Policy Replaced with LCD L34555
Effective February 26, 2018

BlueCross BlueShield of Alabama

Name of Blue Advantage Policy:
Injectable Bulking Agents for the Treatment of Fecal Incontinence

Policy #: 455
Category: Surgery

Latest Review Date: September 2017
Policy Grade: B

Background/Definitions:

Blue Advantage *medical policy does not conflict with Local Coverage Determinations (LCDs), Local Medical Review Policies (LMRPs) or National Coverage Determinations (NCDs) or with coverage provisions in Medicare manuals, instructions or operational policy letters. In order to be covered by Blue Advantage the service shall be reasonable and necessary under Title XVIII of the Social Security Act, Section 1862(a)(1)(A). The service is considered reasonable and necessary if it is determined that the service is:*

1. *Safe and effective;*
2. *Not experimental or investigational*;*
3. *Appropriate, including duration and frequency that is considered appropriate for the service, in terms of whether it is:*
   - *Furnished in accordance with accepted standards of medical practice for the diagnosis or treatment of the patient's condition or to improve the function of a malformed body member;*
   - *Furnished in a setting appropriate to the patient's medical needs and condition;*
   - *Ordered and furnished by qualified personnel;*
   - *One that meets, but does not exceed, the patient's medical need; and*
   - *At least as beneficial as an existing and available medically appropriate alternative.*

Routine costs of qualifying clinical trial services with dates of service on or after September 19, 2000 which meet the requirements of the Clinical Trials NCD are considered reasonable and necessary by Medicare. Providers should bill* ***Original Medicare* *for covered services that are related to* ***clinical trials*** *that meet Medicare requirements (Refer to Medicare National Coverage Determinations Manual, Chapter 1, Section 310 and Medicare Claims Processing Manual Chapter 32, Sections 69.0-69.11).*

Description of Procedure or Service:

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. A number of products have been developed, and there are several U.S. Food and Drug Administration (FDA)-approved options for treating urinary incontinence and 1 for fecal incontinence.

Injectable bulking agents are space-filling substances used to increase tissue bulk. When used to treat stress urinary incontinence (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 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 post-prostatectomy 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 (IAS) 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 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 the U.S. 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 be absorbed over time and symptoms could recur, requiring additional injections. Contigen production was discontinued in 2011. Other periurethral bulking agents cleared by the FDA for urinary incontinence include carbon-coated beads (e.g., Durasphere®), spherical particles of calcium hydroxylapatite (CaHA) in a gel carrier (Coaptite®), polydimethylsiloxane (silicone, Macroplastique®), and ethylene vinyl alcohol copolymer implants (e.g., Uryx®, marketed under the trade name Tegress® starting in 2005). Tegress was later 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, etc. have been studied for the treatment of fecal incontinence. To date, only one bulking agent has been approved by the FDA for treating fecal incontinence. This is a formulation of 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 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.

Coverage criteria for Periurethral Bulking Agents for the treatment of Urinary Incontinence see Incontinence Control Devices (230.10) PM

Policy:

Effective for dates of service on or after February 26, 2018 refer to LCD L34555

Effective for dates of service prior to February 26, 2018:
Blue Advantage will treat the use of **perianal bulking agents to treat fecal incontinence** as a **non-covered benefit** and as **investigational**.

Blue Advantage does not approve or deny procedures, services, testing, or equipment for our members. Our decisions concern coverage only. The decision of whether or not to have a certain test, treatment or procedure is one made between the physician and his/her patient. Blue Advantage administers benefits based on the members' contract and medical policies. Physicians should always exercise their best medical judgment in providing the care they feel is most appropriate for their patients. Needed care should not be delayed or refused because of a coverage determination.

Key Points:

The most recent literature review searched MEDLINE through June 22, 2017.

The literature on injectable bulking agents includes randomized controlled trials (RCTs) that compare bulking agents versus 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. Following is a summary of literature to date.

Urinary incontinence
A 2012 Cochrane review on periurethral bulking agents for urinary incontinence in women identified 14 randomized controlled trials (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 an urodynamic diagnosis of stress incontinence, and seven 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 two bulking agents, two compared bulking agents to surgery, one compared a bulking agent to pelvic floor exercise, and one trial used a placebo comparison group. Several of the studies required that women had experienced incontinence for a specified period of time, e.g., six or 12 months, and/or had already used conservative therapy; one study further specified that

conservative therapy had to have been used for at least three 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 stress urinary incontinence and published in English). Nine studies (total n=682) 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 two years, and 30% to 43% at more than four years. There were eight trials (n=507) using cross-linked 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 one year, but results, particularly with older agents, diminish over time, and repeated injections can restore or enhance improvement.

Bulking Agents Approved by the U.S. Food and Drug Administration (FDA)

Cross-Linked Collagen (Contigen®)

The 1996 Clinical Practice Guidelines for Urinary Continence in Adults, developed by the Agency for Health Care Policy and Research (AHCPR, now Agency for Healthcare Research and Quality [AHRQ]), concluded that periurethral collagen is curative in 32% of men and 62% of women. A randomized controlled trial published in 2005 compared the efficacy of collagen injections with surgery in 133 women. Eligibility criteria included stress incontinence for at least six months or one 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 stress urinary incontinence. 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 double-blind randomized study comparing carbon-coated beads to cross-linked 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.

Ethylene Vinyl Alcohol Copolymer (EVA, e.g., Uryx™ marketed as Tegress™)

The copolymer implant (Uryx™/ Tegress™) received FDA approval based on a study that randomly assigned 237 women with stress urinary incontinence to undergo periurethral bulking with Uryx or to a "currently marketed absorbable bulking agent." The effectiveness at 12 months was similar in the two groups, with 18.4% of those receiving Uryx reporting that they were dry and 48.7% reporting improvement by one grade, compared to 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 non-inferiority 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 calcium hydroxylapatite and 57 (57%) control patients treated with collagen showed an improvement of one grade or more on the four-grade Stamey Urinary Incontinence Scale at 12-month follow-up. Similar results were obtained by intent-to-treat analysis, with non-inferiority of calcium hydroxylapatite to collagen for improvement of at least one Stamey grade (58% vs. 51%, respectively) and decrease in pad weight (51% vs. 38%, respectively) of 50% or more.

Polydimethylsiloxane (Silicone, Macroplastique®)
FDA approval of Macroplastique® (polydimethylsiloxane) was also partly based on a randomized non-inferiority comparison with collagen in women with stress urinary incontinence (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 non-inferior 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 one Stamey grade ($p<0.001$ for non-inferiority). 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 one Stamey grade compared to 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 one 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 (Dx/HA, Zuidex™) with an Injection System (Implacer™)
The Zuidex-Implacer is a system to inject Dx/HA in the outpatient clinic without the need for endoscopy. An industry-sponsored (Q-Med) randomized non-inferiority trial that compared the Zuidex/Implacer system to Contigen conducted in North America was published in 2009. Patients were blinded to treatment group. The primary study outcome was the proportion of women who had an equal to or greater than 50% reduction in urinary leakage on provocation testing from baseline to 12 months after the final treatment (up to three treatments were permitted). The primary outcome was achieved by 65% of Zuidex-treated women compared to 84% in the Contigen group; non-inferiority of Zuidex was not established. The study is limited by a high rate of missing data; primary outcome data were missing for 35% of randomly assigned patients.

A 2005 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% 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 an RCT that was performed under an FDA-regulated investigational device exemption (IDE). This single-blind multicenter randomized non-inferiority trial compared Bulkamid with Contigen (collagen gel) in 345 women. Up to three injections were given. Patients completed the outcome measures at one, three, six, nine, and twelve 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 series (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 VAS quality of life (QOL) and the International Consultation on Incontinence Questionnaires (ICIQ). 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 one episode of incontinence daily. Ninety-eight (73%) completed the 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 at six and 12 months was 71% and 66%, respectively. Corresponding cure rates were 16% and 24%. There were 32 treatment-related adverse effects including two cases of urinary retention requiring hospitalization and ten cases of urinary tract infection (UTI).

A 2013 two-center prospective series included 82 women who had stress incontinence lasting at least 12 months. Patients received an injection of Bulkamid and non-responders were offered a second injection after three months. A total of 80 (98%) women were evaluated at three and six months and 78 (95%) completed the one-year follow-up. The primary efficacy outcome was the subjective success rate at one year, defined as answering one or two on the Patient Global Improvement Impression (PGI-I) questionnaire, which has a range from one (very much better)

to seven (very much worse). In an intention-to-treat analysis, the subjective success rate at one year was 74% (61 of 82 patients). Seven patients reported no change, and none reported worsening of symptoms. At one 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 eight 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, one received a second treatment with hydrogel, and seven 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.

Bulking Agents That Do Not Require FDA Approval
Autologous fat and autologous ear chondrocytes
Other materials have been used as bulking agents but have not demonstrated sustained effectiveness comparable to cross-linked collagen or carbon-coated beads. In a double-blind randomized clinical trial of 56 female patients that compared periurethral injections of autologous fat (treatment group) to saline (placebo group), Lee and colleagues found that periurethral fat injections did not appear to be more efficacious than placebo for treating stress incontinence. At three months, only 6 of 27 patients (22.2%) in the treatment group and six of 29 (20.7%) in the placebo group were cured or improved. In addition, one death occurred as a result of a pulmonary fat embolism. In another clinical trial of 32 female patients, Bent and colleagues 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 non-immunogenic 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."

Pooled data from 80 patients in two phase I/II dose response trials from Cook MyoSite were reported in 2014. Completion of a phase III trial (NCT01382602) with 150 patients is expected December 2016.

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 in the bulking agent

used and the comparison intervention e.g., 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 to alternative treatments. Cross-linked collagen is the most established bulking agent that is currently available, but it has been withdrawn from the market. Results from available trials suggest that carbon-coated spheres, calcium hydroxylapatite, 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

Systematic Reviews

A 2016 comparative effectiveness review for AHRQ evaluated treatments for fecal incontinence. The review found low-strength evidence from 2 RCTs that dextranomer anal bulking injections (NASHA/DX, Solesta) were more effective than sham injections on some outcome measures (i.e., 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 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 five 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 four RCTs. The five identified 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 five 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, two compared different bulking agents and the fifth trial compared two methods of injecting the same agent. Length of follow-up ranged from three 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, two 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 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, included in the 2011 Cochrane, was an industry-sponsored multicenter RCT (2011) 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 one 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 one 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 three 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, two patients (3%) in the sham group reported proctalgia. Moreover, 10 patients (7%) in the active treatment group and one patient (1%) in the sham group had rectal hemorrhage. Infection site bleeding occurred in 12 patients (17%) in the sham group and seven patients (5%) in the active treatment group. Two serious adverse events were reported, both in the active treatment group; there was one rectal abscess and one prostate abscess.

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 receive 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 six 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 two bulking agents for fecal incontinence. Neither of the two bulking agents is FDA-approved for use in the U.S. Moreover, the study was terminated early because one of the two agents was removed from the Australian Pharmaceutical Benefits Scheme. The study found no difference in efficacy between the two 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 (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 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 two 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 Solesta 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 whether 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 stress urinary incontinence who receive injectable bulking agents, the evidence includes randomized controlled trials (RCTs) and systematic reviews of RCTs.

Relevant outcomes are symptoms, functional outcomes, quality of life, and treatment-related morbidity. There is sufficient evidence to conclude that cross-linked collagen improves the net health outcome (i.e., effective in some patients who 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, calcium hydroxylapatite, and polydimethylsiloxane have efficacy for treating incontinence and have efficacy and safety 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 (AHRQ) evaluated 2 RCTs with the FDA-approved product NASHA Dx (Solesta) and 2 RCTs with Durasphere (off-label in the United States). 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 (Solesta) and biofeedback. Two additional RCTs with 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.

Practice Guidelines and Position Statements

Society of Obstetricians and Gynecologists of Canada

In 2010, the Society of Obstetricians and Gynecologists of Canada Urogynecology Committee published a guideline on the evaluation and treatment of recurrent urinary incontinence after pelvic floor surgery. The guideline recommends that conservative management be used as first-line therapy. It also stated that patients with significantly decreased urethral mobility may be managed with periurethral bulking agents as one of several treatment options.

National Institute for Health and Care Excellence

In 2013, NICE amended its 2006 clinical guideline on urinary incontinence in women. The guideline now recommends considering intramural bulking agents (silicone, carbon-coated zirconium beads or hyaluronic acid/dextran copolymer) for the management of SUI if conservative management has failed. Women should be made aware that repeat injections may be needed to achieve efficacy and that efficacy diminishes with time and is inferior to that of synthetic tapes or autologous rectus fascial slings.

In 2007, the National Institute for Health and Clinical Excellence (NICE) in the U.K. published guidance on injectable bulking agents for treating fecal incontinence. The guidance stated that there is insufficient evidence to support the safety and efficacy of injectable bulking agents for fecal incontinence, and use of these products should take place in the context of a clinical trial.

American Society of Colon and Rectal Surgeons

In 2015, the American Society of Colon and Rectal Surgeons (ASCRS) published practice parameters for the treatment of fecal incontinence. ASCRS gave a weak recommendation based on moderate-quality evidence (2B) that injection of bulking agents into the anal canal may help

to decrease episodes of passive fecal incontinence. Studies reviewed showed modest short-term improvements, and no study was identified that the long-term benefit of bulking agents.

American College of Obstetricians and Gynecologists

In 2016, the American College of Obstetricians and Gynecologists issued an updated practice bulletin on urinary incontinence in women. The practice bulletin states that "urethral bulking injections are a relatively noninvasive treatment for stress urinary incontinence that may be appropriate if surgery has failed to achieve adequate symptom reduction, if symptoms recur after surgery, in women with symptoms who do not have urethral mobility, or in older women with comorbidities who cannot tolerate anesthesia or more invasive surgery. However, urethral bulking agents are less effective than surgical procedures such as sling placement and are rarely used as primary treatment for stress urinary incontinence." There was insufficient evidence to recommend any specific bulking agent.

U.S. Preventive Services Task Force Recommendations

Not applicable.

Key Words:

Collagen, Treatment of Urinary Incontinence; Durasphere; Incontinence, Treatment with Bulking Agents; Teflon®, Periurethral Injection for Urinary Incontinence, Uryx, Treatment of Urinary Incontinence, Tegress, Treatment of Urinary Incontinence, Ethylene Vinyl Alcohol Copolymer, Treatment of Urinary Incontinence, Coaptite®, CalciumH, Treatment of Urinary Incontinence; Macroplastique®, Polydimethylsiloxane, Treatment of Urinary Incontinence Dextranomer/ Hyaluronic Copolymer, Treatment of Urinary Incontinence, Zuidex™, Implacer™, Solesta

Approved by Governing Bodies:

Several periurethral bulking agents have been approved by the U.S. Food and Drug Administration (FDA) through the premarket approval process for the treatment of stress urinary incontinence due to intrinsic sphincter deficiency; other than Contigen, approval is only for use in adult women. Products include:

- In 1993, Contigen (Allergan, Inc.), 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. 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 calcium hydroxylapatite, suspended in a gel carrier, was approved for soft tissue augmentation in the treatment of stress urinary incontinence due to intrinsic sphincter deficiency in adult females.
- In 2006, Macroplastique (Uroplasty), polydimethylsiloxane, was approved.

In 2011, non-animal stabilized hyaluronic acid/dextranomer in stabilized hyaluronic acid (NASHA Dx) marketed as Solesta® (Q-Med) is indicated for the treatment of fecal incontinence in patients 18 years and older who have failed conservative therapy.

Benefit Application:

Coverage is subject to member's specific benefits. Group specific policy will supersede this policy when applicable.

Coding:

CPT Codes:

46999	Unlisted procedure, anus
51715	Endoscopic injection of implant material into the submucosal tissues of the urethra and/or bladder neck
0377T	Anoscopy with directed submucosal injection of bulking agent for fecal incontinence **(Effective 01/01/15)**

HCPCS:

L8603	Injectable bulking agent, collagen implant, urinary tract, 2.5 ml syringe, includes shipping and necessary supplies
L8605	Injectable bulking agent, dextranomer/hyaluronic acid copolymer implant, anal canal, 1 ml, includes shipping and necessary supplies
L8606	Injectable bulking agent synthetic implant, urinary tract, 1ml syringe, includes shipping and necessary supplies
Q3031	Collagen skin test

Previous Coding:

HCPCS:

C9735	Anoscopy; with directed submucosal injection(s), any substance **(Deleted 12/31/2014)**

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Policy History:

Adopted for Blue Advantage, February 2015
Medical Policy Group, February 2015
Medical Policy Group, September 2016
Medical Policy Group, September 2017
Medical Policy Group, February 2018

This medical policy is not an authorization, certification, explanation of benefits, or a contract. Eligibility and benefits are determined on a case-by-case basis according to the terms of the member's plan in effect as of the date services are rendered. All medical policies are based on (i) research of current medical literature and (ii) review of common medical practices in the treatment and diagnosis of disease as of the date hereof. Physicians and other providers are solely responsible for all aspects of medical care and treatment, including the type, quality, and levels of care and treatment.

This policy is intended to be used for adjudication of claims (including pre-admission certification, pre-determinations, and pre-procedure review) in Blue Cross and Blue Shield's administration of plan contracts.