DE NOVO CLASSIFICATION REQUEST FOR
NEOTRACT'S UROLIFT SYSTEM

REGULATORY INFORMATION

FDA identifies this generic type of device as:

> **Implantable Transprostatic Tissue Retractor System.** An implantable transprostatic tissue retractor system is a prescription use device that consists of a delivery device and implant. The delivery device is inserted transurethrally and deploys the implant through the prostate. It is designed to increase prostatic urethral patency by providing prostate lobe tissue retraction while preserving the potential for future prostate procedures and is intended for the treatment of symptoms due to urinary outflow obstruction secondary to benign prostatic hyperplasia (BPH) in men.

NEW REGULATION NUMBER: 21 CFR 876.5530

CLASSIFICATION: II

PRODUCT CODE: PEW

BACKGROUND

DEVICE NAME: UROLIFT SYSTEM

SUBMISSION NUMBER: K130651

DATE OF DE NOVO: MARCH 7, 2013

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REQUESTER'S RECOMMENDED CLASSIFICATION: II

INDICATIONS FOR USE

The UroLift System is indicated for the treatment of symptoms due to urinary outflow obstruction secondary to benign prostatic hyperplasia (BPH) in men age 50 and above.

LIMITATIONS

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

2. The UroLift® System should not be used if the patient has:
   - Prostate volume of >80 cc
   - An obstructive or protruding median lobe of the prostate
   - A urinary tract infection
   - Urethra conditions that may prevent insertion of delivery system into bladder
   - Urinary incontinence
   - Current gross hematuria
   - A known allergy to nickel

3. The safety of the delivery system has not been evaluated in the MR environment, and therefore, the delivery system should not be used within the MR environment.

4. The UroLift® Implant has been shown to be MR Conditional and can be scanned under the following conditions:
   - Static magnetic field strength of 3 Tesla or less
   - Maximum spatial gradient magnetic field of 720 Gauss/cm
   - A maximum whole-body-averaged specific absorption rate (SAR) of 4 W/kg for 15 minutes of scanning

PLEASE REFER TO THE LABELING FOR A MORE COMPLETE LIST OF WARNINGS, PRECAUTIONS AND CONTRAINDICATIONS.

DEVICE DESCRIPTION

Device Name: UroLift® System

Device Model(s): UL400

The UroLift® System is composed of two main components: the UroLift® Delivery Device and UroLift® Implant (Figure 1). Each Delivery Device comes pre-loaded with one UroLift® Implant. The insertion of the UroLift® Delivery Device into the male urethra is performed under direct visualization using standard surgical technique, using a standard cystoscopy sheath and a Karl Storz 10324AA telescope. The UroLift® Delivery Device is designed to access the prostatic urethra and deliver one UroLift Implant through a lateral lobe of the prostate. The UroLift® Delivery Device is inserted into the urethra through the penile orifice and used to displace the urethra toward the prostatic capsule. A UroLift® Implant is then deployed transversely through the prostatic tissue. The Implants secure the retracted position of the urethra thereby maintaining an expanded urethral lumen, reducing fluid obstruction and improving lower urinary tract symptoms (LUTS). This is accomplished by holding the approximated position of the inner (urethral) tissue and the outer (capsular) tissue of the prostate with the UroLift® Implant (Figure 2).

Figure 1: UroLift® System

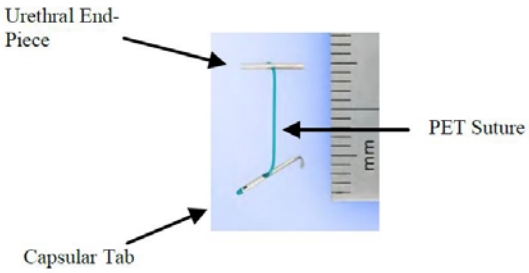
UroLift® Delivery Device	UroLift® Implant
	

Figure 1. The two main components of the UroLift® System, the UroLift® Delivery Device (Left) and the UroLift® Implant (Right). Each Delivery Device comes pre-loaded with one UroLift® Implant.

Figure 2: Male Prostatic Urethra - Pre/Post UroLift System Treatment

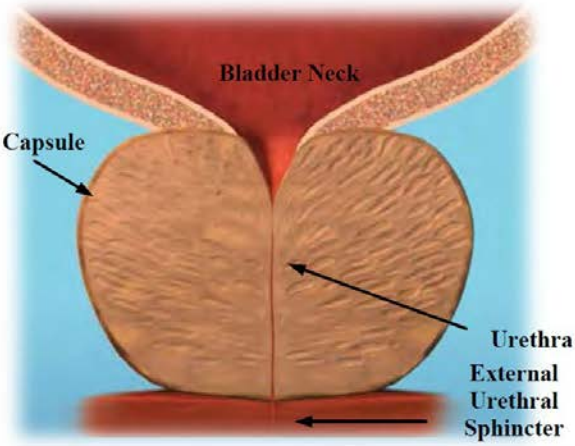
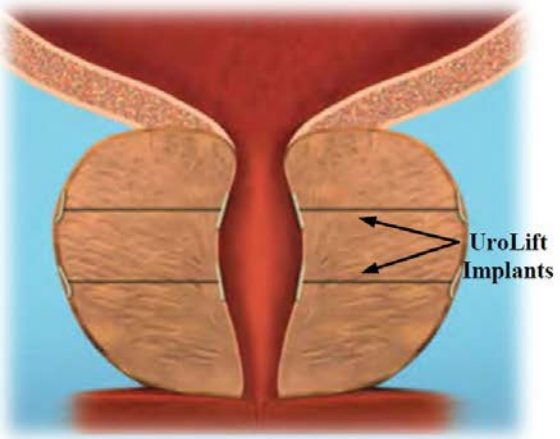
Pre-Treatment	Post-Treatment
	

Figure 2. Illustrations of coronal cross-sections of the male prostatic urethra, pre- and post-UroLift System treatment (Left and Right, respectively), demonstrating how the UroLift Implants can effect separation of the lobes and open the prostatic urethra.

UroLift® Delivery Device

The UroLift® Delivery Device, shown in greater detail in Figures 3 and 4, is a single-use device that delivers one permanent UroLift Implant. The key design elements of the Delivery Device are: i) the hollow nitinol Needle, which penetrates the urethra and prostatic lobe to access the prostatic capsule and then places the Capsular Tab; ii) the stainless steel Shaft Assembly with Distal Tip, which guides the hollow nitinol needle and stores the Urethral End-Piece; and iii) the Handle Assembly, which contains a Needle Safety Lock and three actuators (the Needle Trigger, the Retraction Lever, and the Urethral Release) that allow the user to deploy the UroLift Implant.

Figure 3: UroLift Delivery Device - Shown with the Needle Extended

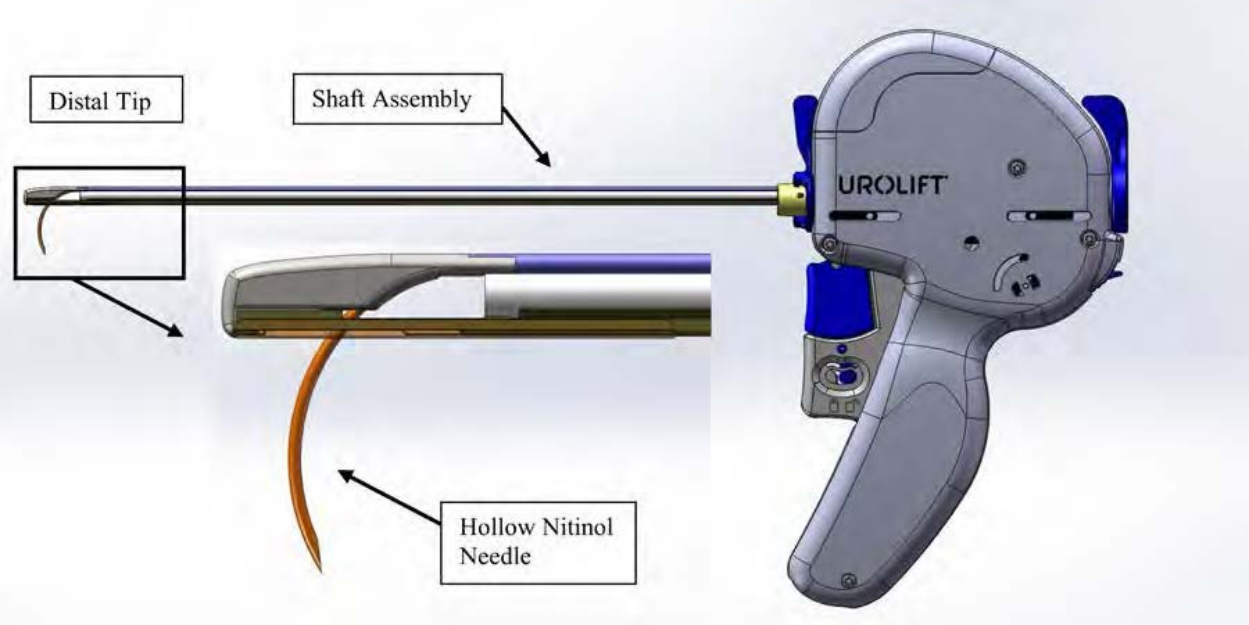


Figure 3. Details of the UroLift® Delivery Device, identifying the Distal Tip, The Shaft Assembly and, in a magnified view, the Hollow Nitinol Needle as it appears when protruding from the Distal Tip.

The Handle Assembly of the UroLift Delivery Device is the primary user interface and contains all of the actuators that are used to deploy the UroLift Implant. The Handle geometry is a pistol-style grip with actuators located on the front and rear of the handgrip portion. The pistol-style grip design of the Handle Assembly provides a user interface familiar to urologists and incorporates several safeguards for the user and the patient.

The Delivery Device user interface comprises seven elements, all part of the Handle Assembly, as shown in Figure 4: 1) the Handle, 2) the Scope Lock, 3) the Sheath Lock, 4) the Needle Safety Lock, 5) the Needle Trigger, 6) the Retraction Lever, and 7) the Urethral Release. These elements are used to connect the UroLift Delivery Device to the ancillary equipment and complete the implantation process. Additional aspects of the user interface are provided via the ancillary equipment. The telescope, light source, and endoscopy camera provide a video image of the urethra. The video is used to select the proper locations to place the UroLift Implants.

Figure 4: UroLift Delivery Device - User Interface Elements

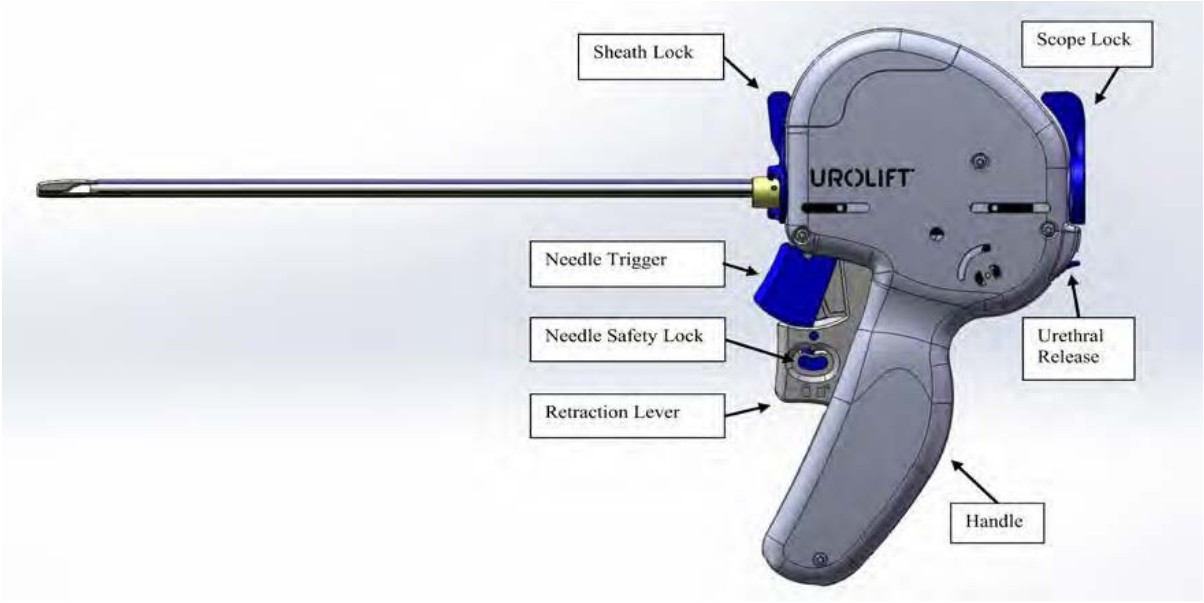


Figure 4. Details of the UroLift® Delivery Device, identifying the Handle, Scope Lock, Sheath Lock, Needle Safety Lock, Needle Trigger, Retraction Lever, and Urethral Release.

UroLift® Implant

The UroLift® Implant is a permanent implant delivered transurethrally into the prostate (Figure 2). The UroLift Implant comprises a nitinol Capsular Tab, a stainless steel Urethral End-Piece, and a monofilament Poly Ethylene Terephthalate (PET) suture. All of the materials and methods of fabrication utilized to produce the UroLift ®Implant are commonly used in the construction of other medical implants that have been cleared/approved for use in various markets, including the United States.

Refer to the Instructions for Use for additional details.

SUMMARY OF NONCLINICAL/BENCH STUDIES

The sponsor conducted a series of non-clinical performance testing to demonstrate that the UroLift System would perform as anticipated. Non-clinical testing included biocompatibility, shelf-life, toxicological, sterility, package integrity, transit, MR compatibility, bench performance, implant corrosion, animal and cadaveric testing, as summarized in Table 1, below.

Test	Purpose	Results
Biocompatibility - Implant		
Cytotoxicity (ISO 10993-5) - Deployed	To evaluate the biocompatibility of the test article (deployed and undeployed UroLift Implant) extract using an in vitro mammalian cell culture test by determining whether leachables extracted from the test article would cause cytotoxicity.	Pass
Cytotoxicity (ISO 10993-5) - Undeployed		Pass
Sensitization (ISO 10993-10) -	To evaluate the potential of the test article (undeployed UroLift Implant) to	Pass

Undeployed	cause delayed contact sensitization in the guinea pig maximization test.	
Intracutaneous Reactivity (ISO 10993-10) - Undeployed	To evaluate the local dermal irritant effects of leachables extracted from the test article (non-deployed UroLift Implant) following intracutaneous injection into rabbits.	Pass
Systemic Toxicity (ISO 10993-11) - Undeployed	To evaluate the acute systemic toxicity of leachables extracted from the test article (UroLift Implant) following a single intravenous or intraperitoneal injection in mice.	Pass
Genotoxicity (ISO 10993-3) - Ames Bacterial Reverse Mutation - Undeployed	To evaluate whether an extract of the test material (UroLift Implant) will cause mutagenic changes in a tryptophan-dependent strain of Escherichia coli or one or more strains of histidine-dependent Salmonella typhimurium in the presence or absence of S9 metabolic activation.	Pass
Genotoxicity (ISO 10993-3) - Mouse Lymphoma Assay - Implant	To evaluate the mutagenic potential of a test material extract using the mouse lymphoma forward mutations assay procedure.	Pass
Genotoxicity (ISO 10993-3) - Mouse Peripheral Blood Micronucleus - Implant	To evaluate the potential for a test article extract to cause damage to chromosomes or the mitotic apparatus of murine erythroblasts by measuring the frequency of micronucleated reticulocytes (MN-RET) of treated mice.	Pass
Implantation – 4 week (ISO 10993-6) - Undeployed	To evaluate the local tissue response to the test article implanted in muscle tissue. This test was performed twice, once with a four week endpoint and once with a twelve week endpoint.	Pass
Implantation – 12 week (ISO 10993-6) - Undeployed		Pass
Biocompatibility - Delivery Device		
Cytotoxicity (ISO 10993-5)	To evaluate the biocompatibility of the test article (patient-contacting portion of the UroLift Delivery Device) extract using an in vitro mammalian cell culture test by determining whether leachables extracted from the test article would cause cytotoxicity.	Pass
Sensitization (ISO 10993-10)	To evaluate the potential of the test article (patient-contacting portion of the UroLift Delivery Device) to cause delayed contact sensitization in the guinea pig maximization test.	Pass
Intracutaneous Reactivity (ISO 10993-10)	To evaluate the local dermal irritant effects of leachables extracted from the test article (patient-contacting portion of the UroLift Delivery Device) following intracutaneous injection into rabbits.	Pass
Shelf Life	After aging conditions, test articles were subjected to Joint and Materials Testing, System Compatibility and Simulated Use Testing and Package Integrity Testing.	Pass
Implant Extractables and Immersion	Comprehensive toxicological assessment of UroLift Implant to determine the degradation products on the sterilized and deployed UroLift Implant.	NA
Exhaustive Extraction Testing – UroLift Implant	This supplemental testing was conducted for information purposes only. This exhaustive extraction testing evaluated extractables and leachables from materials in the UroLift suture.	NA
Exaggerated Extraction (60 Day Immersion) Testing – UroLift Implant	Define the method for identifying and quantifying ions leached from finished NeoTract Urolift ®Suture Implants under simulated in vivo conditions. Provide a standardized method based on ISO 10993-15 "Biological Evaluation of Medical Devices- Part 15: Identification and Quantification of Degradation Products from Metals and Alloys" to assess ion release from the devices.	Pass
Total Digestion – Suture Only	In order to evaluate the overall toxicity of the Neotract implant, this test identifies and quantifies the residual metallic content that may have been used during the production of the suture.	NA
Extractions Study – Suture Only	The purpose of this test was to repeat extraction studies completed on the PET suture with test methods demonstrated to be capable of measuring trace quantities of PET extractables and degradation products in biorelevant extraction media.	NA
Toxicological Assessment	To evaluate the risks to patients associated with exposure to substances identified as potential leachables from components of the UroLift® Implant.	Pass

Sterility		
Sterilization Validation	To ensure that 25 kGy gamma irradiation is an adequate minimum dose to achieve an SAL of 10^{-6} (validation). To determine the appropriate dose map and ensure reproducibility of same. ANSI/AAMI/ISO 11137-1 ANSI/AAMI/ISO 11137-2 ANSI/AAMI/ISO 11137-3	Pass
Pyrogenicity	Evaluate whether a material extraction of the UroLift Implant induced a pyrogenic response following intravenous injection in rabbits.	Pass
Packaging	See Package Integrity testing.	
Package Integrity		
Bubble Emission	Sterile Barrier Testing via bubble emission, dye penetration and lid peel strength.	Pass
Dye Penetration		Pass
Lid Peel strength		Pass
Labels		Pass
Transit Testing	Climatic conditioning and transit simulation per ASTM D4169-09. Test articles were subjected to Joint and Materials Testing, System Compatibility and Simulated Use Testing and Package Integrity Testing.	Pass
Magnetic Resonance (MR) Compatibility	MR compatibility per ASTM F2052, ASTM F2213, ASTM F2182, ASTM F2119	Pass
Performance Testing - Bench		
Joint and Materials Strength	Implant strengths, critical device Joint and Material strength.	
• Capsular Tab-Suture Joint Strength		Pass
• Urethral End-Piece-Suture Joint Strength		Pass
• Suture Material Strength		Pass
• Suture and Ferrule to Suture Spool Assembly		Pass
• Suture to Ferrule Assembly		Pass
• Needle to Needle End Overmold		Pass
• Shaft to Shaft Overmold		Pass
• Lever Lock and Tape		Pass
• Distal Tip Lateral Load		Pass
• Distal Tip Axial Tensile Load		Pass
• Atraumatic Tape to Shaft Bond Function		Pass
System Compatibility and Simulated Use	System Compatibility, Simulated Use Testing, Needle Depth, Suture Tag Length.	
• Compatible with commercially available 20F Storz Sheath minimum		Pass
• Compatible with commercially		Pass

available 2.9mm scope		
• Deploy one UroLift® Implant		Pass
• Suture Tag Length on Urethral End-Piece		Pass
• Needle depth		Pass
Implant Corrosion		
SEM/Auger – Capsular Tab	To determine the oxide layer thickness and composition of NeoTract Capsular Tab component.	Pass
SEM/Auger – Urethral End-Piece	To document the oxide layer composition and thickness of the SS Urethral End-Piece.	Pass
Potentiodynamic – Capsular Tab	To determine the corrosion behavior of the NeoTract UroLift Nitinol Capsular Tab.	Pass
Potentiodynamic – Urethral End-Piece	To determine the corrosion behavior of the NeoTract UroLift stainless steel Urethral End-Piece components.	Pass
Potentiostatic – Capsular Tab	To determine the resistance to crevice corrosion of overlapped NeoTract Capsular Tab to suture assembly.	NA
Potentiostatic – Urethral End-Piece	To determine the resistance to crevice corrosion of overlapped Neotract Stainless Steel Urethral End-Piece components.	NA
Performance Testing - Animal Canine	Long term safety of the UroLift Implant in mammalian prostate.	Pass
Chronic Animal Study (6 months)	Initial safety and feasibility of luminal restoration of the prostatic urethra procedure and the UroLift Implant (1, 3, 6 months)	
Chronic Animal Study (1 month)	Feasibility and safety of the UroLift Implant at 1 month	
Chronic Animal Study (Dog, GLP, 90 and 180 Days)	Systemic and local tissue safety evaluation of the UroLift Implant at 3 and 6 months	
Chronic Animal Study (Dog, GLP, 12 months)	To confirm the safety of long-term effect on the prostate and surrounding urinary tract tissues presence of the UroLift Implant.	NA
Performance Testing - Cadaver	Assessment of procedural success and potential device safety	Pass

Table 1. A summary of non-clinical testing conducted on the UroLift System.

BIOCOMPATIBILITY/MATERIALS

The UroLift System is comprised of two main components, UroLift Implant and the UroLift Delivery Device. The biocompatibility and materials testing included those tests recommended by both FDA memorandum G95-1 entitled "Required Biocompatibility Training and Testing Profiles for Evaluation of Medical Devices" and the current revision of the International Standard ISO 10993, Biological Evaluation of Medical Devices. In addition, UroLift Implant leachables were evaluated through immersion testing.

Biocompatibility

The materials selected for use in the UroLift System are well characterized, used for similar medical device applications, and appropriate for gamma sterilization.

Leachables and Extractables

A review was conducted of the results of various studies in which the amounts of extracted metals and polymer-related organic substances were determined following extractions conducted

with the UroLift Implant and its PET suture component. These studies were performed for different durations of time and with various extraction solvents (hexane, isopropyl alcohol, purified water, and/or artificial urine) to provide a range of solubility conditions. Some of these conditions mimicked the physiological environment in which the UroLift Implant is implanted in male patients while others represented unrealistically aggressive worst-case conditions. As summarized in Table 1, the results of the studies indicate that none of the metals or polymer-related organic substances would be expected to leach from the implant or the PET suture in amounts that would be of toxicological concern to the patient, even in the event that 10 UroLift Implants were to be implanted on a single occasion. The available data do not suggest a toxicological risk to the patient due to the possible leaching of metals or polymer-related organic substances from the UroLift Implant.

Conclusions

In summary, the UroLift System has been evaluated to determine the potential for toxicity resulting from contact of the device component materials with the body. The results of this testing demonstrated the UroLift System is biocompatible when used as intended.

SHELF LIFE, PACKAGE INTEGRITY AND TRANSIT

The shelf life/stability of the UroLift System and its packaging has been demonstrated via real time aging at multiple time points including 18 months. The shelf life testing consisted of demonstrating that the UroLift System and its packaging meet all key design requirements, including joint and materials strength testing, system compatibility and simulated use, and package integrity, after gamma sterilization and aging for a specified time period. The successful completion of these tests demonstrated that the product meets the applicable design requirements and supports the device bearing a shelf life of 18 months.

Package integrity testing was performed on the UroLift System after gamma sterilization, climatic conditioning and transit simulation and demonstrated that the sterile barrier is maintained after these challenge conditions. Label integrity was visually inspected to confirm that labels are intact and legible. The UroLift System packaging test demonstrated that the packaging components met all design requirements.

Transit testing was performed on the UroLift System after gamma sterilization, climatic conditioning and transit simulation in accordance with the appropriate Assurance Levels of ASTM D4169-09 (Standard Practice for Performance Testing of Shipping Containers and Systems.) The test battery comprehensively assessed the key design requirements with the exception of the shelf life and MR conditional requirements and sterility). The UroLift System met all design requirements after the transit simulation.

STERILITY

The UroLift System is gamma sterilized via a validated minimum dose of (b)(4) kGy. The validation was conducted in accordance with the ISO11137-2: Sterilization of health care products – Radiation - Part 2: Establishing the sterilization dose, and resulted in a sterility assurance level (SAL) of 10-6. The packaging configuration of a tray, lid, sealed to a Tyvek cover has been shown to maintain the sterile barrier. In addition, the UroLift System has been found to be non-pyrogenic in accordance with ISO 10993-11. Based on this, the UroLift System will be labeled

and provided as “sterile”.

MAGNETIC RESONANCE (MR) COMPATIBILITY

Testing was conducted by an independent laboratory to evaluate the magnetic resonance (MR) safety and compatibility of the UroLift Implant. Three (3) UroLift Implants were used to test for implant displacement, implant torque, magnetic resonance imaging (MRI) related heating, and image artifacts. In magnetic field interaction tests, the UroLift Implant showed a translational attraction of (b)(4) and (b)(4) torque. The MRI-related heating test resulted in a physiologically inconsequential implant temperature rise of (b)(4) °C. The Implant displayed an artifact that appeared moderate in size in relation to the size and shape of this device. Based on all the test results, the UroLift Implant was assigned a status of MR Conditional. The safety of the delivery system has not been evaluated in the MR environment and therefore the delivery system should not be used within the MR environment.

PERFORMANCE TESTING – BENCH

The UroLift System, comprising the UroLift Delivery Device and the UroLift Implant, as packaged, labeled and gamma sterilized, has been tested in accordance with a comprehensive test plan that was derived in accordance with the FDA 2010 Guidance for the Non-Clinical and Clinical Investigation of Devices Used for the Treatment of Benign Prostatic Hyperplasia (BPH) and applicable ISO, ASTM and USP standards.

Joint and materials strength testing was performed on the UroLift System after gamma sterilization, climatic conditioning and transit simulation and demonstrates that these design requirements were met after challenge conditions. The UroLift System components and subsystems met all design requirements for joint and materials strength.

Simulated use testing was performed on the UroLift System after gamma sterilization, climatic conditioning and transit simulation and demonstrates that these design requirements are met after challenge conditions. These tests required demonstrating fit and mechanical connection to a cystoscope sheath and telescope and deploying the delivery device in a simulated use environment. The UroLift System met all design requirements for system compatibility and simulated use.

PERFORMANCE TESTING – ANIMAL

NeoTract has conducted multiple animal studies to demonstrate the safety of the UroLift System when implanted into mammalian prostates. Several studies were conducted prior to 2012 (Prior Studies) and were reviewed by FDA as part of the Investigation Device Exemption (IDE). The progression of the Prior Studies served to refine critical study methods, such as surgical approach and urine collections techniques, as well as obtain on-going safety data for the UroLift System.

NeoTract conducted an additional study (New GLP Study) to confirm the safety of the UroLift Implant with regard to the long-term effect on the prostate and surrounding tissue and with regard to chronic systemic toxicity. The control arm of the study used animals that received the full surgical procedure including deployment of the Needle from the UroLift Delivery Device, though no UroLift® Implant was delivered. The New GLP Study included five animals in each

group (test and control) at each timepoint: 1, 6, and 12 months (30 animals total).

The results show that the local tissue reaction attributed to the UroLift® Implant up to 6 months post-implantation was characterized by minimal chronic inflammation and minimal to mild fibrosis and was considered to be a steady-state end-stage response typical for a biocompatible chronic implant (New GLP Study). No proliferative changes including urothelial or glandular hyperplasia or neoplasia in the prostate attributable to UroLift® Implant were observed (New GLP Study). In Summary, the results from these studies demonstrated the following:

- Minimal chronic inflammation associated with the UroLift® Implant.
- Prostate tissue responds to physical pressure via local atrophy that relieves the applied pressure over time. The New GLP Study demonstrated a stable, end-stage atrophy at 6 months with no evidence of any proliferative changes. Prior Studies demonstrated no meaningful difference in induced proliferation or apoptosis between UroLift® Implant-treated animals and untreated control animals as previously presented by NeoTract.
- Minimal chronic inflammation associated with the UroLift® Implant. This was demonstrated in the New GLP Study and in Case Reports of clinical subjects who progressed to transurethral resection of the prostate (TURP).

PERFORMANCE TESTING – CADAVER

As part of the design development of the UroLift® System, a series of cadaver studies were performed. Cadaveric evaluations allowed early assessments of procedural success to be made. All devices performed as intended and met the established product specifications. A cumulative total of thirteen UroLift® Implants were deployed within the prostatic tissue resulting in an observed increase in luminal area in all three cadaver studies. The Delivery Device was easily inserted and withdrawn. The overall time per deployment was approximately 5 minutes. All deployments were performed by a board-certified urologist. Both urologists made observations that the System was simple to use. As confirmed by cystoscopy, there was no evidence of damage to the urethra. All devices performed as intended and no safety issues were observed. The results from this cadaver study further confirm the safety and ability to deploy the UroLift® Implant.

SUMMARY OF CLINICAL INFORMATION

Two clinical studies were conducted to confirm the safety, feasibility and effectiveness of the UroLift® System.

Feasibility Study - Australia, 2005

In 2005, a feasibility study was initiated in Australia with the objective of determining whether the placement of UroLift® transprostatic implants was feasible and safe for the effective treatment of lower urinary tract symptoms (LUTS) secondary to benign prostatic hyperplasia (BPH). Safety and feasibility of the device was evaluated on the 64 subjects enrolled and followed out to 5 years. All subjects have reached their two year follow-up. For the intent to treat (ITT) population, all procedures were completed successfully and symptomatic improvement was seen at follow up intervals compared to baseline based on subject questionnaire responses. No unanticipated adverse events have been recorded for this study. Site reported adverse events reported early in the study were typical postoperative symptoms. An independent reviewer adjudicated one event to be both a

procedure and a device related event. No other events were adjudicated as device related in this study. Twenty-four (24) month results from this study demonstrated that placement of the UroLift® implants into the prostate was feasible and that it was sufficiently safe to support continuation onto a broader randomized controlled trial.

Pivotal Study - US/OUS, 2010

The L.I.F.T. (**L**uminal **I**mprovement **F**ollowing Prostatic **T**issue Approximation for the Treatment of Lower Urinary Tract Symptoms) Pivotal Study was an FDA approved Investigational Device Exemption (IDE) Study (G090012), designed as a prospective, multicenter, multinational, 2:1 randomized, single-blinded controlled clinical trial of the UroLift® System. The study had two phases, a randomized single-blind period followed by a non-randomized open-label period. The blinded randomized trial portion of the study started at the time of the procedure and ended at the subject's three-month visit. Once the 3-month follow-up was completed, the subjects were unblinded. After unblinding, if their symptoms returned and treatment was required, subjects were allowed to receive treatment/retreatment (either de novo treatment if originally in the Control group or as a retreatment if originally treated with UroLift) with the UroLift® System or any other approved BPH treatment.

The primary endpoints of this study were to establish safety of the device, test the superiority of UroLift® system effectiveness when compared at 3 months to the randomized Control group, and to test UroLift® system durability at 1 year. At 3 months, the effectiveness of the UroLift® System was demonstrated by comparison of the change from baseline of the International Prostate Symptom Score (IPSS) of the treated group to the Control group. At 12 months, the long-term effectiveness for subjects in the UroLift® group was demonstrated by comparison of the IPSS at 12 months to baseline. The effectiveness assessment was double blinded in terms of both the subject and the assessor. The primary safety endpoint was an assessment of the proportion of subjects requiring extended post-operative urinary catheterization, defined as an occurrence of a subject requiring catheterization within the first 3 days as part of a postoperative management for inability to void and requiring the catheter for more than 7 days.

The UroLift® System would be considered effective if the mean IPSS improvement from baseline at 3 months demonstrates a minimum statistical margin of 25% compared to cystoscopy alone, and the lower bound of a one-sided 97.5% confidence interval of mean percent change (improvement) from baseline in IPSS at 12 months in the UroLift® group is $\geq 30\%$. The primary safety endpoint was to demonstrate that the upper bound of a one-sided 97.5% confidence interval of the observed rate of post-operative urinary catheterization > 7 days is $\leq 10\%$. The secondary effectiveness endpoints were: 1) peak flow rate (Qmax) at 3 and 12 months; 2) IPPS at 2 weeks; 3) Quality of Life (QoL) at 12 months; and 4) BPHII at 12 months.

A total of 206 subjects were randomized in a 2:1 ratio, (UroLift: 140; Control: 66) at 19 investigational sites. Fourteen U.S. sites and five non-U.S. sites (three in Australia and two in Canada) participated in the investigation. Subjects in the UroLift® group underwent the UroLift® System procedure. Subjects in the Control group underwent a sham procedure, which included standard cystoscopy with perioperative sounds and verbal comments that mimicked the UroLift® group procedure.

All study co-primary effectiveness and safety endpoints were achieved. The UroLift® System group was superior to control at 3 months and improvement of the treated group at 12 months was statistically significant as compared to their baseline IPSS. All secondary endpoints were clinically and statistically improved. International Index of Erectile Function (IIEF) showed preservation of function with no statistical change from baseline at 12 months. Symptom relief began as early as 2 weeks and subjects returned to normal activity by 8.6 days. IPSS was reduced from baseline by 50.0% at 3 months and by 45.5% at 12 months. QoL improved from 4.9 at baseline to 1.8 at 6 weeks and 2.4 at 12 months. BPHII decreased 73% at 6 weeks and remained close out to 1 year (64.6 % and 66.7% respectively). Urine Outflow demonstrated a 63.5% increase at 3 months over baseline and 54.8% was achieved at 12 months.

The majority of subjects experienced a greater than 83% and 87% responder rate (>3 point IPSS) at 12 months in the Intent to Treat (ITT) and Per Protocol (PP) groups, respectively. There were no appreciable differences in the treatment effect noted in co-primary effectiveness endpoint 1 based on geographical region. Based on sub-group analyses, it was determined that younger patients (< 66 years) allowed for greater improvement in IPSS score. Also, higher baseline IPSS scores allowed for greater improvement.

The risks of the device include a less than 20% chance that a patient will experience no benefit and a low risk of serious adverse events, though mild, transient, adverse events may be expected. All reported adverse events occurred within the first 30 days post procedure. Of 20, only 6 were adjudicated to be procedure or device related. No unanticipated adverse events have been recorded for this study. The adverse reactions associated with the UroLift® were comparable to other minimally invasive surgical therapies as well as standard cystoscopy, as shown here: Dysuria (35.0 %); Hematuria (26.4 %); Urgency (9.3 %); Incontinence (7.9 %); Calculus Urinary (6.4 %); Retention (5.7 %); Constipation (5.0 %); Nocturia (5.0 %); Bladder spasms (4.3 %); and PSA increase (4.3 %).

The probability of a harmful event was approximately 1.4% for a device or procedure related serious adverse event. There was a 1.4% chance of catheterization > 7 days and a 10% chance of return of lower urinary tract symptoms (LUTS) significant enough to seek medications or additional surgical intervention. Most events were mild or moderate, transient, and resolved without sequelae or intervention. The adverse events had an onset within 7 days of procedure and resolved within 30 days following the procedure.

The L.I.F.T. pivotal clinical study demonstrated a 12 months improvement of the primary and secondary endpoints with a high compliance rate, few significant deviations and low loss to follow-up. The results of this study corroborate the Australian Feasibility results.

LABELING

The labeling for the UroLift® System is consistent with the clinical data and covers all the hazards and other clinically relevant information that may impact safe and effective use of the device. The labeling is sufficient and satisfies the requirements of 21 CFR Part 801.109 Prescription devices.

The following summarizes how the UroLift® System labeling addresses the special controls related to labeling:

1. To address failure to deploy the device or misdeployment, the labeling includes an explanation of how proper implant depth is achieved during deployment will be included in the Instructions for Use (IFU) document and other product labeling.

2. To address infection due to presence of foreign body, an expiration date is included in the IFU document.

3. To address failure to deploy the device or misdeployment, failure of the implanted device, improperly placed implants, the occurrence of genito-urinary adverse events, and the presence of implants adversely affecting subsequent interventions, a detailed description of the training required prior to use of the device is included in the IFU document.

RISKS TO HEALTH

The table below identifies the risks to health that may be associated with the use of an implantable transprostatic tissue retractor system and the measures necessary to mitigate these risks.

Identified Risk	Mitigation Measure
Adverse Tissue Reaction to the Device	1. Biocompatibility Testing 2. *In Vivo* Testing
Infection Due to Presence of Foreign Body	1. Sterilization Validation 2. Labeling (including expiration dating) 3. Shelf life testing
Migration of Implanted Device	1. *In Vivo* Testing 2. MR Compatibility Testing
Failure to Deploy Device or Misdeployment	1. Non-clinical Testing 2. *In Vivo* Testing 3. Labeling
Failure of Implanted Device	1. Non-clinical Testing (Mechanical) 2. Non-clinical Testing (Resistance to Degradation) 3. Shelf life testing 4. *In Vivo* Testing 5. Labeling
Improperly Placed Implants	1. *In Vivo* Testing 2. Labeling
Occurrence of Genito-Urinary Adverse Events	1. *In Vivo* Testing 2. Labeling
Presence of Implants Adversely Affects Subsequent Interventions	1. Non-clinical Testing 2. *In Vivo* Testing 3. Labeling

Table 2. The identified risks that may be associated with the use of an implantable transprostatic tissue retractor system and the measures necessary to mitigate these risks.

SPECIAL CONTROLS:

In combination with the general controls of the FD&C Act, the UroLift® System is subject to the following special controls:

(1) The elements of the device that may contact the patient must be demonstrated to be biocompatible.
(2) Performance data must demonstrate the sterility of the patient-contacting components of the device.
(3) Performance data must support shelf life by demonstrating continued sterility of the device (of the patient-contacting components), package integrity and device functionality over the requested shelf life.
(4) Non-clinical testing data must demonstrate that the device performs as intended under anticipated conditions of use. The following performance characteristics must be tested:
    (A) Deployment testing must be conducted
    (B) Mechanical strength must be conducted
    (C) Resistance-to-degradation testing must be conducted
(5) Non-clinical testing must evaluate the compatibility of the device in a magnetic resonance (MR) environment
(6) *In vivo* testing must demonstrate safe and effective use, assess the impact of the implants on the ability to perform subsequent treatments, document the adverse event profile associated with clinical use, and demonstrate that the device performs as intended under anticipated conditions of use. The following performance characteristics must be tested:
    (A) Deployment testing must be conducted
    (B) Implant migration must be conducted
(7) Labeling must bear all information required for safe and effective use of the device, and must include:
    (A) Specific instructions, warnings, cautions, limitations, and the clinical training needed for the safe use of the device
    (B) Information on the patient population for which the device has been demonstrated to be effective
    (C) A detailed summary of the device technical parameters
    (D) Information on how the device operates and the typical course of treatment
    (E) An expiration date/shelf life
    (F) A detailed summary of the device- and procedure-related complications or adverse events pertinent to use of the device.

BENEFIT/RISK DETERMINATION

The results of the L.I.F.T. Study showed that the UroLift® System is effective in improving symptoms associated with LUTS as shown by the significant improvement in mean IPSS score at three months when compared to Control, and at 12 months when compared to baseline IPSS value. Corresponding, significant improvements in other relevant clinical parameters, Qmax, BPHII, and IPSS QoL support the conclusion. Further, the study demonstrates a favorable safety profile associated with the UroLift® System.

The low rate of extended catheterization, and of catheterization rates in general, as well as the demonstration of no occurrences of de novo sustained erectile dysfunction or anejaculation are cited as evidence for the conclusion. The low rate of SAEs associate with the UroLift® procedure, and the rates and duration of the observed adverse events are deemed acceptable. In fact, the observed procedure-related adverse events are the same as those commonly associated with transurethral

procedures, such as dysuria, hematuria, pelvic pain, urinary retention, and elevated prostate specific antigen (PSA).

There are significant benefits provided by the UroLift® System including improvement in lower urinary tract symptoms (LUTS) as measured by IPSS, low catheterization rate, improvement in Qmax, Quality of Life, and BPHII with a correspondingly low risk of complications. In addition patients are interested in the preservation of sexual function provided by this technology. It offers a less invasive procedure that can be performed under local anesthesia in an outpatient setting with rapid recovery and relief. Finally, the risks associated with the device are not significant and are lower than those for other BPH interventions. The risks can be mitigated by limiting the device to prescription use only, through the Instructions for Use (IFU) which provides instructions, contraindications, warnings and precautions, and through a training program which is available for qualified physicians (e.g. urologists).

In conclusion, given the available information above, the data support that, for the treatment of symptoms due to urinary outflow obstruction secondary to benign prostatic hyperplasia (BPH) in men age 50 and above, the probable benefits outweigh the probable risks for the UroLift® System. The device provides substantial benefits and the risks can be mitigated by the use of general and the identified special controls.

CONCLUSION

The *de novo* for the UroLift® System is granted and the device is classified under the following:

Product Code:	PEW
Device Type:	Implantable Transprostatic Tissue Retractor System
Class:	II
Regulation:	21 CFR 876.5530