



# CIGNA MEDICAL COVERAGE POLICY

The following Coverage Policy applies to all plans administered by CIGNA Companies including plans administered by Great-West Healthcare, which is now a part of CIGNA.

**Subject** **Injectable Bulking Agents for Urinary Conditions**

**Effective Date** ..... 12/15/2009  
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## Table of Contents

Coverage Policy .....	1
General Background .....	1
Coding/Billing Information .....	6
References .....	7
Policy History .....	10

## Hyperlink to Related Coverage Policies

Biofeedback  
 Electrical Stimulators  
 Extracorporeal Electromagnetic Stimulation for Urinary Incontinence  
 Physical Therapy  
 Sacral Nerve Stimulation for Urinary Voiding Dysfunction  
 Surgical Interventions for Urinary Incontinence

### INSTRUCTIONS FOR USE

Coverage Policies are intended to provide guidance in interpreting certain **standard** CIGNA HealthCare benefit plans as well as benefit plans formerly administered by Great-West Healthcare. Please note, the terms of a participant's particular benefit plan document [Group Service Agreement (GSA), Evidence of Coverage, Certificate of Coverage, Summary Plan Description (SPD) or similar plan document] may differ significantly from the standard benefit plans upon which these Coverage Policies are based. For example, a participant's benefit plan document may contain a specific exclusion related to a topic addressed in a Coverage Policy. In the event of a conflict, a participant's benefit plan document **always supercedes** the information in the Coverage Policies. In the absence of a controlling federal or state coverage mandate, benefits are ultimately determined by the terms of the applicable benefit plan document. Coverage determinations in each specific instance require consideration of 1) the terms of the applicable group benefit plan document in effect on the date of service; 2) any applicable laws/regulations; 3) any relevant collateral source materials including Coverage Policies and; 4) the specific facts of the particular situation. Coverage Policies relate exclusively to the administration of health benefit plans. Coverage Policies are not recommendations for treatment and should never be used as treatment guidelines. Proprietary information of CIGNA. Copyright ©2009 CIGNA

## Coverage Policy

**CIGNA covers ANY of the following injectable bulking agents as medically necessary for the treatment of adult 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®) in men or women
- Carbon-coated zirconium oxide particles (e.g., Durasphere™), calcium hydroxylapatite [CaHA] particles (e.g., Coaptite®), or silicone elastomer (e.g., Macroplastique®) in women

**CIGNA covers the endoscopic injection of Deflux® as medically necessary for the treatment of severe vesicoureteral reflux (i.e., stage II–IV) in children age one year or older.**

**CIGNA does not cover bulking agents for the treatment of stress urinary incontinence or vesicoureteral reflux other than those specified above as they 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 mental disability.
- Mixed incontinence refers to a combination of types of incontinence; most commonly stress and urge incontinence.

### **Injectable Bulking Agents**

If conservative medical treatments such as bladder training, pelvic floor muscle exercises, biofeedback, or medication fail to improve the condition, additional intervention may be necessary. Researchers have proposed the use of injectable bulking agents in lieu of surgical intervention for patients diagnosed with urinary incontinence due to stress urinary incontinence (SUI) / intrinsic sphincter deficiency (ISD) that is unresponsive to a minimum of 12 months of conservative medical management.

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. 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 include:

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

### **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 bulking agent (e.g., Deflux<sup>®</sup>, Oceana Therapeutics, Inc., Edison, NJ, USA) is injected around the opening of the affected ureter to try to strengthen the valve's ability to close properly. This method is minimally invasive and compared to open surgery and presents fewer surgical risks. This procedure also

requires general anesthesia, but generally can be performed as outpatient surgery. The American Urological Association states “the significantly lower morbidity associated with the use of Deflux, compared to open surgery, indicates Deflux must be considered as an important option in VUR management. The choice of management options remains with the informed family and the physician, based upon multiple factors including age, sex, reflux grade, voiding patterns, risk of renal injury, and parental preferences” (2007).

### **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 2002 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).

At the present time, Deflux (Oceana Therapeutics, Inc., Edison, NJ, USA) is the only FDA-approved injectable bulking agent for use in children diagnosed with 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.

Tegress™ (C.R. Bard, Covington, GA, USA) formerly known as URYX® (Genyx Medical, Inc., Aliso Viejo, CA) received PMA from the FDA in December 2004 for the treatment of SUI due to ISD in adult women. It is made of ethylene vinyl alcohol (EVOH) copolymers. Bard voluntarily discontinued sales of Tegress™ in 2007.

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. Permacol® porcine dermal implant (Covidien, Dublin, Ireland) is not FDA-approved for urinary use. The FDA states it is intended for use as a soft tissue patch to reinforce soft tissue where weakness exists and for the repair of damaged or ruptured soft tissue membranes. It is specifically indicated for the repair of abdominal wall defects and hernias, including but not limited to parastomal hernias.

### **Literature Review**

The safety and clinical utility of 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. At this time, collagen is the only injectable agent that has been approved for use in men.

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. All patients must have a skin test before injection. 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). 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). Anderson (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  $\geq 1$  continence grade at 2.6 and 2.8 years, respectively. This difference was not statistically significant. 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  $\geq 1$  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%).

**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 (Stenberg, et al., 2007; Puri, et al., 2006; Capozza, et al., 2002; Capozza, et al., 2001; Lackgren, et al., 2001)

**Other:** Tegress (ethylene vinyl alcohol) (C.R. Bard, Covington, GA, USA) formerly known as URYX (Genyx Medical, Inc., Aliso Viejo, CA) is no longer for sale in the United States due to safety concerns such as erosion rate (Hurtado, et al., 2007). C.R. Bard voluntarily withdrew Tegress from the market in 2007.

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 2 or more injectables. In the database 47 articles (75%) pertained to children, 6 (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 1 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 antireflux surgery is necessary. The authors concluded that future studies pertaining to endoscopic therapy should include data on rates of UTI and renal scarring, with prolonged follow-up.

There is limited evidence to support polytetrafluoroethylene (PTFE, Teflon) or autologous myoblasts injections or other non-FDA-approved agents, for use in SUI; or agents other than Deflux for use in VUR; or Deflux for use in SUI (Kotb, et al., 2009; Chertin and Kocherov, 2009; Dyer, et al., 2007; Yucel, et al., 2007; Lottmann, et al., 2006).

## **Professional Societies/Organizations**

### **American Urological Association (AUA)**

AUA Policy Statement on Use of Deflux<sup>®</sup> in the Management of Vesicoureteral Reflux states “It is the current position of the American Urological Association that endoscopic injection of the dextranomer/hyaluronic compound Deflux is an option in the management of pediatric vesicoureteral reflux (VUR). The absence of inclusion of Deflux in the 1997 Pediatric Reflux Guidelines simply reflects the fact that it had not been introduced at that time and therefore could not have been evaluated. The contention that Deflux has not been proven to reduce urinary infections associated with reflux is inappropriate to the same extent that no other treatment modality has been shown to reduce all urinary tract infections. The resolution of reflux has been shown to reduce the incidence of pyelonephritis. Therefore to the extent that Deflux can correct VUR, it will reduce the incidence of pyelonephritis. The significantly lower morbidity associated with the use of Deflux, compared to open surgery, indicates Deflux must be considered as an important option in VUR management. The choice of management options remains with the informed family and the physician, based upon multiple factors including age, sex, reflux grade, voiding patterns, risk of renal injury, and parental preferences. To attempt to dictate specific treatment modality based upon concrete evidence is simply impossible based upon the current state of evidence. Any claim that current evidence can guide such a decision reflects a lack of understanding of the state of current evidence. As more evidence emerges, selection of specific therapy for specific patients may become more appropriate. At present, Deflux must be considered an option in the care of the pediatric patient with VUR” (October 2007).

### **American College of Obstetricians and Gynecologists (ACOG)**

The ACOG guideline entitled ‘Urinary incontinence in women’ lists the following “Major Recommendations”:

Level B evidence:

- Bulking agents are a relatively noninvasive method of treatment for stress incontinence and can be used in women for whom any form of operative treatment is contraindicated.

Levels of Recommendations:

Level A — Recommendations are based on good and consistent scientific evidence.

Level B — Recommendations are based on limited or inconsistent scientific evidence.

Level C — Recommendations are based primarily on consensus and expert opinion (ACOG, 2005).

### **National Institute for Health and Clinical Excellence (NICE)**

NICE and the National Collaborating Centre for Women’s and Children’s Health Guideline on urinary incontinence in women (October, 2006) notes the following:

Intramural bulking agents (glutaraldehyde cross-linked collagen, silicone, carboncoated zirconium beads or hyaluronic acid/dextran copolymer) should be considered for the management of stress UI if conservative management has failed. Women should be made aware that:

- repeat injections may be required to achieve efficacy
- efficacy diminishes with time
- efficacy is inferior to that of retropubic suspension or sling.

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

NICE guidance on the use of intramural urethral bulking procedures for SUI in women (November 2005) states “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 provided that normal arrangements are in place for clinical governance and for audit or research.”

### Summary

Certain injectable bulking agents have been proven effective in treating stress urinary incontinence (SUI) due to intrinsic sphincter deficiency (ISD) in patients who meet specific selection criteria. Although the long-term efficacy of these agents is not known, studies have shown that the use of an injectable bulking agent may provide relief (improvement of one continence grade or more) of ISD in individuals refractory to conservative therapy in 50-80% of patients.

Studies of children treated for severe vesicoureteral reflux (VUR) (grades, II–IV) with Deflux injections have shown this bulking agent to be a safe and effective alternative to antibiotic prophylaxis or open surgical repair.

There is insufficient evidence to support the use of bulking agents for the treatment of stress urinary incontinence (SUI) or vesicoureteral reflux (VUR) other than those specified above (e.g., the use of polytetrafluoroethylene [PTFE, Teflon] or autologous myoblasts injections or other non-FDA-approved agents for SUI; the use of bulking agents other than Deflux for VUR; the use of Deflux for SUI).

## Coding/Billing Information

**Note:** This list of codes may not be all-inclusive.

**Covered when medically necessary:**

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

HCPCS Codes	Description
L8603†	Injectable bulking agent, collagen implant, urinary tract, 2.5 ml syringe, includes shipping and necessary supplies
L8606†	Injectable bulking agent, synthetic implant, urinary tract, 1 ml syringe, includes shipping and necessary supplies

†**Note:** Covered when medically necessary only for the bulking agents specified in the Coverage Policy section of the policy.

ICD-9-CM Diagnosis Codes	Description
599.81	Urethral hypermobility
599.82	Intrinsic (urethral) sphincter deficiency (ISD)
599.83	Urethral instability

625.6	Female stress incontinence
788.31	Urge incontinence
788.32	Stress incontinence, male
788.33	Mixed incontinence urge and stress (male)(female)
788.34	Incontinence without sensory awareness
788.35	Post-void dribbling
788.37	Continuous leakage
788.38	Overflow incontinence

**\*Current Procedural Terminology (CPT®) ©2008 American Medical Association: Chicago, IL.**

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## Policy History

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<b>Pre-Merger Organizations</b>	<b>Last Review Date</b>	<b>Policy Number</b>	<b>Title</b>
CIGNA HealthCare	12/15/2007	0206	Injectable Bulking Agents for Urinary Conditions

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Connecticut General Life Insurance Company has acquired the business of Great-West Healthcare from Great-West Life & Annuity Insurance Company (GWLA). Certain products continue to be provided by GWLA (Life, Accident and Disability, and Excess Loss). GWLA is not licensed to do business in New York. In New York, these products are sold by GWLA’s subsidiary, First Great-West Life & Annuity Insurance Company, White Plains, N.Y.