



Food and Drug Administration
9200 Corporate Boulevard
Rockville MD 20850

MAY 29 1998

Ms. Carol Wernecke
Director, Regulatory and Clinical Affairs
Dornier Medical Systems, Inc.
1155 Roberts Boulevard
Kennesaw, Georgia 30144

Re: P970044
Urowave® Microwave Thermotherapy System
Filed: September 8, 1997
Amended: October 15, December 19 and 24, 1997; January 6, 8, and 13,
February 17, 18, and 25, and May 15, 1998

Dear Ms. Wernecke:

The Center for Devices and Radiological Health (CDRH) of the Food and Drug Administration (FDA) has completed its review of your premarket approval application (PMA) for the Urowave® Microwave Thermotherapy System. This device is indicated as a non-surgical treatment alternative to transurethral resection of the prostate (TURP) for the treatment of symptomatic benign prostatic hyperplasia (BPH) in men with prostatic lengths between 30 mm and 55 mm. We are pleased to inform you that the PMA is approved subject to the conditions described below and in the "Conditions of Approval" (enclosed). You may begin commercial distribution of the device upon receipt of this letter.

The sale, distribution, and use of this device are restricted to prescription use in accordance with 21 CFR 801.109 within the meaning of section 520(e) of the Federal Food, Drug, and Cosmetic Act (the act) under the authority of section 515(d)(1)(B)(ii) of the act. FDA has also determined that to ensure the safe and effective use of the device that the device is further restricted within the meaning of section 520(e) under the authority of section 515(d)(1)(B)(ii), (1) insofar as the labeling specify the requirements that apply to the training of practitioners who may use the device as approved in this order and (2) insofar as the sale, distribution, and use must not violate sections 502(q) and (r) of the act.

In addition to the postapproval requirements in the enclosure, the postapproval reports must include annual progress reports on the following postapproval study:

Your postapproval study should collect 5-year follow-up data to evaluate the long-term effects of the Urowave® Microwave Thermotherapy System treatment on a minimum of 100 patients. The postapproval study should assess the rates of adverse events that occurred during the 5-year follow-up period, as well as the rates of repeat and alternative treatments that were administered. In addition, your study should also collect information on the re-epithelialization of the prostatic urethra.

CDRH will notify the public of its decision to approve your PMA by making available a summary of the safety and effectiveness data upon which the approval is based. The information can be found on the FDA CDRH Internet HomePage located at <http://www.fda.gov/cdrh/pmapage.html>. Written requests for this information can also be made to the Dockets Management Branch (HFA-305), Food and Drug Administration, 12420 Parklawn Dr., rm. 1-23, Rockville, MD 20857. The written request should include the PMA number or docket number. Within 30 days from the date that this information is placed on the Internet, any interested person may seek review of this decision by requesting an opportunity for administrative review, either through a hearing or review by an independent advisory committee, under section 515(g) of the act.

Failure to comply with the conditions of approval invalidates this approval order. Commercial distribution of a device that is not in compliance with these conditions is a violation of the act.

You are reminded that, as soon as possible and before commercial distribution of your device, you must submit an amendment to this PMA submission with copies of all approved labeling in final printed form.

All required documents should be submitted in triplicate, unless otherwise specified, to the address below and should reference the above PMA number to facilitate processing.

PMA Document Mail Center (HFZ-401)
Center for Devices and Radiological Health
Food and Drug Administration
9200 Corporate Blvd.
Rockville, Maryland 20850

If you have any questions concerning this approval order, please contact Laura J. Byrd at (301) 594-2194.

Sincerely yours,



Kimber C. Richter, M.D.
Deputy Director
Clinical and Review Policy
Office of Device Evaluation
Center for Devices and
Radiological Health

Enclosure

1) Conditions of Approval

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Issued: 3-4-98

CONDITIONS OF APPROVAL

APPROVED LABELING. As soon as possible, and before commercial distribution of your device, submit three copies of an amendment to this PMA submission with copies of all approved labeling in final printed form to the PMA Document Mail Center (HFZ-401), Center for Devices and Radiological Health, Food and Drug Administration (FDA), 9200 Corporate Blvd., Rockville, Maryland 20850.

ADVERTISEMENT. No advertisement or other descriptive printed material issued by the applicant or private label distributor with respect to this device shall recommend or imply that the device may be used for any use that is not included in the FDA approved labeling for the device. If the FDA approval order has restricted the sale, distribution and use of the device to prescription use in accordance with 21 CFR 801.109 and specified that this restriction is being imposed in accordance with the provisions of section 520(e) of the act under the authority of section 515(d)(1)(B)(ii) of the act, all advertisements and other descriptive printed material issued by the applicant or distributor with respect to the device shall include a brief statement of the intended uses of the device and relevant warnings, precautions, side effects and contraindications.

PREMARKET APPROVAL APPLICATION (PMA) SUPPLEMENT. Before making any change affecting the safety or effectiveness of the device, submit a PMA supplement for review and approval by FDA unless the change is of a type for which a "Special PMA Supplement-Changes Being Effected" is permitted under 21 CFR 814.39(d) or an alternate submission is permitted in accordance with 21 CFR 814.39(e). A PMA supplement or alternate submission shall comply with applicable requirements under 21 CFR 814.39 of the final rule for Premarket Approval of Medical Devices.

All situations which require a PMA supplement cannot be briefly summarized, please consult the PMA regulation for further guidance. The guidance provided below is only for several key instances.

A PMA supplement must be submitted when unanticipated adverse effects, increases in the incidence of anticipated adverse effects, or device failures necessitate a labeling, manufacturing, or device modification.

A PMA supplement must be submitted if the device is to be modified and the modified device should be subjected to animal or laboratory or clinical testing designed to determine if the modified device remains safe and effective.

A "Special PMA Supplement - Changes Being Effected" is limited to the labeling, quality control and manufacturing process changes specified under 21 CFR 814.39(d)(2). It allows for the addition of, but not the replacement of previously approved, quality control specifications and test methods. These changes may be implemented before FDA approval upon acknowledgment by FDA that the submission is being processed as a "Special PMA Supplement - Changes Being Effected." This acknowledgment is in addition to that issued by the PMA Document Mail Center for all PMA supplements submitted. This procedure is not applicable to changes in device design, composition, specifications, circuitry, software or energy source.

Alternate submissions permitted under 21 CFR 814.39(e) apply to changes that otherwise require approval of a PMA supplement before implementation of the change and include the use of a 30-day PMA supplement or annual postapproval report. FDA must have previously indicated in an advisory opinion to the affected industry or in correspondence with the applicant that the alternate submission is permitted for the change. Before such can occur, FDA and the PMA applicant(s) involved must agree upon any needed testing protocol, test results, reporting format, information to be reported, and the alternate submission to be used.

POSTAPPROVAL REPORTS. Continued approval of this PMA is contingent upon the submission of postapproval reports required under 21 CFR 814.84 at intervals of 1 year from the date of approval of the original PMA. Postapproval reports for supplements approved under the original PMA, if applicable, are to be included in the next and subsequent annual reports for the original PMA unless specified otherwise in the approval order for the PMA supplement. Two copies identified as "Annual Report" and bearing the applicable PMA reference number are to be submitted to the PMA Document Mail Center (HFZ-401), Center for Devices and Radiological Health, Food and Drug Administration, 9200 Corporate Blvd., Rockville, Maryland 20850. The postapproval report shall indicate the beginning and ending date of the period covered by the report and shall include the following information required by 21 CFR 814.84:

(1) Identification of changes described in 21 CFR 814.39(a) and changes required to be reported to FDA under 21 CFR 814.39(b).

(2) Bibliography and summary of the following information not previously submitted as part of the PMA and that is known to or reasonably should be known to the applicant:

(a) unpublished reports of data from any clinical investigations or nonclinical laboratory studies involving the device or related devices ("related" devices include devices which are the same or substantially similar to the applicant's device); and

(b) reports in the scientific literature concerning the device.

If, after reviewing the bibliography and summary, FDA concludes that agency review of one or more of the above reports is required, the applicant shall submit two copies of each identified report when so notified by FDA.

ADVERSE REACTION AND DEVICE DEFECT REPORTING. As provided by 21 CFR 814.82(a)(9), FDA has determined that in order to provide continued reasonable assurance of the safety and effectiveness of the device, the applicant shall submit 3 copies of a written report identified, as applicable, as an "Adverse Reaction Report" or "Device Defect Report" to the PMA Document Mail Center (HFZ-401), Center for Devices and Radiological Health, Food and Drug Administration, 9200 Corporate Blvd., Rockville, Maryland 20850 within 10 days after the applicant receives or has knowledge of information concerning:

(1) A mix-up of the device or its labeling with another article.

(2) Any adverse reaction, side effect, injury, toxicity, or sensitivity reaction that is attributable to the device and

(a) has not been addressed by the device's labeling or

(b) has been addressed by the device's labeling, but is occurring with unexpected severity or frequency.

(3) Any significant chemical, physical or other change or deterioration in the device or any failure of the device to meet the specifications established in the approved PMA that could not cause or contribute to death or serious injury but are not correctable by adjustments or other maintenance procedures described in the approved labeling. The report shall include a discussion of the applicant's assessment of the change, deterioration or failure and any proposed or implemented corrective action by the applicant. When such events are correctable by adjustments or other maintenance procedures described in the approved labeling, all such events known to the applicant shall be included in the Annual Report described under "Postapproval Reports" above unless specified otherwise in the conditions of approval to this PMA. This postapproval report shall appropriately categorize these events and include the number of reported and otherwise known instances of each category during the reporting period. Additional information regarding the events discussed above shall be submitted by the applicant when determined by FDA to be necessary to provide continued reasonable assurance of the safety and effectiveness of the device for its intended use.

REPORTING UNDER THE MEDICAL DEVICE REPORTING (MDR) REGULATION. The Medical Device Reporting (MDR) Regulation became effective on December 13, 1984. This regulation was replaced by the reporting requirements of the Safe Medical Devices Act of 1990 which became effective July 31, 1996 and requires that all manufacturers and importers of medical devices, including in vitro diagnostic devices, report to the FDA whenever they receive or otherwise become aware of information, from any source, that reasonably suggests that a device marketed by the manufacturer or importer:

- (1) May have caused or contributed to a death or serious injury; or
- (2) Has malfunctioned and such device or similar device marketed by the manufacturer or importer would be likely to cause or contribute to a death or serious injury if the malfunction were to recur.

The same events subject to reporting under the MDR Regulation may also be subject to the above "Adverse Reaction and Device Defect Reporting" requirements in the "Conditions of Approval" for this PMA. FDA has determined that such duplicative reporting is unnecessary. Whenever an event involving a device is subject to reporting under both the MDR Regulation and the "Conditions of Approval" for a PMA, the manufacturer shall submit the appropriate reports required by the MDR Regulation within the time frames as identified in 21 CFR 803.10(c) using FDA Form 3500A, i.e., 30 days after becoming aware of a reportable death, serious injury, or malfunction as described in 21 CFR 803.50 and 21 CFR 803.52 and 5 days after becoming aware that a reportable MDR event requires remedial action to prevent an unreasonable risk of substantial harm to the public health. The manufacturer is responsible for submitting a baseline report on FDA Form 3417 for a device when the device model is first reported under 21 CFR 803.50. This baseline report is to include the PMA reference number. Any written report and its envelope is to be specifically identified, e.g., "Manufacturer Report," "5-Day Report," "Baseline Report," etc. Any written report is to be submitted to:

Food and Drug Administration
Center for Devices and Radiological Health
Medical Device Reporting
PO Box 3002
Rockville, Maryland 20847-3002

Copies of the MDR Regulation (FOD # 336&1336) and FDA publications entitled "An Overview of the Medical Device Reporting Regulation" (FOD # 509) and "Medical Device Reporting for Manufacturers" (FOD #987) are available on the CDRH WWW Home Page. They are also available through CDRH's Fact-On-Demand (F-O-D) at

800-899-0381. Written requests for information can be made by sending a facsimile to CDRH's Division of Small Manufacturers Assistance (DSMA) at 301-443-8818.

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SUMMARY OF SAFETY AND EFFECTIVENESS

I. GENERAL INFORMATION

Generic Name: Transurethral Microwave Thermotherapy System

Trade Name: Urowave® System

Applicant: Dornier Medical Systems, Inc.
1155 Roberts Boulevard
Kennesaw, Georgia 31044

PMA Number: P970044

Date of Notice of Approval to Applicant: MAY 29 1998

II. INDICATIONS FOR USE

The Urowave system is a non-surgical treatment alternative to transurethral resection of the prostate (TURP) for the treatment of symptomatic benign prostatic hyperplasia (BPH) in men with prostatic lengths between 30 mm and 55 mm.

III. DEVICE DESCRIPTION

The Urowave system is a computer-controlled device designed to deliver microwave energy to the prostate for the treatment of BPH. The Urowave system consists of (1) a 915 MHz microwave subsystem; (2) a fiberoptic thermometry subsystem; and (3) a temperature controlled cooling subsystem. The subsystems are controlled by dedicated computer hardware and software designed by Dornier.

The Urowave is used in conjunction with sterile, single use disposable accessories: (1) a flexible urethral therapy probe (which encloses the microwave antenna); and (2) interstitial accessories.

In addition, the Urowave is used in conjunction with non-sterile reusable accessories: (1) an interstitial thermosensor array (for insertion within the closed end sheath of the interstitial accessory); (2) a urethral thermosensor (for insertion within the urethral therapy probe); and (3) a rectal thermosensor probe (with three built-in thermosensors). The thermosensors in the urethral therapy probe and rectal thermosensor probe monitor the mucosal temperature of the urethra and rectum, respectively. The interstitial thermosensor array monitors the interstitial temperature of the prostate.

The thermotherapy treatment is applied transurethrally by using the urethral therapy probe which contains two interconnected compartments that are in contact with the urethra; one to circulate cooling water directly over the antenna and the other to circulate

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water within the outer membrane. An inflatable anchor balloon, located at the distal end of the urethral therapy probe, retains the probe at the bladder level throughout treatment. The flow rate and temperature of the water in the cooling subsystem are microprocessor-controlled. Thermosensors monitor temperature levels in the surrounding tissue. The microwave power is discontinued if the temperature rises above preset limits in any of the thermosensors.

The rectal thermosensor probe monitors the temperature of the rectal mucosa immediately adjacent to the prostate. Integrated into the length of the probe is a linear array of three thermosensors, positioned for intimate contact with the mucosal lining. The thermosensors provide feedback to the Urowave system controls.

Once the urethral therapy probe and rectal probe are properly inserted, treatment begins according to an internal algorithm by delivering microwave power (maximum of 90 watts) and coolant water (30° C default, user adjustable) simultaneously to the urethral therapy probe. The maximum urethral and rectal temperatures permitted by the system are 50° C and 42.5° C, respectively. The power shuts off after the predetermined treatment time has elapsed, not to exceed 60 minutes from the onset of treatment.

IV. CONTRAINDICATIONS, WARNINGS, AND PRECAUTIONS

Contraindications

1. Patients with peripheral arterial disease with intermittent claudication or Leriche's syndrome (*i.e.*, claudication of the buttocks and perineum).
2. Patients with clinical or histological evidence of prostatic cancer or bladder cancer.
3. Patients with severe urethral stricture preventing easy catheterization.
4. Patients with a cardiac pacemaker, an implantable defibrillator, or a metallic implant in the region of the hip, pelvis, or femur.
5. Patients with a prostatic urethra less than 30 mm in length.

Precautions

Physician/Patient Related:

1. The use of the Urowave system must be prescribed and administered under the direct supervision of a qualified and trained physician, after appropriate urologic evaluation of the patient.
2. The safety and effectiveness of treatment with the Urowave system have not been established in patients with the following conditions:

- Interest in the preservation of future fertility.
 - Coagulation disorders.
 - Renal impairment.
 - Neurological disorders which might affect bladder function.
 - Post-void residual volume (PVRV) of urine greater than 250 mL.
 - Urinary retention requiring an indwelling catheter.
 - Large median lobe of the prostate protruding into the bladder.
 - Active urinary tract infections.
 - Bacteriological evidence of bacterial prostatitis.
 - Bladder stones.
 - Previous pelvic surgery or pelvic radiotherapy.
 - Previous rectal surgery (other than hemorrhoidectomy).
 - Prostatic urethra greater than 55 mm in length.
3. Substantial changes in prostate specific antigen (PSA) levels may be seen after transurethral microwave thermotherapy. Physicians are cautioned to measure the serum PSA level before treatment for future comparisons. PSA levels should return to baseline by 6 months following thermotherapy and may once again be used as a diagnostic test.
 4. It is recommended that Urowave treated patients be followed on an annual basis to assess for any prostatic changes, since treatment with the Urowave system does not result in removal or total destruction of the prostate.

Urethral/Rectal Probe Related:

5. The Urowave system must not be initiated without assurance that the urethral therapy probe is properly positioned in the patient. The correct positioning of the urethral therapy probe must always be checked by imaging prior to commencing treatment. Improper placement of the urethral therapy probe could result in inaccurate delivery of microwave energy during therapy, heating non-targeted tissues such as the bladder neck, external sphincter, or penile urethra, and may cause injury to these surrounding structures. Start delivery of microwave power only after checking the position of the urethral therapy probe inside the patient.
6. Do not use the urethral therapy probe if it appears damaged.
7. The material used in the anchor balloon of the urethral therapy probe contains natural rubber latex which may cause allergic reactions.
8. The treatment must not be commenced until the rectal probe is properly placed into the patient's rectum and secured.

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Microwave/Electrical Related:

9. Remove all jewelry and metallic elements of patient's and user's clothing. Metals affect microwave absorption and reflection.
10. Exposing eyes to microwave energy may damage eyes.
11. Operators must remain at least 8 inches (20 cm) from the patient during thermotherapy in order to avoid excessive exposure to electromagnetic fields.
12. Electromagnetic compatibility (EMC) between microwave emissions from the Urowave antenna and all other medical devices has not been tested. The Urowave cart and ultrasound *Performa* cart have been tested. Keep all other medical devices at least 9.8 feet (3 meters) from the Urowave antenna. Remember that EMI can travel through walls into adjacent rooms.
13. Avoid stray microwave radiation by pressing MICROWAVE PAUSE during any treatment interruption. Re-positioning or removing the urethral therapy probe must direct no microwave energy toward the patient's eyes, the patient's testes, or the user.
14. Use of the Urowave system results in the deposition of microwave energy within the patient's prostate and into adjacent regions of the body. Some animal studies in the literature suggest that there may be, as yet unknown, health effects from exposure to microwave radiation, including an increased incidence of tumors. Although it is not possible to extrapolate these studies to humans, they suggest that unnecessary microwave radiation exposure should be avoided.
15. Do not remove any external panel from the Urowave system. Lethal voltages exist on the internal modules. Only properly trained service personnel may open electrical components.

V. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

A total of 220 patients (147 in the Active group and 73 in the Sham group) were treated and 194 of the treated patients were available for evaluation at 12 months for adverse events in the clinical study of the Urowave system. See the safety results in Section IX, item 7.

VI. ALTERNATE PROCEDURES

The treatment of BPH has been directed predominantly to a reduction of patient symptomatology and degree of associated urinary obstruction. The following are the currently available BPH treatment options, listed in order from least to most invasive:

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- Observation without treatment (watchful waiting)
- Alpha blocker therapy
- Finasteride therapy
- Balloon dilation
- Heat therapy (i.e., using laser, radiofrequency, or microwave energy)
- Transurethral incision of the prostate
- Transurethral resection of the prostate (TURP)
- Open prostatectomy

VII. MARKETING HISTORY

Approximately 55 Urowave systems have been marketed in Europe, Japan and Canada since October, 1992. Over 8,000 patients have been treated with the Urowave. The Urowave system has not been withdrawn from marketing for any reason relating to its safety or effectiveness.

VIII. SUMMARY OF NONCLINICAL STUDIES

A. Performance Studies

Electrical safety testing (e.g., leakage current, grounding, and isolation) demonstrated that the Urowave meets all applicable electrical safety requirements specified in the latest version of IEC 60601-1. The Urowave system was also tested to electromagnetic compatibility standards specified in the latest version of IEC 60601-1-2 with deviations. Deviation from the standard's testing more adequately addressed the EMC concerns for the device. Immunity testing was performed to demonstrate that the device functions satisfactorily in the intended use environment. Emissions testing between the Urowave antenna and other medical devices has not been conducted. The Urowave cart and ultrasound *Performa* cart have been tested. Keep all other medical devices at least 9.8 feet (3 meters) from the Urowave antenna.

Catheter/balloon performance testing was conducted using ASTM F 623 Standard Performance Specification for Foley Catheters as a model. The ASTM standard was modified to customize certain portions of the testing to the specific intended application of the urethral therapy probe. All samples tested met stated requirements.

B. Tissue Studies

In vitro tissue studies indicated that the heating pattern of the Urowave microwave helical coil antenna is symmetrical about its axis for all power level settings, demonstrating tissue destruction in a confined area relative to the antenna.

Phantom studies were conducted to evaluate the homogeneity of the heating pattern of the urethral therapy probe. A tissue equivalent phantom Plexiglas test chamber was

assembled incorporating a Urowave urethral therapy probe, as well as multiple thermosensors placed radially outward from the wall of the urethral therapy probe. The chamber was filled with a gel which has electromagnetic and thermal properties that are similar to those of human tissue.

The testing demonstrated that the thermosensors recorded temperatures which increased in a linear fashion; the thermosensors closest to the urethral therapy probe consistently recorded the highest temperatures, with the temperature progressively decreasing as the distance from the probe increased.

C. Spatial Specific Absorption Rate

Spatial specific absorption rate (SAR) measurements were performed to determine the SAR distributions for the Urowave microwave antenna in longitudinal and transverse planes. The testing was performed in a liquid muscle tissue equivalent phantom. Measurements were taken both with and without the urethral therapy probe. The results of these studies demonstrated that the Urowave system delivers microwave energy in a reproducible, uniform, and controlled fashion.

D. Animal Studies

Dornier utilized the canine animal model to verify device safety and functional operation and to study the extent of histological damage to the prostate proper and its surrounding tissues. Three separate canine studies were conducted in which a total of 14 dogs were treated. An initial canine study served only as a pilot study to develop the surgical technique required for mapping and to finalize technical details of the device operation and treatment algorithm. This study was not conducted in compliance with the Good Laboratory Practices Regulation. Several conclusions were derived from this study. First, there was no evidence of significant damage outside the prostate (i.e., in the bladder or the rectum), except for some mechanical injury to the outer longitudinal muscle layer of the rectum induced in some dogs by the placement of the angiographic catheter needle (the introducer used for placement of interstitial temperature sensors). Second, significant intraprostatic damage was seen histologically in all dogs in which the recorded temperatures exceeded 45° C. Third, in dogs in which the recorded temperatures did not exceed 45° C, no damage was visible on routine Hematoxylin and Eosin stains obtained immediately following the procedure. Thus, based on this preliminary series of dogs studied, it appeared that a recorded threshold temperature of 45° C was required in order to yield tissue damage in the canine prostate.

For a more definitive and well controlled study following GLP regulations, a series of five dogs was initially treated with the Urowave system. The actual tissue temperatures achieved within the prostate and in the surrounding areas differed considerably because of the size variation in the prostate between the individual dogs. Based on the recorded temperatures obtained during the study, it was found that recorded intraprostatic temperatures in larger prostates were not as high as in smaller prostates. In most dogs,

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the level of heating observed appeared sufficient to result in tissue necrosis. Extensive temperature mapping was performed in the periprostatic tissues and the anterior rectal wall. Histological sectioning of the rectum demonstrated no identifiable damage to the rectal mucosa in any of the dogs.

The canine testing was repeated on an additional seven dogs. Several modifications were made to the urethral therapy probe during this phase of canine testing. Based on testing, the maximum intraprostatic temperature setpoint inside the gland was established at 55° C which assures that the temperature at the capsule will not exceed 45° C.

E. Biocompatibility Testing

The only Urowave components or peripheral hardware that come into direct patient contact are: (1) the interstitial accessories; and (2) the urethral therapy probe. The interstitial accessories are marketed devices whose biocompatibility has already been established.

A series of tests were conducted to characterize the biocompatibility of the materials used in the urethral therapy probe. The following biocompatibility tests were conducted on the composite of the urethral therapy probe: delayed contact sensitization; hemolysis; cytotoxicity; implant; implantation; intracutaneous toxicity; physico-chemical; pyrogen; and acute systemic toxicity. The test results demonstrated that the probe is biocompatible for its intended use.

IX. SUMMARY OF CLINICAL STUDIES

A. Summary of Pilot Clinical Study

A total of 62 patients were treated during the pilot studies. The purpose of the initial pilot phase was to evaluate whether therapeutic temperatures could be reached with adequate tolerance in humans. Twenty-one patients were treated with the final device configuration and treatment protocol with intraprostatic temperatures measured both at 1 cm from the urethra and at the periphery of the prostate gland. Based on the data obtained with the final pilot group, a sufficient safety margin exists for maintaining peripheral prostatic temperatures below therapeutic levels. The current therapy parameters were considered safe.

B. Pivotal Clinical Study

1. Study Design

This multicenter, prospective, randomized clinical study was conducted to determine whether a single, outpatient therapeutic heat treatment with the Urowave can safely and effectively relieve the symptoms of benign prostatic hyperplasia (BPH). The study design was a double blind, sham controlled, randomized study with two groups:

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a group receiving treatment with the Urowave, and a control group receiving a sham treatment. A total of 220 patients were enrolled at five clinical centers (Table 1). The allocation ratio was 2:1, i.e., 2 active patients to 1 sham patient. This study was conducted in compliance with FDA's *Draft Guidance for the Clinical Investigation of Hyperthermia Devices Used for the Treatment of Benign Prostatic Hyperplasia* (BPH) dated November 11, 1994.

Table 1. Study Participants

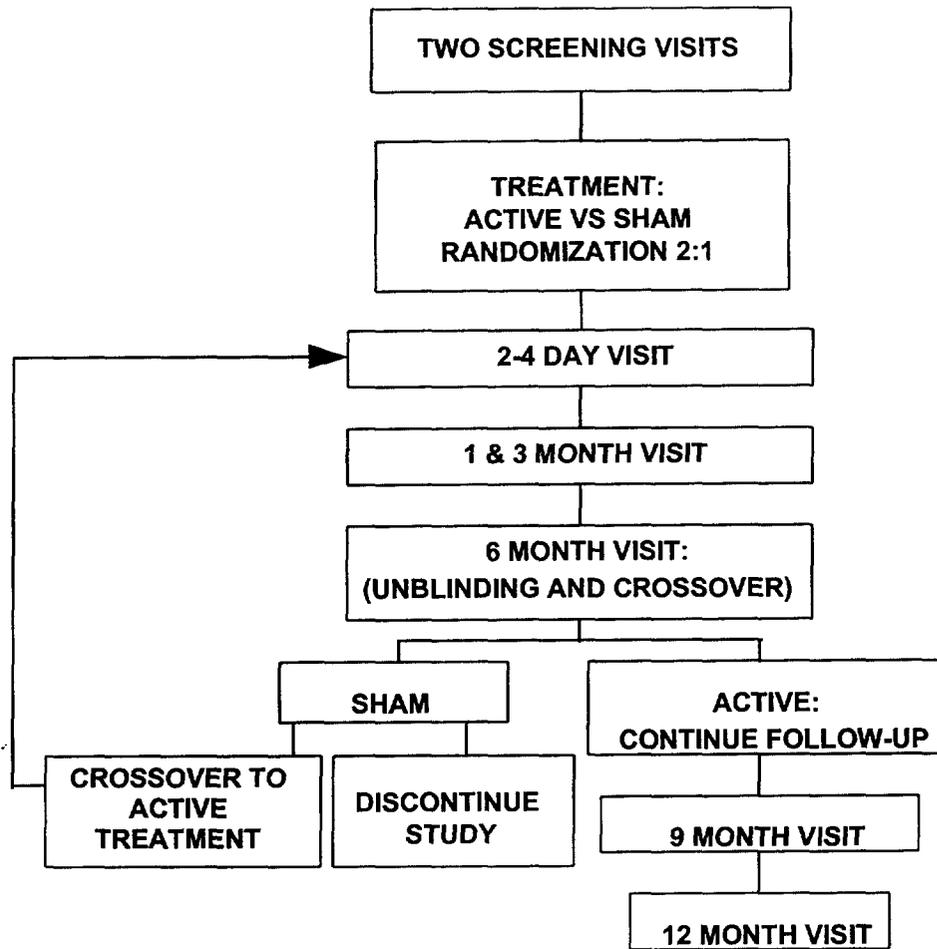
| STUDY SITE | SITE NO. | NUMBER OF PATIENTS | | | PRINCIPAL INVESTIGATOR |
|--|----------|--------------------|------|-------|--------------------------------------|
| | | Active | Sham | Total | |
| Department of Veteran's Affairs Medical Center ¹ Dallas, Texas | 1 | 28 | 13 | 41 | Claus Roehrborn, MD |
| The New York Hospital & Cornell Medical Center New York, New York | 2 | 27 | 14 | 41 | Aaron Perlmutter, MD |
| Duke University Medical Center Durham, North Carolina | 3 | 33 | 17 | 50 | Glenn Preminger, MD |
| Urology Consultants Sarasota, Florida | 4 | 35 | 17 | 52 | Willet Whitmore, MD |
| St. Joseph's Health Centre London, Ontario, CANADA | 9 | 24 | 12 | 36 | Hasan Razvi, MD John Denstedt, MD |
| Total Number Patients Enrolled/Treated | | 147 | 73 | 220 | |

2. Study Methodology

Follow-up visits were scheduled for 2-4 days, 1, 3, 6, 9 and 12 months post-treatment. Sham patients who met the original inclusion/exclusion criteria at their 6 month follow-up visit were eligible for an active Urowave treatment.

¹ A subset of 41 patients at this site underwent pressure flow studies at baseline, 6 and 12 months post-treatment.

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At screening and follow-up, data collection included: peak flow rate (two flows at screening, 6 and 12 months), post void residual urine, cystoscopy (screening, 6 and 12 months), transrectal ultrasound (screening, 6 and 12 months), voiding cystometrogram (subset only), AUA Symptom Score, AUA Bother Score, Quality of Life Score, Sexual Function Questionnaire, laboratory measurements, and digital rectal exam.

3. Study Population

A total of 220 patients were enrolled in this study. Out of these 220 patients, 147 were randomized to the Active group and 73 were randomized to the Sham group. There were five patients with protocol deviations. The deviations were considered minor and all five patients were included in the analysis.

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By the date of database closure, almost all patients completed their 6-month follow-up visit (i.e., 144/147 Active patients, and 72/73 Sham patients) and 110 patients had completed their 12-month follow-up visit according to the protocol. Discontinuations at 6 months included 3 Active patients (felt worse (1), started Proscar (1), moved (1)) and 1 Sham patient (TURP). Twenty-two (22) patients had been discontinued from the study at 12 months (death (1), worsening symptoms (1), felt worse (1), prostate carcinoma (1), started medication (6), withdrew consent (1), lost interest (2), transportation problems (2), elected to see private physician (1), moved (1), TURP (3), TUIP (1), and laser prostatectomy (1)).

4. Baseline Characteristics

The evaluated baseline characteristics were not significantly different between groups. The patient population in the study, on the average, was 66.1 years of age. The average length of BPH symptoms was 50.3 months. The average AUA Symptom Score was 23.7. The average AUA Bother Score was 18.6 and the average Quality of Life Score was 11.5. The mean peak flow rate and average flow rate were 7.9 mL/sec and 4.4 mL/sec, respectively. Post void residual volume averaged 75.6 mL among the patients enrolled. Prostate volume ranged from 25 to 100 grams, with the average volume being 48.9 grams. The majority of the patients (52%) had prostates of 45 grams or larger. The majority of patients (95.9%) had prostate lengths between 30 and 55 mm.

Statistically significant differences between study sites were seen in age ($p=0.006$), duration of symptoms ($p<0.001$), AUA Symptom Score ($p=0.030$), and average flow rate ($p=0.04$). The difference was largely associated with a somewhat older and more severe patient population with a longer history of symptoms at Site 4, however, the data were poolable.

5. Operative Characteristics

The Active patients were treated for 60 minutes in accordance with the Urowave treatment algorithm and the Sham patients received a simulated treatment (urethral therapy probe inserted but no microwave power emitted).

Five of the treatments in the Active group were terminated early due to device malfunctions; one of the treatments was rescheduled at a later date. One sham treatment was rescheduled due to a malfunction prior to treatment. During all treatments, the alarms and safety features of the Urowave functioned properly. Corrective actions were implemented, which included minor technical modifications and changes to the Operating Manual.

The mean maximum power delivered during the Active treatments was 82.4 watts. The maximum allowable power during a Urowave treatment is 90 watts. No general

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or regional anesthesia was required for any patient treatment. All treatments were performed on an outpatient basis. In the Active group, 27.2% of the patients received both oral and parenteral sedation and 19.7% received oral and parenteral analgesia, compared to 2.7% and 1.4% in the Sham group, respectively.

6. Effectiveness Results

The primary effectiveness endpoint was the change in AUA Symptom Score from baseline to 6 months post-treatment. The secondary effectiveness endpoints were the change in the peak flow rate (PFR) and the Quality of Life (QOL) Score from baseline to 6 months post-treatment. Individual patient success was defined as an improvement in these variables of $\geq 30\%$ over baseline at 6 months.

Additional effectiveness outcome measures included the AUA Bother Score, cystometrogram, cystoscopy, post void residual volume, prostate volume, patient assessment, and PSA.

Table 2 summarizes the changes in AUA Symptom Score from baseline, between both groups, at 6 months post-treatment. In the Active group, the mean score decreased from 23.6 ± 5.6 to 12.9 ± 7.2 , a decrease of 44%. In the Sham group, the mean score decreased from 23.9 ± 5.6 to 17.7 ± 7.4 , a decrease of 25%. In the Active group, the AUA Symptom Score was maintained at 12 months (11.3 ± 6.8 , 52.5% improvement, $n=109$) ($p < 0.001$).

Table 2 also summarizes the change in peak flow rate (PFR) from baseline, between both groups, at 6 months post-treatment. In the Active group, the PFR increased from 7.7 ± 2.0 mL/sec to 10.7 ± 3.8 mL/sec, an improvement of 41.5%. The Sham group's PFRs improved from 8.1 ± 2.0 mL/sec to 9.7 ± 3.4 mL/sec, a 21.2% improvement. In the Active group, the peak flow rate improvement was maintained at 12 months (10.5 ± 4.3 , 40.9% improvement, $n=110$) ($p < 0.001$).

Lastly, Table 2 summarizes the change in QOL Score from baseline, between both groups, at 6 months post-treatment. In the Active group, the mean QOL Score decreased (improved) from 11.5 ± 3.4 to 5.4 ± 4.4 , a decrease of 54%. In the Sham group, the mean score decreased from 11.5 ± 3.9 to 7.9 ± 4.6 , a decrease of 29%. In the Active group, the improvement in QOL Score was maintained at 12 months (4.7 ± 4.2 , 61.6% improvement; $n=107$) ($p < 0.001$).

As Table 2 shows, both the Active and Sham groups met the success criteria of improvement by $\geq 30\%$. However, the improvement in the Active group was significantly greater than the Sham group.

Table 2. Effectiveness Results at 6 Months Follow-up for Active and Sham Groups

| | Active Group | Sham Group | Between Group P-Value |
|------------------------------|--------------|------------|-----------------------|
| AUA SYMPTOM SCORE | | | |
| % Change from Baseline | -44% | -25% | <0.001 ² |
| % Improved by ≥30% | 72% | 40% | 0.001 ³ |
| PEAK FLOW RATE | | | |
| % Change from Baseline | 41.5% | 21.2% | 0.003 ² |
| % Improved by ≥30% | 51.7% | 31.9% | 0.007 ³ |
| QUALITY OF LIFE SCORE | | | |
| % Change from Baseline | -54% | -29% | <0.001 ² |
| % Improved by ≥30% | 74.6% | 45.1% | 0.001 ³ |

The changes from baseline of the primary and secondary endpoints at 6 months were analyzed and no significant differences were noted among sites. The results of the analyses further justify the pooling of data across investigational sites. In addition, the 47 sham patients who received a crossover treatment, had similar results to the patients in the original Active treatment group.

There were a total of 88 patients (88/140; 62.9%) who achieved interstitial temperatures of ≥ 45° C. Table 3 presents the mean change in the primary and secondary endpoints (AUA Symptom Score, QOL Score, and PFR) which were evaluated in accordance with three categorizations of peak interstitial temperatures (< 45° C, 45-54° C, and ≥ 55° C). The number of patients listed are those patients who had data available for that particular outcome parameter. Not all 88 patients who had interstitial temperatures ≥ 45° C had data for each outcome parameter. For example, only 86 of the 88 patients with interstitial temperatures ≥ 45° C had AUA data.

Table 3. Peak Interstitial Temperature Compared to 6 Month Change From Baseline Effectiveness Outcome (n=140)*

| Peak Interstitial Temp | AUA Symptom Score | | QOL Score | | PFR (ML/sec) | |
|------------------------|-------------------|-------------|-----------|-------------|--------------|-------------|
| | n | Mean Change | n | Mean Change | n | Mean Change |
| < 45° C | 51 | -11.0 | 49 | -5.8 | 51 | 2.6 |
| 45-54° C | 67 | -9.9 | 65 | -5.9 | 67 | 3.2 |
| ≥ 55° C | 19 | -12.7 | 18 | -8.0 | 19 | 3.5 |

*Only 140/147 Urowave patients (95.2%) were evaluated for interstitial temperatures.

² 2-way ANOVA

³ Cochran-Mantel-Haenzel

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7. Safety Results

The safety of the Urowave treatment was evaluated by the data collected at the time of treatment and during each patient's follow-up visit throughout the course of the study. In addition, safety was assessed through the following measures: laboratory measurements, cystoscopy and TRUS evaluations, digital rectal exams, and questions regarding urinary and sexual dysfunction.

Table 4 summarizes the Urowave treatment-related events at Treatment through 2-4 Day follow-up.

Table 4: Adverse Events Related to Treatment at Treatment/2-4 Day Follow-up

| Adverse Experience | Active Group (n=147) | | Sham Group (n=73) | | Between Groups p-value |
|--|----------------------|-------------------|--------------------|-------------------|------------------------|
| | Number of Patients* | Patient Incidence | Number of Patients | Patient Incidence | |
| URINARY | 81 | 55.1% | 34 | 46.6% | 0.234 |
| Bladder Spasm | 32 | 21.8% | 17 | 23.3% | 0.799 |
| Hematuria ^a | 31 | 21.1% | 12 | 16.4% | 0.414 |
| Urethral Bleeding ^b | 26 | 17.7% | 12 | 16.4% | 0.818 |
| Dysuria | 18 | 12.2% | 6 | 8.2% | 0.368 |
| Urinary Retention ^c | 15 | 10.2% | 0 | 0.0% | 0.005 |
| Urinary Incontinence | 4 | 2.7% | 0 | 0.0% | 0.156 |
| Burning In Penis | 3 | 2.0% | 0 | 0.0% | 0.220 |
| Urinary Frequency | 3 | 2.0% | 0 | 0.0% | 0.220 |
| Urinary Urgency | 3 | 2.0% | 0 | 0.0% | 0.220 |
| Catheter Not Draining | 1 | 0.7% | 0 | 0.0% | 0.481 |
| Bladder Distention | 1 | 0.7% | 0 | 0.0% | 0.481 |
| Urinary Tract Infection | 1 | 0.7% | 0 | 0.0% | 0.481 |
| Urethral Pain | 1 | 0.7% | 0 | 0.0% | 0.481 |
| REPRODUCTIVE | 11 | 7.5% | 4 | 5.5% | 0.580 |
| Penis Pain | 7 | 4.8% | 4 | 5.5% | 0.819 |
| Hematospermia | 4 | 2.7% | 0 | 0.0% | 0.156 |
| Painful Ejaculation | 1 | 0.7% | 0 | 0.0% | 0.481 |
| RECTUM | 2 | 1.4% | 0 | 0.0% | 0.318 |
| Rectal Disorder | 1 | 0.7% | 0 | 0.0% | 0.481 |
| Rectal Bleeding | 1 | 0.7% | 0 | 0.0% | 0.481 |
| OTHER | 28 | 19.0% | 3 | 4.1% | 0.003 |
| Pain During Treatment ^e | 19 | 12.90% | 1 | 1.40% | 0.005 |
| Hypertension | 2 | 1.40% | 0 | 0.00% | 0.318 |
| Bleeding From Interstitial Needle Site | 2 | 1.40% | 0 | 0.00% | 0.481 |
| Syncope | 1 | 0.70% | 0 | 0.00% | 0.481 |
| Nausea And Vomiting | 1 | 0.70% | 0 | 0.00% | 0.481 |
| Dizziness | 1 | 0.70% | 0 | 0.00% | 0.481 |
| Apnea | 1 | 0.7% | 0 | 0.0% | 0.481 |
| Sweating | 1 | 0.7% | 0 | 0.0% | 0.481 |
| Flank Pain | 0 | 0.0% | 1 | 1.4% | 0.156 |
| Rash | 0 | 0.0% | 1 | 1.4% | 0.156 |
| TOTAL | 96 | 65.3% | 35 | 47.9% | 0.014 |

* Note: Some patients experienced more than one acute adverse event.

For the Active group, 96/147 patients (65.3%) experienced 185 acute treatment related adverse events. For the Sham group, 35/73 patients (47.9%) experienced 54 acute treatment related adverse events.

The most common treatment related adverse events occurring on the day of treatment were bladder spasms, hematuria, and urethral bleeding. These were equally common in both the Active group and the Sham group and can be attributed to instrumentation rather than thermotherapy. Table 5 summarizes the events determined to be related to

treatment and/or instrumentation associated with the procedure from day 4 through 6 months.

Table 5: Adverse Events Related to Treatment Between 4 days and 6 Month Follow-Up

| Adverse Experience | Active Group (n=147) | | Sham Group (n=73) | | Between Groups p-value |
|-------------------------------------|----------------------|-------------------|--------------------|-------------------|------------------------|
| | Number of Patients* | Patient Incidence | Number of Patients | Patient Incidence | |
| URINARY | 39 | 26.5% | 2 | 2.7% | 0.001 |
| Dysuria | 13 | 8.8% | 0 | 0.0% | 0.009 |
| Urinary Retention ^c | 9 | 6.1% | 0 | 0.0% | 0.031 |
| Hematuria ^a | 9 | 6.1% | 1 | 1.4% | 0.112 |
| Urethral Bleeding ^b | 6 | 4.1% | 0 | 0.0% | 0.081 |
| Urinary Frequency | 4 | 2.7% | 0 | 0.0% | 0.156 |
| Urinary Urgency | 4 | 2.7% | 0 | 0.0% | 0.156 |
| Urinary Tract Infection | 3 | 2.0% | 0 | 0.0% | 0.220 |
| Urinary Incontinence | 2 | 1.4% | 0 | 0.0% | 0.318 |
| Pelvic Pain | 1 | 0.7% | 0 | 0.0% | 0.481 |
| Catheter Not Draining | 1 | 0.7% | 0 | 0.0% | 0.481 |
| Mucous In Bladder | 1 | 0.7% | 0 | 0.0% | 0.481 |
| Urethral Necrosis | 1 | 0.7% | 0 | 0.0% | 0.481 |
| Bladder Spasm | 1 | 0.7% | 0 | 0.0% | 0.481 |
| Urethral Stricture | 2 | 1.4% | 0 | 0.0% | 0.318 |
| Nocturia | 1 | 0.7% | 0 | 0.0% | 0.481 |
| Split Urinary Stream | 1 | 0.7% | 1 | 1.4% | 0.613 |
| REPRODUCTIVE | 33 | 22.4% | 1 | 1.4% | 0.001 |
| Hematospermia | 17 | 11.6% | 0 | 0.0% | 0.003 |
| Abnormal Ejaculation ^d | 12 | 8.2% | 0 | 0.0% | 0.012 |
| Painful Ejaculation | 5 | 3.40% | 1 | 1.40% | 0.385 |
| Penis Pain | 3 | 2.0% | 0 | 0.0% | 0.220 |
| Libido Decreased | 2 | 1.4% | 0 | 0.0% | 0.318 |
| Penoscrotal Ulceration ⁴ | 1 | 0.7% | 0 | 0.0% | 0.481 |
| Pain After Orgasm | 1 | 0.7% | 0 | 0.0% | 0.481 |
| Balanitis | 1 | 0.7% | 0 | 0.0% | 0.481 |
| Corporal Fibrosis ^{4 f} | 1 | 0.7% | 0 | 0.0% | 0.481 |
| Corporal Induration ^{4 f} | 1 | 0.7% | 0 | 0.0% | 0.481 |
| Erectile Dysfunction ^{4 f} | 1 | 0.7% | 0 | 0.0% | 0.481 |
| Prostatic Disorder | 1 | 0.7% | 0 | 0.0% | 0.481 |
| Prostatic Firmness | 1 | 0.7% | 0 | 0.0% | 0.481 |
| Pain In Prostate | 1 | 0.7% | 0 | 0.0% | 0.481 |
| Scrotal Inflammation | 1 | 0.7% | 0 | 0.0% | 0.481 |
| TOTAL | 59 | 40.1% | 2 | 2.7% | 0.001 |

* Note: Some patients experienced more than one acute adverse event.

⁴ All events occurred in one patient.

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Table Notes:

- ^a Believed to be related to the instrumentation effect. No patient required a blood transfusion. One patient experienced clot formation requiring catheter irrigation.
- ^b Attributed to instrumentation. One patient experienced bleeding requiring intervention (hospitalization for irrigation of clot retention).
- ^c Patients were discharged home with a Foley catheter which was removed within 4 days of treatment. Therefore, urinary retention immediately post-treatment was 100%. Urinary retention following removal of the Foley catheter occurred as stated in the tables. Temporary urinary retention is attributed to urethral edema and/or instrumentation.
- ^d Abnormal ejaculation was described as a decrease in the amount of ejaculate or no ejaculate.
- ^e Discomfort during treatment that required intravenous and/or intramuscular medication.
- ^f These events were not anticipated following a Urowave treatment, but were due to a misplaced urethral therapy probe.

For the Active group, 59/147 patients (40.1%) experienced 114 treatment related adverse events. For the Sham group, 2/73 patients (2.7%) experienced 3 treatment related adverse events.

Adverse events that occurred statistically more frequently in the Active group were dysuria ($p=0.009$) and urinary retention ($p=0.031$). These events are likely to be attributed to the placement of interstitial needles, instrumentation, and/or urethral edema related to microwave thermotherapy.

Differences in the incidence of hematospermia ($p=0.003$) and abnormal ejaculation (0.012) were also statistically significant. Most events were transient and not clinically associated with clinical morbidity.

For the Active group, between 6 months and 1 year post-treatment, three patients (3/127; 2.4%) experienced 4 treatment related adverse events. All 4 events affected the reproductive system (abnormal ejaculation and pain after orgasm).

Cystoscopic Abnormalities: Abnormalities found with cystoscopy performed at 6 months included: trabeculation of the bladder (in both the Urowave (87.5%) and Sham (86.1%) groups), defect in prostatic fossa (Urowave: 37.5%), partial/complete/no re-epithelialization (Urowave: partial (14.6%); complete (27.1%); no re-

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epithelialization (58.3%), and alteration to the bladder neck (Urowave (16%); Sham (15.3%)).

Cystoscopic abnormalities at 12 months included: bladder trabeculation (96.4% (106/110)), defect in prostatic fossa (26.4% (29/110)); depression to verumontanum (2.7% (3/110)), alteration to bladder neck (13.6% (15/110)), and other findings (33.6% (37/110)). Complete re-epithelialization was detected in 94.5% of the Urowave patients (104/110).

Note: A notable defect in the prostatic fossa was found in Urowave treated patients.

Serious adverse events were defined as any complication of health or safety, or a life threatening problem caused by or associated with the device. Two deaths were reported during the study; however, both deaths were not related to treatment.

At Treatment through 2-4 Day Follow-Up Events: For the Urowave Group, 3/147 (2.0%) patients experienced 3 serious adverse events (bladder distention, hematuria, and syncope (vaso-vagal response)). For the Sham Group, 1/73 (1.4%) patients experienced 1 serious adverse event (urethral bleeding with clot). All events were believed to be related to treatment (except for the vaso-vagal response), transient, and resolved. See additional explanation for the vaso-vagal response under Unanticipated adverse events.

Six Months Follow-Up Events: For the Urowave Group, 10/147 (6.8%) patients experienced 14 serious adverse events (Urinary: UTI and urethral stricture; Reproductive: penoscrotal ulceration, corporal fibrosis, corporal induration, erectile dysfunction, and prostate cancer; Rectum: intestinal obstruction; Other: fever, accidental injury, arrhythmia, myocardial infarct, appendicitis, and lung disorder). For the Sham Group, 4/73 (5.5%) patients experienced 5 serious adverse events (myocardial infarct, chest pain, pancreatitis, dyspnea, and respiratory mass). All events were believed not to be related to treatment (except for the patient who experienced a UTI and the patient who experienced a urethral stricture and penoscrotal ulceration, corporal fibrosis, corporal induration, and erectile dysfunction), transient, and resolved (except for the corporal fibrosis and erectile dysfunction, and prostate cancer). See additional explanation for the urethral stricture and penoscrotal ulceration, corporal fibrosis, corporal induration, and erectile dysfunction under Unanticipated adverse events. No serious adverse events were reported after the 6 months follow-up visit.

Unanticipated adverse events were defined as any complication of health or safety, or a life threatening problem caused by, or associated with, the device and not prospectively identified in nature, severity, or degree of incidence. Two patients reported adverse events that were determined to be serious and unanticipated. One patient experienced a severe vaso-vagal reaction (syncope, drop in blood pressure and pulse) during the Urowave treatment. Medication and hospitalization overnight were

required. Another patient reported a group of events after the Urowave treatment that were serious and unanticipated. This patient experienced penoscrotal ulceration on the ventral side of the penis, corporal fibrosis, corporal induration, and erectile dysfunction. The penoscrotal ulceration healed by 3 months post-treatment; the other events persisted through 12 months post-treatment. It is believed that these events were secondary to thermotherapy. The cause was determined to be a misplaced therapy probe or the therapy probe becoming dislodged during treatment.

X. CONCLUSIONS DRAWN FROM THE STUDIES

The laboratory, animal, and clinical data provide reasonable assurance of the safety and effectiveness of the Dornier Urowave® System for the treatment of symptomatic BPH, when used as indicated.

XI. PANEL RECOMMENDATIONS

Persuant to section 515(c)(2) of the Food, Drug, and Cosmetic Act as amended by the Safe Medical Devices Act of 1990, this PMA was not referred to the Gastroenterology and Urology Devices Panel, an FDA advisory panel, for review and recommendation because the information in the PMA substantially duplicates information previously reviewed by this panel.

XII. CDRH DECISION

FDA inspections of were conducted at the Urowave manufacturing facilities (Germany) and the Pharmaceutical Solutions Manufacturing Division, Inc., and it was determined that the manufacturers were in compliance with the Good Manufacturing Practices (GMP) regulation.

Based on a review of the data contained in the PMA, CDRH has determined that the Urowave system is safe and effective for the indication of relief of symptoms associated with BPH in men with prostatic lengths between 30 mm and 55 mm. Furthermore, the applicant agreed to the postapproval requirement that they collect data on the long-term (5 year) effect of their device.

CDRH issued an approval order for the stated indication for the applicants PMA for the Urowave system on MAY 29 1998 .

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XIII. APPROVAL SPECIFICATIONS

Directions For Use: See the labeling.

Hazards to Health from Use of the Device: See Indications, Contraindications, Warnings, Precautions, and Adverse Events in the labeling.

Postapproval Requirements and Restrictions: See approval order.



1 Introduction

Section 1 presents basics about Dornier UrowaveR Microwave ThermoTherapy System. Clinical information includes indications and usage, contraindications, warnings and precautions, adverse effects and clinical studies. An explanation of thermoTherapy outlines how Urowave delivers energy to the patient.

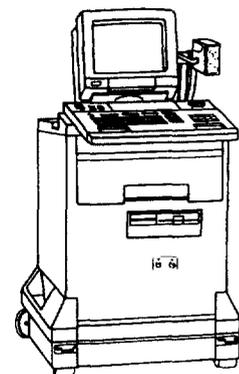
Section 1 includes the following subsections:

| Section | Title | Page |
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| 1.14 | Energy from Urowave Antenna | 1.30 |

1.1 Brief Device Description

The Dornier Urowave Microwave ThermoTherapy system is a cart, to which peripherals are added, for delivery of microwave thermoTherapy to the human prostate gland. Figure 1-1, below, shows the cart, ready to prepare for treatment.

Figure 1-1 Front view, Urowave cart



The Urowave system consists of three subsystems: a 915-MHz microwave subsystem; a fiberoptic thermometry subsystem; a temperature-controlled cooling subsystem. The subsystems are controlled by dedicated computer hardware and software designed by Dornier.

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1.1 Brief Device Description (continued)

The Urowave system is used in conjunction with the following sterile, single-use disposable accessories:

- 1 a flexible urethral therapy probe (which encloses the microwave antenna)
- 2 interstitial accessories

In addition, the Urowave system is used in conjunction with the following non-sterile reusable accessories:

- 1 an interstitial thermosensor array (for insertion within the closed-end sheath of the interstitial accessory)
- 2 a urethral thermosensor (for insertion within the urethral therapy probe)
- 3 a rectal thermosensor probe (with three built-in thermosensors).

In addition, an interstitial thermometry system (ITS) and free standing ultrasound system are used during operation of the Urowave system.

The thermosensors in the urethral therapy probe and rectal thermosensor probe monitor the mucosal temperature of the urethra and rectum, respectively. The interstitial thermosensor array monitors the interstitial temperature of the prostate.

The thermotherapy treatment is applied transurethrally by using a sterile urethral therapy probe containing the microwave antenna. The urethral therapy probe contains two interconnected compartments which are in contact with the urethra: one to circulate cooling water directly over the antenna and the other to circulate water within the outer membrane. An inflatable anchor balloon, located at the distal end of the urethral therapy probe, retains the probe at the bladder level through treatment. The flow rate and temperature of the water in the cooling subsystem are microprocessor-controlled. Thermosensors monitor temperature levels in the corresponding surrounding tissue. The microwave power is discontinued if the temperature rises above preset limits in any of the thermosensors.

The rectal thermosensor probe monitors the temperature of the rectal mucosa immediately adjacent to the prostate. Integrated into the length of the probe is a linear array of three thermosensors, positioned for intimate contact with the mucosal lining. The thermosensors provide feedback to the Urowave system controls.

Once the urethral therapy probe and rectal probe are properly inserted, treatment begins according to an internal algorithm by delivering microwave power (maximum of 90 Watts) and coolant water simultaneously to the urethral therapy probe. The maximum urethral and rectal temperatures permitted by the system are 50 °C and 42.5 °C, respectively. The power shuts off after the predetermined treatment time has elapsed, not to exceed 60 minutes from the onset of treatment.

By combining effects of radiative heating and conductive cooling, Urowave targets highest energy within the prostate at a depth of 4 to 10 mm, rather than at the urethral surface. (See Figure 1-10, on page 1.24.)

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1.2 Indications

The UrowaveR is a non-surgical treatment alternative to transurethral resection of the prostate (TURP) for the treatment of symptomatic benign prostatic hyperplasia (BPH) in men with prostatic lengths of between 30 and 55 mm.

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1.3 Contraindications

- Patients with peripheral arterial disease with intermittent claudication or Leriche's syndrome (i.e., claudication of buttocks and perineum).
- Patients with clinical or histological evidence of prostatic cancer or bladder cancer.
- Patients with severe urethral stricture, preventing easy catheterization.
- Patients with a cardiac pacemaker, implantable defibrillator, or metallic implant in the region of the hip, pelvis, or femur.
- Patients with a prostatic urethra < 30 mm in length.

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1.4

Precautions

1.4.1

Physician/Patient Related

- 1 The use of the Urowave system must be prescribed and administered under the direct supervision of a qualified and trained physician, after appropriate urologic evaluation of the patient.

- 2 The safety and effectiveness of treatment with the Urowave system have not been established in patients with the following conditions:
 - Interest in preserving future fertility
 - Coagulation disorders
 - Renal impairment
 - Neurological disorders which may affect bladder function
 - Post-void residual volume (PVRV) of urine greater than 250 ml
 - Urinary retention requiring indwelling catheter
 - Large median lobe of the prostate protruding into the bladder
 - Active urinary tract infections
 - Bacteriological evidence of bacterial prostatitis
 - Bladder stones
 - Previous pelvic surgery or pelvic radiotherapy
 - Previous rectal surgery (other than hemorrhoidectomy)
 - Prostatic urethra > 55 mm in length

- 3 Substantial changes in prostate specific antigen (PSA) level may be seen after transurethral microwave thermotherapy. Physicians are cautioned to measure the serum PSA level before treatment for future comparisons. PSA levels should return to baseline by six months following thermotherapy, and may once again be used as a diagnostic test.

- 4 It is recommended that Urowave treated patients be followed on an annual basis to assess for any prostatic changes, since treatment with the Urowave system does not result in removal or total destruction of the prostate.

1.4.2 Urethral/Rectal Probe Related

- 1 The Urowave system must not be initiated without assurance that the urethral therapy probe is properly positioned in the patient. The correct positioning of the urethral therapy probe must always be checked by imaging prior to commencing treatment. Improper placement of the urethral therapy probe could result in inaccurate delivery of microwave energy during therapy, heating non-targeted tissues such as the bladder neck, external sphincter, or penile urethra, and may cause injury to these surrounding structures. Start delivery of microwave power only after checking the position of the urethral therapy probe inside the patient.
- 2 Do not use the urethral therapy probe if it appears damaged.
- 3 The material used in the anchor balloon of the urethral therapy probe contains natural rubber latex which may cause allergic reactions.
- 4 The treatment must not be commenced until the rectal probe is properly placed into the patient's rectum and secured.

1.4.3 Microwave/Electrical Related

- 1 Remove all jewelry and metallic elements of patient's and users' clothing. Metals affect microwave absorption and reflection.
- 2 Exposing eyes to microwave energy may damage eyes.
- 3 Operators must remain at least 8 inches (20 cm) from the patient during thermotherapy. Avoid excessive exposure to and interference from electromagnetic fields. (For complete citation, see Bibliography, under IEEE.)
- 4 Electromagnetic compatibility (EMC) between microwave emissions from the Urowave antenna and all other medical devices has not been tested. The Urowave cart and ultrasound *Peforma* cart have been tested. Keep all other medical devices at least 9.8 feet (3 meters). Keep all other medical devices at least 9.8 feet (3 meters) from the Urowave antenna. Remember that EMI can travel through walls into adjacent rooms.
- 5 Avoid stray microwave radiation by pressing MICROWAVE PAUSE during any treatment interruption. Re-positioning or removing the urethral therapy probe must direct no microwave energy toward the patient's eyes, the patient's testes, or the user.
- 6 Use of the Urowave system results in the deposition of microwave energy within the patient's prostate and into adjacent regions of the body. Some animal studies in the literature suggest that there

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may be, as yet unknown, health effects from exposure to microwave radiation, including an increased incidence of tumors. Although it is not possible to extrapolate these studies to humans, they suggest that unnecessary microwave radiation exposure should be avoided.

7 Do not remove any external panel from the Urowave system. Lethal voltages exist on internal modules. Only properly trained service personnel may open electrical components.

1.5 Adverse Events (AEs)

The clinical study of the Dornier Urowave included 220 patients (147 in the Active group and 73 in the Sham group), of whom 194 patients were treated with the Urowave system and remained available for evaluation of adverse events. The clinical study indicates the following adverse events, observed and recorded.

The following table includes all adverse events reported through the 6 months follow-up visit.



Table 1.1: Adverse Events

| Adverse Events | ACTIVE GROUP ¹ of 194 Patients | SHAM GROUP of 73 Patients |
|-------------------------------------|--|--|
| | Number of Patients (Patient Incidence, %) | Number of Patients (Patient Incidence, %) |
| URINARY | | |
| Bladder Spasm | 42 (21.6) | 17 (23.3) |
| Hematuria | 51 (26.3) | 13 (17.8) |
| Urethral Bleeding | 40 (20.6) | 12 (16.4) |
| Dysuria | 42 (21.6) | 6 (8.2) |
| Urinary Retention ² | 29 (14.9) | 0 (0) |
| Urinary Incontinence | 6 (3.1) | 0 (0) |
| Burning In Penis | 3 (1.5) | 0 (0) |
| Urinary Frequency | 9 (4.6) | 0 (0) |
| Urinary Urgency | 12 (6.2) | 0 (0) |
| Catheter Not Draining | 2 (1.0) | 0 (0) |
| Bladder Distention | 1 (0.5) | 0 (0) |
| Urinary Tract Infection | 4 (2.1) | 0 (0) |
| Urethral Pain | 1 (0.5) | 0 (0) |
| Pelvic Pain | 1 (0.5) | 0 (0) |
| Mucous in Bladder | 1 (0.5) | 0 (0) |
| Urethral Necrosis | 1 (0.5) | 0 (0) |
| Urethral Stricture | 2 (1.0) | 0 (0) |
| Nocturia | 1 (0.5) | 0 (0) |
| Split Urinary Stream | 1 (0.5) | 1 (1.4) |
| Urination Impaired | 1 (0.5) | 0 (0) |
| Dribbling | 1 (0.5) | 0 (0) |
| RECTUM | | |
| Rectal Disorder | 1 (0.5) | 0 (0) |
| Rectal Bleeding | 1 (0.5) | 0 (0) |
| REPRODUCTIVE | | |
| Penis Pain | 12 (6.2) | 4 (5.5) |
| Hemospermia | 24 (12.4) | 0 (0) |
| Painful Ejaculation | 8 (4.1) | 1 (1.4) |
| Abnormal Ejaculation | 13 (6.7) | 0 (0) |
| Libido Decreased | 2 (1.0) | 0 (0) |
| Penoscrotal Ulceration ³ | 1 (0.5) | 0 (0) |
| Pain After Orgasm | 1 (0.5) | 0 (0) |
| Balanitis | 1 (0.5) | 0 (0) |
| Corporal Fibrosis ³ | 1 (0.5) | 0 (0) |
| Corporal Induration ³ | 1 (0.5) | 0 (0) |
| Erectile Dysfunction ³ | 1 (0.5) | 0 (0) |
| Prostatic Disorder | 1 (0.5) | 0 (0) |
| Prostatic Firmness | 1 (0.5) | 0 (0) |
| Pain in Prostate | 2 (1.0) | 0 (0) |
| Scrotal Inflammation | 1 (0.5) | 0 (0) |
| Swollen Scrotum | 1 (0.5) | 0 (0) |
| Scrotal Bruising | 1 (0.5) | 0 (0) |
| OTHER | | |
| Pain During Treatment | 23 (11.9) | 1 (1.4) |
| Hypertension | 2 (1.0) | 0 (0) |

¹ Includes 47 Sham patients who had a crossover treatment at 6 months.

² All patients were discharged with a Foley catheter which was removed within 4 days of treatment. Therefore, urinary retention immediately post-treatment was 100%. Urinary retention following removal of the Foley catheter occurred as stated in the table. Temporary urinary retention is attributed to urethral edema and instrumentation.

³ All events occurred in one patient.

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| | | |
|--|---------|---------|
| Bleeding From Interstitial Needle Site | 2 (1.0) | 0 (0) |
| Syncope | 1 (0.5) | 0 (0) |
| Nausea And Vomiting | 1 (0.5) | 0 (0) |
| Dizziness | 2 (1.0) | 0 (0) |
| Apnea | 1 (0.5) | 0 (0) |
| Sweating | 2 (1.0) | 0 (0) |
| Flank Pain | 0 (0) | 1 (1.4) |
| Rash | 0 (0) | 1 (1.4) |
| Pain | 2 (1.0) | 0 (0) |
| Back Pain | 1 (0.5) | 0 (0) |

Note: Some patients experienced more than one (1) acute adverse event.

For the Active Group, between 6 months and 1 year, three patients (3/127; 2.4%) experienced 4 treatment related adverse events. All 4 events affected the reproductive system (abnormal ejaculation and pain after orgasm).

Cystoscopic Abnormalities: Abnormalities found with cystoscopy performed at 6 months included: trabeculation of the bladder (in both the Urowave (87.5%) and Sham (86.1%) groups), defect in prostatic fossa (37.5%), partial/complete/no re-epithelialization (Urowave: partial (14.6%); complete (27.1%); no re-epithelialization (58.3%)), and alteration to the bladder neck (Urowave (16%); Sham (15.3%)).

Cystoscopic abnormalities at 12 months included: bladder trabeculation (96.4% (106/110)), defect in prostatic fossa (26.4% (29/110)); depression to verumontanum (2.7% (3/110)), alteration to bladder neck (13.6% (15/110)), and other findings (33.6% (37/110)). Complete re-epithelialization was detected in 94.5% of the Urowave patients (104/110).

Note: A notable defect in the prostatic fossa was found in Urowave treated patients.

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1.6 Clinical Study

1.6.1 Introduction

A multi-center, prospective, double blinded, sham controlled, randomized clinical trial was conducted to determine whether the Urowave system can relieve the symptoms of benign prostatic hyperplasia (BPH) in men. The primary endpoint was the change from baseline of the American Urological Association's (AUA's) symptom score, in both groups at 6 months with continued follow-up to 1 year in the treatment group. The secondary endpoints were the changes from baseline of both peak flow rate and Quality-of-Life Score. At 6 months, sham patients were unblinded and could elect to undergo the Urowave treatment.

1.6.2 **Methods (of Clinical Study)**

A total of 220 patients were enrolled in this study - 147 were randomized to the Active group and 73 were randomized to the Sham group. There were 47 Sham patients that received a crossover treatment. Findings of the crossover group were similar to those of the Active group.

The mean maximum power delivered during the Active treatments was 82.4 watts. The maximum allowable power during a Urowave treatment is 90 watts. The mean interstitial temperature achieved was 47.6° C.

The majority of patients (62.9%) reached peak interstitial temperatures of 45° C or greater.

No general or regional anesthesia was required for any patient treatment. All treatments were performed on an outpatient basis. In the Active group, patients received both oral and parenteral sedation and 19.7% received oral and parenteral analgesia, compared to 2.7% and 1.4% in the Sham group, respectively.

All patients (Active and Sham) were discharged with a Foley catheter which was removed within 4 days of treatment.

1.6.3 **Effectiveness Results (of Clinical Study)**

Results of the Urowave clinical study are summarized in Table 1-1, below.



Table 1-1 Effectiveness

| | Active Treatment Group | | | | Sham Group | |
|-------------------------------|------------------------|----------------|----------------------|-------------|-----------------------|---------------|
| | Baseline | 6 Months | 12 Months | Improvement | Baseline | 6 Months |
| Total Patients Treated | 147 | 144 | 110 | | 73 | 72 |
| AUA Symptom Score | 23.6±5.6 | 12.9±7.2 | 11.3±6.8 | 52.5% | 23.9±5.6 | 17.7±7.4 |
| Success* | | 103/143 (72 %) | | | | 28/70 (40%) |
| Peak Flow Rate (ml/s) | 7.7±2.0 | 10.7±3.8 | 10.5±4.3 | 40.9% | 8.1±2.0 | 9.7±3.4 |
| Success* | | 74/143 (52 %) | | | | 22/69 (31.9%) |
| Quality-of-Life Score | 11.5±3.4 ¹ | 5.4±4.4 | 4.7±4.2 ² | 61.6% | 11.5±3.9 ³ | 7.9±4.6 |
| Success* | | 106/142 (75%) | | | | 32/71 (45%) |

* Success = Improvement > or = 30%

The results of the clinical study demonstrate a substantial improvement with instrumentation alone (i.e., Sham treatment) at 6 months. However, the improvement in the actively treated group was significantly improved over the Sham group and this improvement was durable out to 1 year.

1.6.4 Safety Results (of Clinical Study)

Refer to Section 1.5 for a comprehensive list of adverse events. Although there were a significant number of adverse events, they were mostly transient and minor in nature. A few were categorized as serious and/or unanticipated.

Serious adverse events: Two deaths were reported during the study; however, both deaths were not related to treatment.

¹ QOL data only available on 143 Active group patients at baseline.

² QOL data only available on 107 Active group patients at 12 months.

³ QOL data only available on 72 Sham group patients at baseline.

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The “treatment through the 2-4 day follow-up” serious adverse events included: 3/147 (2.0%) Urowave patients who experienced 3 serious adverse events (bladder distention, hematuria, and syncope (vaso-vagal response)) and 1/73 (1.4%) Sham patients who experienced 1 serious adverse event (urethral bleeding with clot). All events were believed to be related to treatment (except for the vaso-vagal response), transient, and resolved. See additional explanation for the vaso-vagal response under Unanticipated adverse events.

The “through 6 months follow-up” serious adverse events included: 10/147 (6.8%) Urowave patients who experienced 14 serious adverse events (Urinary: UTI and urethral stricture; Reproductive: penoscrotal ulceration, corporal fibrosis, corporal induration, erectile dysfunction, and prostate cancer; Rectum: intestinal obstruction; Other: fever, accidental injury, arrhythmia, myocardial infarct, appendicitis, and lung disorder) and 4/73 (5.5%) Sham patients who experienced 5 serious adverse events (myocardial infarct, chest pain, pancreatitis, dyspnea, and respiratory mass). All events were believed not to be related to treatment (except for the patient who experienced a UTI and the patient who experienced a urethral stricture and penoscrotal ulceration, corporal fibrosis, corporal induration, and erectile dysfunction), transient, and resolved (except for the corporal fibrosis and erectile dysfunction, and prostate cancer). See additional explanation for the urethral stricture and penoscrotal ulceration, corporal fibrosis, corporal induration, and erectile dysfunction under Unanticipated adverse events. No serious adverse events were reported after the 6 months follow-up visit.

Unanticipated adverse events: Two patients reported adverse events that were determined to be serious and unanticipated. One patient experienced a severe vaso-vagal reaction (syncope, drop in blood pressure and pulse) during the Urowave treatment. Medication and hospitalization overnight were required. Another patient reported a group of events after the Urowave treatment that were serious and unanticipated. This patient experienced penoscrotal ulceration on the ventral side of the penis, corporal fibrosis, corporal induration, and erectile dysfunction. The penoscrotal ulceration healed by 3 months post-treatment; the other events persisted through 12 months post-treatment. It is believed that these events were secondary to thermotherapy. The cause was determined to be a misplaced therapy probe or the therapy probe becoming dislodged during treatment.

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What happens to me before Urowave therapy?

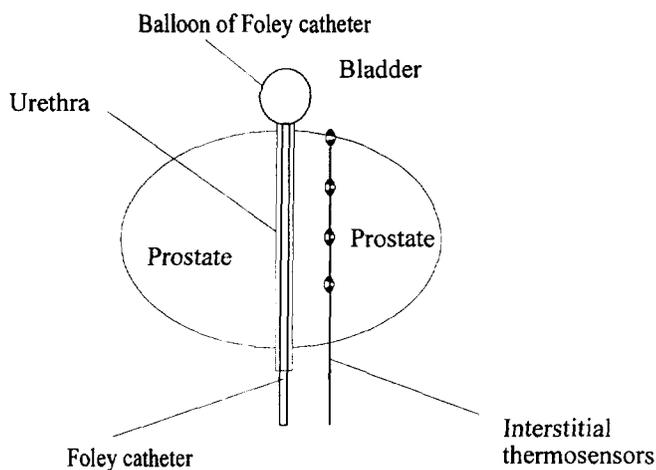
Prior to treatment, your doctor will have assessed your conditions and discussed the treatment options available to you, include the Urowave therapy.

On the day of your treatment, you will undress and put on a gown. You will lie down on an examining table.

Your doctor will give you a local anesthetic. A rectal thermometer measures your body temperature. The measured temperature becomes the standard for calibrating equipment.

A Foley catheter, through your urethra, ensures that your bladder is empty. Without urine inside, the bladder image in ultrasound is clear. An ultrasound probe in your rectum provides the first images.

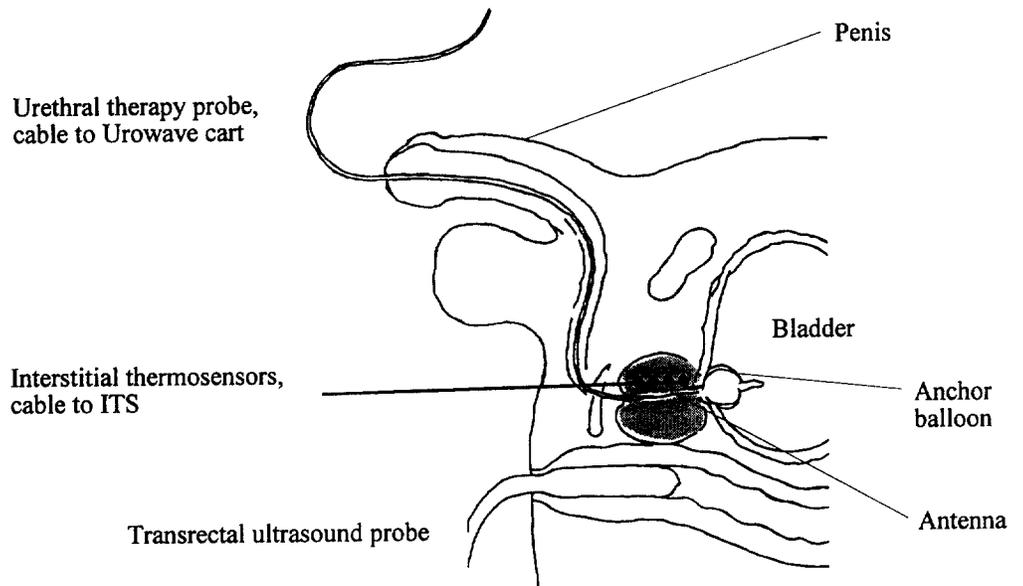
The doctor inserts the needle accessories through your perineum. Needle thermosensors go into your prostate. The figure shows their positions.



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The doctor will deflate the balloon of your Foley catheter and will remove your catheter.

Your doctor will insert the therapy probe. The anchor balloon inflates. The equipment is in position. (Remember, now you have reclined.)



Your doctor will check the final images and removes the ultrasound probe.

The thermosensor probe will go into your rectum. The staff will prepare to start thermotherapy.

The staff will remove all your jewelry.

Your doctor will ensure safe positions of all persons and equipment. Your doctor will tell you when thermotherapy can begin.

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What will I feel during Urowave therapy?

The antenna delivers heat into the prostate. Microwave power slowly increases to heat the prostate. Thermosensors monitor the temperatures in three of your organs:

- Prostate
- Urethra
- Rectum

You may feel a sensation of warmth or the urge to urinate.

Tell your doctor about any discomfort. Your doctor will take appropriate action.

The staff will continue with several safety checks about microwave energy in the treatment room.

After one hour of thermotherapy, you will be finished the treatment.

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What can I expect after treatment?

After the treatment, you will go home with a catheter in your urethra. The catheter keeps your bladder empty.

Dornier *MedTech* conducted a study of the Urowave. About half of all study patients reported side effects. Most reported minor inconvenience that ended within 4 days. You may notice the most common temporary effects:

- Bladder spasms
- Blood in your urine, or hematuria
- Urethral bleeding

During your follow-up visit, 2 to 4 days after treatment, your doctor will remove your catheter.

Tell your doctor if any side effects continue.

You should be able to resume normal activities.

Later, the prostate shrinks, relieving pressure. Lower pressure allows the bladder to empty more completely.

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What are the risks of this treatment?

Every medical treatment may have side effects, or adverse events. The same is true for Urowave therapy. You will want to know these risks before treatment.

The Urowave system was studied. The study reported adverse events. Discuss these adverse event with your urologist for details.

| Adverse Events | ACTIVE GROUP ¹ of 194 Patients | SHAM GROUP of 73 Patients |
|--------------------------------|--|--|
| | Number of Patients (Patient Incidence, %) | Number of Patients (Patient Incidence, %) |
| URINARY | | |
| Bladder Spasm | 42 (21.6) | 17 (23.3) |
| Hematuria | 51 (26.3) | 13 (17.8) |
| Urethral Bleeding | 40 (20.6) | 12 (16.4) |
| Dysuria | 42 (21.6) | 6 (8.2) |
| Urinary Retention ² | 29 (14.9) | 0 (0) |
| Urinary Incontinence | 6 (3.1) | 0 (0) |
| Burning In Penis | 3 (1.5) | 0 (0) |
| Urinary Frequency | 9 (4.6) | 0 (0) |
| Urinary Urgency | 12 (6.2) | 0 (0) |
| Catheter Not Draining | 2 (1.0) | 0 (0) |
| Bladder Distention | 1 (0.5) | 0 (0) |
| Urinary Tract Infection | 4 (2.1) | 0 (0) |
| Urethral Pain | 1 (0.5) | 0 (0) |
| Pelvic Pain | 1 (0.5) | 0 (0) |
| Mucous in Bladder | 1 (0.5) | 0 (0) |
| Urethral Necrosis | 1 (0.5) | 0 (0) |
| Urethral Stricture | 2 (1.0) | 0 (0) |
| Nocturia | 1 (0.5) | 0 (0) |
| Split Urinary Stream | 1 (0.5) | 1 (1.4) |
| Urination Impaired | 1 (0.5) | 0 (0) |
| Dribbling | 1 (0.5) | 0 (0) |
| RECTUM | | |
| Rectal Disorder | 1 (0.5) | 0 (0) |
| Rectal Bleeding | 1 (0.5) | 0 (0) |
| REPRODUCTIVE | | |
| Penis Pain | 12 (6.2) | 4 (5.5) |
| Hemospermia | 24 (12.4) | 0 (0) |
| Painful Ejaculation | 8 (4.1) | 1 (1.4) |
| Abnormal Ejaculation | 13 (6.7) | 0 (0) |

¹ Includes 47 Sham patients who had a crossover treatment at 6 months.

² All patients were discharged with a Foley catheter which was removed within 4 days of treatment. Therefore, urinary retention immediately post-treatment was 100%. Urinary retention following removal of the Foley catheter occurred as stated in the table. Temporary urinary retention is attributed to urethral edema and instrumentation.

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| | | |
|-------------------------------------|-----------|---------|
| Libido Decreased | 2 (1.0) | 0 (0) |
| Penoscrotal Ulceration ³ | 1 (0.5) | 0 (0) |
| Pain After Orgasm | 1 (0.5) | 0 (0) |
| Balanitis | 1 (0.5) | 0 (0) |
| Corporal Fibrosis ³ | 1 (0.5) | 0 (0) |
| Corporal Induration ³ | 1 (0.5) | 0 (0) |
| Erectile Dysfunction ³ | 1 (0.5) | 0 (0) |
| Prostatic Disorder | 1 (0.5) | 0 (0) |
| Prostatic Firmness | 1 (0.5) | 0 (0) |
| Pain in Prostate | 2 (1.0) | 0 (0) |
| Scrotal Inflammation | 1 (0.5) | 0 (0) |
| Swollen Scrotum | 1 (0.5) | 0 (0) |
| Scrotal Bruising | 1 (0.5) | 0 (0) |
| OTHER | | |
| Pain During Treatment | 23 (11.9) | 1 (1.4) |
| Hypertension | 2 (1.0) | 0 (0) |
| Bleeding From | | |
| Interstitial Needle Site | 2 (1.0) | 0 (0) |
| Syncope | 1 (0.5) | 0 (0) |
| Nausea And Vomiting | 1 (0.5) | 0 (0) |
| Dizziness | 2 (1.0) | 0 (0) |
| Apnea | 1 (0.5) | 0 (0) |
| Sweating | 2 (1.0) | 0 (0) |
| Flank Pain | 0 (0) | 1 (1.4) |
| Rash | 0 (0) | 1 (1.4) |
| Pain | 2 (1.0) | 0 (0) |
| Back Pain | 1 (0.5) | 0 (0) |

Note: Some patients experienced more than one (1) acute adverse event.

³ All events occurred in one patient.

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