Executive Summary

Enterra® Therapy System

H990014

Prepared by the Center for Devices and Radiological Health

for the September 16, 2015 Pediatric Advisory Committee meeting

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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 2014 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) used to treat gastroparesis. There are currently no other devices available that are indicated for the management or treatment of gastroparesis refractory to standard medical interventions. 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

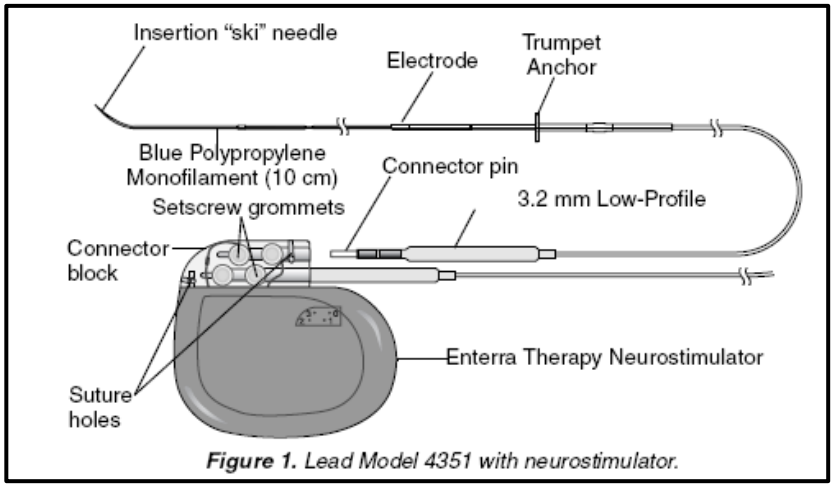
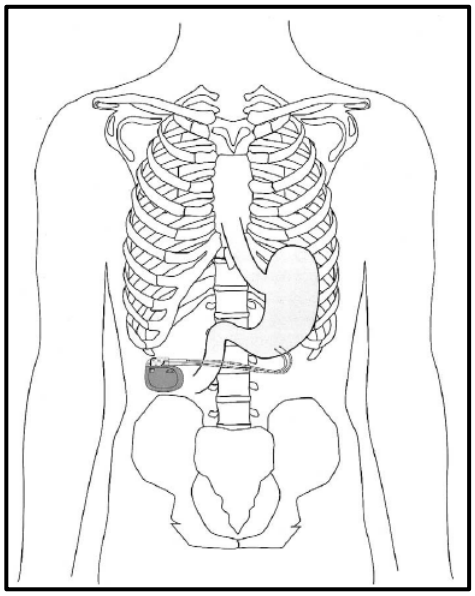


Figure 1. Lead Model 4351 with neurostimulator.

FIGURE 2: Device placement



INDICATIONS FOR USE

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.

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	**Number of Devices Sold in Current Reporting Period 02/01/14 – 01/31/15**	**Number of Devices Sold in Previous Reporting Period 02/01/13 – 01/31/14**
37800 Implantable Neurostimulator (INS)	1,391	1,318
3116 Implantable Neurostimulator	95	n/a
4351 Intramuscular Lead	2,151	1,928

TABLE 2: Number of devices implanted in pediatric patients

	Total	Female		Male		Gender Unknown	
		<18	18-21	<18	18-21	<18	18-21
Number of pediatric patients implanted with Enterra during this reporting period (02/01/14 – 01/31/15)	90	33	41	13	3	0	0
Total number of pediatric patients currently implanted with Enterra	240	71	111	37	21	1	2

MEDICAL DEVICE REPORT REVIEW

Overview of the Manufacturer and User Facility Device Experience (MAUDE) Database

MAUDE is one of several important postmarket surveillance data sources used by the FDA. Each year, the FDA receives several hundred thousand MDRs of suspected device-associated deaths, serious injuries, and malfunctions. The MAUDE database houses MDRs submitted to the FDA by mandatory reporters (i.e., manufacturers, importers, and device user facilities) and voluntary reporters (e.g., health care professionals, patients, and consumers). The FDA uses the information in MDRs to:

- establish a qualitative snapshot of adverse events for a specific device or device type,
- monitor device performance,
- contribute to benefit-risk assessments, and
- detect actual or potential safety issues or other problems with devices used in "real world" settings, including rare or unexpected adverse events, such as those associated with:
  - long-term device use,
  - vulnerable populations, or
  - user error.

Although MAUDE data provide valuable information, this passive surveillance system has limitations, including the potential submission of incomplete, inaccurate, untimely, unverified, or biased data. Other limitations of MAUDE data include the following:

- Under-reporting of events.
- Lack of information about the frequency of device use.
- Reporting bias can occur because of such things as manufacturer reporting practices, increased media attention, and/or FDA's regulatory actions.
- It is not representative of all known safety information for a reported medical device, and therefore should be interpreted in the context of other available information when making device-related or treatment decisions.
- The number of MDR reports cannot be interpreted or used in isolation to reach a conclusion about the existence, severity, or frequency of problems associated with a device.
- MDRs alone cannot be used to determine changes in the rates of events over time or to compare device event rates.
- 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.

MDRs Associated with Enterra

MDR Search Methodology

We searched the database using the following search criteria:

- Product Code: LNQ
- Report Entered: 04/02/14 – 04/30/15

This resulted in 440 MDRs: 438 submitted by the manufacturer and 2 submitted by voluntary reporters. None of these MDRs were submitted by user facilities or distributors.

Event Type by Patient Age

The Event Type distribution reported within the 440 MDRs for pediatric patients <18 years of age, pediatric patients 18-21 years of age, adult patients, and patients with indeterminate age ("Blank") is shown in TABLE 3. Twelve were pediatric (<18 and 18-21 years old) patient reports, including 8 MDRs describing injuries and 4 MDRs describing malfunctions. No death reports were identified in the reports that cited pediatric use.

TABLE 3: Event type by patient age

Event Type	Total MDR Count 04/02/14 –04/30/15	MDR Count by Patient Age (years)			
		Pediatric (<18)	Pediatric (18-21)	Adult (≥22)	Indeterminate (Age blank)
Death	**4**	0	0	1	3
Injury	**315**	4	4	206	101
Malfunction	**121**	4	0	72	45
Total MDR Count	**440**	**12**		**279**	**149**

Event Type Distribution: Comparison between the Current Review Period, 2012, and 2013

TABLE 4 compares the Event Type distribution found in this year's analysis to the distribution within each of the past two calendar years (2012 and 2013). The rates of injuries and malfunctions originally appeared to have largely increased. However, the manufacturer addressed this in the HDE Annual Report Review Form, citing its remedial review of adverse events from 2000 to 2012, which identified 102 incidents that were then submitted as MDRs in 2014. Within this document, these reports are referred to as "remediated reports."

TABLE 4: Event type by year

Event Type	Total MDR Count		
	2012	2013	04/02/14 - 04/30/15
Death	4	4	4
Injury	152	161	315
Malfunction	53	99	121
Total MDR Count	**209**	**264**	**440**

Further review of the 2014-2015 reports determined that 3 of the 4 reported deaths, 91 of the 315 injuries, and 5 of the 121 malfunctions were remediated reports submitted by the manufacturer in 2014, but that were related to events that occurred several years ago. Examination of these remediated reports found that they did not change the complexion of the findings in either last year's or this year's analysis. All events and problems were similar to the findings of the remaining MDRs and have been incorporated into the following discussion of this year's findings.

Patient Gender and Age Information

Of the 440 MDRs reviewed during this analysis, 294 noted the gender of the patient. The pediatric patients' ages ranged from 9 to 22 years, with a mean age of 18 years. This analysis shows that there continues to be a large disparity between the number of reports involving female patients and the number involving male patients. In the adult population, the ratio of reports about females to reports about males is approximately 6:1; in the pediatric population, this ratio is about 4:1. The issue of gender bias was re-addressed with the Office of Device Evaluation (ODE) and Division of Epidemiology (DEPI). Information from the literature review suggests the following theories remain unchanged:

- 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 it does men.

Death Reports

None of the 4 reports of death found during this year's review of MDRs submitted between 04/02/14 and 04/30/15 appear to involve pediatric patients, and none of the reports name the device as the cause of death. Three reports were about patients of indeterminate age with no indication of pediatric involvement identified based on review of the event descriptions and manufacturer narratives. In these reports, we cannot definitively determine the relationship of the patient outcomes to the device, because the reports also indicate multiple co-morbidities (e.g., renal failure, deep vein thrombosis (DVT), pneumonia) as other factors involved in these reported deaths. The remaining report was about an adult (59 years of age) who committed suicide. TABLE 5 summarizes the four MDRs identified as death reports.

TABLE 5: Summary of death reports

MDR Number	Summary of report
6000032-2014-00179	Intentional overdose. History of depression and patient reported as suicidal.
3007566237-2014-03408	INS explanted secondary to lack of symptom relief. Leads left in place – no visible abnormalities. Weeks later, leads eroded – this lead to stomach injury and multiple reoperations. Pt died due to multiple medical problems.
3007566237-2014-02610	Device implanted along with other extensive gastrointestinal procedures. Pt remained hospitalized due to medical comorbidities and DVT. Patient had history of DVTs. Post-op complications – gastroparesis post device placement, DVT, hypertension, chronic Enterococcus infection, cardiac arrest secondary to possible aspiration and/or pulmonary edema.
6000032-2014-00235	Hospitalized for persistent nausea and vomiting secondary to gastroparesis status post device placement; suffered also from serious comorbidities. Later developed pleural effusions, pulmonary vein congestion and persistent atelectasis/or pneumonitis. Pt removed from life-support post chest x-ray, revealing a respiratory syncital virus and unresolvable infiltrates.

Time to Event Occurrence

An analysis of the Time to Event Occurrence (TTEO) was performed for the 440 MDRs reviewed this year. The TTEO is based on the implant duration, and was calculated as the time between the date of implant and the date of event. The TTEO could be determined for 95 MDRs, including 4 of the 12 pediatric reports. TABLE 6 provides the MDR count for various TTEOs for the pediatric, adult, and indeterminate age patient populations.

Review of the four pediatric reports revealed:

- Three pediatric patients (aged 12/13 years) noted the TTEO as the same day as implant, with complaints of shocking and pain without relief from interventions.
- The fourth patient (aged 21 years) complained of a return of symptoms of nausea, vomiting and abdominal pain with a loss of therapeutic effect at 1 year and 8 months.

In the remaining 83 adult MDRs and 8 indeterminate age MDRs, issues with the device occurred most frequently within 1 month to 1 year, with the next common timeframe being within the first 5 years from date of implant. The exception to these involved 4 reports, which listed a TTEO of between 5.1 to 8 years.

The number of pediatric-patient MDRs that provide TTEO information is limited. The TTEO information available for both pediatric patients and adult patients suggests that early onset of events (0 to 1 year) often involved events of injury and the patient's degree of intolerance to any foreign object implanted in the body as characterized below:

- Pain and lack of therapeutic effect with symptom return resolved by medication, replacement of device &/or leads, or reprogramming.
- Infection, migration, and erosion issues, treated with antibiotics for the infection and removal or revision of the device, as warranted.
- Accidents, falls, and trauma to the abdomen continue to be factors that result in increased pain and will often require surgical intervention for replacement or revision, depending on the extent of injury.
- Electromagnetic interference (EMI) (e.g., airport security gates, cell phones) also contributes to the episodes of pain secondary to increased shocking, but this normally resolved over time without needed intervention.

Events of late onset (1 to 5 years) tended to be characterized by malfunction and injury, and are often device related, as described below:

- Device operates differently than expected, often due to battery depletion or a lead malfunction, resulting in decreased effectiveness; replacement of the device &/or its leads is required.
- Discomfort due to slipping or migration, requiring surgical repositioning.
- EMI related to medical procedures (e.g., computed tomography (CT) scans, transcutaneous electrical nerve stimulation (TENS) units, heart monitors), typically resolving without intervention.

TABLE 6: MDR count for the TTEO by patient age

Time to Event Occurrence (TTEO)	MDR Count by Patient Age (years)			
	Pediatric (<18)	Pediatric (18-21)	Adult (≥22)	Indeterminate (Age blank)
Perioperative	0	0	0	0
≤30 days	3	0	21	2
31 days – 1 year	0	0	31	4
1 – 5 years	0	1	27	2
>5 years	0	0	4	0

Most Commonly Reported Patient Problem Codes by Patient Age

Every MDR should include at least one patient problem code to indicate the effects that an event may have had on the patient, including signs, symptoms, syndromes, or diagnosis. TABLE 7 provides the most commonly reported patient problem codes found in the MDRs reviewed during this year's analysis, differentiated by patient age. "Pain and Discomfort" was often characterized by "Unexpected Electrical Shocks" and reported as "Therapeutic effects, unexpected." These MDRs typically involve EMI, accidents, falls, trauma, lead malfunctions, and impedance settings that are too high. Reports with return of symptoms such as "Nausea," "Vomiting," "Complaints, Ill-defined," and "Paresis" most often involve therapeutic response decreases due to battery depletion, device or leads left in place beyond the use-by date (UBD), or accidents or trauma that render the device therapeutically ineffective. When examined collectively, the patient problems in this analysis present issues and complaint types similar to those found during our last analysis, and they present no new concerns.

TABLE7: Most commonly reported <u>patient</u> problem codes by patient age

Patient Problem Code(s)	Total Occurrences in MDRs	Occurrences in MDRs by Patient Age (years)			
		Pediatric (<18)	Pediatric (18-21)	Adult (≥22)	Indeterminate (Age blank)
Vomiting/Nausea/ Complaint, Ill-Defined*	171	2	4	113	52
Pain/Discomfort/ Pain, Abdominal	120	2	3	82	33
Therapeutic Effects, Unexpected**	71	1	0	54	16
Therapeutic Response, Decreased	71	2	1	52	16
No Known Impact or Consequence to Patient***	64	0	0	36	28
Electric Shock	51	3	2	33	13
Paresis	31	0	0	19	12
Infection	28	0	0	15	13
Malaise	19	1	1	13	4
Weight Fluctuations	18	0	0	14	4
Total Patient Problem Count	**644**	**11**	**11**	**431**	**191**

Note: The number of occurrences of patient problem codes in MDRs (644) is greater than the total number of MDRs reviewed (440) because several MDRs include multiple patient problem codes. The submitter of the report uses these codes to describe patient issues, effects and outcomes.

**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 as a result of the reported device behavior.*

Patient Problem Codes Identified in Last Year's Analysis (03/30/00 – 04/01/14)

"Decreased Therapeutic Response," "Electric Shock," and "Pain" were the most frequently reported patient problems found during last year's MDR analysis. "Decreased Therapeutic Response" was most often attributed to lead malfunction/breakage, EMI, and extreme body movements. "Electric Shock" was attributed to the device itself, and most often required recalibration or lead/battery replacement. "Pain" was secondary to migration or flipping of the device.

Most Commonly Reported Device Problem Codes by Patient Age

Every MDR should include at least one device problem code to describe device failures or issues related to the device that are encountered during the event. TABLE 8 provides the most commonly reported device problem codes found in the MDRs reviewed during this year's analysis, differentiated by patient age.

The three most common device problem codes reported are "No Known Device Problem," "Device operates differently than expected," and "Inappropriate Shock." Most frequently observed during this analysis is the "No Known Device Problem" code. This typically involves patient-related issues in which the device appears to be functioning as expected but the patient presents with possible device intolerance issues. Some of these intolerance issues were presented as anxiety, depression, nausea, vomiting, the body's attempt to reject a foreign material, or migration of the device, not related to the device functionality. "Inappropriate Shock" and "Device operates differently than expected" are often related to high or low impedance readings, pain, and loss of therapeutic effects. Adjustments to the device, its placement, or impedance levels, as well as replacement of the leads or device, are noted as bringing relief to patients in these situations.

TABLE 8: Most commonly reported device problem codes by patient age

Device Problem Code(s)	Total Occurrences in MDRs	Occurrences in MDRs by Patient Age (years)			
		Pediatric (<18)	Pediatric (18-21)	Adult (≥22)	Indeterminate (Age blank)
No Known Device Problem*	159	3	1	90	65
Device operates differently than expected	114	3	1	82	28
Inappropriate shock	60	3	2	39	16
Migration of device or device component	24	0	1	14	9
Break	23	0	0	12	11
Electromagnetic compatibility issue	22	0	0	14	8
Low battery	19	0	0	14	5
High impedance/ Impedance issues	19	0	0	15	4
Malposition of device	13	0	0	10	3
Unintended collision	12	1	0	9	2
Electro-magnetic interference (EMI)	12	0	0	10	2
Total Device Problem Count	**477**	**10**	**5**	**309**	**153**

Note: The total number of occurrences of device problems in MDRs (477) is greater than the total number of MDRs reviewed (440) because several MDRs include multiple device problem codes. The submitter of the report uses these codes to describe device related effects, issues and outcomes.

**The code "No Known Device Problem" indicates the device was found to have operated as intended.*

Device Problem Codes Identified in Last Year's Analysis (03/30/00 – 04/01/14)

The three most commonly reported device problems found during last year's MDR analysis were the same as the three most commonly reported device problems found during this year's review; however, last year's analysis found that "Device operates differently than expected" was the most frequently reported problem followed by "No Known Device Problem" and "Inappropriate Shock." "Device operates differently than expected" usually involved electric shock, loss of therapeutic effect, and/or pain. Reports with "No Known device issue" included patients with infections or unconfirmed complaints. "Inappropriate Shock" was often reported as the result of increasing device stimulation secondary to the patients feeling a lack of therapeutic effect. "Inappropriate Shock" was also attributed to accidents and EMI from metal detectors and security gates.

Pediatric Patient Problems as they relate to Device Problem Information

In comparison to TABLES 7 and 8, which provide a listing of patient and device problem codes for all ages, TABLE 9 identifies the MDR occurrences of the most common patient problems and issues in pediatric patients in comparison to last year's findings.

TABLE 9: Clinical events identified with pediatric patients, year-to-year comparison

Clinical Events 03/30/00 – 04/01/14	Occurrences in MDRs	Clinical Events 04/02/14 – 04/30/15	Occurrences in MDRs
Inappropriate Electrical Shock	9	Nausea/Vomiting [Complaints, Ill-Defined]	6
Return of Symptoms [Therapeutic Response, Decreased]	7	Pain/Discomfort/ Abdominal Pain	5
Movement/Flipping of Device	4	Inappropriate Electric Shock	5
Electromagnetic Interference (EMI)	3	Return of Symptoms [Therapeutic Response, Decreased]	3

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.

The most common complaints found in the pediatric MDRs reviewed for this analysis were "Nausea," "Vomiting," and "Complaints, Ill-Defined" (the narratives of many of which mention nausea or vomiting), followed by "Pain" and "Inappropriate Shock." Most often the "Pain" in these reports was characterized by shocking which occurred at a higher-than-expected frequency and/or intensity. "Electrical Shock" is a potential side effect, and supervising adults need to be aware of when the pediatric patient's subjective interpretation of the degree of shock is other than what is

expected. These events were often attributable to the device itself and resolved with time or recalibration. As we found during last year's review, this year we found complaints of "Nausea" or "Vomiting;" these complaints are often associated with both reports of "Decrease in therapeutic response" and "Inappropriate Shocking." The manufacturer characterizes these as "Known Inherent Complaints" with the use of this device.

In comparison, last year's analysis (03/30/00 – 04/01/14), noted that complaints were more often related to device functionality and pediatric activity, with the most commonly reported complaint in pediatric patients being "Inappropriate Electrical Shock." This was followed by "Return of Symptoms" and "Movement or Flipping of the Device." Each of these was characterized as pediatric patients having an increased likelihood of extreme body movements and trauma, which can cause the device leads or the device itself to break and/or dislodge.

With these findings, a need continues for consideration to be given to the individual pediatric patient's cognitive ability to present information with accuracy to healthcare professionals. Close adult supervision of pediatric patients implanted with Enterra is needed to assist with the accurate assessment and labeling of complaints for future monitoring and analysis.

Further Analysis of the MDR Narratives of Pediatric Events from 04/02/14 through 04/30/15

The 12 pediatric MDR narratives were individually reviewed to identify noted patient problems and issues related to each adverse event. Because a single MDR can contain multiple adverse events, some of the MDRs are discussed in more than one of the following sections that summarize our findings.

Inappropriate Electric Shock

The 5 MDRs that identified "Inappropriate Electric Shock" in pediatric patients were individually reviewed to determine whether the electric shock was attributed to the device. It should be noted here that Enterra 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. The "Warnings" section of the device labeling includes shock as a potential side effect: "The voltage induced through the lead and neurostimulator may cause uncomfortable jolting or shocking levels of stimulation."

The 5 reports are further characterized here in terms of reported location of electrical shock, and type of intervention, as applicable:

- The locations of shock sensations were identified as the stomach (2 reports), the right side under the breast/rib cage (2 reports), and the abdominal wall (1 report).
- Interventions involved replacement of the INS (2 reports), explant with no replacement of the INS (1 report), and no intervention (2 reports).

- The manufacturer noted that electrical shock was unable to be confirmed or not attributed to the device itself with no mention of user error.

Pain/Discomfort

The 5 MDRs that identified "Pain"/"Discomfort" in pediatric patients were individually reviewed to determine the reported cause of the described pain. The reported events distinguished the pain as consistent with varying duration, and it was primarily referred to as shocking sensations.

- Three reports involved complaints of shocking sensations without complaint confirmation from the manufacturer.
  - One report noted a 50% reduction in pain post removal of the device.
  - The remaining 2 reports noted the symptoms to be unresolvable, and diagnostic testing of the device found it to be within normal limits.
- One report stated that the health care provider believed the increase in shocking sensations was secondary to excessive walking exercises the patient was doing for a secondary condition. The report also noted this patient would pass out and fall regularly. In last year's analysis, inappropriate shock was a factor attributable to a patient fall and/or device trauma.
- The remaining report involved pain with infection at the incision site for which the patient was being treated with pain medication and antibiotics.

Complaints, Ill-Defined

The 4 MDRs that identified "Complaint-Ill Defined" in pediatric patients were individually reviewed to verify that the device did not harm the patient. MDRs with this code referenced symptoms such as nausea, vomiting, twitching and pain, which are commonly reported complaints and referred by the manufacturer as known inherent risks.

- One report involved a patient with an incision site infection.
- The other 3 reports had no resolution to general complaints despite replacement, diagnostic testing, or impedance setting changes.

Decreased Therapeutic Response

"Decreased Therapeutic Response" was noted in 3 reports, and each was individually reviewed for possible causes.

- One report involved a patient who was in a motor vehicle accident and noted a subsequent loss of therapeutic response following the accident.
- The remaining 2 reports note hospitalization for the return of symptoms (e.g., nausea, vomiting, pain, diarrhea, inability to eat) within 18-21 months of implant.
  - One report noted replacement with a temporary device for complaints of constant shocking. This INS device was then set at a higher impedance. The patient then

experienced nausea, vomiting, and inability to eat 2 days later. The INS was turned down, with relief of the vomiting; however, the patient was later hospitalized again one month later for vomiting and diarrhea, and scheduled for replacement surgery.

- The remaining report included a request for the manufacturer representative to evaluate the device. The manufacturer noted an inability to confirm the complaint, and no report of evaluation was made.

Re-interventions in Pediatric Patients from 04/02/14 through 04/30/15

Re-interventions addressing the types of clinical incidences reported above are listed in TABLE 10. 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. Both last year's and this year's analyses have shown that close monitoring and interventions, as warranted, are necessary with the use of this device.

TABLE 10: Re-interventions in pediatric patients (04/02/14 – 04/30/15)

Re-interventions	Number of MDRs reporting re-interventions	Causal Events
Replacement • Device, • Battery, and/or • Lead	2	• Return of symptoms with decreased therapeutic effects • Shocking
Explant • Permanent, or • Temporary	3	• Lead erosion • Increased shocking
Reprogramming/ Calibration	3	• Loss of therapeutic effect
Hospitalization for follow-up	3	• Incision site infection • Loss of therapeutic effect • Chronic infections not device related
Office follow-up treatment	2	• Increased shocking

Note: The total number of incidences does not equal the number of MDRs since a single MDR can include multiple re-interventions.

Conclusions Based on the MDR Review

- Of the 440 MDRs involving Enterra submitted between 04/02/14 and 04/30/15, twelve MDRs were known to be about pediatric patients; none of these 12 pediatric MDRs involved death.

- We continue to see higher numbers of reports involving female patients. Consultation with CDRH's Office of Device Evaluation and Division of Epidemiology re-confirms that there remains no conclusive information to explain the increased incidence of gastroparesis in females over males.

- The group of reports about patients of indeterminate age ("blank") presented similarly to the group of reports about adults; there were no definitive distinctions between the events, patient problem codes, and device problem codes reported.

- The TTEO was available and analyzed for 95 of the 440 MDRs, including 4 of the 12 pediatric reports. Review of the pediatric reports with TTEO showed:
  - For 3 of the pediatric patients (all less than 18 years of age), TTEO happened the day of implant. Complaints included shocking and pain without relief from interventions.
  - The remaining pediatric patient (21 years of age) complained of a return of symptoms of nausea, vomiting and abdominal pain with a loss of therapeutic effect at 1 year and 8 months after implant.

- The most commonly reported pediatric patient problems found in this year's analysis have similar themes to those found in last year's analysis. They include:
  - "Pain"/"Discomfort" often related to "Electric Shock," and
  - "Complaint, Ill-Defined" and "Decreased Therapeutic Response" most often attributed to the return of symptoms (e.g., "Nausea," "Vomiting").

- Device problems remain unchanged from last year's analysis and present no new significant device concerns to patient safety. Pediatric reported device problems referred most frequently to complaints of "Shock" without relief post evaluation and treatment. Often these devices were not returned or the manufacturer found no definitive issue with the device.

- A pediatric patient's cognitive ability to present information with accuracy to the healthcare professionals continues to be a need of consideration. Close adult supervision of pediatric patients implanted with Enterra is necessary to assist with the accurate assessment and labeling of complaints for future monitoring and analysis.

- Overall, patient problems and device problems observed among pediatric patients were similar to those observed in adult patients. These issues are known inherent risks for the device and do not represent any new or previously unknown concerns regarding patient safety.

LITERATURE REVIEW

Purpose

FDA conducted a systematic literature review to evaluate the safety and probable benefit of Enterra for any indication in the pediatric population. This literature review addresses 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 due to treatment with Enterra are reported in the literature?

Methods

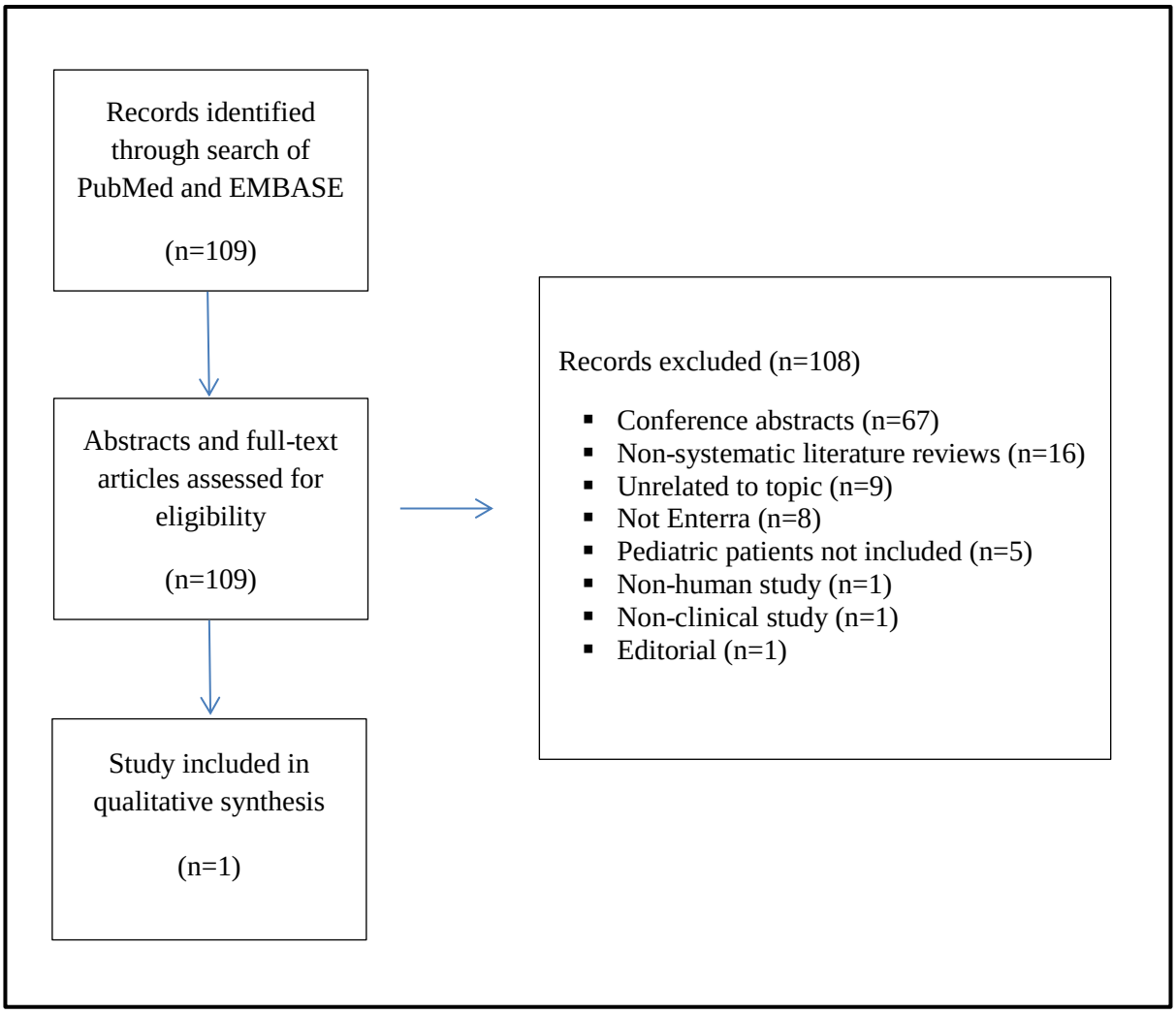
Searches of PubMed and EMBASE were performed using the following search terms:

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

The searches were limited to studies published 04/02/14 through 04/30/15 in human subjects and in the English language. This search yielded a total of 109 citations (7 in PubMed and 102 in EMBASE).

A review of the abstracts and full-texts of each citation was conducted and exclusions were made. Of the 109 articles, 108 were excluded, leaving 1 article for full epidemiological review and assessment. FIGURE 3 diagrams the article retrieval and selection process, including the criteria for exclusion.

FIGURE 3: Article Retrieval and Selection



Results

The study by Brody et al. is a retrospective review of a prospectively maintained database of patients undergoing GES at a single institution in the U.S.[1] This study included 79 subjects with gastroparesis who were implanted with Enterra between November 2003 and June 2013, and followed for up to 8 years. Nearly eighty-four percent (83.5%) of subjects were female (n=66) and 16.5% were male (n=13). Subjects had a mean ± standard deviation age of 43±10.9 years (range: 16 to 75 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 79 participants were pediatric, and did not present the data separately for pediatric and adult subjects. In this cohort, gastroparesis was caused by diabetes in 47% of subjects and due to idiopathic causes in the remaining 53%.

Probable Benefit Results

GI symptoms were assessed using a Total Symptom Score (TSS) questionnaire that assessed 9 parameters (5 functional components and 4 pain symptom components) in terms of severity and frequency.[2] The functional components included vomiting, nausea, early satiety, bloating, and postprandial fullness, and the pain components assessed chest burning, epigastric burning, epigastric pain, and chest pain. The TSS is a 5-point scale ranging from 0 to 4. The severity score was defined as follows: 0 = absent, 1 = present and not inhibiting daily activities, 2 = mildly altering daily activities, 3 = significantly altering daily activities, and 4 = significantly prohibiting most daily activities. The frequency score was rated as follows: 0 = absent, 1 = rare, 2 = 2 to 3 times per week, 3 = 4 to 6 times per week, and 4 = more than 7 times per week.

TSS data were available for 60 the 79 subjects at baseline, 52 subjects at 1-year, 14 subjects during years 2 to 3, and 18 subjects during years 4 to 8. Mean pain and functional TSS scores decreased at 1, 2 to 3, and 4 to 8 years postoperatively (all $p < 0.0001$). Individual component scores also decreased across all time periods for nausea, vomiting, early satiety, postprandial fullness, epigastric pain, and epigastric burning. One year after Enterra placement, 44% and 31% of subjects reported having at least a 25% reduction in symptom distress for functional and pain symptoms, respectively.

The Brody et al. study also reported on change in the need for nutritional support after Enterra treatment. Before device implantation, 9 subjects received nutrition supplementation, with 6 subjects requiring total parenteral nutrition (TPN) and 3 subjects requiring tube feeding. Following device placement, 4 subjects required TPN; 2 of these 4 subjects were reportedly transitioning to daily intravenous fluid of normal saline at last follow-up.

Safety Results

After initial Enterra placement, 34 subjects (43%) underwent a total of 73 additional surgical procedures, with a mean of 2.15 operations per patient. The most common reason for reoperation was due to generator-related causes, which accounted for 45% of all reoperations. Of all generator-related causes, 18 operations were required for battery exchange and 10 operations were performed to re-position the generator to alleviate pain or shocking at the implant site. In addition, 5 subjects underwent device explant due to the following reasons: psychiatric illness (n=2), panceaticoduodenectomy for pancreatic cancer (n=1), symptom resolution after oophorectomy (n=1), and lack of symptom improvement (n=1). Other causes for reoperation included gastrectomy for refractory nausea and vomiting (n=8) and median arcuate ligament release for persistent abdominal pain (n=7).

The study also noted the following: 2 operations for non-resolving small bowel obstructions in a patient with multiple previous operations, and 2 subjects requiring surgeries within 30 days of device placement for incarcerated Hasson port-site hernias.

There were no 30-day mortalities reported; however, 11 subjects died (14%) over the 8-year study period, with 8 deaths occurring in diabetic subjects and 3 deaths in the idiopathic group. All deaths were determined to be unrelated to Enterra.

The age of the subject was not reported for any of the adverse events described in the Brody et al. study. Therefore, it is not known if these safety events occurred in pediatric or adult subjects.

Discussion of the Literature

The retrospective review of pediatric and adult gastroparesis subjects by Brody et al. reported probable benefits of Enterra in improved upper GI symptoms and reduced need for nutritional support. Effects on gastric emptying and retention were not evaluated.

The results of this systematic literature review should be interpreted in light of key limitations. First, our review included only one paper. The quality of the evidence was low, as the study was a retrospective analysis of a small sample of pediatric and adult subjects at a single investigational site. Because the study included both pediatric and adult subjects, it is not clear if benefits derived by the mixed cohort were experienced specifically by 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. Similarly, it is not clear if any of the reported adverse events occurred in pediatric subjects.

Conclusions Based on Literature Review

Results of the one study included in our systematic literature review suggest probable benefits of Enterra with respect to improved upper GI symptoms and reduced need for nutritional support. However, gastroparesis subjects who are implanted with Enterra are likely to require additional surgery.

Although we identified one study describing device performance, the low quality of the evidence limits our ability to make conclusions about the probable benefits and safety of Enterra in the pediatric population.

These findings are consistent with results of last year’s systematic literature review of Enterra.

ACTIONS TAKEN BASED ON 2014 PAC RECOMMENDATIONS

During its initial review of Enterra in 2014, the PAC expressed concerns about off-label use in the <18 year old population, issues with safe use of this device that are unique to this pediatric population, the device's limited efficacy, and the number of adverse events. The PAC recommended the following in addition to the FDA's routine safety monitoring of annual reports, MDRs, and published literature:

1. Medtronic should systematically collect AE data in Enterra patients who are less than 21 years of age.
2. Patient labeling should be evaluated to determine whether information from the physician labeling should be added to the patient labeling. During the discussion, the PAC specifically noted three areas: dental visits, cell phone use, and proximity to theft detectors and security screening devices.

Medtronic submitted information about AEs that occurred in patients less than 21 years old in its latest annual report for Enterra. This data show that the incidence of pediatric AEs for the current reporting period is similar to that of the previous reporting period, and that there are no new, unexpected, or previously unreported types of AEs.

Currently, the patient labeling contains warnings equivalent to those in the physician labeling about dental visits and cell phone use. The FDA requested that Medtronic add information to the patient labeling advising patients (1) to request to bypass theft detectors and security devices and (2) of precautions they should take when bypass requests are not granted.

Additionally, Medtronic agreed to make the following labeling changes recommended by the FDA based on the AEs reported:

1. Add a warning regarding stomach wall perforation that contains information similar to the warning regarding bowel obstruction/perforation (i.e., "The lead can become entangled with or erode into the bowel, which can result in bowel obstruction and perforation. Either may lead to life threatening intra-abdominal infections and may require laparotomy, bowel resection, and system revision. Avoid excess lead slack in the abdominal cavity. Post implant, consider lead entanglement or erosion as a possible etiology in patients with bowel obstruction symptoms.")
2. Consider making the "Upper and lower gastro-intestinal (GI) symptoms" listed in the labeling under "Adverse Events Summary" more specific based on what patients are experiencing (e.g., nausea, vomiting).
3. Include terms like "shocking and jolting" when discussing change in stimulation under "Adverse Events Summary."
4. Include instances in which battery issues and complications may lead to surgical revision.

The FDA has also asked Medtronic to consider performing a study for the approved indication in patients <18 years of age in an effort to expand the labeling to include information about how to safely use this device in that age group.

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. Both Medtronic and the FDA have taken actions to address the PAC's 2014 recommendations.

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. Brody, F., et al., *Follow-up after gastric electrical stimulation for gastroparesis.* J Am Coll Surg, 2015. **220**(1): p. 57-63.
2. Lin, Z., et al., *Treatment of diabetic gastroparesis by high-frequency gastric electrical stimulation.* Diabetes Care, 2004. **27**(5): p. 1071-6.

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