# FDA Executive Summary

Prepared for the
Fall 2021, Meeting of the
FDA's Pediatric Advisory Committee

# 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 the FDA reviewed in the year following our 2020 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**

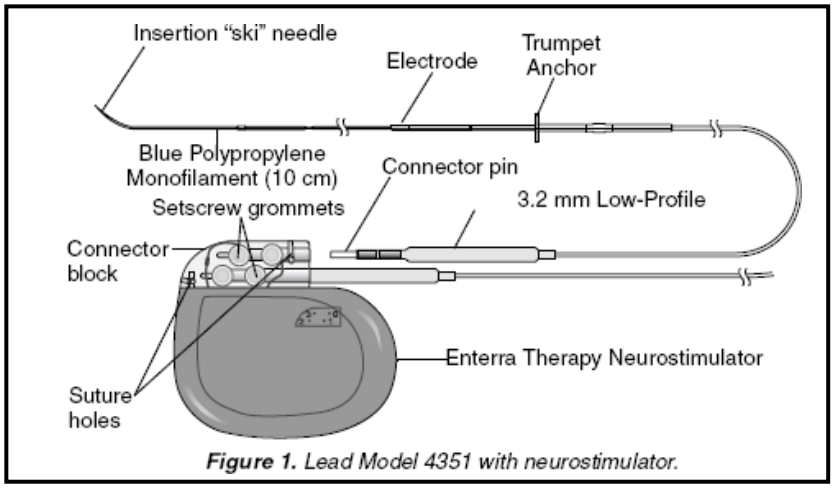
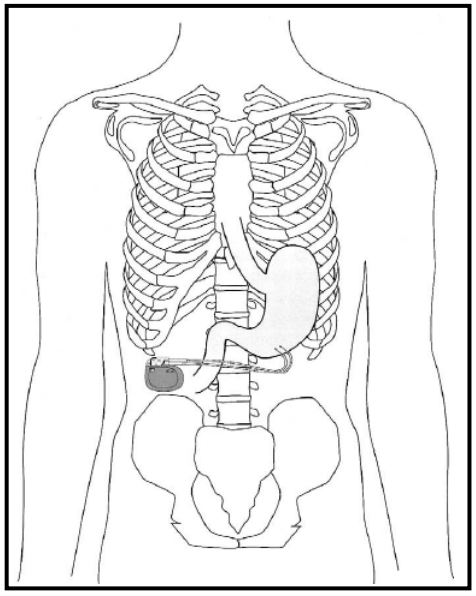



*Figure 1. Lead Model 4351 with neurostimulator.*

**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) 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 02/01/20 – 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 (INS) | 1,895 | 2,053 | 1,951 | 2,017 | 1,865 | 1,611 |
| 3116 Implantable Neurostimulator | 0 | 0 | 0 | 0 | 0 | 208 |
| 4351 Intramuscular Lead | 1,874 | 1,988 | 2,106 | 2,535 | 2,462 | 2,151 |

**TABLE 2: Number of devices implanted in pediatric patients**

| Reporting Period: 02/01/20 – 01/31/21 | Total N (newly implanted this period) | Female | | | Male | | | Gender Unknown | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | <2 | 2<18 | ≥18<22 | <2 | 2<18 | ≥18<22 | <2 | 2<18 | ≥18<22 |
| Newly implanted Pediatric patients implanted during this reporting period | 63 | 0 | 10 | 38 | 0 | 5 | 8 | 0 | 0 | 2 |
| Total Pediatric implant base this period | 235 | 0 | 49 | 116 | 0 | 35 | 30 | 0 | 1 | 4 |

## 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 (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 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

### MDR Search Methodology

The MDR database was searched using the following search criteria:

A. Search 1
- Product Code: LNQ
- Report Entered: between May 1, 2020 and April 30, 2021

B. Search 2
- Brand name: ENTERRA%
- Report Entered: between May 1, 2020 and April 30, 2021

C. Search 3
- Premarket submission number: H990014
- Report Entered: between May 1, 2020 and April 30, 2021

The MDR search yielded 191 MDRs. Of the 191 reports, 183 were manufacturer reports and 1 was a voluntary report. The remaining 7 MDRs were excluded from further MDR analysis since these reports described events reported in six journal articles. The journal articles are discussed in the Literature Review section of this document.

The remaining 184 MDRs involved MDRs received between May 1, 2020 and April 30, 2021. They included 0 deaths, 127 injuries, and 57 device malfunction reports. These 184 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. Three reports identified pediatric patients from 18.0 to 21.9 years old at the time of the event. These reports have been placed into age category of 18-21 years old, and included 3 injury MDRs.

TABLE 3: Overall event type distribution by patient age

| Event Type | Total MDR Count 5/1/2020 – 4/30/2021 | MDR Count by Patient Age (years) | | | |
|---|---|---|---|---|---|
| | | Pediatric (< 18) | Pediatric (18-21) | Adult (≥ 22) | Indeterminate (Age blank) |
| Death | 0 | 0 | 0 | 0 | 0 |
| Injury | 127 | 0 | 3 | 112 | 12 |
| Malfunction | 57 | 0 | 0 | 43 | 14 |
| Total MDR Count | 184 | 3 | | 155 | 26 |

**Comparison of Current Patient Event Type Information Previous Data**

Table 4 below compares the Event Type distribution for this analysis to that of prior years. The current period represents a 9% increase in injury MDR submissions and a 7% decrease in malfunction reports compared to the 2020 PAC presentation period. Pediatric MDR reports remained the same with 3 reports.

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 |
| Death | 0 | 1 | 0 | 0 |
| Injury | 285 | 184 | 117 | 127 |
| Malfunction | 150 | 120 | 61 | 57 |
| Total MDR Count | 435 | 305 | 178 | 184 |

**Patient Gender and Age Information**

In the 184 MDRs received from May 2020 to April 2021, 155 patients were noted as adult (≥22 years old) and 24 MDRs did not provide a patient age (indeterminate age reports). Three MDRs contained pediatric patients' ages that ranged from 18 to 21.3 years, with a mean age of 19.3 years. Of the three pediatric reports, two were for the same patient.

There were 164 MDRs, which noted the gender of the patient: 137 MDRs were identified as female (including 2 pediatric patients), and 27 MDRs were identified as male. The remaining 20 MDRs did not include the patient's gender. Individual review of the 20 reports narrative sections to determine gender identifiers (male or female, she or her, he or him, etc.) did not result in identifying additional female or male noted events, instead these reports identified the individual involved in the event only as "the patient".

**Time to Event Occurrence**

An analysis of the Time to Event Occurrence (TTEO) 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 91 MDRs (out of 184 MDRs) provided a valid event date or explant date, including the 3 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 (n=22) | 0 | 0 | 19 | 3 |
| 31 days - ≤ 1 year (n=34) | 2 | 1 | 31 | 0 |
| > 1 year – ≤ 5 years (n=68) | 0 | 0 | 66 | 2 |
| > 5 years (n=11) | 0 | 0 | 11 | 0 |
| Totals (N=135) | 2 | 1 | 127 | 5 |

**Characterization of the MDR Narratives of Pediatric Events from May 1, 2020 – April 30, 2021 as it relates to TTEO:**

A. TTEO between 31 days and ≤ 1 year of implant. (N=3)

- An 18-year-old male patient's INS implanted 9/7/2016 was explanted improperly in 2017, and had 2 suture anchors that were left in. The suture anchors were removed in clinic during two separate visits. The patient's symptoms resolved when the explant was completed 2/7/2017.
- A report from the same 18-year-old male patient with the event date unknown had a suspected infection. A specimen sample was cloudy, but the culture came back negative for infection. A physician explanted the device. It is unknown exactly when the site became red and swollen but it was 1-2 months before explant on 2/7/2017.
- A 21.9-year old female patient was admitted to the hospital due to abdominal pain and vomiting. The patient stated they felt 'something popped' where the INS is placed. Technical services advised the patient to reach the managing doctor and provided the number.

**Characterizations of the Time to Event Occurrences (TTEO) in the adult and indeterminate age populations from May 1, 2020 – April 30, 2021**

For the adult (N=127) and indeterminate age (N=5) populations with TTEO data, issues with the use of this device continue to 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", then "≤ 30 days" in the adult group. In comparison to last year's analysis of reports for these TTEO groups, the same types of 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 common complaint of pain continues to occur because of inappropriate stimulation/shocking as well as positioning/migration of the device or its components. The inappropriate stimulation/shocking, is often caused by patient device interaction problems, such as patient losing weight after implant; device battery/lead positions; or setting of the devices. Device reposition, battery or leads revision/replacement, or turning down the voltage setting relieve the problems in most cases.

There were 41 reports associated with complaints of pain and 31 reports that specified shocking. In one report, a patient complained of pain and burning in the clinic. Surgery was scheduled to explore the pocket. Fibrotic tissue was discovered due to lead wire contact with tissue. It was believed that the lead coating may have been missing causing the issue. It was noted there was no infection. Impedance checks and parameter changes were performed. It was noted that the leads had been cut from the stimulator and partially explanted. It was reported the issue was resolved at the time of the report.

Infection, migration, and erosion issues also continued to occur as in the previous year. Infection was specifically mentioned in 19 MDRs, with 16 being unspecified infection reports. These events typically occurred within the first three years of device placement with most of occurring in the first six months after device placement.

Infections associated with the device or component (i.e. "pocket", "lead", "INS" and "battery") were found in 19 MDRs, while one report mentioned a patient having sepsis in 2014. It was reported that in 2014 a patient was hospitalized and had to have their Enterra Device removed because the wires were wrapped around the patients small intestine.

Four reports noted lead erosion into the stomach or through the skin, and one report noted pocket erosion through the skin. The erosions occurred between one year and three years of implantation. In one report the impedance readings were normal at 520 Ohms, but the patient was still having nausea and vomiting symptoms. An esophagogastroduodenoscopy (EGD) was performed on 6/26/20 which discovered that the leads had migrated into the mucosa of the stomach. This was the reason for explant of the leads and INS on 6/30/20. The patient stated they had been rough

housing with their kids. The event was resolved and no further patient complications were reported.

As noted in the previous year, adult and indeterminate age patients continue to predominantly experience nausea and vomiting with decrease in therapeutic effectiveness.

12 MDRs discussed battery depletion, which led to patient complaints of "therapy effectiveness, decreased." These events continue to occur from 1 year after placement to 8 years, with typical resolution noted as reprogramming or replacement of the battery.

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

Table 6 below provides the most prevalent reported patient problem codes found in the MDRs reviewed during this year's analysis differentiated by patient age. The top reported patient problem is "Pain" (n=65), which is increased from the previous year analyses of (n=51) and is characterized as inappropriate stimulation/shocking/burning as well as cramping/discomfort and migration of the device or its component. "No Known Impact or Consequence to Patient and Clinical Signs and Symptoms " is ranked second (n=53), which increased from the previous year of (n=43). "Nausea and Vomiting" is ranked third (n=50), which increased from the previous year of (n=41). "Insufficient Information/ Complaint, Ill-Defined is ranked forth (n=42), which increased from the previous year (n=24). New patient codes in the current reporting year include: Gangrene (n=1), and Sepsis (n=1). Overall, this year's patient problem codes do not present significantly new or increased safety concerns as compared to prior analysis period.

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

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

| Patient Problem | Total Patient Problem Code in MDR | Total Patient Problem Code in MDR by Patient Age (years) | | | |
|---|---|---|---|---|---|
| | | Pediatric (< 18) | Pediatric (18 to 21) | Adults (≥ 22) | Indeterminate (Age blank) |
| Pain/ Discomfort/ Abdominal Pain/Muscle Spasms/Burning | 65 | 0 | 2 | 60 | 3 |
| No known impact or consequence to patient*** | 53 | 0 | 0 | 43 | 10 |
| Vomiting/Nausea | 50 | 0 | 1 | 44 | 5 |
| Electric Shock/Nerve Stimulation, Undesired | 34 | 0 | 0 | 30 | 4 |
| Unspecified Infection/ Gangrene/Sepsis | 29 | 0 | 0 | 27 | 2 |
| Therapeutic Response, Decreased/Paresis | 24 | 0 | 1 | 21 | 2 |
| Therapeutic Effects, Unexpected** | 16 | 0 | 1 | 11 | 4 |
| Weight changes | 8 | 0 | 0 | 6 | 2 |
| Malaise | 6 | 0 | 0 | 6 | 0 |
| Insufficient Information/Complaint Ill-Defined | 43 | 0 | 1 | 38 | 4 |
| Total Patient Problem Code Count | 327 | 0 | 6 | 285 | 36 |

*Note: The total MDR Occurrences does not equal the total MDR count since one MDR might have multiple patient problems.*
**MDRs coded with "Complaint, Ill-Defined" often included reports of nausea and/or vomiting.*

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

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

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

Table 7 below provides the most reported Device Problems for all MDRs differentiated by patient age. The top reported device problem codes are consistent as in the previous analysis period with "Adverse event without identified device or use problem" (n=53) ranking first, and "Insufficient information" (n=39) ranking the second. "Inappropriate shock" (n=32) continues to be ranked third and "Battery problem" continues to rank fourth (n=34). There was an increase in the use of code "High"/ "Low impedance"/ "Impedance issues" (n=28), which now ranks fifth, and "Migration or expulsion of device/ "Unstable" (n=27) dropped to the sixth rank code. There was an increase in the use of code "Electromagnetic Compatibility Problem/Electromagnetic Interference" (n=9) compared to prior analysis period.

The reports with "Adverse event without identified device or use problem" are related to patient issues in which the device is functioning or has no identified device problems, but the patient complained of ill-defined, pain, infection, or device intolerance issues. A review of reports found that the device problem code "Insufficient information" was commonly associated with a device not properly functioning but did not provide detailed information of the malfunction. Most of the corresponding patient problem codes were nausea, vomiting, and shocking sensation. Adjustments to the device voltage, its placement, and replacement of the leads or battery were interventions used for these patients.

The reports of "Inappropriate Shock" typically involved the position of device, or electromagnetic compatibility/interference. The device problem codes "Battery problem"/ "Premature Discharge of battery"/ "Low battery issue", and "High"/ "Low impedance"/ "Impedance issues"/ are associated with reports of battery problems or device high or low impedance issues. "Energy output problem"/ "Failure to deliver energy are related to nausea, vomiting, shocking, and decreased therapeutic effect issue; The reports of "Patient device interaction problem" are related to pain and positional shocking. Reprogramming, replace, or revision of device are interventions for these patients.

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

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

| Device Problem | Total Device Problem Code in MDR | Total Device Problem Code in MDR by Patient Age (years) | | | |
|---|---|---|---|---|---|
| | | Pediatric (< 18) | Pediatric (18 to 21) | Adults (≥ 22) | Indeterminate (Age blank) |
| Adverse event without identified device or use problem | 53 | 0 | 2 | 47 | 4 |
| Insufficient information | 39 | 0 | 1 | 33 | 5 |
| Inappropriate shock | 32 | 0 | 0 | 27 | 5 |
| Battery problem/ Premature Discharge of battery /Low/Battery issue | 34 | 0 | 0 | 32 | 2 |
| High/Low impedance/ Impedance issues | 28 | 0 | 0 | 23 | 5 |
| Migration or expulsion of device/Unstable | 27 | 0 | 0 | 24 | 3 |
| Electromagnetic compatibility issue/ Electromagnetic interference (EMI) | 9 | 0 | 0 | 9 | 0 |
| Break/Material deformation | 9 | 0 | 0 | 6 | 3 |
| Energy output problem/failure to deliver energy | 8 | 0 | 0 | 4 | 4 |
| Patient device interaction problem | 8 | 0 | 0 | 8 | 0 |
| Total Device Problem Code Count | 247 | 0 | 3 | 213 | 31 |

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

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

Table 8 identifies the MDR occurrences of the top patient problems and issues in pediatric patients only, in comparison to the prior analysis period's findings. As in the prior analysis period, the clinical events for the three pediatric MDRs found in this analysis also involve complaints of nausea, vomiting and pain. These complaints and device problems are most often due to device setting or battery and lead issues. Adjustments of the device settings, following up with treating physician, hospitalization, and request to explant the device were the noted interventions.

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

| Clinical Events | Occurrences in MDRs** 5/1/2020-4/30/2021 | Occurrences in MDRs** 5/1/2019 – 4/30/2020 | Occurrences in MDRs** 5/1/2018 – 4/30/2019 | Occurrences in MDRs** 5/1/2017 – 4/30/2018 |
|---|---|---|---|---|
| Nausea/Vomiting [Complaint ill- defined] | 1 | 1 | 6 | 15 |
| Therapeutic Response, unexpected/Paresis | 1 | 3 | 4 | 3 |
| Pain/Discomfort/ Abdominal pain/ Burning sensation | 2 | 2 | 3 | 6 |
| Electric Shock/Nerve Stimulation, Undesired/ [Inappropriate Electric Shock] | 0 | 1 | 3 | 3 |
| Infection | 0 | 1 | 2 | 0 |
| Therapeutic Effects, Unexpected | 1 | 0 | 0 | 0 |
| Insufficient Information/Complaint Ill-Defined | 1 | 0 | 0 | 0 |

*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 since one MDR might have multiple clinical events.

## Re-Interventions in Pediatric Patients from 5/1/2020 through 4/30/2021

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

TABLE 9: Re-interventions in pediatric patients* (5/1/2020-4/30/2021)

| Re-Interventions | Number of Re-Interventions | Causal Event |
|---|---|---|
| Replacement/Repositioning<br>• Device or Battery | 0 | • Shocking/burning<br>• Battery depletion |
| Explant<br>• Device or INS | 0 | • Infection<br>• Pain |
| Reprogramming/ Calibration | 0 | • Loss of therapeutic effect<br>• Shocking/jolting/burning |
| Hospitalization/Emergency room | 1 | • Infection<br>• Loss of therapeutic effect<br>• Pain/discomfort<br>• Vomiting/hematemesis |
| Surgery (gastrostomy) /Feeding tube | 0 | • Loss of therapeutic effect<br>• Nausea/vomiting/poor intake |
| Office follow-up treatment | 1 | • Loss of therapeutic effect<br>• Nausea/vomiting<br>• Shocking |

*Note that the total counts do not equal the number of MDRs since one MDR might have multiple noted re-interventions.
** Temporary involves the mention of temporary removal of the device and has no comment of actual replacement in the report.

## MDR Review Conclusions

- There were 3 pediatric MDRs (out of 184) submitted for the Enterra Therapy System between May 1, 2020 and April 30, 2021. The pediatric MDRs were patient injury events.

- The Time to Event Occurrence (TTEO) was calculated for 91 reports (out of 184) MDRs based on the available information contained in the reports, including all three pediatric reports. Review of the pediatric reports with TTEO identified all 3 pediatric events occurring between 31 days - ≤ 1 year. Two of the events occurred in the same patient that had the Enterra device explanted. A second 21.9-year old female patient was

admitted to the hospital due to abdominal pain and vomiting.

- The reported pediatric patient problems are similar to last year's analyses and include "Pain", "Nausea/Vomiting" and "Decreased Therapeutic Response".

- The number of reported pediatric device problems is similar to last year's analysis.

- The patient problems and device problems observed among pediatric patients were similar to those observed in adult patients.

- The types and number of adverse events reported in the current reporting period are similar to the previous reporting period.

# LITERATURE REVIEW

## 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 in 2014, 2015, 2016, 2017, 2018, 2019 and 2020. 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?

The search was limited to studies published since the last PAC meeting update (May 1, 2020 to April 30, 2021), in human subjects, and in the English language. This search yielded a total of 97 citations (17 in PubMed, 73 in Embase, and 7 in MDRs). After a review of titles, abstracts, and selected full texts, 7 articles were selected for full review and assessment as shown in "Figure 1. Article Retrieval and Selection" below.

## Methods

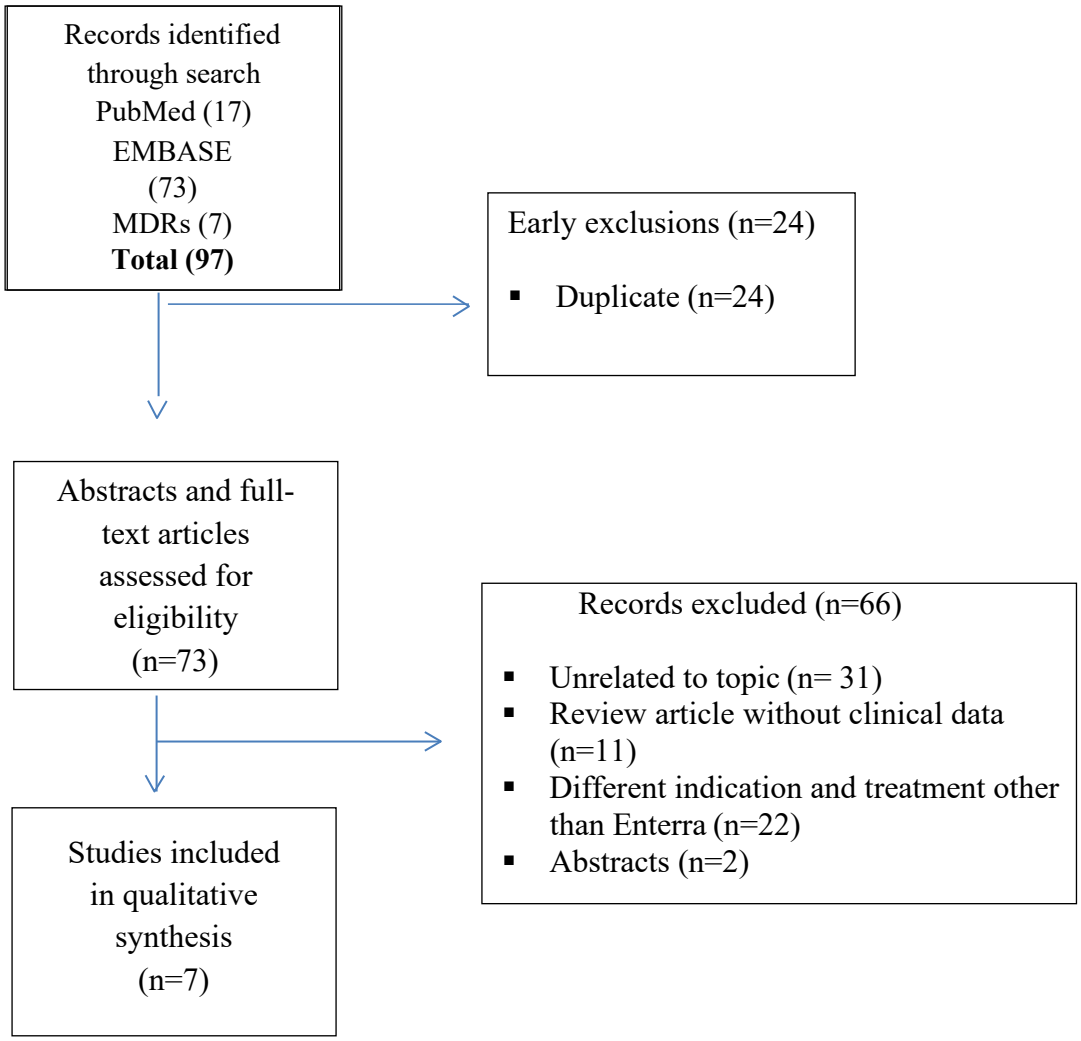
On June 10, 2021, searches in PubMed, Embase and from MDRs were performed using the following search terms:

- 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 neuromodulation"
  Filters: Publication date from 2020/05/01 to 2021/04/30; Humans; English; clinical study, clinical trial, clinical trial, Phase III, control clinical trial, randomized controlled trial.

- 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 [humans]/lim AND [2020-2021]/py AND [english]/lim AND ([young adult]/lim OR [adult]/lim OR [aged]/lim) AND [1-5-2020]/sd NOT [1-5-2021]/sd.

- MDRs
  Karen M. Taylor, BSN, RN, MDR Analyst found seven (7) titles/citations included in MDRs; one of them was excluded because it was out of date range; published before May 1, 2020 (Feb 21, 2020) and was already included in the previous review and PAC presentation of 2020.

Figure 1. Article Retrieval and Selection



**Summaries from Pertinent Articles**

1. **Thompson JS, Hewlett A, Lyden E, Scott JR, McBride C *(2020) Patient factors influence surgical options in gastroparesis. Am J Surg. 2020. doi: 10.1016/j.amjsurg.2020.02.022. MDR # 2182207-2020-00178**

Introduction:
Patient selection for the diverse surgical procedures for gastroparesis remains poorly defined.

Methods:
This is a retrospective study. The aim was to evaluate how patient factors have determined the surgical approach to gastroparesis. Ninety-five (95) patients undergoing 105 surgical procedures for gastroparesis were reviewed. Patient factors were compared across six (6) surgical procedures: 36 gastric neurostimulator (GES), 13 pyloroplasty, 18 neurostimulator plus pyloroplasty, 18 sleeve gastrectomy, 6 gastric bypass and 4 gastrectomy. Global symptom severity was determined preoperatively and at last follow-up.

Results:
There were significant differences in etiology, BMI and gastroesophageal reflux across the various operations. Overall, there were 83% female patients and 74% patients less than fifty years of age. Patients undergoing pyloroplasty and gastrectomy were more likely to have a postsurgical etiology ($p < 0.05$). Patients undergoing sleeve gastrectomy and gastric bypass were more likely to have BMI >35 ($p < 0.05$). Those undergoing sleeve gastrectomy were less likely to have gastroesophageal reflux preoperatively ($p <0.05$). There was no difference in preoperative clinical stage across the procedures. Patient factors influence choice of procedure in the surgical treatment of gastroparesis. Etiology of gastroparesis, BMI >35 and gastroesophageal reflux are important determinants.

Reported Adverse Events:
Four (11%) patients that underwent GES alone underwent a subsequent pyloroplasty. Six devices had been replaced due to battery failure. Six devices were removed for complications and/or failure to improve symptoms.

Conclusion:
Patient factors influence choice of procedure in the surgical treatment of gastroparesis. Etiology of gastroparesis, BMI >35 and gastroesophageal reflux are important determinants. Careful attention should be placed when comparisons between treatments are carried out because patient factors introduce selection bias.

Note:
This article was published on February 16, 2020. Although it is out of date range for this literature review, it was not excluded because it was not part of the previous PAC Executive Summary.

2. **Hedjoudje, Abdellah; Huet, Emmanuel; Leroi, Anne-Marie; Desprez, Charlotte; Melchior, Chloé; Gourcerol, Guillaume (2020) Efficacy of gastric electrical stimulation in intractable nausea and vomiting at 10 years: A retrospective analysis of prospectively collected data. Neurogastroenterology and motility. 2020, Vol.32 (11). ISSN: 1350-1925, 1365-2982; DOI: 10.1111/nmo.13949. MDR # 2182207-2021-00097 00178.**

Introduction:
Gastric electrical simulation has been shown to relieve nausea and vomiting in medically refractory patients. Efficacy of gastric electrical stimulation has been reported mostly in short-term studies, but none has evaluated its efficacy beyond 10 years after implantation.

Methods
This is a retrospective study. Patients implanted at our center for medically refractory severe and chronic nausea

and/or vomiting were evaluated before and over 10 years after implantation using symptomatic scale and quality of life (GIQLI) score. Improvement was defined as a reduction of more than 50% in vomiting frequency.

Results
A total of 50 patients were implanted from January 1998 to December 2009. Among them, 7 were explanted due to a lack of efficacy and/or side effects, 2 died, and 4 were lost to follow-up. Mean follow-up was 10.5 ± 3.7 years. In intention-to-treat analysis, 27/50 (54%) patients reported an improvement. Beyond 10 years, an improvement in early satiety (3.05 vs 1.76, p<0.001), bloating (2.51 vs 1.70, P=0.012), nausea (2.46 vs 1.35, P= 0.001), and vomiting (3.35 vs 1.49 P<0.001) scores were observed. Quality of life improved over 10 years (GIQLI score: 69.7 vs. 86.4, P=0.005) and body mass index (BMI: 23.4 vs. 26.2 kg/m2; P=0.048).

Reported Adverse Events:
At the end of follow-up in 2018, 5 patients were explanted due to device inefficacy and 2 patients were explanted due to side effects (pain).

Conclusions
Gastric electrical simulation is effective in the long-term in patients with medically refractory nausea and vomiting, with an efficacy of 54% at 10 years on an intention-to-treat analysis. Other long-term observational studies are warranted to confirm these results.

3. **Kim, D, Gedney, R, Allen, S *et al.* Does etiology of gastroparesis determine clinical outcomes in gastric electrical stimulation treatment of gastroparesis?. *Surg Endosc* (2020). https://doi.org/10.1007/s00464-020-07928-3https://doi.org/10.1007/s00464-020-07928-3. MDR # 2182207-2021-00098.**

Introduction:
Background Gastroparesis is a condition characterized by impaired gastric motility that may result in weight loss and malnutrition. There have been promising studies demonstrating improvement in symptoms after gastric electrical stimulation (GES) implantation for medically refractory gastroparetics. With the heterogeneous population of gastroparetics, the aim of this study was to assess if etiology correlated with response to GES.

Methods:
A retrospective review and analysis were performed on patients who underwent GES over a 10-year period at a single institution. Each patient was stratified into an etiological subset (diabetes, idiopathic, post-surgical). Patients were compared by demographics, medical and surgical history, subsequent GES explantation vs continued therapy, need for supplemental nutrition postoperatively, weight gain, weight loss or weight maintenance, and readmission rates.

Results:
One hundred and eighty-three (183) patients underwent GES from 2005 to 2015; 50% were diabetic (n = 91), 42% idiopathic (n = 76), and 9% postsurgical (n = 16). Diabetic patients (DM) demonstrated the highest likelihood of continued therapy compared to post-surgical (PS) and idiopathic patients (ID) (54.7% vs 9.5% vs 35.8%, respectively, $p < 0.05$). DM patients saw a greater incidence of weight gain > 4 kg, compared to PS and IS patients (67.6% vs 8.1% vs. 24.3%, respectively, $p < 0.05$). ID patients were most likely to have it removed compared to DM and PS patients (65.7% vs 28.6% vs 5.7%, respectively, $p = < 0.05$). PS patients were least likely to have their GES removed. They were also least likely to utilize supplemental nutrition compared to DM and ID (9.4% vs 49.1% vs 41.51%, respectively, $p < 0.05$).

Reported Adverse Events:
Eighteen (18) patients had their device removed due to continued symptoms despite GES implantation (9.8%). Nine (9) patients had their device removed due to pain associated with the stimulator (4.9%). Five (5) patients had their device removed due to an infection (2.7%).

Conclusions: Patients with gastroparesis had different clinical outcomes after GES therapy based on underlying etiology. By gaining a better understanding of the effects of GES, it can be offered to the appropriate patient.

4. **Marowski, S., Xu, Y., Greenberg, J.A. et al. Both gastric electrical stimulation and pyloric surgery offer long-term symptom improvement in patients with gastroparesis. Surg Endosc (2020). https://doi.org/10.1007/s00464-020-07960-3. MDR # 2182207-2021-00105**

Introduction:
Background Gastroparesis (GP) is hallmarked by nausea, vomiting, and early satiety. While dietary and medical therapy are the mainstay of treatment, surgery has been used to palliate symptoms. Two established first-line surgical options are gastric electrostimulation (GES) and pyloric procedures (PP) including pyloroplasty or pyloromyotomy. We sought to compare these modalities' improvement in Gastroparesis cardinal symptom index (GCSI) subscores and potential predictors of therapy failure.

Methods:
All patients undergoing surgery at a single institution were prospectively identified and separated by surgery: GES, PP, or combined GESPP. GCSI was collected preoperatively, at 6 weeks and 1 year. Postoperative GCSI score over 2.5 or receipt of another gastroparesis operation were considered treatment failures. Groups were compared using Pearson's chi-squared and Kruskal–Wallis one-way ANOVA.

Results:
Eighty-two (82) patients were included: 18 GES, 51 PP, and 13 GESPP. Mean age was 44, BMI was 26.7, and 80% were female. Preoperative GCSI was 3.7. The PP group was older with more postsurgical gastroparesis. More patients with diabetes underwent GESPP. Preoperative symptom scores and gastric emptying were similar among all groups. All surgical therapies resulted in a significantly improved GCSI and nausea/vomiting subscore at 6 weeks and 1 year. Bloating improved initially but relapsed in the GES and GESPP group. Satiety improved initially but relapsed in the PP group. Fifty-nine (72%) had surgical success. Ten (10) underwent additional surgery (7 crossed into the GESPP group, 3 underwent gastric resection). Treatment failures had higher preoperative GCSI, bloating, and satiety scores. Treatment failures and successes had similar preoperative gastric emptying.

Reported Adverse Events:
When determining clinical success of surgery, 59 of 82 patients (71.9%) were deemed a clinical success based upon symptom scores and no need for further surgery for gastroparesis. Of those who experienced clinical failure, thirteen were considered treatment failures using a GCSI of greater than 2.5 in the postoperative period. ten (12.2%) had elevated postoperative GCSI and also underwent additional surgery for gastroparesis.

Conclusions:
Both gastric electrical stimulation and pyloric surgery are successful gastroparesis treatments, with durable improvement in nausea and vomiting. Choice of operation should be guided by patient characteristics and discussion of surgical risks and benefits. Combination GESPP does not appear to confer an advantage over GES or PP alone.

5. **Alex Pontikos, Priyanga Jayakumar, Cristian Rios Perez, Heather Barker, Michael Hughes, Xiu Yang, Mostafa Fraig, Abigail Stocker, Lindsay McElmurray, Christina Pinkston, Abell Thomas (2020) Gastric Electrical Stimulation Has an Effect on Gastric Interstitial cells of Cajal (ICC) That is Associated With Mast Cells. Cureus 12(11): e11458. doi:10.7759/cureus.11458. MDR # 2182207-2021-00273.**

Introduction:
Gastric electrical stimulation (GES) is an emerging therapy for gastric motility disorders, showing improvement of gastroparesis related symptoms in previous studies. Interstitial cells of Cajal (ICC) and mast cells have been shown to have a relevant role in gastroparesis pathogenesis. However, the exact effects of GES in those cells is relatively unknown.

Methods:
Full thickness biopsies (FTBx) of 20 patients with refractory gastroparesis were obtained at the time of GES placement and repeated when the device was exchanged (mean of 22.5 months between biopsies). A patient-reported outcomes survey was obtained during each office visit during this period. All biopsies were stained with cluster of differentiation 117 (CD117), S100, and mast cell tryptase antibodies and were analyzed.

Results:
Half of the patients had a significant increase of ICC during the repeated biopsy compared with baseline (p=0.01) and the other half had significant decrease in ICC levels (p=0.006) but there was no noticeable difference in mast cells counts at baseline between groups. Mast cells analysis was performed in two different groups depending on ICC change from the baseline biopsy (CD117 increase vs CD117 decrease). There was only a significant increase of mast cells count within the CD117 worsened ICC group (p=0.007).

Reported Adverse Events:
All patients had FTBX with GES placement for symptoms of gastroparesis uncontrolled with the conventional dietary and medication recommendation (the initial system) and then subsequently had another FTBX (the repeat system) when GES was replaced for technical reasons (usually symptoms of electrical shocking).

Conclusion:
No significant increase in the number of mast cells count seen in patients who received a GES may indicate an improvement in overall inflammation in patients with refractory gastroparesis after GES placement.

6. **Guillaume Gourcerol, Benoit Coffin, Bruno Bonaz, Hélène Hanaire, Stanislas Bruley Des Varannes, Frank Zerbib, Robert Caiazzo, Jean Charles Grimaud, François Mion, Samy Hadjadj, Paul Valensi, Lucine Vuitton, Guillaume Charpentier, Alain Ropert, Romain Altwegg, Philippe Pouderoux, Etienne Dorval, Michel Dapoigny, Henri Duboc, Pierre Yves Benhamou, Aurélie Schmidt, Nathalie Donnadieu, Philippe Ducrotte, Bruno Guerci, and ENTERRA Research Group (2021) Impact of Gastric Electrical Stimulation on Economic Burden of Refractory Vomiting: A French Nationwide Multicentre Study. Clinical Gastroenterology and Hepatology 2021. https://doi.org/10.1016/j.cgh.2020.11.011 Article in Press. MDR # 2182207-2021-00322.**

Introduction:
Medico-economic data of patients suffering from chronic nausea and vomiting are lacking. In these patients, gastric electrical stimulation (GES) is an effective, but costly treatment. The aim of this study was to assess the efficacy, safety and medico-economic impact of Enterra therapy in patients with chronic medically refractory nausea and vomiting.

Methods:
Data were collected prospectively from patients with medically refractory nausea and/or vomiting, implanted with an Enterra device and followed for two years. Gastrointestinal quality of life index (GIQLI) score, vomiting frequency, nutritional status, and safety were evaluated. Direct and indirect expenditure data were prospectively collected in diaries.

Results:
Complete clinical data were available for 142 patients (60 diabetic, 82 non-diabetic) and medico-economic data were available for 96 patients (36 diabetic, 60 non-diabetic), 24 months after implantation. GIQLI score increased by 12.1 – 25.0 points ($p < 0.001$), with a more significant improvement in non-diabetic than in diabetic patients (D15.8 – 25.0 points, $p < 0.001$ versus 7.3 – 24.5 points, $p < 0.027$, respectively). The proportion of patients vomiting less than once per month increased by 25.5% ($p < .001$). Hospitalizations, time off work and transport were the main sources of costs. Enterra therapy decreased mean overall healthcare costs from 8,873 US$ to 5,525 US$ /patient/year ($p < 0.001$), representing a saving of 3,348 US$ per patient and per year. Savings were greater for diabetic patients (4,096 US$

/patient/year) than for nondiabetic patients (2,900 US$ /patient/year).

Reported Adverse Events:
Thirty-nine (39) patients (27.5%) experienced gastrointestinal disorders, 3 patients (21.1%) experienced pain at the implantation site, 16 patients (11.3%) experienced a pocket infection.

Conclusions:
Enterra therapy is an effective, safe and cost-effective option for patients with refractory nausea and vomiting. ClinicalTrials.gov Identifier: NCT00903799.

7. **Sarosiek I, Davis BR, Espino K, Sarosiek J, Vega N, Dominguez KA, et al. Lessons learned from 8 years of follow up of drug refractory gastroparetic patients who underwent simultaneous implantation of gastric electrical stimulation system and surgical pyloroplasty. Gastroenterology. 2020;158(6): S-626-S-7. doi: 10.1016/S0016-5085(20)32265-4. http://dx.doi.org/10.1016/S0016-5085(20)32265-4.**

Introduction:
Gastric electrical stimulation (GES) therapy is utilized by certain centers based on its HDE status since March of 2000. GES does not improve gastric emptying (GE) in gastroparetic (GP) patients and this unmet need triggered our interest to supplement implantation of GES with simultaneously performed pyloroplasty (PP) in qualified patients. The aim of our investigation was to assess the long-term symptoms outcome and gastric emptying results in all our drug refractory GP patients undergoing GES and surgical PP.

Methods:
Overall 53 GP drug refractory patients (39 diabetics (DM) mean 16.5±5.6 years of diabetes, 14 idiopathic (ID), underwent surgical implantation of GES together with Heineke-Mikulicz PP. GP total symptoms score (TTS) of encompassing 6 components: vomiting, nausea, early satiety, bloating, fullness and epigastric pain, was assessed with 5-point Likert scale, a standardized (egg beater) GE 4-hour scintigraphy test was performed before surgery as well as at the last follow up visit.

Results:
Fifty-three (53) patients, mean age 47 (range 20-78); 38F; with mean 5.5 (range 1-20) years of GP symptoms were enrolled, and the mean follow up is 42 (range 6-89) months. The TTS improved a mean of 56% at last follow up compared to before surgical intervention (Table 1). Overall, 50% of GP patients improved their symptoms by ≥70% after GES+PP. GE tests were available from 39 GP at their last follow up visit. GE results showed 74% (range 44-100) retention at 2 hour and 48% (13-100) at 4 hour before the therapies, and these results improved significantly to 48% (3-98) at 2, and 19% (0-68) at 4 hour, with 70% of patients actually normalizing their GE at 2 hour, and 45% at 4 hour (< 10% retention) after GES +PP surgeries (Table 2). Weight was stable with mean value of 149 (SD±30) lbs before and 150 (SD±17) lbs after. Mean HA1c levels were similar, 9.0 vs.8.8.

Reported Adverse Events:
There were no unanticipated SAEs or technical problems reported by patients during their participation in this study.

Conclusions:
(1) GP patients of diabetic and idiopathic etiologies not responding to all previous therapies, who were treated by combining GES and surgical PP show significant symptomatic improvement ≥70%, and significantly accelerated and often normalized GE (60%), sustained over a long term follow up of mean 3.5 years. (2) These results indicate that this combination surgery provides the best long term follow up outcome, both subjective and objective, which has been previously reported for refractory GP patients.

Table 1

| | Baseline Symptoms | Follow Up Symptoms | P value |
|---|---|---|---|
| Vomiting | 3.2 | 1.4 | <0.001 |
| Nausea | 3.7 | 1.5 | <0.001 |
| Early Satiety | 3.2 | 1.3 | <0.001 |
| Bloating | 2.9 | 1.4 | <0.001 |
| Fullness | 3.2 | 1.4 | <0.001 |
| Epigastric Pain | 2.6 | 1.1 | <0.001 |
| Total Symptoms Score (mean TSS) | 17.9 (3.4) | 7.9 (1.3) | <0.001 |

Table 2

| | 1HR | 2HR | 3HR | 4HR |
|---|---|---|---|---|
| Baseline | 84.9 | 74.3 | 60.6 | 47.3 |
| Follow Up | 64.2 | 45.5 | 30.5 | 17.5 |
| P value | <0.001 | <0.001 | <0.001 | <0.001 |

**Literature Review Results**

In the seven articles selected for this review, the studies may have included pediatric or adolescent patients. These papers were included in this review to be as inclusive as possible, given the limited literature on the Enterra device. Because these studies included adult subjects along with possible pediatric subjects, it is not possible to determine whether the safety results or the probable benefits derived by the mixed cohort were experienced specifically by pediatric subjects.

**a. Probable Benefit Results found in the Literature**

Gastric electric stimulation has short-term and long-term (10 years) effectiveness significantly reducing medically refractory nausea and vomiting (**Hedjoudje et al 2020, Marowski et al 2020, Sarosiek, et al 2020**), and as **Gourcerol et al 2020** reported, it is cost-effective. **Pontikos et al 2020**, stated that interstitial cells of Cajal (ICC) and mast cells have been shown to have a relevant role in gastroparesis pathogenesis. No significant increase in the number of mast cells count were seen in patients who received a GES, which may indicate an improvement in overall inflammation in patients with refractory gastroparesis after GES placement. **Sarosiek et al 2020**, found that GP patients of diabetic and idiopathic etiologies not responding to all previous therapies, and who were treated by combining GES and surgical PP, showed significant symptomatic improvement, ≥70% had significantly accelerated and often normalized GE (60%).

**b. Safety Results found in the Literature**

**Hedjoudje et al, 2020** reported 10% explants due to device inefficacy and 4% were explanted due to side effects (pain). **Kim et al, 2020** reported 2.7% of patients had their device removed due to an infection. These authors agree that clinical outcomes after GES therapy are based on underlying etiology. **Marowski et al, 2020** reported that patients experiencing clinical failure, 16% were considered treatment failures using a GCSI of greater than 2.5 in the postoperative period while 12.2% had elevated postoperative GCSI and underwent additional surgery for gastroparesis. These authors concluded that the combination GESPP does not appear to confer an advantage over GES or PP alone. **Gourcerol et al, 2021,** in a study of 142 patients, found 27.5% patients experienced gastrointestinal disorders, 21.1% experienced pain at the implantation site, and 11.3% a pocket infection. However, since these are expected adverse events for this type of patients, the authors concluded that "*Enterra therapy is an effective, safe and cost-effective option for patients with refractory nausea and vomiting.*" **Sarosiek et al 2020**, found no unanticipated SAEs in their 53 patient study. GP patients of diabetic and idiopathic etiologies not responding to all previous

therapies, who were treated by combining GES and surgical PP, showed significant symptomatic improvement ≥70%, and significantly accelerated and often normalized GE (60%), sustained over a long term follow up of mean 3.5 years. These results indicate that this combination provides the best long term follow up outcome, which has been previously reported for refractory GP patients.

## c. Critical Assessment of the Literature

The current systematic literature review found seven (7) pertinent articles including a total of 625 patients treated with Enterra. All of articles provide evidence of the probable benefit of Enterra reducing gastroparesis symptoms. Device-related adverse events included gastrointestinal disorders, abdominal wall pain at the implantation site, infections at the abdominal pouch level and hematoma. There were approximately 10% of patients in which the device-related adverse events were serious enough to prompt device removal.

The results of this systematic literature review should be interpreted with consideration of its key limitations. First, our review only identified seven (7) articles, and it could not be confirmed that these studies included pediatric patients (< 22 years-of-age) because no age ranges were reported. The Thompson et al (2020) article was published before May 1, 2020; however, the paper was included in this review to be as inclusive as possible, given the limited literature on Enterra. Secondly, there are study design limitations such as retrospective study design in three of the studies, lack of randomization, and unknown sample size for pediatric patients.

### Literature Review Conclusion

The studies found in this literature review suggest probable benefits of Enterra with respect to improvement in long-term gastroparesis symptoms. Despite the reduction of symptoms, some patients with gastroparesis who are implanted with Enterra may experience device-related adverse events that require additional surgery. The findings of this systematic literature review should be interpreted with caution considering the insufficient evidence reported in terms of small number of articles, and with an unknown sample size of pediatric patients treated with the Enterra System. These factors limit our ability to make any firm conclusions about the probable benefits and safety of Enterra in the pediatric population. Although it is difficult to determine if these findings are consistent with results of the Enterra systematic literature reviews presented at the previous PAC meetings, the current findings do not raise safety concerns and support the probable benefit of this device.

## 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 2021.

•Annual distribution number
•Literature review
• MDR review

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