

LABELING

URYX[®]
Urethral Bulking Agent**DRAFT 5****Instructions for Use**

CAUTION: Federal law (USA) restricts this device to sale by or on the order of a physician trained in diagnostic and therapeutic cystoscopy and in the use of this device.

DESCRIPTION

URYX[®] Urethral Bulking Agent is a sterile, non-pyrogenic implant composed of Ethylene Vinyl Alcohol copolymer (EVOH) dissolved in a Dimethyl Sulfoxide (DMSO) carrier. The device is terminally sterilized by dry heat.

URYX is provided as part of the URYX Urethral Bulking Kit, consisting of one vial of URYX (2.8 ml) and one syringe (3 ml) with attached drawing needle (20 G X 1"). The syringe is DMSO compatible. Delivery needles for URYX are supplied separately.

MODE OF ACTION

URYX is injected in the urethral submucosa. Upon injection, the DMSO carrier rapidly dissipates from the EVOH copolymer, forming a cohesive, spongy mass that serves to bulk surrounding tissue. The EVOH copolymer is not subject to absorption or enzymatic breakdown within the body.

INDICATIONS FOR USE

URYX is indicated for transurethral injection in the treatment of adult women diagnosed with stress urinary incontinence (SUI) due to intrinsic sphincter deficiency (ISD).

CONTRAINDICATIONS

URYX urethral bulking procedure is contraindicated in patients with the following conditions:

- acute cystitis, urethritis, other acute or chronic genitourinary tract infections, or
- fragile urethral mucosal lining.

WARNINGS

- Do not inject URYX into blood vessels. This may cause vascular occlusion or embolic phenomena.
- URYX should not be used in patients with bladder neck or urethral strictures or obstructive conditions, until such strictures or obstructive conditions have been corrected. Use of URYX in patients with uncorrected strictures/obstructions may cause occlusion of the urethra.
- The safety and effectiveness of URYX urethral bulking procedures have not been established in patients who are pregnant or lactating.
- The effect of URYX on subsequent pregnancy and delivery, and the impact of subsequent pregnancy on the effect of URYX, is unknown. Therefore, the risks and benefits of the device in women of childbearing potential should be carefully assessed.
- URYX has been shown in clinical study to have increased complications when injected periurethrally, most notably urge incontinence.
- URYX should only be used by someone properly trained with this product.

PRECAUTIONS

- Submucosal placement, slow, deliberate implantation, and measured volume are necessary to avoid exposure of the implant through tissue. Shallow placement, rapid injection, or injection of large volumes may result in exposure of the implanted material.
- After injection of URYX, hold the needle at the injection site for an additional 60 seconds. This step is necessary to allow the implant to solidify into a spongy mass and to minimize leakage of URYX from the injection site.
- Patients should be counselled that one or more repeat URYX injection procedures may be required to achieve dryness or a satisfactory level of improvement in incontinence.
- There is a trend of increased complications in patients receiving repeat URYX treatments, particularly urinary urgency, delayed voiding, urinary tract infection, and pelvic pain.
- The safety and effectiveness of URYX treatment have not been established in patients with any of the following conditions: uncontrolled bladder instability, uterine prolapse > stage II, post-void residual urine volume > 60 mL, or morbid obesity.
- The long-term safety and effectiveness of URYX treatment have not been established.
- To reduce the risks of infection and bleeding, the usual precautions associated with cystoscopic procedures should be followed.
- Do not freeze (i.e., < 0° C / 32° F). Temperatures below 0° C / 32° F can cause the URYX vials to break.
- Refrigeration of URYX is neither necessary nor recommended. The URYX solution undergoes a reversible phase change from a liquid to solid state at approximately 19° C / 66° F. If the solution changes to the solid phase, maintain at room temperature until URYX has returned to a liquid state.
- URYX should be stored at room temperature (i.e., > 19° C / 66° F) to ensure that it is in a liquid state at the time of use.
- URYX must be used only with DMSO compatible needles, syringes, and other accessories.
- URYX is intended as a single-use, disposable device. Do not resterilize any portion of the URYX Kit.
- Do not use the URYX if the integrity of the vial, aluminium seal, or outer packaging appears compromised, or if there is any evidence of leakage.

ADVERSE EVENTS

Observed Adverse Events:

The URYX clinical trial involved 374 URYX treatment injections in 174 subjects (mean follow-up of approximately 14 months). There were no deaths among study patients.

The following table lists the treatment related adverse events reported during the clinical study (incidence $\geq 2\%$). Treatment related events are those events that were deemed to be related to either the device or the procedure. All genitourinary events were classified as treatment related.

Number (%) Subjects Reporting Treatment Related Adverse Events	
Event Category	URYX (n=174)
Urinary tract infection (UTI)	50 (29%)
Delayed voiding	32 (18%)
Dysuria	31 (18%)
Exposed material	28 (16%)
Urinary urgency	24 (14%)
Urinary frequency	22 (13%)
Genitourinary (infection, tenderness)	20 (11%)
Hematuria	19 (11%)
Urge incontinence	16 (9%)
Worsening of incontinence (onset of urge)	14 (8%)
Outlet obstruction	13 (7%)
Pain at injection site	13 (7%)
Pelvic pain	13 (7%)
Yeast infection	12 (7%)
Leakage of urine/stress incontinence	9 (5%)
Bulking material injected into bladder	7 (4%)
Fatigue	3 (2%)
Abnormal urinalysis	3 (2%)
Bladder fullness	3 (2%)
Nocturia	3 (2%)
Pelvic heaviness	3 (2%)
Uterine fibroids	3 (2%)
Other (<2%)	38 (N/A)*

* "Other" treatment related adverse events in URYX patients, occurring at frequencies of < 2%, were as follows (listed alphabetically): abdominal upset, bladder spasms, bladder stones, body aches, burning pain, cold and shivering, cyst, cystitis, feeling of decreased sensation with urination, feeling of bladder not emptying, felt faint during bulking injection, fever, garlic odor, genital pain, kidney stones, labia with erythema, lower back pain, medicinal smell to urine, nausea, partial urinary retention due to dementia, pyuria, removal of URYX, urethral burning sensation, urethral irritation, urethral redness, urethral soreness, urethral spasm, vaginal bleeding, and vulvar burning.

Most treatment related adverse events occurred within 24 hours of treatment and subsequently resolved within 30 days. At the time of database closure, 92% of treatment related adverse events were resolved. The following events were persistent or resolution was unconfirmed at the time of database closure (the number of events is shown in parentheses): urge incontinence (6); leakage of urine/stress incontinence (5); worsening of incontinence (onset of urge) (5); exposed material (4); uterine fibroids (3); urinary tract infection (2); urinary frequency (2); urinary urgency (2) and one event each of genitourinary (infection/tenderness), kidney stones, nocturia, pelvic pain, urethral redness, and URYX removal.

Of the treatment related adverse events, 39% were classified as mild, 58% were classified as moderate, and 3% were classified as severe. The severe treatment related adverse events included: bladder spasms, bladder stones, bulking material injected into the bladder, delayed voiding, exposed bulking material, hematuria, pelvic pain, urge incontinence, and urinary frequency.

The clinical study consisted of a pilot or feasibility phase (n=28), followed by the expanded study phase (n=146). There was higher overall rate of genitourinary adverse events in the feasibility phase of the study than in the expanded phase. In particular, the rate of "exposed material" was higher (32% vs. 13%). This reduction in the rate of exposed material was achieved as a result of modifications to the URYX injection instructions and investigator training.

During the course of the clinical investigation (both study phases), 28 subjects (16%) receiving URYX treatment experienced exposed bulking material in the urethral mucosa. Patients experiencing exposed material often reported other events, particularly dysuria, delayed voiding, urinary tract infection, hematuria, urinary frequency, and urinary urgency. Exposed URYX material was associated with shallow placement and injection too proximal to the bladder neck. Over time, the urethra healed spontaneously as the mucosal surface re-epithelialized. The physician may choose to remove exposed material cystoscopically with graspers or forceps to facilitate healing.

The majority of patients were injected via the transurethral approach, while a small proportion of patients were injected periurethrally. There were significantly more adverse events among URYX patients treated periurethrally; as a result, the URYX instructions for use are limited to transurethral administration.

Potential Adverse Events:

Although not reported in the clinical study, other potential adverse events which may occur include erosion, erythema, embolic phenomena, and vascular occlusion.

CLINICAL STUDIES

Purpose and Design of the URYX Clinical Study

A randomized, masked, multicenter clinical investigation was performed to evaluate the safety and effectiveness of URYX for the treatment of stress urinary incontinence due to intrinsic sphincter deficiency (ISD). Control patients were treated with a commercially available absorbable bulking agent. Patients were adult women diagnosed as having stress urinary incontinence due to ISD. To be eligible for enrollment, subjects were required to have a viable mucosal lining at the injection site and normal bladder capacity. Subjects with uncontrolled bladder instability, high post-void residual urine volume, uterine prolapse greater than stage II, confounding bladder pathology, UTI, and morbid obesity were excluded. Following enrollment, patients were randomized 2:1 between URYX and control.

A maximum of three treatments were permitted over a period of 90 days from initial treatment, and results were assessed versus baseline at 3, 6, and 12 months from final treatment. Treatment results are reported for all subjects who received treatment.

Outcome Parameters

The assessment of safety and effectiveness of URYX was based on testing for equivalence to the control bulking agent.

1. Effectiveness Parameters

Subjects were assessed for improvement of incontinence based on Stamey Grade and Pad Weight at 12 months following final treatment. Additionally, patient quality of life was measured pre- and post-treatment using the "Incontinence Quality of Life Questionnaire" (IQOL; maximum score = 110 points; Wagner et al, 1996). The results for URYX-treated subjects were compared to the control group.

Primary Effectiveness Endpoint:

The primary effectiveness endpoint was improvement in Stamey Grade, defined as a decrease of at least one continence grade from baseline. The Stamey Grade is based on a defined scale with the following designations:

- Grade 0 – Continent or dry;
- Grade 1 – Patient loses urine with sudden increases in abdominal pressure (e.g. coughing, sneezing, laughing) but never in bed at night;
- Grade 2 – Patient's incontinence worsens with lesser degrees of stress (e.g. walking, standing erect from a sitting position, or sitting up in bed);
- Grade 3 – Patient has total incontinence (urine is lost without any relationship to physical activity or position).

Patient success was defined as Stamey Grade improvement at 12 months post-treatment. The criterion for study success was equivalence (Blackwelder formula; 20% delta) between the URYX and control groups in the rates of Stamey Grade improvement at 12 months.

Secondary Effectiveness Endpoints:

The secondary effectiveness endpoints were as follows:

- Improvement in pad weight at 12 months, defined as a decrease of at least 50% in pad weight from baseline.
- Dryness at 12 months, defined alternatively as (i) Stamey Grade 0 or (ii) pad weight ≤ 2 grams.
- Improvement in IQOL at 12 months, defined as an increase of at least 50% in IQOL score from baseline.

2. Safety Parameters

All adverse events associated with the clinical study were summarized and classified according to severity, duration, and relationship to the device and/or the treatment.

Results

A total of 253 subjects were enrolled and treated in two phases of the study: (1) a feasibility phase, during which initial experience with URYX was gained; and (2) an expanded phase, during which the majority of patients were enrolled and treated. Of this total, 174 received URYX treatments, and 79 received treatment with the control bulking agent.

There were no deaths among the URYX patients during the study. Refer to the Adverse Events Section on page 3 for more information on the safety of URYX.

Of the 174 subjects treated with URYX, 16 were treated in a non-randomized fashion to give investigators experience with the injection technique. Therefore, the effectiveness of URYX is based on the 158 patients randomized to URYX, compared to the control subjects. Since 30% of URYX subjects (28% control group) discontinued the study prior to 12 months, primarily to seek alternate treatment, the effectiveness results are reported using an intent-to-treat approach, where all missing data were imputed using the last observation carried forward (LOCF). This method of handling missing data is consistent with the protocol's statistical analysis plan. In addition to comparison of the LOCF results, the effectiveness endpoints are also compared among the subset of subjects who completed the 12-month study. In both analyses, i.e., the intent-to-treat (LOCF) and subjects completing the 12-month study, effectiveness of URYX was statistically equivalent to that of the control bulking agent. The occurrence of exposed material (n=28 URYX patients; see the "Adverse Events" section) did not impact device effectiveness.

The following tables summarize the patient population, treatment information, and effectiveness data collected in the clinical study evaluating URYX urethral bulking therapy:

Patient Accountability

Clinical Study Patient Accountability	URYX	Control
Number of subjects treated	174	79
Number of subjects with 12-month follow-up after final treatment	120	57
Number of subjects with less than 12 months follow-up	54	22

Baseline Profile

Subject Baseline Profile	URYX N=174	Control N=79
Mean age (range)	61 years (35-91)	61 years (30-83)
Mean duration of incontinence	9.5 years	9.9 years
Mean baseline incontinence grade*	2.0	2.0
Subjects with baseline incontinence grade = 1 (%)	19 (12%)	12 (15%)
Subjects with baseline incontinence grade = 2 (%)	113 (72%)	57 (72%)
Subjects with baseline incontinence grade = 3 (%)	26 (16%)	10 (13%)
Mean baseline pad weight*	32.0 g	28.2 g
Mean baseline IQOL score*	63	58

*Baseline information shown for randomized subjects, only

Treatment Profile

Subject Treatment Profile	URYX N=174	Control N=79
Mean number of treatments	2.1	2.1
Subjects receiving 1 treatment (%)	41 (24%)	19 (24%)
Subjects receiving 2 treatments (%)	66 (38%)	32 (41%)
Subjects receiving 3 treatments (%)	67 (38%)	28 (35%)
Mean volume injected per subject per treatment (range)	2.2 ml (1.0 - 5.8)	3.4 ml (1.0 - 7.5)
Mean volume injected per subject for all treatments (range)	4.7 ml (1.5 -17.5)	7.3 ml (1.0 - 20.0)

Effectiveness

Intent-to-Treat (LOCF)

Summary of Effectiveness Outcomes 12-Months After Final Treatment	URYX	Control
Stamey Grade		
Dry	18% (29/158)	16% (13/79)
Dry + Improved	49% (77/158)	53% (42/79)
Same	47% (75/158)	37% (29/79)
Worse	4% (6/158)	10% (8/79)
Pad Weight		
Dry	38% (59/156)	32% (25/78)
≥ 50% Improvement	50% (78/156)	49% (38/78)
1 – 49% Improvement	12% (18/156)	14% (11/78)
No Improvement or Worse	38% (60/156)	37% (29/78)
IQOL		
≥ 50% Improvement	22% (35/158)	29% (23/79)
<50% Improvement	78% (123/158)	71% (56/79)
Mean Improvement	9 points	16 points

Completed Study

Summary of Effectiveness Outcomes 12-Months After Final Treatment for those patients that reached 12 months	URYX	Control
Stamey Grade		
Dry	24% (27/111)	21% (12/57)
Dry + Improved	59% (66/111)	56% (32/57)
Same	39% (43/111)	39% (22/57)
Worse	2% (2/111)	5% (3/57)
Pad Weight		
Dry	59% (46/78)	39% (17/44)
≥ 50% Improvement	71% (55/78)	57% (25/44)
1 – 49% Improvement	11% (9/78)	11% (5/44)
No Improvement or Worse	18% (14/78)	32% (14/44)
IQOL		
≥ 50% Improvement	37% (31/84)	33% (16/48)
<50% Improvement	63% (53/84)	67% (32/48)
Mean Improvement	20 points	21 points

INJECTION PROCEDURE

Physician Training

To use URYX, physicians are required to have experience in diagnostic and therapeutic cystoscopy, and be trained in the use of this device. Physicians experienced in the use of injectable bulking agents are advised to pay particular attention to the directions on injection site selection, depth and angle of needle placement, rate of injection, and needle hold time during the procedure.

Patient Counselling

Prior to URYX therapy, the risks and benefits associated with URYX and urethral bulking procedures should be thoroughly discussed with the patient. The patient should be fully apprised of the indications, contraindications, warnings, precautions, expected clinical outcomes, adverse events, and methods of implantation. The patient should be advised that bulking agent therapy with URYX is a course of treatment that may require more than one injection procedure to achieve dryness or a desired level of improvement in incontinence. There is a minimum of four weeks between retreatment (based on the clinical study). The patient should be counselled to report adverse events to the treating physician, and physicians are advised to report adverse events to Genyx. The Patient Information Brochure may be beneficial in providing additional information to the patient.

Injection Technique

URYX should be delivered to the urethral submucosa using a transurethral injection method. The unique physical characteristics of URYX require injection techniques that may differ slightly from techniques employed with alternative bulking agents. The low viscosity of the URYX solution and the cohesive mass of the resulting implant require specific attention to the injection site, needle orientation, depth of needle placement, rate of injection, and injected volume, in order to achieve the highest rate of success.

Injection Site

- The recommended needle entry site is a minimum of 2 cm distal to the bladder neck.

Needle Orientation and Depth of Injection

- A 30-45 degree oblique angle relative to the urethral wall is the recommended needle orientation to achieve optimal sub-mucosal placement.
- The needle should be positioned between the mucosal and muscle layers. To ensure proper depth of the injection, insert the injection needle into the urethral wall up to the shoulder of the needle.

Rate of Injection

- The unique characteristics of URYX require a consistent, slow rate of injection, of approximately 1 ml per minute. The slow injection rate permits the DMSO carrier to dissipate as designed and the polymer to solidify into a soft, coherent, spongy mass.
- The low viscosity of URYX facilitates ease of injection through a 25-gauge needle, using modest hand pressure.

Injection Volume

- Clinical test experience confirmed the recommended injection volume for URYX is ≤ 1 ml per site, and ≤ 2.5 ml total, in a single treatment session.
- The spongy mass that forms in the mucosa following implantation of URYX has approximately the same volume as the liquid injected at each site.
- Complete coaptation of the urethral walls is not a goal of treatment with URYX. Due to the unique properties of the inert URYX copolymer, the implant will remain a spongy mass in a moist tissue environment, and will not be broken down or absorbed into tissue following implantation.

Injection Method

Transurethral injection of URYX requires the following:

- URYX Urethral Bulking Kit (Model No. 10000)
- Genyx Flexible Needle (Model No. 20100) or URYX Injection Needle (Model No. 20200)
- Cystoscopic instruments of choice

Operative Preparation:

Place the patient in the lithotomy position, anesthetize, and prepare for surgery using standard operative procedures. URYX may be injected using local, regional, or general anesthesia.

1. Prepare the cystoscope according to manufacturer's Instructions for Use. Select a cystoscope with a minimum working channel diameter of 5 Fr. for the Genyx Flexible Needle and a minimum working channel diameter of 3 Fr. for the Genyx Injection Needle.
2. Remove the aluminium tab from the URYX vial and swab the stopper with alcohol.
3. Aspirate the entire volume of the URYX vial into the 3cc syringe provided in the URYX Kit. Place the syringe on the sterile procedure tray until needed.
4. Attach the injection needle to the syringe containing URYX and remove the protective sleeve from the needle tip. Prime the needle with smooth, light but consistent pressure on the URYX syringe. While holding the needle vertical with the tip up, vigorously tap the needle hub during the priming process to remove visible air bubbles. Repeat the tapping process along the length of the needle if necessary to remove air bubbles.
5. When the liquid URYX reaches the needle tip, wipe the tip with a dry sterile wipe to remove any excess.
6. If using a cystoscope assembly that includes a bridge, place the flexible needle guide tube within the working channel of the sheath. Firmly seat the sealing cap at the end of the guide tube over the working channel port to prevent leakage of irrigation fluid during the procedure.
7. Insert the injection needle through the guide tube into the working channel of the cystoscope.
8. Insert the cystoscope into the anesthetized urethra and conduct a standard cystoscopic examination of the tissues.
9. **Visualize and select the desired needle placement site, approximately 2 cm distal to the bladder neck.**
10. Advance the needle tip through the urethral wall at an oblique angle of approximately 30-45 degrees.
11. Insert the needle tip until its shoulder (at the junction of the needle tip and the taper of the catheter) is embedded into tissue. This helps to create a seal around the needle.
12. Close off the fluid irrigation supply. Inject URYX slowly, at a rate of 1 ml per minute. **Continue the injection until the desired level of bulk is achieved or a maximum of 1.0 ml has been injected at the initial site.** If blanching of the urethral wall occurs, stop the injection but do not immediately withdraw the needle from the site.
13. **Hold the needle at the injection site for an additional 60 seconds (minimum) post injection,** to allow the implant to solidify into a spongy mass. This hold time is important to minimize leakage of URYX around the needle or through the injection site, and to ensure a successful implant.
14. Re-establish irrigation and inspect the injection site. If residual URYX is visible outside the injection site, use the cystoscope sheath or the injection needle tip to gently work the material free. Remove the excess material or allow it to be flushed out with the irrigation fluid.
15. Proceed to the next injection site, as required, and repeat steps 10-14, until the procedure is complete. Do not inject more than 2.5 ml of URYX during any single treatment session.
16. Upon completion of the injection, withdraw the needle and cystoscope from the urethra.

SUPPLY

- Contents supplied sterile. Do not use if the integrity of the packaging appears compromised.
- For single use only. Do not reuse, reprocess or resterilize. Reuse, reprocessing, or resterilization may compromise the integrity of the product, which may result in device failure or risk of contamination.
- The URYX Urethral Bulking Kit and all components are latex free.

SYMBOLS

	It is important to read the instructions for use with careful attention to cautions, notes and warnings prior to using this product.
	STERILE: This device is provided sterile. URYX is sterilized using dry heat.
	STERILE: This device is provided sterile. The syringe and drawing needle provided in each URYX Kit are sterilized using radiation.
	DO NOT REUSE OR RESTERILIZE
REF	Catalogue number
	Use by date
	Batch code

STORAGE

Do not freeze (i.e., < 0° C / 32° F). Temperatures below 0° C / 32° F can cause the URYX vials to break. Refrigeration of URYX is neither necessary nor recommended. The URYX solution undergoes a reversible phase change from a liquid to solid state at approximately 19° C / 66° F. If the solution changes to the solid phase, maintain at room temperature until URYX has returned to a liquid state. URYX should be stored at room temperature (i.e., > 19° C / 66° F) to ensure that it is in a liquid state at the time of use.

Do not use the device past the last day of the labelled month of expiration.

Upon receipt of shipment, ensure that the packaging is not open or damaged and retains its sealed integrity. Do not use the device if the integrity of the packaging appears compromised.

Manufactured by



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