Periurethral bulking agents are substances that are injected periurethrally to increase tissue bulk as a treatment of stress urinary incontinence (SUI). Patients receive one or several treatment sessions. A number of products have been developed and are commercially available; key factors in determining the optimal product are biocompatibility, durability, and absence of migration.

Improvement in stress incontinence with bulking agents is achieved by increasing the tissue bulk and thereby increasing 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. Except for Contigen®, however, bulking agents are indicated by the U.S. Food and Drug Administration (FDA) for use only in women, specifically those with stress urinary incontinence due to intrinsic sphincter deficiency.

Biocompatibility, durability, and absence of migration are key factors in the success of bulking agents. 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. Carbon-coated beads (e.g., Durasphere) and ethylene vinyl alcohol copolymer implants (e.g., Uryx®, marketed under the trade name Tegress® starting in 2005) received approval (1999 and 2004, respectively) from the FDA for use as periurethral bulking agents. Both were thought to be more durable than collagen. Tegress was later voluntarily removed from the market due to safety concerns.

In 2005, a bulking agent composed of spherical particles of calcium hydroxylapatite (CaHA) in a gel carrier (Coaptite®) received FDA approval for use in women. Polydimethylsiloxane (silicone, Macroplastique®) received FDA approval in 2006 “for transurethral injection in the treatment of adult women diagnosed with stress urinary incontinence (SUI) primarily due to intrinsic sphincter deficiency.” The FDA approvals are conditional on the enrollment of a minimum of 200–250 patients in a 5-year registry to further evaluate safety and efficacy.
In Europe, Q-Med has marketed a dextranomer/hyaluronic (Dx/HA) copolymer (Zuidex™) together with an injection system (Implacer™) for treatment of urinary incontinence. A Dx/HA formulation (Deflux™) from the same company has been commercially available for a number of years for the treatment of vesicoureteral reflux in children (see policy No. 7.01.102 on the treatment of vesicoureteral reflux with bulking agents).

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.

Policy

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.

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 investigational.

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

Policy Guidelines

There are HCPCS codes for the bulking agents used in this procedure. L8603 describes collagen implant material, such as Contigen, and 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. See coding section below.

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 was performed in 1995. The policy was updated regularly with a literature review using MEDLINE; most recently, the literature was searched from July 2011 through August 2012. Following is a summary of literature to date on use of periurethral bulking agents to treat 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 an 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, 6) 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.” (7) 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, (8) 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. (9) 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 SUI. Results of this trial were published in 2009. (10) 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. (11) 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. (12) 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. (13) 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. (14) 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. (15) 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. (16) 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. (17) 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. (18) 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. (19) 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.

**Summary**

A number of RCTs and a Cochrane review of RCTs evaluating periurethral bulking agents for the treatment of urinary incontinence have been published. The trials vary in the bulking agent used and the comparison intervention 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 risk 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. These agents may be considered medically necessary for patients who
have failed appropriate 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; thus, these are considered investigational.

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. (20) 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 2005 (reaffirmed 2009), the American College of Obstetricians and Gynecologists (ACOG)
issued a practice bulletin on urinary incontinence in women. (21) 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.

Medicare National Coverage

The Medicare National Coverage Determination for Incontinence Control Devices (230.10)
dresses collagen implants but not other types of bulking agents. (22) Specific information on
coverage of collagen implants is, as follows:

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

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

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

References:


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<td>Surgical, urinary system, supplement, bladder neck, via natural or artificial opening endoscopic, codes for autologous tissue substitute, synthetic substitute, and nonautologous tissue substitute</td>
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