

Deflux
Package Insert
September 24, 2001

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

11) 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 (NASHA, 17 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 NASHA 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 sub-mucosally 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.

11) Intended Use/Indications

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

11) Contraindications

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

- Non-functional kidney(s)
- Hutch diverticuli
- Duplicated ureters
- Active voiding dysfunction
- Ongoing urinary tract infection

11) Warnings

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

11) Precautions

- Deflux should only be administered by qualified physicians experienced in the use of a cystoscope and trained in subureteral injection procedures.
- 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 prefilled 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. Immediately return damaged product to Q-Med AB.
- 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 must be stored at 2°C – 8°C, 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.

11) Adverse Events

The safety of Deflux in the treatment of VUR is based on a randomized study in which 39 children were treated with Deflux for VUR, and two nonrandomized studies in which 170 children were treated with Deflux for VUR. Follow-up for all three studies was 12 months. No patients died during the course of these studies.

A list of the treatment related adverse events from the randomized and the nonrandomized studies is presented in **Table 1**.

Table 1: List of treatment-related adverse events for the 39 patients from the randomized study and the 170 patients from the nonrandomized studies.

Adverse Event Category	Randomized Study (n=39 Deflux patients)	Nonrandomized Studies (n=170 Deflux patients)
UTI ⁽ⁱ⁾	6 (15.4%) ^(ii, iii)	13 (7.6%) ^(ii, iii)
Ureteral dilatation ^(iv)	1 (2.6%)	6 (3.5%)
Nausea/Vomiting/Abdominal pain ^(v)	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 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 potential risks of subureteral injection procedures were not reported in any of the studies: vascular occlusion, urinary retention, dysuria, bleeding/hematuria, urgency, and urinary frequency.

11) Clinical studies

Introduction

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

- one randomized study (pivotal study)
- two nonrandomized studies (supporting studies)

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

Table 2: Brief background information for each study performed

	Randomized study	Nonrandomized study 1	Nonrandomized study 2
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, 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, 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.
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.
Endpoints	Effectiveness: Reflux grade on voiding cystourethrogram (VCUG). Safety: Complications, UTI, ureteral dilatation, renal function.	Effectiveness: Reflux grade on VCUG. Safety: Complications, UTI, ureteral dilatation, renal function.	Effectiveness: Reflux grade on VCUG. Safety: Complications, UTI, ureteral dilatation, renal function.
Location	Ospedale Bambino Gesù, Rome, Italy	University Hospital Uppsala, Sweden	Ospedale Bambino Gesù, Rome, Italy
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.
Basic demographics and baseline characteristics	<u>Deflux group:</u> <ul style="list-style-type: none"> • 60% girls; • Mean age = 4.1 yrs (range: 1-13 yrs); • 67% unilateral reflux; • 62% grade III-IV. <u>Antibiotic group:</u> <ul style="list-style-type: none"> • 62% girls; • Mean age = 3.9 yrs (range: 1-10 yrs); • 57% unilateral reflux; • 38% grade III-IV. 	<ul style="list-style-type: none"> • 66% girls; • Mean age = 4.9 yrs (range: 1-18 yrs); • 72% unilateral reflux; • 98% grade III-IV. 	<ul style="list-style-type: none"> • 74% girls; • Mean age = 4.4 yrs (range: 0.9-15.6 yrs); • 60% unilateral reflux; • 70% grade III-IV.

Treatment Information

Deflux:

The Deflux injection procedure was the same in each of the three studies. All treatments were performed under general anesthesia. The injection was administered endoscopically (via cystoscope) and placed submucosally a few millimeters from 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 three studies ranged from 0.8 to 1.1 ml (overall range of 0.2 to 3.0 ml). All treatments were performed on an outpatient basis.

Antibiotic Prophylaxis:

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

Retreatment Information

In all three 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 these studies were 28% for the randomized study, 20% for study 1, and 12% for study 2.

Effectiveness

In each of the three studies, the effectiveness of treatment was based on the 12-month VCUG findings. Treatment success was defined as improvement to grade 0 (no reflux) in all refluxing ureters. The effectiveness results per patient for the three studies are presented in Table 3.

Table 3: The effectiveness results (VCUG after 12 months) per patient for the three studies

	Randomized study	Nonrandomized study 1	Nonrandomized study 2
Number of patients available for analysis at 12 months (Including failures carried forward)	<u>Deflux group</u> : n=39 <u>Antibiotic group</u> : n=21	n=43	n=107
12-month success rate (i.e., patients grade 0 in all treated ureters)	<u>Deflux group</u> : 69% (27/39) <u>Antibiotic group</u> : 33% (7/21) (p=0.0041)	54% (23/43)	60% (65/107)

As expected, the success rate of Deflux treatment is 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

	Randomized study	Nonrandomized study 1	Nonrandomized study 2
Long-term success rate (i.e., grade 0)	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).	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.	No data available.
Long-term surgery rate	No patients had to undergo open surgery.	8% (4/50) of patients underwent open surgery due to persistent reflux (> grade III).	No data available.

11) Directions for use

It is recommended to use the Deflux metal needle (3,7F x 23G tip x 350mm, article No. 10-35798) for safe and accurate administration of Deflux®.

Deflux® can be injected with any common paediatric cystoscope with a minimum 4 French working channel. A new 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 anaesthesia 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.

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

The bladder is semi-filled to allow good visualization and to prevent flattening and spreading of the injected material by high intravesical pressure, but not over-full as this would render ureteral orifices less easy to inject.

The needle is introduced under the bladder mucosa 2–3 mm below the refluxing ureteral orifice at a 6 o'clock position. The needle tip is positioned just under the urothelium and is advanced 4–5 mm in the submucosal plane of the ureter. Deflux® is then injected until a prominent bulge appears, and the orifice has assumed a crescent-like shape. Only a small volume (0.5-1.0 ml) is needed to create a sufficient bolus. Please observe that approximately 0.2 ml remains in the needle.

After the injection the needle should be kept in position for 15–30 seconds to prevent extrusion of the product.

For patients previously treated with Deflux™, the bulge from the previous procedure may still be clearly visible. The needle is introduced in the same manner as previously: 2–3 mm below the orifice at a 6 o'clock position. The objective is to create a more distinct bulge with a slit-like orifice.

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

Deflux is to be administered only by qualified surgeons experienced in the use of a cystoscope and trained in the technique for subureteric injections (with Deflux or other materials).

After three months or so, another VCUG is taken which shows whether the reflux remains. If the 'bulge' needs to be reinforced, further treatments are carried out.

11) 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.

11) 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 (3.7 F x 23G tip x 350 mm, Art No 10-35798) for safe and accurate administration of Deflux.

Storage: Store at 2 to 8°C (35 to 47°F) protected from sunlight and freezing.

11) Manufacturer information

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