Executive Summary

Enterra® Therapy System

H990014

Prepared by the Center for Devices and Radiological Health

for the September 12, 2017 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

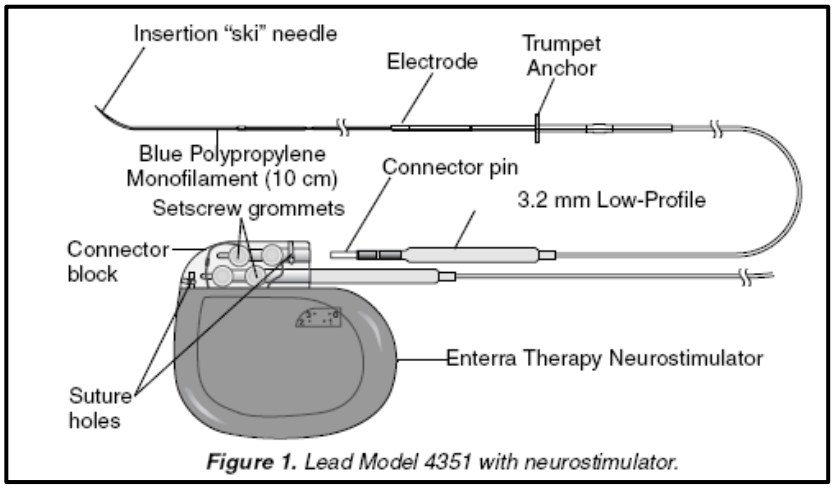
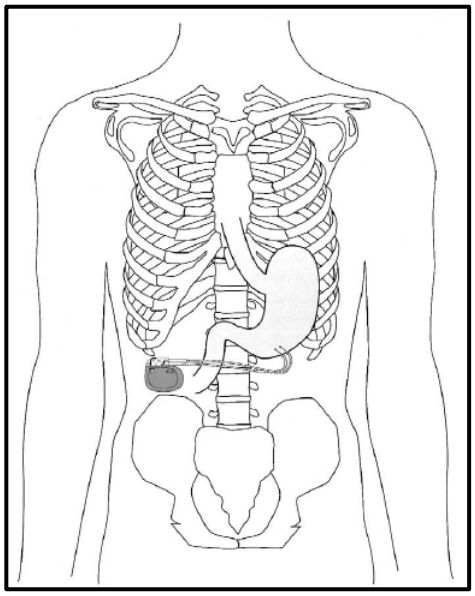


Figure 1. Lead Model 4351 with neurostimulator.

FIGURE 2: Device placement



INDICATIONS FOR USE

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

REGULATORY HISTORY

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

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

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

DEVICE DISTRIBUTION DATA

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 02/01/16 – 01/31/17	Devices Sold from 02/01/15 – 01/31/16	Devices Sold From 02/01/14 – 01/31/15	Devices Sold from 02/01/13 – 01/31/14
37800 Implantable Neurostimulator (INS)	1865	1,611	1,391	1,381
3116 Implantable Neurostimulator	0	208	95	N/A
4351 Intramuscular Lead	2462	2,151	2,151	1.928

TABLE 2: Number of devices implanted in pediatric patients (by gender and years of age)

Reporting Period: 1-Feb-2016 to 31-Jan-2017	Total N (newly implanted this period)[a]	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	56	0	10	29	0	9	3	0	0	5
Total Pediatric implant base this period	290	0	66	152	0[b]	41[b]	23	0	2	6

[a]There were 56 newly implanted pediatric patients in the current reporting period. Additionally, there were 37 pediatric patients that received a replacement device during the current reporting period, for a total of 93 pediatric implants in the current reporting period. Two patients are included in both the newly implanted and replacement totals in the current reporting period. This results in 91 pediatric patients receiving 93 implanted devices in the reporting period.

[b]After reviewing the (b) data, the table was updated to reflect one male patient who moved from the <2 age category to the ≥2<18 category (1 was changed to 0; 40 was changed to 41).

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 Entered:** between May 1, 2016 and April 30, 2017

B. Search 2
   - **Brand name:** Enterra
   - Report Entered: between May 1, 2016 and April 30, 2017

The searches resulted in identifying 404 MDRs: 403 submitted by the manufacturer, and a single voluntary report. There were no User Facilities or Distributor reports submitted during this timeframe.

Three (3) MDRs were excluded from further analysis since these MDRs described events reported in two (2)-journal articles.[1, 2] These articles were also excluded from the **Literature Review** as they were published in April 2016, which is outside of the defined date range for this analysis. In addition, both papers were excluded in last year's literature secondary to the following reasons:

- "THE LONG-TERM EFFICACY AND SAFETY OF PYLOROPLASTY COMBINED WITH GASTRIC ELECTRICAL STIMULATION THERAPY IN GASTROPARESIS", 2016 [1]
    - This article was excluded because this was a conference abstract (not a peer-reviewed journal)

- "MINI-LAPAROTOMY WITH ADJUNCTIVE CARE VERSUS LAPAROSCOPY FOR PLACEMENT OF GASTRIC ELECTRICAL STIMULATION", 2016.[2]
    - This article was excluded because the focus of the study was not related to the safety and effectiveness of the Enterra device. Instead, the study was designed to compare 2 techniques for implanting Enterra (mini-laparotomy vs. laparoscopy). The main outcomes in the study were surgical/procedural variables such as operation duration, hospital length of stay, and hospital readmission rates.

The remaining 401 MDRs involved events occurring between May 1, 2016 and April 30, 2017. They included 2 death, 255 injury, and 144 device malfunction reports (reflective of one MDR being re-categorized as a death report from an injury based on information contained in the MDR). These 401 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. Fifteen (15) reports identified a pediatric patient from 12 to 21 years old. These have been placed into two age categories of < 18 and 18-21 years old, and included 13 injury MDRs and 2 malfunction MDRs.

[1] Davis, B. R., Bashashati, M., Alvarado, B., McCallum, R. W., & Sarosiek, I. (2016). The Long-Term Efficacy and Safety of Pyloroplasty Combined With Gastric Electrical Stimulation: A Single Academic Center Experience. *Gastroenterology*, S1184.

[2] Smith , A., Cacchione, R., Miller, E., McElmurray, L., Allen, R., Stocker, A., et al. (2016). Mini-laparotomy with Adjunctive Care versus Laparoscopy for Placement of Gastric Electrical Stimulation. *The American Surgeon*, Volume 82, Number 4, pp. 337-342(6).

TABLE 3: Overall event type distribution by patient age

Event Type	Total MDR Count 5/2016 - 4/2017	MDR Count by Patient Age (years)			
		Pediatric (< 18)	Pediatric (18-21)	Adult (≥ 22)	Indeterminate (Age blank)
Death*	**2**	0	0	1	1
Injury	**255**	7	6	159	83
Malfunction	**144**	0	2	109	33
Total MDR Count	**401**	**15**		**269**	**117**

* 1 MDR was re-categorized as Death event types from Serious Injury, after review of the event narratives containing the word death (or its variants).

Comparison of Current Patient Event Type Information with 2014 and 2015 Data

Table 4 below compares the Event Type distribution for this analysis to that of prior years 2014 and 2015. As noted in last year's analysis of reports received, the manufacturer had an increase in volume of reported injuries and malfunctions in their 2014 HDE Annual Report Review Form, citing a remedial review of adverse events from 2000 to 2012, which identified 102 reports that were then submitted in 2014 (The numbers are identified in parenthesis). With this in mind, the current period (5/2016 to 4/2017) appears to reflect about a 21% increase of MDR submissions the 5/2015 to 4/2016 period, in the numbers of serious injury and malfunction reports. This increase coincides with an increase of sales for the year (see Table 1). In comparison, pediatric MDR submissions decreased from 17 in the previous analysis period (5/2015 to 4/2016) to 15 in this analysis period (5/2016 to 4/2017).

TABLE 4: Overall event type distribution by year

	Total MDR Count		
Event Type	**PAC Meeting 2015 4/2014 – 4/2015** (including Remediated reports)	**PAC Meeting 2016 5/2015 - 4/2016**	**PAC Meeting 2017 5/2016 - 4/2017**
Death	4 (3)	0	2
Injury	315 (91)	203	255
Malfunction	121 (5)	112	144
Total MDR Count	**440 (102)**	**315**	**401**

Patient Gender and Age Information

In the 401 MDRs submitted from May 2016 to April 2017, 269 patients were noted as adult (≥22 years old) and 117 MDRs did not provide a patient age (indeterminate age reports). Fifteen (15) MDRs contained pediatric patients' ages that ranged from 12 to less than 22 years, with a mean age of 16.6 years (SD ± 3.17 years). Only one (1) of the 401 MDRs noted the gender of the patient – as female. The remaining 400 MDRs did not include the patient's gender in the designated section of the MDR report. However, individual review of the report narrative sections did result in identifying 29 MDRs for "female" patients, and 1 MDR as a "male" patient, based on gender identifiers such as male or female, she or her, he or him, etc. FDA is following up with the manufacturer to understand why patient gender was not available for all but one of the MDRs.

Time to Event Occurrence

An analysis of the Time to Event Occurrence (TTEO) was performed. The TTEO is based on the implant duration and was calculated as the time between the Date of Implant and the date of event, or the date the implant was removed. The TTEO was determined for 294 MDRs, including all of the 15 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	3	3	46	2
31 days – ≤1 year	2	2	65	8
1 year – ≤5 years	2	3	113	18
>5 years	0	0	20	7
Totals (N=294)	7	8	244	35

Characterizations of the 15 MDR Narratives of Pediatric Events from 5/2016 – 4/2017 as it Relates to TTEO:

A. TTEO within the first 30 days of implant. (N=6)
- Three (3) patients (ages 12, 16 and 20) reported post – operative infections
  - The 12-year-old "female" patient required removal/replacement of the leads and battery because of an infection that was "never really eradicated when they got the original infection".
  - The 16-year-old patient had their system removed due to an infection, "first observed post –operation".

- The 20-year-old developed and infection "after implant and the device was completely removed" and re-implanted later with resolution of the infection.

- A 14-year-old patient had her battery replaced due to lack of efficacy. The replacement then migrated "down over the inguinal ligament" requiring intervention and repositioning.
- One (1) patient (age 21) complained of a return of symptoms that began when he/she "smoked a cigarette and has been sick ever since". The patient reported "resolution of their symptoms" without intervention.
- Another 21-year-old patient complained of abnormal contractions, which could be visualized and made their abdomen sore. Adjustments were made to the impedance without resolution. The physician felt "it could be a wire issue".

B. TTEO between 30 days and 1 year of implant. (N=4)

- Two (2) patients (ages 14, and 21) had a return of symptoms with impedance issues and ineffective adjustments. Lead replacement was planned for one (1) of the patients.
- In another patient (age 20) the impedances were found to be out of range during routine interrogation, which was felt to possibly be due to a previous fall in which the patient landed on the device. Lead tips were removed and cleaned during surgery and issues were resolved.
- One (1) patient (age 14) complained of pain at the pocket site determined to be secondary to a migration of the device "over the inguinal ligament" requiring repositioning.

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

- One (1) patient (age 20) was awakened by a sudden onset of vomiting followed by trauma to the device implant site, causing the device to stop working and symptom return. The device was turned off and surgery was pending at the time of the MDR report.
- A 16-year-old had lead migration 1 year after placement. Leads were replaced.
- Another 16-year-old reported an "INS (implantable neurostimulator) was removed due to erosion through the skin" which was believed to be caused by the patient manipulating the INS in the pocket. Replacement was anticipated in 6 weeks post wound healing.
- A 20-year-old complained of pain and cramping, later determined to be secondary to other gastric issues of inflammation and excess bile production. Medication was prescribed, with relief.
- Another 20-year-old complained of a sudden onset of symptoms and loss of therapy that worsened when the patient ate. The manufacturer representative was requested for INS testing.

Characterizations of the Time to Event Occurrences (TTEO) in the adult and indeterminate age populations from 5/2016 – 4/2017

For the adult (N=244) and indeterminate age (N=35) populations with TTEO data, issues with the use of this device continue to occur most frequently after 1 year and up to 5 years from the date of implant, followed by issues occurring between 1 month and 1 year from date of implant. In comparison to last year's analysis of reports for these TTEO groups, the same types of issues continue:

- Sudden return of symptoms of nausea and vomiting and/or loss of therapy secondary to premature battery depletion commonly related to high impedance settings
- Pain and inappropriate simulation/shocking secondary to high impedance
- Infection, migration and erosion issues
- Electromagnetic Interference (EMI)

In this current analysis, the complaints of pain occurred secondary to positioning/ migration of the device or its components, or more commonly, due to inappropriate simulation/shocking. Both problem types occurred between 1 and 9 years after placement. These problems were usually the result of abnormal changes in impedance. In these incidences, impedance issues were attributed to high impedance settings, patient falls and/or trauma to the device site. Electromagnetic interference (EMI) from shopping center and airport security gates, as well as some electronically controlled household items (i.e. "air condition remote") were another cause of abnormal changes in device impedance.

Infection, migration and erosion issues also continued to occur as in the previous years' analyses. Reports of infection (n=31) continue to typically occur within the first 2 years of device placement. Infection was specifically described associated with the device or component (i.e. "pocket", "lead", "INS" and "battery") in 15 reports, while four (4) reports mentioned infections not related to the device and12 reports did not specify the exact location or cause of the infection. Reports noting erosion occurred between 2 weeks and 2 years of implant. These events involved lead erosion into the stomach or INS/battery erosion through the skin possibly secondary to "rejection" of the device by the body. Lead migration, the most reported form of migration in this analysis, as well as INS/battery migration, occurred most often during the first 2-3 years of device placement. Pain, nausea and vomiting (uncontrollable at times) were reported symptoms of lead migration, and interventions to address these symptoms included removal or revision of the leads and /or device.

As noted for the pediatric patients described above, adult and indeterminate age patients also experienced return of symptoms (nausea and vomiting) with decrease in therapeutic effectiveness. Low device impedances or battery depletion (which can be caused by high impedance issues (n=33)), lead to patient complaints of "therapy effectiveness, decreased". These complaints were reported as occurring at 30 days after placement and beyond. Resolution typically required reprogramming or replacement of the battery and/or leads.

Review of Death reports (n=2)

There are two (2) reports of patient death in this year's analysis. One (1) report involved a 38-year-old (adult) patient who was undergoing treatment in a clinical study and passed away in their home, with no information to confirmatively conclude the cause of death. The manufacturer's evaluation determined the device operated within specification and no failure was detected. The second report was originally submitted by the manufacturer as a serious injury report, and upon review, re-characterized by the analyst as a death report. This report involved a "female" patient of indeterminate age with coronary artery disease who reported to the emergency room with complaints of abdominal and chest pain. The patient also complained of nausea and vomiting "aggravated" by

oral intake. The patient died 7 days later from "cardiopulmonary arrest" and "heart failure". The device was not returned to the manufacturer for evaluation.

Most Commonly Reported Patient Problem Codes[3]

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 four patient problem codes remain the same as seen in last year's analysis, and these problems were noted to be related to changes in device impedance (i.e. high or low). Overall, the patient problems in this year's analysis present no significant changes as compared to last year. The unintended impedance changes were the result of lead breaks/issues in 67 MDRs in the current data set, in addition to battery issues (normal or premature), as noted last year. The majority of these reports (n=65) also continue to state the device was not returned for evaluation.

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	**152**	1	5	124	22
Therapeutic Response, Decreased/Paresis	**122**	2	3	93	24
Pain/ Discomfort/ Pain, Abdominal	**113**	3	3	82	25
Complaint, Ill-Defined*/Malaise	**108**	0	3	86	19
No known impact or consequence to patient***	**95**	1	1	58	35
Electric Shock/Nerve Stimulation, Undesired	**66**	0	2	45	19
Therapeutic Effects, Unexpected**	**61**	1	0	40	20
Infection/ Wound Infection, Post-Operative	**23**	2	1	12	8
Weight Fluctuations	**17**	0	0	14	3
Burning Sensation	**13**	0	0	10	3
Total Patient Problem Code Count	**770**	10	18	564	178

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.*

[3] Patient problem codes indicate the effects that an event may have had on the patient, including signs, symptoms, syndromes, or diagnosis.

***MDRs coded with "Therapeutic Effects, Unexpected" typically involved issues of the device not operating as the patient anticipated.*

****A code of "No Known Impact or Consequence to Patient" indicates that while a device behavior was identified in the report, the manufacturer or reporter did not report any patient impact or consequence because of the reported device behavior.*

Most Commonly Reported Device Problem Codes[4]

Table 7 below provides the most commonly reported Device Problems for all MDRs differentiated by patient age. The same two leading device problem codes as noted in last year's analysis predominant in the current analysis, specifically:

- "Device operates differently than expected" and
- "No Known Device Problem"

"Failure to deliver energy"/"Premature Discharge of battery"/"Low"/ "Battery issue" ranked third (n=72) in this analysis whereas "Inappropriate Shock" ranked third in last year's analysis. A review of reports with the "Failure to deliver energy…" device problem code found that this device problem was the cause of low impedance or battery issues. As seen last year's analysis, "Inappropriate Shock", typically involved high impedance readings and electromagnetic interference (EMI).

"Device operates differently than expected" was commonly reported along with patient problem codes of "pain", "nausea" and "therapeutic response, decreased" or "unexpected". 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. "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 such as erosions or "Complaints Ill-Defined". As noted previously in the patient problem section, 139 of the reports state evaluation of the device could not be completed as the devices were not returned.

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	**154**	0	4	112	38
No Known Device Problem	**84**	5	2	41	36
Failure to deliver energy/Premature Discharge of battery/Low/Battery issue	**72**	1	0	62	9
High/Low impedance/ Impedance issues	**50**	0	2	32	16
Inappropriate shock	**48**	0	2	32	14
Electromagnetic compatibility issue/ Electro-magnetic interference (EMI)	**40**	0	0	37	3
Migration of device or device component	**34**	2	1	18	13
Break	**23**	0	0	19	4

[4] Device problem codes describe device failures or issues related to the device that are encountered during the event.

Unintended collision	**18**	0	1	16	1
Overheating of device or device component	**7**	0	0	6	1
Total Device Problem Code Count	**530**	**8**	**12**	**375**	**135**

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 last year's findings.

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

Clinical Events 5/2015 – 4/2016	Occurrences in MDRs*	Clinical Events 5/2016 – 4/2017	Occurrences in MDRs**
Electric Shock/Nerve Stimulation, Undesired/ [Inappropriate Electric Shock]	6	Nausea/Vomiting [Complaint ill- defined]	9
Nausea/Vomiting [Complaint ill- defined]	4	Pain/Discomfort/ Abdominal Pain	6
Pain/Discomfort/ Abdominal Pain	2	Therapeutic Response, Decreased/Paresis	5
Infection/Erosion	2	Infection/ Wound Infection, Post-Operative	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=15) since one MDR might have multiple clinical events.

This year's findings for the fifteen (15) pediatric MDRs, as it relates to clinical events, primarily center on the device issue of "Therapeutic Response, Decreased"/ "Paresis". This correlates to the main complaints in this analysis of nausea, vomiting and pain. Testing of, and adjustments to, the device settings, hospitalization, repositioning of the device and lead revision were the noted interventions. The notations of "Infection" and "Wound Infection, Post-Operative" involved both implanted leads and/or the device and the manufacturer's evaluation found "No Known Device Problem" and concluded these infections were "Known Inherent Risk of Procedure".

In last year's analysis, the most common complaint found in the pediatric reports focused on "Inappropriate Shock". These were directly related to issues of high impedance or a lead connection problem. Again, this year, the manufacturer's investigations of these events were limited because the devices were not returned for analysis.

Re-Interventions in Pediatric Patients from 5/2016 through 4/2017

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

TABLE 9: Incidences of re-interventions in pediatric patients *(5/2016 -4/2017)

Re-Interventions	Number of Re-Interventions	Causal Event
Replacement/Repositioning • Device, • Battery, and/or • Lead	6	• Return of symptoms with decreased therapeutic effects • Erosion • Migration

Explant • Permanent or • Temporary**	4	• Lead erosion • Infection
Reprogramming/ Calibration	1	• Loss of therapeutic effect
Hospitalization for follow-up	1	• Incision site infection • Loss of therapeutic effect
Office follow-up treatment	3	• Impedance issues • Pain/Contractions

*Note that the total Number of Incidences Count does 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.

Review of Supplements Submitted by the Manufacturer from 5/2016 To 4/2017 on Previously Submitted Reports (N=56)

The manufacturer also submitted 56 supplemental reports to MDRs previously submitted between April 2010 and April 2016, which were reviewed and discussed at previous Pediatric Advisory Committee meetings. Most of the supplemental reports provided report follow up and outcomes to the initial complaints. In most instances, the devices involved were replaced, removed or recalibrated for reported problems of loss of therapeutic effect, impedance issues, INS malfunction, and device/lead migration. There are six (6) reports originally submitted in February 2016, whose supplemental reports discusses information received from healthcare providers stating that since Medtronic moved to the newer model INS with a "torque limiting hex- wrench", they have seen an increased number of patients who return post- implant with "unhappy outcomes". The reports state "setscrews were not making good contact with the lead" causing high impedances. Resolution suggested by the manufacturer representative was to "open the pocket and use a high torque on the retention screws to re-tighten". If this was unsuccessful, then lead replacement was required. FDA is following up with the manufacturer to better understand the lead connection issue and the use of the "torque limiting hex- wrench", user mitigation strategies and any additional actions taken or indicated.

Conclusions Based on MDR Review

- There have been 15 out of 401 pediatric MDRs submitted for the Enterra Therapy System between May 1, 2016 and April 30, 2017, 13 were injuries, and 2 were device malfunctions.

- The Time to Event Occurrence (TTEO) was calculated for 294 MDRs based on the available information contained in the reports, including all 15 pediatric reports. Review of the pediatric reports with TTEO showed:
    - Six (6) pediatric patients (ages 12-21), had TTEO of less than 30 days involving three (3) incidences of infection, one (1) abnormal abdominal contractions, one (1) device migration and one (1) return of symptoms since smoking a cigarette after implant.
    - Four (4) of the pediatric patients (ages 14 - 21), had TTEO occurrences of 31 days to 1 year of implant. These involved two (2) complaints of return of symptoms, one (1) impedance issue secondary to a fall, and one (1) migration of device.
    - Five (5) pediatric patients (ages 16-20), had TTEO of 1 to 5 years of implant. Two (2) sudden loss of therapy – one (1) secondary to trauma to the device and the other without noted determination of cause, one (1) pain caused by other gastric issues, and one (1) lead migration and replacement.

- The most common reported pediatric patient problems share similar complaints as identified in previous year's analyses:
    - "Nausea"/ "Vomiting", "Complaints Ill-Defined" and "Decreased Therapeutic Response"/ Paresis".
    - "Pain"/ "Discomfort" associated with migration, infection, return of symptoms and high impedances.
    - Infections/Erosions

- Device Problems in pediatric patients remain unchanged from the previous two (2) year's analyses, with the most frequently reported device problems being:
    - "Device operates differently than expected" - normally associated with pain, return of symptoms and low therapeutic response.

  These 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.

- In analyses prior to 2015, the pediatric patient or device problems were related to child-type activity (i.e. running, jumping, and sports) and device functionality (i.e. premature battery depletion). This and last year's analysis identified 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 the majority of cases (352 of 401 MDRs). FDA is following up with the manufacturer to better understand their efforts towards obtaining devices back for return product analysis.

- Throughout this analysis complaints of return of symptoms (nausea, vomiting), decreased therapeutic effect as well as continued incidences of high impedance appear to center around malfunctions with leads and/or connection issues involving the leads. FDA is following up with the manufacturer for an explanation of this as it relates to the use of the "torque limiting hex- wrench" which, appears in a number of cases, not to be effective in tightening the setscrews in order to make good contact in the newer model INS - 37800.

- 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 this year's analysis are consistent with prior years and no unexpected event types have been reported.

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) meeting

on September 23, 2014, September 16, 2015, and September 14, 2016. 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 June 9, 2016, a search in PubMed and EMBASE was performed using the following search terms:
Enterra OR "gastric electric stimulation" OR "gastric electrical stimulation" OR "gastric electrostimulation" OR "gastric pacemaker" OR "gastric pacing" OR (stimulation AND gastroparesis) OR "gastrointestinal neuromodulation"

The search was limited to studies published from last PAC meeting update between May 1, 2016 and April 30, 2017 in human subjects and in the English language. This search yielded a total of 124 citations (13 in PubMed and 111 in EMBASE). After an initial exclusion of 7 duplicate articles and 42 articles that were published outside of the specified date range, 75 citations were reviewed.

A review of abstracts and full-texts of each citation was conducted and further exclusions were made. Of the 75 articles, 74 were excluded for the following reasons: conference abstracts (n=20); not related to the safety and probable benefit of Enterra (n=24); non-systematic literature reviews (n=10); not clinical study (n=8); treatment other than Enterra (n=7); and pediatric patients not included (n=5). These exclusions left 1 article for full epidemiological review and assessment (Figure 1. Article Retrieval and Selection), which is comparable to the systematic literature review results from last year (two articles were included out of 132).

Results

The paper by Lee et al. is a systematic literature review article on the therapeutic uses of neuromodulation treatment for disorders involving the autonomic nervous system that are not currently approved by the FDA. Neuromodulation treatment modalities included: cavernous nerve stimulation, gastric electrical stimulation, deep brain stimulation, and vagus nerve stimulation. The conditions under review included: erectile dysfunction, gastroparesis, gastroesophageal reflux disease, obesity, asthma, and heart failure. For the purpose of our systematic review, we will focus only on the results of GES for treatment of gastroparesis.

The methods outlined in the Lee et al. study resulted in 4 papers that met the search criteria. Of the 4 included papers, only 2 papers included pediatric patients [2] [3]. Therefore, the current literature review will focus only these 2 papers that included pediatric patients by Abell et al. [2] and by McCallum et al. [3].

It should be noted that the literature review by Lee et al. was included in this review because it met all of the search criteria. However, the individual papers included in the Lee review by Abell et al. and McCallum et al. did not meet our search criteria, as they were published in 2003 and 2010, respectively, which is outside of our defined range of publication dates. The papers by Abell et al. and McCallum et al. were notably included in our previous literature review presented at the PAC meeting in 2014. The assessments of these two papers below are same as those appearing in 2014 PAC Executive Summary.

In the Abell et al. study, 33 patients with chronic gastroparesis (17 diabetic and 16 idiopathic) were randomized in a double-blind crossover design to "ON" or "OFF" stimulation for 1-month periods

[2]. After 2 months (including 1 month "ON" and 1 month "OFF"), all patients were programmed to "ON" stimulation for 10 months, for a total of 12 months of follow-up. Patients were evaluated at 6 and 12 months for vomiting frequency, upper GI symptoms, and gastric emptying. Study participants were 19 to 65 years old. Based on the age range provided in the paper, at least 1 pediatric subject was included. However, it is unclear how many pediatric subjects were included or what the characteristics or outcomes of the pediatric patients were.

The McCallum et al. study is also a controlled, prospective study evaluating Enterra therapy in patients with chronic intractable nausea and vomiting due to diabetic gastroparesis [3]. Fifty-five patients with refractory diabetic gastroparesis were implanted with the Enterra device. After the implantation procedure, all patients had the stimulator turned ON for 6 weeks. After this 6-week period, the subjects were randomly were assigned to groups that had consecutive 3-month, cross-over periods with the device ON or OFF. After this period, the device was turned ON in all patients for an additional 4.5 months, for a total follow-up time of 12 months since Enterra placement. The age range of study participants was 20 to 63 years. Based on the age range provided in the paper, at least 1 pediatric subject was included. However, it is unclear how many pediatric subjects were included or what the characteristics or outcomes of the pediatric patients were.

Probable Benefit Results

In the Abell et al. study, probable benefit was assessed using the following measures: total symptom severity (TSS) score; vomiting frequency; vomiting severity score; nausea severity score; SF-36 physical and mental composite scores; requirement for nutritional support; and gastric emptying [2]. In the double-blinded portion of the study (first 2 months), a 50% reduction in median vomiting frequency was reported between the ON vs. OFF periods. Symptom improvement was also observed in the diabetic and idiopathic subgroups, as patients with diabetic and idiopathic gastroparesis reported a decreased median vomiting frequency of 53% and 7%, respectively. Improvements in vomiting symptoms was also observed in the longer term, with median vomiting frequency decreased 85% at 6 months and 72% at 12 months compared to baseline. Symptom severity scores were also improved at 6 and 12 months, whereas gastric emptying was only modestly accelerated.

In the McCallum et al. study, probable benefit was assessed using the following measures: total symptom severity score; weekly vomiting frequency; and gastric emptying [3]. After the first 6 weeks of Enterra treatment, there was a 57% reduction in median weekly vomiting frequency, compared to baseline. There was no observed difference in vomiting frequency between patients who had the device turned ON or OFF during the cross-over period (median reduction of 0%). At 12 months follow-up, a 67.8% reduction in median weekly vomiting frequency was reported (compared to baseline values). Patients also reported improvements in the total symptom score and gastric emptying.

Safety Results

In the Abell et al. study, several device-related adverse events requiring surgical intervention were reported. In 2 patients, infection of the neurostimulator pocket necessitated surgical removal of the device. In 2 other patients, the device was removed because of pain related to lead perforation of the stomach and erosion of the pulse generator through the skin. In another patient, migration of the pulse generator (leading to patient discomfort) necessitated surgical intervention to reposition the pulse generator. No other types of adverse events (such as non-device-related AEs) were reported in this study.

In the McCallum et al. study, 732 adverse events were reported in 55 subjects over 12 months of follow-up, including 687 patient-related events and 45 therapy- or device-related events. Fifteen of 45

therapy/device-related events were rated as serious (3 lead migration/ dislodgements; 2 device migration; 1 implant site hematoma; 1 implant site infection; the remaining 8 serious AEs were not directly related to the device but were coded as therapy-related because they occurred within 2 weeks of device implantation). Of the 55 patients enrolled in this study, 3 patients required surgical intervention and implant site infection was the only event resulting in a device explantation.

Of the 687 patient-related events in the McCallum et al. study, 438 events were rated as being serious. Hospitalizations related to gastroparesis symptoms (i.e. nausea and vomiting) occurred 225 times in 40 patients, comprising 32.8% of all serious patient-related AEs. Other serious patient-related AEs included: ketoacidosis (n=21), vomiting (n=10), hematemesis (n=8), hypoglycemia (n=7), and hypertension (n=7).

The McCallum et al. study also reported 7 deaths over the course of the 12-month study. The causes of death were cardiovascular (n=5), cerebral aneurysm (n=1), and Staphylococcus infection of knee/septicemia (n=1). None of the deaths was considered to be related to the device or therapy.

CRITICAL ASSESSMENT OF THE LITERATURE

The studies by Abell et al. and McCallum et al. reported probable benefits of Enterra in improved upper GI symptoms. Effects on the need for nutritional support were not evaluated.

The results of this systematic literature review should be interpreted in light of key limitations. First, our review only included one paper (a systematic literature review) that met the search criteria. The quality of the evidence was low, as the 2 pediatric studies included in the Lee et al. review had small sample size and a relatively short follow-up period for what is considered to be a long-term use device. Because these two studies 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 patients at large for treatment of gastroparesis. Similarly, it is not clear if any of the reported adverse events occurred in pediatric subjects.

CONCLUSION

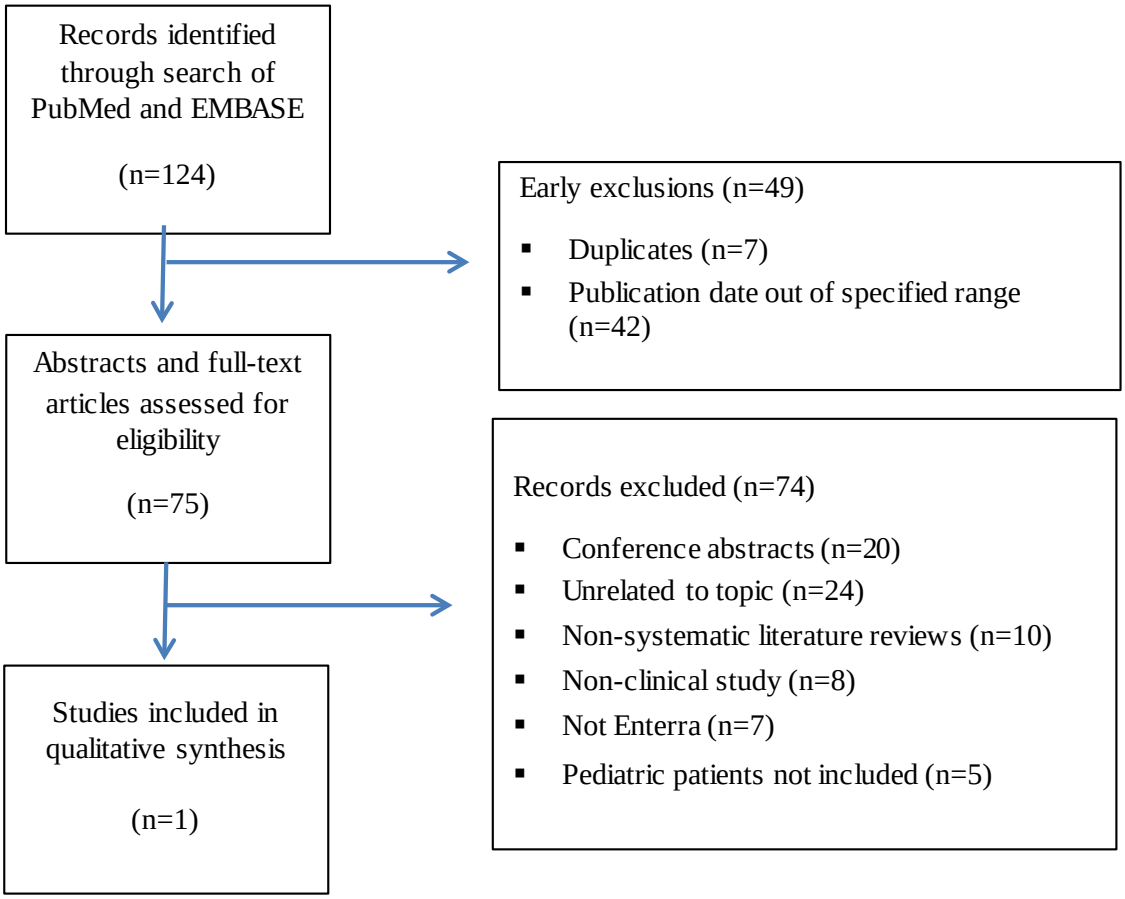
Our systematic literature review included one study (a systematic literature review) which included two studies of mixed pediatric and adult patients. These two studies reported device-related event types which were identified in previous literature reviews and do not raise new safety concerns. Reported adverse events include the following: lead perforation of the stomach; skin erosion; lead and/or device migration; implant site infection; implant-site hematoma; and pain at implant site. With the exception of hematoma, all other AEs are included in the product labeling. A total of 8 patients (across the two studies) required surgical intervention to address one or more of these AEs.

These two 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 gastroparesis subjects implanted with Enterra may experience device-related adverse events that require additional surgery. The findings of this systematic literature review should be interpreted in light of the insufficient evidence presented, 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 on September 23, 2014, September 16, 2015, and September 14, 2016.

Figure 1. Article Retrieval and Selection



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.

REFERENCES

1. Lee S, et al. Some non-FDA approved uses for neuromodulation in treating autonomic nervous system disorders: A Discussion of the preliminary support. Neuromodulation 2016; 19:791-803
2. Abell T, et al. Gastric electrical stimulation for medically refractory gastroparesis. Gastroenterology 2003; 125:421–428.
3. McCallum RW, et al. Gastric electrical stimulation with Enterra therapy improves symptoms from diabetic gastroparesis in a prospective study. Clin Gastroenterol Hepatol 2010; 8:947–954.
4. Islam S, et al. Long-term outcomes of gastric electrical stimulation in children with gastroparesis. J Ped Surg, 2016. 51:67-71.
5. Heckert J, et al. Gastric electric stimulation for refractory gastroparesis: A prospective analysis of 151 patients at a single center. Dig Dis Sci, 2016. 61:168-175.