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Subject: Injectable Bulking Agents for the Treatment of Urinary and Fecal Incontinence

THIS MEDICAL COVERAGE GUIDELINE IS NOT AN AUTHORIZATION, CERTIFICATION, EXPLANATION OF BENEFITS, OR A GUARANTEE OF PAYMENT, NOR DOES IT SUBSTITUTE FOR OR CONSTITUTE MEDICAL ADVICE. ALL MEDICAL DECISIONS ARE SOLELY THE RESPONSIBILITY OF THE PATIENT AND PHYSICIAN. BENEFITS ARE DETERMINED BY THE GROUP CONTRACT, MEMBER BENEFIT BOOKLET, AND/OR INDIVIDUAL SUBSCRIBER CERTIFICATE IN EFFECT AT THE TIME SERVICES WERE RENDERED. THIS MEDICAL COVERAGE GUIDELINE APPLIES TO ALL LINES OF BUSINESS UNLESS OTHERWISE NOTED IN THE PROGRAM EXCEPTIONS SECTION.

DESCRIPTION:

Injectable bulking agents are space-filling substances used to increase tissue bulk. When used to treat stress urinary incontinence, bulking agents are injected periurethrally to increase tissue bulk and thereby increase resistance to the outflow of urine. The bulking agent is injected into the periurethral tissue as a liquid that solidifies into a 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.

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

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

Summary and Analysis of Evidence: Hoe et al (2021) completed a systematic review that compared the efficacy and safety of all urethral bulking agents for the treatment of women with SUI. The review included 56 articles. Since there was substantial heterogeneity of patient cohorts across studies and variability in outcomes reported, only a qualitative data analysis was performed. Overall, the authors concluded that the data support the use of Bulkamid and Macroplastique for the treatment of SUI with a short-term efficacy of 30% to 90% and 40% to 85%, respectively. Long-term efficacy for these bulking agents is 42% to 70% and 21% to 80%, respectively. Of all available bulking agents, Bulkamid appears to have the more favorable safety profile, with no cases of erosion or migration associated with its use. Of note, direct comparisons of the urethral bulking agents have not been performed. Pivazyan et al (2021) assessed the efficacy and safety of bulking agents compared to surgical methods for the management of women with SUI, with 6 studies included in the final analysis. The included studies (N=710) had 288 women receiving a urethral bulking agent and 317 undergoing a surgical procedure (eg, midurethral sling, retropubic tape, tension-free vaginal tape). Results revealed bulking agents to be less effective than surgical procedures with regard to subjective improvement after treatment with no difference between the 2 interventions regarding post-intervention complications. A double-blind, RCT comparing carbon-coated beads with cross-linked collagen was reported by Lightner et al (2001) as part of the U.S. Food and Drug Administration (FDA) approval process for Durasphere. The trial found no difference in efficacy or in the number of treatments between groups, although the trial duration (12 months) might not have been sufficient to assess comparative durability. Calcium hydroxylapatite (Coaptite) received FDA approval based partly on results from a single-blind, randomized, noninferiority comparison of collagen products among women with SUI. This trial was later published by Mayer et al (2007) and reported on 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 an intention-to-treat analysis, with noninferiority 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. Polyacrylamide hydrogel (Bulkamid; Contura International A/S) is a gel containing 2.5% cross-linked polyacrylamide and 97.5% apyrogenic water. Sokol et al (2014) reported on an RCT performed under an FDA-regulated investigational device exemption. This single-blind, multicenter, randomized, noninferiority trial compared Bulkamid with collagen gel (Contigen) in 345 women from 33 study sites in the US and Canada. Up to 3 injections were given. Patients had failed at least 2 previous non-invasive therapies for 3 months each (e.g., behavioral modification, electrical stimulation, pelvic muscle exercise, biofeedback, and/or drug therapy). 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. Similar rates of patients completed the study (87.8% vs. 87.9%). Bulkamid met the noninferiority margin, with a minimum 50% decrease in leakage and incontinence episodes in 45.9% of patients in the hydrogel group and 41.4% of patients in the collagen gel group according to the intention-to-treat analysis. At 12 months, 47% of patients treated with hydrogel and 50% of patients treated with collagen gel reported no stress incontinence episodes. Urinary Incontinence Quality of Life Scale scores improved similarly in both groups (+31.4 vs +26.3 points; p-value not reported). A treatment-related serious adverse event occurred in a single patient in the Bulkamid group and involved an episode of transient hematuria. A possible study design and conduct

limitation is that bias due to inadequate allocation concealment cannot be ruled out as methods were not described. Itkonen Freitas et al (2020) evaluated whether Bulkamid is noninferior to tension-free vaginal tape in 224 women with primary SUI not responsive to conservative treatment recruited between September 2015 and March 2017. Enrollees were randomly assigned to tension-free vaginal tape (n=111) or Bulkamid (n=113). The primary outcome was patient treatment satisfaction as measured on a visual analogue scale with 0 representing extremely unsatisfied and 100 extremely satisfied. This outcome was measured at postoperative visits and a patient satisfaction score ≥80 was defined as a good satisfaction rating. In the Bulkamid group, 46 (43%) women requested additional injection at the 3-month visit while 11 (10%) women did not request additional Bulkamid but preferred to receive tension-free vaginal tape. An additional 5 women eventually underwent tension-free vaginal tape after 2 Bulkamid treatments. In the tension-free vaginal tape group, 2 (2%) women underwent Bulkamid treatment with none undergoing a repeat tension-free vaginal tape procedure. Results revealed that the primary patient satisfaction outcome was achieved by more patients in the tension-free vaginal tape group as compared to the Bulkamid group (96 vs. 64). Bulkamid therapy did not attain the noninferiority threshold set in the study. Objective cure via the cough stress test was also better in the tension-free vaginal tape group as compared to Bulkamid. Additionally, more women who underwent tension-free vaginal tape would choose the therapy again or recommend it to a friend. The majority of perioperative complications and all reoperations due to complications were associated with tension-free vaginal tape surgery. FDA approval of polydimethylsiloxane (Macroplastique) was also partly based on a randomized, noninferiority comparison with collagen in women with SUI. The results of this trial were published by Ghoneim et al (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, and improvement in the Stamey Urinary Incontinence Scale. Seventy-five (61%) of 122 patients in the Macroplastique group and 60 (48%) of 125 patients in the collagen group improved at least 1 Stamey grade. Twelve of the 247 randomized patients were excluded from the analysis. Two-year data on 67 of the 75 women who responded to treatment with Macroplastique were published Ghoneim et al (2010). Fifty-six (84%) of the 67 patients had sustained treatment success at 24 months, defined as an improvement of at least 1 Stamey grade over baseline. Forty-five (67%) of the 67 patients evaluated at 24 months were dry (Stamey grade 0). The long-term analysis was limited because it only included a portion of responders from 1 arm of the trial. The analysis included 67 (55%) of 122 patients originally randomized to Macroplastique and did not provide data on the comparison group. Dextranomer/hyaluronic acid (Zuidex®; AstraZeneca) with an injection system (Implacer®; Q-Med AB) is used to deliver the bulking agent in the outpatient clinic setting without endoscopy. An industry-sponsored (Q-Med) randomized noninferiority trial conducted in North America compared the Zuidex system plus the Implacer with Contigen. As reported by Lightner et al (2009), patients were blinded to treatment group. The primary study outcome was the proportion of women who had a 50% or greater reduction in urinary leakage on provocation testing from baseline to 12 months after the final treatment (up to 3 treatments were permitted). The primary outcome was achieved by 65% of Zuidex-treated women compared with 84% in the Contigen group; noninferiority of Zuidex was not established. The trial was limited by a high rate of missing data; primary outcomes data were missing for 35% of randomized patients. Other materials have been used as bulking agents but have not demonstrated the same sustained effectiveness as cross-linked collagen or carbon-coated beads. In a double-blind RCT of 56 women that compared periurethral injections of autologous fat (treatment group) with saline (placebo group), Lee et al (2001) found that periurethral fat injections were not more efficacious than

placebo for treating stress incontinence. At 3 months, only 6 (22.2%) of 27 patients in the treatment group and 6 (20.7%) of 29 in the placebo group were cured or improved. In addition, 1 death occurred as a result of a pulmonary fat embolism. In another clinical trial of 32 women, Bent et al (2001) reported that 50% of patients remained dry for 12 months after receiving a single outpatient injection of harvested autologous auricular cartilage. While autologous substances have a nonimmunogenic advantage, their use may be limited by resorption and fibrous replacement along with local discomfort associated with harvesting procedures. Pooled safety data from 80 patients in 2 phase 1/2 dose-response trials from Cook MyoSite were reported by Peters et al (2014). Additionally, in 2018, Jankowski et al (2018) conducted a randomized, double-blind, placebo-controlled, multicenter trial of intra-sphincteric autologous muscle-derived cells that aimed to enroll 150 female subjects with predominant SUI. Results of an interim analysis revealed an unexpectedly high placebo response rate (90%) using the composite primary outcome, which prevented assessment of the treatment effect as designed and thus enrollment was halted at 61% of planned subjects. Maeda et al (2013) updated a Cochrane review assessing perianal injectable bulking agents for treating fecal incontinence. Reviewers identified 5 RCTs (N=382) comparing bulking agents with placebo, no intervention, or an alternative intervention. The 5 trials all included adults with internal anal sphincter dysfunction or passive fecal incontinence who had failed previous conservative treatments (eg, pelvic floor muscle training). One of the 5 trials [Quiroz et al (2023)] used the FDA-approved bulking agent dextranomer in stabilized hyaluronic acid (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. The length of follow-up ranged from 3 to 12 months. Four trials were judged to be of high or uncertain risk of bias. The greatest potential source of bias was the lack of (or unclear) blinding of outcome assessment and the lack of blinding of surgeons performing the procedure. Due to heterogeneity among trials, study findings were not pooled. Overall, conclusions on efficacy were limited by the small number of RCTs identified, most of which had methodologic limitations, and lack of long-term follow-up. Quiroz et al (2023) published an open-label, single-arm, FDA-mandated, long-term study evaluating the long-term efficacy and safety of Solesta in patients (N=283) who had failed conservative therapy. The study was conducted at 18 sites in the US, and patients received 1 dose of Solesta within 3 months of baseline and a repeat dose at approximately 3 months after the first dose if necessary. The primary endpoint evaluated the need for fecal incontinence reintervention at 36 months. The enrolled patients were largely White (91.8%) and female (85.5%). The majority of patients (76.7%) received 2 treatments. At 36 months the need for reinterventions was 20.8%. CCFIS scores decreased from 13.5 at baseline to 9.2 at the final visit. There were no serious device-related adverse events or death, but 15.2% of patients reported 92 nonserious device-related adverse events with gastrointestinal-related events the most commonly reported. Limitations of this study include a high dropout rate (32%), limited demographic variability, and lack of a comparison group.

UpToDate review “Female urinary incontinence: Treatment” (Lukacz, 2024) states, “Although urethral bulking injections, also known as periurethral or transurethral injection therapy, result in lower cure rates than other surgeries and often require additional "top-off" injections to achieve maximum efficacy, these procedures have been increasingly used for the primary treatment of stress urinary incontinence (SUI) because of their less-invasive nature and rapid recovery. Historically, these procedures were reserved for patients with intrinsic sphincteric dysfunction in the setting of a fixed immobile urethra, for those with persistent/recurrent stress urinary incontinence after a standard anti-incontinence surgery, or for individuals unwilling or unable to tolerate a more invasive surgical procedure.” UpToDate review

"Stress urinary incontinence in women: Persistent/recurrent symptoms after surgical treatment" (Morgan, 2024) states, "Periurethral injection therapy is a reasonable option for women who cannot tolerate surgery and for whom conservative measures are not effective or acceptable." UpToDate review "Urgency urinary incontinence/overactive bladder (OAB) in females: Treatment" (Lukacz, 2024) recommends the following treatments for urge urinary incontinence: pelvic floor exercises, modifying contributory medical and lifestyle (eg, obesity) factors, bladder training, treating vulvovaginal atrophy (if present) with topical estrogen therapy, supervised pelvic floor physical therapy by a physical therapist specifically trained in the modalities, and pharamacotherapy. The review does not include a recommendation for the use of periurethral bulking agents to treat urge urinary incontinence. UpToDate review "Fecal incontinence in adults: Management" (Limbo, Spivak, 2024) states, "Treatment <with injectable anal bulking agents> is still available at select locations, however, it is no longer recommended routinely. It is hypothesized that injection of anal bulking agents (eg, dextranomer stabilized in hyaluronic acid) may enhance resting anal pressures and thereby improve fecal continence, especially in patients with passive fecal incontinence. Studies have suggested limited efficacy in the treatment of fecal incontinence."

POSITION STATEMENT:

The use of carbon-coated spheres (Durasphere®), calcium hydroxylapatite (Coaptite®), polyacrylamide hydrogel (Bulkamid®), or polydimethylsiloxane (Macroplastique®) (refer to Other section for additional proprietary product names) **meets the definition of medical necessity** to treat stress urinary incontinence in men and women who have failed at least 3 months of appropriate conservative therapy [e.g., pelvic floor muscle exercises, behavioral changes (such as fluid management, moderation of physical activities that provoke incontinence); intravaginal estrogen therapy, use of a pessary, or treatment of other underlying causes of incontinence in those amenable to these treatments].

The use of any other periurethral bulking agent, including, but not limited to Teflon (polytetrafluoroethylene), to treat stress urinary incontinence is considered **experimental or investigational**.

The use of autologous cellular therapy (eg, myoblasts, fibroblasts, muscle-derived stem cells, adipose derived stem cells), autologous fat, and autologous ear chondrocytes to treat incontinence, including but not limited to stress urinary incontinence, is considered **experimental or investigational**.

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

The use of perianal bulking agents, including, but not limited to dextranomer/hyaluronic acid, to treat fecal incontinence is considered **experimental or investigational**.

There is a lack of clinical scientific evidence published in peer-reviewed literature to permit conclusions on safety and net health outcomes.

BILLING/CODING INFORMATION:

CPT Coding:

51715	Endoscopic injection of implant material into the submucosal tissues of the urethra and/or bladder neck

HCPCS Coding:

L8603	Injectable bulking agent, collagen implant, urinary tract, 2.5 mL syringe, includes shipping and necessary supplies
L8604	Injectable bulking agent, dextranomer/hyaluronic acid copolymer implant, urinary tract, 1 ml, includes shipping and necessary supplies (**Investigational**)
L8605	Injectable bulking agent, dextranomer/hyaluronic acid copolymer implant, anal canal, 1 ml, includes shipping and necessary supplies (**Investigational**)
L8606	Injectable bulking agent synthetic implant, urinary tract, 1 ml syringe, includes shipping and necessary supplies

ICD-10 Diagnosis Codes That Support Medical Necessity:

N39.3	Stress incontinence (female) (male)

REIMBURSEMENT INFORMATION:

Refer to section entitled **POSITION STATEMENT**.

PROGRAM EXCEPTIONS:

Federal Employee Program (FEP): Follow FEP guidelines.

State Account Organization (SAO): Follow SAO guidelines.

Medicare Advantage products: The following National Coverage Determination (NCD) was reviewed on the last guideline review date: National Coverage Determination (NCD) for Incontinence Control Devices (230.10), located at cms.gov.

DEFINITIONS:

Fecal incontinence: loss of bowel control, causing stool to leak involuntarily from the rectum.

Stress urinary incontinence: involuntary loss of urine caused by dysfunction of the muscles and tissues around the bladder (eg, pelvic floor, sphincter). Coughing or sneezing often causes urine leak.

Urge urinary incontinence: unintentional loss of urine following sudden, overwhelming urge to urinate due to involuntary contractions of the muscular wall of the bladder.

RELATED GUIDELINES:

Pelvic Floor Stimulation as a Treatment of Incontinence, 01-97000-06

Percutaneous Tibial Nerve Stimulation, 02-64000-01

Transvaginal Radiofrequency Bladder Neck Suspension and Transurethral Radiofrequency Tissue Remodeling for Urinary Stress Incontinence, 02-50000-16

OTHER:

Other terms for injectable bulking agents:

Note: The use of specific product names is illustrative only. It is not intended to be a recommendation of one product over another, and is not intended to represent a complete listing of all products available.

Bulkamid® (polyacrylamide hydrogel)
Coaptite® (calcium hydroxylapatite)
Contigen (bovine collagen cross-linked with glutaraldehyde)
Dextranomer/hyaluronic acid (Zuidex; Deflux™)
Durasphere® (carbon-coated spheres)
Macroplastique® (polydimethylsiloxane)
NASHA Dx (marketed as Solesta®; bulking agent to treat fecal incontinence)

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    a. NCT01110681- Study to Evaluate Solesta for Treatment of Fecal Incontinence Condition: Fecal Incontinence.
    b. NCT00971269 - Pilot Study of NASHA/Dx Gel for Fecal Incontinence Condition: Fecal Incontinence.
    c. NCT00303030 - A Randomized, Controlled, Clinical Trial of Biofeedback and Anal Injections as First Treatment of Fecal Incontinence Condition: Fecal Incontinence.
    d. NCT01380132 - Safety and Efficacy of Anorectal Application of Dx-gel for Treatment of Anal Incontinence Condition: Fecal Incontinence.
    e. NCT00605826 - ClinicalTrials.gov – A Randomized, Blinded, Multicenter Study to Evaluate NASHA/Dx for the Treatment of Fecal Incontinence.
    f. NCT01647906 - Long Term Safety and Efficacy of Solesta® Injectable Bulking Agent for the Treatment of Fecal Incontinence (SoFI).
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COMMITTEE APPROVAL:

This Medical Coverage Guideline (MCG) was approved by the Florida Blue Medical Policy and Coverage Committee on 09/26/24.

GUIDELINE UPDATE INFORMATION:

02/15/12	New Medical Coverage Guideline.
01/01/13	Annual HCPCS coding update: added L8605.
02/15/13	Scheduled review; position statement unchanged, references updated.

02/15/14	Annual review; position statement unchanged; Program Exceptions section updated; references updated.
01/01/15	Annual coding update; added 0377T.
02/15/15	Annual review; position statement unchanged, references updated.
11/01/15	Revision: ICD-9 Codes deleted.
12/15/18	Scheduled review. Revised MCG title, CPT, HCPCS, and ICD10 coding sections; Program Exceptions section, definitions section, related guidelines, and index terms. Added coverage for carbon-coated spheres, calcium hydroxylapatite, or polydimethylsiloxane (urinary stress incontinence). Added (E/I) coverage statements for autologous cellular therapy, autologous fat, autologous ear chondrocytes, and treatment of urge urinary incontinence. Updated references.
01/01/20	Annual CPT/HCPCS coding update. Deleted 0377T.
10/15/20	Scheduled review. Maintained position statement and updated references.
12/15/21	Scheduled review. Added coverage statement for Bulkamid® (polyacrylamide hydrogel). Revised OTHER section and updated references.
11/15/23	Scheduled review. Revised description, maintained position statement, and updated references.
10/15/24	Scheduled review. Revised description, maintained position statement and updated references.