Flourish™ Pediatric Esophageal Atresia Device: H150003

Pediatric Advisory Committee - September 17, 2021

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Humanitarian Device Exemption (HDE) Program

- For devices intended to benefit patients in diagnosis or treatment of diseases in < 8,000 in the US per year
- Criteria:
  - Device will not expose patients to unreasonable or significant risk of injury
  - Probable benefit outweighs the risk, taking into account the benefits and risks of alternative forms of treatment

Disease Description

- Esophageal atresia (EA) is a developmental arrest of the esophagus resulting in absence of normal esophageal lumen

- Five types of EA, with and without concurrent TEF, are recognized

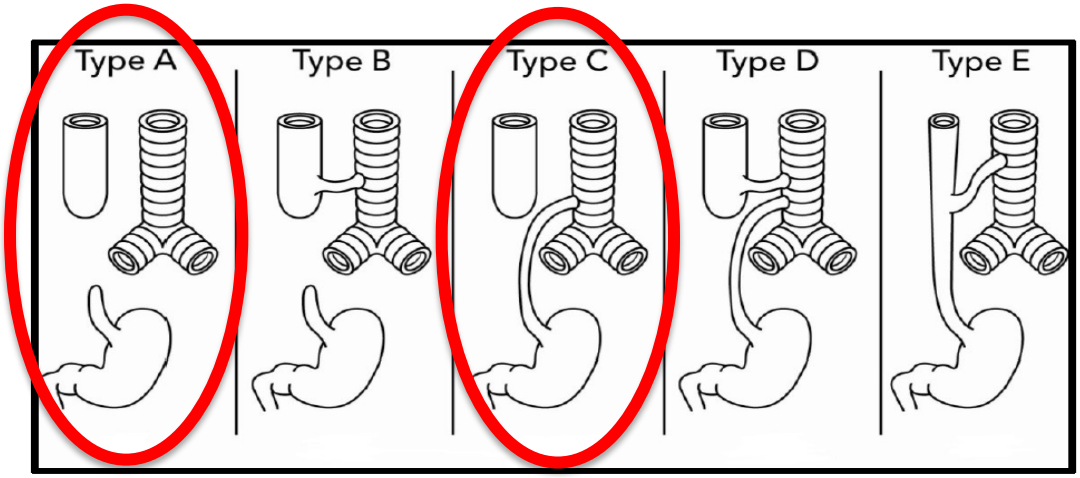


Figure 1: Types of Atresia

- Flourish to be used in patients with Type A EA (7.6% of cases) and patients for whom a concurrent TEF has been closed as a result of a prior procedure (Type C, 85%)

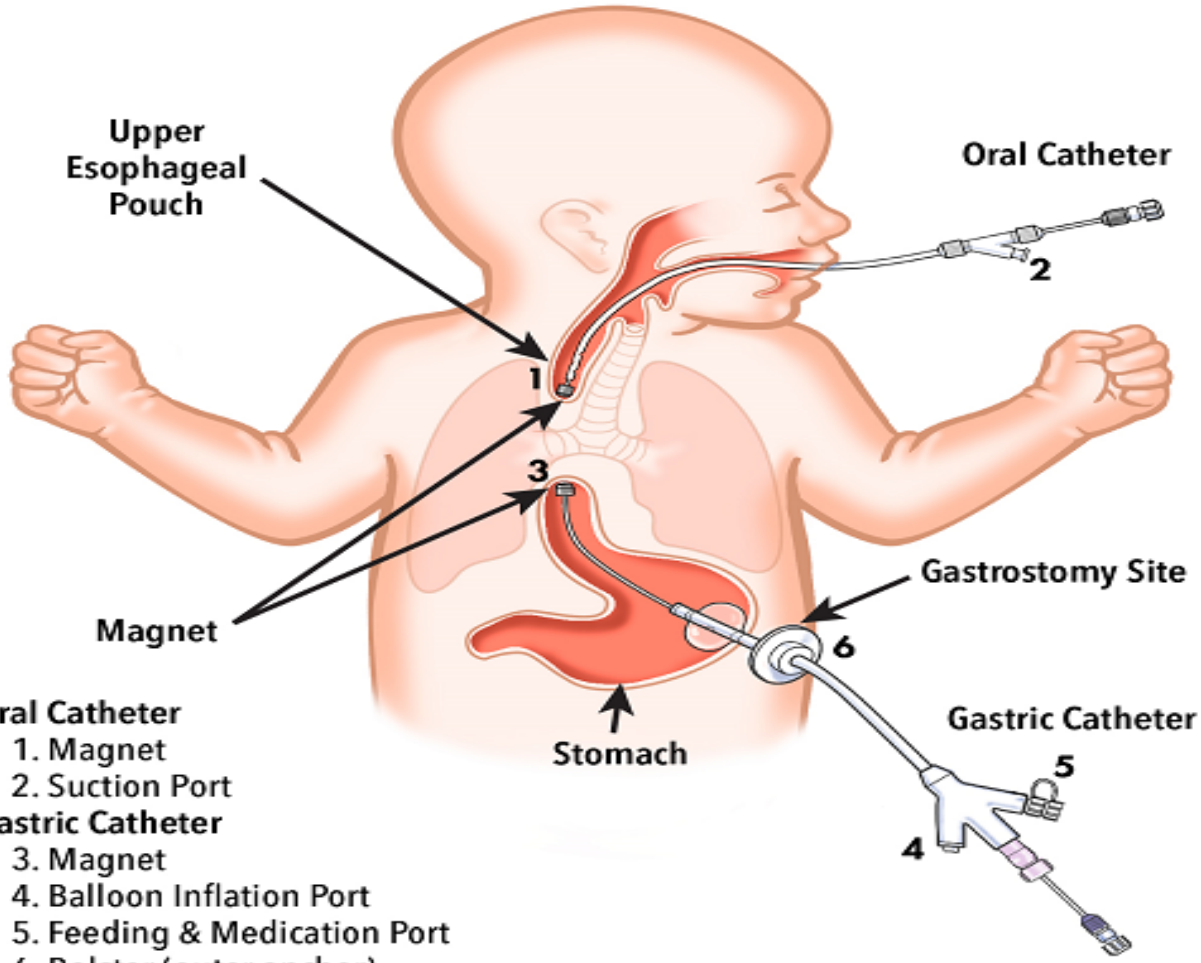
Current Standard of Care

- Surgical repair via thoracotomy or thoracoscopy to create anastomosis
  - Risks include:
    - Anesthesia
    - Post-op pain
    - Leak and stenosis of the anastomosis, GER, esophageal dysmotility, fistula recurrence
    - Cosmesis, shoulder weakness, winged scapula, thoracic scoliosis and/or other deformities of the thoracic wall
- If surgical repair is unsuccessful, colonic, gastric, jejunal interposition performed

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.

Flourish Device Description



Oral Catheter
1. Magnet
2. Suction Port

Gastric Catheter
3. Magnet
4. Balloon Inflation Port
5. Feeding & Medication Port
6. Bolster (outer anchor)

Data Used for HDE Granting

- Two articles from literature
  - Article 1: N= 9 from single center in Argentina
    - 9/9 formed an anastomosis, 8/9 developed stricture
  - Article 2: N= 2 case reports
    - 2/2 formed an anastomosis, 2/2 developed stricture
- Emergency use in the US
  - N= 5
  - N= 5/5 formed an anastomosis, 3/5 developed stricture
- Anastomosis Formation Rate: 100% (16/16)
- Stricture Rate: 81% (13/16)
- Probable benefits of earlier anastomotic repair and fewer surgical complications outweigh risks of a higher anastomotic stricture rate requiring intervention

Systematic Literature Review

Purpose: Evaluate Flourish safety and probable benefit for EA with or without TEF

Methods: PubMed, Embase, Google Scholar searched between 6/1/20 & 4/30/21

Results: 2 articles met selection criteria

- Wolfe et al. 2020
  - 2 of 3 patients achieved anastomosis with Flourish
  - Flourish anastomosis associated with more post-intervention dilatations than conventional anastomotic techniques due to more frequent and/or more resilient anastomotic strictures
- Liu SQ et al. 2020
  - Case report of long-gap (3.0 cm) EA with TEF type IIIa in an infant.
  - Magnetic compression anastomosis achieved on day 36 using customized ring magnets instead of Flourish

Conclusion:

- Current literature is limited to 4 patients reported in 2 articles
- Safety findings not different from information known at time of HDE approval

Post-Approval Device Use

Overview of PAS

- Single-arm, RWD collection from medical records
- 20 subjects followed for up to 2 years
- 1º outcomes: stricture formation, peri-anastomotic leaks, adverse events related to device or procedure
- 2º outcome: Successful anastomosis

Device use during reporting period:

Reporting Period	Total Sales	Total Implanted	Non-PAS Patients	PAS Patients
6/1/20 to 4/30/21	34	9 *	9	0

- PAS was revised in 2020 due to lagging patient enrollment
- Zero PAS patients enrolled during this reporting period
- Revised PAS expected to be completed in December 2022

Clinical Data Outside of PAS

Patients (in chronological order)	Non-PAS?	Pre-procedure gap measurement	Anastomosis Achieved?	Type of Esophageal Atresia
1	Yes	4 cm	Yes	Unknown
2	Yes	3 cm	Yes	A
3	Yes	1 cm	Yes	C
4	Yes	2.5 cm	No	A
5	Yes	1.0 cm	No	Unknown
6	Yes	2.3 cm	No	Unknown
7	Yes	2.2 cm	Yes	Unknown
8	Yes	2.4 cm	Yes	A
9	Yes	<1cm	Yes	Unknown

Clinical Data Summary

- Anastomosis Rates:
  - Pre-approval total: 100% (16/16)
  - Post approval total: 58% (18/31)
    - PAS: 33% (2/6)
    - Non-PAS: 64% (16/25)
  - Current Reporting Period: 67% (6/9)

- Complete information about stricture formation unavailable in the 9 patients

- Some of the nine patients treated within this reporting period experienced AEs that were reported in MDRs

Strength and Limitations of MDR Data

- The FDA uses Medical Device Reports (MDRs) to monitor device performance, detect potential device-related safety issues, and contribute to benefit-risk assessments of these products.
  - Detect actual or potential device problems in a “real world” setting
  - a qualitative snapshot of adverse events for a specific device/device type
  - Off-label use; Use error

- MDRs comprise one of the FDA's several important postmarket surveillance data sources.

- MDRs are a valuable source of information, but this passive surveillance system has limitations, including the potential submission of incomplete, inaccurate, untimely, unverified or biased data.

- Other limitations:
  - potential under-reporting of events
  - lack of information about frequency of device use

MDR Update

Purpose: Search MDR database to identify MDRs associated with Flourish Device.

Methods: Search criteria: Product Code: PTK, Brand name: FLOURISH, Premarket submission number: H150003

Results:

- 7 MDRs reported between 6/1/2020 and 5/31/2021.
- The Time to Event Occurrence (TTEO) ranged from 0 to 35 days, with an average of 11 days (SD± 10.8 days).
- 5/7 MDRs reported anastomosis failure.
- 2 patients were reported to have esophageal perforation (1 was unconfirmed perforation).
- 1 patient had a Tracheoesophageal fistula (TEF) identified after Flourish was removed. The root cause is unknown.
- 1 patient had a device placement failure- insufficient magnet strength.
- 1 patient had a stenosis (stricture) that required dilation

Perforation Case 1

- **MDR 5*** An under one-year old patient was reported to have an esophageal perforation in the lower esophageal area.

- The gastric feeding tube was left in the distal pouch. On day 4, the patient experienced a fever. Contrast study showed contrast draining into the right bronchus, likely indicating perforation of distal pouch.

- The magnets were removed without further incident. A chest tube was placed. A thoracotomy was scheduled for further assessment and treatment.

- The root cause for perforation has not been identified.

*The MDR number and the MDR numbers in the following slides refer to the MDR numbers in the executive summary.

Perforation Case 2

- **MDR 4** A 7-month-old patient: a potential esophageal perforation.
- Altered use of device: inconsistent with the IFU
  - both inner catheters locked through the treatment and pushed on the inner catheters.
  - Introduced the feeding tube into the lower esophageal pouch
- The esophagram: the magnets had likely perforated through the esophageal pouch. An endoscopy was performed to dilate the anastomosis area under fluoroscopy, but unable to confirm if a perforation occurred.
- The physician statement: without the pushing and locking of the device, the magnets would not have come together
- The Cook representative's comments:
  - 1st time any user had left the magnets in longer than 13 days.
  - 1st time putting tension on the inner catheters and locking both catheters

Labeling Change

Cook submitted a supplement for labeling revisions in response to MDRs of perforations and was approved in December 2020. Completed labeling changes included the following:

- Added potential complications: "Potential complications during the device indwelling period also include perforation/leak of one or both esophageal pouches or anastomotic site, which could result in additional procedures and/or death."
- Added two warnings:
  - "(1) Do not insert the feeding/gastric tube into the lower esophageal pouch, doing so may result in pressure on the magnet and subsequent perforation;
  - (2) Do not apply any force onto the esophageal pouches to approximate them, as this may result in perforation."
- Clarified the locking status of the catheters:
  - "**During approximation, always ensure that at least one of the inner magnet catheters is in the unlocked position, so that the magnets can continue to slowly move towards each other**."

Case 3 TEF

- **MDR 7** A 4.4-month-old: a life-threatening tracheoesophageal fistula.
- Altered use of device: inconsistent with the IFU
  - Left a wire guide in the lower catheter for support.
  - Applied force to the magnets to bring them together
- On day 14, the esophagram had no leaks, the device was removed that day.
- Four days after the device removal, a surgical consult indicated a potential TEF.
  - Bronchoscopy & esophagoscopy: a large TEF.
  - The patient's medical history: a pure esophageal atresia.
- The manufacturer investigation: related to the improper use of device.
  - the user applied force to the device to try to bring the magnets together and left the wire guide in place.

Additional Information Response

- In response to the MDR on TEF, a definitive root cause was not identified.
- The esophagogram had no apparent leaks upon Flourish removal, however, a TEF was identified 4 days after removal. It is possible that the device could cause an acquired TEF.
- Cook identified the most likely root cause, if the Flourish caused or contributed to the TEF, to be improper use of the device by the user.
- Cook intends to submit a new HDE Supplement for the labeling change.

Case 4 Insufficient Magnet Strength

- **MDR 6** An 8-month-old patient: a Flourish device placement failure
- The lower esophagus was very thin and short, and the magnet placed kept sliding out. The procedure was aborted.
- The atretic gap distance was 2.3cm (within the range of indication for use) but could not approximate the pouches less than 2 cm without some tension.
- The magnets was tested ex vivo; they did not connect until they were about 1.5-1.7 cm apart.
- The manufacturer tested a device from the same lot
  - the magnets showed attraction towards each other when within 4 cm but do not fully connect at this distance.
  - This is the expected behavior of the device per the manufacturer.

Additional Information Response

- In response to MDR on insufficient magnet strength, Cook stated that
  - the force with which the magnets are pulling towards each other increases exponentially as the distance between them is reduced.
- This intrinsic characteristic of the magnets:
  - allows the esophageal pouches to stretch towards each other over time
  - mitigates the risk of perforation.
- To maintain safe use, Cook noted that the device must not provide an excessive magnetic compression pressure
  - Such that the tissue between the magnets necroses before an adequate fusion of the esophageal pouches to achieve anastomosis, which may lead to anastomotic leaks.

Meeting with Cook

- Study by Lambe et al. (2014)*: an optimal compression pressure should not exceed 60 N/cm2 (at 2 mm inter-magnet distance).

- The Flourish device exerts a mean compression pressure of approximately 37.3 N/cm2 (STDEV = 2.7 N/cm^2)

- The exponential force:
  - a slight increase in force at small distances has very little impact on force at larger distances.
  - a higher potential for perforation at smaller distances without significantly impacting forces at larger distances.

- Multiple clinical factors: impact effectiveness of magnet attraction and subsequent anastomosis, such as
  - patient anatomy
  - length of esophageal pouches
  - location of PEG placement
  - fibrous tissue

Lambe T, Ó Ríordáin MG, Cahill RA, et al. Magnetic compression in gastrointestinal and bilioenteric anastomosis: how much force? *Surg Innov*. 2014;21(1):65-73

Additional Action Plan

- Cook will provide a new HDE supplement to improve the current labeling including
  - potential new complications
  - clarification of repositioning the device after placement
  - additional warnings of improper use of device
  - Editing the device description
  - update the physician training

- Patient specific information is difficult to be recreated in a benchtop model. For this reason, patient specific factors will be assessed at the conclusion of the post-approval study.

- Cook and FDA are engaged in discussions regarding the proposed action plan.

MDR Conclusion

- New serious adverse events of esophageal perforation, and tracheoesophageal fistula.
- Recurrent improper use of device that was inconsistent with the instructions for use. The added force could cause a perforation.
- Cook identified multiple clinical factors that could potentially impact effectiveness of magnet attraction and subsequent anastomosis.
- The device has exponential property. A slight increase in force at small distances has very little impact on force at larger distances but could result in a higher potential for perforation at smaller distances.

Conclusions

- Flourish was approved with limited clinical data demonstrating successful anastomosis formation in all described cases
- Data in current reporting period show evolving benefit-risk profile
  - Successful anastomosis formation in 6 of 9 patients in the 2021 reporting period, compared to 16 of 16 patients in premarket data
  - Reports of perforations, TEF, stricture formation, and insufficient magnet strength
- Limited data in non-PAS patients does not allow for definitive conclusions
- Expect to gain a clearer picture of device's benefit-risk profile with completion of PAS and continued evaluation of non-PAS patients

Conclusions

- Probable benefits of Flourish outweighs risk when used as indicated
- With Flourish, anastomotic repair can occur earlier than thoracotomy and avoids potential surgical complications.
- FDA and Cook discussing potential labeling and training revisions to reduce SAE risk
- FDA recommends continued surveillance of Flourish device and plans to report the following to the PAC in 2022:
  - Annual distribution number
  - PAS results
  - MDR review
  - Literature review
  - Additional device/labeling changes or manufacturer communications

Question 1

Recurrent improper use of device was observed in the new serious adverse events. Also, the attractive force of the magnet increases as the distance is reduced. Does the committee agree that

- additional warnings about improper device use, including excess user manipulations of the device, and explanation of the magnet behavior would address and mitigate the risk of perforations or TEFs?

    a) Yes
    b) No
    c) Abstain

Question 2

There are multiple clinical factors that can impact the effectiveness of the anastomosis. Does the committee agree that

- physicians should be given additional information regarding the clinical variables to better identify suitable candidates for treatment with the Flourish device?

a) Yes
b) No
c) Abstain

Question 3

The FDA will report on the following to the PAC in 2022:

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

Does the Committee agree with the FDA's plan for continued surveillance of the Flourish device?

a) Yes
b) No
c) Abstain

Thank You