Executive Summary

Enterra® Therapy System

H990014

Prepared by the Center for Devices and Radiological Health

for the September 16, 2016 Pediatric Advisory Committee meeting

TABLE OF CONTENTS

INTRODUCTION

In accordance with the Pediatric Medical Device Safety and Improvement Act, this document provides the Pediatric Advisory Committee (PAC) with postmarketing safety information to support its annual review of the Enterra® Therapy System ("Enterra"). The purpose of this annual review is to (1) ensure that the Humanitarian Device Exemption (HDE) for this device remains appropriate for the pediatric population for which it was granted, and (2) provide the PAC an opportunity to advise FDA about any new safety concerns it has about the use of this device in pediatric patients.

This document summarizes the safety data the FDA reviewed in the year following our 2015 report to the PAC. It includes data from the manufacturer's annual report, postmarket medical device reports (MDR) of adverse events, and peer-reviewed literature.

BRIEF DEVICE DESCRIPTION

Enterra is a surgically-implanted gastric electrical stimulator (GES). The mechanism(s) by which Enterra works is not well understood, but may involve indirect neuromodulation of parasympathetic nerves and/or ganglia which regulate gastric function.

Enterra 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. The neurostimulator contains a sealed battery and electronic circuitry.
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.

Schematic diagrams of the implantable components and device placement are provided in FIGURE 1 and FIGURE 2, respectively.

FIGURE 1: Implantable components

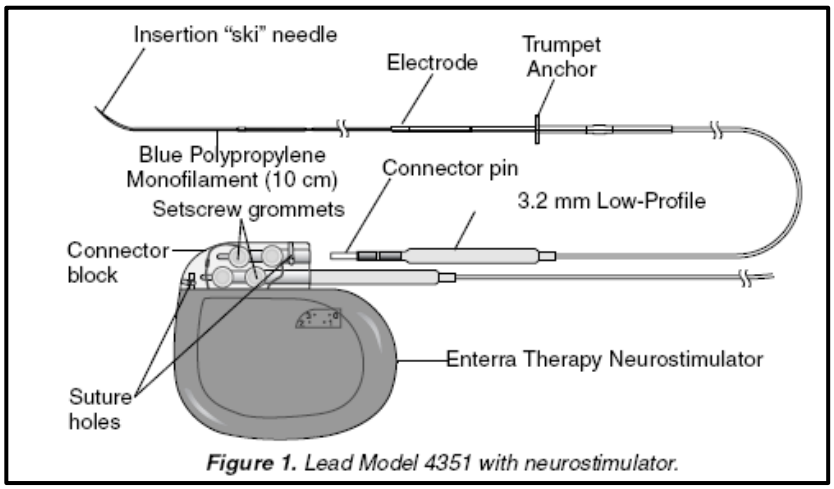
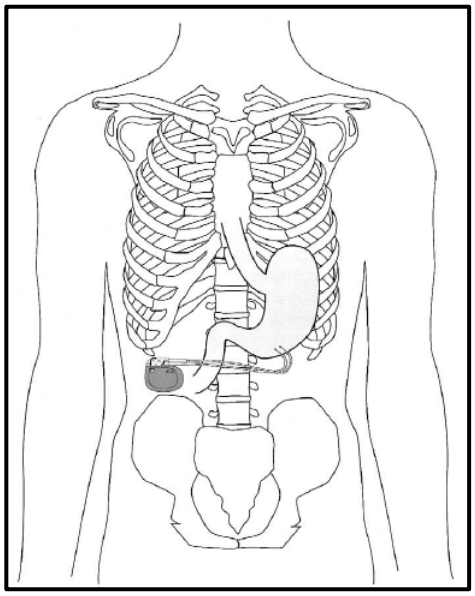


Figure 1. Lead Model 4351 with neurostimulator.

FIGURE 2: Device placement



INDICATIONS FOR USE

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

REGULATORY HISTORY

September 23, 1999: Granting of Humanitarian Use Device (HUD) designation for Enterra (HUD #990014)

March 30, 2000: Approval of Enterra HDE (H990014)

March 25, 2013: Approval to profit on the sale of Enterra

DEVICE DISTRIBUTION DATA

FDASIA amended section 520(m) of the FD&C Act to allow devices with HDEs indicated for use in pediatric patients or a pediatric subpopulation to be sold for profit; the number of devices distributed in any calendar year cannot exceed the Annual Distribution Number (ADN) for each device. The 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 FDA has interpreted this to mean that the calculation of the ADN should be 4,000 multiplied by the number of devices reasonably necessary to treat an individual. For Enterra, one device is reasonably necessary to treat an individual, therefore the ADN for this device is 4,000. Annual distribution of Enterra has not yet exceeded the ADN.

The total number of Enterra devices *sold* in the U.S. for the current and previous reporting periods is detailed in TABLE 1; the number of devices *implanted* in pediatrics is detailed in TABLE 2.

TABLE 1: Distribution numbers

Model Number & Component Name	Devices Sold from 02/01/15 – 01/31/06	Devices Sold From 02/01/14 – 01/31/15	Devices Sold from 02/01/13 – 01/31/14
37800 Implantable Neurostimulator (INS)	1,611	1,391	1,381
3116 Implantable Neurostimulator	208	95	N/A
4351 Intramuscular Lead	2,151	2,151	1.928

TABLE 2: Number of devices implanted in pediatric patients

Reporting Period	Total N	Female		Male		Gender Unknown	
		<18	18 to <22	<18	18 to <22	<18	18 to <22
Newly implanted Pediatric patients implanted during this reporting period	71*	24	35	7	4	1	0
Total Pediatric implant base this period	268**	71	137	36	21	2	1

*There were 71 newly implanted pediatric patients in the current reporting period. Additionally there were 32 previously implanted pediatric patients that received a replacement device during the current reporting period, for a total of 103 pediatric implants in the current reporting period.
**After reviewing the 2015-16 data, the table was updated to reflect the addition of one pediatric female patient with previously unknown date of birth.

MEDICAL DEVICE REPORT REVIEW

Overview of MDR database

The MDR database is one of several important postmarket surveillance data sources used by the FDA. Each year, the FDA receives several hundred thousand medical device reports (MDRs) of suspected device-associated deaths, serious injuries and malfunctions. The MDR database houses MDRs submitted to the FDA by mandatory reporters (manufacturers, importers and device user facilities) and voluntary reporters such as health care professionals, patients and consumers. The FDA uses MDRs to monitor device performance, detect potential device-related safety issues, and contribute to benefit-risk assessments of these products. MDR reports can be used effectively to:

- Establish a qualitative snapshot of adverse events for a specific device or device type
- Detect actual or potential device problems in a "real world" setting/environment, including:
  - rare, serious, or unexpected adverse events
  - adverse events that occur during long-term device use
  - adverse events associated with vulnerable populations
  - off-label use
  - use error

Although MDRs are a valuable source of information, this passive surveillance system has limitations, including the potential submission of incomplete, inaccurate, untimely, unverified, or biased data. In

addition, the incidence or prevalence of an event cannot be determined from this reporting system alone due to potential under-reporting of events and lack of information about frequency of device use. Because of this, MDRs comprise only one of the FDA's several important postmarket surveillance data sources. Other limitations of MDRs include, but are not necessarily limited to:

- MDR data alone cannot be used to establish rates of events, evaluate a change in event rates over time, or compare event rates between devices. The number of reports cannot be interpreted or used in isolation to reach conclusions about the existence, severity, or frequency of problems associated with devices.
- Confirming whether a device actually caused a specific event can be difficult based solely on information provided in a given report. Establishing a cause-and-effect relationship is especially difficult if circumstances surrounding the event have not been verified or if the device in question has not been directly evaluated.
- MDR data is subjected to reporting bias, attributable to potential causes such as reporting practice, increased media attention, and/or other agency regulatory actions.
- MDR data does not represent all known safety information for a reported medical device and should be interpreted in the context of other available information when making device-related or treatment decisions.

MDRs Associated with Enterra Therapy System

MDR Search Methodology

The database was searched using the following search criteria:

- **Product Code:** LNQ
- **Report Entered:** between May 1, 2015 and April 30, 2016.

Results

The search resulted in 351 MDRs, of which 350 were submitted by the Manufacturer and 1 was submitted by a Voluntary reporter. Neither User Facilities nor Distributors submitted any MDRs. In 25 events two or more reports (N=35) were submitted for the same event, where multiple device components were implanted in the same patient. One (1) MDR was excluded from the MDR data analysis since this MDR described an event reported in a journal article; "Long-Term Outcomes of Gastric Electrical Stimulation in Children with Gastroparesis, 2016." That article is discussed in the LITERATURE REVIEW section of this document. Therefore, there were 315 unique events identified. These events included 203 injuries, and 112 device malfunctions and these are further discussed below.

Event Type by Patient Age

The distribution of event type by reported age grouping is found in Table 1 below. Seventeen reports (17) identified a pediatric patient (< 18 and 18 to <22 years old), and included 13 injury MDRs and 4 malfunction MDRs.

TABLE 3: Overall Event Type Distribution by Patient Age.

Event Type	Total MDR Count 5/2015 - 4/2016	MDR Count by Patient Age (years)			
		Pediatric (< 18)	Pediatric (18 to <22)	Adult (≥ 22)	Indeterminate (Age blank)
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**

Comparison of Current Patient Event Type Information with 2013 and 2014 Data

Table 4 below compares the Event Type distribution for this analysis to years 2013 and 2014. Last year in the HDE Annual Report Review Form, the manufacturer addressed an increase in rates of reporting for injuries and malfunctions, citing a remedial review of adverse events from 2000 to 2012, which identified 102 reports that were then submitted in 2014. Ninety-nine (99) of these reports submitted by the manufacturer in 2014 related to events that occurred several years ago. (These numbers are identified in parenthesis). When correcting for remedial reports submitted in the previous two years, this year's total number of MDRs appears to fall in line with the previous submissions.

TABLE 4: Overall Event Type Distribution by Year.

Event Type	Total MDR Count		
	3/30/13-4/1/14	4/2/14-4/30/15 (Remediated reports)	5/2015 - 4/2016
Death	4	4 (3)	0
Injury	161	315 (91)	203
Malfunction	99	121 (5)	112
Total MDR Count	**264**	**440 (99)**	**315**

Patient Gender and Age Information

The pediatric patients' ages ranged from 12 to 21.9 years, with a mean age of 17.8 years old. In the review of the 315 MDRs, 249 noted the gender of the patient, where there continues to be a large gender disparity. This disparity is greater in the reports for pediatric patients (14:1 female to male ratio) compared with adult patient reports (5:1 female to male ratio). Information based on previous literature reviews indicates the following theories:

- Gastroparesis is more commonly diagnosed in females than males, in all age categories
- Gender-specific (female: male) incidence of definite gastroparesis was found to be at a rate of 4:1 however, through all studies and MDR reviews there is no information to substantiate concrete reasons for the increased incidence of gastroparesis in females over males.
- Idiopathic gastroparesis affects women at a much higher frequency than men.

Time to Event Occurrence

An analysis of the Time to Event Occurrence (TTEO) was performed. The TTEO is based on the implant duration and was calculated as the time between the Date of Implant and the Date of Event or the date the implant was removed. The TTEO could be determined for 129 MDRs, including 10 of the 17 pediatric reports.

Table 5 below provides the MDR count for the TTEO for the pediatric, adult, and indeterminate patient populations.

TABLE 5: MDR count for the TTEO by patient age

Time to Event Occurrence (TTEO)	MDR Count by Patient Age (years)			
	Pediatric (<18)	**Pediatric (18 to <22)**	**Adult (≥22)**	**Indeterminate (Age blank)**
≤30 days	0	3	25	1
31 days – 1 year	3	4	14	8
1 – 5 years	0	0	45	10
>5 years	0	0	15	1
Totals (N=129)	3	7	99	20

Review of the ten (10) pediatric reports:

A. TTEO within the first 30 days of implant. (N=3)
   - One (1) patient (age 18) had complaints of lack of therapeutic effect since implant.
   - Two (2) patients (both age 21) had lead erosion.

B. TTEO between 30 days and 1 year of implant. (N=7)
   - One (1) patient (age 12) developed an infection at the pocket site.
   - Five (5) pediatric patients had a return of symptoms and electrical shock.
     - One (1) patient (age 14) complained of a return of symptoms of nausea and vomiting. His/her physician felt the issue was related to increased impedance.
     - One (1) patient (age 15) reported a return of nausea, occurring "24 hours after a lightning strike outside of the barn the patient was in". Settings on the device were noticed to be changed and later the device stopped working completely. Patient was scheduled for INS (Intestinal Nerve Stimulator) replacement.

        - One (1) patient (age 18) reported a "sudden return of vomiting symptoms" because of premature battery depletion. Patient was scheduled for INS replacement.
        - One (1) patient report (age 18) noted, "Stimulator was not working" without providing additional information.
        - One (1) patient report (age 20) noted vomiting with shocking and inappropriate stimulation pain without relief from interventions.
    - One (1) patient (age 21 years) required a revision of a jejunostomy and duodenal rotation initially thought to be secondary, in some way, to the device and later confirmed there was "no device issue".

For the adult (N=99) and indeterminate age (N=20) populations with TTEO data, issues with the device occurred most frequently after 1 year and up to 5 years from the date of implant, followed by issues occurring between 1 month and 1 year from date of implant. This year's review also noted an increase in reports with TTEO between 5 and 10 years. This period coincides with normal battery depletion so complaints of return of symptoms (nausea, vomiting) or decreased therapeutic response would be expected. Also, with normal activities as well as unforeseen accidents (falls, motor vehicle), issues of device or lead migration are also occurring.

Last year's TTEO analysis, identified the period between 1 month and 1 year as the most prevalent time for reported device issues occurring in the adult and indeterminate age populations.

Further review of occurrences in this TTEO group reveals:

The early onset of events (0 to 1 year) often involved unexpected outcomes of the device implantation which resulted in injury to the patient as characterized below:

- Sudden return of symptoms of nausea and vomiting and/or loss of therapy secondary to premature battery depletion often related to high impedance settings.
- Pain and inappropriate simulation/shocking secondary to high impedance issues without relief from interventions.
- Infection, migration and erosion issues, in which the treatment was antibiotics for the infection and removal or revision of the device as warranted.
- Reports noting "expired implantable neurostimulators and/ or leads".

In comparison to last year's reports of events with TTEO up to 1 year, the notable difference are reports of accidents, falls and trauma as well as incidences of electromagnetic interference (EMI) which were not reported this year in the events occurring from 0 to 1 year after implant.

Incidences occurring after 1 year tend to commonly characterize adjustable or resolvable device related issues such as:

- Impedance issues after falls and motor vehicle accidents attributed to complaints of "jolting", "shocks "and "pain". These incidences often require adjustments or surgical intervention for replacement/revision depending on the extent of injury.
- Electromagnetic Interference (EMI) (shopping center and airport security gates) resulting in loss of therapy and return of symptoms.
- Normal and premature battery depletion or high impedance issues resulting in decreased effectiveness of the device and requires reprogramming or replacement of the battery &/or leads.

In last year's analysis, for events occurring one (1) year and beyond, the same types of complaints were noted.

Most Commonly Reported Patient Problem Codes

Table 6 below provides the most commonly reported patient problem codes found in the MDRs reviewed during this year's analysis, differentiated by patient age. The most prevalent complaints were "Nausea" and "Vomiting" (N=98), which were characterized often as a return of symptoms and "Complaints Ill-defined" /"Malaise" (N=95). Included with these were complaints of "Therapeutic Response, Decreased"/Paresis (N=90). Most of these complaints were attributed to battery depletion, often because of impedance issues that drained the battery prematurely, as well as falls and accidents which rendered the device therapeutically ineffective.

Following these, the most commonly reported problems were "Pain and Discomfort" (N=88) and "Therapeutic Effects, Unexpected" (N=79), often characterized by "Electrical Shocks" or "Nerve Stimulation, Undesired" (N=73), "Infection/Erosions" (N=23) and "Burning" (N=13). These MDRs typically involved impedance settings that were too high, lead malfunctions and incidents of EMI. Collectively, in comparison to last year's analysis, the patient problems in this analysis present no new elements; however, there are more references to impedance issues (high and low) as well as premature battery depletion issues. The review of MDRs did not provide a contributing reason for why there is an increase in the numbers of events citing battery impedance issues or why the infections/erosions were occurring. The majority of the devices were not returned to the manufacturer for evaluation.

TABLE 6: Most Commonly Reported Patient Problem Codes received by Patient Age.

Patient Problem	Total Occurrences in MDR	MDR occurrences by Patient Age (years)			
		Pediatric (< 18)	Pediatric (18 to <22)	Adults (≥ 22)	Indeterminate (Age blank)
Vomiting/ Nausea	**98**	1	2	10	85
Complaint, Ill-Defined*/Malaise	**95**	0	1	11	83
Therapeutic Response, Decreased/Paresis	**90**	1	0	18	71
Pain/ Discomfort/ Pain, Abdominal	**88**	1	1	25	61
Therapeutic Effects, Unexpected**	**79**	1	0	14	64
Electric Shock/Nerve Stimulation, Undesired	**73**	0	2	17	54
No known impact or consequence to patient***	**65**	0	1	41	23
Infection/Erosion	**23**	1	1	11	10
Burning	**13**	0	0	3	10
Total Patient Problem Count	**624**	5	8	150	461

Note: The total MDR Occurrences does not equal the total MDR count since one MDR might have multiple patient problems.
***MDRs coded with "Complaint, Ill-Defined" often included reports of nausea and/or vomiting.*
****MDRs coded with "Therapeutic Effects, Unexpected" typically involved issues of the device not operating as the patient anticipated.*
*****A code of "No Known Impact or Consequence to Patient" indicates that while a device behavior was identified in the report, the manufacturer or reporter did not report any patient impact or consequence because of the reported device behavior.*

Comparison of Patient Problem Codes with last year's analysis (4/2014 – 4/2015)

Last year's analysis of patient problem codes noted, "Pain and Discomfort" and return of symptoms ("Nausea", "Vomiting", or the more general, "Complaints, Ill-defined" and "Paresis") as the most commonly reported Patient Problems. The "Pain and Discomfort" was attributed to "Unexpected Electrical Shocks" and reported as "Therapeutic effects, unexpected". As observed in this year's analysis, the return of symptoms last year also involved decreases in therapeutic response secondary to battery depletion, device or leads in place beyond use by date (UBD), and accidents or trauma which renders the device therapeutically ineffective.

Most Commonly Reported Device Problem Codes

Table 7 below provides the most commonly reported Device Problems for all MDRs differentiated by patient age. As has been seen in the past two (2) yearly MDR analyses, the top three device problem codes reported are "Device operates differently than expected" (N=111), "No Known Device Problem" (N=67), and "Inappropriate Shock" (N=54).

It was observed in this year's analysis, that "Device operates differently than expected", was most often attributed to losses in therapeutic effects secondary to low impedance readings and battery depletion. "Inappropriate Shock" (N=54) typically involved high impedance readings and electromagnetic interference (EMI) from metal detectors and security gates, both causing pain and discomfort. Adjustments to the device, its placement, impedance levels and replacement of the leads or device were noted to bring relief in these situations. As noted last year, "No Known device Problem" continues to relate to patient issues in which the device is functioning as expected but the patient presents with device intolerance issues such as erosions or "Complaints Ill-Defined" (nausea, vomiting, weight fluctuations).

TABLE 7: Most Commonly Reported Device Problem Codes Received by Patient Age.

Device Problem	Total Occurrences in MDR	MDR occurrences by Patient Age (years)			
		Pediatric (< 18)	Pediatric (18 to <22)	Adults (≥ 22)	Indeterminate (Age blank)
Device operates differently than expected	**111**	0	2	45	64
No Known Device Problem	**67**	1	2	38	26
Inappropriate shock	**54**	1	3	11	39
Failure to deliver energy/Premature Discharge of	**46**	0	0	13	**33**

battery/Low/Battery issue					
High/Low impedance/ Impedance issues	**40**	0	0	6	34
Electromagnetic compatibility issue/ Electro-magnetic interference (EMI)	**36**	0	1	11	24
Migration of device or device component	**25**	0	1	14	10
Break	**19**	0	0	8	11
Unintended collision	**13**	0	0	4	**9**
Overheating of device or device component	**11**	0	0	7	**4**
Total Device Problem Count	**422**	**2**	**9**	**157**	**254**

Note: The total MDR Occurrences does not equal the total MDR count since one MDR might have multiple device problems.

Discussion of the Top Four reported Pediatric Problems

Similar to last year's analysis, the three most common complaints found in the pediatric MDRs were "Electrical Shock" ("Nerve Stimulation, Undesired"), "Nausea", "Vomiting", ("Complaints, Ill-defined) followed by Pain and Discomfort . On further examination of the clinical events involving these pediatric complaints, most were attributable to high or low impedance issues and commonly associated with a battery depletion or lead malfunction. New to the top reported pediatric clinical events this year is Infection/ Erosion . This type of event occurred in the pocket for one patient in addition to lead erosion requiring medical intervention in another. Root causes of these infections/erosions were not mentioned in the reports.

In comparison, previous analyses noted that most pediatric complaints were related to device functionality and pediatric activity with the primary reported complaint in pediatric patients being "Inappropriate Electrical Shock". The complaints of "Nerve Stimulation, Undesired"/ "Electric Shock" in this year's analysis however, were directly related to issues of high impedance or a lead connection problem.

Further analysis of the MDR narratives of Pediatric Events from 5/2015 – 4/2016

The seventeen (17) pediatric MDR narratives were individually reviewed to identify patient problems and issues related to each MDR adverse event.

Nausea/ Vomiting/ Complaint-Ill Defined
There were five (5) MDRs that identified "Nausea"/"Vomiting"/"Complaint-Ill Defined" in pediatric patients. Use of "Complaint-Ill Defined" referenced symptoms such as nausea, vomiting, twitching and pain, which are commonly reported complaints and referred by the manufacturer as known inherent risks.

- One (1) report involved a patient (age 14) with return of symptoms of nausea and vomiting related to impedance issues. Battery was changed and symptoms improved.
- The 4 other reports (ages 15 to 21) involved patients with complaints of nausea and/or vomiting. Impedance levels were checked and found to be acceptable in two (2) of these events. Impedance setting changes and a complete system change in the other two (2) patient's resolved the issues.

Electrical Shock/ Nerve Stimulation, Undesired/ Inappropriate Electric Shock
Four (4) MDRs identified "Electrical Shock", "Nerve Stimulation, Undesired and "Inappropriate Shock" in pediatric patients. Each report was individually reviewed to determine if electric shock was attributed to the device or a non-device related event. It should be noted here that the Enterra Therapy System is designed to use electrical stimulation to treat the secondary symptoms of gastroparesis and thus, patients may experience shocking sensations at times when the device is operating as intended. Medtronic mentions shock as a potential side effect in the device labeling under Warnings:

> "The voltage induced through the lead and Neurostimulator may cause uncomfortable jolting or shocking levels of stimulation."

The four (4) reports are characterized here in terms of suspected cause and type of intervention, as applicable:

- One (1) report involved the 14 year old mentioned above with complaints of nausea and vomiting. Increased impedance was found to increase this patient's symptoms therefore the physician made an attempt at turning off one of the three leads. This then caused shocking sensations and a determination was made to replace the battery which improved the patient's symptoms.
- Two (2) reports involve patient (each age 20) complaints of inappropriate stimulus secondary to impedance issues and required programming adjustments.
- One (1) report noted a patient (age 21) with complaints of jolting sensations in the stomach area. The lead was found to be "too far from the INS". It was suggested the "device and leads be replaced with the most recent generation of the system", however no outcomes were reported.

Pain/ Discomfort/ Abdominal Pain
The two (2) events that identified "Pain"/ "Discomfort" in pediatric patients were individually reviewed to determine the reported cause of the described pain.

- One (1) report involved a patient (age 12) with complaints of nausea, vomiting, chest and incision site pain since implant. The patent was very thin and placement of the device was lower than typical placement. Reduction of the voltage and pain medication resolved these issues.
- One (1) report involved a 20 year old whose pain was primarily referred to as "pain from gastroparesis" and shocking. At the time, the patient was seeking a healthcare provider to make impedance adjustments as she had recently moved. No outcome was reported regarding this event.

Therapeutic Response, Decreased or Therapeutic Response, Unexpected
"Therapeutic Response, Decreased" and /or "Therapeutic Response, Unexpected" were noted in four (4) reports.

- Two (2) reports noted "Therapeutic Response, Unexpected".

- One (1) patient (age 15) "developed an allergic/inflammatory reaction to the gastric/pacer components". An abscess was found at the location of one of the lead sites. The cause of the abscess was not determined and the device relationship to the event was not determined.
- One (1) patient (age 18) complained of nausea and vomiting, it was determined after hospitalization to be related to a different gastrological issue. The INS was found to have appropriate device settings.

- Two (2) reports noted a "Decrease in Therapeutic Response.
  - One (1) patient (age 16) had the leads moved to a different location without resolution.
  - Another patient (age 18) complained of premature battery depletion this contributed to her return of vomiting symptoms.

Re-interventions in Pediatric patients from 5/2015 through 4/2016

Re-interventions addressing types of clinical incidences reported above are listed below in Table 9. This table summarizes the re-interventions identified in the narratives and the causal events leading to these re-interventions.

Literature by Brody et al., *"Follow-up after gastric electrical stimulation for gastroparesis"*[1] notes that patients receiving this type of therapy have a high likelihood of requiring additional surgery. This year's analysis continues to show that close monitoring and interventions, as warranted, are necessary with the use of this device

TABLE 9: MDR Reported Re-Interventions in Pediatric patients (5/2015 -4/2016)

Re-Interventions	Number of Incidences	Causal Event
Replacement • Device, • Battery, and/or • Lead	6	• Return of symptoms with decreased therapeutic effects • Shocking • Erosion
Explant • Permanent or • Temporary	3	• Lead erosion • Increased shocking • Infection
Reprogramming/ Calibration	2	• loss of therapeutic effect
Hospitalization for follow-up	2	• Incision site infection • Loss of therapeutic effect • Device becoming randomly hot
Office follow-up treatment • Examination • Prescriptions	2	• Increased shocking • Pain • Lead erosion

*Note that the total Number of Incidences Count does not equal the number of MDRs since one MDR

[1] Brody, F., et al., *Follow-up after gastric electrical stimulation for gastroparesis.* J Am Coll Surg, 2015. **220**(1): p. 57-63.

might have multiple noted re-interventions.

Conclusions Based on MDR Review

- There have been 17 pediatric MDRs submitted for the Enterra Therapy System between May 1, 2015 and April 30, 2016, with 13 injuries, and 4 device malfunctions.

- We continue to see higher numbers of reports involving female patients both in the adult population (5:1 female to male ratio) as well as amongst pediatric patients (14:1 female to male ratio).

- Reports found to be within the indeterminate age group (Age Blank) aligned most closely with the events, patient and device problem codes of those found in the adult population group (≥ 22 years). There were no definitive distinctions between the age groups aside from the numbers presented.

- The TTEO was available and analyzed for 129 MDRs, including 10 of the 17 pediatric reports. Three pediatric patients (ages 18 to <22) had TTEO of less than 30 days while seven (7) of the pediatric patients (ages 12 - 20), had TTEO occurrences of 31 days to 1 year of implant.

- The most common reported pediatric patient problems share similar themes as identified in last year's analysis. However, there are more reported impedance issues noted in this year's analysis than in previous years associated with reported patient complaints of :
    - "Nausea"/ "Vomiting", "Complaints Ill-Defined" and "Decreased Therapeutic response"
    - "Pain"/ "Discomfort" characterized by "Electrical Shocks" or "Nerve Stimulation, Undesired" or "Burning" sensations.
    - Infections/Erosions

- Device Problems in pediatric patients remain unchanged from the previous two (2) year's analyses with the most frequently reported device problems being:
    - "Device operates differently than expected" with low impedance readings and battery depletion.
    - "Inappropriate Shock" involving high impedance readings and electromagnetic interference (EMI) from metal detectors/security gates.
    - Adjustments to the device impedance settings, its positioning or complete replacement of the leads or device generally resulted in relief of these complaints.

- Device problems directly related to the impedance issues often had to do with battery issues and/or lead placement connections this year. The manufacturer's evaluations of these device issues were hindered due to devices not being returned in the majority of cases (284 of 315 MDRs).

- Active adult involvement and awareness of issues of complaint by pediatric patients implanted with the Enterra device, continues to be needed to assist with the accurate assessment and labeling of those complaints for future monitoring and analysis.

- Overall, the types of Patient Problems and Device Problems observed among pediatric patients were similar to those observed in adult patients.

LITERATURE REVIEW

Purpose of literature review

A systematic literature review was conducted to evaluate the safety and probable benefit of Enterra gastric electrical stimulator (GES) for any indication in the pediatric population (<22 years old). This is an update from the literature review presented at the Pediatric Advisory Committee (PAC) meeting on September 23, 2014 and September 16, 2015. Specifically, the literature review was conducted to address the following questions:

1. What is the probable benefit of Enterra for the following clinical endpoints: improvement in upper GI symptoms; reduction in need for nutritional support; and improved gastric emptying time (GET)?
2. What adverse events are reported in the literature after treatment with Enterra?

Literature Search Methodolgy

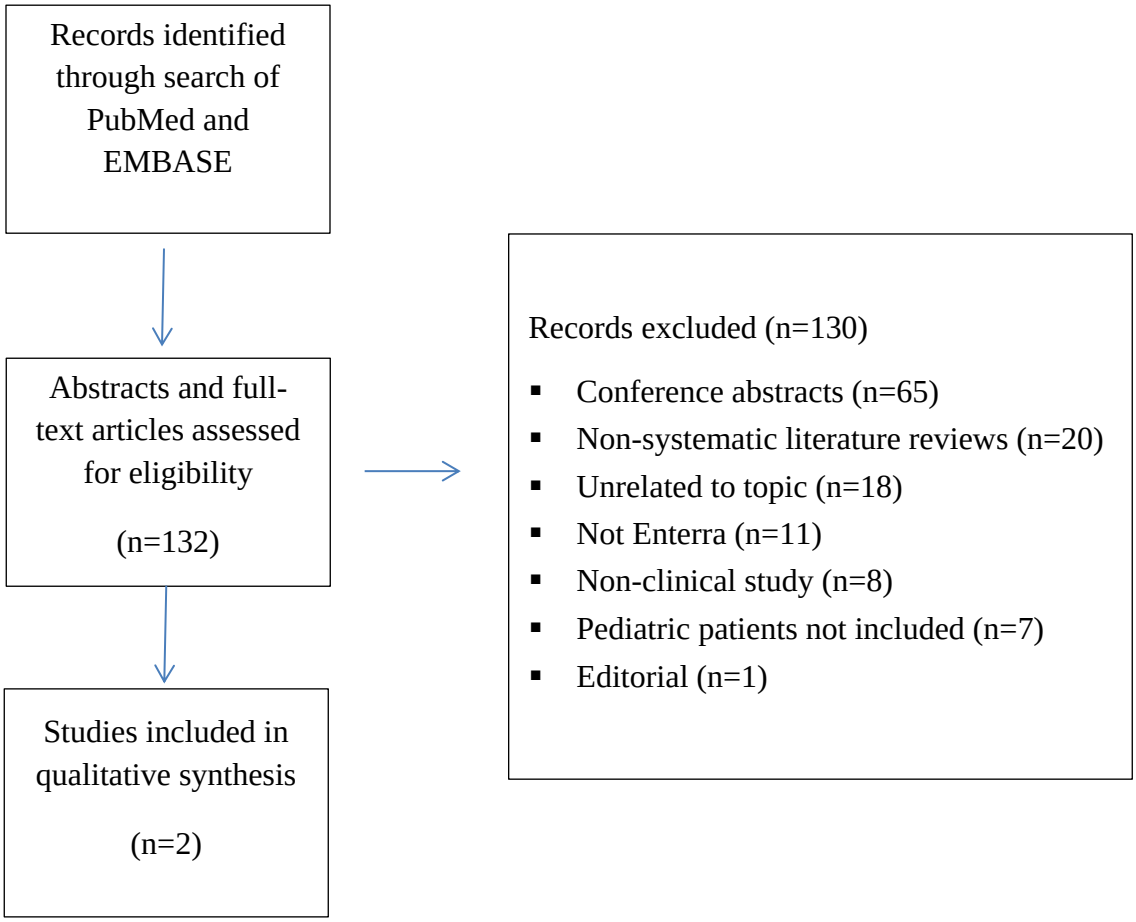
On June 5, 2016, a search in PubMed and EMBASE was performed using the following search terms:

Enterra OR "gastric electric stimulation" OR "gastric electrical stimulation" OR "gastric electrostimulation" OR "gastric pacemaker" OR "gastric pacing" OR (stimulation AND gastroparesis) OR “gastrointestinal neuromodulation”

The search was limited to studies published between May 1, 2015 and April 30, 2016 in human subjects and in the English language. This search yielded a total of 132 citations (13 in PubMed and 119 in EMBASE).

A review of abstracts and full-texts of each citation was conducted and exclusions were made. Of the 132 identified articles, 130 were excluded for the following reasons: conference abstracts (n=65); non-systematic literature reviews (n=20); not related to the safety and effectiveness of Enterra (n=18); treatment other than Enterra (n=11); not clinical study (n=8); pediatric subjects not included (n=7); and editorial (n=1). These exclusions left 2 articles for full epidemiological review and assessment (Figure 3. Article Retrieval and Selection), which is comparable to the systematic literature review results from last year (one article was included out of 109).

FIGURE 3: Article Retrieval and Selection



Results

The study by Islam et al. is a retrospective review of a prospectively maintained database of patients undergoing GES at two U.S. sites (University of Mississippi and University of Florida Health). [1] This study included 67 pediatric subjects with medically refractory gastroparesis (GP) who were implanted with Enterra between 2004 and 2014 and followed for an average of 3.5 years (range of 1-9 years). The 67 subjects were a subset of a larger group of 97 pediatric patients who responded favorably to temporary gastric stimulation prior to permanent Enterra placement (96 patients received temporary GES prior to Enterra placement and 1 patient received Enterra without temporary GES). In the overall cohort of 97 patients, the mean age was 13.7 years (range 2-19 years); seventy-six percent were female and 85.6% were Caucasian. Demographic information was not provided for the subset of 67 patients who were implanted with Enterra.

The study by Heckert et al. is a case series of 151 consecutive GP patients who were implanted with Enterra at a single U.S. site (Temple University) between July 2010 and December 2013 and were followed for 12 months. [2] Seventy-nine percent of subjects (n=120) were female and the mean age was 38.2 years (range 18-69 years) at the time of device implantation. Therefore, 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 the Islam et al. study, GI symptoms were assessed using the Gastroparesis Cardinal Symptom Index (GCSI), a validated Likert based scale that evaluates the severity of symptoms from 0 (none) to 5 (very severe) for anorexia, nausea, emesis, pain, and bloating. A combined total symptom scores (TSS) was also calculated. Of the 67 subjects included in this study, outcome data were available for 56 subjects at 1 month, 52 subjects at 6 months, 40 subjects at 12 months, and 34 subjects beyond 12 months post-implant. Improvements in all individual symptoms (pain, nausea, emesis, bloating, and satiety) were reported at all follow-up time points ($P<0.005$). A reduction in TSS was also reported at 1-, 6-, 12-, and >12 months compared to baseline ($P<0.005$).

Of the 67 subjects included in the Islam et al. study, symptom scores could not be obtained in 11 subjects due to very young age and developmental delays. Of these 11 subjects, the study reported in very general terms that 10 reported improved food intake, parental report of symptoms, and reduced need for parenteral nutrition. The one remaining patient responded favorably to Enterra after repositioning of the leads.

The Heckert et al. study assessed GI symptoms using Patient Assessment of GI Symptoms (PAGI-SYM) questionnaires which include GCSI scores and additional questions about abdominal pain, constipation, and diarrhea. Changes in PAGI-SYM scores indicated improvement in all symptoms ($P<0.05$). Symptoms that improved the most were nausea, early satiety, and loss of appetite; symptoms with the least improvement included constipation, diarrhea, & abdominal distension. For the assessment of a global clinical response, 75% of patients reported improved overall symptoms and this favorable response was greater in diabetics than in idiopathic patients ($p<0.05$). Of the 65 diabetic patients included in this study, 85 % reported improved overall symptoms compared to 68% of idiopathic patients. The Heckert et al. study did not report on changes in need for nutritional support and gastric emptying time following Enterra placement.

Safety Results

The following adverse events were reported in the Islam et al. study:

- 10 patients underwent device explant for the following reasons:
    - Failure of long-term stimulation (after mean 13.2 months post-implant) to improve symptoms (n=5)
    - Improvement in the condition no longer requiring stimulation after 6 to 24 months of treatment (n=4)
    - Traumatic disruption of the pocket (n=1)
- 13 patients underwent device replacement due to expired battery life. In all 13 patients, symptom recurrence prompted further evaluation and symptom improvement was observed following device replacement.
- 5 patients underwent repositioning of the leads for the following reasons:
    - Symptom recurrence during the first month of GES treatment (n=2)
    - Long-term failure of stimulation after 4 to 18 months of treatment (n=3)
- In 2 patients, the leads eroded through the gastric mucosa, requiring reoperation.
- 1 patient developed a seroma within 1 month of device implantation, which was drained without recurrence.
- Flowchart detailing the patients with GES (labeled Figure 1 in article) indicated that there were 4 deaths with the following: “Died (N=4)”.

- 3 patients died of progressive respiratory insufficiency; 2 patients were post-lung transplant and 1 had severe cystic fibrosis. The paper noted that Enterra had provided relief of GP symptoms in all 3 patients who died.
- However, no detail information was provided for the fourth death in the paper.

The following adverse events were reported in the 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%)
- 2 diabetic patients had Enterra removed for infection (one at 6 months and the other at 7 months post-implantation)
- "One diabetic patient died due to unrelated causes."

For the adverse events described in the Heckert et al. study, the age of the subject experiencing the event was not reported. Therefore, it is not known if these safety events occurred in pediatric or adult subjects.

Critical Assessment of the Literature

The studies by Islam et al. and Heckert et al. reported probable benefits of Enterra in improved upper GI symptoms. Effects on the need for nutritional support and gastric emptying/retention were not systematically evaluated.

The results of this systematic literature review should be interpreted in light of key limitations. First, our review only included two papers that met the search criteria and the quality of evidence in these 2 studies was relatively low. Although the Islam et al. study focused on the pediatric population, as retrospective analysis, it may subject to recall bias. Furthermore, the probable benefit and safety of Enterra was evaluated in a selected group of patients who previously responded well to temporary gastric stimulation which lasted 1-3 days for endoscopic leads and 3-28 days for trans-gastrostomy leads. Therefore, the true safety and probable benefit of Enterra in the pediatric GP population at large may have been over-estimated. The Heckert et al. study was a larger study of 151 subjects; however, it included both pediatric and adult subjects. Therefore, it is not clear if benefits derived by the mixed age cohort were experienced specifically by pediatric subjects. Similarly, it is not clear if any of the reported adverse events occurred in pediatric subjects. Despite the favorable results demonstrating probable benefits of Enterra therapy, these study design factors limit the generalizability of the results to the pediatric gastroparesis population at large.

Conclusions based on literature review

The two studies included in our systematic literature review suggest probable benefits of Enterra with respect to improved upper GI symptoms. GES effects on the need for nutritional support and GET are less clear. These findings are in contrast to 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. [3] It should be noted that the Levinthal et al. study was captured in our literature search but was not included in our review because all of the included studies were published before the designated timeframe for this review. Our review also indicated that, despite reduction of symptoms, subjects with idiopathic or diabetic gastroparesis who are implanted with Enterra may require additional surgery. The findings of this systematic literature review should be interpreted in light of the low quality of evidence, which limits our ability to make any firm conclusions about the

probable benefits and safety of Enterra in the pediatric population.

These findings are consistent with results of the Enterra systematic literature reviews that were presented at the PAC on September 23, 2014 and September 16, 2015.

SUMMARY

The FDA did not identify any new safety signals during this review of the Enterra annual report received, the MDRs received, and the peer-reviewed literature published since our last report to the PAC.

The FDA believes that the HDE for this device remains appropriate for the pediatric population for which it was granted. The FDA will continue to implement the PAC's recommendations in addition to our routine monitoring of the safety and distribution information for this device.

References

1. Islam S, et al. Long-term outcomes of gastric electrical stimulation in children with gastroparesis. J Ped Surg, 2016. 51:67-71.
2. Heckert J, et al. Gastric electric stimulation for refractory gastroparesis: A prospective analysis of 151 patients at a single center. Dig Dis Sci, 2016. 61:168-175.
3. Levinthal DJ et al. Systematic review and meta-analysis: Gastric electrical stimulation for gastroparesis. Auton Neurosci, 2015 (In press), http://dx.doi.org/10.1016/j.autneu.2016.03.004.