Clinical Policy Title: Injectable bulking agents for fecal incontinence

Clinical policy number: 08.02.04

Effective Date: October 1, 2015
Initial Review Date: May 20, 2015
Most Recent Review Date: June 22, 2017
Next Review Date: June 2018

Related policies:
CP# 08.02.06 Cecostomy for fecal incontinence
CP# 13.02.02 Pelvic floor stimulation for incontinence

Policy contains:
- Non-animal stabilized hyaluronic acid/dextranomer (NASHA Dx).
- Fecal incontinence.

ABOUT THIS POLICY: AmeriHealth Caritas Pennsylvania has developed clinical policies to assist with making coverage determinations. AmeriHealth Caritas Pennsylvania’s clinical policies are based on guidelines from established industry sources, such as the Centers for Medicare & Medicaid Services (CMS), state regulatory agencies, the American Medical Association (AMA), medical specialty professional societies, and peer-reviewed professional literature. These clinical policies along with other sources, such as plan benefits and state and federal laws and regulatory requirements, including any state- or plan-specific definition of “medically necessary,” and the specific facts of the particular situation are considered by AmeriHealth Caritas Pennsylvania when making coverage determinations. In the event of conflict between this clinical policy and plan benefits and/or state or federal laws and/or regulatory requirements, the plan benefits and/or state and federal laws and/or regulatory requirements shall control. AmeriHealth Caritas Pennsylvania’s clinical policies are for informational purposes only and not intended as medical advice or to direct treatment. Physicians and other health care providers are solely responsible for the treatment decisions for their patients. AmeriHealth Caritas Pennsylvania’s clinical policies are reflective of evidence-based medicine at the time of review. As medical science evolves, AmeriHealth Caritas Pennsylvania will update its clinical policies as necessary. AmeriHealth Caritas Pennsylvania’s clinical policies are not guarantees of payment.

Coverage policy

AmeriHealth Caritas Pennsylvania considers the use of injectable bulking agents for fecal incontinence (FI) to be investigational and, therefore, not medically necessary.

For Medicare members only:

In accordance with local coverage articles A52920, A52921, A52922, and A52923, injectable bulking agents for the treatment of FI will undergo manual review for medical necessity and reasonableness. See applicable codes at the end of this policy.

Limitations:

Other uses of injectable bulking agents may be medically necessary for other gastro-urinary indications,
such as urinary incontinence.

**Alternative covered services:**
- Biofeedback.
- Dietary management.
- Pharmacotherapy.
- Strengthening exercises.
- Surgery (e.g., post-anal repair, sphincteroplasty, artificial anal sphincter implantation, total pelvic floor repair, or bowel diversion).
- Sacral nerve stimulation.

**Background**

The strongest independent risk factors for FI in community populations are bowel disturbances such as diarrhea, the symptom of rectal urgency, and burden of chronic illness. Groups at high risk of FI include (Norton, 2007; Bharucha, 2015):
- Frail older people.
- Patients with loose stools or diarrhea from any cause.
- Symptom of rectal urgency.
- Women who have recently given birth (especially after third- or fourth-degree obstetric injury).
- Patients with neurological or spinal cord disease or injury.
- Patients with severe cognitive impairment or learning disabilities.
- Patients with urinary incontinence; pelvic organ or rectal prolapse; or perianal soreness, itching, or pain.
- Patients who have had colonic resection, anal surgery, or pelvic radiotherapy.

The pathophysiological mechanisms responsible for FI include diarrhea, anal and pelvic floor weakness, reduced rectal compliance, and reduced or increased rectal sensation; many patients have multifaceted anorectal dysfunctions. The type (urge, passive, or combined), etiology (anorectal disturbance, bowel symptoms, or both), and severity classify FI (Bharucha, 2015). The diagnosis of FI encompasses a detailed medical history, physical exam, and a range of tests to assess the structure and function of the rectum, anus, and pelvic floor muscles (National Institute of Diabetes and Digestive and Kidney Diseases [NIDDK], 2015).

Current treatments for FI range from conservative medical therapy aimed at reducing symptoms to surgical interventions intended to correct anal sphincter or pelvic floor abnormalities (NIDDK, 2015). The goal of medical therapy is to reduce stool frequency and improve stool consistency. Conservative measures include dietary changes, fiber additives, anti-motility medications, bowel training, and pelvic floor exercises with or without biofeedback. Electrical nerve stimulation (neuromodulation) is an emerging treatment option.
Surgery may be an option for FI that fails to improve with other treatments or for FI caused by pelvic floor or anal sphincter muscle injuries. Several surgical procedures are available: pelvic reconstructive surgery to restore normal anatomy; artificial anal sphincter implantation; and bowel diversion such as colonostomy or ileostomy (NIDDK, 2015). Minimally invasive procedures such as radiofrequency ablation to the anal sphincter and injectable perianal bulking agents have emerged as potential treatment alternatives for FI (Wald, 2014).

Injectable, perianal bulking agents:

Injectable bulking agents are potential treatments for FI following their reported success in treating urinary incontinence. A biocompatible material is injected into the anal submucosa or intersphincteric space to close the anal canal or raise the pressure inside the anal canal to avoid FI. Typically, a colorectal surgeon or gastroenterologist performs the procedure under local anesthesia, and the procedure may be done in an outpatient clinic setting. The simplicity and minimal invasiveness of this procedure makes it an attractive treatment alternative for FI.

Several different materials have been used to treat urinary incontinence, but to date, the U.S. Food and Drug Administration (FDA) has approved only one bulking agent for treatment of FI: dextranomer in stabilized sodium hyaluronate, also known as non-animal stabilized hyaluronic acid/dextranomer in stabilized hyaluronic acid or NASHA Dx. NASHA Dx is available in the United States under the trade name Solesta®. FDA-approved NASHA Dx as a class III medical device (product code LNM; agent, bulking, injectable for gastro-urology use) for the treatment of FI in patients 18 years and older who have failed conservative therapy (e.g., diet, fiber therapy, anti-motility medications) (FDA, 2011). The physician injects 1 milliliter (mL) of NASHA Dx through an anoscope into each quadrant of the deep submucosal layer of the proximal anal canal, approximately 5 to 10 millimeters (mm) above the dentate line.

According to product labeling, NASHA Dx is contraindicated in patients with the following conditions (FDA, 2011):

- Active inflammatory bowel disease.
- Immunodeficiency disorders or ongoing immunosuppressive therapy.
- Previous radiation treatment to the pelvic area.
- Significant mucosal or full-thickness rectal prolapse.
- Active anorectal conditions, including abscess, fissures, sepsis, bleeding, proctitis, or other infections.
- Anorectal atresia, tumors, stenosis, or malformation.
- Rectocele.
- Rectal varices.
- Patients who were pregnant, breast feeding, or without adequate contraception within the first year, or within one year postpartum.
- Presence of existing implant (other than NASHA Dx) in the anorectal region.
- Allergy to hyaluronic acid-based products.
As a condition of approval, FDA requires manufacturers to provide data regarding numbers of devices sold and distributed with necessary context for FDA to ascertain the frequency and prevalence of adverse events. FDA also mandated two additional studies to assess the long-term safety and durability of NASHA Dx (FDA, 2011):

- A single-arm, multicenter observational study of safety and durability through 36 months.
- A substudy to show the anatomic stability of NASHA Dx in at least 30 subjects by comparing anatomical positioning via transrectal ultrasonography at time of injection to positioning at six and 36 months.

**Searches**

AmeriHealth Caritas Pennsylvania searched PubMed and the databases of:

- UK National Health Services Centre for Reviews and Dissemination.
- Agency for Healthcare Research and Quality’s (AHRQ) National Guideline Clearinghouse and other evidence-based practice centers.
- The Centers for Medicare & Medicaid Services (CMS).

We conducted searches on April 26, 2017. Search terms were: “fecal incontinence (MeSH),” “bulking agent,” “NASHA,” and “dextranomer.”

We included:

- **Systematic reviews**, which pool results from multiple studies to achieve larger sample sizes and greater precision of effect estimation than in smaller primary studies. Systematic reviews use predetermined transparent methods to minimize bias, effectively treating the review as a scientific endeavor, and are thus rated highest in evidence-grading hierarchies.
- **Guidelines based on systematic reviews.**
- **Economic analyses**, such as cost-effectiveness, and benefit or utility studies (but not simple cost studies), reporting both costs and outcomes — sometimes referred to as efficiency studies — which also rank near the top of evidence hierarchies.

**Findings**

AmeriHealth Caritas Pennsylvania identified two systematic reviews (Hayes, 2014; Maeda, 2013), one cost-effectiveness analysis (Bernstein, 2014) and two evidence-based guidelines (NICE, 2007; Wald, 2014) for this policy. The overall quality of the evidence is low given the scarcity of controlled studies and high risk of bias among uncontrolled studies. Methodological limitations of the uncontrolled studies included small sample sizes, lack of blinding, and high numbers of dropouts.

The majority of studies evaluated NASHA Dx for treating FI. The evidence consists of one randomized controlled trial (RCT) comparing NASHA Dx to sham controls (the PIVOTAL study; clinicaltrials.gov).
identifier NCT00605826), one RCT comparing NASHA Dx to anal sphincter training with biofeedback (clinicaltrials.gov identifier NCT00303030), and several small uncontrolled studies using NASHA Dx and other bulking agents. The Pivotal Study is the primary data set that demonstrated the safety and effectiveness of NASHA Dx to FDA, along with supporting evidence of safety and effectiveness from one uncontrolled, multisite open-label study (clinicaltrials.gov identifier NCT01110681) and one single-site, proof-of-concept study (clinicaltrials.gov identifier NCT01380132) (FDA, 2011). All but one of the NASHA Dx studies were industry sponsored.

The study populations comprised patients with FI who had not responded to conservative treatment (21 to 206 patients per study). All patients received four injections of 1 mL of NASHA Dx in each quadrant of the anal submucosa. Patients were generally discharged from the treatment setting after a brief period of observation. After one month, patients without improvement of symptoms were offered a second treatment. Efficacy endpoints included the change in the number of incontinence episodes. A significant treatment response was defined as a 50 percent or greater decrease in FI episode frequency compared with baseline, the number of incontinence-free days and changes in incontinence scores using validated instruments. Patients recorded FI episodes and patterns in diaries when warranted. The duration of follow-up ranged from three months to three years.

**The evidence is insufficient to support the use of injectable bulking agents for treatment of FI in adults.** A limited number of uncontrolled studies of bulking agents other than NASHA Dx are insufficient to permit conclusions regarding their safety and efficacy for FI. The results for NASHA Dx suggest the procedure was well tolerated, with the majority of treatment-related adverse events considered mild or moderate in intensity. These included mild or moderate pain or discomfort in the rectum or anus, minor to moderate bleeding or spotting from the rectum, fever, abdominal pain, diarrhea, and constipation after treatment.

NASHA Dx is associated with some modest but statistically significant symptomatic improvements and may be a cost-effective alternative up to three years of follow-up in persons who have not responded to conservative treatment. However, improvement in many incontinence scores and general health was not statistically significant, and it is unclear if improvement in incontinence scores correlated with practical symptom improvements that mattered to the patients. Results of the sham-controlled study suggest a significant placebo effect, and the other controlled study suggested comparable results between NASHA Dx and anal sphincter training with biofeedback.

**Additional research is needed to determine the clinical value of bulking agents for FI.** Given the large placebo effect observed, larger, independent, randomized, sham-controlled studies are needed to further evaluate the efficacy, durability, and safety of this treatment. Future studies should compare NASHA Dx with standard therapies such as sacral nerve stimulation and other minimally invasive alternatives. There is also a need to better define the patient selection criteria by examining variables that predict which patients will derive the most clinical benefit from this therapy. To fulfill FDA conditions for continued approval, one observational study is underway to evaluate the long-term safety and effectiveness of NASHA Dx through three years in a real-world setting (clinicaltrials.gov identifier...
According to a horizon scanning report, tissue-bulking agents have potential to improve health outcomes, but would not always completely resolve FI (ECRI Institute, 2012). Those with muscle disruptions will probably need surgery. The intervention might become widely accepted because it is a noninvasive alternative to surgery that would appeal to patients, but most experts wanted to see additional trial results. Similarly, evidence-based guidelines confirmed the potential of bulking agents for treating FI in patients who are refractory to conservative therapy, but further studies are needed (NICE, 2007; Wald, 2014).

Policy updates:

In 2016, we found one new evidence-based guideline by the American Society of Colon and Rectal Surgeons (ASCRS) for treatment of FI (Paquette, 2015). The ASCRS made a weak recommendation for injection of biocompatible bulking agents into the anal canal to help decrease episodes of passive FI. Their recommendation was based on limited, moderate-quality evidence showing modest improvements in short-term outcomes, although long-term follow-up with regard to safety and efficacy awaits further experience.

AHRQ conducted a comprehensive systematic review of surgical and nonsurgical treatments for FI (Forte, 2016). Low-quality evidence at six months’ follow-up suggests dextranomer anal bulking injections are more effective than sham injections on outcome measures of QOL, the number of FI-free days, and the percent of adults with at least 50 percent reduction from baseline in FI episodes. They are not more effective than pelvic floor muscle training plus biofeedback with or without electrostimulation on measures of FI severity and quality of life, and not more effective than sham injection on FI severity or episode frequency.

Moderate-quality evidence suggests another injectable bulking agent Durasphere® (Coloplast Corp., Minneapolis, Minnesota), which is approved for stress urinary incontinence and represents an off-label use for FI, reduced FI severity for up to six months, but gains diminished thereafter. The authors stress that there is little high-quality evidence to guide decisions about the optimal surgical or nonsurgical treatment options for FI beyond standard care (i.e., dietary fiber supplements or stool-modifying drugs). These findings do not change earlier conclusions. Therefore, no changes to the policy are warranted.

Summary of clinical evidence:

<table>
<thead>
<tr>
<th>Citation</th>
<th>Content, Methods, Recommendations</th>
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<tbody>
<tr>
<td>Forte (2016) for AHRQ Surgical and nonsurgical</td>
<td>Key points:</td>
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<tr>
<td></td>
<td>• Systematic review of 63 studies with comparator or control groups, and an additional 53 surgical case series were examined for adverse effects. Enrollees were mostly adult females with mixed FI etiologies.</td>
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<tr>
<td>Citation</td>
<td>Content, Methods, Recommendations</td>
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| treatments for FI     | • Overall quality: very low to low for all treatment options. Limited by short-term follow-up (three to six months), numerous outcome measures, and inadequate study reporting standards.  
• Low-quality evidence suggests dietary fiber, clonidine, and pelvic floor muscle training with biofeedback with or without electrostimulation, and injectable bulking agents) show either no change or modest short-term improvements in some FI outcomes.  
• Insufficient evidence for all other nonsurgical and surgical procedures.  
• More substantial complications with surgical interventions, often requiring reoperation or permanent colostomy.  
• Future studies should focus on longer-term effects and attempt to identify subgroups of adults by FI etiology that might benefit from specific interventions. |
| Bernstein (2014)      | **Key points:**  
• Expected costs in year 2013 for Solesta ($14,962); conservative therapy ($9,053); and sacral nerve stimulation (SNS) ($33,201).  
• The incremental costs per quality-adjusted life-year gained were $37,036 for Solesta versus conservative therapy; $244,509 for SNS versus Solesta; and $103,066 for SNS versus conservative therapy. The model did not include indirect costs.  
• Funded by Salix Pharmaceuticals Inc. |
| Three-year cost        |                                                                                                                                                                                                                                                                                                                                                                      |
| effectiveness analysis |                                                                                                                                                                                                                                                                                                                                                                      |
| Hayes (2014)           | **Key points:**  
• Systematic review of two RCTs and six prospective uncontrolled studies. All but one study was manufacturer-sponsored.  
• Overall quality: low due to low numbers of controlled studies, small study sizes, high numbers of dropouts, and lack of blinding in uncontrolled studies.  
• Uncontrolled studies: Statistically significant improvements in 44% to 57.1% of patients at six months, 64% to 74% at one year, 59% to 63% at two years, and 45% at three years. No significant differences in incontinence scores or general health scores.  
• NASHA Dx versus sham control at six months' post treatment: ≥ 50% reduction in number of incontinence episodes (53% versus 32%); but similar median decrease in number of incontinence episodes between groups; significant benefit for coping behavior; no significant differences between groups in other QOL measures.  
• NASHA Dx versus anal sphincter training with biofeedback: no significant differences in improvements in FI and QOL during two years of follow-up.  
• Strong likelihood of placebo effect noted in studies.  
• Adverse events (AEs): mostly mild or moderate and transient with low incidence of serious AEs (~4% to 12%), mainly infections that required antibiotics or surgical drainage, which resolved spontaneously or with treatment. No late complications in studies reporting two- and three-year follow-up of patients. |
| Maeda (2013)           | **Key points:**  
• Systematic review of five RCTs (n = 382 patients).  
• Overall quality: low. Four of five trials had an uncertain or high risk of bias.  
• Short-term benefit from injections regardless of material used. Long-term data lacking. Unclear if improvement in FI scores matched practical symptom improvements that mattered to the patients.  
• One RCT of NASHA Dx versus sham (n = 206): NASHA Dx was more effective than sham |
injection at six months, but with more adverse effects.

- 48% versus 69% participants not improved, defined as < 50% reduction in FI episodes (relative risk [RR] 0.70, 95% confidence interval [CI] 0.55 to 0.88).
- More incontinence-free days (3.1 days versus 1.7 days, mean difference 1.40 days, 95% CI 0.33 to 2.47).

**References**

**Professional society guidelines/other:**


**Peer-reviewed references:**


**CMS National Coverage Determinations (NCDs):**

No NCDs were identified as of the writing of this policy.

**Local Coverage Determinations (LCDs):**

No LCDs were identified as of the writing of this policy.

**Local coverage articles:**


Commonly submitted codes

Below are the most commonly submitted codes for the service(s)/item(s) subject to this policy. This is not an exhaustive list of codes. Providers are expected to consult the appropriate coding manuals and bill accordingly.

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<td>0377T</td>
<td>Anoscopy with directed submucosal injection of bulking agent for fecal incontinence</td>
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<tr>
<td>R15.9</td>
<td>Full incontinence of feces</td>
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<tbody>
<tr>
<td>L8605</td>
<td>Injectable bulking agent dextranomer/hyaluronic acid copolymer implant, anal canal, 1 mL, includes shipping and necessary supplies</td>
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