Injectable Bulking Agents for the Treatment of Urinary and Fecal Incontinence

Policy # 00095
Original Effective Date: 01/27/2003
Current Effective Date: 11/21/2018

Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc.(collectively referred to as the "Company"), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

Note: Sacral Nerve Neuromodulation/Stimulation is addressed separately in medical policy 00108.

Note: Posterior Tibial Nerve Stimulation for Voiding Dysfunction is addressed separately in medical policy 00415.

When Services Are Eligible for Coverage
Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:

- *Benefits are available in the member's contract/certificate, and*
- *Medical necessity criteria and guidelines are met.*

Based on review of available data, the Company may consider the use of carbon-coated spheres, calcium hydroxylapatite (CaHA), or polydimethylsiloxane to treat stress urinary incontinence (SUI) in men and women who have failed appropriate conservative therapy to be **eligible for coverage**.

When Services Are Considered Investigational
Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Company considers 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 (SUI) to be **investigational.***

Based on review of available data, the Company considers the use of any other periurethral bulking agents, including, but not limited to Teflon®‡ to treat stress urinary incontinence (SUI) to be **investigational.***

Based on review of available data, the Company considers the use of periurethral bulking agents to treat all other indications, including urge urinary incontinence, to be **investigational.***

Based on review of available data, the Company considers the use of perianal bulking agents to treat fecal incontinence to be **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.

Background/Overview

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 and 17% issues with fecal incontinence.

Treatment

Urinary Incontinence

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 postprostatectomy incontinence.

After the success of periurethral bulking agents for treating stress urinary incontinence, 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.

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 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 (eg, 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 (eg, Durasphere), spherical particles of calcium hydroxylapatite (CaHA) in a gel carrier (Coaptite), polydimethylsiloxane (silicone, Macroplastique), and ethylene vinyl alcohol copolymer implants (eg, Tegress, formerly Uryx). Tegress was voluntarily removed from the market due to safety concerns.

Fecal Incontinence
Several agents identical or similar to those used for urinary incontinence (eg, Durasphere, silicone biomaterial) have been studied for the treatment of fecal incontinence. To date, only 1 bulking agent has been approved by FDA for fecal incontinence. This formulation is a non-animal-stabilized hyaluronic acid/dextranomer in stabilized hyaluronic acid (NASHA Dx), 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 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.

FDA or Other Governmental Regulatory Approval

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

- In 1993, Contigen (Allergan), 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.

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In 2011, NASHA Dx, marketed as Solesta®‡ (Q-Med), was approved by FDA through the premarket approval process as a bulking agent to treat fecal incontinence in patients 18 years and older who have failed conservative therapy. FDA product code: LNM.

Centers for Medicare and Medicaid Services (CMS)
The 1996 Medicare National Coverage Determination for Incontinence Control Devices (230.10) addressed collagen implants but not other types of bulking agents. Specific coverage information on 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 H_2O 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 (eg, 6-12 months previously) may benefit from additional treatment sessions. Coverage of additional sessions may be allowed but must be supported by medical justification."

No national coverage determination was identified on injectable bulking agents for treating fecal incontinence.

Rationale/Source

Evidence reviews assess the clinical evidence to determine whether the use of a 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 to 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 a technology, 2 domains are examined: the relevance and the quality and credibility. To be relevant, studies must represent one 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.

URINARY INCONTINENCE

Clinical Context and Therapy Purpose

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

The question addressed in this evidence review is: Does the use of injectable bulking agents improve the net health outcome in patients with stress urinary incontinence?

The following PICOTS were used to select literature to inform this review.

Patients

The relevant population of interest is patients with stress urinary incontinence.

Interventions

The therapy being considered is injectable bulking agents.

Comparators

The following therapies are currently being used to make decisions about stress urinary incontinence: conservative therapy and surgery.

Outcomes

The general outcomes of interest are symptom reduction, symptom recurrence, and treatment-related adverse events (eg, pain, infection).

Timing

Bulking agents may or may not be curative, and follow-up injection may be necessary within 6 months. Beneficial effects may last between 3 and 12 months.

Setting

Injectable bulking agents are administered under local anesthesia in an outpatient setting.

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Systematic Reviews
A Cochrane review by Kirchin et al (2012) evaluating periurethral bulking agents for urinary incontinence in women identified 14 RCTs (sample ranges, 30-355 patients) that included bulking agents in at least 1 study arm. This review updated 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 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 one used a placebo comparison group. Several studies required that women had experienced incontinence for a specified period of time (eg, 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 stress urinary incontinence [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

Cross-Linked Collagen (Contigen)
Contigen is no longer commercially available. 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. An RCT by Corcos et al (2005) compared the efficacy of collagen injections with surgery in 133 women. Twelve-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).

Carbon-Coated Beads (eg, 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 number of treatments between groups, although trial duration (12 months) might not have been sufficient to assess comparative durability.

Ethylene Vinyl Alcohol Copolymer (eg, Tegress)
Tegress, a copolymer implant, was voluntarily withdrawn from the market by its manufacturer, CR Bard, in 2007, following reports of adverse effects. Tegress (formerly Uryx) had previously received FDA approval based on a trial that randomized 237 women with SUI to periurethral bulking with Uryx or to another absorbable bulking agent. Efficacy at 12 months was similar between groups, with 18.4% of those receiving Uryx reporting that they were dry and 48.7% reporting improvement by 1 grade, compared with 16.5% and 53.2%, respectively, in the control group. A repeat injection was necessary for 75% of these patients to achieve satisfactory results.

Calcium Hydroxylapatite (eg, 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 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.

Polydimethylsiloxane (eg, Silicone, Macroplastique)
FDA approval of polydimethylsiloxane (Macroplastique) was also partly based on a randomized noninferiority comparison with collagen in women with SUI. 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 the 122 patients in the Macroplastique group and 60 (48%) of 125 patients in the collagen group improved at least 1 Stamey grade ($p<0.001$ 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-FDA-Approved Bulking Agents

Dextranomer/Hyaluronic Acid (eg, Zuidex) With an Injection System (eg, 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) 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.

An open multicenter study from Europe by Chapple et al (2005) reported on a 12-month 77% positive response rate (reduction ≥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.

Polyacrylamide Hydrogel (eg, 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. A single RCT was identified that compared Bulkamid with an FDA-approved bulking agent (Contigen).

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. Up to 3 injections were given. 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. Bulkamid met the noninferiority margin, with a minimum 50% decrease in leakage and incontinence episodes in 53% of patients in the hydrogel group and 55% of patients in the collagen gel group. At 12 months, 47% of patients treated with hydrogel and 50% of patients treated with collagen gel reported no stress incontinence episodes.

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 the 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 a 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 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 symptom 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 by 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.

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

Bulking Agents Not Requiring FDA 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). A phase 3 trial (NCT01382602) with 150 patients was completed in 2017, but trial results were not identified.

Section Summary: Urinary Incontinence
A number of RCTs and a Cochrane review of RCTs evaluating periurethral bulking agents for the treatment of urinary incontinence have been published. The trials vary by bulking agents used and comparator interventions (eg, placebo, conservative therapy, 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. Cross-linked collagen is the most well established bulking agent, but it was withdrawn from the market. Results from available trials have suggested that carbon-coated spheres, calcium hydroxylapatite, and polydimethylsiloxane have efficacy for treating incontinence that is similar to cross-linked collagen. For other agents (eg, autologous cellular therapy, autologous fat, autologous ear chondrocytes, Teflon), there are few RCTs and little evidence of efficacy.

FECAL INCONTINENCE

Clinical Context and Therapy Purpose
The purpose of injectable bulking agents in patients who have fecal incontinence is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The question addressed in this evidence review is: Does the use of injectable bulking agents improve the net health outcome in patients with fecal incontinence?

The following PICOTS were used to select literature to inform this review.

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Patients
The relevant population of interest is patients with fecal incontinence.

Interventions
The therapy being considered is injectable bulking agents.

Comparators
The following therapies are currently being used to make decisions about fecal incontinence: conservative therapy, sacral nerve stimulation, and surgery.

Outcomes
The general outcomes of interest are symptom reduction, symptom recurrence, and treatment-related adverse events.

Timing
Bulking agents may or may not be curative, and follow-up injection may be necessary within 6 months. Beneficial effects may last between 3 and 12 months.

Setting
Injectable bulking agents are administered under local anesthesia in an outpatient setting.

Systematic Reviews
A comparative effectiveness review, conducted by Forte et al (2016) for the Agency for Healthcare Research and Quality, evaluated treatments for fecal incontinence. Reviewers found low strength of evidence from 2 RCTs that dextranomer anal bulking injections (NASHA Dx, Solesta) were more effective than sham injections on some outcome measures (ie, 50% reduction in episodes, number of incontinence-free days, quality of life) but not more effective than sham on fecal incontinence severity or frequency, and no more effective than pelvic floor muscle training with biofeedback on fecal incontinence severity or quality of life. There was moderate strength of evidence from 2 RCTs comparing Durasphere with a non-FDA-approved bulking agent that off-label use of Durasphere reduced fecal incontinence severity for up to 6 months, with diminishing improvements after that time.

Maeda et al (2013) updated a Cochrane review assessing perianal injectable bulking agents for treating fecal incontinence. Reviewers identified 5 RCTs (total N=382 patients) 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 (detailed next) 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. 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 lack (or unclear) blinding of outcome assessment and lack of blinding of surgeons performing the procedure. Due to heterogeneity among trials, study findings were not pooled. Overall, conclusions on efficacy were limited by the small number of RCTs identified, most of which had methodologic limitations, and lack of long-term follow-up.

Previously, 2 systematic reviews were published that included observational studies and RCTs evaluating bulking agents for treating fecal incontinence. Hussain et al (2011) included 1070 patients from 39 studies in a safety analysis. Adverse events occurred in 139 (13.5%) patients. The most common complication was pain, which occurred in 67 (6.5%) patients, followed by leakage of injected material, which was reported by 58 (5.6%) patients. Reviewers did not report the number of serious adverse events.

Randomized Controlled Trials

The RCT evaluating Solesta, included in the 2011 Cochrane review, was an industry-sponsored multicenter trial, reported by Graf et al (2011), that compared Solesta with sham treatment in 206 adults. To be eligible for inclusion, patients had to have a Cleveland Clinic Florida Fecal Incontinence Score of 10 or higher, at least 4 documented incontinence episodes in 2 weeks, symptoms for at least 12 months, and failure of 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 (86%) patients in the active treatment group and 61 (87%) patients in the sham group received a second procedure. Response to treatment was defined as a reduction in the number of incontinence episodes by 50% or more compared with baseline. The trial 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 (96%) of 206 randomized patients completed 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, 2.36; 95% confidence interval, 1.24 to 4.47; p=0.009). Findings for secondary outcomes at 6 months were mixed. For example, the mean increase in the number of incontinence-free days was significantly higher in the active treatment group (3.1) than the sham group (1.7; p=0.016), but the median decrease in the number of incontinence episodes did not differ significantly between groups (6.0 vs 3.0, respectively; p=0.09). Moreover, change in the Cleveland Clinic Florida Fecal Incontinence Score did not differ significantly between groups at 6 months (2.5 points for active treatment vs 1.7 points for sham treatment). Quality of life was measured by the Fecal Incontinence Quality of Life instrument, which has 4 subscales. One of the 4 subscales (coping and behavior) improved significantly more in the treatment group than in the sham group at 6 months. Change in scores on the other 3 subscales (lifestyle, depression and self-perception, embarrassment) did not differ significantly between

groups at 6 months. Trialists did not report the proportion of patients 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 (14%) patients (vs 2 [3%] patients in the sham group). Moreover, 10 (7%) patients in the active treatment group and 1 (1%) patient in the sham group had a rectal hemorrhage. Injection site bleeding occurred in 12 (17%) patients in the sham group and in 7 (5%) patients in the active treatment group. Two serious adverse events were reported, both in the active treatment group (1 rectal abscess, 1 prostate abscess).

Subsequent to the Cochrane reviewers' search of the literature, Dehli et al (2013) published findings of an RCT evaluating Solesta. A total of 126 adults with fecal incontinence were randomized to 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 Fecal Incontinence Grading System score, which ranges from 0 (perfect continence) to 24 (maximal incontinence). A St. Mark's score of at least 4 was required for study participation. Ten (8%) patients 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 to 13.8) at baseline to 9.2 points (95% CI, 7.9 to 10.5). In the bulking agents group, mean scores were 12.9 (95% CI, 11.8 to 14.0) at baseline and 8.9 (95% CI, 7.6 to 10.2) at 6 months. This difference between groups in St. Mark's score reduction was not statistically significant. In addition, change in St. Mark's score did not differ between groups at 24 months, and only 61 (49%) patients completed the 24-month follow-up. Three of the first 10 patients in the bulking agent group developed infections at the injection site and underwent treatment; subsequent patients in this group received prophylactic antibiotics.

Another RCT, conducted by Morris et al (2013) in Australia, compared 2 bulking agents for fecal incontinence. Neither agent was FDA-approved for use in the United States. The trial was terminated early because one of the agents was removed from the Australian Pharmaceutical Benefits Scheme. The trial found no difference in efficacy between agents. The trial lacked a comparison group of patients not receiving bulking agents, which limits the ability to draw conclusions about the relative efficacy of bulking agents to sham or alternative treatments.

Uncontrolled Trials

Longer term data on Solesta are available from an uncontrolled study conducted by La Torre et al (2013). A total of 115 patients with fecal incontinence received 4 injections of Solesta. Eighty-three (72%) of 115 patients completed the 24-month follow-up. The primary efficacy end point was a response to treatment, defined as a minimum 50% reduction from baseline in the number of fecal incontinence episodes recorded

in a 28-day diary. At the 24-month follow-up, 52 (63%) of 83 patients with data available had responded to treatment. The median number of incontinence-free days in a 28-day period increased from 14.6 at baseline to 21.7 at 24 months. The study lacked a comparison group and had a high dropout rate.

Section Summary: Fecal Incontinence
Several RCTs and systematic reviews of RCTs on bulking agents for the treatment of fecal incontinence have been published. A 2016 comparative effectiveness review from the Agency for Healthcare Research and Quality evaluated 2 RCTs with the FDA-approved product NASHA Dx (Solesta) and 2 RCTs with Durasphere. One RCT using NASHA Dx found that, compared with sham, NASHA Dx improved some outcomes but not others. The other RCT did not find a significant difference in efficacy between NASHA Dx and biofeedback. Two other RCTs evaluating Durasphere (off-label in the U.S.) found short-term improvements in fecal incontinence severity. Overall, the evidence is not sufficient to conclude that bulking agents are an effective treatment for fecal incontinence. Corroboration of the single positive trial is needed, and controlled trials with longer follow-up are important to determine the durability of any treatment effect.

SUMMARY OF EVIDENCE
For individuals who have stress urinary incontinence who receive injectable bulking agents, the evidence includes RCTs and systematic reviews of RCTs. Relevant outcomes are symptoms, functional outcomes, quality of life, and treatment-related morbidity. Studies have shown that cross-linked collagen improves the net health outcome (ie, it is effective in some patients 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 FDA-approved carbon-coated spheres, calcium hydroxylapatite, and polydimethylsiloxane have efficacy for treating incontinence, 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 a meaningful improvement in the net health outcome.

For individuals who have fecal incontinence who receive injectable bulking agents, the evidence includes RCTs and systematic reviews of RCTs. Relevant outcomes are symptoms, functional outcomes, quality of life, and treatment-related morbidity. A comparative effectiveness review from the Agency for Healthcare Research and Quality evaluated 2 RCTs with the FDA-approved product NASHA Dx (Solesta) and 2 RCTs with Durasphere (off-label in the United States). One RCT comparing NASHA Dx with sham found that NASHA Dx improved some outcomes but not others. The other RCT did not find a significant difference in efficacy between NASHA Dx and biofeedback. Two additional RCTs evaluating Durasphere found only short-term improvements in fecal incontinence severity. Controlled trials with longer follow-up are needed to determine the durability of any treatment effect. The evidence is insufficient to determine the effects of the technology on health outcomes.

Injectable Bulking Agents for the Treatment of Urinary and Fecal Incontinence

Policy # 00095
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References

1. Blue Cross-and Blue Shield Association, Medical Policy Reference Manual, "Injectable Bulking Agents for Treatment of Urinary Incontinence", 7.01.19, 9:2018.
2. Gorina Y, Schappert S, Bercovitz A, et al. Prevalence of incontinence among older Americans. *Vital Health Stat 3.* Jun 2014(36):1-33. PMID 24964267
3. Kirchin V, Page T, Keegan PE, et al. Urethral injection therapy for urinary incontinence in women. *Cochrane Database Syst Rev.* Feb 15 2012;2(2):CD003881. PMID 22336797
4. Davila GW. Nonsurgical outpatient therapies for the management of female stress urinary incontinence: long-term effectiveness and durability. *Adv Urol.* 2011;2011:176498. PMID 21738529
5. Agency for Health Care Policy and Research. *Clinical Practice Guideline. Urinary Incontinence in Adults.* Rockville, MD: Department of Health and Human Services; 1996.
6. Corcos J, Collet JP, Shapiro S, et al. Multicenter randomized clinical trial comparing surgery and collagen injections for treatment of female stress urinary incontinence. *Urology.* May 2005;65(5):898-904. PMID 15882720
7. Lightner D, Calvosa C, Andersen R, et al. A new injectable bulking agent for treatment of stress urinary incontinence: results of a multicenter, randomized, controlled, double-blind study of Durasphere. *Urology.* Jul 2001;58(1):12-15. PMID 11445471
8. Hurtado E, McCrery R, Appell R. The safety and efficacy of ethylene vinyl alcohol copolymer as an intra-urethral bulking agent in women with intrinsic urethral deficiency. *Int Urogynecol J Pelvic Floor Dysfunct.* Aug 2007;18(8):869-873. PMID 17103121
9. Food and Drug Administration. Summary of Safety and Effectiveness: URYX Urethral Bulking Agent. 2004; https://www.accessdata.fda.gov/cdrh_docs/pdf3/P030030b.pdf. Accessed July 12, 2018.
10. Mayer RD, Dmochowski RR, Appell RA, et al. Multicenter prospective randomized 52-week trial of calcium hydroxylapatite versus bovine dermal collagen for treatment of stress urinary incontinence. *Urology.* May 2007;69(5):876-880. PMID 17482925
11. Ghoniem G, Corcos J, Comiter C, et al. Cross-linked polydimethylsiloxane injection for female stress urinary incontinence: results of a multicenter, randomized, controlled, single-blind study. *J Urol.* Jan 2009;181(1):204-210. PMID 19013613
12. Ghoniem G, Corcos J, Comiter C, et al. Durability of urethral bulking agent injection for female stress urinary incontinence: 2-year multicenter study results. *J Urol.* Apr 2010;183(4):1444-1449. PMID 20171691
13. Lightner D, Rovner E, Corcos J, et al. Randomized controlled multisite trial of injected bulking agents for women with intrinsic sphincter deficiency: mid-urethral injection of Zuidex via the Implacer versus proximal urethral injection of Contigen cystoscopically. *Urology.* Oct 2009;74(4):771-775. PMID 19660800
14. Chapple CR, Haab F, Cervigni M, et al. An open, multicentre study of NASHA/Dx Gel (Zuidex) for the treatment of stress urinary incontinence. *Eur Urol.* Sep 2005;48(3):488-494. PMID 15967568
15. Lone F, Sultan AH, Thakar R. Long-term outcome of transurethral injection of hyaluronic acid/dextranomer (NASHA/Dx gel) for the treatment of stress urinary incontinence (SUI). *Int Urogynecol J.* Nov 2010;21(11):1359-1364. PMID 20571764
16. Sokol ER, Karram MM, Dmochowski R. Efficacy and safety of polyacrylamide hydrogel for the treatment of female stress incontinence: a randomized, prospective, multicenter North American study. *J Urol.* Sep 2014;192(3):843-849. PMID 24704117
17. Pai A, Al-Singary W. Durability, safety and efficacy of polyacrylamide hydrogel (Bulkamid((R))) in the management of stress and mixed urinary incontinence: three year follow up outcomes. *Cent European J Urol.* Feb 2015;68(4):428-433. PMID 26855795
18. Lose G, Sorensen HC, Axelsen SM, et al. An open multicenter study of polyacrylamide hydrogel (Bulkamid(R)) for female stress and mixed urinary incontinence. *Int Urogynecol J.* Dec 2010;21(12):1471-1477. PMID 20645077
19. Leone Roberti Maggiore U, Alessandri F, Medica M, et al. Outpatient periurethral injections of polyacrylamide hydrogel for the treatment of female stress urinary incontinence: effectiveness and safety. *Arch Gynecol Obstet.* Jul 2013;288(1):131-137. PMID 23371485
20. Mouritsen L, Lose G, Moller-Bek K. Long-term follow-up after urethral injection with polyacrylamide hydrogel for female stress incontinence. *Acta Obstet Gynecol Scand.* Feb 2014;93(2):209-212. PMID 24372312
21. Lee PE, Kung RC, Drutz HP. Periurethral autologous fat injection as treatment for female stress urinary incontinence: a randomized double-blind controlled trial. *J Urol.* Jan 2001;165(1):153-158. PMID 11125386
22. Bent AE, Tutrone RT, McLennan MT, et al. Treatment of intrinsic sphincter deficiency using autologous ear chondrocytes as a bulking agent. *Neurourol Urodyn.* 2001;20(2):157-165. PMID 11170190
23. Strasser H, Marksteiner R, Margreiter E, et al. Autologous myoblasts and fibroblasts versus collagen for treatment of stress urinary incontinence in women: a randomised controlled trial. *Lancet.* Jun 30 2007;369(9580):2179-2186. PMID 17604800
24. Kleinert S, Horton R. Retraction--autologous myoblasts and fibroblasts versus collagen [corrected] for treatment of stress urinary incontinence in women: a [corrected] randomised controlled trial. *Lancet.* Sep 6 2008;372(9641):789-790. PMID 18774408

25. Peters KM, Dmochowski RR, Carr LK, et al. Autologous muscle derived cells for treatment of stress urinary incontinence in women. *J Urol.* Aug 2014;192(2):469-476. PMID 24582537
26. Forte ML, Andrade KE, Butler M, et al. *Treatments for Fecal Incontinence (Comparative Effectiveness Review No. 165).* Rockville, MD: Agency for Healthcare Research and Quality; 2016.
27. Maeda Y, Laurberg S, Norton C. Perianal injectable bulking agents as treatment for faecal incontinence in adults. *Cochrane Database Syst Rev.* Feb 28 2013;2(2):CD007959. PMID 23450581
28. Hussain ZI, Lim M, Stojkovic SG. Systematic review of perianal implants in the treatment of faecal incontinence. *Br J Surg.* Nov 2011;98(11):1526-1536. PMID 21964680
29. Leung FW. Treatment of fecal incontinence - review of observational studies (OS) and randomized controlled trials (RCT) related to injection of bulking agent into peri-anal tissue. *J Interv Gastroenterol.* Oct 2011;1(4):202-206. PMID 22586538
30. Graf W, Mellgren A, Matzel KE, et al. Efficacy of dextranomer in stabilised hyaluronic acid for treatment of faecal incontinence: a randomised, sham-controlled trial. *Lancet.* Mar 19 2011;377(9770):997-1003. PMID 21420555
31. Dehli T, Stordahl A, Vatten LJ, et al. Sphincter training or anal injections of dextranomer for treatment of anal incontinence: a randomized trial. *Scand J Gastroenterol.* Mar 2013;48(3):302-310. PMID 23298304
32. Morris OJ, Smith S, Draganic B. Comparison of bulking agents in the treatment of fecal incontinence: a prospective randomized clinical trial. *Tech Coloproctol.* Oct 2013;17(5):517-523. PMID 23525964
33. La Torre F, de la Portilla F. Long-term efficacy of dextranomer in stabilized hyaluronic acid (NASHA/Dx) for treatment of faecal incontinence. *Colorectal Dis.* May 2013;15(5):569-574. PMID 23374680
34. Kobashi KC, Albo ME, Dmochowski RR, et al. Surgical treatment of female stress urinary incontinence: AUA/SUFU Guideline. *J Urol.* Oct 2017;198(4):875-883. PMID 28625508
35. Chapple CR, Cruz F, Deffieux X, et al. Consensus Statement of the European Urology Association and the European Urogynaecological Association on the Use of Implanted Materials for Treating Pelvic Organ Prolapse and Stress Urinary Incontinence. *Eur Urol.* Sep 2017;72(3):424-431. PMID 28413126
36. Lovatsis D, Easton W, Wilkie D, et al. Guidelines for the evaluation and treatment of recurrent urinary incontinence following pelvic floor surgery. *J Obstet Gynaecol Can.* Sep 2010;32(9):893-904. PMID 21050525
37. National Institute for Health and Care Excellence (NICE). Urinary incontinence in women: management [CG171]. 2015; https://www.nice.org.uk/guidance/CG171/chapter/introduction. Accessed July 12, 2018.
38. American College of Obstetricians and Gynecologists (ACOG). Practice Bulletin No. 155: Urinary Incontinence in Women. *Obstet Gynecol.* May 2016;127(5):e66-81. PMID 27548423
39. Paquette IM, Varma MG, Kaiser AM, et al. The American Society of Colon and Rectal Surgeons' clinical practice guideline for the treatment of fecal incontinence. *Dis Colon Rectum.* Jul 2015;58(7):623-636. PMID 26200676
40. National Institute for Health and Care Excellence (NICE). Injectable bulking agents for faecal incontinence [IPG210]. 2007; https://www.nice.org.uk/guidance/ipg210/chapter/1-guidance. Accessed July 12, 2018.
41. Centers for Medicare & Medicaid Services. National Coverage Determination (NCD) for Incontinence Control Devices (230.10). 1996; https://www.cms.gov/medicare-coverage-database/details/ncd-details.aspx?NCDId=241&ncdver=1&DocID=230.10&bc=gAAAAAgAAAAAAA%3D%3D&. Accessed July 12, 2018.

Policy History

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01/27/2003	Managed Care Advisory Council approval
01/04/2005	Medical Director review
01/18/2005	Medical Policy Committee review. Format revision. Coverage eligibility unchanged.
01/31/2005	Managed Care Advisory Council approval
01/04/2006	Medical Director review
01/17/2006	Medical Policy Committee review. Format revision.
02/23/2006	Quality Care Advisory Council approval
01/10/2007	Medical Director review

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01/17/2007	Medical Policy Committee approval. Coverage eligibility unchanged.
01/09/2008	Medical Director review
01/23/2008	Medical Policy Committee approval. Policy statement revised to include newly FDA-approved bulking agents.
01/07/2009	Medical Director review
01/14/2009	Medical Policy Committee approval. Autologous cellular therapy was added as investigational.
01/07/2010	Medical Director review
01/20/2010	Medical Policy Committee approval. Ethylene vinyl alcohol copolymers were deleted from coverage.
01/06/2011	Medical Director review
01/19/2011	Medical Policy Committee approval. No change to coverage.
03/01/2012	Medical Policy Committee review
03/21/2012	Medical Policy Implementation Committee approval. Added "Urinary" to the policy title. Added that men and women who have failed appropriate conservative therapy are eligible for coverage to treat stress urinary incontinence. Stress urinary incontinence added to the investigational statements. The use of periurethral bulking agents to treat all other indications, including urge urinary incontinence, is considered investigational.
03/07/2013	Medical Policy Committee review
03/20/2013	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
06/05/2014	Medical Policy Committee review
06/18/2014	Medical Policy Implementation Committee approval. Changed the policy title from "Periurethral Bulking Agents for the Treatment of Urinary Incontinence" to "Injectable Bulking Agents for the Treatment of Urinary and Fecal Incontinence". Added that the use of perianal bulking agents to treat fecal incontinence is considered to be investigational.
08/03/2015	Coding update: ICD10 Diagnosis code section added; ICD9 Procedure code section removed.
10/08/2015	Medical Policy Committee review
10/21/2015	Medical Policy Implementation Committee approval. Contigen (cross-linked collagen) removed from eligibility statement as it has been withdrawn from the market.
10/01/2016	Coding update
11/03/2016	Medical Policy Committee review
11/16/2016	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
01/01/2017	Coding update: Removing ICD-9 Diagnosis Codes
11/02/2017	Medical Policy Committee review
11/15/2017	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
11/08/2018	Medical Policy Committee review
11/21/2018	Medical Policy Implementation Committee approval. Coverage eligibility unchanged. Added Policy Guidelines section.

Next Scheduled Review Date: 11/2019

Coding

The five character codes included in the Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines are obtained from Current Procedural Terminology (CPT®)‡, copyright 2017 by the American Medical Association (AMA). CPT is developed by the AMA as a listing of descriptive terms and five character identifying codes and modifiers for reporting medical services and procedures performed by physician.

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Codes used to identify services associated with this policy may include (but may not be limited to) the following:

Code Type	Code
CPT	0377T, 46999, 51715
HCPCS	L8603, L8604, L8605, L8606
ICD-10 Diagnosis	N36.42-N36.43, N39.3, R15.0-R15.9, T83.713A-T83.713S, T83.714A-T83.714S, T83.723A-T83.723S, T83.724A-T83.724S

*****Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. Food and Drug Administration (FDA) and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or
B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:
    1. Consultation with the Blue Cross and Blue Shield Association technology assessment program (TEC) or other nonaffiliated technology evaluation center(s);
    2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
    3. Reference to federal regulations.

**Medically Necessary (or "Medical Necessity") - Health care services, treatment, procedures, equipment, drugs, devices, items or supplies that a Provider, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury, disease or its symptoms, and that are:

A. In accordance with nationally accepted standards of medical practice;
B. Clinically appropriate, in terms of type, frequency, extent, level of care, site and duration, and considered effective for the patient's illness, injury or disease; and
C. Not primarily for the personal comfort or convenience of the patient, physician or other health care provider, and not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient's illness, injury or disease.

For these purposes, “nationally accepted standards of medical practice” means standards that are based on credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community, Physician Specialty Society recommendations and the views of Physicians practicing in relevant clinical areas and any other relevant factors.

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