02.01.76 Periurethral Bulking Agents for the Treatment of Stress Urinary Incontinence

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Related Policies:

- 02.01.51 Fecal Incontinence Management
- 02.01.73 Biofeedback as a Treatment of Urinary Incontinence
- 02.01.75 Artificial Urinary Sphincter
- 02.01.77 Periureteral Bulking Agents as a Treatment of Vesicoureteral Reflux
- 02.01.78 Percutaneous and Implantable Posterior Tibial Nerve Stimulation
- 02.01.79 Miscellaneous Investigational Therapies and Tests for Urinary Incontinence/Urinary Dysfunction
- 08.01.21 Sacral Nerve Neuromodulation/Stimulation

Summary

Description

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

Summary of Evidence

For individuals who have stress urinary incontinence (SUI) 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 (QOL), and treatment-related morbidity. The trials vary by bulking agents used and comparator interventions (e.g., placebo, conservative therapy, surgical procedure, another bulking agent). Due to this heterogeneity across studies, and the small number of studies in each category, Cochrane reviewers were unable to draw specific conclusions about the efficacy of specific bulking agents compared with alternative treatments. Additionally, authors of another recent systematic review concluded that bulking agents were less effective than surgical procedures regarding subjective improvement after treatment, with no difference between the interventions with regard to complications. Studies have shown that cross-linked collagen improves the net health outcome (i.e., it is effective in some individuals who have 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 the US Food and Drug Administration (FDA) approved Durasphere® (carbon-coated spheres), Coaptite® (calcium hydroxylapatite), Bulkamid® (polyacrylamide hydrogel), and Macroplastique® (polydimethylsiloxane) have efficacy for treating SUI, and further that they produce outcomes with a safety profile similar to cross-linked collagen. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

OBJECTIVE

The objective of this evidence review is to determine whether injectable bulking agents improve the net health outcome for individuals with stress urinary incontinence (SUI).

PRIOR APPROVAL

Not applicable.

POLICY

Medically Necessary

The following periurethral bulking agents may be considered **medically necessary** to treat stress urinary incontinence (SUI) for individuals who are unresponsive to conservative therapy* for at least 3 months:

- Durasphere® (carbon-coated spheres)
- Coaptite® (calcium hydroxylapatite)
- Macroplastique® (polydimethylsiloxane)
- Bulkamid® (polyacrylamide hydrogel)

Additional Treatment Sessions

Individuals with SUI and do not improve with 5 injection procedures (5 separate treatment sessions) are considered treatment failures, and any further treatment of SUI with a medically necessary periurethral bulking agent(s) above is considered **not medically necessary**. Individuals who have a recurrence of stress urinary incontinence (SUI) following successful treatment (5 separate treatment sessions) with a medically necessary periurethral bulking agent above 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 documentation (e.g., documentation must be provided regarding the individual's response from prior treatment[s]).

Investigational

The use of periurethral bulking agents not meeting the above criteria, and including but not limited to the following, as a treatment for SUI and any other types of urinary incontinence, including urge incontinence, is considered **investigational** due to the lack of clinical evidence demonstrating an impact on improved net health outcomes:

- Autologous cellular therapy (e.g., myoblasts, fibroblasts, muscle-derived stem cells, adipose derived stem cells), autologous fat or autologous ear chondrocytes
- Dextranomer/hyaluronic acid (Zuidex® with an injection system (Implacer®; Q-Med AB)
- Polytetrafluoroethylene (Teflon®)

POLICY GUIDELINES

Individuals should have had inadequate response to conservative therapies; in general, these treatments should have been used for at least 3 months:

*Conservative therapy for SUI may include:

- Pelvic floor muscle exercises (Kegel exercises)/supervised pelvic floor therapy

- Behavioral changes, such as:
  - Fluid management
  - Weight loss
  - Moderation of physical activities that provoke stress urinary incontinence

- Additional Options might include:
  - Intravaginal estrogen therapy
  - Use of pessary

- Treatment of other underlying causes of stress incontinence in individuals amendable to these treatments

Coding

See the Codes table for details.

BACKGROUND

Incontinence

Incontinence, especially urinary, is a common condition and can have a substantial impact on quality of life. Estimates from the National Center for Health Statistics have suggested that, among noninstitutionalized persons 65 years of age and older, 44% have reported issues with urinary incontinence.

Treatment

Urinary Incontinence

Injectable bulking agents are space-filling substances used to increase tissue bulk. When used to treat SUI, bulking agents are injected periurethrally to increase 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 genotypic XX individuals. Genotypic XY individuals have also been treated, typically those with postprostatectomy incontinence.

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 to be absorbed over time and symptoms could recur, requiring additional injections. Contigen® production was discontinued in 2011. Other periurethral bulking agents cleared by FDA for urinary incontinence include carbon-coated beads (e.g., Durasphere®), spherical particles of calcium hydroxylapatite (CaHA®) in a gel carrier (Coaptite®), polydimethylsiloxane (silicone, Macroplastique®), cross-linked polyacrylamide hydrogel (Bulkamid®), and ethylene vinyl alcohol copolymer implants (e.g., Tegress®, formerly Uryx®). Tegress® was voluntarily removed from the market due to safety concerns.

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).

Regulatory Status

Several periurethral bulking agents have been approved by FDA through the premarket approval process for the treatment of SUI due to intrinsic sphincter deficiency; other than Contigen®, approval is only for use in adult women. Products include:

- In 1993, Contigen® (Allergan), a cross-linked collagen, was approved. A supplemental approval in 2009 limited the device's indication to the 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. Allergan ceased production in 2011; no reason for discontinuation was provided publicly.
- In 1999, Durasphere® (Advanced UroScience), a pyrolytic carbon-coated zirconium oxide sphere, was approved.
- In 2004, Uryx® (CR Bard), a vinyl alcohol copolymer implant, was approved. In 2005, approval was given to market the device under the name Tegress®. In 2007, Tegress® was voluntarily removed from the market due to safety concerns.

- In 2005, Coaptite® (Merz Aesthetics, previously BioForm Medical), spherical particles of calcium hydroxylapatite, suspended in a gel carrier, was approved.
- In 2006, Macroplastique® (Cogentix Medical), polydimethylsiloxane, was approved.
- In 2020, Bulkamid® Urethral Bulking System (Axonics Modulation Technologies, Inc.), a soft hydrogel that consists of 97.5% water and 2.5% polyacrylamide, was approved

RATIONALE

This evidence review was created in September 2010 with searches of the PubMed database. The most recent literature update was performed through October 2025.

Evidence reviews assess the clinical evidence to determine whether the use of technology improves the net health outcome. Broadly defined, health outcomes are length of life, quality of life, and ability to function, including benefits and harms. Every clinical condition has specific outcomes that are important to patients and managing the course of that condition. Validated outcome measures are necessary to ascertain whether a condition improves or worsens; and whether the magnitude of that change is clinically significant. The net health outcome is a balance of benefits and harms.

To assess whether the evidence is sufficient to draw conclusions about the net health outcome of technology, 2 domains are examined: the relevance, and quality and credibility. To be relevant, studies must represent 1 or more intended clinical use of the technology in the intended population and compare an effective and appropriate alternative at a comparable intensity. For some conditions, the alternative will be supportive care or surveillance. The quality and credibility of the evidence depend on study design and conduct, minimizing bias and confounding that can generate incorrect findings. The randomized controlled trial (RCT) is preferred to assess efficacy; however, in some circumstances, nonrandomized studies may be adequate. RCTs are rarely large enough or long enough to capture less common adverse events and long-term effects. Other types of studies can be used for these purposes and to assess generalizability to broader clinical populations and settings of clinical practice.

Clinical Context and Therapy Purpose

The purpose of injectable bulking agents in individuals who have stress urinary incontinence (SUI) is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The following PICO was used to select literature to inform this review.

Populations

The relevant population of interest is individuals with SUI.

Interventions

The therapy being considered is injectable bulking agents.

Comparators

The following therapies are currently being used to make decisions about SUI: conservative therapy, other injectable bulking agents, and surgery.

Although Contigen® is no longer commercially available, it continues to be a common and acceptable comparator for subsequently developed injectable bulking agents. Previously, a clinical practice guideline (1996) for urinary continence in adults concluded that periurethral collagen is curative in 32% of men and 62% of women. Additionally, an RCT by Corcos et al (2005), compared the efficacy of collagen injections with surgery in 133 women and found 12-month success rates for collagen treatment (53%) were lower than for surgery (72%), but the collagen-treated group had significantly fewer adverse events (36% vs 63%, respectively).

Outcomes

The general outcomes of interest are symptom reduction, symptom recurrence, and treatment-related adverse events (e.g., pain, infection). Bulking agents may or may not be curative, and follow-up injections may be necessary within 6 months. Beneficial effects may last between 3 and 12 months.

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies;
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought;
- Studies with duplicative or overlapping populations were excluded.

Review of Evidence

Systematic Reviews

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 supports 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 (e.g., 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 (risk ratio: 0.70; 95% confidence interval [CI], 0.53 to 0.92, p=.01) with no difference between the 2 interventions regarding post-intervention complications (risk ratio: 1.30; 95% CI, 0.30 to 5.66; p=.73).

A Cochrane review by Kirchin et al (2017) evaluating periurethral bulking agents for urinary incontinence in women identified 14 RCTs (sample ranges, 30 to 355 patients) that included bulking agents in at least 1 study arm. This review updated a 2012 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 trials varied by types of bulking agent and comparator interventions used. Eight studies compared 2 bulking agents, 2 compared bulking agents with surgery, 1 compared a bulking agent with pelvic floor exercise, and 1 used a placebo comparison group. Several 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; 1 study further specified that conservative therapy had to have been used for at least 3 months. Reviewers determined that the data were unsuitable for pooling due to heterogeneity across trials. They concluded that there was insufficient evidence to guide practice and recommended that additional RCTs with a placebo group or conservative treatment arm be conducted.

A systematic review by Davila (2011) identified 20 studies meeting inclusion criteria (prospective clinical studies or RCTs conducted among women with SUI and published in English. Nine studies (n=682 patients) 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. Eight trials (n=507 patients) used cross-linked polydimethylsiloxane injection. Cure rates ranged from 20% to 71% at 12 months and 18% to 40% at long-term follow-up (to 60 months). Reviewers concluded that bulking agents had demonstrated effectiveness at 1 year, but results, particularly with older agents, diminished over time and required repeated injections to restore or enhance improvement.

U.S. Food and Drug Administration-Approved Bulking Agents

Carbon-Coated Beads (e.g., Durasphere®)

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 (e.g., Coaptite®)

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 (e.g., Bulkamid®)

Randomized Controlled Trials

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 $\geqslant$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 (difference: 35.2%; 95% CI, 24.4 to 45.1, p<.001). Objective cure via the cough stress test was also better in the tension-free vaginal tape group as compared to Bulkamid® (95% vs. 66.4%; difference: 28.6%; 95% CI, 18.4 to 38.5). 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.

Case Series

Several case series, conducted in Europe, have been published. The largest (N=256) is by Pai and Al-Singary (2015). Women with stress or mixed urinary incontinence (>1 episode per 24 hours) who received injections of Bulkamid® were assessed yearly with quality of life measured by visual analog scale and incontinence by the International Consultation on Incontinence Questionnaire. 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 for 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 multicenter series by Lose et al (2010) included 135 adult women with symptomatic stress (n=67) or mixed (n=68) incontinence. Eligibility included the presence of symptoms for at least 12 months, including at least 1 episode of incontinence daily. Ninety-eight (73%) patients completed 12-month follow-up. The primary outcome was response to treatment, defined as patients self-reporting that they considered themselves "improved" or "cured." The response rate was 71% at 6 months and 66% at 12 months. Corresponding cure rates were 16% and 24%. There were 32 treatment-related adverse effects including 2 cases of urinary retention requiring hospitalization and 10 cases of urinary tract infection.

A 2-center prospective series by Maggiore et al (2013) included 82 women who had had stress incontinence for at least 12 months. Patients received an injection of Bulkamid®, and nonresponders were offered a second injection after 3 months. A total of 80 (98%) women were evaluated at 3 and 6 months, and 78 (95%) completed a 1-year follow-up. The primary efficacy outcome was the subjective success rate at 1 year, defined as answering 1 or 2 on the Patient Global Improvement Impression questionnaire, which is scored from 1 (very much better) to 7 (very much worse). In an intention-to-treat analysis, the subjective success rate at 1 year was 74% (61/82 patients). Seven patients reported no change, and none reported symptoms worsening. At 1 year, 87% (71/78) of patients were considered to be responders (answer of 1, 2 or 3 on the Patient Global Improvement Impression). Twenty-one (26%) patients had adverse events attributable to the injection procedure. The most common adverse event was urinary tract infection, reported by 8 patients. Four patients reported de novo urinary urgency; in all cases, this resolved within 3 months.

Eight-year outcomes were reported by Mouritsen et al (2014) for 24 women, of whom 15 (62.5%) had no further treatment, 1 received a second treatment with hydrogel, and 7 had placement of mid-urethral slings. Subjectively, 44% considered their incontinence to be cured or much improved. Vaginal ultrasonography showed visible hydrogel deposits in all patients.

Polydimethylsiloxane (e.g., Silicone, Macroplastique®)

FDA approval of polydimethylsiloxane (Macroplastique®) was also partly based on a randomized, noninferiority comparison with collagen in women with stress urinary incontinence (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 (p<.001 for noninferiority). 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.

Non-Food and Drug Administration-Approved Bulking Agents

Dextranomer/Hyaluronic Acid (e.g., Zuidex®) With an Injection System (e.g., Implacer®)

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) RCT 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.

An open multicenter study from Europe by Chapple et al (2005) reported on a 12-month 77% positive response rate (reduction $\geq$50% for provocation test urinary leakage) with the dextranomer/hyaluronic acid (Zuidex® system with Implacer) in 142 women who met strict inclusion and exclusion criteria. Similar to the North American trial, this study had a high dropout rate (24%), an unrepresentative patient population, and lacked a comparison group. Twenty-one women in this study were followed for a mean of 6.7 years after treatment with the Zuidex® system. At this long-term follow-up, 7 (33%) of 21 were continent, but 6 of the 7 had had other continence procedures since their Zuidex® injections.

Polytetrafluoroethylene (e.g., Teflon®)

No published clinical trials were identified on polytetrafluoroethylene (Teflon®) as a bulking agent.

Bulking Agents Not Requiring Food and Drug Administration Approval

Autologous Fat and Autologous Ear Chondrocytes

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.

Autologous Cellular Therapy

Strasser et al (2007) published the first RCT using autologous cell therapy to treat SUI. While widely cited as an important advance in the field, the Lancet retracted publication of this trial in 2008 due to ethical and quality concerns.

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.

Kaufman et al (2024) conducted a double-blind RCT using autologous cell therapy to treat SUI. Adult women (N=297) were randomized 2:1 to either autologous cell therapy or placebo, respectively, and stratified by severity of incontinence and prior SUI surgery. After 12 months, patients receiving placebo could opt to receive open-label autologous cell therapy. At 12 months, the proportion of patients achieving the primary endpoint of ≥50% SUI episode reduction was not statistically significant between treatment groups (52% vs 53.6%; p=.798). Adverse events related to treatment were reported in 9.5% of patients receiving autologous cell therapy compared to 6.1% of patients receiving placebo.

Section Summary

A number of RCTs and a Cochrane review of RCTs evaluating periurethral bulking agents for the treatment of urinary incontinence have been published. The trials vary by bulking agents used and comparator interventions (e.g., placebo, conservative therapy, surgical procedure, another bulking agent). Due to this heterogeneity across studies, and the small number of studies in each category, Cochrane reviewers were unable to draw specific conclusions about the efficacy of specific bulking agents compared with alternative treatments. Additionally, authors of another recent systematic review concluded that bulking agents were less effective than surgical procedures regarding subjective improvement after treatment, with no difference between the interventions with regard to complications. Cross-linked collagen is the most well-established bulking agent, but it was withdrawn from the market. Results from available trials have suggested that Durasphere® (carbon-coated spheres), Coaptite® (calcium hydroxylapatite), Macroplastique® (polyacrylamide hydrogel), and Bulkamid® (polydimethylsiloxane) have efficacy for treating SUI that is similar to cross-linked collagen. For other agents (e.g., autologous cellular therapy, autologous fat, autologous ear chondrocytes, Teflon®), there are few RCTs and little evidence of efficacy.

SUPPLEMENTAL INFORMATION

The purpose of the following information is to provide reference material. Inclusion does not imply endorsement or alignment with the evidence review conclusions.

Practice Guidelines and Position Statements

Guidelines or position statements will be considered for inclusion in ‘Supplemental Information' if they were issued by, or jointly by, a US professional society, an international society with US representation, or National Institute for Health and Care Excellence (NICE). Priority will be given to guidelines that are informed by a systematic review, include strength of evidence ratings, and include a description of management of conflict of interest.

American College of Obstetricians and Gynecologists

In 2015, (reaffirmed in 2025), the American College of Obstetricians and Gynecologists (ACOG) updated its practice bulletin on urinary incontinence in women. The practice bulletin stated 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.

American Urological Association and Society of Urodynamics

In 2017, Joint guidelines on the surgical treatment of female SUI from the American Urological Association and Society of Urodynamics, Female Pelvic Medicine and Urogenital Reconstruction stated bulking agents are an option of patients considering surgery for SUI. The guidelines also stated that there are few long-term on the efficacy of bulking agents and that retreatment is common. These recommendations are consistent in the 2023 update to the guidelines

American Urogynecologic Society

In 2024, the American Urogynecologic Society published a clinical practice statement on urethral bulking. They recommended that urethral bulking agents are indicated in cases of stress urinary incontinence (SUI), and that intrinsic sphincter deficiency is not predictive of outcomes (Grade B evidence; strength of recommendation [SOR]: strong recommendation). They also stated that urethral bulking agents may be considered for initial management of SUI, however, the grade and evidence and strength of recommendation were weaker (Grade C evidence; SOR: recommendation).

National Institute for Health and Care Excellence

In 2019, NICE updated its guidance on urinary incontinence in women. The updated guidance recommends "intramural bulking agents to manage stress urinary incontinence if alternative surgical procedures are not suitable for or acceptable to the woman." The patient should be educated that these are permanent injectable materials, repeat injections may be needed, and there is limited evidence on long-term effectiveness and adverse events.

Ongoing and Unpublished Clinical Trials

Some currently ongoing and unpublished trials that might influence this review can be located at clinicaltrials.gov.

REFERENCES

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CODES

To report provider services, use appropriate CPT codes, HCPCS codes, Revenue codes, and/or ICD diagnosis codes.

Codes	Number	Description
CPT		
	51715	Endoscopic injection of implant material into the submucosal tissues of the urethra and/or bladder neck
HCPCS		

	L8604	Injectable bulking agent, dextranomer/hyaluronic acid copolymer implant, urinary tract, 1 ml, includes shipping and necessary supplies
	L8606	Injectable bulking agent synthetic implant, urinary tract, 1 ml syringe, includes shipping and necessary supplies
Type of Service	Surgery	
Place of Service	Inpatient/Outpatient	

POLICY HISTORY

Date	Action	Action
October 2025	Annual Review	Policy Renewed
October 2024	Annual Review	Policy Revised
August 2023	Annual Review	Policy Revised
July 2022	Interim Review	Policy Revised
June 2022	Annual Review	Policy Revised
April 2022	Interim Review	Policy Revised
June 2021	Annual Review	Policy Revised
June 2020	Annual Review	Policy Revised
June 2019	Annual Review	Policy Revised
June 2018	Annual Review	Policy Revised
June 2017	Annual Review	Policy Revised
July 2016	Annual Review	Policy Revised
July 2015	Annual Review	Policy Revised
August 2014	Annual Review	Policy Renewed
May 2014	Interim Review	Policy Revised
September 2013	Annual Review	Policy Revised
October 2012	Annual Review	Policy Renewed

Date	Action	Action
October 2011	Annual Review	Policy Renewed
September 2010	Annual Review	Policy Renewed

New information or technology that would be relevant for Wellmark to consider when this policy is next reviewed may be submitted to:

Wellmark Blue Cross and Blue Shield
Medical Policy Analyst
PO Box 9232
Des Moines, IA 50306-9232

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