Cogentix
Medical

REF **MPQ-2.5**

Macroplastique®

URETHRAL BULKING AGENT

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

MACROPLASTIQUE® IMPLANTS
Instructions for Use

SYMBOL DESCRIPTION


Consult Instructions for Use


Do not reuse


Use by

Sterilized using irradiation


Store at room temperature

REF **Product reference number**

LOT **Lot Number**

Not made with natural rubber latex

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

PRODUCT DESCRIPTION

Macroplastique® Implants is a sterile, nonpyrogenic, latex-free, injectable tissue bulking agent comprised of flexible, soft textured implants of heat-vulcanized polydimethylsiloxane (a solid silicone elastomer) suspended in a bio-excretable polyvinylpyrrolidone (PVP) carrier gel. When implanted in the urethral wall between the mid-urethra and the bladder neck, the implants bulk tissue and create coaptation of the urethra.

Macroplastique is supplied sterile in a pre-filled polypropylene syringe containing approximately 2.5 ml of product. The Macroplastique product is implanted using an administration device and an endoscopic injection needle recommended by Cogentix Medical.

Macroplastique is a biocompatible, nonresorbable implant that allows tissue healing to occur. The synthetic implants remain in place at the implantation site as a result of the naturally occurring tissue response. The carrier gel is exchanged for tissue fluids containing host fibroblasts that subsequently deposit a collagen matrix around the individual implants, as well as around the periphery of the implanted material. After the exchange, the carrier gel is removed by the reticuloendothelial system and excreted unmetabolized from the body through the kidneys.

INDICATIONS FOR USE

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

CONTRAINDICATIONS FOR USE

Macroplastique must not be used in patients with:

» Acute urogenital tract inflammation or infection.

» Fragile urethral mucosal lining (e.g., post radiation therapy, post-surgery to the bladder neck).

WARNINGS

» Do not inject Macroplastique into blood vessels. This may cause vascular occlusion or embolic phenomena.

» Avoid using Macroplastique in patients with non-viable tissue, e.g. history of significant pelvic irradiation, multiple pelvic surgeries, etc. Scar tissue and significantly compromised tissue will not coapt appropriately.

» Do not use within 12 weeks of a previous Macroplastique treatment or within 12 weeks of a previous sling placement. Reimplantation prior to 12 weeks may not allow enough time for the initial inflammatory response to subside.

» Macroplastique should not be used in patients with obstructive conditions, such as bladder neck or urethral strictures, until such conditions have been corrected. Use of Macroplastique in patients with uncorrected urinary obstruction may cause occlusion of the urethra.

» Overcorrection using Macroplastique may lead to urinary obstruction.

» Macroplastique should only be used by someone properly trained in diagnostic and therapeutic cystoscopy.

PRECAUTIONS

» Safety and effectiveness of periurethral injection of Macroplastique have not been established.

» Safety and effectiveness of Macroplastique in men have not been established.

» The long-term safety and effectiveness of Macroplastique treatment have not been established.

» The safety and effectiveness of Macroplastique have not been established in patients with any of the following conditions:
- Urinary incontinence due to uncontrolled bladder instability or hyperreflexia,
- Neuropathic bladder,
- Prolapsed bladder,
- Nocturnal enuresis (bed wetting),
- Overflow incontinence,
- Functional incontinence, or
- Morbid obesity

» The safety and effectiveness of Macroplastique in patients who are pregnant or lactating have not been established.

» The effect of Macroplastique on subsequent pregnancy and delivery, and the impact of subsequent pregnancy on the effect of Macroplastique, is unknown. Therefore, the risks and benefits of the device in women of childbearing potential should be carefully assessed.

» The safety and effectiveness of more than one retreatment with Macroplastique, and retreatment administered less than 12 weeks after the initial treatment, are unknown.

» Patients should be counseled that a repeat Macroplastique injection procedure may be required to achieve dryness or a satisfactory level of improvement in incontinence.

» Dysuria, hematuria, and frequency of micturition are to be expected post-treatment. If any of these conditions persist past 48 hours, the patient should be instructed to contact the treating Physician immediately.

» Post-treatment retention may occur which may necessitate intermittent catheterization. If the patient remains unable to void freely, continued intermittent catheterization may be necessary.

» To reduce the risks of infection and bleeding, the usual precautions associated with cystoscopic procedures should be followed.

» There are risks associated with any implant procedure including, but not limited to, complications associated with anesthesia and patient tolerance to implanted foreign material.

» Macroplastique is supplied radiation sterilized in a sealed package and is for single use only. Do not reuse, reprocess, or resterilize.

» Do not use Macroplastique product if the integrity of the syringe or outer packaging has been damaged or compromised.

ADVERSE EVENTS

The Macroplastique clinical trial involved 186 Macroplastique treatments in 122 subjects. A total of 303 treatment related adverse events (including transient symptoms) in 96 patients were reported in the Macroplastique arm. In order to reduce potential bias, all genitourinary adverse events were analyzed as treatment related regardless of time period reported (i.e., a urinary tract infection occurring at either 1 month or 12 months post treatment was considered a treatment related adverse event). The severity of treatment related adverse events was noted as "serious" or "not serious"; there were no serious treatment related adverse events reported in the Macroplastique arm. There was one death of a Macroplastique patient due to respiratory failure secondary to cancer, which was determined to be not related to the treatment.

In the randomized trial comparing Macroplastique to a control urethral bulking agent, the proportion of patients experiencing treatment related and/or genitourinary adverse events were similar across treatment groups with no significant differences found either overall or for any specific event. The incidence for the most prevalent treatment related adverse events reported in the multicenter evaluation is listed in Table 1.

Table 1: Number (%) of Subjects Reporting Treatment Related Adverse Events

Event Category	Macroplastique (n = 122)
Post-procedure catheterization (see paragraph below)	53 (43.4%)
Urinary tract infection (UTI) (including bladder infection)	31 (25.4%)
Urinary retention	26 (21.3%)
Dysuria	23 (18.9%)
Hematuria (including transient hematuria)	19 (15.6%)
Pain at implantation site	16 (13.1%)
Frequency	14 (11.5%)
Urgency	14 (11.5%)
Slowed urine stream	9 (7.4%)
Incomplete bladder emptying	7 (5.7%)
Urge incontinence	7 (5.7%)
Hesitancy	6 (4.9%)
Vaginal bleeding	4 (3.3%)
Yeast infection	4 (3.3%)
Bladder pain	3 (2.5%)
Increased/worsening nocturia	3 (2.5%)
Overactive bladder (OAB)	3 (2.5%)
Cystitis	3 (2.5%)
Number of Other Events[1]	29 (N/A)

[1] "Other" treatment related adverse events in Macroplastique subjects, occurring at frequencies of < 2%, were as follows (listed alphabetically): abdominal pain, allergic reaction – control bulking agent skin test, bolus ruptured, change in urine stream, diarrhea, dizziness, filling defect, headache, increased AM urge incontinence, joint pain during urination, nausea, partial urethral closure, pelvic tenderness, perineal discomfort/pain, sleep disturbance, spotting between periods, tiredness, urethral erosion, uterine polyp, vaginal discharge, vaginal itching, visible product, and vulvar lesion.

Placement of an in/out catheter immediately post-procedure is commonly performed and was included in the clinical trial protocol as a way to drain the bladder at the end of the procedure. The duration of placement was brief and did not disrupt the newly placed bulking agent bolus. Five subjects (4 Macroplastique, 1 Control) were sent home with an indwelling catheter, which was removed the next day. An additional Macroplastique subject had a Foley catheter placed for 48 hours to address her retention. While the proportion of Macroplastique patients with in/out catheters was statistically higher when compared with Control, this event is not clinically significant, particularly since the protocol allowed for this practice.

Two cases of urethral erosion were observed in the Macroplastique arm. Neither case was reported due to patient complaint, but rather was observed during regular patient follow-up visit by study-related cystoscopy. One of the cases resolved spontaneously while the other case's resolution status was not specifically evaluated on follow-up cystoscopy and is listed as unknown. The patient in each case received subsequent reimplantation with Macroplastique.

Excluding transient symptoms reported during treatment, a total of 154 treatment related/genitourinary adverse events reported for Macroplastique subjects were analyzed for time-to-onset and resolution. This information was not typically reported for transient symptoms. Of these 154 events, 89 (57.8%) occurred within 30 days of the most recent treatment date, 35 (22.7%) occurred more than 30 days from the most recent treatment date and 30 (19.5%) had an unknown onset date. The resolution status at the time of database closure of the 154 treatment related events was as follows: 124 resolved (80.5%), 15 were reported as ongoing (9.7%) and 15 had unknown resolution status (9.7%). Of those reported as resolved, 73 resolved within 30 days of onset, 30 resolved after more than 30 days from onset and 21 had unknown onset dates/resolution dates. The 30 events reported as ongoing or unresolved at closure are: abdominal pain (1), bladder infection (1), bladder infection symptoms (1), change in urine stream (2), dysuria (2), filling defect (1), frequency (1), hesitancy (2), incomplete bladder emptying (2), overactive bladder (1), pelvic tenderness (1), spotting between periods (1), sleep disturbance (1), slowed urine stream (2), tenderness at implant site (1), transient hematuria (2), urethral erosion (1), urgency (3), urge incontinence (3), vaginal discharge (1).

Potential Adverse Events

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

CLINICAL STUDY

Study Design

The Macroplastique clinical study was a prospective, multicenter, single-blind, randomized controlled trial. This study was designed to evaluate Macroplastique in a pivotal trial and was conducted to determine the safety and effectiveness of Macroplastique implants as a minimally invasive, transurethral endoscopic treatment of female stress urinary incontinence (SUI) primarily due to intrinsic sphincter deficiency (ISD).

To be eligible for enrollment, subjects were required to be adult women diagnosed with SUI primarily due to ISD, and to have viable mucosal lining and normal bladder capacity. Subjects with urinary tract infections, uncontrolled bladder instability, high post void residual urine volume, prolapse greater than stage II, confounding bladder pathology, as well as subjects who were pregnant or morbidly obese were excluded.

Two hundred sixty subjects were enrolled in the study, of which, two hundred forty-eight patients were randomized 1:1 and treated with either Macroplastique or a Control device (a commercially available absorbable urethral bulking agent). Two hundred forty-seven subjects were treated in accordance with their randomization.

Only one subsequent treatment was allowed. If performed, the second treatment took place within one month after patients' 3-month follow-up in both study arms. Evaluation of study endpoints was performed 12 months after the patient's last treatment.

Primary Effectiveness Endpoint

Continence status was determined by evaluating patients prior to treatment through twelve months follow-up using the Stamey incontinence grading described as follows:

Grade 0: Continent or dry
Grade 1: Patient loses urine with sudden increases in abdominal pressure, but never in bed at night
Grade 2: Patient's incontinence worsens with lesser degrees of stress, such as walking, standing erect from a sitting position, or sitting up in bed
Grade 3: Patient has total incontinence and urine is lost without any relation to physical activity or position

The primary endpoint in the study was the percentage of patients demonstrating improvement of at least one Stamey Grade from baseline to 12 months after last treatment. The primary endpoint was analyzed using a non-inferiority hypothesis with a 15% delta for Macroplastique versus Control. Pad weight, dryness, and quality of life (I-QoL) were assessed as secondary endpoints at 12 months.

Safety Endpoint

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. In order to minimize potential bias, all genitourinary adverse events were conservatively classified as treatment related.

Results

All study objectives were met in the Macroplastique trial. Tables 2 through 5 present data from the multicenter clinical trial for the Intent-to-Treat and Per Protocol patient populations. The Intent-to-Treat population includes all 260 subjects enrolled in the study (130 Macroplastique and 130 Control); the Per Protocol population excludes those subjects who were neither implanted nor followed and also excludes 1 subject treated contrary to her randomization for 122 Macroplastique and 125 Control subjects. Patients whose outcomes were unknown at 12 months are automatically analyzed as failures using both the Intent-to-Treat and Per Protocol analysis methods.

Table 2: Patient Baseline Information

Patient Baseline Information	Macroplastique	Control
Mean age (range)	60.5 years (27-85)	61.6 years (34-90)
Mean duration of incontinence	11.3 years	11.0 years
Patients with baseline Stamey grade = 1	30%	39%
Patients with baseline Stamey grade = 2	68%	54%
Patients with baseline Stamey grade = 3	2%	7%
Baseline pad weight	28 grams	28 grams
Baseline I-QoL score	49.3	48.2

Table 3: Treatment Information

Treatment Information	Macroplastique	Control
Mean number of treatments per patient during study	1.5	1.6
Patients receiving a single treatment	47.5%	41.3%
Patients receiving two treatments	52.5%	58.7%
Mean initial volume injected per patient	4.6 ml	4.6 ml
Mean retreatment volume injected per patient	4.3 ml	4.5 ml
Mean total volume injected per patient	6.8 ml	7.2 ml

Analysis of the primary endpoint demonstrated that Macroplastique was statistically non-inferior to the Control bulking agent for the endpoint of improvement in Stamey Grade at 12 months, where 'non-inferior" is defined statistically as the study arm is not worse than the control arm (with a tolerable margin of 15%).

Table 4: Key Effectiveness Results at 12 Months (Intent-to-Treat)

	Macroplastique	Control
Stamey Grade		
Dry	34.6% (45/130)	23.8% (31/130)
Improvement of $\geq$ 1 grade	57.7% (75/130)	46.9% (61/130)
Same	19.2% (25/130)	24.6% (32/130)
Worse / Unable to assess*	23.1% (30/130)	28.5% (37/130)
Pad Weight		
$\geq$ 50% improvement	60.0% (78/130)	53.1% (69/130)
0-49% improvement	6.9% (9/130)	7.7% (10/130)
Worse / Unable to assess*	33.1% (43/130)	39.2% (51/130)

* No 12-month data was available for the Unable to Assess group; these subjects were analyzed as failures.

Table 5: Key Effectiveness Results at 12 Months (Per Protocol)

	Macroplastique	Control
Stamey Grade		
Dry	36.9% (45/122)	24.8% (31/125)
Improvement of $\geq$ 1 grade	61.5% (75/122)	48.8% (60/125)
Same	20.5% (25/122)	25.6% (32/125)
Worse / Unable to assess*	18.0% (22/122)	26.4% (33/125)
Pad Weight		
$\geq$ 50% improvement	63.9% (78/122)	54.4% (68/125)
0-49% improvement	7.4% (9/122)	8.0% (10/125)
Worse / Unable to assess*	28.7% (35/122)	37.6% (47/125)
Quality of Life (As Followed)		
Mean improvement in I-QoL	28.7	26.7

* No 12-month data was available for the Unable to Assess group; these subjects were analyzed as failures.

Twenty-four month follow-up Stamey Grade data were available on 84 Macroplastique subjects. Of these 84 subjects, 63 had improvement in Stamey Grade at 24 months, 28 of whom were dry.

FDA POST-MARKET SURVEILLANCE PROGRAM

During the two years following FDA approval, Macroplastique users were surveyed quarterly to report erosions or other adverse events associated with Macroplastique use. In total, 99.1% (222/224) of physician responses reported no erosions or adverse events. Two separate cases of temporary urinary retention, a known potential transient side effect of urethral bulking agent treatment, were reported. This surveillance program demonstrates that Macroplastique is being used safely in the field and is associated with no new safety issues.

PHYSICIAN TRAINING

Macroplastique should only be used by someone properly trained in diagnostic and therapeutic cystoscopy.

PATIENT COUNSELING

Cogentix Medical relies on the physician to advise the patient of all potential risks and benefits associated with the Macroplastique implant procedure. 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 Macroplastique is a course of treatment that may require more than one injection procedure to achieve dryness or a desired level of improvement in incontinence. Patients should be counseled to report adverse events to the treating physician and physicians are advised to report adverse events to Cogentix Medical. The Macroplastique Patient Brochure may be beneficial in providing additional information to the patient.

TREATMENT WITH MACROPLASTIQUE

A complete medical history and urological examination should be obtained to determine whether the patient is an appropriate candidate for treatment with Macroplastique.

INSTRUCTIONS FOR USE

Patient Pretreatment

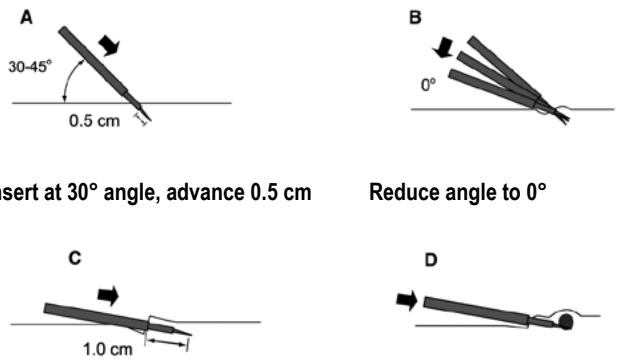
1. Perform appropriate pretreatment evaluation to ensure the absence of urinary tract infection.
2. Broad-spectrum antibiotics should be administered prior to implantation consistent with current surgical implant procedures (i.e., levofloxacin, ciprofloxacin). Physicians are cautioned not to allow antibiotics to interfere with pretreatment microbiological cultures.
3. Using standard procedure, prepare the patient for cystoscopy and inject a local anesthetic into the urethra. Fill the bladder to approximately 50% of its capacity with sterile water or sterile saline.

Macroplastique Implantation Procedure

1. Macroplastique is implanted transurethrally through a cystoscope with an endoscopic needle recommended by Cogentix Medical (e.g., Cogentix Medical Rigid Endoscopic Needle).
2. Place the syringe collar over the Macroplastique syringe flanges, then firmly grasp the collar and lock the syringe/collar assembly securely onto the rotating hub of the Control Flow AD.
3. Firmly twist and fasten the Cogentix Medical endoscopic needle hub onto the luer lock tip of the syringe to achieve a tight connection. Remove the protective sleeve from the needle.

4. Prime the needle with Macroplastique by engaging the Control Flow AD. To stop the flow, depress the release mechanism located on top of the Control Flow AD.
5. Insert the cystoscope into the urethra and advance the needle through the working channel of the scope to visualize the needle tip.
6. Retract the needle tip and scope back into the urethra 1.5 to 2.0 cm distal from the bladder neck.
7. Advance the needle with the bevel facing the center of the urethra.
8. In all positions, use the tissue tunneling technique (Figures A-D) and wait approximately 30 seconds before withdrawing the needle from the tissue to limit product loss from the implantation site.

Figures A-D: Tissue Tunneling Technique



Insert at 30° angle, advance 0.5 cm **Reduce angle to 0°**

Advance another 0.5 cm **Implant bolus**

9. Locate the 6 o'clock position within the urethral lumen and tilt the scope to a 30-45° angle (Figure A). Insert the needle tip into the urethral tissue at this angle, and then advance the needle 0.5 cm in depth. Angle the scope to 0°, parallel with the urethra, (Figure B) and advance the needle another 0.5 cm to create a tissue tunnel (Figure C).

Recommended Treatment Locations & Volumes			
6 o'clock	**10 o'clock**	**2 o'clock**	**Total Volume**
≤ 2.5 ml	≤ 1.25 ml	≤ 1.25 ml	5 ml

10. Implant a small amount of Macroplastique to confirm correct needle placement within the mucosa (Figure D). If the needle is properly placed, a bleb (tissue bulking) in the urethral mucosa should immediately be visible with the cystoscope. If it does not appear, withdraw and reposition the needle more superficially. Then, inject again.
11. Implant product slowly. Wait a few seconds between each pull of the Control Flow AD lever.
12. Repeat the implantation procedure at the 2 o'clock and 10 o'clock positions to achieve urethral coaptation.
13. Depending on the patient's history of previous incontinence surgery (i.e., bladder neck suspension, sling procedures, etc.), the Macroplastique implantation sites and injected volume may be adjusted according to the morphology of the bladder neck and urethra to achieve urethral coaptation.

14. Use caution and avoid passing the cystoscope over the implantation site, which could potentially disrupt product placement.
15. Use a small intermittent catheter (8-12 Fr.) to drain the bladder when necessary.

Needles and treatment syringes may be potential biohazards. After use, handle accordingly and dispose of all materials in accordance with accepted medical practice and all applicable local, state and federal laws and regulations.

Post-Implantation

Confirm that a patient's voiding function is satisfactory before she leaves the clinic. If the patient is unable to spontaneously void following the procedure, pass an intermittent catheter (8-12 Fr.) to relieve any symptoms of delayed voiding. If necessary, instruct the patient in the technique of clean intermittent self-catheterization.

Upon discharge, prescribe a broad-spectrum antibiotic (i.e., levofloxacin, ciprofloxacin, etc.), and provide analgesia to manage any possible post-treatment discomfort.

Counsel the patient to report adverse events to the treating physician. Physicians should report serious device-related adverse events to Cogentix Medical.

Subsequent Treatment

Some patients may require additional treatments to enhance their improvement or achieve dryness. It is recommended to delay further Macroplastique treatment for 12 weeks to allow tissue healing to occur.

For subsequent treatment, implant distal to the initial Macroplastique placement and follow the prescribed tunneling procedure and recommended treatment locations and volumes as described above.

STORAGE CONDITIONS

Carefully examine the sterile packaging and contents prior to use to confirm neither has been damaged in shipment. If damaged, do not use and immediately return damaged product to Cogentix Medical.

Store at room temperature (59-86˚F; 15-30˚C). See product labeling for expiration date.

WARRANTY

Cogentix Medical warrants that reasonable care has been used to design and manufacture this product. Product will be replaced if Cogentix Medical determines its material or workmanship is defective. This is Cogentix Medical's only warranty, and it excludes all other warranties (including those implied by operation of law). Cogentix Medical is not responsible for matters within the control of the user or others, such as product handling and storage, patient selection and diagnosis and treatment procedures.

This Limited Warranty is limited to its express terms. In particular:

(1) Except as expressly provided by this Limited Warranty, COGENTIX MEDICAL IS NOT RESPONSIBLE FOR ANY DIRECT, INCIDENTAL OR CONSEQUENTIAL DAMAGES BASED ON ANY DEFECT, FAILURE OR MALFUNCTION OF THE PRODUCT, WHETHER THE CLAIM IS BASED ON WARRANTY, CONTRACT, TORT OR OTHERWISE.

(2) This Limited Warranty is made only to the purchaser of the Product. AS TO ALL OTHERS, COGENTIX MEDICAL MAKES NO WARRANTY, EXPRESS OR IMPLIED, INCLUDING, BUT NOT LIMITED TO, ANY IMPLIED WARRANTY OF MERCHANTABILITY OR FITNESS FOR A PARTICULAR PURPOSE WHETHER ARISING FROM STATUTE, COMMON LAW, CUSTOM OR OTHERWISE. THIS LIMITED WARRANTY SHALL BE THE EXCLUSIVE REMEDY AVAILABLE TO ANY PERSON.

Any implied warranties of merchantability or fitness are specifically excluded. Statements and descriptions in marketing literature, while generally describing product, do not constitute any warranties.

DISCLAIMER OF WARRANTIES

Cogentix Medical excludes all warranties and responsibilities for:

» Improper use of or tampering with the product, and/or
» Failure to follow instructions provided in this insert

Macroplastique is a registered trademark. Contigen and Bard are registered trademarks.

U.S. Patent Numbers 5,258,028; 5,336,263 and 5,571,182. Canadian Patent Number 2,133,756. French, Italian and United Kingdom Patent Number 0,636,014. German Patent Number 69,318,835.9. Japanese Patent Number 3,004,724. Spanish Patent Number 2,118,953.

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PN 4226 Rev D - 09/15