Pediatric Population

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September 14, 2016

Purpose

- Systematic literature review of Enterra to address the following in pediatric patients (<22 years old):
 - What are the probable benefits of Enterra for the following clinical endpoints?
 - Improvement in upper GI symptoms
 - Reduction in need for nutritional support
 - Improved gastric emptying time (GET)
 - What adverse events are reported in the literature after treatment with Enterra?

Methods

- Searched PubMed and EMBASE using the following terms:
 - Enterra
 - "gastric pacing"
 - "gastric pacemaker"
 - "gastric electrostimulation"
 - "gastric electric stimulation"
 - "gastric electrical stimulation"
 - (stimulation AND gastroparesis)
 - "gastrointestinal neuromodulation"
- Inclusion Criteria
 - Published between May 1, 2015 and April 30, 2016
 - Human studies
 - Includes pediatric patients
 - English language
- Search yielded 132 citations
 - 130 articles excluded
 - 2 articles included for full epidemiological review and assessment

Results

Islam et al. Study (Article #1)

- Retrospective review of a prospectively maintained database of patients undergoing GES at two US sites (University of Mississippi and University of Florida Health)
- 67 pediatric patients implanted with Enterra, 2004 to 2014
- Average 3.5 years of follow-up (range 1-9 years)
- 67 subjects were a subset of 97 patients who responded favorably to temporary GES prior to Enterra placement.
- In the overall cohort of 97 patients:
 - Mean age 13.7 years (range 2-19 years)
 - 76% female
 - 85.6% Caucasian

Probable Benefit Results in Islam et al. Study

- Improvements in all individuals symptoms (pain, nausea, emesis, bloating, and satiety) and total symptom score (TSS) at 1-, 6-, 12-, and >12 months compared to baseline
- Of the 67 subjects included in this study, outcome data were available in a decreasing number of subjects a 1 month (n=56), 6 months (n=52), 12 months (n=40), and beyond 12 months (n=34)
- Symptom scores not obtained in 11 subjects
 - Improved food intake, parental report of symptoms, and reduced need for parenteral nutrition (n=10)
 - Favorable response to Enterra after repositioning of leads (n=1)

Safety Results in Islam et al. Study

- Device explant (n=10)
 - Failure of long-term stimulation (after mean 13.2 months post-implant) to improve symptoms (n=5)
 - No longer requiring stimulation due to improved condition after 6-24 months of treatment (n=4)
 - Traumatic disruption of pocket (n=1)
- Device replacement due to expired battery life (n=13)
- Repositioning of the leads (n=5)
 - Symptom recurrence during the first month of GES (n=2)
 - Long-term failure of stimulation after 4 to 18 months of treatment (n=3)
- Lead erosion through gastric mucosa requiring reoperation (n=2)
- Seroma within 1 month of device implantation (n=1)
- Deaths (n=4)
 - Progressive respiratory insufficiency (n=3)
 - No additional information provided for the fourth death

Heckert et al. Study (Article #2)

- 151 consecutive GP patients implanted with Enterra at a single US site (Temple University) between July 2010 and December 2013
- Followed for 12 months
- 79% female
- Mean age 38.2 years (range 18-69 years)
- This study included both pediatric and adult subjects; however, the study did not report how many of the 151 participants were pediatric or present the data separately for pediatric and adult subjects.

Probable Benefit Results in Heckert et al. Study

- Improvement in all symptoms with the greatest reported improvement in nausea, early satiety, and loss of appetite; symptoms with the least improvement included constipation, diarrhea, & abdominal distension
- 75% of patients reported improved overall symptoms and this response was greater in diabetics than in idiopathic patients.
 - Of 65 diabetic patients, 85 % reported improved overall symptoms compared to 68% of idiopathic patients.
- Did not report on changes in need for nutritional support and GET

Safety Results in Heckert et al. Study

- Most common adverse event was pain or sensation at the stimulator site, which was reported in 15 of 138 patients (11%)
- Two diabetic patients had Enterra removed for infection (one at 6 months and the other at 7 months post-implantation)
- One death, in a diabetic patient due to “unrelated causes”

Discussion and Conclusion of the Literature Review

- Reduced upper GI symptoms after Enterra treatment; effects on need for nutritional support and GET less clear
- Commonly reported need for additional surgical procedures for battery replacement and repositioning of device
- Our findings contrast a recent systematic review and meta-analysis by Levinthal et al. which concluded that controlled trials did not demonstrate a clinical effect of GES above and beyond sham controls.
- Limitations
 - Only 2 studies included
 - Retrospective review
 - Enterra evaluated in responders to temporary GES
 - Mixed pediatric and adult subjects in Heckert et al. study
- Study design factors limit our ability to make any conclusions about probable benefits and safety of Enterra in the pediatric population
- Findings consistent with Enterra systematic literature reviews presented at PAC on September 23, 2014 and September 16, 2015

Overall Conclusion

- No new adverse event types have been reported in the pediatric population in the MDRs and in the literature
- FDA believes that Enterra should remain in HDE designation.

CDRH Recommendation

- FDA will continue surveillance and report the following to the PAC in 2017:
 - Distribution numbers
 - MDR review results
 - Literature review results

Question to the PAC

- Does the Committee agree with CDRH's conclusions and recommendation?

