FDA Executive Summary

Prepared for the
FDA Pediatric Advisory Committee
Fall 2023 Review Cycle

H990014

Enterra® Therapy System

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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 post-marketing 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 FDA reviewed in the year following our 2022 report to the PAC. It includes data from the manufacturer's annual report, post-market 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

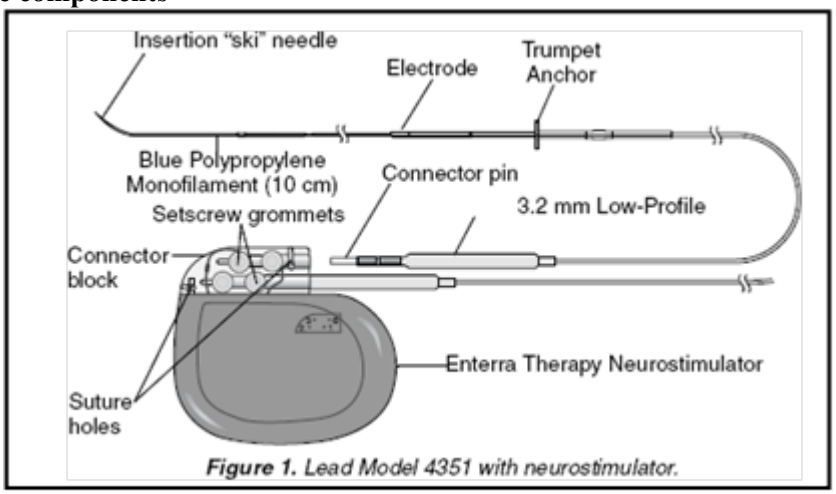
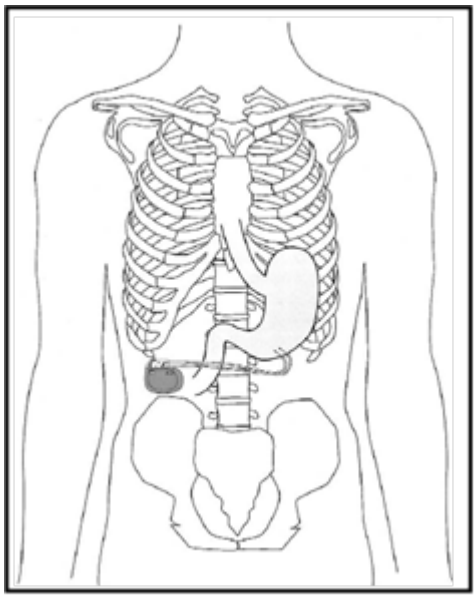


Figure 1. Lead Model 4351 with neurostimulator.

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 Act) 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. The approved ADN for Enterra is 8,000 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 02/01/22 – 01/31/23	Devices Sold From 02/01/21 – 01/31/22	Devices Sold From 02/01/20 – 01/31/21	Devices Sold From 02/01/19 – 01/31/20	Devices Sold From 02/01/18 – 01/31/19	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
37800 Implantable Neurostimulator	2410	2,127	1,895	2,053	1,951	2,017	1,865	1,611
3116 Implantable Neurostimulator	0	0	0	0	0	0	0	208
4351 Intramuscular Lead	2345	2,131	1,874	1,988	2,106	2,535	2,462	2,151

TABLE 2: Number of devices implanted in pediatric patients

Reporting Period: 02/01/22 – 01/31/23	Total N (newly implanted this period)	Female by age in years			Male by age in years			Gender Unknown by age in years		
		<2	2<18	≥18<22	<2	2<18	≥18<22	<2	2<18	≥18<22
Newly implanted pediatric patients during this reporting period	43	0	7	28	0	1	0	0	0	7
Total pediatric patients with active implants this reporting period	225	0	40	119	0	29	25	0	3	9
Estimated total number of patients receiving Medtronic® Enterra™ Therapy in this reporting period	11,509									

ANNUAL REPORT REVIEW

This year's annual report included annual distribution information; a summary changes including design, manufacturing and labeling; reports of scientific investigations and literature; clinical experience including medical device reports; and a pediatric safety report. The annual report did not include any information that affects the safety of the Enterra System. FDA conducted the independent MDR and literature reviews that follow.

MEDICAL DEVICE REPORT REVIEW

Overview of MDR database

The MDR database is one of several important post-market surveillance data sources used by the FDA. Each year, the FDA receives several hundred thousand medical device reports 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 important post-market 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 rate 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 subject 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

The Enterra System labeling includes a summary of known adverse events. The Enterra labeling summary includes the following adverse events that were reported as MDRs in the current reporting year: impedance out of range, change in stimulation (described as a shocking, jolting, or tingling sensation), loss of therapeutic effect, neurostimulator system ceases to function due to battery depletion or telemetry issues, lead or neurostimulator erosion or migration, infections, stomach wall perforation, upper gastro-intestinal (GI) symptoms including nausea, vomiting, abdominal pain, discomfort, persistent pain at the neurostimulator site.

MDR Search Methodology

The MDR database was searched using the following search criteria:

- Product Code: LNQ
- Brand name: Enterra
- Manufacturer: Medtronic
- Report Entered: between May 1, 2022, and April 30, 2023

The MDR search yielded 228 reports received between May 1, 2022, and April 30, 2023. The MDRs included 0 deaths, 172 injuries and 56 device malfunction reports. Two of the MDRs identified using the search methodology were reported in the literature. These MDRs are excluded from the analysis because the MDRs did not involve pediatric patients and the events occurred outside of the current reporting period. The remaining 226 MDRs are reviewed below.

Event Type by Patient Age

Table 3 provides the distribution of the MDRs by reported event type and age grouping. In this year's reporting period, there were two patients in the pediatric age category of 18-21 years old with injury MDR reports. There were no pediatric reports of deaths or malfunctions this reporting period.

TABLE 3: Overall event type distribution by patient age

Event Type	Total MDR Count 5/1/2022 – 4/30/2023	MDR Count by Patient Age (years)			
		Pediatric (< 18)	Pediatric (18-21)	Adult (≥ 22)	Indeterminate (Age blank)
Death	0	0	0	0	0
Injury	170	0	2	125	43
Malfunction	56	0	0	46	10
Total MDR Count	226	2		171	53

Comparison of Current Patient Event Type Information with Previous Years

Table 4 compares the event type distribution for this year's results to prior years. There was a 48% increase in injury MDR reports and no change in death or malfunction reports compared to last year's PAC reporting period. The number of injury reports this year is within the historical range over the last six years.

TABLE 4: Overall event type distribution by reporting year

	Total MDR Count					
Event Type	**2018 PAC Meeting 5/2017 - 4/2018**	**2019 PAC Meeting 5/2018 4/2019**	**2020 PAC Meeting 5/2019 - 4/2020**	**2021 PAC Meeting 5/2020 - 4/2021**	**2022 PAC Meeting 5/2021 - 4/2022**	**2023 PAC Meeting 5/2022 - 4/2023**
Death	0	1	0	0	0	0
Injury	285	184	117	127	116	170
Malfunction	150	120	61	57	57	56
Total MDR Count	435	305	178	184	173	226

Patient Gender and Age Information

In the 226 MDRs received from May 2022 to April 2023, 171 patients were identified as adult (≥22 years old) and 53 MDRs did not provide a patient age (indeterminate age reports). Two MDRs contained pediatric patients.

There were 176 MDRs that noted the gender of the patient: 158 MDRs were identified as female (2 reports involved the same patient) and 18 MDRs were identified as male. The remaining 52 MDRs did not include the patient gender. Review of the 52 unknown gender 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. 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) 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. A total of 141 MDRs (out of 226) provided a valid event date and date of implant. The remaining reports did not include a valid event or explant date. A TTEO could not be determined for these reports.

Table 5 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	0	21	3
31 days - ≤ 1 year	0	1	37	5
> 1 year – ≤ 5 years	0	0	50	7
> 5 years	0	0	16	1
Totals	0	1	124	16

Characterization of the MDR Narratives of the Pediatric Events

On March 19, 2023 information was received from a healthcare provider regarding a 19-year-old patient who was implanted with an implantable neurostimulator (INS) for gastric stimulation and gastrointestinal/pelvic floor stimulation. The heath care provider stated the patient was admitted because the device was causing shocking pain (for the last three days), and the patient was experiencing nausea and vomiting and had free fluid in the pelvis. Additional information was received from the healthcare provider who stated the patient was transferred out of ICU the next day and there were no further details provided. No implant or explant dates were provided.

On November 11, 2022 information was received from a 21-year-old patient who was implanted with an implantable neurostimulator (INS) for Diabetic Gastroparesis and Gastroparesis. The patient stated they met with their doctor recently and was unable to communicate with the implant. The patient reported they were scheduled to have replacement surgery but was scared to have the surgery again. The patient reported the therapy has been working well and was told the settings were too low. The patient asked about the warranty and for information on the low settings.

Characterization of the Time to Event Occurrences in the adult and indeterminate age populations

For the adult the population with TTEO data, issues with the use of the device occur most frequently from "> 1 year up to ≤ 5 years" from the date of implant, followed by issues occurring between "31 days up to ≤ 1 year". Similar to last year's analysis, the following issues continue to be reported:

- Pain and inappropriate simulation/shocking secondary to positioning of the device or battery and lead issues
- Symptoms of nausea and vomiting and/or loss of therapeutic effect secondary to impedance issues or battery issues

- Infection, lead, battery and erosion issues

In the current analysis, the most common complaint of pain continues to occur. The MDR narratives often note inappropriate stimulation/shocking as well as positioning/migration of the device or its components. The inappropriate stimulation/shocking is also often noted in the MDR narrative as being caused by patient device interaction problems, such as patient losing weight after implant; device battery/lead position; or setting of the device. Device repositioning, battery or leads revision/replacement or turning down the voltage setting relieve the problems in most cases.

There were 46 reports associated with complaints of pain and 42 reports that specified shock. In one report, a patient was implanted with an implantable neurostimulator (INS) for gastroparesis and idiopathic gastroparesis. It was reported that when the patient was sitting at their desk they felt a shock where the INS is located, and they noticed some of their symptoms returning. The patient called Medtronic to see if the system can be checked remotely. Patient was advised the device cannot be checked remotely and was directed to their doctor. The issue was resolved at the time of the report.

There were 74 reports of "No Clinical Signs or Symptoms or Conditions". This type of report can mean there were no health consequences or impact to the patient. These MDRs can also vary and include reports of patients needing a physician to tighten a screw, reports of patients with batteries depleted and replaced and patients with devices out of range and requiring the voltage adjustment. This reporting year also included reports with insufficient information, reports not device related and reports with no lasting health impact to patients.

Electric shock, pain and discomfort reports continued to occur this reporting period. A challenge many patients face with these painful clinical symptoms include obtaining relief from the shock events after multiple emergency department visits. For example, one report stated a patient's device was causing problems, and the patient was trying to find a doctor that would see them. Patient stated they did not want to go back the original surgeon, but the device was causing intermittent painful shocks in the lower abdomen. Patient stated the issue began approximately 2 years ago. The patient was directed to their healthcare provider to address the issue. The issue was not resolved at the time of the report and no surgical intervention occurred at time of report.

Nausea/vomiting continued to occur this reporting period. There were 33 reports of nausea/vomiting, which often lead to weight loss. Pocket erosion and decreased therapeutic effectiveness also continued to occur this reporting period. There were 17 MDRs that reported battery depletion, which led to patient complaints of decreased therapeutic effectiveness. These events generally occur from 1 year after placement to 5 years, with typical resolution noted as reprogramming or replacement of the battery.

Infection was reported in 22 MDRs this reporting period. In one report received on October 6, 2022, information was received from a healthcare provider regarding a patient who was implanted with an implantable neurostimulator (INS) for gastric stimulation. It was reported the patient's device was replaced due to eroded gastric stimulator leads. The leads were removed successfully. On August 27th, 2021, the patient was not wearing the binder and there was fluid around the stimulator. The doctor advised the patient to wear the binder to prevent infection. The doctor noted mild serous

drainage from the umbilicus and treated the patient with silver nitrate. No further complications were reported/anticipated at that time.

Most Commonly Reported Patient Problem Codes (PPC)[1]

Table 6 provides the most prevalent reported patient problem codes found in the MDRs reviewed during this reporting period classified by patient age. The top reported patient problem this reporting period is "No Clinical Signs, Symptoms or Conditions/ Insufficient Information" (n=73), which increased from the previous year (n=50). No Clinical Signs, Symptoms or Conditions Insufficient Information code is characterized by no findings and/or problem being detected after an investigation. The second highest category is Pain (n=46), which is characterized by inappropriate stimulation/shocking/burning as well as cramping/discomfort and migration of the device or its component. "Pain" decreased slightly when compared to last year (n=50). "Nausea/Vomiting" is the third most prevalent code (n=33). The other identified patient problem codes included erosion and infection. Overall, this year's patient problem codes do not present significantly new or increased safety concerns when compared to last year.

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

Patient Problem	Total Patient Problem Code	Total Patient Problem Code by Patient Age (years)			
		Pediatric (< 18)	Pediatric (18 to 21)	Adults (≥ 22)	Indeterminate (Age blank)
No Clinical Signs, Symptoms or Conditions/ Insufficient Information	73	0	0	53	20
Pain/ Electric Shock/ Abd Pain/ Discomfort/ Burning Sensation/ Und Nerve Stimulation/ Shaking/Tremors/ Twitching/ Convulsion/Seizure	46	0	1	40	5
Nausea/Vomiting	33	0	1	29	3
Unspecified Infection/ Sepsis/ Post Operative Wound Infection/ Fluid Discharge/ Purulent Discharge	22	0	0	17	5

[1] The total patient problem code (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.

Erosion/ Device Embedded in Tissue or Plaque	17	0	0	15	2
Seroma/ Swelling/ Edema	9	0	0	8	1
Internal Organ Perforation/ Bowel Perforation	7	0	0	6	1
Muscle Weakness/Atrophy/ Ambulation Difficulties/ Nerve Damage/ Paresis	7	0	0	6	1
Scar Tissue/ Adhesion(s)	5	0	0	1	4
Total Count	219	0	2	175	42

Most Commonly Reported Device Problem Codes (DPC)[2]

Table 7 provides the most prevalent reported device problems for all MDRs classified by patient age. The top three reported device problem codes this year are "Adverse event without identified device or use problem" (n=59) ranking first, "Insufficient Information" (n=58) ranking second, and "Inappropriate/Inadequate Shock/Stimulation/ Pocket Stimulation" (n=44) ranking third. The reports with "adverse event without identified device or use problem" are related to patient issues in which the device was functioning or had no identified device problems. The other reports most often included reports of pain with device intolerance issues. Most of the corresponding patient problem codes were nausea/vomiting, shocking sensation and infection. Adjustments to the device voltage, device placement and replacement of the leads or battery were reported interventions in these patients. The reports of "Inappropriate Shock" typically involved the position of device, or electromagnetic compatibility/interference. "Energy output problem" and "Failure to deliver energy are related to nausea, vomiting, shocking and decreased therapeutic effect issues. Recognized Device or Procedural Complication are Hospitalizations or Prolonged Hospitalizations are common health impact codes associated interventions as well as Device Revision or Replacement in many of the reports.

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

Device Problem	Total Device Problem Code	Total Device Problem Code by Patient Age (years)			
		Pediatric (< 18)	Pediatric (18 to 21)	Adults (≥ 22)	Indeterminate (Age blank)

[2] The total Device Problem Codes (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.

Adverse Event Without Identified Device or Use Problem	59	0	0	46	13
Insufficient Information	58	0	0	44	14
Inappropriate/Inadequate Shock/Stimulation/ Pocket Stimulation	44	0	1	37	6
Battery Problem/ Premature Discharge of Battery	33	0	0	18	15
Migration or Expulsion of Device	30	0	0	24	6
Electromagnetic Compatibility Problem/ Electromagnetic Interference	20	0	0	15	5
Break/ Material Deformation/ Degraded/ Disconnection	19	0	0	13	6
Failure to Interrogate/ Failure to Deliver Energy/ Energy Output Problem/ Connection Problem/ Communication or Transmission Problem/ Data Problem	16	0	1	14	1
Total Device Problem Code Count	279	0	2	211	66

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 reporting periods. There were two pediatric MDRs this reporting period. Previous pediatric MDRs have involved complaints of nausea, vomiting, pain, shock and infection, corresponding to device issue related to "Therapeutic Response, unexpected/decreased", and "inappropriate shock." These complaints and device problems were most often due to device setting, battery and lead issues. Adjustments of the device settings, follow up with the treating physician, hospitalization and request to explant the device were noted interventions.

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

Clinical Events	Occurrences in MDRs** 5/1/2022- 4/30/2023	Occurrences in MDRs** 5/1/2021- 4/30/2022	Occurrences in MDRs** 5/1/2020- 4/30/2021	Occurrences in MDRs** 5/1/2019– 4/30/2000
Nausea/Vomiting	1	1	1	1
Therapeutic Response, unexpected/Paresis	0	0	1	3
Pain/Discomfort/Abdominal pain/ Burning sensation	0	0	2	2
Electric Shock/Nerve Stimulation, Undesired/ [Inappropriate Electric Shock]	1	0	0	1
Infection	0	0	0	1
Therapeutic Effects, Unexpected	0	0	1	0
Insufficient Information/Complaint Ill-Defined	0	1	1	0

**Only the most observed patient problems and issues in pediatric MDR narratives are included.*
***The total MDR Occurrences may not equal the total pediatric MDR count since one MDR might have multiple clinical events.*

Re-Interventions in Pediatric Patients this reporting period

Re-interventions addressing clinical events are listed in Table 9. This table summarizes the re-interventions identified in the narratives and the causal events leading to these re-interventions. Re-interventions are events that required an additional procedure after the initial placement of the device. There were two pediatric MDRs this reporting period.

TABLE 9: Re-interventions in pediatric patients* (5/1/2022-4/30/2023)

Re-Interventions	Number of Re- Interventions	Causal Event
Replacement/Repositioning Device or Battery	2	• Shocking/burning • Battery depletion
Explant Device or INS	0	• Infection • Pain
Reprogramming/ Calibration	0	• Loss oftherapeutic effect • Shocking/jolting/burning

Hospitalization/Emergency room	1	• Infection • Loss of therapeutic effect • Pain/discomfort • Vomiting/hematemesis
Surgery/impedance check	1	• Loss of therapeutic effect • Minor Injury/ Illness/ Impairment • Poor Intake
Surgery (gastrostomy) /Feeding tube	0	• Loss of therapeutic effect • Nausea/vomiting/poor intake
Office follow-up treatment	1	• Loss of therapeutic effect • Nausea/vomiting • Shocking

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

MDR Review Conclusions

- There were two pediatric MDR reports submitted for the Enterra Therapy System between May 1, 2022 and April 30, 2023.
- The number and type of pediatric MDRs this year are similar to previous reporting periods.
- The type and number of overall MDRs reported in the current reporting period are similar to previous reporting periods.
- The TTEO was calculated for 141 reports based on the available information contained in the reports. MDRs continue to occur most frequently from > 1 year up to ≤ 5 years from the date of implant.
- Patient problems observed this reporting period were similar to patient problem codes observed in the last reporting period. Complaints of pain and incidences of shock appear to be related to the position of device and/or connection/malfunction issues involving the leads or batteries.
- Device problems observed this reporting period were similar to device problem codes observed in the last reporting period. Reports continue to identify device functionality issues with the device including migration, malfunction and battery depletion issues.

LITERATURE REVIEW

Purpose

A systematic literature review was conducted to evaluate the safety and probable benefit of the Enterra gastric electrical stimulator (GES) in the pediatric population (<22 years old). This review is an update to the literature reviews presented at the Pediatric Advisory Committee (PAC) meetings from 2014 through 2022. 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

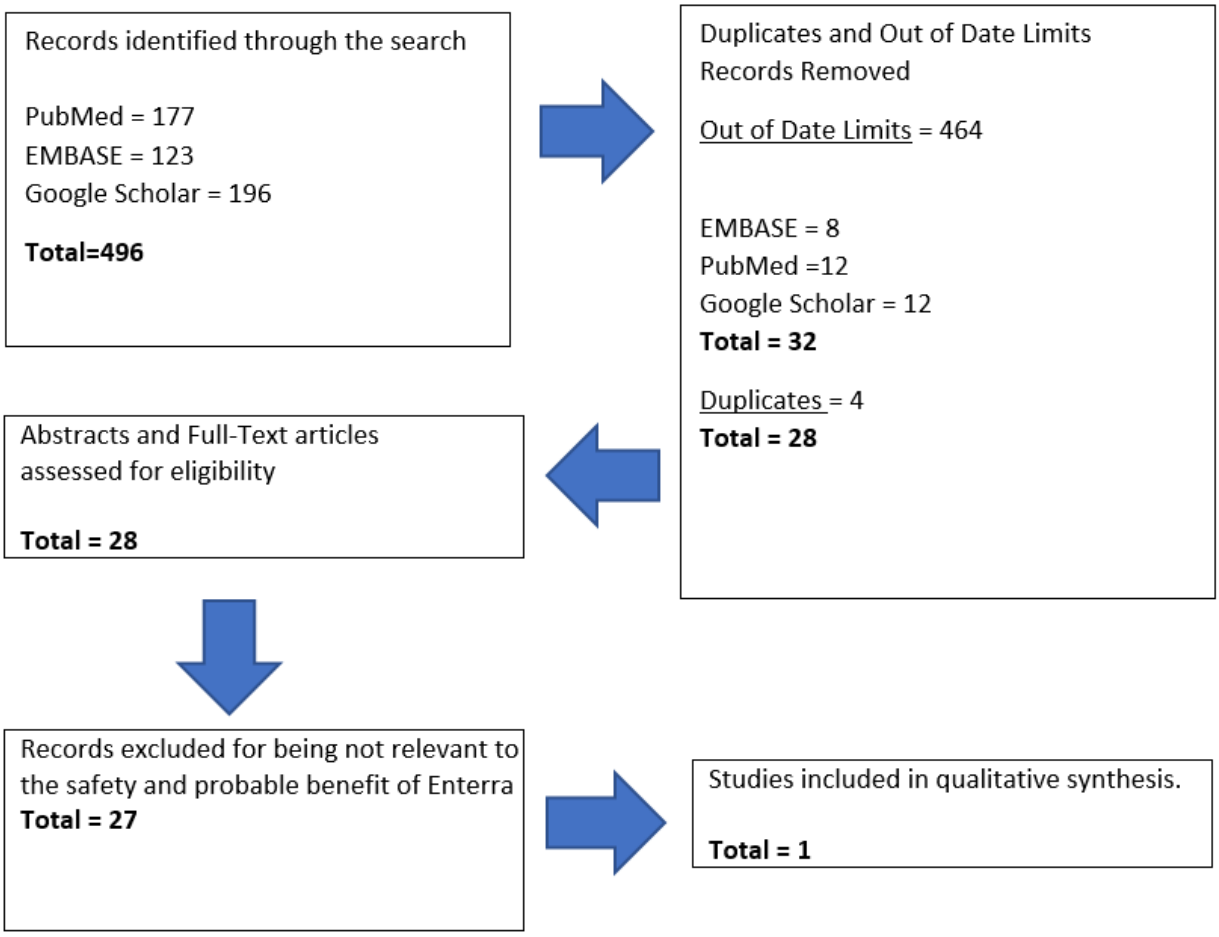
The search was limited to studies published since the last PAC meeting update (May 1, 2022 to April 30, 2023). The results were filtered for studies in human subjects, studies published in English, and excludes articles indexed to animals when not also indexed to humans. This search yielded a total of 496 citations (177 in PubMed, 123 in Embase and 196 in Google Scholar). After a review of titles, abstracts, and selected full texts, 1 article was selected for full review and assessment as shown in "Figure 3 Article Retrieval and Selection". On May 20, 2022, searches in PubMed, Embase, and from MDRs were 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 neuromodulat*)) AND English [la] AND ("infant, newborn" [mh] OR "infant" [mh] OR "child, preschool" [mh] OR "Child"[Mesh] OR "adolescent" [mh] OR "young adult" [mh] OR newborn* OR infant* OR child* OR preschool* OR adolescent* OR "young adult" OR pediatric* OR boy OR girl OR toddler*) AND ("2022/05/01"[Date - Create] : "2023/04/30"[Date - Create] OR "2022/05/01"[Date - Publication] : "2023/04/30"[Date - Publication])) NOT ("animals"[MeSH Terms] NOT "humans"[MeSH Terms]) =12 references

- Embase: (('enterra'/exp OR enterra OR 'gastric pacemaker'/exp OR 'gastric pacemaker' OR 'gastric electrical stimulation'/exp OR 'gastric electrical stimulation' OR 'gastric electric stimulation'/exp OR 'gastric electric stimulation' OR 'gastric electrostimulation' OR 'gastric pacing'/exp OR 'gastric pacing' OR (stimulation AND gastroparesis) OR 'gastrointestinal neuromodulation') AND [english]/lim AND ([newborn]/lim OR [infant]/lim OR [child]/lim OR [preschool]/lim OR [adolescent]/lim OR [young adult]/lim OR newborn* OR neonat* OR infant* OR child* OR preschool* OR adolescen* OR 'young adult' OR pediatric* OR boy OR girl OR toddler*) AND [01-05-2022]/sd NOT [30-04-2023]/sd) NOT ([animals]/lim NOT [humans]/lim) =8 references

- Google Scholar: "Enterra" AND ("gastric electrical stimulation" OR "gastric electrostimulation" OR "gastric pacemaker" OR "gastric pacing" OR gastroparesis OR "gastric neuromodulation") AND (infant OR child OR adolescent OR pediatric OR "young adult"). Limited to 2022-2023 =12 references

Figure 3. Article Retrieval and Selection



Summary of Relevant Article

Wnuk, et al., 2022 Gastric Electrical Stimulation (GES) for Gastroparesis Associated with Mitochondrial Disease and Dysautonomia in Children.

Background: Gastroparesis (GP) is a debilitating condition in many children and is challenging to treat with limited therapies available. Gastric electrical stimulation has been used successfully in children with recalcitrant GP. Patients with dysautonomia syndromes (DA) or mitochondrial disorders (MD) frequently include GP as part of the symptom complex and are especially challenging to manage. We report the use and outcomes of GES in a group of patients with these conditions.

Methods: A retrospective analysis of patients who underwent either temporary or permanent GES was performed, and cases with DA or MD were included for this study. Clinical data including Gastroparesis Cardinal Symptom Index (GCSI) were collected and analyzed with a paired t test.

Results: Overall 275 patients underwent temporary and 152 permanent GES. 50 cases were found to have associated DA. Majority (88%) were female, with a mean age of 15.36 years and 19 had features of both DA and Ehlers-Danlos (EDS). 82% responded to temporary GES and had a permanent implant. In the patients with permanent GES (n=41), 24 patients reported improvement in GCSI scores at all visits with a reduction in mean GCSI score from 16.44 to 9.95, with a mean follow up of 4.88 years. 14 patients improved their route of feeding while 5 maintained the same route of feeding and 2 required supplemental nutrition. 14 patients required device removal due to progression of disease and remission. 12 patients with MD had temporary GES and 7 responders had a permanent implant. Responders were older than non-responders (2.6 vs. 5.6 years). Three of the patients with permanent GES were male, and all 7 had improvement reported symptoms at 3 and 6-months and beyond. All had weight gain post GES placement, and improvement in route/volume of feedings. Hospital utilization was reduced in these cases, with a long-term mean follow up of 5.7 years, with one patient requiring explantation.

Conclusion: Study found GES to be effective in selected patients with quality-of-life improvements and a significant reduction in GP symptoms, improved feeding method, and reduction in antiemetic medications. Consideration should be given to early use of GES in children with MD and DA syndromes with recalcitrant GP.

Probable Benefit from Literature

The single article found in this search is a meeting abstract describing a retrospective study in which 275 patients underwent temporary and 152 permanent GES. These were patients with dysautonomia syndromes (DA) or mitochondrial disorders (MD) that included GP as part of the symptom complex. The study reported subjects responding favorably to GES treatment including quality-of-life improvements, reduction in GP symptoms, improved feeding method and weight gain.

Safety from Literature

Two patients required supplemental nutrition and fourteen patients required device removal due to progression of disease and remission. No other safety data was reported in the study and none of the information included in the abstract indicates the presence of safety signal.

Critical Assessment of the Literature

The current systematic literature review found one relevant citation (meeting abstract), out of 496 publications. The study included a total of 275 patients. The meeting abstract provides evidence Enterra reduced gastroparesis symptoms. There is no indication of a safety signal in the abstract.

The results of this systematic literature review should be interpreted with consideration of the key limitations. First, the literature review only identified one pertinent citation in which Enterra was used for GES. Secondly, the identified citation has study design limitations including retrospective design, lack of methodology to select patients in the study and no treatment randomization. The retrospective study design significantly limits the value of the safety data. In addition, this is a meeting abstract that does not include details regarding safety findings. FDA was not able to obtain additional information on this study.

Literature Review Conclusion

The limitations of the literature review prevent making firm conclusions about the safety of using the Enterra system in the pediatric population. However, the current findings are not different from last year's literature review and thus do not raise safety concerns.

OVERALL SUMMARY

FDA did not identify any new safety signals during this year's review of the Enterra annual report, MDRs or the peer-reviewed literature published since the last report to the PAC. FDA concludes the HDE for this device remains appropriate for the pediatric population for which it was granted. FDA will continue routine surveillance including MDR and literature reviews.

FDA will report the following to the PAC in 2023:

- Annual distribution number,
- Literature review,
- MDR review

REFERENCES

1. Wnuk MT, Jenkins P, Islam A. Gastric Electrical Stimulation for Gastroparesis Associated with Mitochondrial Disease and Dysautonomia in Children. Pediatrics (2022) 149 (1 Meeting Abstracts February 2022): 867.