Injectable Bulking Agents for the Treatment of Urinary and Fecal Incontinence

Policy # 00095
Original Effective Date: 01/27/2003
Current Effective Date: 11/15/2017

Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc. (collectively referred to as the "Company"), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

Note: Sacral Nerve Neuromodulation/Stimulation is addressed separately in medical policy 00108.

Note: Posterior Tibial Nerve Stimulation for Voiding Dysfunction is addressed separately in medical policy 00415.

When Services Are Eligible for Coverage
Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:

- Benefits are available in the member’s contract/certificate, and
- Medical necessity criteria and guidelines are met.

Based on review of available data, the Company may consider the use of carbon-coated spheres, calcium hydroxylapatite (CaHA), or polydimethylsiloxane to treat stress urinary incontinence (SUI) in men and women who have failed appropriate conservative therapy to be eligible for coverage.

When Services Are Considered Investigational
Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Company considers the use of autologous cellular therapy (e.g., myoblasts, fibroblasts, muscle-derived stem cells or adipose-derived stem cells), autologous fat, and autologous ear chondrocytes to treat stress urinary incontinence (SUI) to be investigational.*

Based on review of available data, the Company considers the use of any other periurethral bulking agents, including, but not limited to Teflon® to treat stress urinary incontinence (SUI) to be investigational.*

Based on review of available data, the Company considers the use of periurethral bulking agents to treat all other indications, including urge urinary incontinence, to be investigational.*

Based on review of available data, the Company considers the use of perianal bulking agents to treat fecal incontinence to be investigational.*

Background/Overview
Injectable bulking agents are space-filling substances used to increase tissue bulk. When used to treat SUI, bulking agents are injected periurethrally to increase tissue bulk and thereby increase resistance to the outflow of urine. The bulking agent is injected into the periurethral tissue as a liquid that solidifies into a solid form.
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spongy material to bulk the urethral wall. Bulking agents may be injected over a course of several treatments until the desired effect is achieved. Periurethral bulking agents have been widely used for incontinence in women. Men have also been treated, typically those with postprostatectomy incontinence.

After the success of periurethral bulking agents for treating SUI, bulking agents injected into the anal canal have been proposed to treat fecal incontinence. In particular, bulking agents are a potential treatment for passive fecal incontinence associated with internal anal sphincter dysfunction. The bulking agent is injected into the submucosa of the anal canal to increase tissue bulk in the area, which narrows the opening of the anus. Current treatment options for fecal incontinence include conservative measures (e.g., dietary changes, pharmacotherapy, pelvic floor muscle exercises), sacral nerve stimulation, and surgical interventions to correct an underlying problem.

Key factors in determining the optimal product are biocompatibility, durability, and absence of migration. A number of periurethral bulking agents to treat urinary incontinence have been cleared for marketing by the Food and Drug Administration (FDA); however, products developed to date have not necessarily met all criteria of the ideal bulking agents. The first FDA-approved product was cross-linked collagen (e.g., Contigen). The agent was found to be absorbed over time and symptoms could recur, requiring additional injections. Contigen production was discontinued in 2011. Other periurethral bulking agents cleared by FDA for urinary incontinence include carbon-coated beads (e.g., Durasphere), spherical particles of CaHA in a gel carrier (Coaptite), polydimethylsiloxane (silicone, Macroplastique), and ethylene vinyl alcohol copolymer implants (e.g., Tegress, formerly Uryx). Tegress was voluntarily removed from the market due to safety concerns.

Several agents identical to or similar to those used for urinary incontinence (e.g., Durasphere, silicone biomaterial) have been studied for the treatment of fecal incontinence. To date, only 1 bulking agent has been approved by FDA for fecal incontinence. This formulation is a non-animal-stabilized hyaluronic acid/dextranomer in stabilized hyaluronic acid (NASHA Dx) and is marketed by Q-Med as Solesta. A hyaluronic acid/dextranomer formulation (Deflux™‡) from the same company has been commercially available for a number of years for the treatment of vesicoureteral reflux in children.

Autologous fat and autologous ear chondrocytes have also been used as periurethral bulking agents; autologous substances do not require FDA approval. Polytetrafluoroethylene (Teflon) has been investigated as an implant material but does not have FDA approval. A more recently explored alternative is cellular therapy with myoblasts, fibroblasts, or stem cells (muscle-derived or adipose-derived). In addition to their use as periurethral bulking agents, it is hypothesized that transplanted stem cells would undergo self-renewal and multipotent differentiation, which could result in regeneration of the sphincter and its neural connections.

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FDA or Other Governmental Regulatory Approval
U.S. Food and Drug Administration
Several periurethral bulking agents have been approved by FDA through the premarket approval process for the treatment of SUI due to intrinsic sphincter deficiency; other than Contigen®, approval is only for use in adult women. Products include:

- In 1993, Contigen (Allergan), a cross-linked collagen, was approved. A supplemental approval in 2009 limited the device’s indication to treatment of urinary incontinence due to intrinsic sphincter deficiency in patients (men or women) who have shown no improvement in incontinence for at least 12 months. Allergan ceased production in 2011; no reason for discontinuation was provided publicly.
- In 1999, Durasphere® (Advanced UroScience), a pyrolytic carbon-coated zirconium oxide sphere, was approved.
- In 2004, Uryx® (CR Bard, Murray Hill, NJ), a vinyl alcohol copolymer implant, was approved. In 2005, approval was given to market the device under the name Tegress®. In 2007, Tegress was voluntarily removed from the market due to safety concerns.
- In 2005, Coaptite® (Merz Aesthetics, previously BioForm Medical), spherical particles of CaHA, suspended in a gel carrier, was approved.
- In 2006, Macroplastique® (Cogentix Medical, Minnetonka, MN), polydimethylsiloxane, was approved.

In 2011, NASHA Dx, marketed as Solesta® (Q-Med), was approved by FDA through the premarket approval process as a bulking agent to treat fecal incontinence in patients 18 years and older who have failed conservative therapy. FDA product code: LNM.

Centers for Medicare and Medicaid Services (CMS)
The 1996 Medicare National Coverage Determination for Incontinence Control Devices (230.10) has addressed collagen implants but not other types of bulking agents. Specific coverage information on collagen implants is as follows:

“Coverage of a collagen implant, and the procedure to inject it, is limited to the following types of patients with SUI due to ISD [intrinsic sphincteric deficiency]:

- Male or female patients with congenital sphincter weakness secondary to conditions such as myelomeningocele or epispadias;
- Male or female patients with acquired sphincter weakness secondary to spinal cord lesions;
- Male patients following trauma, including prostatectomy and/or radiation; and
- Female patients without urethral hypermobility and with abdominal leak point pressures of 100 cm H2O or less.

Patients whose incontinence does not improve with 5 injection procedures (5 separate treatment sessions) are considered treatment failures, and no further treatment of urinary incontinence by
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collagen implant is covered. Patients who have a recurrence of incontinence following successful treatment with collagen implants in the past (e.g., 6-12 months previously) may benefit from additional treatment sessions. Coverage of additional sessions may be allowed but must be supported by medical justification."

No national coverage determination was identified on injectable bulking agents for treating fecal incontinence.

Rationale/Source
Assessment of efficacy for therapeutic intervention involves a determination of whether the intervention improves health outcomes. The optimal study design for this purpose is a randomized controlled trial (RCT) that includes clinically relevant measures of health outcomes. Intermediate outcome measures, also known as surrogate outcome measures, may also be adequate if there is an established link between the intermediate outcome and true health outcomes. Nonrandomized comparative studies and uncontrolled studies can sometimes provide useful information on health outcomes, but are prone to biases such as noncomparability of treatment groups, placebo effect, and variable natural history of the condition.

The literature on injectable bulking agents includes RCTs that compare bulking agents with alternative treatments or placebo. Therefore, this evidence review will focus on RCTs and systematic reviews of RCTs on use of injectable bulking agents to treat urinary and fecal incontinence. The following is a summary of key literature to date.

URINARY INCONTINENCE
A 2012 Cochrane review on periurethral bulking agents for urinary incontinence in women identified 14 RCTs (sample ranges, 30-355 patients) that included bulking agents in at least 1 of the study arms. This review updated a 2007 review. All trials included women with a urodynamic diagnosis of stress incontinence, and 7 trials limited eligibility to stress incontinence due to intrinsic sphincter deficiency. The trials varied by types of bulking agent and comparator interventions used. Eight studies compared 2 bulking agents, two compared bulking agents with surgery, one compared a bulking agent with pelvic floor exercise, and one used a placebo comparison group. Several studies required that women had experienced incontinence for a specified period of time (e.g., 6 or 12 months) and/or had already used conservative therapy; 1 study further specified that conservative therapy had to have been used for at least 3 months. Reviewers determined that the data were not suitable for pooling due to heterogeneity across trials. They concluded that there was insufficient evidence to guide practice and recommended that additional RCTs with a placebo group or conservative treatment arm be conducted.

A 2011 systematic review by Davila identified 20 studies meeting inclusion criteria (prospective clinical studies or RCTs conducted among women with [SUI] and published in English). Nine studies (n=682 patients) evaluated the bulking agent cross-linked collagen. Rates of patients considered cured or improved in individual studies ranged from 21% to 81% at 12 months, 7% to 52% at 2 years, and 30% to 43% at more than 4 years. Eight trials (n=507 patients) used cross-linked polydimethylsiloxane injection. Cure rates ranged from 20% to 71% at 12 months and 18% to 40% at long-term follow-up (to 60 months). Reviewers
concluded that bulking agents had demonstrated effectiveness at 1 year, but results, particularly with older agents, diminished over time, and required repeated injections to restore or enhance improvement.

U.S. Food and Drug Administration–Approved Bulking Agents

**Cross-Linked Collagen (Contigen)**
The 1996 clinical practice guidelines for urinary continence in adults concluded that periurethral collagen is curative in 32% of men and 62% of women. A 2005 RCT compared the efficacy of collagen injections with surgery in 133 women. Eligibility criteria included stress incontinence for at least 6 months or 1 year after delivery. Twelve-month success rates for collagen treatment (53%) were lower than for surgery (72%). However, there were significantly fewer adverse events in the collagen-treated group (36% vs 63%, respectively). No randomized trials comparing Contigen with conservative therapy or placebo were identified. Contigen is no longer commercially available.

**Carbon-Coated Beads (e.g., Durasphere)**
A 2001 double-blind, RCT comparing carbon-coated beads with cross-linked collagen was reported as part of the U.S. FDA‒approval process for Durasphere. The trial found no difference in efficacy or in number of treatments between groups, although trial duration (12 months) may not have been sufficient to assess comparative durability.

**Ethylene Vinyl Alcohol Copolymer (e.g., Tegress)**
The copolymer implant (Tegress; formerly Uryx) received FDA approval based on a trial that randomly assigned 237 women with SUI to undergo periurethral bulking with Uryx or to a “currently marketed absorbable bulking agent.” Efficacy at 12 months was similar between groups, with 18.4% of those receiving Uryx reporting that they were dry and 48.7% reporting improvement by 1 grade, compared with 16.5% and 53.2%, respectively, in the control group. A repeat injection was necessary in 75% of these patients to achieve satisfactory results. Following reports of adverse effects, Tegress was voluntarily withdrawn from the market by its manufacturer, CR Bard, in January 2007.

**Calcium Hydroxylapatite (e.g., Coaptite)**
CaHA (Coaptite) received FDA approval based partly on results from a 2007 single-blind randomized noninferiority comparison with collagen among women with SUI. This trial was later published and reported on 231 (78%) of 296 enrolled women. For the primary outcome measure, 83 (63%) patients treated with CaHA and 57 (57%) control patients treated with collagen showed an improvement of 1 grade or more on the 4-grade Stamey Urinary Incontinence Scale at 12-month follow-up. Similar results were obtained by intention-to-treat analysis, with noninferiority of CaHA to collagen for improvement of at least 1 Stamey grade (58% vs 51%, respectively) and decrease in pad weight (51% vs 38%, respectively) of 50% or more.

**Polydimethylsiloxane (e.g., Silicone, Macroplastique)**
FDA approval of polydimethylsiloxane (Macroplastique) was also partly based on a randomized noninferiority comparison with collagen in women with SUI. Results of this trial were published in 2009. The trial was single-blind; patients, but not providers, were blinded. At 12 months, Macroplastique was found to
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be noninferior to collagen in terms of the primary efficacy variable, and improvement in the Stamey Urinary Incontinence Scale. Seventy-five (61%) of the 122 patients in the Macroplastique group and 60 (48%) of 125 patients in the collagen group improved at least 1 Stamey grade (p<0.001 for noninferiority). Twelve of the 247 randomized patients were excluded from the analysis. Two-year data on 67 of the 75 women who responded to treatment with Macroplastique were published in 2010. Fifty-six (84%) of the 67 patients had sustained treatment success at 24 months, defined as an improvement of at least 1 Stamey grade over baseline. Forty-five (67%) of the 67 patients evaluated at 24 months were dry (Stamey grade 0). The long-term analysis was limited because it only included a portion of responders from 1 arm of the trial. The analysis included 67 (55%) of 122 patients originally randomized to Macroplastique and did not provide data on the comparison group.

Non-FDA-Approved Bulking Agents

Dextranomer/Hyaluronic Acid (e.g., Zuidex) With an Injection System (e.g., Implacer)
Dextranomer/hyaluronic acid (Zuidex; AstraZeneca, Cambridge, England) with injection system (Implacer; Q-Med AB, Uppsala, Sweden) is used to deliver the bulking agent in the outpatient clinic setting without need for endoscopy. An industry-sponsored (Q-Med) randomized noninferiority trial (2009) conducted in North America compared the Zuidex system plus the Implacer with Contigen. Patients were blinded to treatment group. The primary study outcome was the proportion of women who had a 50% or greater reduction in urinary leakage on provocation testing from baseline to 12 months after the final treatment (up to 3 treatments were permitted). The primary outcome was achieved by 65% of Zuidex-treated women compared with 84% in the Contigen group; noninferiority of Zuidex was not established. The trial was limited by a high rate of missing data; primary outcomes data were missing for 35% of randomized patients.

A 2005 open multicenter study from Europe reported on a 12-month 77% positive response rate (reduction ≥50% for provocation test urinary leakage) with the dextranomer/hyaluronic acid (Zuidex system with Implacer) in 142 women who met strict inclusion and exclusion criteria. Similar to the North American trial, this study had a high dropout rate (24%), an unrepresentative patient population, and lacked a comparison group. Twenty-one women in this study were followed for a mean of 6.7 years after treatment with the Zuidex system. At this long-term follow-up, 7 (33%) of 21 were continent of urine, but 6 of the 7 had had other continence procedures since their Zuidex injections.

Polyacrylamide Hydrogel (e.g., Bulkamid)
Polyacrylamide hydrogel (Bulkamid; Contura International A/S, Søborg, Denmark) is a gel containing 2.5% cross-linked polyacrylamide and 97.5% apyrogenic water. A single RCT was identified that compared Bulkamid with an FDA-approved bulking agent (Contigen).

In 2014, Sokol et al reported on an RCT performed under an FDA-regulated investigational device exemption. This single-blind multicenter randomized noninferiority trial compared Bulkamid with collagen gel (Contigen) in 345 women. Up to 3 injections were given. Patients completed the outcome measures at 1, 3, 6, 9, and 12 months after the last bulking procedure. The primary outcome measure was the responder rate at 12 months, determined by a composite of a 50% decrease in leakage, as measured by
the 24-hour pad test, and a minimum 50% decrease in self-reported daily incontinence episodes. Bulkamid met the noninferiority margin, with a minimum 50% decrease in leakage and incontinence episodes in 53% of patients in the hydrogel group and 55% of patients in the collagen gel group. At 12 months, 47% of patients treated with hydrogel and 50% of patients treated with collagen gel reported zero stress incontinence episodes.

Several case series, conducted in Europe, have been published. The largest (N=256) is by Pai and Al-Singary (2015). Women with stress or mixed urinary incontinence (>1 episode per 24 hours) who received injections of Bulkamid were assessed yearly with quality of life measured by visual analog scale and incontinence by the International Consultation on Incontinence Questionnaire. The primary outcome was whether patients were completely dry (cured) or leaked once a week or less (significant improvement). At the 3-month follow-up, 110 (42.9%) were cured and 102 (39.8%) patients reported significant improvement. These percentages were maintained through 5 years (median, 38 months). However, only 60 (23.4%) patients were available for follow-up at 60 months, limiting interpretation of the long-term results.

A 2010 multicenter series by Lose et al included 135 adult women with symptomatic stress (n=67) or mixed (n=68) incontinence. Eligibility included presence of symptoms for at least 12 months, including at least 1 episode of incontinence daily. Ninety-eight (73%) patients completed 12-month follow-up. The primary outcome was response to treatment, defined as patients self-reporting that they considered themselves “improved” or “cured.” The response rate was 71% at 6 months and 66% at 12 months. Corresponding cure rates were 16% and 24%. There were 32 treatment-related adverse effects including 2 cases of urinary retention requiring hospitalization and 10 cases of urinary tract infection.

A 2013 two-center prospective series included 82 women who had had stress incontinence for at least 12 months. Patients received an injection of Bulkamid, and nonresponders were offered a second injection after 3 months. A total of 80 (98%) women were evaluated at 3 and 6 months, and 78 (95%) completed 1-year follow-up. The primary efficacy outcome was the subjective success rate at 1 year, defined as answering 1 or 2 on the Patient Global Improvement Impression questionnaire, which has a scoring range from 1 (very much better) to 7 (very much worse). In an intention-to-treat analysis, the subjective success rate at 1 year was 74% (61/82 patients). Seven patients reported no change, and none reported symptom worsening. At 1 year, 87% (71/78) of patients were considered to be responders (answer of 1, 2 or 3 on the Patient Global Improvement Impression). Twenty-one (26%) patients had adverse events attributable to the injection procedure. The most common adverse event was urinary tract infection, reported by 8 patients. Four patients reported de novo urinary urgency; in all cases, this resolved by 3 months.

Eight-year outcomes were reported in 2014 for 24 women, of whom 15 (62.5%) had no further treatment, 1 received a second treatment with hydrogel, and 7 had placement of mid-urethral slings. Subjectively, 44% considered their incontinence to be cured or much improved. Vaginal ultrasonography showed visible hydrogel deposits in all patients.

**Polytetrafluoroethylene (e.g., Teflon)**

No published clinical trials were identified on polytetrafluoroethylene as a bulking agent.
Bulking Agents Not Requiring FDA Approval

**Autologous Fat and Autologous Ear Chondrocytes**

Other materials have been used as bulking agents but have not demonstrated the same sustained effectiveness as cross-linked collagen or carbon-coated beads. In a double-blind RCT of 56 women that compared periurethral injections of autologous fat (treatment group) with saline (placebo group), Lee et al (2001) found that periurethral fat injections were not more efficacious than placebo for treating stress incontinence. At 3 months, only 6 (22.2%) of 27 patients in the treatment group and 6 (20.7%) of 29 in the placebo group were cured or improved. In addition, 1 death occurred as a result of pulmonary fat embolism. In another clinical trial of 32 women, Bent et al (2001) reported that 50% of patients remained dry for 12 months after receiving a single outpatient injection of harvested autologous auricular cartilage. While autologous substances have a nonimmunogenic advantage, their use may be limited by resorption and fibrous replacement along with local discomfort associated with harvesting procedures.

**Autologous Cellular Therapy**

In 2007, Strasser et al published the first RCT on autologous cell therapy for treating SUI. While widely cited as an important advance in the field, the *Lancet* retracted publication of this trial in 2008 due to ethical and quality concerns. The *Lancet* retraction stated: “...in our view, the conclusions of this official investigation pinpoint so many irregularities in the conduct of their (Strasser et al) work that, taken together, the paper should be retracted from the public record.”

Pooled data from 80 patients in 2 phase 1/2 dose-response trials from Cook MyoSite were reported in 2014. A phase 3 trial (NCT01382602) with 150 patients was completed in January 2017.

**Section Summary: Urinary Incontinence**

A number of RCTs and a Cochrane review of RCTs evaluating periurethral bulking agents for the treatment of urinary incontinence have been published. The trials vary by bulking agents used and comparator interventions (e.g., placebo, conservative therapy, another bulking agent). Due to this heterogeneity across studies, and the small number of studies in each category, Cochrane reviewers were unable to draw specific conclusions about the efficacy of specific bulking agents compared with alternative treatments. Cross-linked collagen is the most well established bulking agent, but it was withdrawn from the market. Results from available trials have suggested that carbon-coated spheres, CaHA, and polydimethylsiloxane have efficacy for treating incontinence that is similar to cross-linked collagen. For other agents (e.g., autologous cellular therapy, autologous fat, autologous ear chondrocytes, Teflon), there are few RCTs and little evidence of efficacy.

**Fecal Incontinence**

**Systematic Reviews**

A 2016 comparative effectiveness review for the Agency for Healthcare Research and Quality evaluated treatments for fecal incontinence. Reviewers found low strength of evidence from 2 RCTs that dextranomer anal bulking injections (NASHA Dx, Solest) were more effective than sham injections on some outcome
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measures (i.e., 50% reduction in episodes, number of incontinence-free days, quality of life) but not more effective than sham on fecal incontinence severity or frequency, and no more effective than pelvic floor muscle training with biofeedback on fecal incontinence severity or quality of life. There was moderate strength of evidence from 2 RCTs comparing Durasphere with a non-FDA-approved bulking agent that off-label use of Durasphere reduced fecal incontinence severity for up to 6 months, with diminishing improvements after that time.

In 2013, Cochrane updated a review of perianal injectable bulking agents for treating fecal incontinence. Reviewers identified 5 RCTs (total N=382 patients) comparing bulking agents with placebo, no intervention, or an alternative intervention. The 5 trials all included adults with internal anal sphincter dysfunction or passive fecal incontinence who had failed previous conservative treatments (e.g., pelvic floor muscle training). One of the 5 trials, detailed next, used the FDA-approved bulking agent dextranomer in stabilized hyaluronic acid (marketed as Solesta). Two trials used a placebo or sham control, two compared different bulking agents, and the fifth trial compared two methods of injecting the same agent. Length of follow-up ranged from 3 to 12 months. Four trials were judged to be of high or uncertain risk of bias. The greatest potential source of bias was lack (or unclear) blinding of outcome assessment and lack of blinding of surgeons performing the procedure. Due to heterogeneity among trials, study findings were not pooled. Overall, conclusions on efficacy were limited by the small number of RCTs identified, most of which had methodologic limitations, and a lack of long-term follow-up.

Previously, in 2011, 2 systematic reviews were published that included observational studies and RCTs evaluating bulking agents for treating fecal incontinence. Hussain et al included 1070 patients from 39 studies in a safety analysis. Adverse events occurred in 139 (13.5%) patients. The most common complication was pain, which occurred in 67 (6.5%) patients, followed by leakage of injected material, which was reported by 58 (5.6%) patients. Reviewers did not report the number of serious adverse events.

Randomized Controlled Trials
The RCT evaluating Solesta, included in the 2011 Cochrane review, was an industry-sponsored multicenter trial (2011) that compared Solesta with sham treatment in 206 adults. To be eligible for inclusion, patients had to have a Cleveland Clinic Florida Fecal Incontinence Score of 10 or higher, at least 4 documented incontinence episodes in 2 weeks, symptoms for at least 12 months, and failure of at least 1 medically supervised conservative treatment (which could include dietary modification, fiber supplements, or loperamide hydrochloride). Patients received an initial injection, and those with persistent symptoms and no substantial adverse effects at 1 month were offered a second injection. A total of 112 (86%) patients in the active treatment group and 61 (87%) patients in the sham group received a second procedure. Response to treatment was defined as a reduction in the number of incontinence episodes by 50% or more compared with baseline. The trial was double-blind for the first 6 months of follow-up; at 6 months, patients in the sham group were offered active treatment. Thus, the primary efficacy outcome was assessed at 6 months.

A total of 197 (96%) of 206 randomized patients completed 6-month follow-up and were included in the primary efficacy analysis. Seventy-one (52%) in the active treatment group and 22 (31%) in the sham group had a 50% or greater reduction in incontinence episodes at 6 months. The difference between groups was
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statistically significant (odds ratio, 2.36; 95% confidence interval, 1.24 to 4.47; p=0.009). Findings on secondary outcomes at 6 months were mixed. For example, the mean increase in number of incontinence-free days was significantly higher in the active treatment group (3.1) than the sham group (1.7; p=0.016), but the median decrease in number of incontinence episodes did not differ significantly between groups (6.0 vs 3.0, respectively; p=0.09). Moreover, change in the Cleveland Clinic Florida Fecal Incontinence Score did not differ significantly between groups at 6 months; (2.5 points for active treatment vs 1.7 points for sham treatment). Quality of life was measured by the Fecal Incontinence Quality of Life instrument, which has 4 subscales. One of the 4 subscales (coping and behavior) improved significantly more in the treatment group than in the sham group at 6 months. Change in scores on the other 3 subscales (lifestyle, depression and self-perception, embarrassment) did not differ significantly between groups at 6 months. Trialists did not report the proportion of patients continent at follow-up, either as a primary or secondary outcome.

During the 6-month blinded treatment phase, 128 adverse events were reported in the active treatment group and 29 in the sham group. The most common adverse event in the active treatment group was proctalgia, which occurred in 19 (14%) patients. In contrast, 2 (3%) patients in the sham group reported proctalgia. Moreover, 10 (7%) patients in the active treatment group and 1 (1%) patient in the sham group had rectal hemorrhage. Injection-site bleeding occurred in 12 (17%) patients in the sham group and in 7 (5%) patients in the active treatment group. Two serious adverse events were reported, both in the active treatment group (one rectal abscess and one prostate abscess).

Subsequent to the Cochrane reviewers’ search of the literature, Dehli et al (2013) in Norway published findings of an RCT evaluating Solesta. A total of 126 adults with fecal incontinence were randomized to injectable bulking agents (n=62) or a 6-month biofeedback intervention (n=64). Patients in the bulking agent group who reported minor or no symptom improvement at 3 months received a second injection. The primary efficacy outcome was incontinence severity, as measured by the St. Mark’s Fecal Incontinence Grading System score, which can range from 0 (perfect continence) to 24 (maximal incontinence). A St. Mark’s score of at least 4 was required for study participation. Ten (8%) patients dropped out of the study before 6 months. At the 6-month follow-up, the mean St. Mark’s score in the biofeedback group had decreased from 12.6 points (95% CI, 11.4 to 13.8) at baseline to 9.2 points (95% CI, 7.9 to 10.5). In the bulking agents group, mean scores were 12.9 (95% CI, 11.8 to 14.0) at baseline and 8.9 (95% CI, 7.6 to 10.2) at 6 months. This difference between groups in St. Mark’s score reduction was not statistically significant. In addition, change in St. Mark’s score did not differ between groups at 24 months; only 61 (49%) patients completed the 24-month follow-up. Three of the first 10 patients in the bulking agent group developed infections at the injection site and underwent treatment; subsequent patients in this group received prophylactic antibiotics.

Another 2013 RCT, conducted in Australia, compared 2 bulking agents for fecal incontinence. Neither bulking agent was FDA-approved for use in the United States. The trial was terminated early because one of the agents was removed from the Australian Pharmaceutical Benefits Scheme. The trial found no difference in efficacy between agents. The trial lacked a comparison group of patients not receiving bulking agents, which limits the ability to draw conclusions about the relative efficacy of bulking agents to sham or alternative treatments.
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Uncontrolled Trials
Longer term data on Solesta are available from an uncontrolled study (2013) conducted in Spain. A total of 115 patients with fecal incontinence received 4 injections of Solesta. Eighty-three (72%) of 115 patients completed the 24-month follow-up. The primary efficacy end point was response to treatment, defined as a minimum 50% reduction from baseline in the number of fecal incontinence episodes recorded in a 28-day diary. At the 24-month follow-up, 52 (63%) of 83 patients with data available had responded to treatment. The median number of incontinence-free days in a 28-day period increased from 14.6 at baseline to 21.7 at 24 months. The study lacked a comparison group and had a high dropout rate.

Section Summary: Fecal Incontinence
Several RCTs and systematic reviews of RCTs on bulking agents for the treatment of fecal incontinence have been published. A 2016 comparative effectiveness review from the Agency for Healthcare Research and Quality evaluated 2 RCTs with the FDA-approved product NASHA Dx (Solesta) and 2 RCTs with Durasphere. One RCT using NASHA Dx found that, compared with sham, NASHA Dx improved some outcomes but not others. The other RCT did not find a significant difference in efficacy between NASHA Dx and biofeedback. Two additional RCTs with Durasphere (off-label in the U.S.) found short-term improvements in fecal incontinence severity. Overall, the evidence is not sufficient to conclude that bulking agents are an effective treatment for fecal incontinence. Corroboration of the single positive trial is needed, and controlled trials with longer follow-up are important to determine the durability of any treatment effect.

SUMMARY OF EVIDENCE
For individuals who have SUI who receive injectable bulking agents, the evidence includes RCTs and systematic reviews of RCTs. Relevant outcomes are symptoms, functional outcomes, quality of life, and treatment-related morbidity. Studies have shown that cross-linked collagen improves the net health outcome (i.e., it is effective in some patients who have failed conservative treatment with fewer adverse events than surgery), although products that cross-link in such a way are no longer commercially available. There is evidence that FDA-approved carbon-coated spheres, CaHA, and polydimethylsiloxane have efficacy for treating incontinence, and further that they produce outcomes with a safety profile similar to cross-linked collagen. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have fecal incontinence who receive injectable bulking agents, the evidence includes RCTs and systematic reviews of RCTs. Relevant outcomes are symptoms, functional outcomes, quality of life, and treatment-related morbidity. A comparative effectiveness review from the Agency for Healthcare Research and Quality evaluated 2 RCTs with the FDA-approved product NASHA Dx (Solesta) and 2 RCTs with Durasphere (off-label in the United States). One RCT comparing NASHA Dx with sham found that NASHA Dx improved some outcomes but not others. The other RCT did not find a significant difference in efficacy between NASHA Dx and biofeedback. Two additional RCTs evaluating Durasphere found only short-term improvements in fecal incontinence severity. Controlled trials with longer follow-up are important to determine the durability of any treatment effect. The evidence is insufficient to determine the effects of the technology on health outcomes.
Injectable Bulking Agents for the Treatment of Urinary and Fecal Incontinence

Policy #  00095
Original Effective Date:  01/27/2003
Current Effective Date:  11/15/2017

References


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01/27/2003 Managed Care Advisory Council approval
01/04/2005 Medical Director review
01/31/2005 Managed Care Advisory Council approval
01/04/2006 Medical Director review
01/17/2006 Medical Policy Committee review. Format revision.
02/23/2006 Quality Care Advisory Council approval
01/10/2007 Medical Director review
01/17/2007 Medical Policy Committee approval. Coverage eligibility unchanged.
01/09/2008 Medical Director review
01/23/2008 Medical Policy Committee approval. Policy statement revised to include newly FDA-approved bulking agents.

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01/07/2009 Medical Director review
01/14/2009 Medical Policy Committee approval. Autologous cellular therapy was added as investigational.
01/07/2010 Medical Director review
01/20/2010 Medical Policy Committee approval. Ethylene vinyl alcohol copolymers were deleted from coverage.
01/06/2011 Medical Director review
01/19/2011 Medical Policy Committee approval. No change to coverage.
03/01/2012 Medical Policy Committee review
03/21/2012 Medical Policy Implementation Committee approval. Added “Urinary” to the policy title. Added that men and women who have failed appropriate conservative therapy are eligible for coverage to treat stress urinary incontinence. Stress urinary incontinence added to the investigational statements. The use of perirethral bulking agents to treat all other indications, including urge urinary incontinence, is considered investigational.
03/07/2013 Medical Policy Committee review
03/20/2013 Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
06/05/2014 Medical Policy Committee review
06/18/2014 Medical Policy Implementation Committee approval. Changed the policy title from “Periurethral Bulking Agents for the Treatment of Urinary Incontinence” to “Injectable Bulking Agents for the Treatment of Urinary and Fecal Incontinence”. Added that the use of perianal bulking agents to treat fecal incontinence is considered to be investigational.
08/03/2015 Coding update: ICD10 Diagnosis code section added; ICD9 Procedure code section removed.
10/08/2015 Medical Policy Committee review
10/21/2015 Medical Policy Implementation Committee approval. Contigen (cross-linked collagen) removed from eligibility statement as it has been withdrawn from the market.
10/01/2016 Coding update
11/03/2016 Medical Policy Committee review
01/01/2017 Coding update: Removing ICD-9 Diagnosis Codes
11/02/2017 Medical Policy Committee review

Next Scheduled Review Date: 11/2018

Coding
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Procedure Terminology which contains the complete and most current listing of CPT codes and descriptive terms. Applicable FARS/DFARS apply.

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Codes used to identify services associated with this policy may include (but may not be limited to) the following:

<table>
<thead>
<tr>
<th>Code Type</th>
<th>Code</th>
</tr>
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<tbody>
<tr>
<td>CPT</td>
<td>0377T, 46999, 51715</td>
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<tr>
<td>HCPCS</td>
<td>C9735, L8603, L8604, L8605, L8606</td>
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<td>ICD-10 Diagnosis</td>
<td>N36.42-N36.43, N39.3, R15.0-R15.9, T83.713A-T83.713S, T83.714A-T83.714S, T83.723A-T83.723S, T83.724A-T83.724S</td>
</tr>
</tbody>
</table>

Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is investigational will be based on a consideration of the following:

A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. Food and Drug Administration (FDA) and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or
B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:
   1. Consultation with the Blue Cross and Blue Shield Association technology assessment program (TEC) or other nonaffiliated technology evaluation center(s);
   2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community;
   3. Reference to federal regulations.

**Medically Necessary (or “Medical Necessity”) - Health care services, treatment, procedures, equipment, drugs, devices, items or supplies that a Provider, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury, disease or its symptoms, and that are:

A. In accordance with nationally accepted standards of medical practice;
B. Clinically appropriate, in terms of type, frequency, extent, level of care, site and duration, and considered effective for the patient's illness, injury or disease; and
C. Not primarily for the personal comfort or convenience of the patient, physician or other health care provider, and not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient's illness, injury or disease.

For these purposes, “nationally accepted standards of medical practice” means standards that are based on credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community, Physician Specialty Society recommendations and the views of Physicians practicing in relevant clinical areas and any other relevant factors.

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