Date of approval of the Protocol: August 6, 2003

Product: Male Sling for Urinary Stress Incontinence

Name of the product: ARGUS Adjustable Male Sling

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Place where the suggested research study will take place (performance site):

- Universidad de Unicamp. CAMPINAS. Brasil
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- Centro Médico ULTRALITHO. Florianópolis, Brasil.
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INTRODUCTION

Male urinary Stress incontinence (SUI) can be a complication of prostate surgery whether it is a radical prostatectomy (RP) or an adenomectomy. Besides, UEI can be a sign of neurogenic sphincter incompetence. Ref. 1 Urodynamic studies identify Intrinsic Sphincter Deficiency (ISD) as the etiology of incontinence in most of these patients. Ref. 2

The surgical treatment of post-prostatectomy UEI include transurethral injections, artificial urinary sphincter and bulbourethral Sling operations.

Based on the percentage of successful use of Sling in women, a similar procedure has been implemented in men with sphincter dysfunction after a radical or transurethral prostatectomy. Ref. 3

The male Sling is based on the Stamey Technique, i.e. the transference of a belt that compresses the bulb of the urethra to the suprapubic region with needles, and was later tuned up by a member of his team, Dr. Anthony Schaeffer. For bulbourethral compression, they use 3 segments of 40-mm-long x 6-mm-diameter Cooley vascular prosthesis covered with a Teflon mesh, to which they suture nylon thread Number 1 in the extremes and then are transferred to the abdomen with needles through the perineum. Ref. 3

The only known commercial Sling for men is the system promoted by AMS, which consists of a polypropylene mesh tied to the pubic bone with titanium screws. In 40% of the cases patients were cured, in 40% of the cases patients improved and in 20% of the cases the procedure failed. Ref. 4

The use of screws is associated with the risk of causing osteitis.

Promedon’s male Sling consists of a radiopaque pad made of silicone foam. The pad is 42.0 mm long, 26.0 mm wide and 9.0 mm high. This is placed on the bulbular urethra providing a padded support.

The pad is joined to two silicone columns formed by multiple cones that allow for the possibility of post-surgery readjustment. The total length of the Sling is of 411 mm. The male Sling has two radiopaque silicone rings which are placed over the abdominal wall in the Sling columns and tightened to prevent them from moving downwards and to allow readjusting. Measures: 15 mm in diameter and 2.90 mm thick.

The Sling is implanted using 2 3.5-mm-diameter needles that pass through the perineum (upwards) or the suprapubic region (downwards).
A preliminary experience was performed by the main researcher that included 9 patients who were monitored for an average of 8 months to test efficiency and tolerance of the procedure. The initial results were very encouraging: 100% tolerance (rejection, erosion or infection) and 50% cure. These results were given to the 2002 Argentinean Conference on Urology (Congreso Argentino de Urología). Ref. 5,6

Following these first implants and the experience obtained, some improvements were introduced to the Sling and the surgical technique in order to reach the present model. The background motivated us to launch this multi-site protocol to confirm our preliminary expectations. What follows is a general view of the present Sling:

**PRIMARY OBJECTIVES**

To confirm **effectiveness and safety** of the Sling for treating male UEI

- **Effectiveness**
  The following terms are defined:
  - **Cure**: patients do not require postoperative protection, they do not wet themselves
  - **Improvement**: patients wet up to 1 pad / day
  - **Failure**: patients wet 2 or more pads / day

- **To compare the effect of implanting a male Sling on the patient's quality of life**
  The method will be considered **effective** if a subjective and objective improvement over 50% is achieved compared to preoperative status.

- **Safety**:
  To determine tissue tolerance to Sling and the incidence of infection/erosion
SECONDARY OBJECTIVES

- To achieve a **comfortable urination** and without urodynamic consequences relevant to the urinary system
- To assess the surgical technique used in order to make the implantation of the Sling easier

The results will be assessed immediately (30 days), medium term (6 months) and long term (12 months).

DETAILS OF THE DESIGN AND TYPE OF RESEARCH

**Type of Study:** Non-random, open multi-site study.

**Duration of the Study:** The study will last for one year with a short term assessment of patients implanted 30 days to 1 year before.

**Study Population:**
The population to be studied is made up of at least 30 patients in the different research sites. Each site shall have at least 6 cases.

Post-prostatectomy incontinence can be a devastating situation for the quality of life of those suffering from it, and, even though it is fortunately low (3-30%), at least 5% require surgery.\(^7\)

Based on the low incidence of postoperative incontinence, and on the scant scientific publications on this subject, where the average of reported patients is of 14\(^\text{Ref. 1,8,9,10,11,12}\), we decided that the minimum number of patients making up the population under study during this phase would be 30.

**Inclusion Criteria:**

- Patients with SUI due to post-prostatectomy ISD (Intrinsic Sphincter Deficiency), refractory to the conservative treatment and with a postoperative period no less than 12 months. The surgery causing incontinence could have been performed to treat benign prostatic hyperplasia (BPH) or prostate cancer (PC).

- Patients with neurogenic urethral incompetence (for example, myelomeningocele): these patients will be part of a separate group from patients with prostatectomy. Therefore, the analysis of these patients’ data will be performed separately from the study population of at least 30 patients with previous prostate surgery.

- Consent of the Ethics Committee of each site
The preoperative and postoperative studies include:

1. **Urination Chart**: During 3 days for 24 hours in the preoperative stage and at 7 days, 1 month, 3 months, 6 months and 12 months in the postoperative stage where the date, time and amount of urination appears, including the incontinence episodes.

2. **Absorbent Test**: The patient must collect the pads used during 24 hours in individual bags which must be put in a bigger bag afterwards. This bag shall be taken to the doctor who will weight each pad deducting the weight of the dry pad. In the patient registry, the weight in grams of urine lost per day will be entered.

   **NOTE**: If the patient uses an incontinence urinal, the total volume collected in 24 hours will be measured (equal to the urine lost per day). The patient will be warned that during those 24 hours he shall not urinate voluntarily inside the collector system.

3. **Impact of urinary Incontinence Questionnaire - ICIQ -SF**: The questionnaire must be completed before the surgery and at 7 days, 1 month, 3 months, 6 months and 12 months after the surgery. The ICIQ score obtained must be entered in the patient registry.

4. **Endoscopy**: of the urethra and bladder for strictures which must be stabilized before the Sling surgery.

5. **Urodynamic Examination**: Relevant data for inclusion are:

   - Good vesical **capacity**, that is to say over 300 ml, good accommodation: **compliance > 10 ml /cm H\textsubscript{2}O**.
   - Identify the presence of vesical **instability** / hyperactive detrusor.
   - The ability of a patient to urinate by reflex of the detrusor voluntarily or not must be known: hypoareflexic bladder and **abdominal press miction**, to prevent -in the latter case- the need for intermittent catheterization for the postoperative vesical emptying and the eventual placing of an intraoperative drainage.
   - **Measure the pressure of loss** during exertion while the patient is standing and has no urethral catheter (full vesicle). The total abdominal pressure will be registered at the moment of the loss.
   - **Determination of the back urethral pressure** or passive resistance previous and during the surgery for which a Foley catheter with 2 ml of water is inflated in the navicular fossa and connected by means of a tubulature (guide) to a serum bottle. With **pubic level being 0** (level of water in bottle at pubic level) the bottle starts to rise on a ruler from this point to
the height where the drip starts in the dropper. This height in cm (distance between the 
water level and the pubic area) equals the passive urethral pressure, usually 40 or 50 cm in 
the male UEI.

**NOTE:** This same procedure and the Cystoscopy will be used during the surgery to adjust 
the Sling.

**Exclusion Criteria**
- Patients with untreated urethral stricture.
- Patients with untreated active genitourinary infection.
- Patients that have been irradiated as a treatment for Prostate Cancer, this being interstitial 
or external, neoadjuvant, therapeutic or adjuvant.

**Criteria for Withdrawing a Patient from the Study**
- When the patient is not satisfied and wants to withdraw voluntarily and does not want to 
continue to be part of the examinations and interviews required for the complete study.
- The patient will be taken into account until his/her last visit to the Urology office.

**SURGICAL PROCEDURE**

1) **Assembly of Surgical Instruments:**
Insert the stainless steel needles in the corresponding plastic handles, making sure that the 
arrows in both pieces coincide. Firmly tighten the screw as much as necessary in order to avoid 
rotation of the needle.

2) **Surgical Technique**
Mechanical clearing of the rectum (enemas) and preoperative prophylaxis with Antibiotics 
(Gentamycin + Cephalosporin).

On general or spinal anesthesia, and after brushing the hypogastric and genito-perineal areas 
with soapy povidone, a No 16 or 18 Foley catheter is inserted through the urethra and the 
bladder is completely emptied *. Surgical drapes are placed making sure the area of the anus is 
clear.

*Perform a preoperative endoscopy before introducing the catheter if not done before.

It is recommended to immerse the Sling in an antibiotic solution or cover it with a mixture of 10 
cm³ of Xilocaine gel and 2 ampules of Gentamycin. The use of this mixture is not mandatory and 
it is used in order to minimize contamination during surgery and to improve lubrication of the 
Sling when going through the tissues.
1. **Position**: lithotomy and Moderate Trendelemburg
2. **Suprapubic Incisions**: two 3-cm incisions are performed (over the superior border of the pubis) 2 cm on both sides of the center. Incisions in the cellular tissue up to the aponeurosis shall be deepened being careful not to injure it.
3. **Perineal Incision**: Median or inverted U on the perineum over the urethral bulb. Its center shall be the inferior border of the pubis. A 7-cm-long median incision is recommended.
4. **Dissection**: sharp and blunt dissection of the triangular space between the urethral bulb and the ischiopubic branch to which the root of the cavernous body (crura) is adhered on both sides, towards the inferior side of the pubic area leaving the bulb and ischiocavernous muscles attached (in situ). The pelvic floor must be reached without perforating the perineal aponeurosis (superficial layer).
5. It is here (“floor” described in point 4) where the needles are introduced on both sides, pre-threaded on the end with no hook with a safety thread. Initially, the needles will move horizontally, parallel to the table, until deeply perforating the perineal aponeurosis. Immediately afterwards, move vertically, through the retropubic space, perpendicular to the table, towards the pre-opened suprapubic incisions. It is important to note that, if decided by the surgeon or due to characteristics of the patient, needles may be introduced from the abdomen towards the perineum. However, using this maneuver there are more chances of perforating the urethra. Once the needles are in place, an endoscopic control is performed in order to check the integrity of the bladder and the urethra. If perforation has occurred, the needle shall be reinserted through a different path than the one previously used, keeping the cystoscope in place.

During endoscopy observation using a cystoscope with sheath 17 Fr or smaller, keep the needle handles tensioned so that the ones laterally in the urethra will open and not close against it. This is how injury or damage of the urethral wall will be prevented when handling the cystoscope.

The ends of the safety thread are then tightened with forceps with one end in the perineum and the other one in the abdomen.

If, during the transference, the needle is detached, the column may be reintroduced into the tunnel previously opened by tying its end to the safety thread and pulling it towards the abdomen.

6. **Transference of the Columns of the Sling into the Abdomen**:

Needle handles are changed from the perineal to the abdominal end, and the crochet hook is left uncovered for threading and pulling the columns. Once the columns have been transferred they are held from their ends (perineal and abdominal) and moved upwards and downwards several times (gently, not violently) until they move easily so that traction from the abdomen is
transmitted without difficulties to the end of the pad to apply controlled pressure on the urethra. Both safety threads are then removed.

7. **Placing the washers:** The washer is threaded into a mosquito forceps which will then be used to hold the end of the column in order to transfer the washer from the forceps to the column.

The washers are moved down the column up to the aponeurosis by introducing them into the positioner used for pushing into the cellular tissue up to the aponeurosis.

8. **Adjustment (**)**: The adjustment (upwards and downwards) of the washers with the positioner will be controlled by the cystoscope and a water column, verifying that the opening of the urethra is closed when tightening the Sling. The height of the serum bottle during endoscopy must be 45 cm from the patient’s pubic level up to the water level of the bottle. In this position, the back urethral pressure will be of ~ 45 cm of the water column. The adjustment of the sling will be made through the washers until the dripping in the macrodropper of the line of infusion stops.

It is important to keep the pad centered which can be done by tying one of the wings of the pad in the center of the urethra with an atraumatic hemostatic clamp making sure not to damage or perforate the surface of the pad. Different tensions in the columns shall be avoided as this would cause the pad to move. In the event of puncture or damage of the pad, the Sling must be discarded and replaced.

9. The columns must be cut about 6 cones over the washer and the remainder of the column must be placed in a subcutaneous tunnel as deep as possible away from the skin.

10. **Irrigation with antibiotics:** During the implantation, it is suggested to abundantly irrigate the Sling and the cut with saline and 4-6 Gentamycin ampules, as is the usual procedure in the implantation of other synthetic materials such as the artificial sphincter or the penis prosthesis.

11. **Closure of the cut:** Careful hemostasia and closure of the perineal cut in several cellulo-adipose planes and the skin by means of continuous suture of polyglycolid acid 3-0 without leaving drainage.

12. **Cares after surgery:** It is recommended to administer parenteral antibiotics to the patient for 48 hs after surgery and then continue for 5 more days (7 days in all) with antibiotics such as Quinolones, Cephalosporin or Aminoglycosides. Analgesic / anti-inflammatory will be used as needed.

13. **Urethral probe:** A 16 or 18 FR urethral probe will be removed 24 hs after surgery. In the event of urethral or vesical lesion the probe will be removed 7 days after the surgery.

14. **After surgery:** 24 hs after surgery and depending on the general state of the patient, spontaneous mictions will start and the satisfactory emptying of the bladder will be checked. X-ray of the pelvis will be useful to check the final position of the Sling to compare it with subsequent controls.
Note: (*) To criterion of the surgeon and for an easy location of the washers on the aponeurosis a single incision of 7 cm instead of 2 cm, type phanestiel, can be made

(**) Argus is a sling that can be readjusted after the surgery. For that reason, during the surgery it is recommended to fit it up to 45 cm of water or less to avoid the risk of early urethral erosion. In case the patient lose tinkles, after 4 weeks the sling can be readjusted.

3) Postoperative Tightening-Loosening Procedure: the second washer positioner in the kit will be used for this procedure. The first positioner must be disposed of after surgery. What follows is the description of a series of steps to adjust tension of the Sling (tighten or loosen). This procedure is recommended within 30 days after surgery.

A) Adjustment of the Sling
1. Identify the end of the columns and detach tissue. Columns will be covered by thin fibrous tissue which must be carefully detached so as not to puncture the columns or rings. Ideally, this should be done with an electrical knife.
2. Hold the washer with the positioner designed for that purpose.
3. Hold the remainder of the column over the washer, preferably with your fingers and move the washer downwards one cone using the positioner. Repeat this procedure in the other column. Endoscopic control of tightening is suggested. Depending on the degree of fibrosis and compression of tissues on the column, the washers on each side could be tightened more than one cone. However, this should be done carefully making sure the column is not excessively stretched so as to avoid tearing it.

B) Releasing tension of the Sling
1. Steps 1 and 2 same as previous one
2. Use a mosquito forceps with protected branches (with polyethylene tubes: K30) to press the two superior cones close to the ring. Then, using a forceps, introduce 1 cone in the center of the washer pushing it down exerting countertraction with the positioner. Repeat the procedure on the other column. Repeat the maneuvers if more than one cone needs to be loosened.
3. Using the cystoscope, push down the urethra. If the tension on the urethra is still not released, it shall be approached from the perineum up to the pad-column attachment. Hold the area of the attachment with forceps or fingers and move downwards.
FOLLOW-UP

- Periodic controls will be performed with Urination Control Charts, Absorbent Test, Quality of Life Questionnaire and Urodynamic Examination in the event of failure. These controls are essential 7 days after urination starts and at 1, 3, 6 and 12 months.
- 30% of the patients is expected to need a tension readjustment of their Sling. This can be performed with local anesthesia and will be facilitated by the prosthesis adjustable system. The back urethral pressure must be recorded before and after the Sling readjustment, and an endoscopy is suggested.

DATA COLLECTION

The data collected are summarized in the “Patient Registry” attached hereto. This is sent to Promedon by e-mail (osvaldoriguol@promedon.com.ar) or by fax (54-(0)351-4663379) every time it is updated.

PATIENT CONSENT

Before the surgery, the patient and a relative will be informed about the characteristics of the prosthesis, advantages and disadvantages, risks and alternatives of this type of procedure. They will also be duly informed about how and where to go in the event of doubts or postoperative urgencies which shall be dealt with by the corresponding team members.

This consent shall be signed by both, the patient and the witness (relative) authorizing the doctor and his team to perform the procedure.
## Results - September 2004

<table>
<thead>
<tr>
<th>TOTAL Nº of cases : 49</th>
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</thead>
<tbody>
<tr>
<td><strong>Dry :</strong></td>
</tr>
<tr>
<td>35 cases → 71.4 %</td>
</tr>
<tr>
<td><strong>Improved : (up to 1 pad/day)</strong></td>
</tr>
<tr>
<td>7 cases → 14.3 %</td>
</tr>
<tr>
<td><strong>Failure : (over 1 pad/day)</strong></td>
</tr>
<tr>
<td>7 cases → 14.3 %</td>
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</tbody>
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**Failures Summary :**
- 2 (4%): Use > 2 pad/day
- 1 (2%): Column breakage (sling’s cone of 3 mm). The patient is waiting for a reimplant.
- 2 (4%): Sling withdrawal due to urethral erosion (possible excess of tension in the adjustment)
- 2 (4%): 1 sling withdrawal due to infection after reimplant. 1 sling withdrawal due to column breakage and infection of perineal hematoma

- **Maximum follow Up : 17 months**

- **Mean Follow Up : 11 months for over 41 % of the patients**

- **Impact of Incontinence Questionnaire - ICIQ-SF (0-21) :**
  - Mean ICIQ-SF Pre implant : 19.4 (16-21)
  - Mean ICIQ-SF Post implant : 4 (0-15)

- **Complications** *
  - Dysuria : 10 cases → 20.4 %
  - Perineal pain : 7 cases → 14.3 %
  - Sling column breakage : 7 cases → 14.3 %
  - Resling : 6 cases → 12.2 %
  - Acute retention : 5 cases → 10.2 %
  - Infection : 2 case → 4 %
  - Scrotum - perineal drowsiness : 3 cases → 6.1 %
  - Extrusion/Erosion : 2 case → 4 %
  - Urethral perforation : 1 case → 2 %
  - Vesical perforation : 0 case
  - Chronic retention : 0 case

* The majority of the complications was temporary, being solved in 15 to 20 days of the postoperating one. The cases of breakage of column of sling were solved reinforcing the columns (the inside diameter of the cones was increased from 3 to 3.5 mm). In those patients, a reinforced sling was reimplanted (Resling). One patient is waiting for a reimplant.
5 readjustments were performed postsurgically:

- 3 of them were performed during the first 4 weeks:
  
  o 1 patient changed from failure to dry
  o 1 patient with urine retention, the sling was loosen. Actually the patient is dry and urinates normally.
  o 1 patient did not improve his incontinence

- The fourth case: was adjusted after 6 months of the implant surgery and the patient changed from failure to improved

- The fifth case (use <1 pad/day): one cone of each side was adjusted after 4 months of the implant surgery. Results: without improvement.
References:


4. Dr. Leach “Sling for Post-Prostatectomy Incontinence can help Improve The Quality of Life” http://www.hisandherhealth.com/articles/slingprost.shtml


6. Romano,SV; Carrasco, NE; Cobreros, C; Pelecanachis, D.; Kogan, D.; Belinki, J. y Fredotovich, N. “Operación de Sling para la corrección de la incontinencia de orina de esfuerzo en el hombre. Técnica Quirúrgica” (Video), Congreso Arg. De Urologia, Mar del Plata, Nov 2002


