Injectable Bulking Agents for Urinary Conditions and Fecal Incontinence

Overview

This Coverage Policy addresses injectable bulking agents for certain urinary conditions (e.g., stress urinary incontinence, vesicoureteral reflux) and fecal incontinence.

Coverage Policy

The following injectable bulking agent is considered medically necessary for the treatment of MALE stress urinary incontinence (SUI) secondary to intrinsic sphincter deficiency (ISD) when there is failure, contraindication or intolerance to at least 12 months of conservative medical management:

- Glutaraldehyde cross-linked [GAX] bovine collagen (e.g., Contigen®)

Each of the following injectable bulking agents is considered medically necessary for the treatment of FEMALE stress urinary incontinence (SUI) secondary to intrinsic sphincter deficiency (ISD) when there is failure, contraindication or intolerance to conservative medical management:

- Glutaraldehyde cross-linked [GAX] bovine collagen (e.g., Contigen®)
- Carbon-coated zirconium oxide particles (e.g., Durasphere™)
• Calcium hydroxylapatite [CaHA] particles (e.g., Coaptite®)
• Silicone elastomer (e.g., Macroplastique®)

Endoscopic injection of Deflux® is considered medically necessary for the treatment of severe vesicoureteral reflux (i.e., stage II–IV) in children age one year or older.

Injectable urinary bulking agents other than those specified above are considered experimental, investigational or unproven.

Injectable bulking agents (e.g., Solesta®) for the treatment of fecal incontinence are considered experimental, investigational or unproven.

General Background

Urinary incontinence is the involuntary loss of urine. It is not a disease but rather a symptom that can be caused by a wide range of conditions. There are several types of incontinence:

• Stress incontinence is the most common type of leakage. This occurs when urine is lost during activities such as walking, aerobics or even sneezing and coughing. The primary causes are urethral sphincter weakness (intrinsic sphincter deficiency) or a hypermobile urethra. Urethral hypermobility occurs when there is weakness of pelvic floor and poor support of the vesicourethral sphincter unit. The proximal urethra can be displaced outside the abdominal pressure zone during straining.
• Urge incontinence, often referred to as overactive bladder, is another form of leakage. This can happen when a person has an uncontrollable urge to urinate but cannot reach the bathroom in time.
• Overflow incontinence occurs when the bladder is full, is unable to empty and yet leaks. Frequent small urinations and constant dribbling are symptoms. This is rare in women and more common in men with a history of surgery or prostate problems.
• Functional incontinence is the inability to access a proper facility or urinal container because of physical or intellectual disability.
• Mixed incontinence refers to a combination of types of incontinence; most commonly stress and urge incontinence.

Stress Urinary Incontinence (SUI)

If conservative medical treatments such as bladder training, pelvic floor muscle exercises, biofeedback, or medication fail to improve SUI, additional intervention may be necessary. Injectable therapy using bulking agents composed of synthetic materials, bovine collagen, or an autologous substance augments the urethral wall and increases urethral resistance to urinary flow. Injection of bulking agents to treat a dysfunctional urethra is a minimally invasive method of correcting intrinsic sphincteric deficiency (ISD) that results in SUI. ISD may be caused by aging or scarring.

Bulking agents are materials that are injected into tissue surrounding the urethra to help keep the urethra closed and reduce urine leakage. A bulking agent procedure usually done in a doctor's office requires minimal anesthesia and takes about five minutes. Bulking up the bladder neck with particulate matter effectively closes the lumen of the urethra, which improves urethral coaptation and restores the mucosal seal mechanism of continence. The downside of the procedure is that most available bulking agents lose their effectiveness over time, and repeat injections are usually needed every six to 18 months. New bulking agents are being developed, as well as new ways to make the injection process easier and more efficient. The standard method of injecting a bulking agent is through a needle, which is inserted in different positions with the assistance of a cystoscope. Treatment-related adverse events are uncommon and relatively minor, the most common being dysuria, urinary urgency, transient urinary retention and acute (e.g., < seven days) urinary retention. Injectable agents are contraindicated in the presence of acute cystitis, urethritis, acute genitourinary infection, and bladder neck or urethral stricture. They should not be injected into blood vessels. Materials used as bulking agents for stress urinary incontinence include:

• glutaraldehyde cross-linked [GAX] bovine collagen (i.e., Contigen®)
• carbon-coated zirconium oxide particles (i.e., Durasphere™)
• calcium hydroxylapatite [CaHA] particles (i.e., Coaptite®)
• silicone elastomer/polydimethylsiloxane (i.e., Macroplastique®)
• polytetrafluoroethylene (PTFE; Teflon)

Prior to the FDA approving collagen for treating intrinsic sphincter deficiency (ISD), fat injections were used to treat ISD by bulking the urethra. The short-term result of periurethral fat injection is extremely good. Over time, however, the injected adipocytes tend to be phagocytized by the patient’s own body. This high degree of fat absorption is the major detriment to a long-term cure.

**U.S. Food and Drug Administration (FDA):** Contigen (glutaraldehyde cross-linked [GAX] bovine collagen) (C. R. Bard, Covington, GA, USA) received a premarket approval (PMA) in 1993 from the FDA. Once injected, this bovine collagen begins to degrade within 12 weeks and completely degrades in 9–19 months. One month before receiving the first treatment, the patient must undergo a skin test to exclude hypersensitivity. Per 2009 PMA update, the device was modified and is marketed under the trade name Contigen Bard Collagen Implant and is indicated for use only in the treatment of urinary incontinence due to intrinsic sphincter deficiency (ISD) that may be helped by a locally injected bulking agent. Contigen implant therapy should be initiated only in patients who have shown no improvement in their incontinence for at least 12 months.

Durasphere (carbon bead particles) (Carbon Medical Technologies, St. Paul, MN, USA) was approved by the FDA in 1999 for use in treating ISD in women age 21 and over. The use of carbon-coated zirconium oxide particles is restricted to women, as the studies that were submitted with the PMA application showed no improvement in the small number of male and child participants. Skin testing is not required prior to the use of this product. In 2003 there were bead modifications and a trade name revision to Durasphere EXP, also indicated for use in the treatment of adult women with stress urinary incontinence (SUI) due to ISD.

Coaptite (calcium hydroxylapatite) (BioForm Medical, Inc., San Mateo, CA, USA) was granted PMA by the FDA in November 2005. Coaptite is an injectable, sterile implant composed of spherical particles of calcium hydroxylapatite (CaHA), suspended in an aqueous based gel carrier. The gel carrier is composed of sodium carboxymethyl cellulose, sterile water for injection, and glycerin. It is indicated for soft tissue augmentation in the treatment of SUI due to ISD in adult females. It is contraindicated in patients with 1) significant history of urinary tract infections without resolution, or 2) current or acute conditions of cystitis or urethritis, or 3) fragile urethral mucosal lining.

Macroplastique implants (silicone elastomer/polydimethylsiloxane) (Uroplasty, Inc., Minnetoka, MN, USA) was granted PMA by the FDA in October 2006. Macroplastique is a permanently implanted, injectable bulking agent composed of polydimethylsiloxane particles suspended in a polyvinylpyrrolidone (PVP) carrier gel. It is indicated for transurethral injection in the treatment of adult women diagnosed with SUI primarily due to ISD. Macroplastique is contraindicated in patients with 1) acute urogenital tract inflammation or infection, or 2) fragile urethral mucosal lining (e.g., post-radiation therapy, post-surgery to the bladder neck).

Polytetrafluoroethylene (PTFE; Teflon) is not approved by the US Food and Drug Administration (FDA) for treatment of female SUI because of the risk of migration (Gill, 2018).

URYX® (Genyx Medical, Inc., Aliso Viejo, CA) received PMA from the FDA in December 2004 and is indicated for the treatment of SUI due to ISD in adult women. It is made of ethylene vinyl alcohol (EVOH) copolymers. Per the 2005 PMA update the device was modified and is marketed under the trade name Tegress Urethral Implant and is indicated for transurethral injection in the treatment of adult women diagnosed with stress urinary incontinence (SUI) due to intrinsic sphincter deficiency (ISD).

Bulkamid® (Contura International, Denmark), Zuidex (Q-MED Uppsala, Sweden) and Vantris (Promedon, Cordoba, Argentina) urethral bulking agents are currently not approved by the FDA. Polytetrafluoroethylene (PTFE, Teflon®) and autologous myoblasts are not addressed by the FDA as urinary bulking agents.

**Literature Review SUI:** The safety and clinical utility of most FDA-approved urethral bulking agents are well-supported in the peer-reviewed scientific literature. While several agents have received approval for use through
the FDA, their clinical efficacy has not been proven in all patient populations (e.g., women, men and/or children). Several manufacturers have printed warnings on their package inserts that their product has not been tested in women who are pregnant, in children or men. While some studies have included males in their study population, outcomes do not support the use of most agents for the treatment of male urinary incontinence.

Collagen injection has been used in the treatment of stress urinary incontinence (SUI) since 1993. Studies in the peer-reviewed scientific literature support the use of Contigen (collagen) injections for SUI with 50%–60% success rates (social continence, 24-hour dry pad test) at 12–24 months follow-up. Studies include men and women. Studies address SUI caused by intrinsic sphincter deficiency (ISD) only, or both ISD and urethral hypermobility. Although collagen injection is considered a safe and effective procedure, most patients need additional treatment sessions to achieve and maintain improvement or cure (Corcos, et al., 2005; Winters, et al., 2000; Smith, et al., 1998; Smith, et al., 1997).

Ghoniem et al. (2012) conducted a systematic review and meta-analysis of the evidence (n=23 cohort studies/958 patients) on the safety and effectiveness of Macroplastique® (polydimethylsiloxane injection). SUI improvement rates were 75% in the short-term, 73% in the mid-term (6–18 months), and 64% in the long-term (> 18 months). Cure/dry rates were 43%, 37%, and 36% during the same respective follow-up periods. No serious adverse events were reported. According to the authors, this meta-analytic evidence is supportive of Macroplastique as a safe and effective urethral bulking agent for treating with SUI primarily due to ISD.

A Cochrane review by Kirchin et al. (2012) assessed the effects of periurethral or transurethral injection therapy on the cure or improvement of urinary incontinence in women in randomized controlled trials (n=14 studies/2004 subjects). The limited data were not suitable for meta-analysis. Trials were small and generally of moderate quality. Of the 14 trials, eight compared different agents and all results had wide confidence intervals suggesting uncertainty. Silicone particles, calcium hydroxylapatite, ethylene vinyl alcohol, carbon spheres and dextranomer hyaluronic acid combination gave improvements which were not shown to be more or less efficacious than collagen. It was summarized that no clear-cut conclusions could be drawn from trials comparing agents. Insufficient evidence was found to show superiority of mid-urethral or bladder neck injection. Further comparative randomized trials with long term follow-up, involving a placebo or conservative treatment arm are required before injection therapy can be recommended as a standard first-line treatment for stress incontinence. An update to this Cochrane review identified no additional studies for inclusion and maintained previous conclusions (Kirchin, et al., 2017).

Ghoniem et al. (2009) randomized 247 patients (122 received Macroplastique; 125 received Contigen). The Contigen group served as the control. At 12 months, the Macroplastique group the dry/cure rate was 36.9% compared to 24.8% in the control group (p<0.05). In the Macroplastique and control groups the 1-hour pad weight decrease was 25.4 and 22.8 ml from baseline (p=0.64), and the mean improvement in Urinary Incontinence Quality of Life Scale score was 28.7 and 26.4 (p=0.49), respectively.

Mayer et al. (2007) compared the safety and effectiveness of Coaptite (calcium hydroxylapatite) to Contigen (collagen) in a randomized controlled trial (n=231). Up to five injections were performed in the first six months of the trial. At 12 months, 63.4% of Coaptite patients compared to 57.0% of Contigen patients showed improvement of ≥ 1 incontinence grade (not statistically significant). Most of the Coaptite and Contigen patients received two to three injections, and the mean number of injections was similar for the Coaptite and Contigen; however, a significantly greater percentage of Coaptite patients (38%) than collagen patients (26.1%) had only one injection (p=0.03). No statistically significant differences were found in the number of patients requiring greater than one injection of the test materials.

A randomized controlled trial (n=45) compared the safety and clinical utility of Macroplastique (silicone elastomer) to pubovaginal sling procedure in the treatment of female SUI (Maher, et al., 2005). Within each group, there was a significant improvement in outcome as documented by the 1-hour pad test and validated urinary incontinence questionnaires. Macroplastique is associated with reduced morbidity when compared to the sling, including significantly decreased operating time, blood loss, hospital stay and a quicker return to normal activity. While the subjective, patient-determined and objective evaluations were all greater in the sling group, the objective evaluation was the only parameter in which the sling demonstrated a statistically superior outcome to the Macroplastique in the short term (81% versus 9%).
Andersen (2002) also conducted a randomized controlled trial (n=46), with a longer average length of follow-up of 32.3 months. A total of 80% of Durasphere patients and 62% of Contigen patients demonstrated an improvement of ≥ 1 continence grade at 2.6 and 2.8 years, respectively. This difference was not statistically significant.

A randomized controlled trial (n=129) compared the safety and clinical utility of Durasphere (carbon-coated zirconium oxide beads) to Contigen (collagen) in the treatment of SUI and found the two materials comparable with respect to the improvement in continence grade and pad weight testing at 12 months (Lightner, et al., 2001). Specifically, when examined one year after the date of the last treatment, 49 (80.3%) of the 61 women treated with Durasphere showed improvement of one continence grade or more compared to 47 (69.1%) of 68 women treated with bovine collagen (p=0.162, this difference was not statistically significant).

**Professional Societies/Organizations**

**American Urological Association (AUA) and Society of Urodynamics, Female Pelvic Medicine (SUFU):** The AUA and SUFU guideline on the surgical treatment of female stress urinary incontinence stated that in patients with SUI and ISD, physicians can offer bulking agents as the injections have been shown to be effective in this setting. However, the risk of SUI recurrence and the likely need for future injections should be discussed with the patient (Kobashi et al., 2017).

**International Consultation on Incontinence (ICI) and International Continence Society (ICS):** The sixth ICI committee on surgical treatment of stress incontinence in men stated that bulking agents remain the most minimally invasive treatment for post-radical prostatectomy incontinence after conservative measures. All agents for which there is peer-reviewed data available, only show modest success rates with low cure rates and the effects tend to deteriorate over time. It remains to be seen if improvements in outcomes can be achieved with alternative agents, or if the concept of urethral bulking has achieved its maximal benefit with the agents available now. It is the opinion of the committee that the use of bulking agents for the treatment of male urinary incontinence should only be utilized when other more effective treatments are contraindicated (Abrams et al., 2017).

**American College of Obstetricians and Gynecologists (ACOG):** The 2015 (reaffirmed 2018) ACOG practice bulletin on urinary incontinence in women stated that urethral bulking injections are a relatively noninvasive treatment for stress urinary incontinence. Urethral bulking injections 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 who cannot tolerate anesthesia or more invasive surgery.

**Vesicoureteral Reflux (VUR)**

VUR is the abnormal flow of urine from the bladder backwards towards the kidneys. Most commonly a condition of infancy and childhood, VUR increases the risk of urinary tract infections and can lead to kidney damage. Children with primary VUR are born with a defect in the valve that normally prevents urine from flowing backward from the bladder into the ureters. Some children with primary outgrow the condition. Secondary vesicoureteral reflux is due to a urinary tract blockage, often caused by infection. Treatment for both primary and secondary VUR is aimed at preventing kidney damage. Depending on the severity of the condition, treatment options include watchful waiting, medication and surgery. Surgery is typically reserved for those children for whom antibiotics are not successful. However, surgery may be a first line therapy option for grades IV and V or when a quicker, more definitive treatment than medication is appropriate.

In endoscopic surgery, a periurethral bulking agent is injected via a cystoscope which changes the angle and perhaps fixation of the intravesical ureter thereby correcting the VUS. This method is a less invasive ambulatory procedure. In the United States, the two most commonly used techniques are the hydrodistension implantation technique (HIT) and the subureteral transurethral injection (STING). Both techniques use a copolymer of dextranomer/hyaluronic acid (Dx/HA or Deflux) but use different injection sites (Mattoo et al., 2018).

**U.S. Food and Drug Administration (FDA):** At the present time, Deflux (Oceana Therapeutics, Inc., Edison, NJ, USA) is the only FDA-approved injectable bulking agent for use in vesicoureteral reflux (VUR). Granted PMA by the FDA in September 2001, it is cross-linked dextran (dextranomer) microspheres in a carrier gel. It is
intended for use in treating children age one year and over diagnosed with vesicoureteral reflux (stage II–IV). It cannot be used in children with a urinary tract infection.

**Literature Review: Vesicoureteral Reflux (VUR):** The overall success rate reported by different groups of authors for use of Deflux ranged between 68% and 92% depending mainly on the VUR grade (Chertin and Kocherov, 2009). Study results indicate that VUR can be treated successfully with Deflux, producing positive short- and long-term outcomes and providing an alternative to antibiotics or open surgery (Friedmacher et al., 2018; FruTaşkinlar, et al., 2016; Stredele, et al., 2013; Stenberg, et al., 2007; Puri, et al., 2006; Capozza, et al., 2002; Capozza, et al., 2001; Lackgren, et al., 2001).

A meta-analysis of the literature on endoscopic therapy for vesicoureteral reflux was conducted by Elder et al. (2006). This analysis included the treatment of 5527 patients. The articles dealt with polytetrafluoroethylene (PTFE, Teflon), collagen, dextranomer/hyaluronic acid (Deflux), polydimethylsiloxane (Macroplastique), chondrocytes, blood and two or more injectables. In the database 47 articles (75%) pertained to children, six (10%) adults, and 10 (16%) children and adults. The number of studies, number of patients, and percent of reflux resolution by bulking agent was as follows:

- **Teflon:** 33 / 361 / 66.86%
- **Collagen:** 10 / 947 / 56.86%
- **Deflux:** 3 / 385 / 68.71%
- **Macroplastique:** 8 / 347 / 76.46%
- **Chondrocytes:** 1 / 47 / 50.48%

Overall, following one treatment, the reflux resolution rate (by ureter) for grades I and II reflux was 78.5%, grade III 72%, grade IV 63% and grade V 51%. If the first injection was unsuccessful, the second treatment had a success rate of 68%, and the third treatment 34%. The aggregate success rate with one or more injections was 85%. The success rate was similar among children and adults. It should be noted that relatively few studies included the incidence of urinary tract infection (UTI) in patients undergoing endoscopic therapy. The authors stated that further study of the rates of UTI and pyelonephritis after endoscopic and open anti-reflux surgery is necessary. It was concluded that future studies pertaining to endoscopic therapy should include data on rates of UTI and renal scarring, with prolonged follow-up (Elder, et al., 2006).

**Professional Societies/Organizations**

**American Urological Association (AUA):** The AUA guideline on the management and screening of primary vesicoureteral reflux in children (Peters, et al., 2010; updated 2017) recommended patients over one year of age who are on continuous antibiotic prophylaxis with a febrile breakthrough urinary tract infection be considered for open surgical ureteral reimplantation or endoscopic injection of bulking agents for intervention with curative intent.

In general, there is limited evidence to support agents other than Deflux for use in VUR (Kotb, et al., 2009; Chertin and Kocherov, 2009; Dyer, et al., 2007; Yucel, et al., 2007; Lottmann, et al., 2006; Chapple, et al., 2005).

**Fecal Incontinence**

Fecal incontinence is the inability to control ones bowel movements in someone who is older than four years old. Common causes of fecal incontinence include constipation, diarrhea, and muscle or nerve damage. Fecal incontinence may be due to a weakened anal sphincter associated with aging or to damage to the nerves and muscles of the rectum and anus from giving birth. Treatment may include dietary changes, medications, special exercises to help better control the bowels, injection of bulking agents, or surgery.

**U.S. Food and Drug Administration (FDA):** Solesta® (Oceana Therapeutics, Inc., Edison, NJ, USA) received FDA-approval (P100014) in May 2011. It is approved for the treatment of fecal incontinence in patients 18 years and older who have failed conservative therapy (e.g., diet, fiber therapy, anti-motility medications). This product was developed under the name “NASHA/Dx Fecal.” Solesta is a sterile, viscous gel contained in a disposable 1 mL assembled glass syringe with a standard luerlock fitting. Solesta consists of dextranomer microspheres, 50 mg/mL, and stabilized sodium hyaluronate, 15 mg/mL, in phosphate buffered 0.9% sodium chloride solution. Deflux, is the same material as Solesta.
Literature Review: There is insufficient evidence in the peer-reviewed scientific literature to demonstrate long term safety and clinical utility of Solesta for fecal incontinence. There is a paucity of studies evaluating other bulking agents (e.g., Coaptite) for fecal incontinence.

An Agency for Healthcare Research and Quality (AHRQ) comparative effectiveness report by Forte et al. (2016) analyzed the evidence (n=117 studies) comparing surgical and nonsurgical treatments for fecal incontinence (FI) in adults. Included in the review were RCTs (n=50 studies), observational studies with comparators (n=14 studies), and case series (n=53 studies). Participants in studies were primarily female with mixed fecal incontinence etiologies. A total of two RCTs (n=332 patients) examined the dextranomer anal sphincter tissue-bulking injection. Outcomes measured included effectiveness of treatment, improvement of fecal incontinence severity and quality of life, and adverse effects. Due to variability in follow-up periods, outcomes evidence was considered short-term (< 3 months), intermediate-term (3–6 months) or long-term (> 6 months). It was noted that meta-analysis was not possible due to the variety and volume of outcomes. The report found low-strength evidence at six months post-treatment to suggest that dextranomer anal tissue-bulking injections are more effective than sham injections resulting in improvements of the fecal incontinence quality of life scale, the number of fecal incontinence-free days, and on the number of patients with fecal incontinence episode reduction of ≥ 50% from baseline, but no more effective than sham injection on fecal incontinence severity, or in reducing the number of fecal incontinence episodes from baseline. Few minor adverse effects were reported. Overall, limited evidence was found to support any fecal incontinence treatment beyond six months. It was summarized that the long-term effects of injected anal bulking agents are unclear, including their effects on adjacent normal tissues and the location of the injected substance itself.

A Hayes Brief reviewed the available literature on Solesta (NASHA/Dx) for fecal incontinence, which included RCTs (n=2 studies) and prospective uncontrolled trials (n=6 studies). Patient populations in studies ranged from 21–206 and consisted of non-responders to conservative treatment. Outcomes included the change in the number of incontinence episodes and the number of days without incontinence. Follow-up ranged from three months to three years. According to the Hayes report, the available evidence showed that NASHA/Dx treatment for fecal incontinence is associated with modest but statistically significant improvements at follow-up compared with pretreatment status in 64%–74% of patients at one year, 59%–63% at two years, and 45% at three years. However, the overall quality of the evidence was found to be low due to the paucity of controlled studies and small sample sizes. Loss to follow-up was also found to be a limitation of the evidence. It was concluded that given the large placebo effect observed in studies of treatments for fecal incontinence, larger, independent, randomized, sham-controlled studies are needed to further evaluate the efficacy, durability, and safety of this treatment (Hayes, 2014; 2016).

A randomized controlled trial (n=206) was conducted to compare injection of dextranomer in stabilized hyaluronic acid with a sham for treatment of fecal incontinence (Graf, et al., 2011). Patients were eligible for inclusion if they were aged 18–75 years, had a Cleveland clinic Florida fecal incontinence score (CCFIS) of 10 or higher and at least four recorded incontinence episodes in two weeks, had symptoms for at least 12 months, had failure of medically supervised conservative treatment (at least one of dietary modification, fiber supplements, or loperamide hydrochloride treatment) ending at least two weeks before the screening period, were able to understand and comply with the requirements of the study, and were available for follow-up. Adults were randomized to receive NASHA Dx (n=136) or sham treatment (n=70). Of the NASHA Dx group, 132 were analyzed at six months, and 125 analyzed at 12 months. In the sham group, 65 were analyzed at six months. After six months, the trial was unmasked, and patients in the sham treatment group were offered active treatment and were thereafter excluded from further analysis. Data from the first six months were used to assess the effect of active treatment compared with sham treatment. The durability of injected NASHA Dx was assessed using 12-month data from individuals in the active treatment group. The primary endpoint was response to treatment based on the number of incontinence episodes. A 50% or greater reduction in the number of incontinence episodes was noted in 71 patients in the active treatment group (52%) compared with 22 (31%) in the sham treatment group (p=0.0089), this is statistically significant. However, the median decrease in number of incontinence episodes was not significantly greater in the active treatment group than in the sham treatment group at both three months and six months. Change in CCFIS compared with baseline did not differ between treatment groups at three months or at six months. Recorded were 128 treatment-related adverse events, of
which two were serious (rectal abscess [n=1]; prostatic abscess [n=1]). Small sample size and short term follow-up are limitations of this study.

Mellgren et al. (2014) published follow-up results of the Graf et al. (2011) study at 36 months. The 136 patients randomized to NASHA Dx treatment in that study represented the patient population reported on in this extension study. A 36-month follow-up assessment was completed by 112/136 patients. Re-treatment one month after initial treatment was performed in 112/136 patients (82%). The decrease of symptoms in 52% of patients at reported at six months was sustained at 36 months. Complete resolution of symptoms was experienced by 13% of patients at 36 months, however 15% of patients also experienced worsening of symptoms during this timeframe. A success rate of 59% was reported for all of 112 patients who were followed up at this time point; the success rate was 44.9% when all missing patients were treated as failures. The number of incontinence episodes recorded in a 14-day diary decreased significantly from baseline to 36-month follow-up (p<0.001). Likewise, the number of incontinence-free days increased significantly (p<0.001). Although this study provides medium-term success data, the results are limited by small sample size and loss to follow-up.

Dodi et al. (2010) conducted a prospective observational study, treating 115 patients with fecal incontinence (FI) with NASHA/Dx gel. Of the 115 patients treated with NASHA/Dx gel, a total of 14 patients withdrew or were lost to follow-up at six months (n=101), and additional 10 patients withdrew or were lost to follow-up at 12 months (n=91). One month after the first treatment visit, the patients were offered retreatment of up to four treatments. The number of FI episodes per 24 hours was recorded in the diaries. Fever was fairly common after treatment. A total of 7% of patients reported pyrexia that was assessed by the investigator as related to treatment. A total of six cases of anorectal abscesses were reported in the study. All of these events resolved after treatment. Results included a ≥ 50% reduction from baseline in the number of FI episodes in 57.1% of patients at six months, and 64.0% at 12 months. The reduction from baseline in number of FI episodes, recorded in the 28-day diary, was statistically significant at both six months (p<0.001) and 12 months (p<0.001) after last treatment. Limitations of this study include small sample size and no comparison group.

A Cochrane systematic review (n=4 RCTs/176 patients) by Maeda et al. (2010) evaluated perianal injectable bulking agents as treatment for fecal incontinence in adults. Most studies reported a short term benefit from injections regardless of the material used as outcome measures improved over time. A silicone biomaterial was found to provide some advantages and was safer in treating fecal incontinence than carbon-coated beads in the short term. There were also short term benefits from injections delivered under ultrasound guidance compared to digital guidance. The silicone biomaterial did not demonstrate clinical benefit compared to control injection of normal saline. Within the available data, the authors found no reliable evidence for effectiveness of one treatment over another in improving fecal incontinence. It was noted that “a definitive conclusion cannot be drawn regarding the effectiveness of perianal injection of bulking agents for fecal incontinence due to the limited number of identified trials together with methodological weaknesses. Larger well-designed trials with adequate numbers of subjects using reliable validated outcome measures are needed to allow definitive assessment of the treatment for both effectiveness and safety” (Maeda, et al., 2010). A 2013 update to this Cochrane review included one additional trial (n=5 RCTs/382 patients). Similar conclusions were made by the authors were similar in that although “one large randomized controlled trial has shown that this form of treatment using dextranomer in stabilized hyaluronic acid (NASHA Dx) improves continence in the short term, the number of identified trials was limited and most had methodological weaknesses” (Maeda, et al., 2013).

**Professional Societies/Organizations**

**American Society of Colon and Rectal Surgeons (ASCRS):** The ASCRS clinical practice guideline for the treatment of fecal incontinence noted that the injection of bulking agents is an option for the treatment of fecal incontinence. The injection of biocompatible bulking agents into the anal canal may help to decrease episodes of passive fecal incontinence. However, long term efficacy has not yet been defined (Paquette et al., 2015)

**Use Outside of the US**

The National Institute for Health and Clinical Excellence (NICE) and the National Collaborating Centre for Women’s and Children’s Health Guideline on urinary incontinence in women noted that intramural bulking agents (glutaraldehyde cross-linked collagen, silicone, carbon coated zirconium beads or hyaluronic acid/dextran copolymer) should be considered for the management of SUI if conservative management has failed. Women should be made aware of the following (NICE, 2013; updated 2015):
Repeat injections may be required to achieve efficacy.
Efficacy diminishes with time.
Efficacy is inferior to that of synthetic tapes or autologous rectus fascial slings.

Autologous fat and polytetrafluoroethylene used as intramural bulking agents are not recommended for the treatment of SUI.

The NICE guidance on the use of intramural urethral bulking procedures for SUI in women (November 2005) stated that current evidence on the safety and short-term efficacy of intramural urethral bulking procedures for stress urinary incontinence is adequate to support the use for these procedures.

The NICE guidance on the use of injectable bulking agents for fecal incontinence stated that the current evidence on the safety and efficacy does not appear adequate for this procedure to be used without special arrangements for consent and for audit or research, which should take place in the context of a clinical trial or formal audit protocol that includes information on well-defined patient groups (NICE, 2007).

**Coding/Billing Information**

**Note:**
1) This list of codes may not be all-inclusive.
2) Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement

**Collagen/Carbon-coated Zirconium Oxide/Calcium Hydroxylapatite/Silicone Elastomer Agents:**

Considered Medically Necessary when criteria in the applicable policy statements listed above are met for a urinary injectable bulking agent for males:

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<tr>
<th>CPT® Codes</th>
<th>Description</th>
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<tr>
<td>51715</td>
<td>Endoscopic injection of implant material into the submucosal tissues of the urethra and/or bladder neck</td>
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<td>52327</td>
<td>Cystourethroscopy (including ureteral catheterization); with subureteric injection of implant material</td>
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<th>HCPCS Codes</th>
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<tr>
<td>L8603</td>
<td>Injectable bulking agent, collagen implant, urinary tract, 2.5 ml syringe, includes shipping and necessary supplies</td>
</tr>
</tbody>
</table>

Considered Medically Necessary when criteria in the applicable policy statements listed above are met for urinary injectable bulking agents for females:

<table>
<thead>
<tr>
<th>CPT® Codes</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>51715</td>
<td>Endoscopic injection of implant material into the submucosal tissues of the urethra and/or bladder neck</td>
</tr>
<tr>
<td>52327</td>
<td>Cystourethroscopy (including ureteral catheterization); with subureteric injection of implant material</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>HCPCS Codes</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>L8603</td>
<td>Injectable bulking agent, collagen implant, urinary tract, 2.5 ml syringe, includes shipping and necessary supplies</td>
</tr>
<tr>
<td>L8606</td>
<td>Injectable bulking agent, synthetic implant, urinary tract, 1 ml syringe, includes shipping and necessary supplies</td>
</tr>
</tbody>
</table>
Deflux®:

Considered Medically Necessary when criteria in the applicable policy statements listed above are met:

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<thead>
<tr>
<th>HCPCS Codes</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>L8604</td>
<td>Injectable bulking agent, dextranomer/hyaluronic acid copolymer implant, urinary tract, 1 ml, includes shipping and necessary supplies</td>
</tr>
</tbody>
</table>

Bulking Agents for Fecal Incontinence (e.g., Solesta®):

Considered Experimental/Investigational/Unproven when used to report anoscopy with directed submucosal injection of bulking agent for fecal incontinence and injectable bulking agents (e.g., Solesta®):

<table>
<thead>
<tr>
<th>CPT® Codes</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>46999</td>
<td>Unlisted procedure, anus</td>
</tr>
<tr>
<td>0377T</td>
<td>Anoscopy with directed submucosal injection of bulking agent for fecal incontinence (Code deleted 12/31/2019)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>HCPCS Codes</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>L8605</td>
<td>Injectable bulking agent, dextranomer/hyaluronic acid copolymer implant, anal canal, 1 ml, includes shipping and necessary supplies</td>
</tr>
</tbody>
</table>


References


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