FDA Executive Summary

Prepared for the
March 23, 2018 meeting of the
FDA's Pediatric Advisory Committee

H150003
Flourish™ Pediatric Esophageal Atresia Device

TABLE OF CONTENTS

I. INTRODUCTION

In accordance with the Pediatric Medical Device Safety and Improvement Act this review can advise the Food and Drug Administration (FDA) on potential safety concerns associated with the use of this device in children. This executive summary will include postmarket follow-up of the premarket clinical study, the peer-reviewed literature associated with the device, and postmarket medical provides a safety update based on the postmarket experience since approval in 2017. The purpose of this review is to provide the Pediatric Advisory Committee with postmarket safety data, so the committee device reporting (MDR) for adverse events.

II. INDICATIONS FOR USE

The Flourish Pediatric Esophageal Atresia Device is indicated for use in lengthening atretic esophageal ends and creating an anastomosis with a non-surgical procedure in pediatric patients, up to one year of age with esophageal atresia without a tracheoesophageal fistula (TEF) or in pediatric patients up to one year of age for whom a concurrent TEF has been closed as a result of a prior procedure. This device is indicated for atretic segments < 4cm apart.

The indication for use statement has been modified from that granted for the HUD designation. The HUD designation was "for lengthening atretic esophageal ends and creating an anastomosis with a non-surgical procedure in pediatric patients, up to one year of age with esophageal atresia without a currently existing tracheoesophageal fistula (TEF), or for whom a concurrent TEF has been closed as a result of a prior procedure." It was modified for the HDE approval to include the device trade name and specify that atretic segments must be < 4cm apart.

DISEASE CONDITION

Esophageal atresia (EA) is a developmental arrest of the esophagus resulting in the absence of normal esophageal lumen The overall incidence of EA/Tracheoesophageal fistula (TEF) ranges from 1/2500 to 1/4500 live birthsFive types of EA, with and without concurrent TEF, are recognized. Infants usually present with excessive oral secretions, feeding intolerance, and/or respiratory difficulties which necessitates suctioning and feed through gastrostomy tube. Morbidity/mortality is dependent on associated conditions; EA/TEF are conditions commonly found in patients with VACTERL syndrome (vertebral, anal, cardiac, tracheal, esophageal, renal, limb) and CHARGE association (coloboma, heart, atresia, choanal, retarded growth, genital hypoplasia, ear deformities).

Current standard of care includes surgical repair via thoracotomy or thoracoscopy to create an anastomosis. If this is unsuccessful, colonic, gastric, or jejunal interposition are options.

III. BRIEF DEVICE DESCRIPTION

The Flourish Pediatric Esophageal Atresia Anastomosis Device consists of an oral/esophageal catheter and a gastric catheter. The oral/esophageal catheter is a 10 Fr two-

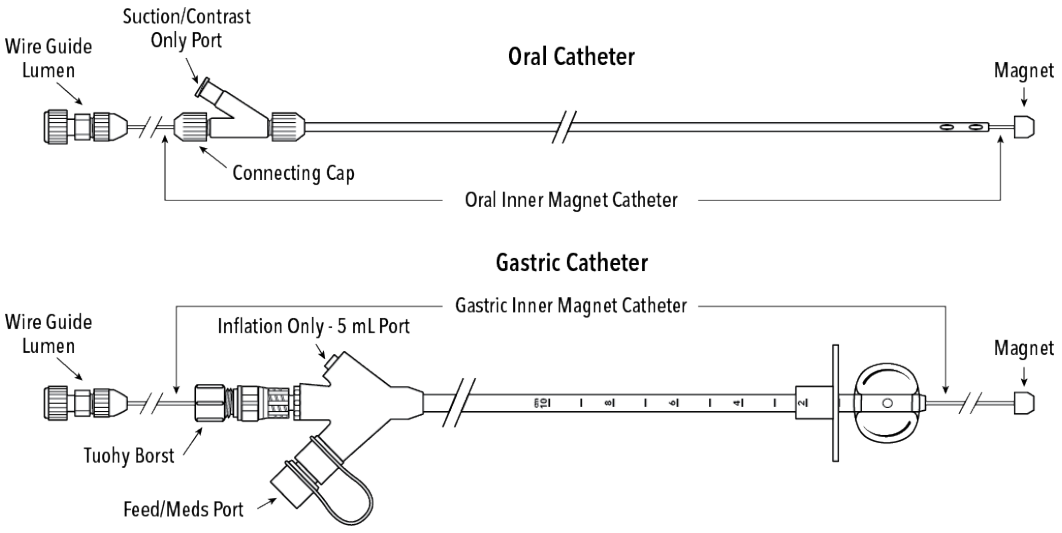
lumen catheter. One lumen is for injection of contrast to confirm anastomosis; the other is for suction of saliva.

The gastric catheter is a modified two-lumen 18 Fr/ 5 cc balloon retention catheter. One lumen is for balloon inflation/deflation. The second lumen is modified by the addition of the gastric magnet catheter, essentially creating a lumen within a lumen. This modified arrangement allows for initial placement of a wire to guide introduction of the gastric magnet catheter assembly. Once the wire guide is removed from the gastric magnet catheter, flushing can occur through this created lumen or through an added accessory lumen.

Feed is delivered through the original accessory feed port adjacent to the adapted central port. The inflated balloon holds 5 mL of liquid.

The distal end of each of the internal catheters is fitted with a bullet-shaped neodymium iron boron (NdFeB) magnet, which features a central hole for insertion of up to a 0.038-inch guide wire. When the two catheters are aligned tip to tip the magnets have opposite polarities; thus attracting each other. They are cylindrically shaped and have a diameter of 6.35 mm. Each magnet catheter is 56.5" in length. Figure 1 illustrates the complete device.

Figure 1- Flourish Pediatric Esophageal Atresia Anastomosis Device:



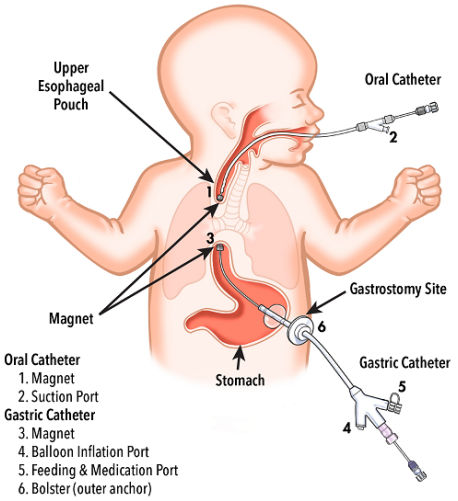
Principles of Operation

In a candidate infant, the distance between the atretic segments is assessed under fluoroscopy using metal probes. After identification of the pouches, the oral/esophageal catheter is inserted orally and advanced until the magnet is located at the distal end of the upper pouch. The gastric catheter is inserted over a wire guide, under fluoroscopy through a mature stoma and advanced until the magnet is located at the distal end of the lower pouch. The gastric catheter is secured to the stomach wall internally with a balloon and externally

with a bolster (Figure 2 - Flourish Pediatric Esophageal Atresia Anastomosis Device Placement, below).

Within three to thirteen days, the traction caused by the magnets allows the esophageal sacs to approximate. Daily biplane chest radiographs are taken to assess the distance between magnets. Once approximated, the surrounding tissues grow together while the tissue between the magnets undergoes necroses, causing development of an anastomosis, thereby creating a connected passage from mouth to stomach.

Once an anastomosis has been confirmed through fluoroscopy, the magnets are removed. The proximal end of the oral/esophageal inner magnet catheter is cut. A new wire is introduced through the oral/esophageal inner magnet catheter through the newly formed anastomosis and exits through the gastrostomy port. The oral/esophageal catheter is pushed distally toward the stomach until magnets are in the stomach, below the anastomosis. Then, the oral/esophageal inner magnet catheter is gently pushed and the gastric catheter is pulled until the system exits from gastrostomy site, thus removing the gastrostomy tube, oral/esophageal and gastric inner magnet catheters and the magnet pair as a unit. A new orogastric tube or nasogastric tube is placed for one to three days.



IV. REGULATORY HISTORY

Flourish™ Pediatric Esophageal Atresia Device received designation as a Humanitarian Use Device (HUD Designation) on October 28, 2010, and on May 12, 2017, the HDE application was approved by the Center for Devices and Radiological Health (CDRH) of the Food and Drug Administration.

V. POSTMARKET DATA: ANNUAL DISTRIBUTION NUMBER

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.

As stated in section 520(m)(8) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), the agency's Pediatric Advisory Committee will annually review all HUDs intended for use in pediatric patients that are approved on or after September 27, 2007, to ensure that the HDE remains appropriate for the pediatric populations for which it is granted.

The table below provides the number of device components distributed by the firm for the calendar year 2017 in the United States

Table 1. Annual Distribution Number

Calendar Year (Jan - Dec)	Total Sales
2017	0

POSTMARKET DATA: ADDITIONAL DATA

There were five emergency use cases, one had to undergo serial dilations and at a year and a few months, had a recalcitrant stricture, one required multiple dilations and three months post anastomosis was receiving training in swallowing and speech, one had no further treatment due to need for ventilator support for a pre-existing congenital anomaly, one had serial dilations and a subsequent esophageal stent, and one required surgery to correct an undiagnosed TEF.

VI. POSTMARKET DATA: POST-APPROVAL STUDY (PAS)

PAS Conditions of Approval:

The Flourish device was approved on May 12, 2017 with the following condition of approval regarding the PAS:

OSB Lead HDE Post-Approval Study – Flourish Post-Approval Study: The Office of Surveillance and Biometrics (OSB) will have the lead for studies initiated after device approval. On April 14, 2017 (by interactive review e-mail), you agreed to conduct a post-approval study as follows:

New Enrollment PAS for the Flourish Pediatric Esophageal Atresia Magnetic Device: The study objective is for continued evaluation of device safety and probable benefit after device approval. This is a prospective, single-arm, new enrollment observational study conducted in a minimum of 15 sites, including 1 site in the United States. A minimum of 20 subjects will be followed for 2 years after treatment with the Flourish Pediatric Esophageal Atresia Magnetic Device. The frequency of follow-up assessments will be consistent with the standard of care. The primary safety endpoint is the rate of the following: stricture at the anastomotic site leading to the need for intervention; peri-anastomotic leaks; and other adverse events and/or complications potentially related to the device or procedure (including, but not limited to: GERD, tracheomalacia, esophageal dysmotility, and/or recurrent asthma or pulmonary infections). The secondary endpoint (for evaluation of probable benefit) is successful anastomosis formation, defined as creation of a lumen connecting the upper esophageal pouch to the lower esophageal pouch as demonstrated by union of the device magnets and an esophagram showing connected flow of contrast agent. Descriptive analyses will be presented for all study endpoints.

PAS Protocol

The PAS study protocol has not yet been approved. As of January 8, 2018, the protocol is under review by FDA.An approved protocol is expected by the end of April 2018.

PAS Study Status

The PAS is expected to begin soon after approval of the PAS study protocol.

Systematic Literature Review on the Safety and Probable Benefit of Flourish in the Pediatric Population

Purpose
To evaluate the safety and probable benefit of the Flourish device for esophageal atresia with or without tracheoesophageal fistula in the medical literature.

Methods
On November 30, 2017, a search was conducted using the PubMed and EMBASE databases with the following search terms:

(Flourish OR magnet*) AND ("esophageal atresia" OR (“trachea-esophageal fistula” OR “tracheoesophageal fistula” OR TEF) OR “magnetic compression anastomosis” OR “short gap atresia”)

The search retrieved articles published through November 30, 2017. There was no early time restriction because a literature review was not previously conducted during Humanitarian Device Exemption (HDE) review for approval of the Flourish device.

To determine the eligibility of the articles for inclusion, the titles and abstracts were first screened, and then relevant full text articles were screened, selected, and reviewed for data extraction and synthesis.

Our search strategy generated 418 unique records after de- duplication. Of these, 8 articles were retained after screening titles and abstracts, and 4 were retained for qualitative synthesis after full text review (Figure 1).

Results

The four articles included in this assessment comprise of case reports/series, originating from the United States (n=2) and Argentina (n=2), and were published from 2009 to 2016, before the approval date for Flourish. Of the four articles, three provided supporting clinical evidence for the HDE approval of Flourish. [1-3] The sample sizes reported in the articles ranged from 1 to 17, and included patients aged 23 days – 11 years who underwent magnetic compression anastomosis (MCA) for esophageal atresia with/without tracheoesophageal fistula (n=12), esophageal stenosis (n=5), rectocolonic stenosis (n=2), and gastric outlet obstruction (n=1). However, none of these articles specified that Flourish was the MCA device used, instead the term “neodymium-iron-boron magnets (Cook Medical, Winston-Salem, NC)” was used.

For this review, we focused on cases (n=12) of MCA treatment for esophageal atresia (EA) in patients less than 1 year old. All 12 cases presented patient experiences prior to device approval. Of the nine patients with EA reported by Zaritzky et al (2014),[1] six patients had EA without tracheoesophageal fistula (type A) and the other three had EA with tracheoesophageal fistula (type C), which had been surgically repaired (converted to type A) prior to MCA treatment. All nine patients had a gap of 4cm or less and had previously underwent surgical gastrostomy and had a mature gastrostomy tract at the time of MCA treatment. The average patient age was 3 months (range 23 days to 5 months). Mid-term outcomes were previously reported for 5 of these patients. [4] The remaining two publications described a total of 3 infants with long-gap EA who were also reported to have underwent a staged esophageal lengthening prior to MCA treatment, including Foker procedure, Bakes dilators approximation or suture-approximation of the two esophageal pouches without anastomosis. [2, 3] The staged repairs resulted in a gap distance that gradually decreased over a 2-month span, with the infants beginning their first lengthening procedure at 2 months, 3.5 months, and 4.5 months of age respectively.

The most common adverse event reported (see Table 1) for all 12 cases was significant and persistent esophageal stricture which required serial endoscopic balloon dilation, [1-4] stent placement, [1] and surgery. [1, 4] The esophageal stricture was reported to have occurred in two

children in as early as 1 day, and 6 weeks after magnet removal respectively, both requiring weekly balloon dilation for 3 – 4 consecutive weeks.[3] Also reported, was signs of sepsis 48 hours following magnet placement in one child. In this case, the magnets were removed, the patient was successfully treated with antibiotics, and the magnets were restored to complete the treatment. [4] Three patients were lost to long-term follow-up. Of the 9 patients with long-term (time range: 4 – 144 months) follow-up data, one child was reported to have gastroesophageal reflux disease, oral aversion requiring therapy, oral consumption of liquids but Gastro-Jejunal (GJ) tube feeds for majority of calories, and required medication with Carafate and PPI.[2] Six children were reported to demonstrate one or a combination of the following comorbidities: gastroesophageal reflux disease, tracheomalacia, esophageal dysmotility requiring treatment, asthma, or recurrent pulmonary infections. [1] One of these patients was reported to have a concurrent diagnosis of all these comorbidities at 17 months of age, and was at the 15th growth percentile for age.

Other reported incidents include: replacement of the distal magnet and catheter after it became dislodged into the stomach,[2] and a baby pulling the oral catheter (with the magnets still coupled) up into her mouth, [3] on day 3 and day 10 following magnet placements (Table 1).

The four articles demonstrated probable benefits (see Table 2) for all 12 patients, with leak-free anastomosis following magnet placement, which was achieved in an average of 7.6 days (range 2-13 days). It was also reported that 8 patients showed an ability to swallow secretions and ingest oral diets normally in the months post procedure. [1, 3] The papers did not specify how long after the procedure these observations were noted.

The results of this systematic literature review should be interpreted in light of key limitations. First, our results are limited by the small number of included publications. In our search of the literature up to the year 2017, there were only 4 papers reporting on the use of Flourish in the pediatric population. Furthermore, the quality of the evidence was low, as all 4 papers were case reports and case series with small sample size describing a single-site experience. These factors limit the generalizability of the results from these studies to the pediatric EA population at large.

Conclusion

In this systematic literature review, we evaluated four published case reports/series reporting clinical outcomes in pediatric patients who underwent MCA. The major adverse event reported in all described cases was recalcitrant esophageal stenosis, which required serial balloon dilatation, and a combination of stent placement and/or surgery in some cases. Probable benefit was also reported, with leak-free anastomosis being achieved in all cases, and ability to swallow secretions and ingest oral diets normally. However, the four articles were published before the approval date for Flourish (May 12, 2017), three of which provided supporting evidence for its HDE approval. [1-3]

Due to the limited information available in the current literature, we recommend continued monitoring of adverse events and probable benefits of the Flourish device in the medical literature.

Figure 1: Flow diagram of the articles retrieved and study selection.

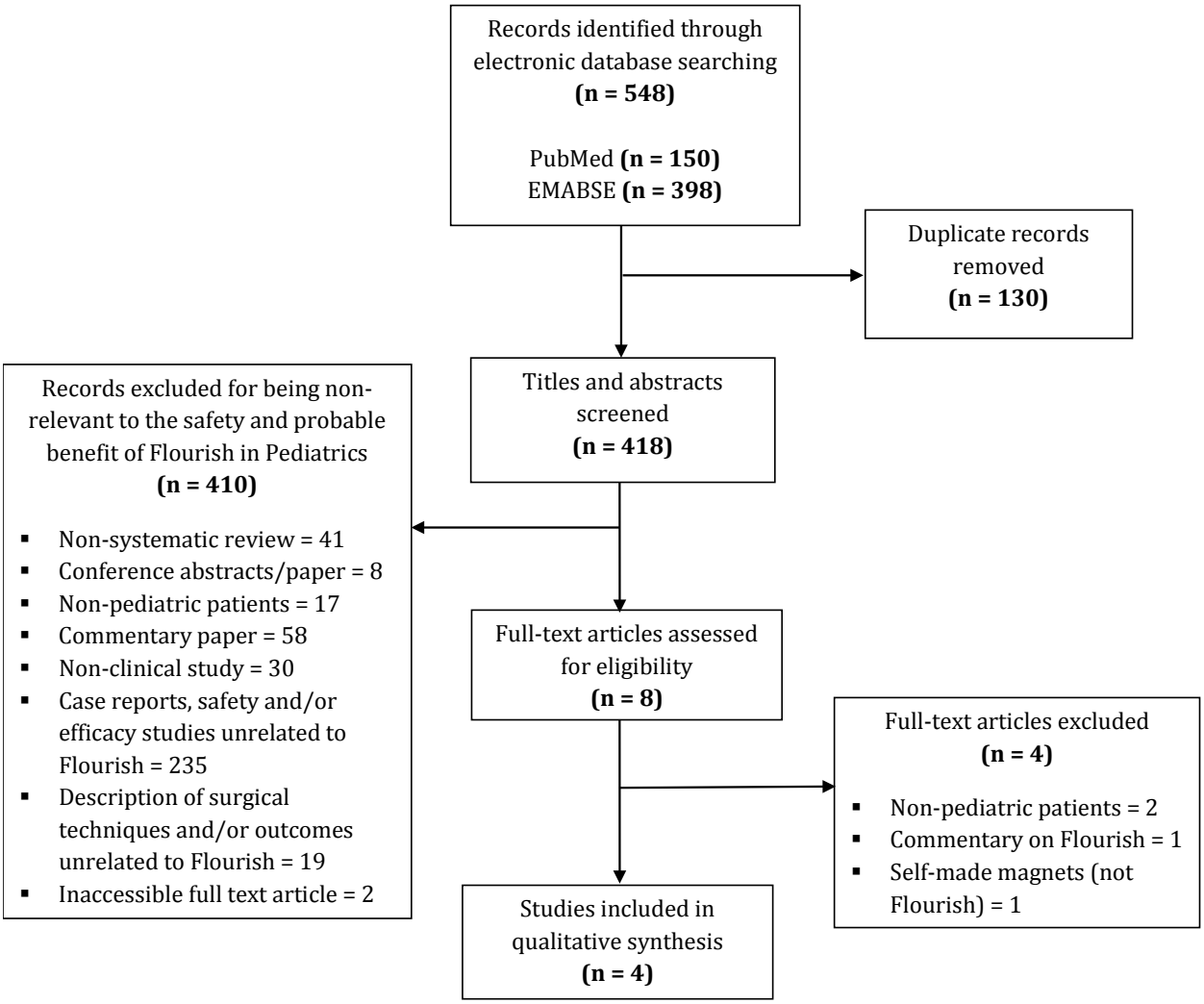


Table 1. Reported Safety Events with Neodymium-iron-boron Magnets	
Short-term Adverse Outcomes	**N (%)**

Stricture at anastomosis site requiring endoscopic balloon dilation	12/12 (100%)
Stricture at anastomosis site requiring surgical intervention	1/12 (8%)
Stricture at anastomosis site requiring stent placement	2/12 (17%)
Sepsis	1/12 (8%)
Long-term Adverse Outcomes	
Gastroesophageal reflux disease	3/9[†] (33%)
Oral aversion requiring therapy	1/9[†] (11%)
GJ tube feeds	1/9[†] (11%)
Tracheomalacia	3/9[†] (33%)
Esophageal dysmotility requiring treatment	3/9[†] (33%)
Asthma	1/9[†] (11%)
Recurrent pulmonary infections	3/9[†] (11%)
Dislodgement of magnets	2/9[†] (22%)

[†] Three patients were lost to long-term follow up.

Table 2. Reported Probable Benefits with Neodymium-iron-boron Magnets	
Clinical Benefits	**N (%)**
Leak-free anastomosis	12/12 (100%)

Ability to swallow secretions	9/9[†] (100%)
Ability to ingest oral diets	7/9[†] (78%)

[†] Three patients were lost to long-term follow up.

VII. Overview of MDR Database

Strengths and Limitations of MDR Data

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 used 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; and
    - use error

Although MDRs are a valuable source of information, this passive surveillance system has limitations, including the potential submission of incomplete, inaccurate, untimely, unverified or biased data. In addition, the incidence or prevalence of an event cannot be determined from this reporting system alone due to potential under-reporting of events and lack of information about frequency of device use. Because of this, MDRs comprise only one of the FDA's several important postmarket surveillance data sources. Other limitations of MDRs and FDA's internal MDR database include:

- MDR data alone cannot be used to establish rates of events, evaluate a change in event rates over time, or compare event rates between devices. The number of reports cannot be interpreted or used in isolation to reach conclusions about the existence, severity, or frequency of problems associated with devices.
- Confirming whether a device actually caused a specific event can be difficult based solely on information provided in a given report. Establishing a cause-and-effect relationship is especially difficult if circumstances surrounding the event have not been verified or if the device in question has not been directly evaluated.
- MDR data is subjected to reporting bias, attributable to potential causes such as reporting practice, increased media attention, and/or other agency regulatory actions.

- MDR data does not represent all known safety information for a reported medical device and should be interpreted in the context of other available information when making device-related or treatment decisions.

MDRs Associated with Flourish™ Pediatric Esophageal Atresia Device - H150003

The MDR Database, was searched on December 5, 2017 for reports with product code PTK received by the Agency on or before November 30, 2017.

The search identified no MDRs. An additional search for reports with "Flourish" brand name came to the same result. The lack of MDR submissions for this device was confirmed by the manufacturer (Cook Medical) in early December 2017.

VIII. SUMMARY

The data support the reasonable assurance of safety and probable benefit of this device when used in accordance with the indications for use. Esophageal anastomosis was achieved in the majority of described cases, both as first line, as well as second line therapy. The probable benefits of earlier anastomotic repair and fewer surgical complications outweigh the risks higher rate of anastomotic strictures requiring balloon dilation and/or esophageal stenting in the appropriate patient. This is coupled with thorough labeling, obtained opinions from experts in the field with the majority favoring device use, and an acceptable training program and post-approval study in place.

Therefore, FDA finds it reasonable to conclude that the probable benefit to health from using the device for the target population outweighs the risk of illness or injury, taking into account the probable risks and benefits of currently available devices or alternative forms of treatment when used as indicated in accordance with the directions for use.

FDA's Review Team has identified no new safety concerns compared to what was known/anticipated at the time of HDE approval in 2003. Based on the available data, and taking into account the probable benefits and risks, FDA concludes that the HDE remains appropriately approved for pediatric use. FDA will continue routine surveillance including MDR and literature reviews. FDA will provide focused updated safety and use data to the PAC in 2019.

Therefore, FDA recommends:

1. Continued surveillance and will report the following to the PAC in 2019:

    - Annual distribution number
    - PAS follow-up results
    - Literature review

- MDR review

References

1. Zaritsky M. Ben R. Johnston K. Magnetic gastrointestinal anastomosis in pediatric patients. J Ped Surg 2014; 49:1131-1137.
2. Dorman RM, Vali K, Harmon CM, Zaritzky M, Bass KD. Repair of esophageal atresia with proximal fistula using endoscopic magnetic compression anastomosis (magnamosis) after staged lengthening. Pediatr Surg Int 2016; 32(5):525-528.
3. Lovvorn H, Baron M, Danko M, et al. Staged repair of esophageal atresia: Pouch approximation and catheter-based magnetic anastomosis. J Ped Surg Case Reports 2014; (2): 170-175.
4. Zaritzky M, Ben R, Zylberg GI, Yampolsky B. Magnetic compression anastomosis as a nonsurgical treatment for esophageal atresia. Pediatric radiology 2009; 39(9): 945-9.