FDA Executive Summary

Prepared for the
April 8, 2019 meeting of the
FDA's Pediatric Advisory Committee

H150003
Flourish™ Pediatric Esophageal Atresia Device

Contents

I. INTRODUCTION

In accordance with the Pediatric Medical Device Safety and Improvement Act this review 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 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 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

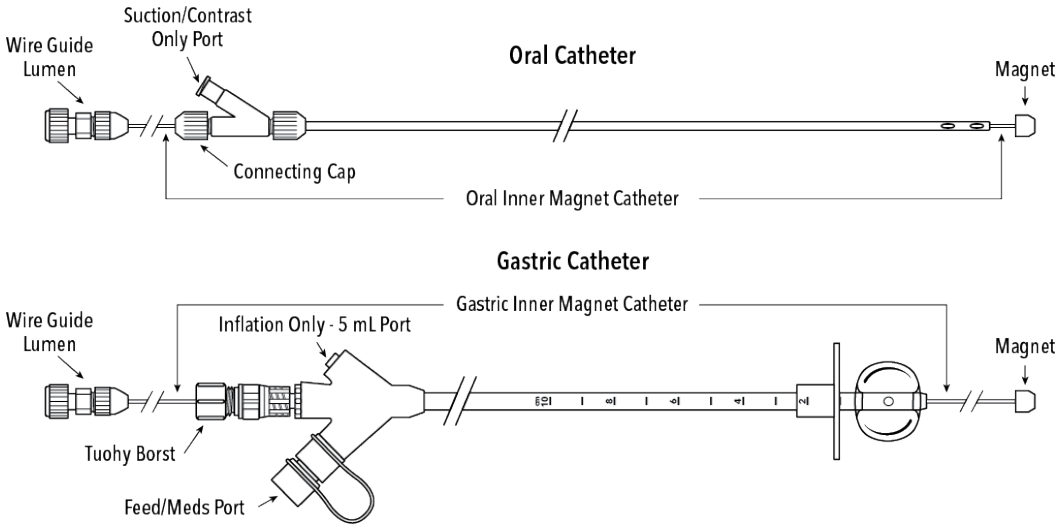
The Flourish Pediatric Esophageal Atresia Anastomosis Device consists of an oral/esophageal catheter and a gastric catheter. The oral/esophageal catheter is a 10 Fr two-lumen catheter. One lumen is for injection of contrast to confirm anastomosis; the other is for suction of saliva.

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:

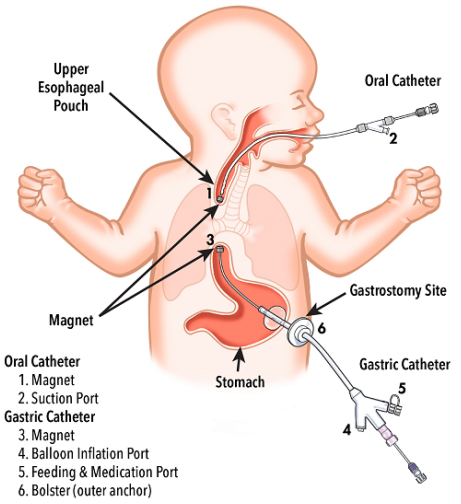


Principles of Operation

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 2018in the United States

Table 1. Annual Distribution Number

Calendar Year (Jan - Dec)	Total Sales
2018	3

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:

> 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 was approved on April 27, 2018.

PAS Study Status

Although the PAS protocol was approved on April 27, 2018, the device was not commercially available until September 30, 2018. Therefore, the most recent interim PAS report (dated November 6, 2018) indicates that the study had been active for approximately 1 month as of the report closing date. During this time, one patient was enrolled in the PAS.

In this one PAS-enrolled patient, the sponsor stated that an anastomosis was not achieved with use of the Flourish device due to an atretic gap of greater than 4 cm. On October 11, 2018 (3.5 weeks prior to surgery), a radiographic exam showed an atretic gap of 3.9 cm. Following device placement on November 5, 2018, the atretic gap was observed to be > 4 cm on radiographic imaging. It was noted that the physician had a difficult time placing the distal magnet of the Flourish device due to the location of the original stoma and patient anatomy (i.e., patient's lower pouch was unusually oriented). The oral catheter was repositioned from the mouth to the nares on November 6, 2018 and the physician repositioned the magnets on November 7, 2018. The device was removed on November 15, 2018 because no movement of the magnets toward each other was observed on x-ray over this period. Operative repair per thoracotomy was performed on November 15, 2018 to correct the esophageal atresia. The sponsor reported that the patient did not experience any adverse events.

The sponsor determined that verification of an atretric gap of no more than 4 cm, as required by the intended use, needs to be confirmed immediately prior to placing the Flourish device as stated in the current labeling. Physician training will continue to emphasize the importance of atretic gap verification prior to placement of a Flourish device.

The study status based on the most recent PAS report is Progress Adequate.

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

Purpose
To conduct a systematic literature review on medical literature that evaluates the safety and probable benefit of the Flourish device for esophageal atresia with or without tracheoesophageal fistula in pediatric patients

Methods
On January 18, 2019, a search was conducted using the PubMed and Embase databases with the following search strategies:

(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 was restricted to articles published between December 1, 2017 and November 30, 2018. 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.

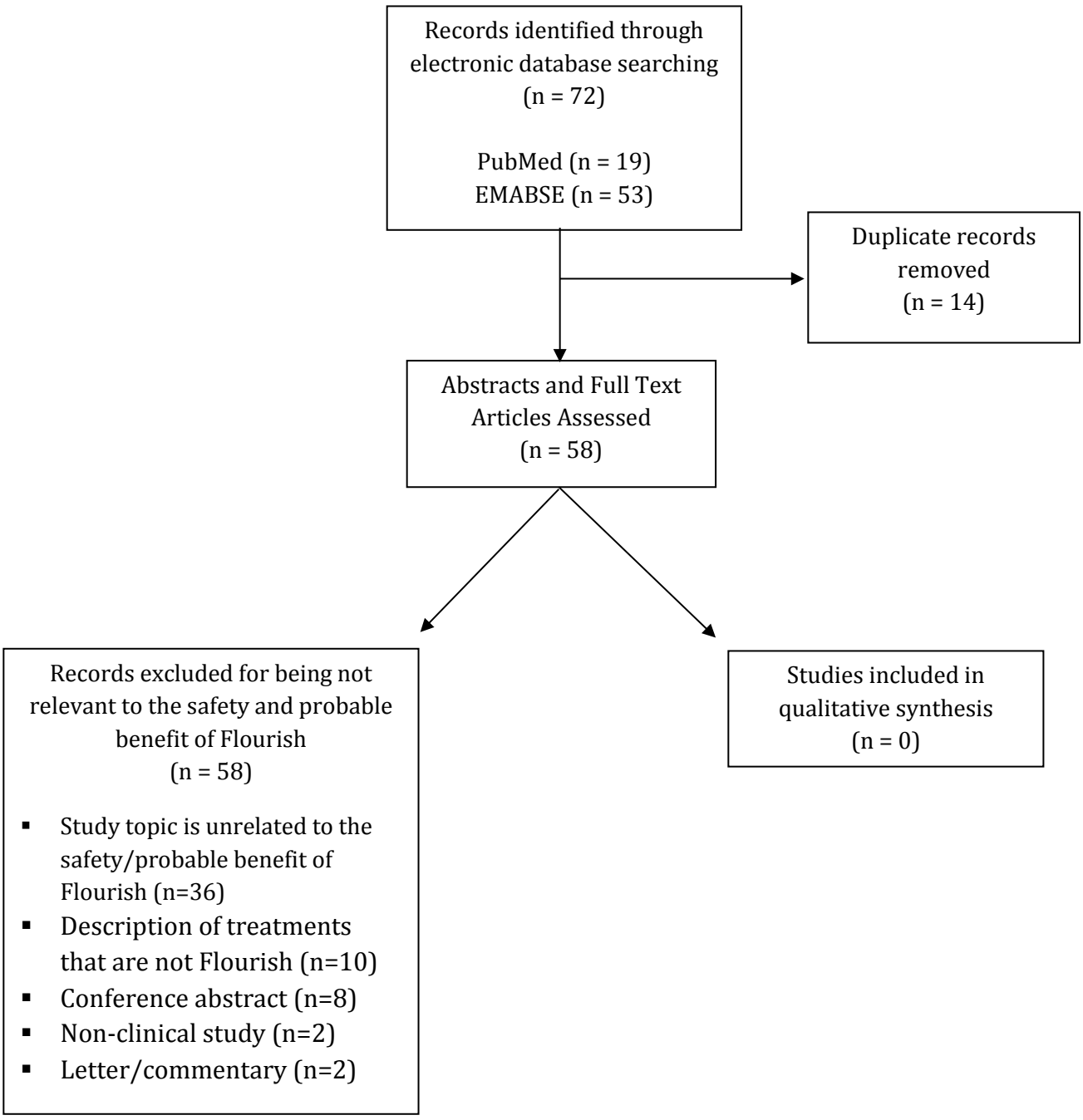
Results

Our search strategy resulted in 19 articles from PubMed and 53 articles from Embase. Removal of 14 duplicate articles resulted in 58 unique records. Abstracts and full-texts of the 58 citations were reviewed and all 58 papers were excluded because they did not provide information on the safety and probable benefit of Flourish for treatment of esophageal atresia. Reasons for exclusion of the 58 articles are provided in Figure 1.

Conclusion

A systematic search of the literature resulted in zero papers on this topic in a 1-year period since device approval on May 12, 2017. Therefore, we recommend continued monitoring of the literature for adverse events and probable benefits of the Flourish device in pediatric patients with esophageal atresia.

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



VIII. 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 17, 2018 for reports with product code PTK received by the Agency from December 1, 2017 through November 30, 2018.

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) at the end of November 2018.

VIX. SUMMARY

FDA's Review Team has identified no new safety concerns compared to what was known/anticipated at the time of HDE approval in 2017. 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 2020.

Therefore, FDA recommends:

1. Continued surveillance and will report the following to the PAC in 2020:

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