Medical Policy

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Title: Periurethral Bulking Agents for the Treatment of Urinary and Fecal Incontinence

See Also: *Periureteral Bulking Agents as a Treatment of Vesicoureteral Reflux (VUR)*

Professional
Original Effective Date: January 21, 2011
Revision Date(s): April 10, 2012; August 19, 2013; December 31, 2013
Current Effective Date: August 19, 2013

Institutional
Original Effective Date: May 10, 2012
Revision Date(s): August 19, 2013; December 31, 2013
Current Effective Date: August 19, 2013

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DESCRIPTION

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. One product is commercially available to date for treating 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). Except for Contigen®, bulking agents are indicated by FDA for use only in women, specifically those with stress urinary incontinence due to intrinsic sphincter deficiency. Cross-linked collagen (e.g., Contigen®) has been commercially available for many years. Collagen is slowly absorbed over time, and symptoms may recur, requiring additional injections. 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.

Regulatory Status

Several periurethral bulking agents have been approved by the FDA through the premarket approval process. These devices are indicated 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.
- 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.

One bulking agent was approved by the FDA through the premarket approval process for treating fecal incontinence. 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.

POLICY

A. The use of cross-linked collagen, carbon-coated spheres, calcium hydroxylapatite, or polydimethylsiloxane may be considered **medically necessary** to treat stress urinary incontinence in men and women who have failed appropriate conservative therapy.

B. 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 is considered **experimental / investigational**.

C. The use of any other periurethral bulking agent, including, but not limited to Teflon®, to treat stress urinary incontinence is considered **experimental / investigational**.

D. The use of periurethral bulking agents to treat urge urinary incontinence is considered **experimental / investigational**.

E. The use of perianal bulking agents to treat fecal incontinence is considered **experimental / investigational.**

Policy Guidelines

Patients should have had inadequate response to conservative therapy or therapies; in general, these treatments should have been used for at least 3 months. Conservative therapy for stress incontinence includes pelvic floor muscle exercises and behavioral changes, such as fluid management and moderation of physical activities that provoke incontinence. Additional options include intravaginal estrogen therapy, use of a pessary, and treatment of other underlying causes of incontinence in patients amenable to these treatments.

RATIONALE

An initial literature search on bulking agents to treat urinary incontinence was performed in 1995. The policy was updated regularly with a literature review using the MEDLINE database. The policy was expanded to include fecal incontinence in 2013. The most recent literature review searched MEDLINE through February 12, 2013. Following is a summary of literature to date on use of injectable bulking agents to treat urinary and fecal incontinence.

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. (1) 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 to surgery, 1 compared a bulking agent to 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, e.g., 6 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 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 stress urinary incontinence and published in English). (2) 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 2 years, and 30% to 43% at more than 4 years. There were 8 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 1 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®)

Contigen® was the first bulking agent approved by the U.S. Food and Drug Administration (FDA) for the treatment of urinary incontinence. No randomized trials comparing Contigen to conservative therapy or placebo were identified. 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. (3) A randomized controlled trial published in 2005 compared the efficacy of collagen injections with surgery in 133 women. (4) 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 stress urinary incontinence.

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™. (5) 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.” (6) 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 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, (7) 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. (8) 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 1 grade or more on the 4-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 1 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. (9) 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 1 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. (10) 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 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. (11) 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 3 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.

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. (12) 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. (13) 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. Findings from a multicenter European case series were published in 2010. (14) A total of 135 adult women with symptomatic stress (n=67) or mixed (n=68) incontinence for at least 12 months and at least 1 episode of incontinence per day were included. Ninety-eight (73%) completed the 12-month follow-up; 4 additional patients were excluded from the per-protocol analysis due to protocol violations. The primary outcome was response to treatment, defined as patients self-reporting that they considered themselves "improved" or "cured". The response rate at 6 and 12 months was 71% and 66%, respectively. Corresponding cure rates were 16% and 24%. The study lacked a comparison group with which to compare these outcomes; a comparison group is particularly important with a subjective outcome such as the one used in the study. There were 32 treatment-related adverse effects including 2 cases of urinary retention requiring hospitalization and 10 cases of urinary tract infection. (UTI)

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 to cross-linked collagen or carbon-coated beads. In a randomized, double-blind 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. (15) 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 and colleagues reported that 50% of patients remained dry for 12 months after receiving a single outpatient injection of harvested autologous auricular cartilage. (16) 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. (17) 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. (18) 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.

Conclusions: 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. The evidence on cross-linked collagen is sufficient to conclude that it is effective in some patients who fail conservative treatment and therefore, is a reasonable alternative to more risky surgical procedures. 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

There have been 3 published RCTs evaluating bulking agents for treatment of fecal incontinence. Two were placebo or sham-controlled trials, and 1 compared injections of bulking agents to biofeedback. The RCTs are described below:

In 2013, Dehli and colleagues in Norway published findings of an RCT evaluating Solesta, an FDA-approved non-animal stabilized hyaluronic acid/dextranomer in stabilized hyaluronic acid (NASHA Dx) bulking agent.(19) 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 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% confidence interval [CI]: 11.4-13.8) at baseline to 9.2 points (95% CI: 7.9-10.5). In the bulking agents group, mean scores were 12.9 (95% CI: 11.8-14.0) at baseline and 8.9 (95% CI: 7.6-10.2) 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. Marks'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.

In 2011, Graf and colleagues published an industry-sponsored multicenter RCT that compared Solesta to sham treatment in 206 adult patients. (20) 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 to 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 197/206 (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% 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 versus 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 versus 1.7 points in the sham treatment group). Quality of life was measured by the fecal incontinence quality of life (FIQL) 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, and 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.

In 2007, Siproudhis and colleagues in France published a small, single center, placebo-controlled, double-blind RCT a non-U.S. Food and Drug Administration (FDA)-approved silicone bulking agent, (polydimethylsiloxane). (21) A total of 44 patients with severe fecal incontinence were treated with a bulking agent or saline control. Follow-up was for 3 months, and the primary outcome was the percent of patients with successful treatment, defined as a CCFIS score of less than 8. A secondary outcome measure was the mean CCFIS score at 3 months. There were not statistically significant differences on either outcome measure. The percent of patients with a successful treatment outcome was 27% in the bulking agent group compared to 23% in the

placebo group (p=0.73). The mean CCFIS score decreased from 13.8 at baseline to 11.7 at 3 months in the bulking agent group compared to a mean score of 14.6 at baseline and 11.4 at 3 months in the placebo group (p=0.79).

Systematic Reviews: At least 3 systematic reviews have been published; all conducted literature searches prior to the publication of the RCTs evaluating the FDA-approved bulking agent for treating fecal incontinence. The systematic reviews included other RCTs that compared different types of bulking agents, and/or different types of delivery of bulking agents.

A 2010 Cochrane review on perianal injectable bulking agents for treating fecal incontinence identified 4 RCTs with a total of 176 patients. (22) The trials included patients with anal sphincter dysfunction or passive fecal incontinence who had failed previous conservative treatments e.g. anti-diarrheal medications, pelvic floor muscle training, etc. One trial was placebo-controlled, 2 compared 2 different bulking agents and another compared 2 methods of injecting the same agent. Due to heterogeneity among trials, study findings were not pooled. The Cochrane investigators stated that the single placebo-controlled trial [the study by Siproudhis et al., described above (21)] was too small to detect between-group differences in any outcome. Of the 2 trials comparing bulking agents, 1 had only 10 participants, which is too few to detect between-group differences. The other trial found significantly greater improvement in fecal incontinence at 6 and 12 months using silicone material compared to carbon-coated beads. A limitation of the latter trial is that injectable bulking agents were not compared to placebo or an alternative treatment. None of the agents used in the RCTs were approved by the FDA.

In 2011, 2 systematic reviews were published that included observational studies and RCTs evaluating bulking agents for treating fecal incontinence. (23, 24) Both systematic reviews identified the 4 RCTs included in the Cochrane review. Additionally, the Hussain review included one RCT that did not publish results for the control group, but only for the treatment group, and therefore does not allow conclusions about comparative efficacy of bulking agents. 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 and colleagues included 1,070 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.

Conclusions: Three RCTs evaluating bulking agents for the treatment of fecal incontinence have been published; 2 of these used the FDA-approved product, NASHA Dx (Solesta). Two of the 3 trials (including 1 evaluating Solesta) did not show that bulking agents provided significant benefit compared to the comparison intervention. One RCT using Solesta found that a significantly greater proportion of patients receiving active treatment compared to sham had at least a 50% reduction in incontinence episodes at 6 months. Secondary outcomes were mixed, and the authors did not report the number of patients who attained continence. Moreover, outcomes were not compared in the treatment and sham groups beyond 6 months, and side effects were more prevalent in the treatment group. Systematic reviews published prior to the largest RCT have concluded that there is little evidence for the efficacy of these agents. Overall, this 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 trials with longer follow-up are important to determine the durability of any treatment effect.

Clinical Input Received through Physician Specialty Societies and Academic Medical Centers

In response to requests, input was received through 4 physician specialty societies and 4 academic medical centers while this policy was under review in 2013. Although 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. 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 the respondents.

Summary

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). Moreover, there is evidence that carbon-coated spheres, calcium hydroxylapatite, and polydimethylsiloxane have efficacy for treating incontinence and have efficacy and safety similar to cross-linked collagen. Thus, these bulking agents may be considered medically necessary for patients with urinary incontinence who have failed conservative therapy. There is insufficient published evidence on the efficacy of autologous cellular therapy, autologous fat, autologous ear chondrocytes, and other treatments such as Teflon. Therefore, use of these agents to treat urinary incontinence is considered investigational.

There is insufficient evidence that injectable bulking agents improve the net health outcome for patients with fecal incontinence. The available evidence from randomized controlled trials has not consistently found that perianal bulking agents improve health outcomes compared to a comparison intervention; 1 of 2 trials evaluating the FDA-approved product found benefit, but had limitations. Thus, injectable bulking agents are considered investigational for treating fecal incontinence.

Practice Guidelines and Position Statements

In 2010, the Society of Obstetricians and Gynaecologists of Canada Urogynaecology Committee published a guideline on the evaluation and treatment of recurrent urinary incontinence after pelvic floor surgery. (25) 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.

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. (26) 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.

In 2007, the American Society of Colon and Rectal Surgeons published practice parameters for the treatment of fecal incontinence. (27) The document included the following statement on bulking agents:

"When passive fecal incontinence caused by internal sphincter dysfunction is the predominant symptom, injectable therapy seems to be effective and safe, although its long-term efficacy has yet to be defined. Level of Evidence: II; Grade of Recommendation: B."

In 2005 (reaffirmed 2009), the American College of Obstetricians and Gynecologists (ACOG) issued a practice bulletin on urinary incontinence in women. (28) The practice bulletin included a recommendation for injection of bulking agents (i.e., collagen, carbon-coated beads, and fat) as second-line therapy or in women with urinary incontinence who are ineligible for surgery. This recommendation was based on limited or inconsistent scientific evidence.

CODING

The following codes for treatment and procedures applicable to this policy are included below for informational purposes. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

CPT/HCPCS

51715	Endoscopic injection of implant material into the submucosal tissues of the urethra and/or bladder neck
C9735	Anoscopy; with directed submucosal injection(s), any substance (new code 07.01.2013)
L8603	Injectable bulking agent, collagen implant, urinary tract, 2.5 ml syringe, includes shipping and necessary supplies
L8605	Injectable bulking agent, copolymer/hyaluronic acid copolymer implant, anal canal, 1 ml, includes shipping and necessary supplies
L8606	Injectable bulking agent, synthetic implant, urinary tract, 1 ml syringe, includes shipping and necessary supplies
Q3031	Collagen skin test

- There are HCPCS codes for the bulking agents used in this procedure.
  - L8603 describes collagen implant material, such as Contigen.
  - L8606 describes synthetic bulking agents, such as carbon-coated beads or copolymers (Durasphere or Uryx)
- The physician services associated with urethral bulking agents are described by CPT code 51715.

DIAGNOSES

599.82	Intrinsic (urethral) sphincter deficiency [ISD]
625.6	Stress incontinence, female
788.32	Stress incontinence, male
787.60-787.63	Incontinence of feces code range

ICD-10 Diagnosis (*Effective October 1, 2014)*

N36.43	Combined hypermobility of urethra and intrinsic sphincter deficiency
N36.42	Intrinsic sphincter deficiency (ISD)

N39.3 Stress incontinence (female) (male)
R15.0 Incomplete defecation
R15.1 Fecal smearing
R15.2 Fecal urgency
R15.9 Full incontinence of feces

REVISIONS

04-10-2012	Effective for Institutional providers 30 days after the Revision Date.
	Policy added to the bcbsks.com web site.
08-19-2013	In the Policy Title, added "and Fecal" to read "Periurethral Bulking Agents for the Treatment of Urinary and Fecal Incontinence"
	Updated Description section.
	In Policy section: ▪ Added Item E, "The use of perianal bulking agents to treat fecal incontinence is considered experimental / investigational."
	Updated Rationale section.
	In Coding section: ▪ Added HCPCS codes: C9735 and L8605 ▪ Added Diagnosis codes: 787.60-787.63
	Updated Reference section.
12-31-2013	In Coding section: ▪ Added ICD-10 Diagnosis *(Effective October 1, 2014)*

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