

Executive Summary

Enterra[®] Therapy System

H990014

Prepared by the Center for Devices and Radiological Health
for the September 23, 2018 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 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

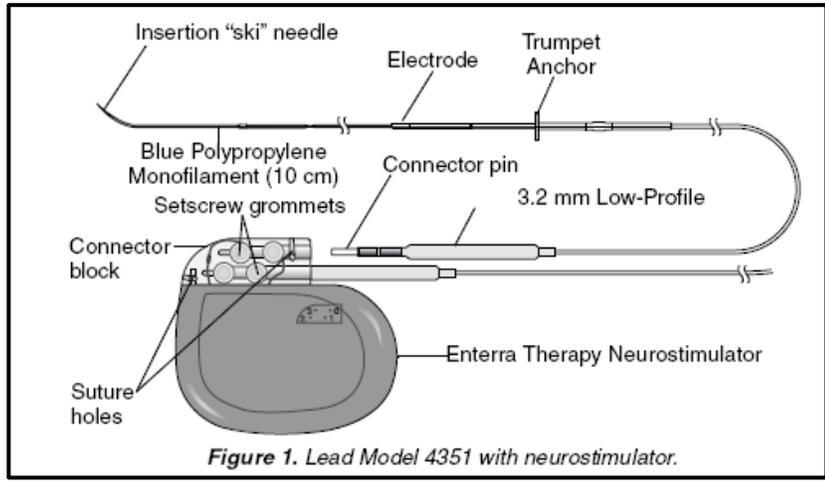
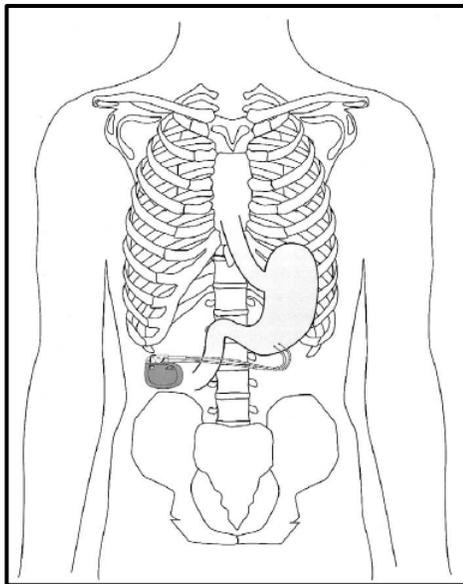


FIGURE 2: Device placement



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

Section 520(m)(6)(A)(ii) of The Food, Drug, and Cosmetic Act (FD&C) allows HDEs indicated for pediatric use to be sold for profit as long as the number of devices distributed in any calendar year does not exceed the annual distribution number (ADN). On December 13, 2016, the 21st Century Cures Act (Pub. L. No. 114-255) updated the definition of ADN to be the number of devices “reasonably needed to treat, diagnose, or cure a population of 8,000 individuals in the United States.” Based on this definition, FDA calculates the ADN to be 8,000 multiplied by the number of devices reasonably necessary to treat an individual. However, it is to be noted that unless the sponsor requests to update their ADN based on the 21st Century Cures Act, the ADN will still be based on the previously approved ADN of 4,000. The approved ADN for Enterra is 4,000 total per year.

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 02/01/17 – 01/31/18	Devices Sold from 02/01/16 – 01/31/17	Devices Sold From 02/01/15 – 01/31/16	Devices Sold from 02/01/14 – 01/31/15
37800 Implantable Neurostimulator (INS)	2,017	1,865	1,611	1,391
3116 Implantable Neurostimulator	0	0	208	95
4351 Intramuscular Lead	2,535	2,462	2,151	2,151

TABLE 2: Number of devices implanted in pediatric patients

Reporting Period: 1-Feb-2017 to 31-Jan-2018	Total N (newly implanted this period)	Female			Male			Gender Unknown		
		<2	2<18	≥18<22	<2	2<18	≥18<22	<2	2<18	≥18<22
Newly implanted Pediatric patients implanted during this reporting period	54	0	10	34	0	5	3	0	0	2
Total Pediatric implant base this period	286	0	57	154	0	44	24	0	2	5

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:

A. Search 1

- **Product Code:** LNQ
- **Report Create Date:** between May 1, 2017 and April 30, 2018

B. Search 2

- **Brand name:** Enterra%
- **Report Create Date:** between May 1, 2017 and April 30, 2018

The searches resulted in identifying 480 MDRs: 444 submitted by the manufacturer, 34 voluntary reports, and two (2) User Facilities reports submitted during this timeframe.

Forty-five (45) MDRs were excluded from further analysis since these MDRs described events reported in twenty-seven (27) journal articles. Twenty-four (24) of these articles were excluded from the MDR analysis and the Literature Review as they are articles discussing off-label indications (i.e. sacral neuromodulation for fecal/urinary

incontinence) and one (1) article was excluded because it was outside the defined search parameters (i.e. did not include pediatric patients) for this analysis. The two (2) remaining journal articles are further discussed in the **Literature Review** section of this document.

The remaining 435 MDRs involved MDRs received between May 1, 2017 and April 30, 2018. They included 0 death, 285 injury, and 150 device malfunction reports. These 435 MDRs are discussed below.

Event Type by Patient Age

Table 3 below provides the distribution of the MDRs by reported event type and age grouping. Twelve (12) reports identified a pediatric patient from 10 to 21 years old.

These have been placed into two age categories of < 18 and 18-21 years old, and included 9 injury MDRs and 3 malfunction MDRs.

TABLE 3: Overall event type distribution by patient age

Event Type	Total MDR Count 5/2017 - 4/2018	MDR Count by Patient Age (years)			
		Pediatric (< 18)	Pediatric (18-21)	Adult (≥ 22)	Indeterminate (Age blank)
Death*	0	0	0	0	0
Injury	285	3	6	241	35
Malfunction	149	1	2	123	24
Total MDR Count	435	12		364	59

Comparison of Current Patient Event Type Information with 2016 and 2017 Data

Table 4 below compares the Event Type distribution for this analysis to that of prior years 2016 and 2017. The current period appears to reflect about an 8.5% increase of MDR submissions compared with the 2017 PAC presentation period (May 1, 2016 to April 30, 2017), in the numbers of serious injury and malfunction reports. This increase coincides with an increase of product sales for the year (see Table 1, Device Distribution data). By comparison, pediatric MDR submissions decreased from 15 in the previous analysis period to 12 in this current analysis period. There was also a decrease in new pediatric implants from 56 in the previous reporting period to 54 in the current reporting period.

TABLE 4: Overall event type distribution by year

Event Type	Total MDR Count		
	PAC Meeting 2016 5/2015 - 4/2016	PAC Meeting 2017 5/2016 - 4/2017	PAC Meeting 2018 5/2017 - 4/2018
Death	0	2	0
Injury	203	255	285
Malfunction	112	144	150
Total MDR Count	315	401	435

Patient Gender and Age Information

In the 435 MDRs received from May 2017 to April 2018, 364 patients were noted as adult (≥22 years old) and 59 MDRs did not provide a patient age (indeterminate age reports). Twelve (12) MDRs contained pediatric patients' ages that ranged from 10.3 to less than 22 years, with a mean age of 18.3 years (SD ± 4.04 years). There were also 364 MDRs which noted the gender of the patient – 317 MDRs as female (including 9 pediatric), and 47 MDRs as male (including 3 pediatric). The remaining 71 MDRs did not include the patient's gender. Individual review of the 71 report narrative sections to determine gender identifiers (male or female, she or her, he or him, etc.), did not result in identifying additional female or male noted events, instead these reports identified the individual involved in the event only as "the patient".

Time to Event Occurrence

An analysis of the Time to Event Occurrence (TTEO) for the adverse event cited in the reports, 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. For those reports without a date of event, the TTEO was calculated using the reported date of implant removal. The TTEO was determined for 300 MDRs, including all 12 of the pediatric reports.

Table 5 below provides the MDR count for the TTEO for the pediatric, adult, and indeterminate age 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 (18-21)	Adult (≥22)	Indeterminate (Age blank)
≤ 30 days	0	1	56	2
31 days - ≤ 1 year	0	4	74	11
> 1 year – ≤ 5 years	4	3	100	11
> 5 years	0	0	28	7
Totals (N=300)	4	8	258	31

Characterizations of the 12 MDR Narratives of Pediatric Events from 5/2017 – 4/2018 as it Relates to TTEO:**A. TTEO within the first 30 days of implant. (N= 1)**

- One 21-year old female, reported symptoms of nausea and vomiting which were more severe than the patient was experiencing prior to the device implant. In response, the device stimulation voltage was increased on two separate occasions and eventually the patient experienced relief of the symptoms. At the time of placement, the patient weighed just 64 lbs, but after the voltage adjustments the patient was able to consume more nutrients and water (via PICC line); and “the patient was actually getting nutrients so their eye sight had been restored” (the blindness had been a pre-existing condition x 4 years). The parents also noted that “the patient started having seizures/passing out related to heart issues”, and wondered if there was a correlation to the device since this started after device placement.

B. TTEO between 31 days and ≤ 1 year of implant. (N=4)

- A 15-year-old male complained of pain in the abdomen and right shoulder after a “battery replacement” procedure. The device was turned off to relieve the pain. The patient was referred to a new healthcare provider (HCP), then had the device leads moved to a “better spot” (location not specified) and the battery was replaced at the same time 2nd battery

replacement). Per the event description, “no further complications were

- reported/anticipated”.
- A 17-year-old female reported an inability to keep “anything in their stomach”, after a “device replacement” procedure for normal battery depletion. The device voltage was increased to resolve the issue. Additional supplemental information received from the healthcare provider indicated that the cause of the complaint was undetermined and there were “no further complications reported as a result of this event.”
 - A 20-year old female reported unintended electrical shocking that led to painful stomach twitches. The device voltage was lowered a few times with no improvement, and nausea and vomiting symptoms returned. The patient’s physician thought the cause of unintended shocking was due to the patient being too thin. The patient was on TPN therapy to gain weight; however, the unintended device shocking has not improved with weight gain.
 - A 21-year-old female experienced a sudden sharp shooting pain accompanied by electrical shocking after he/she bumped into a suitcase, three days prior. The patient had a similar episode three months ago, and her HCP turned off one lead to alleviate the symptoms. The patient stated this was her second implant (first device replaced for a new battery) and they were having more trouble with this device. The patient planned to follow up with a managing HCP.

C. TTEO between >1 year and < 5 years of implant. (N=7)

- A 10 -year old female complained for the past 9 months she had experienced weight gain, nausea and a “return of gastroparesis symptoms”. The device had been in place for 2 years. The settings were increased on the device with no resolution. During a scheduled procedure it was noted the patient had a hernia in the pocket where the stimulator was located and “the leads had grown into the hernia”. No further information was provided regarding the outcome of the event.
- A 11-year-old female had a device showing failure codes during a follow up doctor’s visit. The narrative states the device was less than two weeks old, however the implant date was noted to be October 2015. This event occurred in December of 2017. According to supplemental information, the patient required a device revision, completed in November 2017, after an office visit “determined that one of the codes meant there was a loose screw at the bottom, at the leads” and a disconnected wire was found during the revision. A follow-up with the physician to check and adjust the device settings was scheduled. There were “no further complications reported as a result of this event.
- A 19-year-old male reported having the device damaged during an adrenalectomy surgery completed 2 years post implant. The patient was then “without therapy for a period of time” and had chronic nausea and vomiting until the device was replaced. Therapy was then restored and no further complications were reported.
- A 19-year-old male reported that they had a device implanted in 2013 and later removed “in 2015 or 2014”. The patient initially got relief from the pain but “it didn’t help nausea relief”. The patient reported “referred pain from the device” but the cause was not determined. Eventually the patient had the

device turned off because the pain was not allowing him to sleep. Once the device was turned off, the pain was relieved. The device remained off for 1 year and was later removed. No additional information was provided on the patient outcome.

- A 20-year-old female complained, approximately 1.5 years post placement, “it was found that the leads were misfiring and it was firing way higher than it should have been”. It was reported “they stopped using the affected lead and changed to use the other lead” but then complained of pain and vomiting. Surgery found no issues with the leads and only the device was replaced. The two old leads were connected to the new device and functioned properly. The physician noted that upon removal, the old device was “fried” and suspected EMI interference. The patient stated they “had been around a state of the art wheelchair with a NF22 battery” and questioned if this was the cause. The event narrative continues to explain, “It was reviewed that it would be unexpected. The patient had been around the wheelchair since 2016” and they were “unsure if it was a significant EMI source”. No further information was provided.
- A 20-year-old female reported nausea and vomiting, 2 years after device placement. The HCP decided to replace the leads and placed them in new locations on the stomach and also replaced the battery which “had been depleted from use”, according to additional supplemental information. It was unknown if any factors led to the event. “No further complications were reported/anticipated.”
- During an endoscopy, it was determined that a 21-year-old female had a “lead eroded into the stomach”, 1.5 years after placement of the device. The device and leads were removed. The patient was diagnosed with Cushing’s disease, which the HCP believed to contribute to the erosion.

Characterizations of the Time to Event Occurrences (TTEO) in the adult and indeterminate age populations from May 1, 2017 – April 30, 2018

For the adult (N=258) and indeterminate age (N=31) populations with TTEO data, issues with the use of this device continue to occur most frequently after > 1 year up to < 5 years from the date of implant, followed by issues occurring between 31 days up to ≤ 1 year from date of implant. In comparison to last year’s analysis of reports for these TTEO groups, the same types of issues continue:

- Return of symptoms of nausea and vomiting and/or loss of therapy secondary to impedance issues or battery issues
- Pain and inappropriate stimulation/shocking secondary to impedance or lead issues
- Infection, migration and erosion issues
- Electromagnetic Interference (EMI)

In this current analysis, the common complaint of pain continues to occur because of inappropriate stimulation/shocking as well as positioning/migration of the device or its components. The inappropriate stimulation/shocking, most often caused by abnormal changes in impedance, continue to be attributed to high impedance settings, patient falls and/or trauma to the device site. Electromagnetic interference (EMI) from medical testing (CT Scanner, MRI) as well as patients encountering metal detection devices also caused abnormal shocking and some positioning changes with the device.

Infection, migration and erosion issues also continued to occur as in the previous years' analyses. Infection was specifically mentioned in 26 MDRs, and continues to typically occur within the first 3 years of device placement. Infection associated with the device or component (i.e. "pocket", "lead", "INS" and "battery") was found in 14 reports, while six (6) reports mention a urinary tract infection, one (1) report noted a non-related toe infection, and the remaining five (5) reports did not mention site or cause of the infection.

Sixteen (16) reports note lead erosion occurring between 81 days and 2 years of implant, with one (1) additional outlier report noting lead erosion after 7.5 years. One MDR reported "twisted leads and breakage, and the device was leaking and there was a breakdown of the protective coating which led to an erosion of the generator wall/casing", 21 months after initial implant. This year's analysis identified five (5) reports of lead migration; however, only two (2) reports noted a TTEO (7 and 23 months). Pain/shocking and nausea were reported symptoms of lead migration, and interventions involved revision with replacement and relocation of the leads addressed these symptoms.

As noted last year, adult and indeterminate age patients continue to predominantly experience nausea and vomiting with decrease in therapeutic effectiveness. Thirty-one (31) MDRs discuss battery depletion (6 reports cite normal use battery depletion) which lead to patient complaints of "therapy effectiveness, decreased". These continue to occur from 30 days after placement and beyond, with typical resolution noted as reprogramming or replacement of the battery and/or leads.

Most Commonly Reported Patient Problem Codes (PPC)¹

Table 6 below provides the most prevalent reported patient problem codes found in the

MDRs reviewed during this year's analysis, differentiated by patient age. The top reported patient problem code continues to be Vomiting and Nausea, as seen in previous analyses and is still often characterized as related to changes in device impedance (i.e. high or low). In the current analysis period, there was an increase in the use of the code "No known impact or consequence to patient" (n=110) and a decrease in the use of the code "Therapeutic Response, Decreased/Paresis (n=77), as compared to prior analysis period. Complaints of pain and the more general "Malaise"/ "Complaint, Ill-defined, remain unchanged in relative ranking from last year's analysis. Overall, the top patient problems present nothing significantly new as compared to prior analysis period, and 324/435 reports continue to state the device was not returned for evaluation. However, there are 6 MDRs in the current analysis period in which the wiring from the leads becomes entangled in the bowel of the patients. Two reports (2/6) linked to the same event note that the bowel entanglement caused "cecal volvulus". Labeling for this device does warn about possible entanglement of the leads with the bowel. Each of these events involved migration of the device components.

¹ The total PPC does not equal the total MDR count since one MDR might have multiple patient problems. Patient problem codes indicate the effects that an event may have had on the patient, including signs, symptoms, syndromes, or diagnosis.

TABLE 6: Most commonly reported patient problem codes received by patient age

Patient Problem	Total Patient Problem Code in MDR	Total Patient Problem Code in MDR by Patient Age (years)			
		Pediatric (< 18)	Pediatric (18 to 21)	Adults (≥ 22)	Indeterminate (Age blank)
Vomiting/ Nausea	171	2	11	157	1
No known impact or consequence to patient***	110	1	0	79	30
Pain/ Discomfort/ Pain, Abdominal	100	1	5	87	7
Complaint, Ill-Defined*/Malaise	93	1	1	88	3
Therapeutic Response, Decreased/Paresis	77	1	2	71	3
Electric Shock/Nerve Stimulation, Undesired	71	0	2	60	9
Therapeutic Effects, Unexpected**	50	0	2	46	2
Infection/ Wound Dehiscence	31	0	0	31	0
Weight Fluctuations	20	1	1	18	0
Erosion	14	0	0	8	6
Total Patient Problem Code Count	737	7	24	645	61

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 may have been identified in the report, the manufacturer or reporter did not report any patient impact or consequence because of the reported device behavior.

Most Commonly Reported Device Problem Codes (DPC)²

Table 7 below provides the most commonly reported Device Problems for all MDRs differentiated by patient age. For the third analysis period in a row, the top 2 reported device problem codes are:

- “Device operates differently than expected” and
- “No Known Device Problem”

Additionally, “Failure to deliver energy”/ “Premature Discharge of battery”/ “Low”/ “Battery issue” continues, as in the prior analysis period, to rank third (n=72) along with “High”/ “Low impedance”/ “Impedance issues”/ “Unstable” (n=72). A review of reports with the “Failure to deliver energy” / “Premature Discharge of battery”/ “Low”/ “Battery issue” “High”/ “Low impedance”/ “Impedance issues”/ and “Unstable” device problem codes found that this device problem was associated with reports of low impedance or battery issues. The reports of “Inappropriate Shock”, if located in the device pocket area, typically involved the battery (e.g. depletion) or patient falls/trauma as the cause, otherwise they were reported as the result of faulty leads or electromagnetic interference (EMI).

The device problem code “Device operates differently than expected” was commonly associated with patient problem codes of “pain”, “nausea” and “vomiting” and a corresponding battery or lead issue. Adjustments to the device, its placement, impedance levels and replacement of the leads or device were the interventions used for the patients to bring relief in these situations. The reports with “No Known Device Problem” continues to relate to patient issues in which the device is functioning as expected but the patient has an infection or device intolerance issues (e.g. erosion). As noted previously in the patient problem section, 324/435 reports state the device was not returned for evaluation.

²The total DPC does not equal the total MDR count since one MDR might have multiple patient problems. Device problem codes describe device failures or issues related to the device that are encountered during the event.

TABLE 7: Most commonly reported device problem codes received by patient age

Device Problem	Total Device Problem Code in MDR	Total Device Problem Code in MDR by Patient Age (years)			
		Pediatric (< 18)	Pediatric (18 to 21)	Adults (≥ 22)	Indeterminate (Age blank)
Device operates differently than expected	149	3	5	120	21
No Known Device Problem	86	1	1	74	10
Failure to deliver energy/Premature Discharge of battery/Low/Battery issue	72	1	2	66	3
High/Low impedance/ Impedance issues/Unstable	72	1	0	58	13
Inappropriate shock	59	0	2	48	9
Migration of device or device component	35	1	0	29	5
Electromagnetic compatibility issue/ Electro-magnetic interference (EMI)	31	0	2	26	3
Break/Device or Device Fragments Location Unknown	18	0	0	15	3
Unintended collision	9	0	0	8	1
Entrapment of Device or Device Component	5	0	0	4	1
Total Device Problem Code Count	536	7	12	448	69

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

Discussion of Pediatric Patient Problem as it relates to Device Problem Information

Table 8 identifies the MDR occurrences of the top patient problems and issues in pediatric patients only, in comparison to the prior analysis period's findings.

TABLE 8: Clinical events identified with pediatric patients - year-to-year comparison*

Clinical Events 5/2016 – 4/2017	Occurrences in MDRs**	Clinical Events 5/2017 – 4/2018	Occurrences in MDRs**
Nausea/Vomiting [Complaint ill- defined]	9	Nausea/Vomiting [Complaint ill- defined]	15
Pain/Discomfort/ Abdominal Pain	6	Pain/Discomfort/ Abdominal Pain	6
Therapeutic Response, Decreased/Paresis	5	Therapeutic Response, Decreased/Paresis	3
Infection/ Wound Infection, Post- Operative	3	Electric Shock/Nerve Stimulation, Undesired/ [Inappropriate Electric Shock]	3

*Only the most observed patient problems and issues in pediatric MDR narratives are included.

**The total MDR Occurrences does not equal the total pediatric MDR count (n= 12) since one MDR might have multiple clinical events.

As in the prior analysis period, the clinical events for the twelve (12) pediatric MDRs found in this analysis also involve complaints of nausea, vomiting and pain, corresponding to the device issue of “Therapeutic Response, Decreased”/ “Paresis”. These complaints and device problems are both most often due to battery and lead issues. Testing of, and adjustments to the device settings, hospitalization, repositioning of the device and lead revision were the noted interventions.

There were two (2) reports of “Erosion” amongst the submitted pediatric reports, both involving the device’s leads. The manufacturer’s evaluation found in one report that there was “No Known Device Problem” and concluded this was a “Known Inherent Risk of Procedure”. In the other report the device was not returned for evaluation.

Re-Interventions in Pediatric Patients from 5/2017 through 4/2018

Re-interventions addressing types of clinical events 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.

TABLE 9: Re-interventions in pediatric patients* (5/2017 -4/2018)

Re-Interventions	Number of Re-Interventions	Causal Event
Replacement/Repositioning <ul style="list-style-type: none"> • Device, • Battery, and/or • Lead 	8	<ul style="list-style-type: none"> • Return of symptoms with pain • Lead loose/misfire/shocking • Damage during another surgery • Erosion
Explant - Permanent	1	<ul style="list-style-type: none"> • Lead erosion • Nausea and Pain
Reprogramming/Calibration	2	<ul style="list-style-type: none"> • Loss of therapeutic effect
Hospitalization for follow-up	1	<ul style="list-style-type: none"> • Loss of therapeutic effect
Office follow-up treatment	3	<ul style="list-style-type: none"> • Impedance issues

*Note that the total counts do not equal the number of MDRs since one MDR might have multiple noted re-interventions.

** Temporary involves the mention of temporary removal of the device and has no comment of actual replacement in the report.

Conclusions Based on MDR Review

- There have been 12 pediatric (out of 435) MDRs submitted for the Enterra Therapy System between May 1, 2017 and April 30, 2018. Of these, 9 were injury events, and 3 were device malfunction events.
- The Time to Event Occurrence (TTEO) was calculated for 300 MDRs based on the available information contained in the reports, including all 12 pediatric reports. Review of the pediatric reports with TTEO showed:
 - One (1) severely underweight patient (age 21), had a TTEO of less than 30 days involving a return of symptoms since implant as well as a new onset of “seizures/passing out”. The parent questioned a correlation with this new onset and the device, however no other information was provided.
 - Four (4) of the pediatric patients (ages 15 - 21), had TTEO occurrences of 31 days to 1 year of implant. These involved:
 - two (2) complaints of return of symptoms and pain,
 - one (1) shocking secondary to trauma to the implant site, and
 - one (1) severe “twitching” and unresolved shocking.
 - Seven (7) pediatric patients (ages 10 - 21), had TTEO of 1 to 5 years of implant.
 - Two (2) had a return of symptoms, in one (1) case the leads were relocated and a dead battery replaced and in the other the INS was reported as “fried” secondary to an EMI source (potential EMI sources and effects are addressed in the IFU),

- one (1) had the device removed secondary to pain noted as “referred” from the device,
 - one (1) damage to the device during an adrenalectomy,
 - one (1) noted device error codes due to a faulty connection, and
 - two (2) lead erosion. One (1) secondary to Cushing’s disease diagnosed after placement and the other secondary to a hernia in the pocket site.
- The most common reported pediatric patient problems share similar complaints as identified in previous analyses reported to the PAC in prior years:
 - “Nausea”/ “Vomiting”, and
 - “Unexpected”/ “Decreased Therapeutic Response”/ “Paresis”.
 - “Pain”/ “Discomfort” associated with shocking, return of symptoms and impedance changes.
 - “Infection”/ “Erosion”
 - Device Problems in pediatric patients remain unchanged from the previous two (2) analysis periods, with the most frequently reported device problems being: “Device operates differently than expected” - normally associated with complaints of “pain”, “return of symptoms” and “low therapeutic response”. The device problems in this analysis continue to be related to the impedance issues due to lead issues, connection problems and/or battery issues. Adjustments to the device impedance settings, it’s positioning or complete replacement of the leads or device generally resulted in relief of these complaints.
 - Reports continue to identify other underlying device functionality issues with the device lead (i.e. misconnection, break, migration or malfunction) in addition to battery depletion issues.
 - The manufacturer’s evaluations of the various device issues were hindered due to devices not being returned in most cases (324 of 435 MDRs).

As in prior analysis period, complaints of return of symptoms (nausea, vomiting), decreased therapeutic effect, as well as incidences of shocking, appear to center around malfunctions with leads and/or connection issues involving the leads.

- Overall, the Patient Problems and Device Problems observed among pediatric patients were similar to those observed in adult patients.
- The types of adverse events being seen in the current analysis period analysis are consistent what has been observed in prior analysis periods, with one noted exception. There were 5 reported events (6 MDRs) describing entanglement of the leads within the patient’s bowel/muscle in adult patients in this analysis period. Labeling for this device does warn about possible entanglement of the leads with the bowel. This problem was not reported in any of the pediatric reports submitted.

LITERATURE REVIEW

Purpose

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 reviews presented at the Pediatric Advisory Committee (PAC) meetings on September 23, 2014, September 16, 2015, September 14, 2016, and September 12, 2017. 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?

Methods

On May 31, 2018, a search in PubMed and Embase was performed using the following search terms:

- PubMed
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"
Filters: Publication date from 2017/05/01 to 2018/04/30; Humans; English
- Embase
(enterra OR 'gastric pacemaker'/exp OR 'gastric electrical stimulation'/exp OR 'gastric electric stimulation' OR 'gastric electrostimulation' OR 'gastric pacing'/exp OR '(stimulation and gastroparesis)' OR 'gastrointestinal neuromodulation') AND [humans]/lim AND [english]/lim AND [2017-2018]/py

The search was limited to studies published from the last PAC meeting update (May 1, 2017 and April 30, 2018), in human subjects, and in the English language. This search yielded a total of 68 citations (13 in PubMed and 55 in Embase). After an initial exclusion of 4 duplicate articles and 11 articles that were published outside of the specified date range, 53 citations were reviewed.

A review of abstracts and full-texts of each citation was conducted and further exclusions were made. Of the 53 articles, 50 were excluded for the following reasons: conference abstracts/poster presentations (n=17); not related to the safety and probable benefit of Enterra (n=14); non-systematic literature review (n=8); treatment other than Enterra (n=7); and pediatric patients not included (n=4). These exclusions left 3 articles for full epidemiological review and assessment ([Figure 1](#). Article Retrieval and Selection).

Study Design and Included Population

The study by Arthur et al. [1] is a retrospective review of data collected from electronic medical records for 58 patients with gastroparesis (GP) who were treated at the Ochsner Clinic (New Orleans, LA) between 2010 and 2016. The purpose of this study was to compare the following surgical treatments for GP: GES only (n=33 patients); pyloroplasty only (n=7); both GES and pyloroplasty (n=16); and sleeve gastrectomy (n=2). Patients who received both GES and pyloroplasty were only given a second procedure if there was poor resolution of symptoms with the first procedure. Of the 58 patients included in this study, 33 patients in the 'GES only' group included at least one pediatric patient as indicated by the age range in this group (20-72 years). There were 16 patients in the 'GES

and pyloroplasty' group; however, this group did not include any pediatric patients, as the youngest patient in this group was 26 years old. Therefore, this review will focus on results in the 33 patients who received GES only. Of note, the study did not provide the number of pediatric subjects included or the characteristics or outcomes of the pediatric patients.

The Meleine et al. study [2] is an ancillary study to a large, double-blinded randomized controlled trial (NCT00903799) that is designed to evaluate the efficacy of GES in 220 patients with intractable nausea and vomiting. Meleine et al. reports on a subset of 21 patients who were implanted with the Enterra device in France between 2009 and 2012. The purpose of this study is to assess the effect of GES on gastrointestinal peptide levels in patients with intractable vomiting. The patients were randomly assigned to one of the following treatment groups: 4 months of OFF stimulation followed by 4 months of ON stimulation (n=8); or 4 months of ON stimulation followed by 4 months of OFF stimulation (n=13). The present study compares results after the first 4 months of assigned treatment (prior to cross-over). Clinical and biological evaluations as well as gastric emptying measurements were taken before implantation and after the first four-month period. Clinical endpoints included vomiting episodes and quality of life. Fourteen of the 21 patients completed the 4-month study (10 ON and 4 OFF stimulation). The mean age for OFF stimulation was 39.5 ± 6.1 years while the mean age for ON stimulation was 42.4 ± 34 years. Based on how age was reported in the paper (as mean \pm SEM, standard error of the mean), it is unclear how many pediatric subjects were included if any, or what the characteristics or outcomes of the pediatric patients were.

The paper by Wakamatsu et al. [3] is a retrospective chart review of all patients who underwent surgical treatment of GP from February 2003 to December 2014 at University Hospital (FL, USA). Of the 93 patients, 47 had idiopathic GP and 46 had diabetic GP. A total of 78 patients underwent GES implantation while the remaining 15 patients underwent Roux-en-Y gastric bypass (RYGB) and pre/post-operative symptoms including nausea, vomiting, abdominal discomfort were patient reported. The objective of this study was to compare results of surgical treatment of both diabetic GP and idiopathic GP after GES and RYGB. The median follow-up time was 400 days with an interquartile range (IQR) of 183-865 days. The age of patients was reported as median of 44.5 years (IQR 32.2-55.8). Based on the age range provided in the paper, it is unclear how many pediatric subjects were included if at all, or what the characteristics or outcomes of the pediatric patients were.

The three included studies evaluated various treatment modalities for GP. For this systematic review, results are presented focused on patients who received GES for GP treatment. It should also be noted that the study by Arthur et al. [1] met all search and inclusion criteria, including treatment of pediatric patient(s). However, the papers by Meleine et al. [2] and Wakamatsu et al. [3] did not provide the age range for their included patients; therefore, we could not confirm or exclude that at least one pediatric patient was included in these studies. Given the limited Enterra literature available in the defined time period these papers were included in our review.

Results

Probable Benefit Results

In the Arthur et al. study [1], pre- and post-operative comparisons were made for the severity and frequency of the following symptoms over an average 17 months of follow-up (range 6 weeks to 80 months): vomiting; nausea; early satiety; bloating; postprandial fullness; epigastric pain; and epigastric burning. Each symptom was assigned a score of 0 to 4. Severity scores were as follows: 0= absent; 1= mild (not influencing normal activity); 2= moderate (diverting, but not overly modifying usual activity); 3= severe (influencing usual activity to point of modification); and 4= extremely severe (requiring bed rest). Frequency scores were as follows: 0= absent; 1= rare (1 time/week); 2=

occasional (2-4 times/week); 3= frequent (5-7 times/week); and 4= extremely frequent (>7 times/week). In the 'GES only' group, mean scores improved in each of the 14 symptoms, including: vomiting severity (1.26 ± 1.5), nausea severity (1.14 ± 1.15), early satiety severity (1 ± 1.38), bloating severity (0.53 ± 1.39), postprandial fullness severity (0.91 ± 1.79), epigastric pain severity (1.13 ± 1.48), and epigastric burning severity (0.9 ± 1.78) as well as vomiting frequency (1.10 ± 1.7), nausea frequency (0.82 ± 1.48), early satiety frequency (0.74 ± 1.61), epigastric pain frequency (0.91 ± 1.53), and epigastric burning frequency (0.92 ± 2.02). Frequency of bloating (0.23 ± 1.65) and frequency of postprandial fullness (0.60 ± 1.91) were two reported symptoms with the least improvement.

In the Meleine et al. study [2], probable benefit was assessed using the following measures: vomiting score, quality of life, and gastric emptying time. Vomiting score was quantified using a Likert scale from 0 to 4 (0= absent, 1= mild, 2= moderate, 3= severe, 4= extremely severe). Quality of life was measured by the Gastrointestinal Quality of Life Index (GIQLI), which has scores varying from 0 (worst quality of life possible) to 144 (best quality of life). Gastric emptying was evaluated at both baseline and after four months using C-octanoic acid breath test. Compared to baseline, patients with the ON stimulation for 4 months reported slightly reduced vomiting episodes (from 3.5 ± 0.4 to 2.3 ± 0.5). However, both GIQLI score (from 71.2 ± 6.7 to 74.2 ± 5.9) and gastric emptying (from 207.0 ± 19.8 to 193.0 ± 15.1) were similar to reported baseline values.

In the Wakamatsu et al [3] study, probable benefit was assessed using the following patient reported measures: nausea episodes; vomiting episodes; and abdominal discomfort episodes. The percentage of patients reporting symptoms after GES placement decreased for nausea from 83% (55/66 patients) to 27% (18/66 patients), vomiting with a decrease from 80% (53/66 patients) to 36% (24/66 patients), and abdominal discomfort with a decrease from 37% (25/66 patients) to 20% (13/66 patients).

Safety Results

In the Arthur et al. study [1], the following 30-day complications were reported in the 33 patients who received GES only: hematoma formation (n=1 patient); pain at the stimulator site (n=2) with one patient having their stimulator removed one year after original placement; wound dehiscence (n=1); and post-operative diabetic ketoacidosis (DKA) (n=1). There were no deaths observed during the study.

In the Wakamatsu et al. study [3], of the 78 patients who underwent GES implantation, 16 patients required reoperation: 13 patients required removal or replacement of the device due to abdominal discomfort that resolved after relocation; and 3 patients required removal of the GES device and conversion to RYGB due to refractory nausea and vomiting. No complications were reported.

No adverse events were reported in the Meleine et al. [2] paper.

CRITICAL ASSESSMENT OF THE LITERATURE

The current systematic literature review includes 3 articles which is comparable to results from last year (one article was included out of 124). The studies by Arthur et al. [1], Meleine et al. [2], and Wakamatsu et al. [3] reported the safety and probable benefits of Enterra in improved upper GI symptoms. Effects on the need for nutritional support were not evaluated. The types of reported adverse events were consistent with literature from previous years. Overall, the safety and probable benefit of the Enterra device as reported in these three papers are consistent with what has been reported previously.

The results of this systematic literature review should be interpreted considering key limitations. First, our review only included one paper (Arthur et al.) that clearly met all search criteria, including

treatment of pediatric patient(s). In the papers by Meleine et al. and Wakamatsu et al., it could not be confirmed or excluded that these studies included pediatric patients because of the way patient age was reported. However, these papers were included in this review to be as inclusive as possible, given the limited literature on Enterra. Secondly, common study limitations, including retrospective study design, small sample sizes, and short follow-up duration are present in these studies. A major limitation of the studies by Arthur et al. and Wakamatsu et al. was that data were collected from retrospective chart review, which may be prone to bias, as patients with favorable outcomes remain in the study and those with poor outcomes are likely to exit early, leading to overestimation of probable benefit. Additionally, the Arthur et al. study did not report on any complications occurring after 30 days, even though the follow up period reached up to 80 months. Only mean pre-op symptom scores were reported along with mean improvement in score \pm standard deviation, but no mean post-op symptom scores were reported. The Meleine et al. study was limited with a small sample size of 14 subjects who completed the study (10 ON stimulation, 4 OFF stimulation). In addition, the Wakamatsu et al. study design was a retrospective single-center analysis, with short follow-up duration for what is intended to be a long-term device.

Because all three studies included adult subjects along with possible pediatric subjects, it is not clear if safety and probable benefits derived by the mixed cohort were experienced specifically by pediatric subjects. Despite the favorable results demonstrating probable benefits of Enterra therapy, and that all three publications declared no conflicts of interests, these study design factors limit the generalizability of the results to the pediatric patients at large for treatment of gastroparesis.

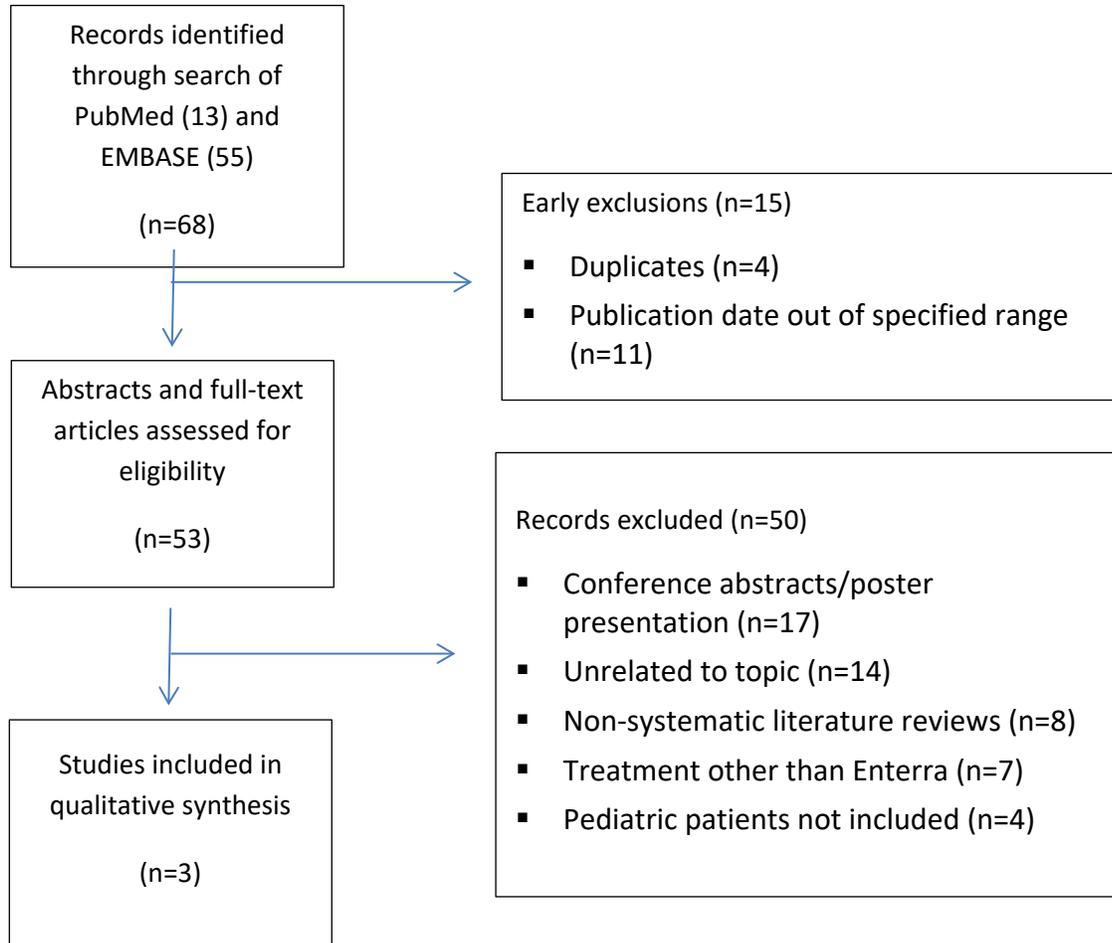
CONCLUSION

Our systematic literature review included one study which met all search criteria (including treatment of pediatric patients) and two studies in which it was not clear if pediatric patients were included. These studies reported device-related adverse events that were identified in previous literature reviews and, therefore, do not raise new safety concerns. Reported adverse events include the following: hematoma formation; pain at stimulator site; wound dehiscence; post-operative DKA; superficial wound infection; and abdominal discomfort, which are all included in the product labeling. While DKA is not specifically listed in the product labeling, it is included under “acute diabetic complications”. A total of 14% (17/121) of patients across the three studies required surgical intervention to address one or more of these AEs.

These three studies 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. Despite possible reduction of symptoms, some patients with GP who are implanted with Enterra may experience device-related adverse events that require additional surgery. The findings of this systematic literature review should be interpreted considering the insufficient evidence reported in terms of inadequate number and quality of papers with adequate sample size of pediatric patients and long-term follow-up. These factors limit 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 meetings on September 23, 2014, September 16, 2015, September 14, 2016, and September 12, 2017.

Figure 1. Article Retrieval and Selection



REFERENCES

1. Arthur, et al. Tailored approach to gastroparesis significantly improves symptoms. *Surgical Endoscopy* 2018; 32:977-982.
2. Meleine, et al. Gastrointestinal Peptides During Chronic Gastric Electrical Stimulation in Patients with Intractable Vomiting Neuromodulation 2017; 20: 774-782.
3. Wakamatsu, et al. Laparoscopic treatment of gastroparesis: a single center experience *Surgery for Obesity and Related Diseases* 14 (2018): 200-205.

OVERALL 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.