Both cases of nausea/vomiting/abdominal pain were resolved.

No case of ureteral dilatation required intervention and most cases resolved spontaneously.

Patients in the nonrandomized studies received antibiotic prophylaxis until the 3-month voiding cystourethrogram (VCUG).

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deflux intravesically. Injection of Deflux into blood vessels may cause vascular occlusion.

Do not inject Deflux intravascularly. Injection of Deflux into blood vessels may cause vascular occlusion.

The safety of Deflux in the treatment of VUR is based on a pivotal randomized study in which 39 children were treated with Deflux, two nonrandomized supportive studies in which 170 children were treated with Deflux, and a nonrandomized post-approval study in which 165 children were treated with Deflux. Follow-up for the pivotal and supportive studies was 12 months; follow-up for the post-approval study was 5 years (5-year data available for 31 of the 165 enrolled subjects (18.8%). No patients died during the course of these studies.

The brief background information for each study is presented in Table 1.

Table 1: List of Treatment-Related Adverse Events Occurring in >1% of Patients in the Pivotal, Supportive and Post-Approval Studies

<table>
<thead>
<tr>
<th>Adverse Event Category</th>
<th>Pivotal Study</th>
<th>Supportive Study</th>
<th>Post-Approval Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deflux group</td>
<td>n=39</td>
<td>n=160</td>
<td>n=165</td>
</tr>
<tr>
<td>Nausea</td>
<td>n=18 (4.6%)</td>
<td>n=73 (4.6%)</td>
<td>n=83 (5.1%)</td>
</tr>
<tr>
<td>Abdominal discomfort</td>
<td>n=11 (2.8%)</td>
<td>n=30 (1.9%)</td>
<td>n=22 (1.3%)</td>
</tr>
<tr>
<td>Dysuria</td>
<td>n=10 (2.6%)</td>
<td>n=48 (3.0%)</td>
<td>n=44 (2.7%)</td>
</tr>
<tr>
<td>Urinary incontinence</td>
<td>n=7 (1.8%)</td>
<td>n=23 (1.4%)</td>
<td>n=16 (1.0%)</td>
</tr>
</tbody>
</table>
| Ureteroceles must be identified.

The incidence of UTIs in the studies supporting the original approval of Deflux ranged from 8% in the nonrandomized studies to 15% in the pivotal randomized study consistent with the occurrence of reflux in these types of patients.

In the studies supporting the original approval of Deflux, 1 subject had pyelonephritis in the randomized study and none had hydronephrosis. In the postapproval study, 2 subjects each had pyelonephritis and hydronephrosis and none had hydronephrosis. The rate of pyelonephritis and hydronephrosis was higher in the 12-month follow-up period compared to the preapproval period. However, the rate of pyelonephritis was the same in the pre- and post-approval periods.

In the pivotal study, patients were assigned to receive prophylactic antibiotics were prescribed legally marketed antibiotic medications for the entire 12-month study period in the pivotal, supportive and post-approval studies.

In all four studies, patients with persistent reflux (i.e., VUR grade still meeting study eligibility) 3 months after initial Deflux treatment were eligible to receive a single retreatment. These retreatments were performed in the same way as the initial injection procedures. The retreatment observed in these studies was 28% for the pivotal study, 30% for supportive study 1, 12% for supportive study 2 and 30% for the post-approval study.

SUCCESS RATES

In the pivotal and two supportive studies, the success rate of Deflux treatment was generally higher for patients with lower baseline reflux grade and unilateral versus bilateral reflux.

SUCCESS RATE

Success rate was defined as improvement to VCUG = 0 (no reflux) at the 12-month post-injection time point. In the post-injection study effectiveness was defined as improvement to VCUG = 0 (no reflux) at 3 months (VCUG assessment in this study was only mandatory at 3 months post-injection). At the 12-month post-injection time point, the success rate was 90% (95% CI 85-94%).

Table 3: Efficacy Results at 3- and 12-Month Post-Injection in the Pivotal, Supportive and Post-Approval Studies

<table>
<thead>
<tr>
<th>Study Design</th>
<th>Pivotal Study</th>
<th>Supportive Study</th>
<th>Post-Approval Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Success rate at 3- and 12-months</td>
<td>n=12 months: Deflux group (n=39)</td>
<td>n=12 months: Antibiotic group (n=21)</td>
<td>n=12 months: Deflux group (n=165)</td>
</tr>
<tr>
<td>Success rate at 3- and 12-months</td>
<td>n=12 months: Deflux group (n=66/279)</td>
<td>n=12 months: Antibiotic group (n=33/171)</td>
<td>n=12 months: Deflux group (n=78/301)</td>
</tr>
<tr>
<td>Success rate at 3- and 12-months</td>
<td>Success rate at 3- and 12-months: Deflux group (n=100/165)</td>
<td>Success rate at 3- and 12-months: Antibiotic group (n=58/165)</td>
<td>Success rate at 3- and 12-months: Deflux group (n=78/301)</td>
</tr>
</tbody>
</table>

SUCCESS RATE

Success rate was defined as improvement to VCUG = 0 reflux at 12 months post-injection time point.

SUCCESS RATE

Success rate was defined as improvement to VCUG = 0 reflux at 12 months post-injection time point. In the pivotal study, success was defined as persistent absence of reflux on VCUG, grade 0 as shown on VCUG assessment following the occurrence of a failed UTI or other event that warranted a repeat VCUG study.

In the pivotal and post-approval studies, the success rate of Deflux treatment was generally higher for patients with lower baseline reflux grade and unilateral versus bilateral reflux.

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Deflux

Deflux is to be administered only by qualified personnel experienced in the use of a cytoscope and trained in the technique of submucosal and/or intra-ureteric injections (with Deflux or other materials).

It is recommended to use the Deflux metal needle (3.7F x 23G tip x 350 mm) for safe and accurate administration of Deflux. To assist the physician in positioning the needle, the Deflux metal needle has a circular mark 6 mm from the needle tip. To show the position of the needle level, there is a square mark 8 mm from the needle tip. The marks are for reference only.

Deflux can be injected with any common pediatric cystoscope with a minimum 4 French working channel. A type of cystoscope with a straight working channel is also well adapted for this type of procedure. The child is placed in a lithotomy position under general anesthesia and cystoscopy is performed to localize the ureteral orifices.

Before injecting Deflux the following is recommended:

1. Flush physiological saline solution through the needle.
2. Fasten the needle tightly to the syringe.
3. Remove the air from the needle by injecting the gel into the needle up to a point where a droplet is visible at the tip.

Please note that the luer lock adapter is snapped onto the syringe and held in place with friction only. It can rotate freely or be pulled off should enough force be applied. Because of this, it is recommended that the thumb and forefinger are held firmly around both the glass syringe barrel and the luer lock adapter when assembling the needle and syringe. To facilitate proper threading/fastening of needle off should enough force be applied. Because of this, it is recommended that the thumb and forefinger are held firmly around both the glass syringe barrel and the luer lock adapter when assembling the needle and syringe. To facilitate proper threading/fastening of needle hub and luer lock adapter, please push and rotate them firmly together (see Fig. 1).

To avoid any interruption in patient treatment or the need to repeat a procedure because of leakage or breakage of a syringe, it is recommended that extra syringes be kept in inventory.

Injection Techniques

Several techniques have been described for the endoscopic treatment of VUR including a submucous injection (STING procedure), a single intra-ureteric injection (HIT procedure) and a double (proximal and distal) intra-ureteric injection (Double-HIT procedure). The Double-HIT procedure is a refinement of the original STING and HIT procedures and has been reported to result in greater clinical success rates.

In general, the bladder is semi-filled to allow for good visualization of the ureteral orifice(s) and to avoid tension within the submucosal layer of the ureter secondary to overdistension. For the HIT procedure, hydrodistention of the ureteral orifice is initiated to define the site of injection within the submucosa of the ureteral orifice. The needle is inserted approximately 4 mm in the submucosa of the mid- to distal ureteral tunnel at the 6 o’clock position (Site 1; Fig. 2). Irrigation should be stopped at this point, and the gel is injected. Only a small volume (0.5-1.0 mL) is needed to create a sufficient bulge. The ureteric tunnel should collapse with injection. The cystoscope is pulled back towards the bladder neck to visualize the full injection. After the injection the needle should be kept in position for 15-30 seconds to prevent extrusion of the product. At termination of the procedure, the ureteral orifice should no longer hydrodistend, indicating complete coaptation of the ureteral orifice and tunnel.

If the ureteral orifice does not completely coapt with a single intra-ureteral injection, a second more distal intra-ureteral injection (Double-HIT) may be contemplated (Site 2; Fig. 2) or a sub-ureteral implantation (STING) can be performed (Site 3; Fig. 2).

Postoperatively it is not necessary to use an indwelling catheter. Patients are usually able to void without any problems after recovery from the anesthesia.

A VCUG is suggested in the post treatment follow up to ascertain whether the reflux remains. If the original injection needs to be reinforced further treatments may be administered.

For patients previously treated with Deflux, the injection sites from the previous procedure may still be visible. An augmentation of prior intra-ureteric injections can be performed or further enhanced with a sub-mucosal injection in order to achieve resolution of persistent reflux.

Deflux Metal Needle

• Follow national local or institutional guidelines for use and disposal of medical sharp devices.
• Do not re-shield used needles. Re-shielding by hand is a hazardous practice and should be avoided.
• Discard unshielded needles in approved sharps containers.
• Obtain prompt medical attention if injury occurs.