FDA Executive Summary

Prepared for the
Fall 2024 Review by the
FDA's Pediatric Advisory Committee

Enterra® Therapy System
(H990014)

Table of Contents

I. 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 2023 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.

II. 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.

III. 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.

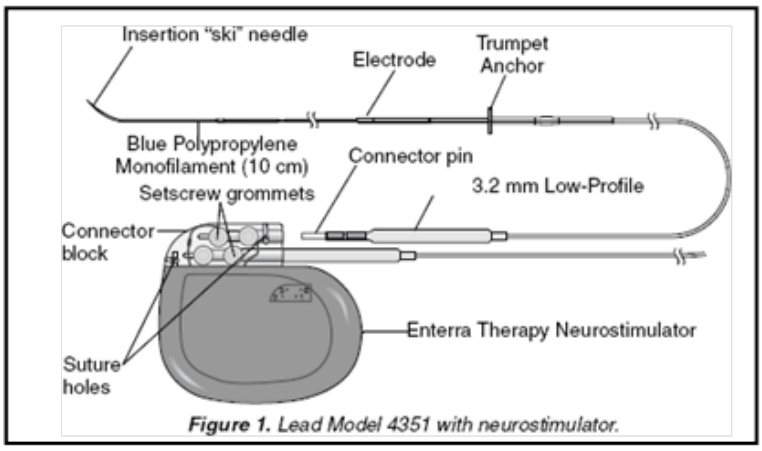

FIGURE 1: Implantable components

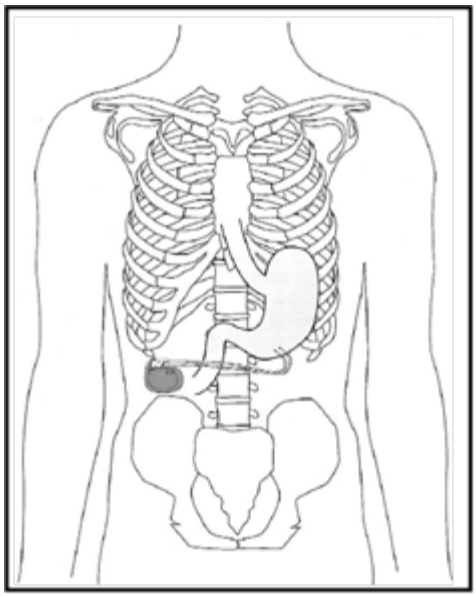

FIGURE 2: Device placement

IV. 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

V. 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.

As of May 10, 2023, Medtronic is no longer responsible for Annual Report activities related to the Enterra product. As such, the information below on Device Distribution is being provided by Enterra for this reporting period.

It should be noted that there has been a decrease in specificity and granularity on the information provided in their Annual Reports compared to the previous reports provided by Medtronic (shown below) which impacted their Device Distribution information. Interactive attempts had been made to request more specificity but Enterra Medical did not have it, and they were informed going forward that more specific information should be captured and included in future reports. While this additional granularity would provide for a more detailed assessment, the available information provided from Enterra was deemed adequate for the scope of this executive summary.

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

TABLE 1: Distribution Numbers

Model Number & Component Name	Devices Sold From 2/01/23 – 01/31/24	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	2923	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	0	208
4351 Intramuscular Lead	3027	2345	2,131	1,874	1,988	2,106	2,535	2,462	2,151

TABLE 2: Estimated Number of Devices Implanted in Pediatric Patients

Reporting Period: 02/01/23 – 01/31/24	Total N (newly implanted this period)	Gender Unknown by age in years	
		<18	≥18<22

Newly implanted pediatric patients during this reporting period	207	0	134
Total pediatric patients with active implants this reporting period	423	166	257
Estimated total number of patients receiving Medtronic® Enterra™ Therapy in this reporting period	15601	N/A	N/A

For reference here is an example of the specificity of data provided in the 2023 PAC Report from Medtronic in Table 3.

TABLE 3: Estimated Number of Devices Implanted in pediatric patients (Reporting by Medtronic in 2023)

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	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A

VI. 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.

VII. 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
- Manufacturer name: Enterra, Enterra Medtronic Inc, Medtronic, Puerto Rico Operations CO
- Report Entered: between May 1, 2023, and April 30, 2024

The MDR search yielded 107 reports received between May 1, 2023, and April 30, 2024. The MDRs included 1 death, 37 injuries and 69 malfunction reports. Of the 107 reports there were 4 pediatric patient reports and one adult report identified as a literature review.

Event Type by Patient Age

Table 4 provides the distribution of the MDRs by reported event type and age grouping. In this year's reporting period, there were three patients in the pediatric age category of <18 years old with malfunction MDR reports and one in the 18-21 age category. There were no pediatric reports of deaths or injury this reporting period.

TABLE 4: Overall event type distribution by patient age

Event Type	Total MDR Count 5/1/2023 – 4/30/2024	MDR Count by Patient Age (years)			
		Pediatric (< 18)	Pediatric (18-21)	Adult (≥ 22)	Indeterminate (Age blank)
Death	1	0	0	1	0
Injury	37	0	0	30	7
Malfunction	69	3	1	49	16

Total MDR Count	107	3	1	80	23

Comparison of Current Patient Event Type Information with Previous Years

Table 5 compares the event type distribution to prior years.

TABLE 5: 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**	**2024 PAC Meeting 5/2023 - 4/2024**
Death	0	1	0	0	0	0	1
Injury	285	184	117	127	116	170	37
Malfunction	150	120	61	57	57	56	69
Total MDR Count	435	305	178	184	173	226	107*

** Interactive Request was made to request the MDRs submitted between May 01, 2023 – April 30, 2024. Enterra Medical noted that since the HDE had officially changed ownership (from Medtronic) on May 10, 2023, there were MDRs that likely were not entered into the Enterra compliant system in May.*

Patient Gender and Age Information

In the 107 MDRs received from May 2023 to April 2024, 80 patients were identified as adult (≥22 years old) and 23 MDRs did not provide a patient age (indeterminate age reports). Four (4) MDRs contained pediatric patients.

There were 71 MDRs that noted the gender of the patient: 66 MDRs were identified as female and 5 MDRs were identified as male. The remaining 36 MDRs did not include the patient gender.

Review of the 36 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 59 MDRs (out of 107) 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 6 provides the MDR count for the TTEO for the pediatric, adult, and indeterminate age patient populations.

TABLE 6: MDR count for the TTEO by patient age

Time to Event Occurrence (TTEO)	MDR Count by Patient Age (years)			
	Pediatric (<18)	Pediatric (18-21)	Adult (≥22)	Indeterminate (Age blank)
≤ 30 days	3	0	5	0
31 days - ≤ 1 year	0	0	24	2
> 1 year – ≤ 5 years	0	0	10	1
> 5 years	0	0	13	1
Totals	3	0	52	4

Characterization of the MDR Narratives of the Pediatric Events

<30 Days
On October 23, 2023, a 10-year-old female patient implanted 6/11/23 is experiencing wound and skin concerns around pocket site where her Enterra device is implanted. The surgeon described it: "there is a rim of discoloration around the perimeter of the generator (not the incision). Yesterday (6/13) it was pink and blanched. Today (6/14) it looks a little more like a bruise. She also has some pink just below the midline wound where the leads are tracking through the abdominal wall." surgeon said after administering antibiotics, the patient showed some overnight improvement, but they are concerned about a potential allergic reaction to the device.

<30 Days
On December 28, 2023, A Mother called the patient liaison line and left a voicemail stating, "my daughter has an implanted Enterra device. She's had it in place for a week and it's sending excruciating shock to her body. She's at a children's hospital and the doctors have never had this happen either." I called and spoke with the mother on 12/6/23 and she states she already spoke

with the rep. She states the 14-year-old female patient was implanted last week by the doctor and started experiencing the shocking about 10 hours after the surgery. She states the device was turned off; it was then turned back on at a lower voltage. The patient then began experiencing the shocking and the device was turned off and is currently off. She states she had an ultrasound yesterday and there was seroma around the battery. She states they were about to go into a GI appointment with the doctor. Discussed issue with the doctor and will send email to the rep.

No Info
On January 17th 2024, after a Gen change the 21-year-old female patient has not been able to achieve the same level of efficacy. Unintended revision surgery to replace device.

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

For the adult the population with TTEO data, issues with the use of the device occur most frequently from "31 days - ≤ 1 year" from the date of implant, followed by issues occurring between "> 5 years". Last year's analysis, issues with the use of the device occurred most often between > 1 year – ≤ 5 years. Three of the four reported pediatric use of device issues occurred ≤ 30 days from the date of implant this reporting period. One pediatric only gave the patients age. The following issues continue for both adult and pediatric patients.

- 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 which causes pain. Patients experiencing pain complained of it most often around the implant site. Patient device interaction problems were reported in some patients due to 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 20 reports associated with complaints of pain and 22 reports that specified shock. In one report (2182207-2023-01237), information was received from multiple sources about a patient who was implanted with an implantable neurostimulator (INS) for unknown indications for use. It is unknown if the device was used off label. It was reported that the shocking from the stimulator can be felt most at night, and it makes them cry. The issue was not resolved at the time of the report and no surgical intervention occurred at time of report. There were 37 reports of "No Clinical Signs or Symptoms or similar 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 replace a lead(s), 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, examples include:

- "Patient is experiencing shocking and cannot lay on their left side without experiencing." "Patient returned call for permanent implant card being returned to sender."
- "Patient stated on the call that they are experiencing shocking problems (did not specify more), they cannot lay on their left side."
- "Patient stated they have been trying to find a new managing physician closer to them and that will help with the device management. The patient verified their last implant and managing doctor to get a new implant card mailed out."
- "Patient was transferred to tech support (855-681-5982) for the issues they are experiencing and to locate a new doctor closer to them. 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 15 MDRs of nausea/vomiting which often led to weight loss. Pocket erosion and decreased therapeutic effectiveness also continued to occur this reporting period. There were six (6) battery problem reports down from last year's nine (9) 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 13 MDRs this reporting period, down from 22 MDRs documented in the annual report from last year. In one report received on October 24, 2023, information was received from a healthcare provider regarding a patient who was implanted with an Enterra Medical implantable neurostimulator (INS) for gastric stimulation. A patient had a battery change about three months ago by the doctor. "The patient's pocket opened a few weeks ago and the doctor widened the pocket today and reclosed it." On January 3, 2024, it was reported explant due to infection.

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

Table 7 provides the most prevalent patient reported problem codes found in the MDRs reviewed

[1] The total patient problem code (PPC) does not equal the total MDR count since one MDR might

during this reporting period classified by patient age. The most common reported patient problems this reporting period are "No Clinical Signs, Symptoms or Conditions/Insufficient Information" (n=37), which decreased from the previous year (n=73). 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 Electric Shock, Shock, Undesired Nerve Stimulation Pain (n=22), which is characterized by inappropriate stimulation/shocking/burning as well as cramping/discomfort and migration of the device or its component. The third most prevalent code "Pain" is just behind slightly at (n=20) decreasing when compared to last year (n=50). The fourth patient problem code is Nausea and Vomiting with weight changes (n=15). The Fifth most reported patient problem code is Infection (n=13). This year's patient problem codes do not present significantly new or increased safety concerns when compared to last year.

TABLE 7: 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	37	0	0	30	7
Pain/Abd Pain/ Discomfort	20	1	0	18	1
Electric Shock, Shock, Undesired Nerve Stimulation	22	2	0	16	4
Nausea/Vomiting/ Weight Changes	15	0	1	13	1
Skin Infection, Unspecified Infection, Post Operative Wound Infection, Post Traumatic Wound Infection, Skin	13	1	0	11	1

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.

Inflammation/ Irritation, Erythema					
Failure of Implant	9	0	0	8	1
Erosion, Pocket Erosion, Internal Organ Perforation	6	0	0	5	1
Muscle Weakness/Atrophy / Numbness	3	0	0	3	0
Total Count	125	4	1	104	16

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

Table 8 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=30) ranking first, "Unintended Electrical Shock, Intermittent Shock/Stimulation" (n=24) ranking second, and "Patient Device Interaction Problem, Patient-Device Incompatibility" (n=19) 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 8: Most commonly reported device problem codes in MDRs received by patient age

[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.

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)
Patient Device Interaction Problem, Patient-Device Incompatibility	19	1	1	17	N/A
Appropriate Term/Code Not Available, Insufficient Information, Adverse Event Without Identified Device or Use Problem	30	0	0	30	N/A
Unintended Electrical Shock, Intermittent Shock/Stimulation, Inappropriate/Inadequate Shock/Stimulation, Pocket Stimulation, Defibrillation/Stimulation Problem, Vibration	25	2	0	23	N/A
Migration or Expulsion of Device, Malposition of Device, Unintended Movement, Entrapment of Device, Device Dislodged or Dislocated, Device Fell, Loosening of Implant Not Related to Bone-Ingrowth, Positioning Problem	17	0	0	17	N/A
Battery Problem, Premature Discharge of Battery, Battery Problem: Low Impedance, Failure to Deliver Energy, Energy Output Problem, Intermittent Continuity	12	0	0	12	N/A
Break, Material Puncture/Hole, Material Perforation, Material Deformation, Material Erosion, Misassembled	13	0	0	13	N/A
Impedance Problem, High impedance	5	0	0	5	N/A

Use of Device Problem, Unexpected Therapeutic Results, Device Difficult to Program or Calibrate, Failure to Interrogate	5	0	0	5	N/A
Electromagnetic Compatibility Problem, Communication or Transmission Problem, Loose or Intermittent Connection	3	0	0	3	N/A
Improper or Incorrect Procedure or Method	1	0	0	1	N/A
Device Appears to Trigger Rejection	1	0	0	1	N/A
Noise, Audible	1	0	0	1	N/A
Total Device Problem Code Count	132	3	1	128	N/A

** There were four pediatric MDRs this reporting period. One shocking sensation experienced by a 14-year-old female pediatric patient did not negatively impact her or delay the neurostimulator procedure.*

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

Table 9 identifies the MDR occurrences of the top patient problems and issues in pediatric patients only in comparison to the prior reporting periods. There were four (4) 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 9: Clinical events identified with pediatric patients - year-to-year comparison*

Clinical Events	Occurrences in MDRs** 5/1/2023-4/30/2024	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	0	1	1	1	1

Therapeutic Response, unexpected/Paresis	0	0	0	1	3
Pain/Discomfort/Abdominal pain/ Burning sensation	0	0	0	2	2
Electric Shock/Nerve Stimulation, Undesired/ [Inappropriate Electric Shock]	3	1	0	0	1
Infection	1	0	0	0	1
Therapeutic Effects, Unexpected	0	0	0	1	0
Insufficient Information/Complaint Ill-Defined	0	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 10. 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 four pediatric MDRs this reporting period.

TABLE 10: Re-interventions in pediatric patients* (5/1/2023-4/30/2024)

Re-Interventions	# of Re-Interventions	Causal Event	Outcome of Intervention
Device Revision or Replacement	1	Appropriate Term/Code Not Available Battery depletion Appropriate Term/Code Not Available	"After a gen change the patient has not been able to achieve the able same level of efficacy. Unintended revision surgery to replace device."
Delay to Treatment/ Therapy	0	Patient Device Interaction Problem Use of Device Problem	N/A
Death	0	Abdominal Pain Material Perforation	N/A

Minor Injury/ Illness / Impairment	1	Loss of therapeutic effect Battery/ Patient Lead Adverse Event Without Identified Device or Use Problem	"After administering antibiotics, the patient showed some overnight improvement, but they are concerned potential allergic reaction to the device"
Surgical Intervention	2	Material Puncture/Hole; Material Perforation Inappropriate/Inadequate Shock/Stimulation Impedance Problem	"Patients experienced some relief after Enterra INS settings re-adjustment"
Change in Therapeutic Response	0	Unintended Electrical Shock Patient Device Interaction Problem	N/A

**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 four pediatric MDR reports submitted for the Enterra Therapy System between May 1, 2023, and April 30, 2024, none involving a death.

- The number and type of pediatric MDRs this year are similar to previous reporting periods.

- The age of the pediatric patients in the MDRs documented for the current reporting period range from 10 to 21 years old, all of these MDRs were attributed to malfunction of the device.

- The TTEO was calculated for a total of 59 MDRs (out of 107) with a valid event date and date of implant. The remaining reports did not include a valid event or explant date, and therefore TTEO could not be determined for these reports.

- 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.

- Enterra has not provided effectiveness data for the Enterra INS device this reporting period. The device remains appropriate for the pediatric population and the FDA has no new safety concerns about the use of this device in pediatric patients.

Purpose

A systematic literature review was conducted to evaluate the safety and probable benefit of 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 2023. 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 1,2023 to April 30, 2024). 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 521 citations (187 in PubMed, 138 in Embase and 196 in Google Scholar). After a review of titles, abstracts, and selected full texts, 40 articles were selected for full review and assessment as shown in "Figure 3. Article Retrieval and Selection". On June 7, 2024, 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 "stomach paresis")) 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 ("2023/05/01"[Date - Create] : "2024/04/30"[Date - Create] OR "2023/05/01"[Date - Publication] : "2024/04/30"[Date - Publication]) NOT ("animals"[MeSH Terms] NOT "humans"[MeSH Terms])
    = 14 references (187 before date limits applied)

- 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'/exp OR gastroparesis OR 'stomach paresis')) 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 [01-05-2023]/sd NOT [30-04-2024]/sd) NOT ([animals]/lim NOT [humans]/lim)

=10 references (138 references before date limits applied)

- 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 2023-2024
    =20 references (215 before date limits applied)

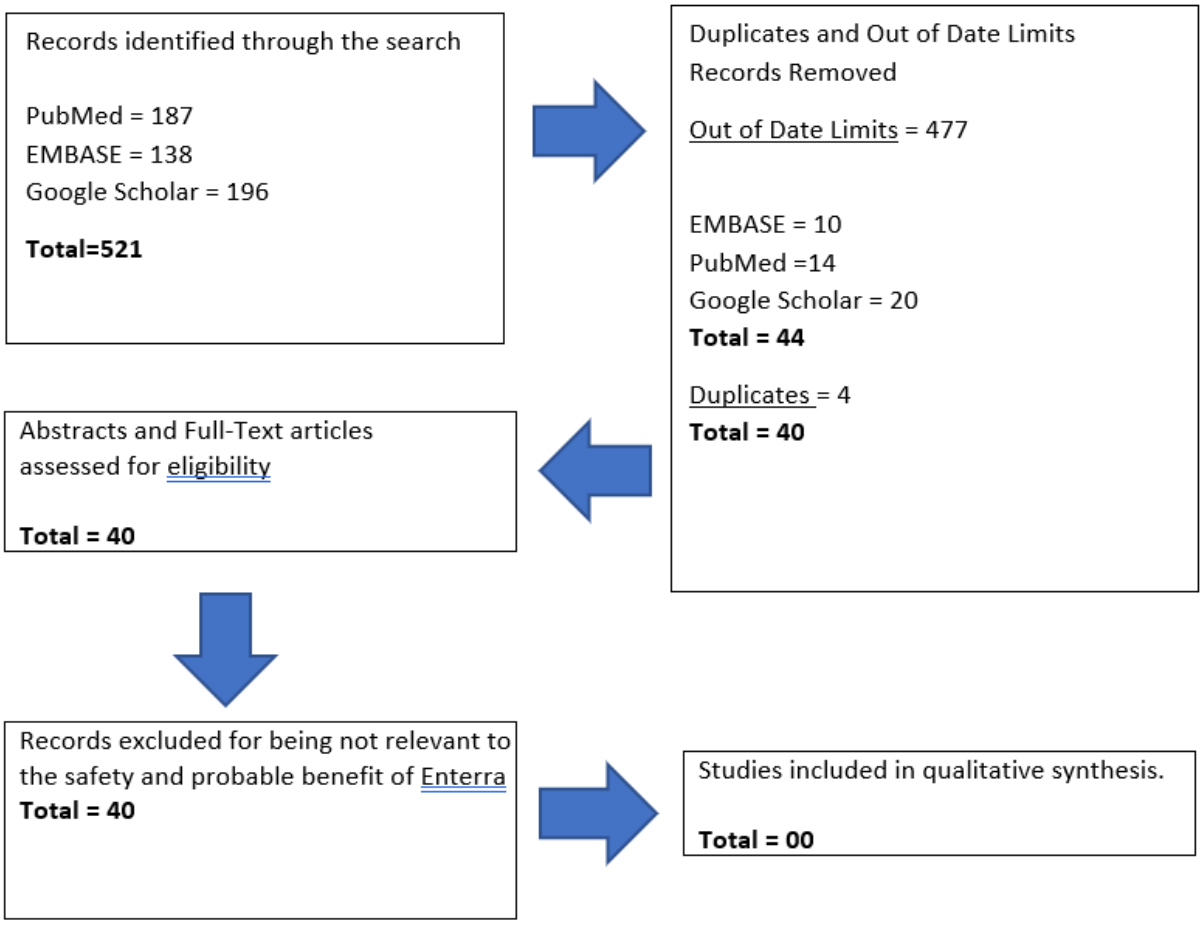

Figure 3. Article Retrieval and Selection

Literature Review Summary

Similar to literature reviews presented at the Pediatric Advisory Committee (PAC) meetings from 2014 through 2023 our identification of relevant articles was determined on finding articles that were:

- Relevant to the safety and probable benefit of Enterra/Gastric Electric Stimulators; and
- Analysis of the pediatric population

Within the period of this search limited to studies published since the last PAC meeting update (May 1, 2023 to April 30, 2024) there were no articles that fit these above criteria.

However, in the effort of a comprehensive search the following five articles from the literature search were considered to see if safety information could be extrapolated from use of Enterra/Gastric Electric Stimulators in adults or studies on pediatric patient populations with gastroparesis (common indication for Gastric Electric Stimulation therapy):

1. *Bills S, Shine A, Williams JC, Mathur P, Kedar A, Daniels M, et al. Difference in Cyclic Versus Non-cyclic Symptom Patterns in Patients with the Symptoms of Gastroparesis Undergoing Bioelectric Therapy. Dig Dis Sci. 2024;69 (5).1722-30. Epub 20240409. doi: 10.1007/s10620-024-08303-1. PubMed PMID: 38594432.*
2. *Soliman H, Schalla MA, Coffin B, Gourcerol G. Gastric electrical stimulation is safe during pregnancy and delivery: Results from a French cohort. Neurogastroenterol Motil. 2023;35 (10).e14657. Epub 20230813. doi: 10.1111/nmo.14657. PubMed PMID: 37574861.*
3. *Naing LY, Baumgarten H, Mathur P, Goodman BR, Mandzhieva B, Gondim DD, et al. USE OF FULL THICKNESS BIOPSIES IN PEDIATRIC PATIENTS WITH SEVERE GASTROPARESIS SYMPTOMS IN COMPARISON TO ADULT PATIENTS. Gastroenterology. 2023;164 (6).S-149. doi: 10.1016/S0016-5085(23)01320-3.*
4. *Nita A, Kadirkamanathan S, Curry J, Lindley K, Nikaki K, Rybak A, et al. EFFICACY OF GASTRIC PACING AS TREATMENT OF PAEDIATRIC SEVERE GASTROPARESIS. Journal of Pediatric Gastroenterology and Nutrition. 2023;76.173. doi: 10.1097/MPG.0000000000003823.*
5. *Konings B, de Barahona LV, Barahona G, Burns R, McKnight M, Chumpitazi BP, et al. THE MORBIDITY AND MORTALITY BURDEN OF PEDIATRIC GASTROPARESIS: A NATION-WIDE ANALYSIS OF ACADEMIC MEDICAL CENTERS. Gastroenterology. 2023;164 (6).S-948. doi: 10.1016/S0016-5085(23)03191-8.*

Critical Assessment of the Literature

The current systematic literature review found no relevant citations (meeting abstract), out of 521 publications.

None of the considered articles raised any safety concerns. However, one article – Konings et. al – did note that greater efforts are needed to ameliorate the negative impact of gastroparesis on pediatric health which noted therapies such as gastric electric stimulation (e.g., Enterra).

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.

Literature Review Conclusion
The current findings were based on the same approach as last year's literature review. No pertinent literature was located during this literature review that would suggest a need to revise prior conclusions about the safety of using the Enterra Medical INS System in the pediatric population or any general safety concerns when utilizing the Enterra Medical INS system.

VIII. 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.

However, we will be requesting Enterra Medical capture more specific data regarding their pediatric safety reports as part of their future annual reports.

FDA will continue routine surveillance including MDR and literature reviews.

FDA will report the following to the PAC in 2024:

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

IX. REFERENCES

1. Bills S, Shine A, Williams JC, et al. Difference in Cyclic Versus Non-cyclic Symptom Patterns in Patients with the Symptoms of Gastroparesis Undergoing Bioelectric Therapy. *Dig Dis Sci*. 2024;69(5):1722-1730.
2. Soliman H, Schalla MA, Coffin B, Gourcerol G. Gastric electrical stimulation is safe during pregnancy and delivery: Results from a French cohort. *Neurogastroenterol Motil*. 2023;35(10):e14657.
3. Nita A, Kadirkamanathan S, Curry J, Lindley K, Nikaki K, Rybak A, et al. EFFICACY OF GASTRIC PACING AS TREATMENT OF PAEDIATRIC SEVERE GASTROPARESIS. *Journal of Pediatric Gastroenterology and Nutrition*. 2023;76.173
4. Naing LY, Baumgarten H, Mathur P, Goodman BR, Mandzhieva B, Gondim DD, et al. USE OF FULL THICKNESS BIOPSIES IN PEDIATRIC PATIENTS WITH SEVERE GASTROPARESIS SYMPTOMS IN COMPARISON TO ADULT PATIENTS. *Gastroenterology*. 2023;164 (6).S-149.
5. Konings B, de Barahona LV, Barahona G, Burns R, McKnight M, Chumpitazi BP, et al. THE MORBIDITY AND MORTALITY BURDEN OF PEDIATRIC GASTROPARESIS: A NATION-WIDE ANALYSIS OF ACADEMIC MEDICAL CENTERS. *Gastroenterology*. 2023;164 (6).S-948.