Deflux® Injectable Gel

CAUTION: Federal law restricts this device to sale by or on the order of a physician.

DEVICE DESCRIPTION

Deflux® is a sterile, highly viscous gel of dextranomer microspheres (50 mg/mL) in a carrier gel of non-animal stabilized hyaluronic acid (15 mg/mL), constituting a biocompatible and biodegradable implant. The dextranomer microspheres range in size between 80-250 microns with an average size of about 130 microns. The stabilized hyaluronic acid acts mainly as a carrier, leaving the dextranomer microspheres at the implant site.

Deflux is contained in a single use disposable syringe. The syringe is equipped with a tip cap, plunger and plunger rod. The syringe is terminally sterilized.

Deflux is injected submucosally in the urinary bladder in close proximity to the ureteral orifice. The injection of Deflux creates increased tissue bulk thereby providing coaptation of the distal ureter during filling and contraction of the bladder. The dextranomer microspheres are gradually surrounded by host connective tissue.

INDICATIONS

Deflux is indicated for treatment of children with vesicoureteral reflux (VUR) grades II-IV.

CONTRAINDICATIONS

Deflux is contraindicated in patients with any of the following conditions:

- Non-functional kidney(s)
- Hutch diverticulum
- Ureterocele
- Active voiding dysfunction
- Ongoing urinary tract infection.

WARNINGS

- Do not inject Deflux intravascularly. Injection of Deflux into blood vessels may cause vascular occlusion.
- Do not inject if the patient is known to be allergic to hyaluronic acid-based products or dextran.

PRECAUTIONS

- Deflux is to be administered only by qualified surgeons experienced in the use of a cystoscope and trained in the technique of subureteric and/or intraureteric injections (with Deflux or other materials).
- Treatment of duplex systems has not been prospectively studied.
- Ureters with grossly dilated orifices may render the patient unsuitable for treatment.
- The risks of infection and bleeding are associated with the cystoscopic procedure used to inject Deflux. The usual precautions associated with cystoscopy (e.g., sterile technique, proper dilation, etc.) should be followed.
- The safety and effectiveness of the use of more than 6 mL of Deflux (3 mL at each ureteral orifice) at the same treatment session have not been established.
- The safety and effectiveness of Deflux in the treatment of children under 1 year of age have not been established.
- Deflux is supplied pre-filled in a 1 mL syringe with a luer lock fitting, and is intended for single use only. Carefully examine the unit to verify that neither the contents nor the package has been damaged in shipment. **DO NOT USE** if damaged.
- Deflux is supplied sterile. Do not re-sterilize, as this may damage or alter the product.
- Deflux is supplied in a syringe ready for use. Never mix Deflux with other products.
- Deflux is stored up to 25°C (77°F), and used prior to the expiration date printed on its label. Do not expose Deflux to either sunlight or freezing, as this may damage or alter the product. Do not use Deflux after its expiration date.
- Deflux is packaged in a glass syringe. Glass is subject to breakage under a variety of unavoidable conditions. Care should be taken with the handling of the glass syringe and with disposing of broken glass to avoid laceration or other injury.
- After use, syringes and needles should be handled as potential biohazards. Disposal should be in accordance with accepted medical practice and applicable local, state and federal requirements.

ADVERSE EVENTS

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.

A list of the treatment -related adverse events occurring in >1% of patients in all four studies is presented in **Table 1**.

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

Adverse Event Category	Pivotal Study (n=39 Deflux patients)	Supportive Studies (n=170 Deflux patients)	Post-Approval Study (n=165 Deflux patients)
Urinary tract infection (UTI)[(i)]	6 (15.4%)[(ii, iii)]	13 (7.6%)[(ii, iii)]	3 (1.8%)
Ureteral dilatation[(iv)]	1 (2.6%)	6 (3.5%)	0 (0%)
Nausea/Vomiting/Abdominal pain[(v)]	0 (0%)	2 (1.2%)	0 (0%)
Abdominal discomfort	0 (0%)	0 (0%)	2 (1.2%)
Dysuria	0 (0%)	0 (0%)	2 (1.2%)
Micturition urgency	0 (0%)	0 (0%)	2 (1.2%)
Pollakiuria	0 (0%)	0 (0%)	2 (1.2%)
Urinary incontinence	0 (0%)	0 (0%)	2 (1.2%)
Vesicoureteric reflux	0 (0%)	0 (0%)	2 (1.2%)

(i) Cases of UTI typically occurred in patients with persistent reflux.
(ii) Patients in the nonrandomized studies received antibiotic prophylaxis until the 3-month voiding cystourethrogram (VCUG). After that only those patients whose treatment had failed received further antibiotic prophylaxis. The patients in the randomized study received antibiotic prophylaxis 1 month post-treatment.
(iii) All UTI cases were successfully treated with antibiotics.
(iv) No case of ureteral dilatation required intervention and most cases resolved spontaneously.
(v) Both cases of nausea/vomiting/abdominal pain were resolved.

The following adverse events were associated with the use of Deflux from spontaneous post-marketing surveillance reporting or from clinical studies (occurring ≤1%) and include but are not limited to: ureteral obstruction with or without hydronephrosis (some cases requiring temporary placement of a ureteric stent, and rare cases of ureteral re-implant procedures), hematuria, urgency, frequency, pyelonephritis, foreign body reaction, calcification, pyrexia, hypertonic bladder, bladder irritation, and Henoch-Schonlein purpura.

Adverse events should be reported to:

Salix Product Information Call Center
Phone: 1-800-508-0024
Fax: 1-510-595-8183
E-mail: Salix@medcomsol.com

CLINICAL STUDIES

Introduction

Four single-center, clinical studies were performed to evaluate the safety and effectiveness of Deflux for the treatment of vesicoureteral reflux (VUR):

- one single-center randomized study (pivotal study)
- two single-center open label studies (supportive studies)
- one multicenter open label study (post-approval study)

The brief background information for each study is presented in **Table 2**.

Table 2: Brief Background Information: Clinical Studies Performed to Evaluate the Safety and Effectiveness of Deflux for the Treatment of Vesicoureteral Reflux (VUR)

	Pivotal Study	Supportive Study 1	Supportive Study 2	Post-Approval Study
Design	A randomized comparative study of submucosal injection of Deflux for VUR grade II-IV. The patients were followed for 12 months for safety and effectiveness.	An open-label, non-comparative study of submucosal injection of Deflux for VUR grade III-IV, where the patients were followed for 12 months for safety and effectiveness.	An open-label, non-comparative study of submucosal injection of Deflux for VUR grade II-IV, where the patients were followed for 12 months for safety and effectiveness.	An open-label, non-comparative study of submucosal injection of Deflux for VUR grade II-IV, where the patients were followed for 5 years for safety and effectiveness.
Purpose	To investigate the safety of Deflux and to compare the effectiveness of Deflux with that of long-term prophylactic treatment with antibiotics in the treatment of VUR 12 months after start of treatment.	To investigate the safety and effectiveness of submucosal injection of the implant Deflux in the treatment of VUR.	To investigate the safety and effectiveness of submucosal injection of the implant Deflux in the treatment of VUR.	To investigate the long-term safety and effectiveness of submucosal injection of the implant Deflux in the treatment of VUR.
Endpoints	Effectiveness: Reflux grade on voiding cystourethrogram (VCUG).	Effectiveness: Reflux grade on VCUG.	Effectiveness: Reflux grade on VCUG..	Effectiveness: • Reflux grade on VCUG at 3 months, 12 months and 5 years. • Comparison of study results to published literature • 18.8% of subjects (31 of 165 subjects) completed the full 5 years of follow-up and the mean duration of post-injection follow-up was 2.4 years (range: 0 to 7.8 years)
	Safety: Complications, UTI, ureteral dilatation, renal function.	Safety: Complications, UTI, ureteral dilatation, renal function.	Safety: Complications, UTI, ureteral dilatation, renal function.	Safety: Complications, UTI, ureteral dilatation, renal function
Location	Ospedale Bambino Gesu, Rome, Italy	University Hospital of Uppsala, Sweden	Ospedale Bambino Gesu, Rome, Italy	12 Centers in the United States
Size	39 children were treated with Deflux. 21 children were treated with antibiotics.	50 children were treated with Deflux.	120 children were treated with Deflux	165 children were treated with Deflux
Basic demographics and baseline characteristics	*Deflux group:* • 60% girls; • Mean age = 4.1 yrs (range: 1-13 yrs) • 67% unilateral reflux • 62% grade III-IV *Antibiotic group:* • 62% girls; • Mean age = 3.9 yrs (range: 1-10 yrs); • 57% unilateral reflux; • 38% grade III-IV	• 66% girls; • Mean age = 4.9 yrs (range: 1-18 yrs) • 72% unilateral reflux; • 98% grade III-IV	• 74% girls; • Mean age = 4.4 yrs (range: 0.9-15.6 yrs) • 60% unilateral reflux; • 70% grade III-IV	• 91% girls; • Mean age = 5.7 yrs (range: 1-16 yrs); • 52% unilateral reflux; • 37% grade III-IV

Cumulative Literature Review

After removing foreign language citations, review articles, or commentary on primary research, and including only articles that showed safety results, a cumulative total of 106 publications (88 clinical studies and 18 case reports) were identified within the 24 September 2001 (approval date) to 23 June 2014 time period.

At least 9100 children received Deflux injections and were followed for up to 13.4 years, with median/mean follow-up durations of 2 to ≥ 5 years for most of the studies. Safety data collected over durations of ≥ 5 years provide substantial information to support the safety profile of Deflux over the longer term.

Most of the adverse events in this population, such as urinary tract infection (UTI), febrile UTI, pyelonephritis, and hydronephrosis, result from the vesicoureteral reflux (VUR) condition for which Deflux is indicated.

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 incidence observed in the postapproval study (18%). The incidence of UTIs in the literature ranges of 2.9% to 55%.

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 ureteral obstruction following Deflux injection. In the published literature, the rate of pyelonephritis ranged from 0.4% to 1%. Ureteral obstruction and hydronephrosis have been reported in 0.7% of patients in a large study (745 patients) and reported rates of ureteral obstruction in the literature range from 0.7% to 5.7%.

Therefore, safety data in the published literature, the postapproval study, and data in the current product label support the conclusion that Deflux is well tolerated and has a favorable safety profile. Reported adverse events are predominantly short-lived and mild in severity.

Treatment Information

***Deflux*:**

The Deflux injection procedure was the same in each of the four studies. All treatments were performed under general anesthesia. The injection was administered endoscopically (via cystoscope) and placed submucosally a few millimeters rom the ureteral orifice at the 6 o'clock position. Each injection was to create a well-defined small bulge and a crescent shaped tightening of the orifice. The mean volume of Deflux injected per ureter in the pivotal and supportive studies ranged from 0.8 to 1.1 mL (overall range of 0.2 to 3.0 mL). In the post-approval study, the volume of Deflux injected per ureter ranged from 0.2 to 2.6 mL. All treatments were performed on an outpatient basis.

Antibiotic Prophylaxis:

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

Retreatment Information

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 manner as the initial injection procedure. The retreatment rates observed in these studies were 28% for the pivotal study, 20% for supportive study 1, 12% supportive for study 2 and 30% for the post-approval study.

Effectiveness

In the pivotal study and two supportive studies, effectiveness of treatment was defined as improvement to VCUG = 0 (no reflux at the 12-month post injection time point. In the post-approval 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; success at later time points was defined as the persistent absence of febrile UTI or VUR Grade 0 as shown on a repeat VCUG assessment following the occurrence of a febrile UTI or other event that warranted a repeat VCUG study). Effectiveness results per patient for all four studies presented in **Table 3** (3- and 12-months post injection) and **Table 4** (long-term success rates).

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

	Pivotal Study	Supportive Study 1	Supportive Study 2	Post-Approval Study
Number of patients available for analysis (including failures carried forward)	12 months: *Deflux group*: n=39 *Antibiotic group*: n=21	12 months: n=43	12 months: n=107	3 months: n=165 12 months: n=139
Success rate[a] at 3- or 12-months	12 months: *Deflux group*: 69% (27/39) *Antibiotic group*: 33% (7/21) (p=0.0041)	12 months: 54% (23/43)	12 months: 60% (65/107)	3 months: 66% (109/165) 12 months: 69% (96/139)

[a] Success was defined as improvement to VCUG = 0 (no reflux) at 12 months in the pivotal and supportive studies and at 3 months in the post-approval study. At 12 months in the the post-approval study, success was defined as persistnet absence of febrile UTI or VUR grade 0 as shown on VCUG assessment following the occurence of a febrile UTI or other event that warranted a repeat VCUG study.

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

Long-Term Follow-up Information

The long-term success (i.e., grade 0) rate and long-term surgery rate are presented in **Table 4.**

Table 4: Long-Term Follow-Up Information for Deflux in the Pivotal, Supportive and Post-Approval Studies

	Pivotal Study	Supportive Studies	Post-Approval Study
Long-term success rate[a] (i.e., grade 0)	3 years: All 27 Deflux patients rated as cured at 12 months had repeat VCUGs performed approximately 3 years post treatment. All but one remained free of reflux. Assuming that all Deflux patients who were study failures at 12 months continue to have reflux, the 3-year success rate is 67% (26/39).	3 years: Study 1: Patients (18/50) were followed 2-6 years after the last Deflux treatment. Based on life table analysis of the whole patient group (n=50), 50% of the patients are cured of their VUR 3 years post treatment. Study 2: No data available	5 years: 40% (32/80)
Long-term surgery rate	No patients had to undergo open surgery.	Study 1: 8% (4/50) of patients underwent open surgery due to persistent reflux (> grade III). Study 2: No data available	No data available.

[a]Success in the pivotal and supportive studies was defined as improvement to VCUG = 0 (no reflux). Success in the post-approval study was defined as persistent absence of febrile UTI or VUR Grade 0 shown on VCUG assessment following the occurrence of a febrile UTI or other event that warranted a repeat study.

Study Strengths and Weaknesses

Although the purpose of the study was to provide 5-year data on a minimum of 180 subjects, only 165 were enrolled and complete 5-year data are available for just 31/165 subjects (18.8%), with partial 5-year data available for 80/165 subjects (48%). However, the data from the study confirm the long-term efficacy and safety of endoscopic correction with Deflux in children with vesicoureteral reflux grade II-IV. The safety of Deflux in this study was consistent with the observations in the studies that supported the approval of Deflux (Pivotal Study) and with data in the literature.

DIRECTIONS FOR USE

Deflux is to be administered only by qualified surgeons experienced in the use of a cystoscope and trained in the technique of subureteric and/or intraureteric injections 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 bevel, 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 hub and luer lock adapter, please both **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.

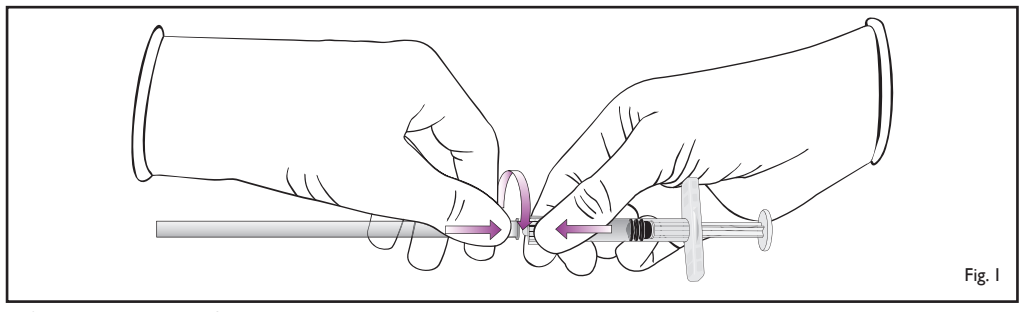

Fig. 1

Deflux is easily injected by finger pressure on a normal syringe with any commonly used pediatric cystoscope. Due to its viscoelastic properties, Deflux can be injected through a fine needle – no special injection device is necessary.

Injection Techniques

Several techniques have been described for the endoscopic treatment of VUR including a subureteric injection (STING procedure), a single intra-ureteric injection (HIT procedure) and a double (proximal and distal) intra-ureteric injection (Double-HIT procedure)[1-6]. 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.

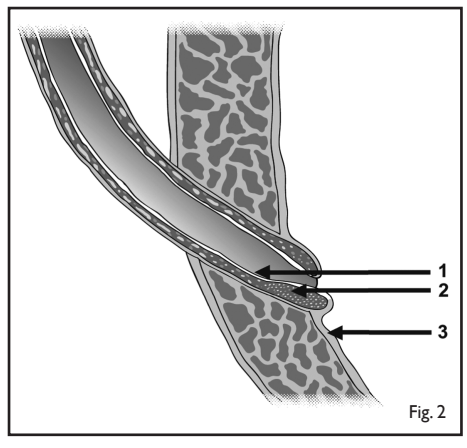

Fig. 2

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 intramural ureter. 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 bolus. The ureteric tunnel should coapt 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 intraureteral 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 leave 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 intraureteric injections can be performed or further enhanced with a subureteral 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. Recapping by hand is a hazardous practice and should be avoided.
- Discard unshielded needles in approved sharps containers.
- Obtain prompt medical attention if injury occurs.

PATIENT COUNSELING INFORMATION

Prior to Deflux implant therapy, the patient must be given the Deflux Patient/Parents Brochure and a thorough presentation of the risks and benefits of Deflux treatment should be made to prospective patients (or parents of prospective patients). As part of this presentation, patients/parents should also be counseled on the risks and benefits of all treatment alternatives (i.e., antibiotic prophylaxis and open surgery).

Prior to treatment, the patient should undergo a physical examination and be thoroughly evaluated to ensure proper patient selection. The patient should be advised that Deflux may not give a permanent therapeutic result and that additional treatment sessions may be required to achieve and maintain the effect of the treatment.

HOW SUPPLIED

Deflux is supplied in a glass syringe containing 1 mL. Each syringe is terminally moist heat sterilized in a Steriking pouch and packed in a paper carton.

It is recommended to use the Deflux metal needle (3.7F x 23G tip x 350 mm) for safe and accurate administration of Deflux.

Storage: Store up to 25°C (77°F) protected from sunlight and freezing.

REFERENCES

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Rev. 04/2016