Injectable Bulking Agents for the Treatment of Urinary and Fecal Incontinence

Policy # 00095
Original Effective Date: 01/27/2003
Current Effective Date: 11/16/2016

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.

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
Bulking agents are injectable substances used to increase tissue bulk. They can be injected periurethrally to treat urinary incontinence and perianally to treat fecal incontinence. The U.S. Food and Drug Administration (FDA) has approved several bulking agent products for treating urinary incontinence and 1 for treating fecal incontinence.

Injectable bulking agents are space-filling substances used to increase tissue bulk. When used to treat SUI, bulking agents are injected periurethrally to increase the tissue bulk and thereby increase resistance to the outflow of urine. The bulking agent is injected into the periurethral tissue as a liquid that then solidifies into a spongy material to bulk the urethral wall. Bulking agents may be injected over a course of several
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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.

Following the success of periurethral bulking agents for treating SUI, bulking agents injected into the anal canal have been proposed for treating 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 eg, dietary changes, pharmacotherapy and 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 FDA; however, products developed to date have not necessarily met all criteria of the ideal bulking agents. The first FDA-approved product was crosslinked collagen (eg, Contigen\textsuperscript{\textregistered}). 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 (eg, Durasphere\textsuperscript{\textregistered}), spherical particles of CaHA in a gel carrier (Coaptite\textsuperscript{\textregistered}), polydimethylsiloxane (silicone, Macroplastique\textsuperscript{\textregistered}), and ethylene vinyl alcohol copolymer implants (eg, Tegress\textsuperscript{\textregistered}, formerly Uryx\textsuperscript{\textregistered}). Tegress was voluntarily removed from the market due to safety concerns.

Several agents identical to or similar to those used for urinary incontinence eg, Durasphere, silicone biomaterial, etc., have been studied for the treatment of fecal incontinence. To date, only 1 bulking agent has been approved by FDA for treating fecal incontinence. This is a formulation of nonanimal stabilized hyaluronic acid/dextranomer in stabilized hyaluronic acid (NASHA Dx) and is marketed by Q-Med as Solesta. A hyaluronic acid/dextranomer formulation (Deflux\textsuperscript{TM}) 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 has not received 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 hoped that transplanted stem cells will undergo self-renewal and multipotent differentiation, which could result in regeneration of the sphincter and its neural connections.

**FDA or Other Governmental Regulatory Approval**

FDA

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 Inc.), a crosslinked 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
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12 months. The manufacturer of the product ceased production in 2011; no reason for discontinuation was provided to the public.

- In 1999, DuraspHERE (Advanced UroScience), pyrolytic carbon-coated zirconium oxide spheres, was approved.
- In 2004, Uryx (CR Bard), vinyl alcohol copolymer implants, was approved. In 2005, approval was given to market the device under the trade name Tegress. In 2007, Tegress was voluntarily removed from the market due to safety concerns.
- In 2005, Coaptite (BioForm Medical Inc.), spherical particles of CaHA, suspended in a gel carrier, was approved.
- In 2006, Macroplastique (Uroplasty), 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 Medicare National Coverage Determination for Incontinence Control Devices (230.10) addresses collagen implants but not other types of bulking agents. Specific information on coverage of 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 H\textsubscript{2}O 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 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
The literature on injectable bulking agents includes randomized controlled trials (RCTs) that compare bulking agents versus alternative treatments or placebo. Therefore, this policy will focus on RCTs and systematic reviews of RCTs on use of injectable bulking agents to treat urinary and fecal incontinence. Following is a summary of key literature to date.
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Urinary Incontinence
A 2012 Cochrane review on periurethral bulking agents for urinary incontinence in women identified 14 RCTs with sample sizes ranging from 30 to 355 patients that included bulking agents in at least one of the study arms. This was an update of 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 studies varied in the type of bulking agent and comparison intervention used. Eight studies compared 2 bulking agents, 2 compared bulking agents with surgery, 1 compared a bulking agent with pelvic floor exercise, and 1 trial used a placebo comparison group. Several of the studies required that women had experienced incontinence for a specified period of time, eg, 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. The authors stated that data from the trials were not suitable for pooling due to heterogeneity among studies. They concluded that the updated review indicates insufficient evidence to guide practice and recommend that additional RCTs with a placebo group or conservative treatment arm be conducted.

A 2011 systematic review by Davila identified 20 studies meeting their inclusion criteria (prospective clinical studies or RCTs conducted among women with SUI and published in English). Nine studies (total N=682) evaluated the bulking agent crosslinked 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. There were 8 trials (n=507) using crosslinked polydimethylsiloxane injection. Cure rates ranged from 20% to 71% at 12 months and 18% to 40% at long-term follow-up up to 60 months. The authors concluded that bulking agents have demonstrated effectiveness at 1 year, but results, particularly with older agents, diminish over time, and repeated injections can restore or enhance improvement.

FDA-Approved Bulking Agents

Cross-linked collagen (Contigen)
The 1996 Clinical Practice Guidelines for Urinary Continence in Adults, developed by the Agency for Health Care Policy and Research (now Agency for Healthcare Research and Quality), concluded that periurethral collagen is curative in 32% of men and 62% of women. An RCT published in 2005 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 were lower than for surgery (53% vs 72%, respectively). However, there were significantly fewer adverse events in the collagen-treated group (36% vs 63%, respectively). Results from this study support informed decision making in the choice between bulking agents and surgical intervention for SUI. No randomized trials comparing Contigen with conservative therapy or placebo were identified. Contigen is no longer commercially available.

Carbon-coated beads (eg, Durasphere)
A double-blind randomized study comparing carbon-coated beads with crosslinked collagen was reported as part of the FDA-approval process for Durasphere. The study found no difference in efficacy or in the number of treatments between the groups, although the trial length of 12 months may not have been long enough to assess comparative durability.
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**Ethylene vinyl alcohol copolymer (EVA, eg, Uryx marketed as Tegress)**
The copolymer implant (Uryx/Tegress) received FDA approval based on a study that randomly assigned 237 women with SUI to undergo periurethral bulking with Uryx or to a "currently marketed absorbable bulking agent." The effectiveness at 12 months was similar in the 2 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 CR Bard as of January 31, 2007.

**Calcium hydroxylapatite, CaHA (Coaptite)**
Coaptite (CaHA) received FDA approval based partly on results from a single-blind randomized noninferiority comparison with collagen among women with SUI. This study was later published and reported on findings from 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 (silicone, Macroplastique)**
The FDA approval of Macroplastique (polydimethylsiloxane) 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 be noninferior to collagen in terms of the primary efficacy variable, improvement in the Stamey incontinence grade. Seventy-five of the 122 patients (61.2%) in the Macroplastique group and 60 of 125 patients (48%) in the collagen group improved at least 1 Stamey grade (p<0.001 for noninferiority). Twelve of the 247 randomly assigned 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 of the 67 (84%) patients had sustained treatment success at 24 months, defined as an improvement of at least 1 Stamey grade compared with baseline. Forty-five of the 67 (67%) patients evaluated at 24 months were dry (Stamey grade 0). The long-term analysis is limited because it only includes a portion of responders from 1 arm of the trial. The analysis included 67 of 122 (55%) patients originally randomly assigned to receive Macroplastique and did not provide data on the patients in the comparison group.

**Non-FDA-Approved Products**

*Dextranomer/hyaluronic Acid (Zuidex™)† With an Injection System (Implacer™)‡*
Dextranomer/hyaluronic Acid (Zuidex) with injection system (Implacer) is used to inject the bulking agent in the outpatient clinic setting without need for endoscopy. An industry-sponsored (Q-Med) randomized noninferiority trial conducted in North America that compared the Zuidex system with Implacer to 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
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established. The study was limited by a high rate of missing data; primary outcome data were missing for 35% of randomly assigned patients.

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

Polyacrylamide hydrogel (Bulkamid®)

Bulkamid is a gel containing 2.5% crosslinked polyacrylamide and 97.5% apyrogenic water. No RCTs or non-RCTs evaluating Bulkamid were identified. A single RCT was identified that compared Bulkamid with an FDA-approved bulking agent (Contigen).

In 2014, Sokol et al reported an RCT that was performed under an FDA-regulated investigational device exemption. This single-blind multicenter randomized noninferiority trial compared Bulkamid with Contigen (collagen gel) 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 53.2% of patients in the hydrogel group and 55.4% of patients in the collagen gel groups. 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 in 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 (QOL) measured by visual analog scale and incontinence by the International Consultation on Incontinence Questionnaires. 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 2-center prospective series included 82 women who had stress incontinence lasting 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 the 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 (PGI-I) questionnaire, which has a 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 of 82 patients). Seven patients reported no change, and none reported worsening of symptoms. At 1 year, 87% of patients (71 of 78) were considered to be responders (answer of 1, 2 or 3 on the PGI-I). Twenty-one patients (26%) had adverse events attributable to the injection procedure. The most common adverse event was a 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 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 (Teflon)**
No published clinical trials were identified.

**Products That Do Not Require FDA Approval**
**Autologous Fat and Autologous Ear Chondrocytes**
These are other materials that have been used as bulking agents but have not demonstrated sustained effectiveness comparable with crosslinked collagen or carbon-coated beads. In a double-blind RCT of 56 female patients that compared periurethral injections of autologous fat (treatment group) with saline (placebo group), Lee et al (2001) found that periurethral fat injections did not appear to be more efficacious than placebo for treating stress incontinence. At 3 months, only 6 of 27 patients (22.2%) in the treatment group and 6 of 29 (20.7%) in the placebo group were cured or improved. In addition, 1 death occurred as a result of a pulmonary fat embolism. In another clinical trial of 32 female patients, Bent et al 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 randomized study on autologous cell therapy for treating SUI. This study has been widely cited as an important advance in the field. However, in September 2008, the Lancet published a statement that they were retracting publication of this study due to ethical and quality concerns. The Lancet retraction states "...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." Because of this retraction, findings from this study will no longer be cited as evidence in this policy.
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Pooled data from 80 patients in 2 phase 1/2 dose response trials from Cook MyoSite were reported in 2014. Completion of a phase 3 trial (NCT01382602) with 150 patients is expected January 2017.

Section summary
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 in the bulking agent used and the comparison intervention eg, placebo, conservative therapy, or another bulking agent. Due to this heterogeneity among studies, and the small number of studies in each category, the Cochrane review was unable to make specific conclusions about the efficacy of specific bulking agents compared with alternative treatments. Crosslinked collagen is the most established bulking agent, but it has been withdrawn from the market. Results from available trials suggest that carbon-coated spheres, CaHA, and polydimethylsiloxane have efficacy for treating incontinence that is similar to cross-linked collagen. For other agents, such as autologous cellular therapy, autologous fat, autologous ear chondrocytes, and Teflon, there are few RCTs and little evidence of efficacy.

Fecal Incontinence
A 2016 comparative effectiveness review for AHRQ evaluated treatments for fecal incontinence. The review found low strength of evidence from 2 RCTs that dextranomer anal bulking injections (NASHA Dx, Solesta) were more effective than sham injections on some outcome measures (ie, 50% reduction in episodes, number of incontinence free days, QOL) 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 QOL. 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, the Cochrane Collaboration published an updated review on perianal injectable bulking agents for treating fecal incontinence. The reviewers identified 5 RCTs with a total of 382 patients comparing bulking agents with placebo, no intervention or an alternative intervention. The previous review, published in 2010, had included 4 RCTs. The 5 identified trials all included adults with internal anal sphincter dysfunction or passive fecal incontinence who had failed previous conservative treatments eg, pelvic floor muscle training. One of the 5 trials, described in more detail next, used the FDA-approved bulking agent dextranomer in stabilized hyaluronic acid (marketed as Solesta). Two trials used a placebo or sham control, 2 compared different bulking agents and the fifth trial compared 2 methods of injecting the same agent. Length of follow-up ranged from 3 to 12 months. Four of the 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; moreover, there was 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. Although data from RCTs are needed to draw conclusions about efficacy of bulking agents, data from observational studies are useful for analysis of safety outcomes. Hussain et al included 1070 patients from 39 studies in a safety analysis. Adverse events
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occurred in 139 patients (13.5%). The most common complication was pain, which occurred in 67 patients (6.5%) followed by leakage of injected material, which was reported by 58 patients (5.6%). The authors did not report the number of serious adverse events.

Randomized Controlled Trials
The RCT evaluating Solesta that was included in the Cochrane review was published in 2011 by Graf et al. This was an industry-sponsored multicenter RCT that compared Solesta with sham treatment in 206 adult patients. To be eligible for inclusion, patients needed to have a Cleveland Clinic Florida Fecal Incontinence Score (CCFIS) of 10 or higher, at least 4 documented incontinence episodes in 2 weeks, symptoms for at least 12 months and have failed 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 patients (86%) in the active treatment group and 61 patients (87%) 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 study 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 of 206 (96%) of randomized patients completed the 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 statistically significant (odds ratio [OR], 2.36; 95% confidence interval [CI], 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 than the sham group (3.1 vs 1.7, respectively; 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 CCFIS did not differ significantly at 6 months; (2.5 points in the active treatment group vs 1.7 points in the sham treatment group). 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 than 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. The authors did not report the proportion of patients who were 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 patients (14%). In contrast, 2 patients (3%) in the sham group reported proctalgia. Moreover, 10 patients (7%) in the active treatment group and 1 patient (1%) in the sham group had rectal hemorrhage. Infection site bleeding occurred in 12 patients (17%) in the sham group and 7 patients (5%) in the active treatment group. Two serious adverse events were reported, both in the active treatment group; there was 1 rectal abscess and 1 prostate abscess.

Subsequent to the Cochrane reviewers’ search of the literature, Dehli et al in Norway published findings of an RCT evaluating Solesta. A total of 126 adults with fecal incontinence were randomized to receive
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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 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 patients (8%) 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. The difference between groups in St. Mark’s score reduction at 6 months was not statistically significant. In addition, change in St. Mark’s score did not differ between groups at 24 months; only 61 patients (49%) completed the 24-month follow-up. Three of the first 10 patients in the bulking agent group got infections at the injection site and underwent treatment; subsequent patients in this group received prophylactic antibiotics.

Another 2013 RCT was conducted in Australia and compared 2 bulking agents for fecal incontinence. Neither of the 2 bulking agents are FDA-approved for use in the U.S. Moreover, the study was terminated early because 1 of the 2 agents was removed from the Australian Pharmaceutical Benefits Scheme. The study found no difference in efficacy between the 2 agents. The trial lacked a comparison group of patients who did not receive bulking agents, which limits the ability to draw conclusions about the relative efficacy of bulking agents to sham or alternative treatments.

Uncontrolled Trials
Longer term data on Solesta are available from an uncontrolled study 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
Several RCTs and a systematic review of RCTs on bulking agents for the treatment of fecal incontinence have been published. A 2016 comparative effectiveness review from AHRQ 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 outcome measures 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.

Ongoing and Unpublished Clinical Trials
Some currently unpublished trials that might influence this review are listed in Table 1.
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Table 1. Summary of Key Trials

<table>
<thead>
<tr>
<th>NCT No.</th>
<th>Trial Name</th>
<th>Planned Enrollment</th>
<th>Completion Date</th>
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<td>NCT01647906</td>
<td>A Prospective, Single Arm, Multicenter, Observational Assessment of the Long Term Safety and Efficacy of Solesta Injectable Bulking Agent for the Treatment of Fecal Incontinence (SoFI)</td>
<td>244</td>
<td>Dec 2017</td>
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<td>NCT02538991</td>
<td>TVT Versus Bulkmid-Injections in Treatment of Stress Urinary Incontinence - Patient Satisfaction and Complications of the Treatment</td>
<td>212</td>
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NCT: national clinical trial.

* Denotes industry-sponsored or cosponsored trial.

Clinical Input Received Through Physician Specialty Societies and Academic Medical Centers

While the various physician specialty societies and academic medical centers may collaborate with and make recommendations during this process, through the provision of appropriate reviewers, input received does not represent an endorsement or position statement by the physician specialty societies or academic medical centers, unless otherwise noted.

In response to requests, input was received from 4 physician specialty societies and 4 academic medical centers while this policy was under review in 2013. There was consensus agreement with all of the policy statements among reviewers who provided responses. In particular, for the statement added in 2013 that perianal bulking agents to treat fecal incontinence is considered investigational, there was unanimous agreement among respondents.

Summary

For individuals who have stress urinary 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. Studies have shown that cross-linked collagen improves the net health outcome (ie, it is effective in some patients who failed conservative treatment with fewer adverse events than surgery), although this product is no longer commercially available. There is evidence that FDA-approved carbon-coated spheres, calcium hydroxylapatite, and polydimethylsiloxane have efficacy for treating incontinence and produce outcomes and have a safety profile similar to cross-linked collagen. The evidence is sufficient to determine qualitatively 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 outcome measures 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.

References

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Injectable Bulking Agents for the Treatment of Urinary and Fecal Incontinence

Policy # 00095
Original Effective Date: 01/27/2003
Current Effective Date: 11/16/2016


Policy History

Original Effective Date: 01/27/2003
Current Effective Date: 11/16/2016

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

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01/23/2008  Medical Policy Committee approval. Policy statement revised to include newly FDA-approved bulking agents.
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 periurethral 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

Next Scheduled Review Date:  11/2017

Coding
The five character codes included in the Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines are obtained from Current Procedural Terminology (CPT®)‡, copyright 2015 by the American Medical Association (AMA). CPT is developed by the AMA as a listing of descriptive terms and five character identifying codes and modifiers for reporting medical services and procedures performed by physician.

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CPT is a registered trademark of the American Medical Association.

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

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<td>Codes added effective 10/1/16: T83.713A-T83.713S, T83.714A-T83.714S, T83.723A-T83.723S, T83.724A-T83.724S</td>
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*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. 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 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; or
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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