Policy
Blue Cross and Blue Shield of Kansas City (Blue KC) will provide coverage for periureteral bulking agents for VUR when it is determined to be medically necessary because the criteria shown below are met.

When Policy Topic is covered
Periureteral bulking agents may be considered medically necessary as a treatment of vesicoureteral reflux grades II–IV when medical therapy has failed surgical intervention is otherwise indicated.

When Policy Topic is not covered
The use of bulking agents as a treatment of vesicoureteral reflux in other clinical situations is considered investigational.

Considerations
The use of bulking agents is contraindicated in patients with non-functioning kidney(s), hutch diverticuli, active voiding dysfunction, and ongoing urinary tract infection.

Description of Procedure or Service

<table>
<thead>
<tr>
<th>Populations</th>
<th>Interventions</th>
<th>Comparators</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Individuals: • With vesicoureteral reflux who have failed medical therapy and are eligible for surgery</td>
<td>Interventions of interest are: • Endoscopic treatment with periureteral bulking agents</td>
<td>Comparators of interest are: • Ureteral reimplantation surgery</td>
<td>Relevant outcomes include: • Symptoms • Morbid events • Treatment-related morbidity</td>
</tr>
<tr>
<td>Individuals: • With vesicoureteral reflux who have not failed medical therapy and/or are not eligible for surgery</td>
<td>Interventions of interest are: • Endoscopic treatment with periureteral bulking agents</td>
<td>Comparators of interest are: • Antibiotic prophylaxis • Ureteral reimplantation surgery • Surveillance only</td>
<td>Relevant outcomes include: • Symptoms • Morbid events • Treatment-related morbidity</td>
</tr>
</tbody>
</table>
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.

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 randomized controlled trials (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 RCTs, 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.

**Background**

**Vesicoureteral Reflux**

Treatment of vesicoureteral reflux (VUR) is based on the assumption that VUR predisposes patients to urinary tract infections (UTIs) and renal infection (pyelonephritis) by facilitating the transport of bacteria from the bladder to the upper urinary tract. Pyelonephritis causes renal scarring in as many as 40% of children, and extensive scarring may lead to renal insufficiency and hypertension. The period between first renal scarring from pyelonephritis and the development of hypertension or end-stage renal disease can be 30 to 40 years.¹

**Diagnosis**

In most cases, VUR is diagnosed during evaluation of UTIs. Approximately one third of children with UTIs are found to have VUR.² The average age for UTI onset is 2 to 3 years, corresponding to the age when toilet training occurs. There also appears to be a genetic predisposition to VUR, and siblings may also be examined. The criterion standard for diagnosis is voiding cystourography, a procedure that involves catheterization of the bladder. The severity of reflux is described by a grade, typically with the International Reflux Study Group grading system, which grades severity from I (reflux partway up the ureter) to V (massive reflux of urine up the ureter with marked tortuosity and dilation of the ureter and calyces).
Determination of VUR grade is not exact, however, due to factors such as bladder pressure, which may vary at the time of measurement. In general, more severe reflux is associated with higher rates of renal injury, and less severe reflux (ie, grade I and II) is associated with higher rates of spontaneous resolution and treatment success. Other factors found to be associated with the likelihood of spontaneous resolution of VUR and/or renal injury include age, sex, laterality, presence of renal scars, presence of voiding dysfunction, and history of UTI.1

**Treatment**

Treatment strategies for VUR include bladder training, antibiotic prophylaxis, and surgical modification of the ureter to correct the underlying reflux. VUR is likely to resolve spontaneously over 1 to 5 years; lower grades of reflux (ie, grades I and II) are associated with a higher probability of spontaneous resolution.3,4 The decision to administer prophylactic antibiotic treatment includes consideration of potential adverse events of long-term antibiotic treatment, which can include allergic reactions and development of treatment-resistant bacteria resulting in breakthrough UTIs.

Open surgical treatment is typically reserved for patients with high-grade reflux (grades III and IV) or as salvage therapy for those who are noncompliant with antibiotic therapy or have breakthrough UTIs while receiving prophylactic therapy. Surgical management involves lengthening the intramural ureter by modification of the ureterovesical attachment with reimplantation of the ureter. Success rates for open surgery are reported to be greater than 95% and nearly 100% for patients with lower grades of reflux. In recent years, there have been advances in surgical technique, including use of a lower abdominal transverse incision that leaves a smaller scar. Combined with a reduction in the use of ureteral stents and prolonged catheterization, the changes have led to shorter hospital stays and reduced surgery-related morbidity. Moreover, surgeries can now be done on an outpatient basis. Surgery, however, still involves risks associated with anesthesia and potential complications, such as ureteral obstruction, infection, and bleeding.1 Some centers have reported using laparoscopic antireflux surgery, but this is technically difficult and has not become widespread. Robotic-assisted laparoscopic methods are being developed to overcome some of the technical difficulties.5

Treatment of VUR remains controversial. There is a lack of good evidence that VUR actually increases the risk of pyelonephritis and renal scarring, and the long period of time before renal scarring, hypertension, and end-stage renal disease makes these serious conditions difficult to study. Moreover, VUR has a relatively high rate of spontaneous resolution, more than 60% over 5 years, so many children may not benefit from treatment.6 An important challenge is to identify the subset of children most likely to benefit from VUR treatment. At present, in the absence of definitive answers on the utility of treating VUR or the best treatment option, antibiotic prophylaxis to prevent recurrent UTIs and surgery to treat the underlying reflux remain accepted management strategies.

The use of bulking agents in the treatment of VUR has been reported for more than 20 years and has been 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 of the compounds used in clinical studies are collagen (Contigen® [Allergan, Coolock, Ireland; note: this product is no longer commercially available], Zyderm®, Zyplast® [Caollagen Corp., Palo Alto, CA]), polytetrafluoroethylene paste (Teflon), polydimethylsiloxane (Macroplastique® [Cogentix Medical, Minnetonka, MN]), calcium hydroxyapatite (Coaptite®), dextranomer/hyaluronic acid copolymer (Deflux® or Dx/HA), and polyacrylamide hydrogel (Bulkamid® [Contura International A/S, Søborg, Denmark]).

**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 urinary tract infection. 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, Raleigh, NC), Macroplastique®, and Tegress™ (CR Bard, Murray Hill, NJ) are categorized by FDA as “Agent, Bulking, Injectable for Gastro-Urology Use.” Tegress™ was voluntarily withdrawn from the market by CR Bard on January 2007.

**Rationale**
The evidence review was created in June 2005 and has been updated regularly with searches of the MEDLINE database. The most recent literature update was performed through June 22, 2017.

Treatment of vesicoureteral reflux (VUR) with periurethral bulking agents is proposed as: (1) an alternative to other types of surgery for patients with high-grade VUR (predominantly grades III and IV) who have failed or are noncompliant with prophylactic antibiotics; and (2) an alternative to prophylactic antibiotics for patients with low-grade or high-grade VUR. Appropriate outcomes for the comparison of bulking agents and other types of surgery are resolution of reflux and reduction in the rate of urinary tract infections (UTIs) and pyelonephritis. Because prophylactic antibiotic use does not treat the underlying reflux, reduction in the rate of UTIs and pyelonephritis are reasonable outcomes
for studies comparing antibiotics with bulking agents. Differences in morbidity are also important outcomes for both proposed uses.

The following is a summary of key literature to date on use of periureteral bulking agents to treat VUR.

### Efficacy of Bulking Agents for VUR

#### Systematic Reviews

A 2011 Cochrane review included randomized controlled trials (RCTs) on treatments for VUR. Reviewers addressed a variety of interventions including long-term antibiotic prophylaxis, open surgery, and use of bulking agents and, thus, had limited ability to evaluate the efficacy of bulking agents because studies on open surgery and bulking agents were combined in the analysis. The review, however, is useful because it examines the assumption that VUR increases the risk of complications. This Cochrane review, last updated in 2011, included 20 trials (total N=2324 children). No statistically significant differences were found in the overall risk of UTI or renal parenchymal injury between groups treated with surgery or bulking agents plus antibiotics and antibiotic prophylaxis alone at any time point between 1 and 24 months. For example, a pooled analysis of data from 5 trials that evaluated repeat positive urine culture at 1 to 2 years found a nonsignificant relative risk (RR) of 0.89 (95% confidence interval [CI], 0.55 to 1.44). In addition, a pooled analysis of 4 trials that evaluated the outcome of new renal parenchymal defects at 4 to 5 years after treatment calculated a pooled RR of 1.09 (95% CI, 0.79 to 1.49). One statistically significant finding was a reduction in febrile UTI by 5 years with surgery or bulking agent treatment compared with antibiotics alone in a pooled analysis of 2 studies (449 children) (RR=0.43; 95% CI, 0.27 to 0.70). These findings challenge the assumptions underlying the treatment of VUR, because one would expect a reduction in UTI if the hypothesis is correct that VUR is a modifiable risk factor for UTI and renal parenchymal damage.

A systematic review published in 2010 identified randomized trials and observational studies evaluating dextranomer/hyaluronic acid (Dx/HA) copolymer treatment for pediatric VUR. A total of 47 studies, mainly retrospective case series, met eligibility criteria. A key inclusion was that studies report the postoperative success rate after a single injection of Dx/HA. Success was defined as resolution of VUR and could also include downgrading to grade 1 VUR. Of 7303 ureters injected with Dx/HA, 5633 (77%) were considered treatment successes. There were higher rates of success in children with low-grade reflux than in those with high-grade reflux. For example, the 164 children whose preoperative VUR was grade 1 had an 89% success rate compared with a 59% success rate among the 1109 children with initial grade IV VUR.

#### Randomized Controlled Trials

**Periureteral Bulking Agents vs Other Types of Surgery**

The first RCT comparing periureteral bulking agents with ureteral reimplantation (UR) was published in 2013. Garcia-Aparicio et al in Spain randomized 41 children
older than 1 year of age with VUR grades I to IV to receive endoscopic treatment with Dx/HA (n=22) or UR (n=19). Indications for surgery included recurrent UTIs, persistent VUR after 2 years of antibiotic prophylaxis, impairment of renal function, or another type of impairment due to VUR. Thirty-five refluxing ureters were treated with bulking agents, and 32 refluxing ureters were treated with UR. One year after treatment, 32 (91.4%) of 35 ureters in the Dx/HA group and 32 (100%) of 32 ureters in the surgical reimplantation group were cured; the difference between groups was not statistically significant (p=0.23). Findings were similar at final follow-up. At 5 years, 30 (85.7%) of 35 ureters in the Dx/HA group and 100% in the UR group were free of VUR (p=0.48). One patient in the Dx/HA group and 2 patients in the UR group experienced treatment complications. Two patients in the Dx/HA group and none in the UR group experienced fevers posttreatment. Rates of complications and adverse events did not differ significantly between groups. The results of this trial supported a finding of no large differences between the 2 treatments, but the study was not powered to detect smaller differences in outcomes and was also likely too small to detect differences in complications and adverse events.

**Periureteral Bulking Agents vs Antibiotic Prophylaxis**

Capozza and Caione (2002) reported on the results of a study of 61 children with VUR (grades II-IV) who were randomized to an endoscopic subureteral implantation (n=40) of Deflux or 12 months of antibiotic prophylaxis (n=21). Entry criteria included grades II, III, or IV reflux present for at least 6 months. The antibiotic therapy was not specified and presumably varied. It was not reported whether patients had been receiving antibiotic therapy during the preceding 6 months and experienced breakthrough UTIs, were noncompliant, or showed no evidence of spontaneous resolution of VUR. Therefore it is unknown whether the Deflux treatment was primarily considered an alternative to medical therapy or to surgical therapy. Partly due to the small numbers in the antibiotic control group, the distribution of the different grades of VUR differed between groups. Outcomes included improvement in reflux grade and measures of renal function; incidence of UTIs was not reported. The only statistically significant outcome reported was improvement in reflux grade at month 12, with 69% of those in the Deflux group reporting a reflux grade of I or less—compared with only 38% in the antibiotic group. However, these results are not surprising, because antibiotic therapy is not intended to improve reflux grade but simply to sterilize the urine while awaiting the spontaneous resolution of VUR. Therefore, the only conclusion is that Deflux results in a higher incidence of VUR resolution than spontaneous resolution.

Findings from the Swedish Reflux Trial in children were published in 2010. This nonblinded multicenter study included 203 children (128 girls, 75 boys) between the ages of 1 and 2 years with grade III, III, or IV reflux. Participants were not required to have failed antibiotic prophylaxis; thus the trial evaluated injection of a bulking agent as an alternative to antibiotic therapy. Most participants (194 [96%]) were identified after a symptomatic UTI. Recruitment was more difficult than expected, and enrollment was stopped after 6 years. Participants were
randomized to 1 of 3 groups: antibiotic prophylaxis (n=69), endoscopic treatment with Deflux (n=66), or surveillance only (n=68).

The study aimed to simulate clinical practice, ie, prophylactic antibiotics were prescribed without monitoring compliance, rather than ensuring that study participants took a known dose of antibiotics. Primary study outcomes included VUR status, and rates of febrile UTI and kidney damage after 2 years. Sixty-four of 66 patients randomized to endoscopy received treatment. Fourteen of 19 patients with ongoing dilating VUR after 1 injection received a second injection; 2 patients received a third injection. Complications occurred in 6 (9%) of the 64 individuals who received endoscopic treatment. Overall, 187 (92%) participants completed at least 6 of the 8 follow-up visits; analysis was intention to treat. Two-year cystourethrography was done in 185 (91%) of the 203 patients. Findings from voiding cystourethrography were that VUR had resolved in 9 (13%) of 68 patients in the prophylaxis group, in 20 (38%) of 52 in the endoscopy group, and in 10 (15%) of 65 in the surveillance group. The proportion of patients in the 3 groups whose VUR was downgraded to grade I or II were 18 (26%) of 68, 17 (33%) of 52, and 21 (32%) of 65, respectively. There was a significantly greater proportion of patients whose VUR had resolved or had been downgraded in the endoscopy group than in the prophylaxis (p<0.001) and the surveillance groups (p=0.003), but no statistically significant differences were found between the prophylaxis and surveillance groups. Thirteen (20%) of the 66 patients randomized to endoscopy whose VUR had initially resolved or been downgraded experienced recurrences and had stage III or IV VUR at 2 years.

Febrile UTI rates by treatment group in girls were 8 (19%) of 43, 10 (23%) of 43, and 24 (57%) of 42, respectively, in the prophylaxis, endoscopic, and surveillance groups. Rates were significantly higher in the surveillance group than either the prophylaxis group (p=0.002) or the endoscopic group (p=0.14); rates did not differ significantly between the prophylaxis and the endoscopic groups. Rates of febrile UTI recurrence during follow-up were dramatically higher in girls (42/128 [33%]) than in boys (7/75 [9%]).

Rates of febrile UTIs in boys were 2 (8%) of 26 in the prophylaxis group, 4 (17%) of 23 in the endoscopic group, and 1 (4%) of 26 in the surveillance group; there were no statistically significant differences between groups. The rate of new renal damage did not differ significantly among groups.

After stratifying findings by sex, the sample sizes in reported analyses were relatively small. For this reason, the study might have been insufficiently powered to evaluate some of the outcomes of interest (eg, kidney damage, febrile UTIs). Moreover, findings might not be applicable to children outside of the restricted age range evaluated or to those with lower grade VUR. Larger studies with a more representative sample of children with VUR are needed to evaluate the effectiveness of this treatment further.
Comparison Among Bulking Agents

Three RCTs have compared Deflux with Macroplastique for treatment of VUR in children. An earlier (2002) study by Oswald et al found similar rates of reflux correction in the 2 groups; however, more recent RCTs have found higher success rates with Macroplastique than with Deflux. Studies varied in their eligibility criteria (eg, grade of VUR, previous use of antibiotics). The RCTs are described next.

Oswald et al (2002) randomized 72 children with VUR to receive Deflux or Macroplastique in addition to antibiotic prophylaxis. Eligible children had grade II, III, or IV reflux (International Reflux Study Group grading system). Because all patients continued to receive antibiotic therapy, presumably, the bulking procedure was primarily considered an alternative to surgical reimplantation of the ureter; however, the patient selection criteria do not indicate whether patients had failed prior antibiotic therapy or had unresolved VUR. Three months postinjection, VUR was corrected in 50 (86%) of 58 ureters in the Macroplastique group and in 40 (71%) of 56 ureters in the Deflux group; the difference between groups was not statistically significant. Rates of maintaining reflux correction at 1 year were also similar in both groups.

In 2011, Kim et al in Korea randomized 85 children ages 2 to 15 years with VUR (grades II-V) to subureteral injections of Macroplastique (n=42) or Deflux (n=43). Eligibility included breakthrough UTI, in addition to persistent VUR; most patients (exact number not reported) had started immediately on antibiotic prophylaxis after diagnosis. Seventy-three (86%) of 85 children were available for the 3-month follow-up. The cure rate, defined as no evidence of reflux, was 69% in the Macroplastique group and 55% in the Deflux group. The difference between groups was statistically significant, favoring Macroplastique (p<0.05).

A 2014 RCT by Moore and Bolduc in Canada randomized 275 children (median age, 50 months) with grade I, II, III, IV, or V VUR to endoscopic treatment with Macroplastique or Deflux. Unlike previous trials, the trial included patients with grade I VUR (9% of ureters) as well as higher grade disease; results were not stratified by VUR grade. Previous endoscopic treatment of VUR was an exclusion criterion but previous use of antibiotics was not reported. Three months after a single injection of bulking agents, VUR was corrected in 104 (85%) of 122 patients in the Macroplastique group and in 101 (76%) of 133 patients in the Deflux group. As in the Kim trial, the difference between groups was statistically significant, favoring Macroplastique (p<0.05).

Children With Duplicated Ureters

No controlled studies have been published comparing bulking agents with other treatments in children with duplicated ureters. However, several case series are available, and these uncontrolled studies suggest reasonable response rates and do not report high complication rates in this population. The largest series to date was published in 2013 by Hunziker et al in Ireland. The study included 123 children with complete duplex systems who were treated with Dx/HA for grade II, III, IV, or V VUR. The mean age of participants was 3 years (range, 1 month to 12
years). Complete duplicated ureters were unilateral in 100 (81%) patients and bilateral in the remaining 13. A total of 136 refluxing ureteral units were treated with endoscopic injections of Dx/HA. Three months after treatment, children were evaluated using voiding cystourethrography and bladder ultrasound. The rate of VUR resolution after 1 injection was 68.4% (93/136 ureters). VUR resolved in an additional 35 (25.7%) ureters after a second injection and in the remaining 8 (5.9%) ureters after a third injection. There was 1 complication associated with the endoscopic injections, which was a case of frank hematuria. No patients needed ureteral reimplantation, and there was no evidence on ultrasound of delayed vesicoureteral junction obstruction. Five (4%) patients developed febrile UTIs during follow-up.

Other smaller case series have evaluated bulking agents as a treatment of VUR in patients with duplicated ureters. For example, Molitierno et al (2008) included 52 children with duplex ureters who had grade II, III, IV, or V VUR. Overall, VUR was cured in 44 (85%) of 52 patients after 1 or 2 treatments with Dx/HA. Moreover, Lackgren et al (2003) evaluated 68 children with duplex ureters and VUR. Forty-three (63%) children had a positive response to treatment, defined as having their reflux resolve to grade 0 or I. There were no complications associated with treatment. Seventeen (25%) children required open surgery.

**Adverse Events**

According to case series data, injection of periureteral bulking agents is associated with low morbidity rates. Temporary postoperative ureteral obstruction may occur in less than 0.7% of patients following injection of bulking agents; this can be treated with ureteral stenting until the problem resolves. In comparison, on average a 2% (range, 0%-9%) ureteral obstruction and reoperation rate has been reported following ureteral reimplantation. A large series published by Puri et al (2012) retrospectively reported on 1551 children injected with Dx/HA for high-grade VUR. The only reported procedure-related complication was hematuria lasting up to 12 hours in 3 patients. There was no evidence of delayed vesicoureteral junction obstruction. Febrile UTIs occurred in 69 (5%) patients during follow-up; median follow-up was 5.6 years. Dwyer et al (2013) compared the rate of febrile UTIs in 2 cohorts of patients with VUR. The incidence of febrile UTI did not differ significantly between patients who had ureter reimplantation (8% [16/210 cases]) and those who had endoscopic injections of Dx/HA (4% [4/106 patients]) (p=0.24).

**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 RCTs, 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
In 2012, The European Association of Urology 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 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
In 2010, the American Urological Association updated its guidelines on 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 trials.

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

Medicare National Coverage
There is no national coverage determination. In the absence of a national coverage determination, coverage decisions are left to the discretion of local Medicare carriers.
## Ongoing and Unpublished Clinical Trials
Some currently unpublished trials that might influence this review are listed in Table 1.

### Table 1. Summary of Key Trials

<table>
<thead>
<tr>
<th>NCT No.</th>
<th>Trial Name</th>
<th>Planned Enrollment</th>
<th>Completion Date</th>
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<tr>
<td>NCT02271035</td>
<td>A Prospective Study Comparing the Success Rate of Injection of (DefluxR) Versus (VantrisR) for VUR in children</td>
<td>100</td>
<td>Dec 2015 (unknown)</td>
</tr>
</tbody>
</table>

NCT: national clinical trial.

### References
(Macroplastique) or dextranomer/hyaluronic acid copolymer (Deflux): a short-term prospective comparative study. Urol Int. 2011;87(3):299-303. PMID 21934268


**Billing Coding/Physician Documentation Information**

<table>
<thead>
<tr>
<th>CPT Code</th>
<th>Description</th>
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<tbody>
<tr>
<td>52327</td>
<td>Cystourethroscopy (including ureteral catheterization); with subureteric injection of implant material</td>
</tr>
<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>L8604</td>
<td>Injectable bulking agent, dextranomer/hyaluronic acid copolymer implant, urinary tract, 1 ml, 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>
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</table>

**ICD10 Codes**

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
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<tbody>
<tr>
<td>N11.0</td>
<td>Nonobstructive reflux-associated chronic pyelonephritis</td>
</tr>
<tr>
<td>N13.70-</td>
<td>Vesicoureteral-reflux code range</td>
</tr>
<tr>
<td>N13.739</td>
<td></td>
</tr>
</tbody>
</table>

**Coding Issues**

CPT code 52327 would apply to the use of any bulking agent, including Deflux, to treat VUR:

Effective 1/1/09, there is a specific HCPCS code for Deflux:
L8604: Injectable bulking agent, dextranomer/hyaluronic acid copolymer implant, urinary tract, 1 ml, includes shipping and necessary supplies

Prior to 2009, HCPCS Code L8606 was sometimes used to describe the use of Deflux; however, the code was not a perfect match, since Deflux is a copolymer that includes some non-synthetic material. HCPCS code L8606 was created for totally synthetic bulking agents (i.e., Macroplastique), while HCPCS code L8603 describes the use of collagen. These codes were originally designed to address the use of bulking agents as a treatment of urinary incontinence.

Additional Policy Key Words
N/A

Policy Implementation/Update Information

5/1/06 New policy; considered investigational.
5/1/07 Policy statement revised adding a medically necessary statement for periureteral bulking agents.
5/1/08 No policy statement changes.
5/1/09 No policy statement changes
5/1/10 Policy statement revised to change the medically necessary from “open surgical procedure” to “surgical procedure.” Also added failed medical therapy to the medically necessary policy statement.
5/1/11 No policy statement changes.
5/1/12 No policy statement changes.
5/1/13 No policy statement changes.
5/1/14 Duplicated ureter removed as contraindication in Policy Guidelines.
5/1/15 No policy statement changes.
5/1/16 No policy statement changes.
5/1/17 No policy statement changes.
5/1/18 No policy statement changes.

State and Federal mandates and health plan contract language, including specific provisions/exclusions, take precedence over Medical Policy and must be considered first in determining eligibility for coverage. The medical policies contained herein are for informational purposes. The medical policies do not constitute medical advice or medical care. Treating health care providers are independent contractors and are neither employees nor agents Blue KC and are solely responsible for diagnosis, treatment and medical advice. No part of this publication may be reproduced, stored in a retrieval system or transmitted, in any form or by any means, electronic, photocopying, or otherwise, without permission from Blue KC.