FEP 7.01.102 Periureteral Bulking Agents as a Treatment of Vesicoureteral Reflux

**Description**
Most commonly seen in children, vesicoureteral reflux (VUR) is the retrograde flow of urine from the bladder upward toward the kidney. The primary management strategies have been prophylactic antibiotics to reduce urinary tract infections and, for higher grade disease, surgical correction of the underlying reflux. Injection of periureteral bulking agents is proposed as an alternative to surgical intervention.

The use of bulking agents in the treatment of VUR has been reported for more than 20 years and suggested as an alternative to antibiotic and surgical therapy. Bulking agents can be injected into tissue around the ureteral orifices to minimize reflux. The STING procedure (subureteral transurethral injection) involves the endoscopic injection of a bulking agent into the submucosal bladder wall just below the ureteral opening. In the more recently used modified STING procedure, the needle is placed in the ureteral tunnel, and the bulking agent is injected into the submucosal intraureteral space. When successfully injected, the compound tracks along the length of the detrusor tunnel and establishes a coapted ureteral tunnel. This endoscopic procedure can be performed in an outpatient setting.

A variety of bulking agents have been tested for biocompatibility and absence of migration. Some compounds used in clinical studies are collagen (Contigen® [Allergan, Coolock; note: this product is no longer commercially available], Zyderm®, Zyplast® [Collagen Corp.]), polytetrafluoroethylene paste (Teflon), polydimethylsiloxane (Macroplastique), calcium hydroxyapatite (Coaptite), dextranomer/hyaluronic acid copolymer (Deflux® or Dx/HA), and polyacrylamide hydrogel (Bulkamid® [Contura International A/S]).

**OBJECTIVE**

The objective of this evidence review is to determine whether endoscopic treatment with periureteral bulking agents improves the net health outcome in individuals who have vesicoureteral reflux and (a) have failed medical therapy and are eligible for surgery or (b) have not failed medical therapy and may be ineligible for surgery.
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POLICY STATEMENT
Periureteral bulking agents may be considered medically necessary as a treatment of vesicoureteral reflux grades II, III, or IV when medical therapy has failed and surgical intervention is otherwise indicated. The use of bulking agents as a treatment of vesicoureteral reflux in other clinical situations is considered investigational.

POLICY GUIDELINES
The use of bulking agents is contraindicated in patients with nonfunctioning kidney(s), Hutch diverticuli, active voiding dysfunction, and ongoing urinary tract infection.

BENEFIT APPLICATION
Experimental or investigational procedures, treatments, drugs, or devices are not covered (See General Exclusion Section of brochure).

FDA REGULATORY STATUS
In 2001, Deflux® was approved by the U.S. Food and Drug Administration (FDA) through the premarket application process for the “treatment of children with vesicoureteral reflux (VUR) grades II-IV.” Contraindications include patients with nonfunctioning kidney(s), active voiding dysfunction, and ongoing UTI. Duplicated ureters were initially considered a contraindication to Deflux® treatment, but this was changed to a precaution in 2007.

Note: Polytetrafluoroethylene may migrate, causing serious adverse events; this agent is not FDA-approved. Coaptite® (Merz Aesthetics), Macroplastique® (Cogentix Medical), and Tegress™ (CR Bard) are categorized by FDA as “Agent, Bulking, Injectable for Gastro-Urology Use.” Tegress™ was voluntarily withdrawn from the market by CR Bard in January 2007.

FDA product code: LNM

RATIONALE
Summary of Evidence
For individuals who have VUR who have failed medical therapy and are eligible for surgery who receive endoscopic treatment with periureteral bulking agents, the evidence includes RCTs and systematic reviews. Relevant outcomes are symptoms, morbid events, and treatment-related morbidity. Overall, studies have reported similar rates of reflux resolution compared with ureteral reimplantation surgery and the body of evidence would suggest that morbidity rates are similar or lower with bulking agents. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have VUR who have not failed medical therapy and may be ineligible for surgery who receive endoscopic treatment with periureteral bulking agents, the evidence includes RCTs. Relevant outcomes are symptoms, morbid events, and treatment-related morbidity. The randomized controlled trials, which had relatively small sample sizes in each arm, compared periureteral bulking agents with antibiotic prophylaxis and/or surveillance only and reported mixed findings. Additional, larger studies are needed before conclusions can be drawn about the efficacy of periureteral bulking agents as first-line treatment for patients with VUR. The evidence is insufficient to determine the effects of the technology on health outcomes.
SUPPLEMENTAL INFORMATION

Practice Guidelines and Position Statements

European Association of Urology
The European Association of Urology (2012) published guidelines on the diagnosis and treatment of vesicoureteral reflux (VUR) in children. The Association recommended continuous antibiotic prophylaxis as initial treatment for children diagnosed with VUR in the first year of life and for children ages 1 to 5 years who present with high-grade VUR. For children ages 1 to 5 with lower grade VUR and no symptoms, surveillance without antibiotic prophylaxis is considered a reasonable option. The guidelines indicated that a surgical correction is a treatment option for patients with persistent symptoms and that endoscopic injection of bulking materials can have satisfactory results in children with lower grades of VUR.

American Urological Association
The American Urological Association (2010) updated its guidelines on the management of primary VUR in children. The Association recommended that patients older than 1 year of age who have a febrile breakthrough urinary tract infection while receiving continuous antibiotic prophylaxis be considered for open surgery or endoscopic injection of bulking agents. Specific bulking agents mentioned were Deflux and Macroplastique. The guidelines were based on a review of the evidence, but its authors acknowledged the lack of robust randomized controlled trial data.

U.S. Preventive Services Task Force Recommendations
The U.S. Preventive Services Task Force has not addressed the use of injectable bulking agents to treat VUR.

Medicare National Coverage
There is no national coverage determination (NCD). In the absence of an NCD, coverage decisions are left to the discretion of local Medicare carriers.

REFERENCES

The policies contained in the FEP Medical Policy Manual are developed to assist in administering contractual benefits and do not constitute medical advice. They are not intended to replace or substitute for the independent medical judgment of a practitioner or other health care professional in the treatment of an individual member. The Blue Cross and Blue Shield Association does not intend by the FEP Medical Policy Manual, or by any particular medical policy, to recommend, advocate, encourage or discourage any particular medical technologies. Medical decisions relative to medical technologies are to be made strictly by members/patients in consultation with their health care providers. The conclusion that a particular service or supply is medically necessary does not constitute a representation or warranty that the Blue Cross and Blue Shield Service Benefit Plan covers (or pays for) this service or supply for a particular member.


### POLICY HISTORY

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<thead>
<tr>
<th>Date</th>
<th>Action</th>
<th>Description</th>
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<tbody>
<tr>
<td>December 2012</td>
<td>New Policy</td>
<td>Policy updated with literature review, References 8-9, 17-19, and 23 added, other references renumbered. Policy statements unchanged.</td>
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<tr>
<td>March 2015</td>
<td>Update Policy</td>
<td>-policy updated with literature review through June 22, 2017; no references added. Policy statements unchanged but “not medically necessary” corrected to “Investigational”</td>
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<tr>
<td>December 2017</td>
<td>Update Policy</td>
<td>Policy updated with literature review through June 7, 2018; no references added. Policy statements unchanged.</td>
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