Flourish™ Pediatric Esophageal Atresia Device: H150003

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Humanitarian Device Exemption (HDE) Program

- For devices intended to benefit patients in the dx or tx of diseases in < 8,000 in the US/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 tx
- Those approved for pediatric patients are required annually to ensure the HDE is still appropriate for the population for which it was approved

Disease Description

- Esophageal atresia (EA) is a developmental arrest of the esophagus resulting in the absence of normal esophageal lumen
  - Overall incidence of EA/Tracheoesophageal fistula (TEF) ranges from 1/2500 to 1/4500 live births

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

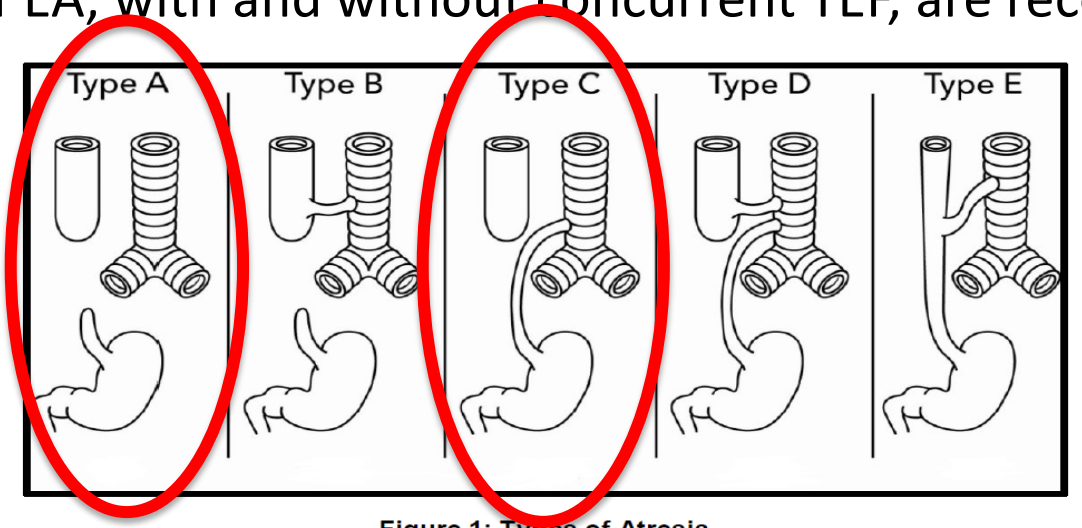
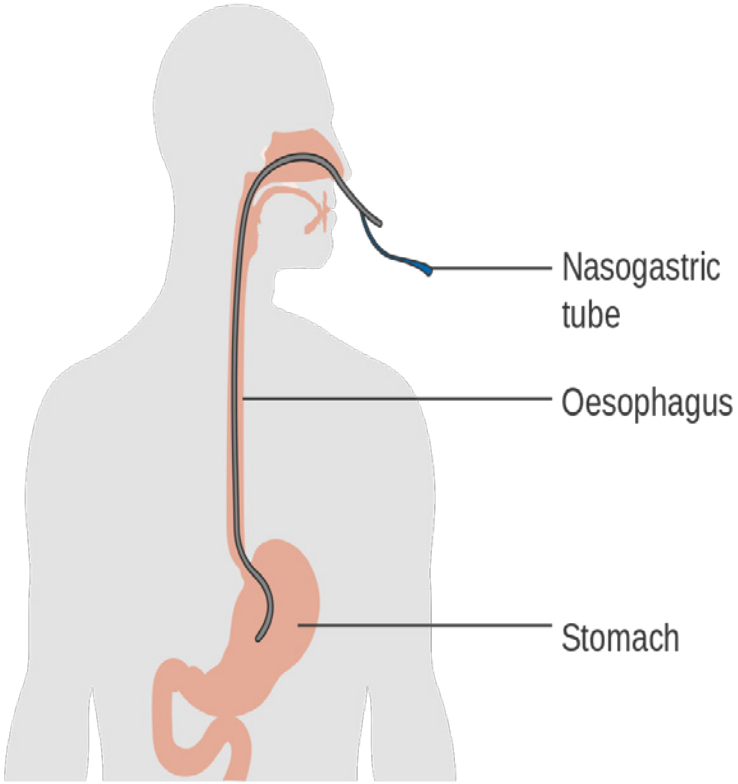


Figure 1: Types of Atresia

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

Disease Description



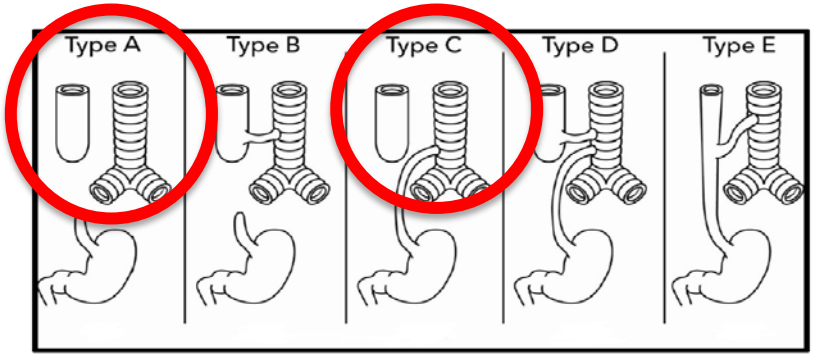
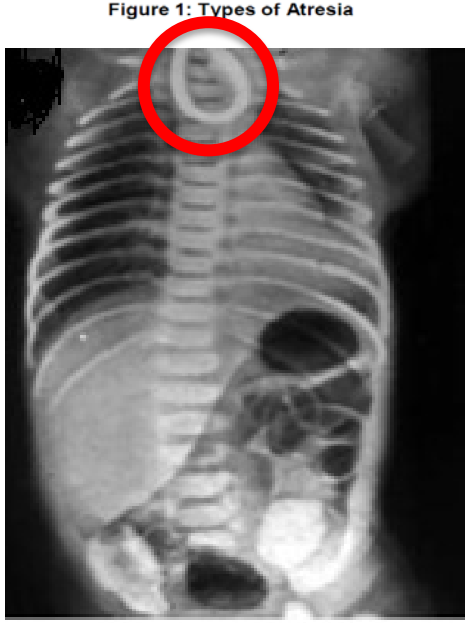


Figure 1: Types of Atresia



Clinical Course

- Infants present with excessive oral secretions, feeding intolerance, and/or respiratory difficulties
  - Necessitates suctioning and feeding through gastrostomy tube
- Morbidity/mortality is also dependent on associated conditions:
  - Condition commonly found in patients with VACTERL syndrome
  - CHARGE association may include EA

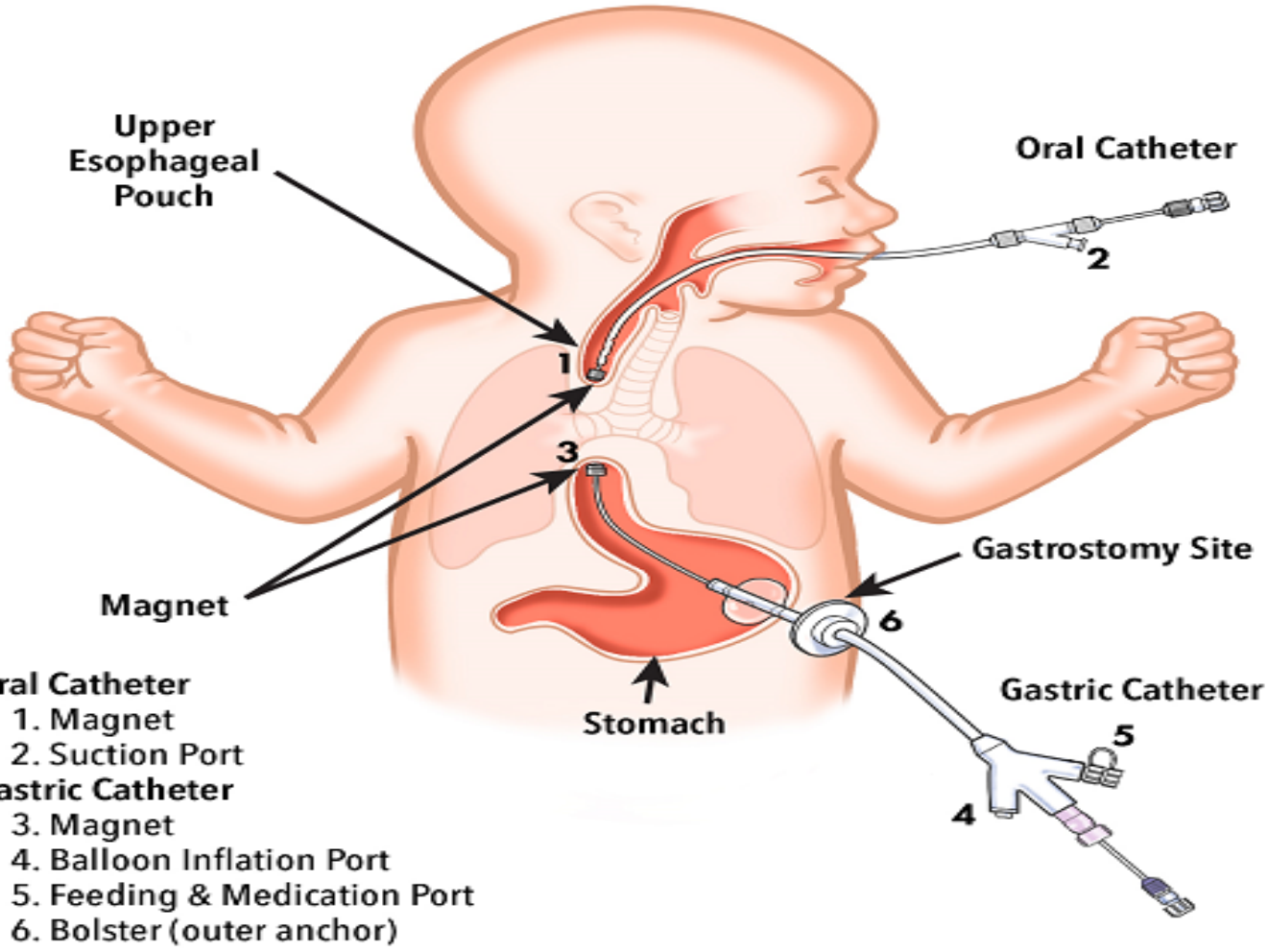
Standard of Care

- 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 unsuccessful, colonic, gastric, jejunal interposition performed

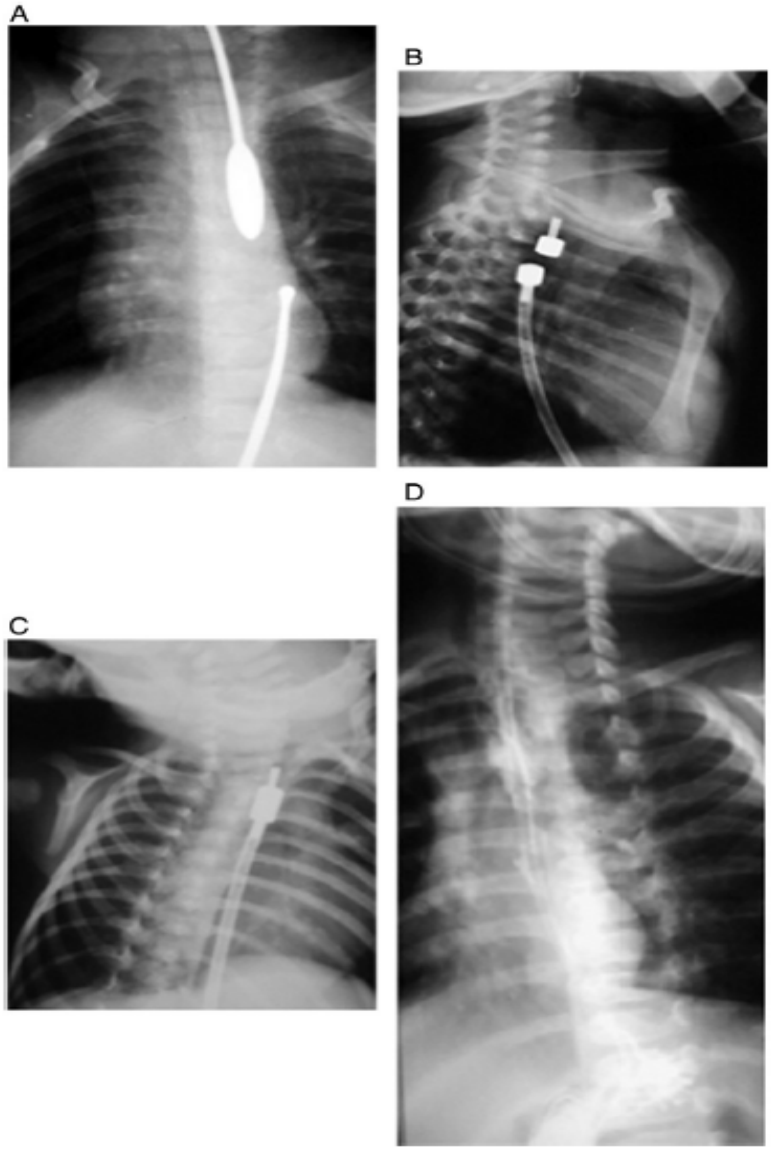
Indications for Use

- 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



Flourish Device Description



Data Used for HDE Granting

- Two articles from the 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)

Post-Approval Use

Post-Approval Study Requirements:

- Prospective, single-arm, new enrollment observational
- 15 sites at least 1 U.S.
- ≥ 20 subjects
- 2 year F/U
- 1º endpt: Safety (stricture leading to the need for dilation or surgery, peri-anastomotic leaks, adverse events possibly, probably, or causally related to the device or procedure)
- 2º endpt: Successful anastomosis

Post-Approval 2018-2020:

Reporting Period	Total Sales	Total Implanted	Patients in Post Approval Study (PAS)
Nov 2018 – May 2020	33	20*,**	6**

*of the 20 devices implanted, 5 patients were treated outside the U.S. (Canada). These patients were not enrolled in the PAS.
** in two patients the device was used in two separate procedures. However each patient was counted once.

- FDA is interactively working with Cook to explore PAS modifications

Post-Approval Clinical Data

Patients (in chronological order)	PAS?	Anastomosis Achieved?
1	Yes	No
2	Yes	No
3	Yes	Yes
4	No	No
5	Yes	No
6	No	Yes
7	No	Yes
8	No	Yes
Labeling Changes Implemented – October 2019		
9	No	Yes
10	Yes	No
11	No	No
12	No	No
13	No	No
14	Yes	Yes
15	No	Yes
16	No	Yes
17	No	No
18	No	Yes
19	No	No
20	No	Yes

Clinical Data Summary

- Anastomosis Rates:
  - Pre approval total: 100% (16/16)
  - Post approval total: 50% (10/20)
  - PAS patients: 33% (2/6)
  - Non PAS patients: 57% (8/14)
  - Pre labeling change: 50% (4/8)
  - Post labeling change: 50% (6/12)

- Stricture:
  - Limited information. Of the 2 PAS patients that achieved anastomosis, they both developed stricture
  - Information not available in non PAS patients

Failure Analysis

- **Non-clinical Testing**:
  - Testing demonstrated that magnet strength was in specification
- **Clinical Assessment:**
  - Atretic gap shouldn't be greater than 4 cm
    - Should be verified and confirmed immediately prior to placement
    - Review of imaging suggested that standard measurement was not being applied
      - Ex. Gap may have been > 4 cm (used a rigid tool under tension)
- **Sponsor Mitigation**:
  - Labeling revision

Labeling Change

- In order to determine if a patient is a suitable candidate for Flourish placement, an accurate measurement of the esophageal gap needs to be made. The following imaging recommendations should be followed:
  - It is essential that the measurement be made by not exerting any pressure over the esophageal pouches to approximate the atretic gap.
  - In order to not exert any pressure, it is better to use radiopaque flexible catheters under fluoroscopic visualization. Radiographs should be taken in AP and lateral incidences. It is also necessary to include a radiopaque ruler in the field of view.
  - Rigid probes are an alternative to the use of flexible catheters, but in this case, special attention should be taken not to push the probes to artificially reduce the gap distance.
  - Before starting the catheter placement procedure, the distance between upper and lower esophageal pouches must be measured and determined to be less than 4 cm in length, without exerting pressure to the pouches in AP and lateral fluoroscopic views.

Systematic Literature Review

Purpose: Evaluate safety and probable benefit of the Flourish device for EA with or without TEF in pediatric patients.

Methods: PubMed, Embase and Google Scholar databases searched between 12/1/18 and 4/31/20

Results: 2 articles met criteria;

- Average length F/U 9.3 years in 14 patients.
- All achieved anastomosis (range: almost immediately to 13 days).
- No anastomotic leaks, majority developed stenosis that required dilation.
- One infection reported with severe respiratory decompensation requiring sedation and pharmacologic paralysis 10 days after procedure. Stenosis observed after 4 weeks.

Conclusion:

- Literature provided valuable information about long-term outcomes.
- All 14 achieved anastomosis.
- Stricture formation was a complication: n=13/14
  - N=6 required esophageal stenting, n=2 required surgery
- Majority (n=11) of patients ultimately tolerated full oral feeds suggesting that patients benefited.
- Data are consistent with pre-market approval data and did not provide new data related to stricture and anastomosis success rates.

MDR Analysis

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:

- 10 MDRs identified between 12/1/2018 and 5/12/2020.
- The Time to Event Occurrence (TTEO) ranged from 4 to 16 days, with an average of 10 days (SD± 3.77 days).
- 8/10 MDRs identified anastomosis failure.
- 2 patients had stenosis that required dilation, 1 esophageal leak, and 1 bronchus fistula reported.

Conclusion:

- MDRs are consistent with the lower rate of successful anastomosis seen in the PAS.

Conclusions

- HDE pre-approval data:
  - 100% anastomosis
  - 1st and 2nd line therapy
  - Probable benefits of earlier repair and fewer surgical complications outweighed the risks of higher rate (80%) of anastomotic strictures
- Post Approval Data:
  - 10/20 (50%) anastomosis with 2 patients developing stricture.
  - Stricture rate is unknown for 8/10 patients treated
- Limited data: does not allow for definitive conclusions
- Potential reasons for differences:
  - Selection bias
  - Measuring technique and timing
  - Scarring of the esophageal ends from previous intervention
  - Age and/or gender of the patient
  - Site where the procedure was performed
  - EA type
  - Physician experience

Conclusions

- Based on review of available information, FDA concludes that the probable benefit to health continues to outweigh the risk as the device provided a benefit of anastomosis (50% of post approval cases vs. 100% of pre approval cases) given that there is insufficient new stricture rate information (unknown for 8/10 patients treated)

- Our analysis considers the probable risks and benefits of currently available devices or alternative forms of treatment; with the Flourish device, anastomotic repair can occur earlier than a thoracotomy and avoids several surgical complications

- Therefore, FDA recommends continued surveillance of the Flourish device. FDA will report the following to the PAC in 2021:

  - Annual distribution number
  - PAS follow-up results
    - Revised PAS study (FDA working in collaboration with Cook)
  - Literature review
  - MDR review

Question

The FDA will report on the following to the PAC in 2021:

- Annual distribution number
- PAS follow-up results
  - Revised PAS study (FDA working in collaboration with Cook)
- Literature review
- MDR review

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

Thank you