Bulkamid®
Urethral Bulking System

Instructions for Use

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

10078-001 January 2020

PRODUCT DESCRIPTION

The Bulkamid Urethral Bulking System contains sterile, single use components for urethral injection for the treatment of stress urinary incontinence (SUI) due to intrinsic sphincter deficiency (ISD) in adult women who have SUI or stress predominant mixed incontinence.

The Bulkamid Urethral Bulking System consists of:

- Two sterile Bulkamid Hydrogel pre-filled 1 mL syringes,
- One sterile Bulkamid Rotatable Sheath,
- Two sterile Bulkamid injection needles.

Bulkamid Hydrogel

Bulkamid Hydrogel is a non-resorbable, injectable, transparent, hydrophilic gel for urethral bulking. The Bulkamid Hydrogel consists of a backbone of cross-linked polyacrylamide, with water molecules loosely bound to the polymer matrix. Nominal proportions of the Bulkamid Hydrogel are 2.5% cross-linked polyacrylamide and 97.5% non-pyrogenic water (w/w). It is biocompatible, non-biodegradable, and non-migrational. Bulkamid is sterilized by moist heat.

Bulkamid Hydrogel is supplied in a pre-filled, sterile, 1 mL syringe, sealed with a Luer lock fitting. It is intended to be injected with the sterile 23G x 12cm needle using a Bulkamid Rotatable Sheath. A 3-part label with the LOT number accompanies each syringe. Attach one of them to the patient's record in order to ensure product traceability.

Bulkamid Needle

The Bulkamid needles are 23G and 12cm in length and intended for the injection of Bulkamid Hydrogel.

The Bulkamid needles are non-pyrogenic, peel packed, and sterilized by ethylene oxide.

Bulkamid Rotatable Sheath

The Bulkamid Rotatable Sheath is a guidance device used for injecting Bulkamid Hydrogel in the urethral submucosal tissue under visual control. The Bulkamid Rotatable Sheath is a 125mm long device with a working channel for the needle, access lumen for the optic device (Cystoscope 2.7x113mm, 0˚, supplied separately), water tubing with flow regulators, and Luer lock connector for the inflow of water. The Bulkamid Rotatable Sheath is peel packed and sterilized by ethylene oxide.

MODE OF ACTION

Bulkamid Hydrogel is injected into the submucosal tissue of the proximal half of the urethra.

Bulkamid Hydrogel is intended to improve urethral coaptation.

INDICATION

Bulkamid Urethral Bulking System is indicated for urethral injection for the treatment of stress urinary incontinence (SUI) due to intrinsic sphincter deficiency (ISD) in adult women who have SUI or stress predominant mixed incontinence.

CONTRAINDICATIONS

Bulkamid Urethral Bulking System must not be used in patients suffering from acute urinary tract infection.

WARNINGS

- Do not inject Bulkamid Hydrogel intravascularly. Injection of Bulkamid Hydrogel into blood vessels may cause vascular occlusion leading to a possible embolism.
- Discontinue injection of Bulkamid Hydrogel if the superficial capillaries of the mucosa start to fade in order to avoid ischemia.
- Prior assessment of the tissue is recommended before introducing Bulkamid Rotatable Sheath into the urethra. Do not force the Bulkamid Rotatable Sheath into the urethra if the tissue is damaged. Do not inject Bulkamid Hydrogel if the tissue is damaged.
- Bulkamid Urethral Bulking System should not be used in patients with urethral or bladder neck strictures until the strictures have been corrected. Use of Bulkamid Urethral Bulking System in patients with strictures may cause injury and/or urethral obstruction.
- Over-correction using Bulkamid Hydrogel may lead to obstruction.
- Patients receiving treatment affecting blood coagulation have an increased risk of hematoma or urethral bleeding, as with any invasive procedure.
- Do not use Bulkamid Hydrogel in male patients. Testicular abnormalities have been observed in some male animals implanted with Bulkamid; however, their relationship with Bulkamid has not been definitively established.

PRECAUTIONS

- Bulkamid Urethral Bulking System is only to be administered by a qualified physician, e.g. gynecologist, urologist, or urogynecologist.
- Safety and effectiveness of Bulkamid has not been established in patients with a fragile urethral mucosal lining.
- Safety and effectiveness of re-injection of Bulkamid Hydrogel less than 4 weeks after initial injection has not been established.
- Safety and effectiveness of Bulkamid have not been established in patients with any of the following conditions:
    - Urethral hypermobility with a straining angle >30º from horizontal bladder neck.
    - Predominant urge incontinence.
    - Detrusor overactivity.
    - Known polyuria (≥ 3L/24h).
    - Unevaluated hematuria.
    - Prolapse stage greater than Stage II using the ICS Pelvic Organ Prolapse Quantification (POPQ) exam.
    - BMI >35 kg/m2.
    - Neurogenic bladder.
- Safety and effectiveness of Bulkamid Urethral Bulking System have not been established in patients less than 18 years.
- The procedure may cause urinary tract infections and scratches in the urethra and bladder. Prophylactic use of antibiotics is recommended.
- Only patients with well-controlled diabetes should be considered for Bulkamid Hydrogel injection.
- Safety and effectiveness have not been established in patients who have active Herpes Genitalis.
- Bulkamid should be used with caution in patients on immunosuppressive therapy. Safety has not been established for patients with autoimmune diseases. Patients with acute or chronic infection in other sites of the body should be treated with caution.
- If the patient has undergone major surgery or dental work, Bulkamid should not be injected until the patient has fully recovered. Please also advise Bulkamid patients that if they need to undergo a surgical procedure in the future, especially a dental procedure, there is a risk of infection developing in Bulkamid or near where the

Bulkamid was placed. This is due to the possibility of bacteria migrating to the implant, which is the case with many other medical implants. Please consider advising patients that if they require a surgical or dental procedure in the future, they should tell the treating physician that they have a permanent implant and that they should discuss the possible need for prophylactic antibiotic therapy with their treating physician.

- The effect of Bulkamid has not been evaluated in women during pregnancy, delivery or lactation.
- The effect of Bulkamid on subsequent pregnancy and delivery, and the impact of subsequent pregnancy on the effect of Bulkamid, is unknown. Therefore, the risks and benefits of the device in women of childbearing potential should be carefully assessed.
- Do not mix Bulkamid Hydrogel with any other substances.
- Do not inject Bulkamid Hydrogel into sites previously injected with another bulking agent, or inject another bulking agent into a site previously injected with Bulkamid Hydrogel.
- Patients should be counseled that one or more repeat Bulkamid Hydrogel injection procedures may be required to achieve dryness or a satisfactory level of improvement in urinary incontinence.
- Do not use any other component of the Bulkamid Urethral Bulking System after the expiration date printed on the packaging.
- All components of the Bulkamid Urethral Bulking System are intended for use in a single patient. Do not re-use. Re-use increases the risk of contamination and thereby increases the risk of infection.
- All components of the Bulkamid Urethral Bulking System are sterile when supplied. Only use the components if the packaging and products are intact and undamaged. Do not re-sterilize any of the components.
- After use, syringes and needles should be handled as potential biohazards. Dispose in accordance with accepted medical practice and applicable local, state and federal requirements.

ADVERSE EVENTS

The Bulkamid clinical study involved 228 patients. There were no deaths or Unanticipated Adverse Device Effects among study patients. One Bulkamid patient experienced hematuria that was determined to be a serious adverse event that was probably related to the procedure and probably not related to the device.

Table 1 lists the treatment-related adverse events reported during the clinical study in the Bulkamid group. The incidence of treatment-related adverse events was similar in the control group in the clinical study. Treatment-related events are those events that were classified to be related to the device and the procedure.

Table 1: Incidence of All Treatment-Related Adverse Events in the Bulkamid Group

Adverse Event Type	Events n	Patients n (%)
Acute retention	14	13 (5.7)
De novo urge incontinence	2	2 (0.9)
Dysuria	2	2 (0.9)
Excreted bulking material	0	0 (0.0)
Hematuria	3	3 (1.3)
Nocturia	0	0 (0.0)
Non-acute urinary retention (> 7 days)	0	0 (0.0)
Outlet obstruction	0	0 (0.0)
Pain at implant site	39	28 (12.3)
Pelvic pain	0	0 (0.0)
Urinary frequency	0	0 (0.0)
Urinary tract infection	10	8 (3.5)
Urinary urgency	2	2 (0.9)
Vaginal infection/irritation/Lichen Sclerosus	1	1 (0.4)
Worsening urinary incontinence	1	1 (0.4)
Other adverse event[1]	7	6 (2.6)
Total events	81	
Patients with at least 1 adverse event		60 (26.3)

[1]Other treatment-related adverse events observed in the Bulkamid group were (in alphabetical order): abnormal laboratory value (elevated total Immunoglobulin E), back/neck pain, dizziness/fainting, extremity nerve pain/tingling, and inflammatory condition (gout).

Most treatment-related adverse events resolved within five days (range: 0.0-88.0 days). At the time of study closure, 93.8% of treatment-related adverse events were resolved. The following 5 events were persistent or resolution was unconfirmed at the time of study closure: de novo urge incontinence (N=2), urinary urgency (N=2), and other inflammatory condition (N=1).

For severity of the treatment-related adverse events, 64.2% were classified as mild, 33.3% were classified as moderate, and 2.5% were classified as severe. The severe treatment-related adverse events were: hematuria (N=1), and pain at implant site (N=1).

Although not observed in the Bulkamid clinical study, the following complications have been reported with the use of competitor urethral bulking agents, some of which may occur with Bulkamid use: embolic phenomena, erythema, excreted material, granuloma, incomplete bladder emptying/outlet obstruction, migration of injected material, urethral erosion, urinary frequency, and vascular occlusion.

PATIENT INFORMATION

The patient should be informed about the intended use, expected results, contraindications, precautions, warnings and potential adverse events.

Patients should inform healthcare professionals of their urethral bulking treatment for accurate future medical assessment.

CLINICAL INFORMATION

Pivotal Study Design

A single-blinded, randomized, multi-center, two-arm clinical trial was conducted to support the safety and effectiveness of the Bulkamid Urethral Bulking System for the treatment of stress urinary incontinence (SUI) in adult women due to intrinsic sphincter deficiency (ISD) compared to another FDA-approved bulking agent (i.e., the Allergan Inc. Contigen Bard Collagen Implant) in the control group.

To be eligible for enrollment, subjects were required to be at least 18 years of age, have SUI due to ISD or stress predominant mixed incontinence for at least six months, have failed two previous non-invasive therapies and have at least three incontinence episodes measured over three days. Subjects with predominant urge incontinence, urethral hypermobility (with a straining angle >30° from horizontal bladder neck), detrusor overactivity, regular use of a urethral catheter, or previous urethral surgery were excluded.

Subjects were randomized in a 2:1 ratio to Bulkamid or the control device at the initial treatment visit. Subjects who were not continent at the first evaluation visit were considered for re-injection of the assigned randomized treatment. A maximum of three injections (initial treatment plus two re-injections) were allowed. After the final injection, subjects attended the 3-month, 6-month and 12-month follow-up visits plus a telephone encounter at 9 months.

Primary Effectiveness Endpoint

The primary effectiveness endpoint was the proportion of subjects with at least 50% reduction from baseline in both urine leakage (as measured by a 24-hr. pad weight test) and daily number of incontinence episodes (as documented in a voiding diary) at 12 months.

Secondary Effectiveness Endpoints

Secondary effectiveness endpoints included change in leakage from baseline, change from baseline in the number of incontinence episodes, the proportion of subjects with no incontinence episodes, responder rate based on subject perception, change from baseline in Incontinence Quality of Life (IQoL) score and change from baseline in International Consultation on Incontinence Questionnaire-Urinary Incontinence (ICIQ-UI) score.

Primary Safety Endpoint

The primary safety endpoint was the incidence of device- and procedure-related serious adverse events over the 12-month follow-up period.

Secondary Safety Endpoints

The secondary safety endpoints were incidence and severity of all procedure- and device-related adverse events and incidence of all adverse events through the 12-month follow-up visit.

Results

Subject Accountability

Eight-hundred and sixty-seven (867) subjects were consented, with 345 subjects randomized and treated (Intent-to-Treat (ITT) population). Two-hundred and twenty-eight (228) subjects were randomized to Bulkamid and 117 subjects were randomized to the control device. The Per Protocol (PP) population, which consisted of subjects with complete primary effectiveness endpoint data and no major protocol deviations, included 238 subjects (159 Bulkamid and 79 control). In addition, the Complete Case (CC) population consisted of ITT subjects with complete data for a specific endpoint at a particular time point (174 Bulkamid and 88 control). Last Observation Carried Forward (LOCF) was used for the primary ITT analyses.

Baseline Characteristics and Treatment Parameters

Table 2 and Table 3 include baseline characteristics and treatment parameters for the ITT population, respectively.

Table 2: Patient Baseline Characteristics (ITT Population)

Baseline Characteristic	Bulkamid (N=228)	Control (N=117)
Mean Age (range)	58.0 years (23.3-93.4)	57.4 (29.5-85.4)
Mean Duration of SUI Symptoms (range)	9.5 years (0.6-51.5)	8.9 (0.7-39.7)
Mean Pad Weight	93.6 g	115.4 g
Mean IQoL Score	49.5	47.3
Type of Urinary Incontinence		
Stress	30 (13.2%)	13 (11.1%)
Mixed	187 (82.0%)	98 (83.8%)

Table 3: Treatment Parameters (ITT Population)

Baseline Characteristic	Bulkamid (N=228)	Control (N=117)
Number of Injection Sessions Received:		
1	52 (22.8%)	39 (33.3%)
2	95 (41.7%)	47 (40.2%)
3	81 (35.5%)	31 (26.5%)
Mean Volume Injected per Patient at Initial Injection Sessions (range)	1.6 mL (0.1-4.0)	4.7 mL (1.0-15.0)
Mean Volume Injected per Patient at First Re-injection Sessions (range)	1.5 mL (0.1-4.0)	4.1 mL (0.9-15.0)
Mean Volume Injected per Patient at Second Re-injection Sessions (range)	1.6 mL (0.4-2.0)	4.4 mL (1.0-15.0)
Mean Volume Injected per Patient for all Injection Sessions (range)	3.3 mL (0.7-6.0)	8.6 mL (1.0-42.5)

Primary Effectiveness Endpoint Results

At 12 months, 46.9% (107/228) of Bulkamid subjects showed at least a 50% reduction in both leakage and number of daily incontinence episodes, compared to 42.7% (50/117) of control subjects (non-inferiority P = 0.0003; ITT population). Similar significant results were observed in the PP and CC populations.

Secondary Effectiveness Endpoint Results (CC analysis set)

Overall improvement was seen in both randomization groups in the secondary effectiveness endpoints, including change in leakage from baseline, change from baseline in the number of incontinence episodes, and proportion of subjects with no incontinence episodes, and change from baseline in ICIQ-UI and IQoL scores (Table 4). There was no meaningful difference between Bulkamid subjects and control subjects for any of these endpoints. Thus, Bulkamid was shown to be as effective and safe as the other FDA-approved bulking agent used in the study.

Table 4: Secondary Effectiveness Endpoint Results at 12 Month Follow-up

Baseline Characteristic	Bulkamid		Control	
	N	Mean (SD) or N (%)	N	Mean (SD) or N (%)
Change from Baseline in Leakage 24 h Pad Test	181	-62.6 (120.5)	89	-60.1 (141.7)
Change from Baseline in Daily Incontinence Episodes	195	-2.6 (2.7)	101	-2.1 (2.4)
Responder Rate Cured/Dry/Much Improved/Improved	187	144 (77.0)	101	71 (70.3)
Change from Baseline in ICIQ-UI	187	-6.9 (5.2)	98	-6.0 (5.6)
Change from Baseline in IQoL Total Score	196	31.1 (23.3)	102	26.8 (23.6)

METHOD OF ADMINISTRATION:

Pre-Operatively

1. Test the patient's urine in order to exclude urinary tract infection (UTI). Do not proceed if a UTI is present.
2. Place the patient in lithotomy position.
3. Disinfect according to local routine procedure.
4. Place anesthetic gel inside the urethra, and/or inject local anesthesia bilaterally to the mucosa along the urethra (3 and 9 o'clock) 5-10 minutes prior to the procedure.
5. To minimize the possibility of urinary tract infection, it is advised to administer prophylactic antibiotics in accordance with local anti-microbial protocol prior to surgery.

Peri-Operatively

Assembly of the Bulkamid Urethral Bulking System

1. Attach the light cable to the Cystoscope 2.7x113mm, 0˚.
2. Place the Cystoscope 2.7x113mm, 0˚ (with camera) into the Bulkamid Rotatable Sheath (ensure the light cable and irrigation tubes are pointing in the same direction). A click will be heard when the optic is fully inserted into the rotatable sheath.
3. Attach the irrigation system to the Bulkamid Rotatable Sheath via the inflow (blue) and outflow (red) tubes (make sure the red and blue taps are closed before opening the water tap on the irrigation system).
4. Remove any air bubbles from the irrigation system by opening the blue inflow tap. Once all air bubbles have been removed the blue inflow tap is closed.
5. Remove the protective tip cap from the Bulkamid Hydrogel syringe and attach the Bulkamid needle firmly into the Luer lock socket. Make sure the needle is firmly mounted onto the syringe to prevent leakage of hydrogel during the procedure and to prevent the needle being pushed off the syringe tip.
6. Remove the protection sheath including the stopper from the needle.
7. Prime the needle by advancing the syringe plunger until hydrogel appears at the tip of the needle.

Bulkamid Procedure

1. Place local anesthetic gel on to the Bulkamid Rotatable Sheath and carefully advance the Bulkamid Urethral Bulking System until the bladder is visualized and inspected (ensure the blue inflow tap is open and the red outflow tap is closed).
2. Close the blue inflow tap and retract the optic from the Bulkamid Rotatable Sheath to allow the bladder to empty (alternatively the red outflow tap can be opened).
3. Reinsert the optic once the bladder is empty.
4. Insert the Bulkamid needle into the needle channel on the Bulkamid Rotatable Sheath until the needle is just visible on the monitor but is not in contact with the urethral tissue. Advance the Rotatable Sheath towards the bladder until the needle tip is adjacent to the bladder neck (fig. 1).

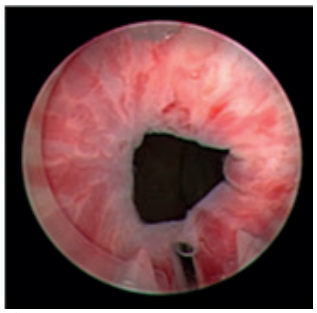


fig 1

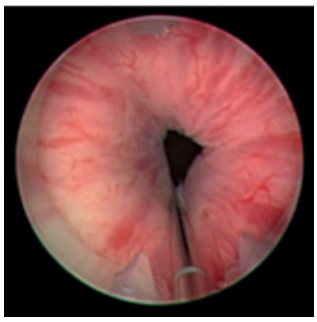


fig 2

5. Rotate the sheath so that the tip of the needle is in line with the first injection site (e.g. at 6 o'clock) and the bevel part of the needle is pointing towards the urethral lumen at all times (fig. 1). Retract the system to approximately 2 cm from the bladder neck (fig. 2).

6. Carefully press the system parallel against the urethral wall in order to get the mucosa placed in front of the tip of the needle (fig. 3). Do not angle the system; angling could lead to the injection being either too deep or too superficial.

7. Insert the needle into the submucosal tissue until the 1 cm marking on the needle is aligned with the mucosal surface (fig. 4).

8. At each injection site, inject Bulkamid Hydrogel until reaching the midline of the urethral lumen, while making sure that the superficial blood vessels remain visible (this is to avoid potential ischemia). Perform the injections with water inflow dilating the urethra, and allow sufficient vision during the injections (fig. 5).

9. Depending on the shape and position of the 1st injection site, repeat the procedure at 2 further sites (e.g. 2 and 10 o'clock or 3 and 9 o'clock) in order to get regular bulking around the circumference of the urethra (fig. 6). When rotating the sheath to the next injection site, ensure that the position of the Bulkamid Urethral Bulking System is maintained within the urethra and only the rotatable portion of the sheath is moved. This will ensure that all injection sites are at the same level/plane. Limit the number of puncture holes to avoid increased risk of extravasation of the material. Make sure the needle is retracted before rotating or removing the Bulkamid Rotatable Sheath.

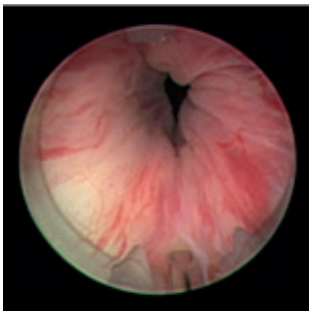
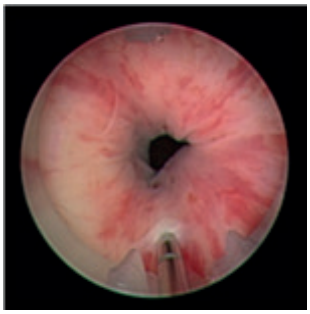


fig 3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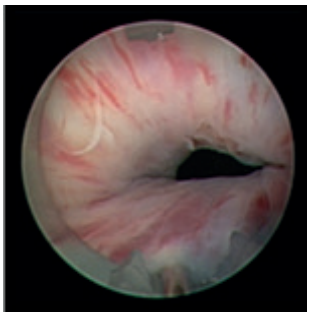
fig 5

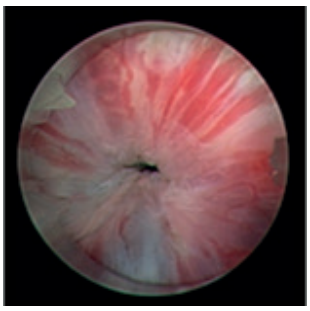
fig 6

10. If necessary, change the syringe during the procedure, and repeat the injections, making sure not to re-inject the same site more than once, as the typical amount of Bulkamid Hydrogel used is 1.5 - 2.0 mL. The maximum recommended total volume of hydrogel is 2 mL per treatment session.

11. If necessary, open the outflow between injections to avoid urgency symptoms. Do this either by closing inflow and opening outflow or by separating the optic from the Bulkamid Rotatable Sheath.

12. Once the final gel deposit has been injected, the bladder should be emptied using a disposable 10-12Fr. catheter. Take care not to use the Bulkamid Rotatable Sheath or any hard tube to empty the bladder.

Post-Operatively

After the patient's first void, the residual urine volume should be measured. If the residual volume is ≤ 100 mL, the patient can be discharged.

If difficulty in voiding postoperatively occurs, the patient may be instructed to perform intermittent catheterization with a disposable 10-12Fr. catheter at home.

If a top-up injection is required to improve treatment efficacy, this can be performed at least 4 weeks after a treatment session. Safety and effectiveness have been demonstrated for up to three treatment sessions up to a maximum of 2 mL per session. Evaluate urethral closure and, if necessary, inject Bulkamid in the same plane as the previous injections.

STORAGE

The Bulkamid Urethral Bulking System must be used prior to the expiration date on the package. Do not freeze. Protect from direct sunlight.

HOW SUPPLIED

The components of the Bulkamid Urethral Bulking System are:

- 2 x sterile Bulkamid Hydrogel prefilled 1 mL syringes
- 1 x sterile Bulkamid Rotatable Sheath
- 2 x sterile Bulkamid Needles 23G (12 cm in length)

Injection of Bulkamid Hydrogel also requires the following accessory (supplied separately)

- Cystoscope 2.7x113mm, 0˚

COMPLAINTS

Please report any malfunction or complaints to Contura at complaints@contura.com.

SYMBOLS DESCRIPTION

Symbol	Description
	Consult Instructions For Use.
	For single use only. Do not re-use.
	Do not re-sterilize
	Sterile. Sterilized by moist heat
	Sterile. Sterilized by ethylene oxide
	Expiry date. Use before the date printed on the label.
	Batch code
	Manufacturer
	Keep out of direct sunlight
	Do not use if package is opened or damaged
	Do not freeze

Symbol	Description
Rx ONLY	Federal (US) law restricts this device to sale by or on the order of a physician
	Non-Pyrogenic (Needle)

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