



PMS

P450014

Memorandum

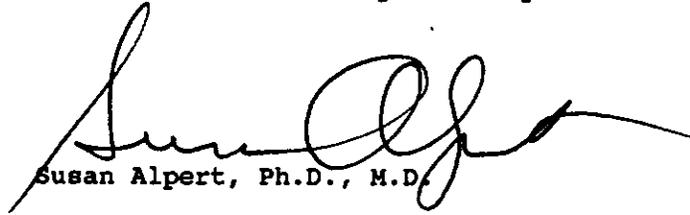
Date MAY - 3 1996  
From Director, Office of Device Evaluation (HFZ-400)  
Center for Devices and Radiological Health (CDRH)  
Subject Premarket Approval of EDAP Technomed Group (U.S.A.), Inc.'s  
Prostatron™ - ACTION  
To The Director, CDRH  
ORA \_\_\_\_\_

**ISSUE.** Publication of a notice announcing approval of the subject PMA.

**FACTS.** Tab A contains a FEDERAL REGISTER notice announcing:

- (1) a premarket approval order for the above referenced medical device (Tab B); and
- (2) the availability of a summary of safety and effectiveness data for the device (Tab C).

**RECOMMENDATION.** I recommend that the notice be signed and published.

  
Susan Alpert, Ph.D., M.D.

Attachments  
Tab A - Notice  
Tab B - Order  
Tab C - S & E Summary

**DECISION**

Approved \_\_\_\_\_ Disapproved \_\_\_\_\_ Date \_\_\_\_\_

Prepared by John H. Baxley, CDRH, HFZ-470, 02-21-96, 594-2194

DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

[DOCKET NO. \_\_\_\_\_]

EDAP TECHNOMED GROUP (U.S.A.), INC.; PREMARKET APPROVAL OF PROSTATRON™

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA) is announcing its approval of the application by the EDAP Technomed Group (U.S.A), Inc., Cambridge, MA, for premarket approval, under section 515 of the Federal Food, Drug, and Cosmetic Act (the act), of the Prostatron™. After reviewing the recommendation of the Gastroenterology and Urology Devices Advisory Panel, FDA's Center for Devices and Radiological Health (CDRH) notified the applicant, by letter on MAY - 3 1996, of the approval of the application.

DATE: Petitions for administrative review by (insert date 30 days after date of publication in the FEDERAL REGISTER).

ADDRESS: Written requests for copies of the summary of safety and effectiveness data and petitions for administrative review, to the Dockets Management Branch (HFA-305), Food and Drug Administration, Rm. 1-23, 12420 Parklawn Drive, Rockville, MD 20857.

FOR FURTHER INFORMATION CONTACT:

John H. Baxley

Center for Devices and Radiological Health (HFZ-470)

Food and Drug Administration

9200 Corporate Blvd.

Rockville, MD 20850

301-594-2194.

SUPPLEMENTARY INFORMATION: On April 17, 1995, the EDAP Technomed Group (U.S.A.), Inc., Cambridge, MA 02139, submitted to CDRH an application for premarket approval of the Prostatron™. The device is a transurethral microwave thermal therapy system and is indicated as a non-surgical treatment alternative to transurethral resection of the prostate (TURP) for the treatment of symptomatic benign prostatic hyperplasia (BPH). The Prostatron™ is indicated for patients with prostatic lengths of 35 to 50 mm. It is intended that the Prostatron™ deliver a complete thermal therapy treatment during a single treatment session.

On October 20, 1995, the Gastroenterology and Urology Devices Advisory Panel, an FDA advisory panel, reviewed and recommended approval of the application.

On MAY - 3 1996, CDRH approved the application by a letter to the applicant from the Director of the Office of Device Evaluation, CDRH.

A summary of the safety and effectiveness data on which CDRH based its approval is on file in the Dockets Management Branch (address above) and is available from that office upon written request. Requests should be identified with the name of the device and the docket number found in brackets in the heading of this document.

OPPORTUNITY FOR ADMINISTRATIVE REVIEW

Section 515(d)(3) of the act (21 U.S.C. 360e(d)(3)) authorizes any interested person to petition, under section 515(g) of the act (21 U.S.C. 360e(g)), for administrative review of CDRH's decision to approve this application. A petitioner may request either a formal hearing under part 12 (21 CFR part 12) of FDA's administrative practices and procedures regulations or a review of the application and CDRH's action by an independent advisory committee of experts. A petition is to be in the form of a petition for reconsideration under 10.33(b) (21 CFR 10.33(b)). A petitioner shall identify the form of review requested (hearing or independent advisory committee) and shall submit with the petition supporting data and information showing that there is a genuine and substantial issue of material fact for resolution through administrative review. After reviewing the petition, FDA will decide whether to grant or deny the petition and will publish a notice of its decision in the FEDERAL REGISTER. If FDA grants the petition, the notice will state the issue to be reviewed, the form of the review to be used, the persons who may participate in the review, the time and place where the review will occur, and other details.

Petitioners may, at any time on or before (insert date 30 days after date of publication in the FEDERAL REGISTER), file with the Dockets Management Branch (address above) two copies of each petition and supporting data and information, identified with the name of the device and the docket number found in brackets in the heading of this document. Received petitions may be seen in the office above between 9 a.m. and 4 p.m., Monday through Friday.

This notice is issued under the Federal Food, Drug, and Cosmetic Act (secs. 515(d), 520(h), (21 U.S.C. 360e(d), 360j(h)) and under authority delegated to the Commissioner of Food and Drugs (21 CFR 5.10) and redelegated to the Director, Center for Devices and Radiological Health (21 CFR 5.53).

Dated: \_\_\_\_\_

\_\_\_\_\_



Food and Drug Administration  
9200 Corporate Boulevard  
Rockville MD 20850

Mr. Eric Poincelet  
Chief Operating Officer  
EDAP Technomed Group (U.S.A.), Inc.  
179 Sidney Street  
Cambridge, Massachusetts 02139

MAY 3 1996

Re: P950014  
Prostatron™  
Filed: April 17, 1995  
Amended: August 18, September 20, 22, and 26,  
October 3 and 24, November 16, 1995; and  
January 17 and April 8, 1996

Dear Mr. Poincelet:

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 Prostatron™. 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). The Prostatron™ is indicated for patients with prostatic lengths of 35 to 50 mm. It is intended that the Prostatron™ deliver a complete thermal therapy treatment during a single treatment session. 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 the annual progress reports on the following postapproval study, which was recommended by the Gastroenterology and Urology Devices Advisory Panel during its October 20, 1995, meeting:

Your postapproval study should collect 5-year follow-up data to evaluate the long-term effects of Prostatron™ treatment on a minimum of 100 patients. This 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.

CDRH will publish a notice of its decision to approve your PMA in the FEDERAL REGISTER. The notice will state that a summary of the safety and effectiveness data upon which the approval is based is available to the public upon request. Within 30 days of publication of the notice of approval in the FEDERAL REGISTER, 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.

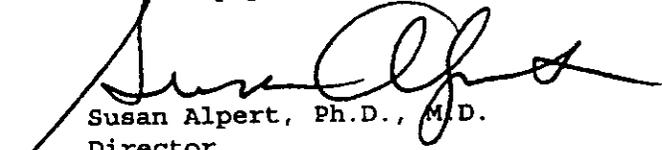
You are reminded that as soon as possible, and before commercial distribution of your device, that you must submit an amendment to this PMA submission with copies of all approved labeling in final printed form.

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 Mr. John Baxley at (301) 594-2194.

Sincerely yours,



Susan Alpert, Ph.D., M.D.  
Director  
Office of Device Evaluation  
Center for Devices and  
Radiological Health

Enclosure

## SUMMARY OF SAFETY AND EFFECTIVENESS DATA: PROSTATRON™

### I. GENERAL INFORMATION

DEVICE GENERIC NAME: Transurethral Microwave Thermal Therapy System

DEVICE TRADE NAME: Prostatron™

APPLICANT: EDAP Technomed Group (USA), Inc.  
179 Sidney Street  
Cambridge, Massachusetts 02139

PREMARKET APPROVAL APPLICATION (PMA) NUMBER: P950014

DATE OF NOTICE OF APPROVAL TO THE APPLICANT: May 3, 1996

### II. INDICATIONS FOR USE

The Prostatron™ is a non-surgical treatment alternative to transurethral resection of the prostate (TURP) for the treatment of symptomatic benign prostatic hyperplasia (BPH). The Prostatron™ is indicated for patients with prostatic lengths of 35 to 50 mm. It is intended that the Prostatron™ deliver a complete thermal therapy treatment during a single treatment session.

### III. DEVICE DESCRIPTION

The Prostatron™ is a computer-controlled device designed to deliver microwave energy to the prostate for the treatment of BPH. In this PMA, this therapy is referred to as transurethral microwave thermal therapy (TUMT) of the prostate. This device utilizes a transurethral microwave antenna, with simultaneous urethral cooling, to heat the prostate. This heating process is regulated through temperature feedback from one sensor mounted on the urethral catheter at the level of the prostate, and three sensors mounted on the surface of a rectal probe. A complete treatment consists of applying microwave energy at 1296 MHz (60 Watts maximum) to the prostate for 60 minutes. The device consists of: (1) a control module which is the operator's interface with the Prostatron™; (2) a treatment module which contains most of the major subassemblies of the Prostatron™, as well as the patient table; and (3) a treatment applicator (called the "Prostaprobe") which is a single use, disposable component of the Prostatron™ system consisting of a urethral catheter and a rectal probe. Although not supplied with the device, the Prostatron™ must be used with a legally marketed, free standing, transrectal ultrasound scanner.

The urethral catheter component of the Prostate probe is 25 Fr, has a distal latex balloon to position the catheter within the urethra, and incorporates the cooling circuit, the microwave antenna, and a fiber optic thermosensor. The microwave antenna consists of a coaxial cable, the active portion of which is positioned immediately proximal to the latex balloon. The rectal probe component of the Prostate probe consists of a plastic tube, upon which are mounted three thermosensors. The rectal thermosensors are positioned on the probe such that they are opposite the prostate.

By combining the effects of radiative heating and conductive cooling, the device targets the highest temperatures within the prostate at a depth of 5 to 10 mm, rather than at the urethral surface. Once the urethral and rectal probes are properly inserted, treatment begins according to an internal algorithm by delivering microwave power and coolant water simultaneously to the urethral applicator. The maximum urethral and rectal temperatures permitted by the system are 44.5°C and 42.5°C, respectively. After 60 minutes have elapsed from the start of the microwave power, the Prostate probe™ shuts off power to the microwave oscillator.

#### **IV. CONTRAINDICATIONS, WARNINGS, AND PRECAUTIONS**

The labeling for the Prostate probe™ contains the following contraindications, warnings, and precautions:

##### Contraindications

1. Peripheral arterial disease with intermittent claudication or Leriche's syndrome (i.e., claudication of the buttocks and perineum).
2. Clinical or histological evidence of prostatic cancer or bladder cancer.
3. Severe urethral stricture preventing easy catheterization.
4. Presence of a cardiac pacemaker, an implantable defibrillator, or a metallic implant in the region of the hip, pelvis, or femur.

##### Warnings

1. Studies have not been conducted on patients with evidence of latex sensitivity and therefore patients with this condition must be treated with caution.
2. In the Prostate probe™ clinical study, patients with a pre-treatment post-void residual urine of greater than 150 mLs and a prostate volume of greater than 40 mLs had a higher incidence of transient urinary retention after TUMT than other patients. The retention is likely to be due to a degree of detrusor failure in these men.

Prior to discharge, such patients should be carefully assessed to determine their risk of experiencing post-treatment retention. A reasonable period of catheterization may be prudent to avoid the occurrence of acute urinary retention post-discharge.

### Precautions

1. The safety and effectiveness of treatment with the Prostatron™ have not been established in patients with the following conditions:
  - Interest in the preservation of future fertility.
  - Disorders of coagulation.
  - Renal impairment.
  - Neurological disorders which might affect bladder function.
  - Post-void residual urine volumes greater than 350 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).
  
2. The use of the Prostatron™ must be prescribed and administered under the direct supervision of a qualified and trained physician, after appropriate urologic evaluation of the patient. The treating physician should be present at all times during the treatment, and the following additional warnings should be observed with respect to the patient's safety:
  - The treatment catheter must be cleaned and high-level disinfected prior to use according to the procedures outlined in the user's manual.
  - Do not use a treatment catheter if it appears to be damaged.
  - Ensure that the treatment catheter is correctly seated within its connection plate on the Prostatron™. Never attempt to turn microwave power on without the treatment catheter connected.
  - The Prostatprobe™ must not, under any circumstances, be connected to the treatment module before the treatment applicator has been carefully passed into the patient's urethra. The correct positioning of the treatment applicator must always be checked by ultrasound imaging prior to commencing treatment.

- The treatment must not be commenced until the rectal probe is introduced into the patient's rectum after the removal of the ultrasound probe. The probe's orientation must be verified, and its position secured using adhesive tape.
- Do not start microwave emission until all jewelry or metallic elements on the patient's clothes are removed.
- The emission of microwaves must be switched off during treatment applicator positioning or premature removal to avoid stray microwave radiation, directed either towards the patient's eyes or testes, or the operator.
- Operators must remain at a distance of at least 15 cm from the patient during microwave exposure in order to avoid excessive exposure to electromagnetic fields.
- Substantial changes in prostate specific antigen (PSA) levels--up to 470 percent after 1 week--may be seen in the first few weeks after TUMT. The use of PSA testing during this period will be unreliable. Physicians are cautioned to measure the serum PSA level before treatment for future comparisons. PSA levels should return to baseline by 6 months following TUMT and may once again be used as a diagnostic test.
- It is recommended that TUMT-treated patients be followed on an annual basis to assess for any prostatic changes, since treatment with the Prostatron™ does not result in removal or total destruction of the prostate.
- The electrical equipment inside the Prostatron™ uses voltages which are capable of causing serious injury or death from electric shock. To avoid this hazard, operators must never remove any of the Prostatron's™ cabinet covers.
- To minimize the risk of electromagnetic interference between the Prostatron™ and any nearby electrical equipment, any electrical devices should be placed at least 3.25 m (10.6 ft) from the Prostatron's™ microwave antenna while the Prostatron™ is in operation. Since some medical equipment may not meet the 3 V/m standard and could potentially be affected at distances greater than 3.25 m (10.6 ft), periodic monitoring of the equipment for erratic operation is recommended. Similarly, since the emissions of some medical equipment may be high enough to affect the operation of the Prostatron™ at distances greater than 3.25 m (10.6 ft), periodic monitoring of the Prostatron™ for erratic

operation is also recommended. If it is necessary to operate an electrical device closer than 3.25 m (10.6 ft) while the Prostatron™ is in operation, the device and the Prostatron™ should be completely tested for proper simultaneous operation prior to its clinical use.

Since microwave energy can travel through walls, ceilings, and floors to affect other devices, it is important to understand that the 3.25 m safety distance applies not only to the treatment room, but also to all adjacent rooms in the building, including the rooms above and below the treatment room.

- Use of the Prostatron™ results in the deposition of microwave energy within the patient's prostate and in 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.

## **V. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH**

A total of 375 patients were evaluated for adverse events in the clinical investigation of the Prostatron™. The studies that were conducted recorded the following adverse events: (1) hematuria (52.0%), (2) urinary retention requiring catheterization (32.0%), (3) urethral bleeding (13.3%), (4) urinary/rectal discomfort (12.0%), (5) urinary tract infection (8.5%), (6) minor ejaculatory disturbances (6.7%), (7) inflammation/pain in the reproductive tract (6.1%), (8) urethral discharge (5.3%), (9) abnormalities by proctoscopy (2.7%), (10) urethral trauma (2.4%), (11) elevated blood pressure (2.1%), (12) discomfort during treatment (2.1%), and (13) decreased sexual function and impotence (1.9%).

## **VI. ALTERNATE PRACTICES OR PROCEDURES**

The treatment of BPH has been based predominantly on 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 (AHCPR; 1994): watchful waiting, alpha blocker therapy, finasteride therapy, balloon dilation, transurethral incision of the prostate, transurethral resection of the prostate, and open prostatectomy.

## VII. MARKETING HISTORY

Approximately 100 Prostatron™ devices have been marketed in 27 countries since June, 1990. The Prostatron™ has not been withdrawn from marketing for any reason relating to its safety or effectiveness.

## VIII. SUMMARY OF PRECLINICAL STUDIES

### A. Biocompatibility Testing

Biocompatibility tests were performed using the mucosal-contacting components of the Prostaprobe, and include: sensitization assay in guinea pigs, mucosal irritation in rabbits, cytotoxicity (MEM elution), acute systemic toxicity in mice, intracutaneous toxicity in rabbits, hemolysis, muscle implantation in rabbits (7 days), mutagenicity, and protein Lowry assay. Furthermore, dermal irritation testing in rabbits was performed for the components that are skin-contacting. With the exception of the cytotoxicity and acute systemic toxicity (cotton seed oil extract only) tests that were conducted on the Prostaprobe's latex balloon, the results submitted showed no significant toxicity. Furthermore, since latex is frequently used as a positive control in cytotoxicity tests and is soluble in cotton seed oil, these results were not unexpected. To address this issue, a warning is included in the labeling of the Prostatron™ which states that the latex may cause a reaction in latex-sensitive individuals.

### B. Laboratory Studies

#### Electromagnetic Compatibility (EMC) Testing

Testing was conducted to assess the potential of the device causing electromagnetic interference (EMI) in other devices, or being susceptible to such interference. This testing demonstrated that the Prostatron™ meets the EMC standards of IEC 601-1-2.

#### Safety Levels with Respect to Operator Exposure

Testing was conducted to characterize the strength of the electromagnetic field being emitted from the Prostatron™ during operation. These measurements indicated that it is safe for medical personnel to be  $\geq 15$  cm from the emitting portion of the treatment applicator, based on the recommendations from the American National Standards Institute (ANSI) which lists a human exposure limit of  $4.32 \text{ mW/cm}^2$  for 1296 MHz.

#### Phantom Studies

In vitro phantom studies were performed to characterize the microwave antenna applicator with regard to (i) the spatial distribution of the specific absorption rate (SAR),

and (ii) the spatial distribution of the microwave-induced temperature patterns. The phantom material consisted of a gel which has electromagnetic and thermal properties that are similar to those of human tissue. Each of these experiments was conducted using arrays of fiber optic thermosensors spaced known distances from the catheter's tip. The results measured a 50% iso-SAR volume which is 38 mm in the axial direction and 4 mm in the radial direction, with the "hot spot" located 1 mm from the center of the antenna's active region. The temperature pattern measured in this set-up demonstrated the following: (i) the cooling system is able to lower temperature at the surface of the catheter, allowing the maximum temperature to be achieved several millimeters radial from the catheter; (ii) past the effects of cooling, temperature decreases with radial distance; and (iii) the location of the maximum temperature, as well as the volume of significant heating, is symmetrical about the catheter's axis.

### C. Animal Studies

Four animal studies were conducted to evaluate the effects of treatment with the Prostatron™ upon the canine prostate from December 1988 to April 1991. Each of these studies were conducted by Marion Devonec, M.D., in Lyon, France.

The first study examined the safety of several early Prostatron™ prototypes (each emitting 1296 MHz) using various treatment parameters in nine dogs. The primary conclusions drawn from this study were: (1) it is possible to achieve therapeutic temperatures within the dog's prostate using transurethral microwave heating while preserving the rectum and surrounding extraprostatic tissues; (2) if urethral cooling is not used, tissue swelling and necrosis are produced adjacent to the catheter; (3) cooling of the catheter produces symmetrical, therapeutic heating beyond the periurethral zone, while preserving the urethral tissue to a depth of several millimeters; (4) the maximum temperature reached at any point within the prostate is dependent upon the degree of tissue perfusion, the distance from the antenna, the power level, the duration of power, and prostate size; (5) the histologic data support using 42.5°C as the rectal regulating temperature; and (6) where therapeutic temperatures (i.e., 45°C) were exceeded, thermal injury to the prostatic tissue was demonstrated at 3 days and a cavity was seen after 7 days.

The second study was performed to compare the effects of 1296 MHz heating with 915 MHz heating using two prototype systems and to evaluate which frequency was best suited for heating the prostate while preserving the rectum. This study involved 17 dogs. Although the variation of the treatment parameters prohibited an independent assessment of the optimum value of each, these results enabled the sponsor to reach the following conclusion: the histology findings demonstrated greater rectal necrosis with the use of 915 MHz as compared to 1296 MHz. (However, since the actual conditions of treatment varied from dog to dog, it is unclear if the results can be attributed to frequency alone.) Based on this conclusion, coupled with the theoretical

expectations that 1296 MHz (1) provides a greater margin of safety (i.e., heating is better confined), and (2) activates the rectal temperature thermosensors less frequently (thereby increasing the average power delivered to the prostate), an emissions frequency of 1296 MHz was chosen for the Prostatron™.

The third animal study was performed using the final Prostatron™ design to obtain thermal maps of the heated volume, and for verification that the device delivers therapeutic temperatures to the prostate while maintaining safe temperatures within the surrounding tissues. These thermal maps were obtained in six dogs using transperineal, interstitial thermosensors. The results of this study supported the following conclusions: (1) despite the dog being the best animal model available, there are several significant differences between the dog and the human anatomy that must be considered when evaluating such data (e.g., the dog has a smaller prostate, a shorter urethra-to-rectum distance, and a different cellular composition); (2) the hottest area along the catheter surface is between 0 and 10 mm distal to the antenna's shielding junction, which is within the prostate when the balloon is seated at the bladder neck; (3) the volume of therapeutic heating is spherical with a radius of 4 to 13 mm; (4) cooling of the urethral wall preserves the urethra's integrity; and (5) the rectal wall can withstand temperatures up to 42.5°C without damage.

The fourth study was conducted to justify the safety of using 42.5°C as the rectal set-point temperature. To investigate this hypothesis, 10 dogs were treated with the final Prostatron™ design. This study demonstrated that the canine rectal wall can withstand temperatures up to 47°C for up to 46 minutes without histologic damage, while rectal temperatures in excess of 47°C were associated with tissue necrosis. Based on these data, the device's rectal limit of 42.5°C was justified for use in human clinical trials.

## **IX. SUMMARY OF CLINICAL INVESTIGATIONS**

### **A. Pre-IDE Clinical Studies**

Prior to initiation of large-scale clinical trials, the sponsor conducted three pre-IDE clinical studies. These studies were performed in Europe from October 1989 to December 1990. These studies were conducted to (1) optimize the device design and treatment algorithm, (2) to support the hypothesis that target temperatures are limited to the prostate gland, and (3) to demonstrate sufficient improvements in objective and subjective criteria to justify further study in a controlled clinical trial.

## B. IDE Clinical Investigations

### Overview of Studies

#### 1. Study Design

Clinical investigations were conducted to determine the safety and effectiveness of the Prostatron™ in the treatment of BPH. Overall, four separate clinical studies were conducted at a total of seven institutions: five sites in the United States; one site in the United Kingdom; and one site in Sweden. These sites enrolled a total of 455 patients, of which 444 actually received their assigned treatment (i.e., either treatment with the Prostatron™ (i.e., TUMT) or control therapy). Of these 444 patients, 375 actually received TUMT therapy. These data were collected between December 4, 1990 and June 30, 1993.

The design of the clinical investigation of the Prostatron™ is consistent with the recommendations made in the FDA guidance document entitled "Draft Guidance for the Clinical Investigation of Hyperthermia Devices Used for the Treatment of Benign Prostatic Hyperplasia." However, since these clinical trials were underway prior to the first release of this guidance document, there are some minor differences.

FDA granted expedited review status to the premarket approval application. The decision to expedite the review of the PMA was based on the belief that the Prostatron™ represented a breakthrough device for the treatment of BPH, when compared to existing treatment options. Specifically, this device appeared to offer a clinically significant level of symptomatic relief without the morbidity that is commonly associated with traditional surgical procedures.

Table 1 summarizes each investigational site, as well as the distribution of patients enrolled and treated under each of the four clinical study protocols.

TABLE 1. Clinical Sites

|  | Patients Enrolled/Treated by Study Component |                 |                  |                    | Total   |
|--|--|-----------------|------------------|--------------------|---------|
|  | General Study                                | Sham/TUMT Study | TUMT/TUR-P Study | Interstitial Study |         |
| Mayo Clinic Rochester, MN                        | 30/30  | 55/55           | 0                | 0                  | 85/85   |
| Rush Presbyterian Hospital Chicago, IL           | 55/55  | 0               | 0                | 0                  | 55/55   |
| Mayo Clinic Jacksonville, FL                     | 30/30  | 61/60           | 0                | 0                  | 91/90   |
| Rocky Mountain Kidney Stone Center Denver, CO    | 48/48  | 0               | 0                | 0                  | 48/48   |
| Georgetown University Hospital Washington, D.C.  | 54/53  | 0               | 0                | 0                  | 54/53   |
| Charing Cross Hospital London, United Kingdom    | 0  | 0               | 0                | 44/43              | 44/43   |
| University of Goteberg Hospital Goteberg, Sweden | 0  | 0               | 78/70            | 0                  | 78/70   |
| Patients Enrolled/Treatment with TUMT            | 217/216                                      | 77/78           | 39/38            | 44/43              | 377/375 |
| Total Patients Enrolled/Treated                  | 217/216                                      | 116/115         | 78/70            | 44/43              | 455/444 |

In all four studies, the primary endpoints for effectiveness were improvements in the Madsen Symptom Score (MSS; a 0-27 point scale rating the typical urinary symptoms associated with BPH) and in peak urine flow rates (PFRs). Other effectiveness endpoints assessed during the studies were improvements in quality of life measures; changes in post-void residual urine volume (PVR), prostate specific antigen (PSA) levels, prostate volume, and global assessments of treatment affects by the patients and physicians.

These four studies were all performed using the same general protocol. However, each was designed with different goals to address specific issues regarding the safety and effectiveness of TUMT with the Prostatron™, as follows:

### Sham/TUMT Study

The Sham Study was designed as a prospective randomized double-blind study to compare the therapeutic effects and adverse events of the Prostatron™ to those of instrumentation alone. Patients were randomized in a 2:1 ratio to receive either an actual Prostatron™ treatment or a simulated, sham treatment. Patients were unblinded after their 3-month evaluation, after which sham patients were given an opportunity to undergo TUMT. Patient improvement and morbidity were compared between the two arms after 3 months of follow-up. This study was performed at the Mayo Clinics in Rochester, MN, and Jacksonville, FL, where a total of 116 patients were enrolled.

### General Study

The General Study was a multi-center, uncontrolled study designed to assess the therapeutic benefit of TUMT in a larger population than the Sham/TUMT Study, to evaluate the durability of the results over a 12-month follow-up period; and to assess the long-term (i.e., 12 months) safety of the device. The study was conducted at five U.S. investigational sites and enrolled 217 patients.

### TUMT/TURP Study

The TUMT/TURP Study was a randomized study where the principal objective was to compare the overall morbidity of patients treated with the Prostatron™ to patients treated with TURP. A total of 78 patients were randomly assigned on a 1:1 basis to receive either TUMT or TURP for their BPH. Symptom score and uroflow improvements achieved by these two modalities, as well as the morbidity rates associated with each of these two treatments, were compared after 12 months of follow-up. This study was conducted in Sweden.

### Interstitial Thermometry Study

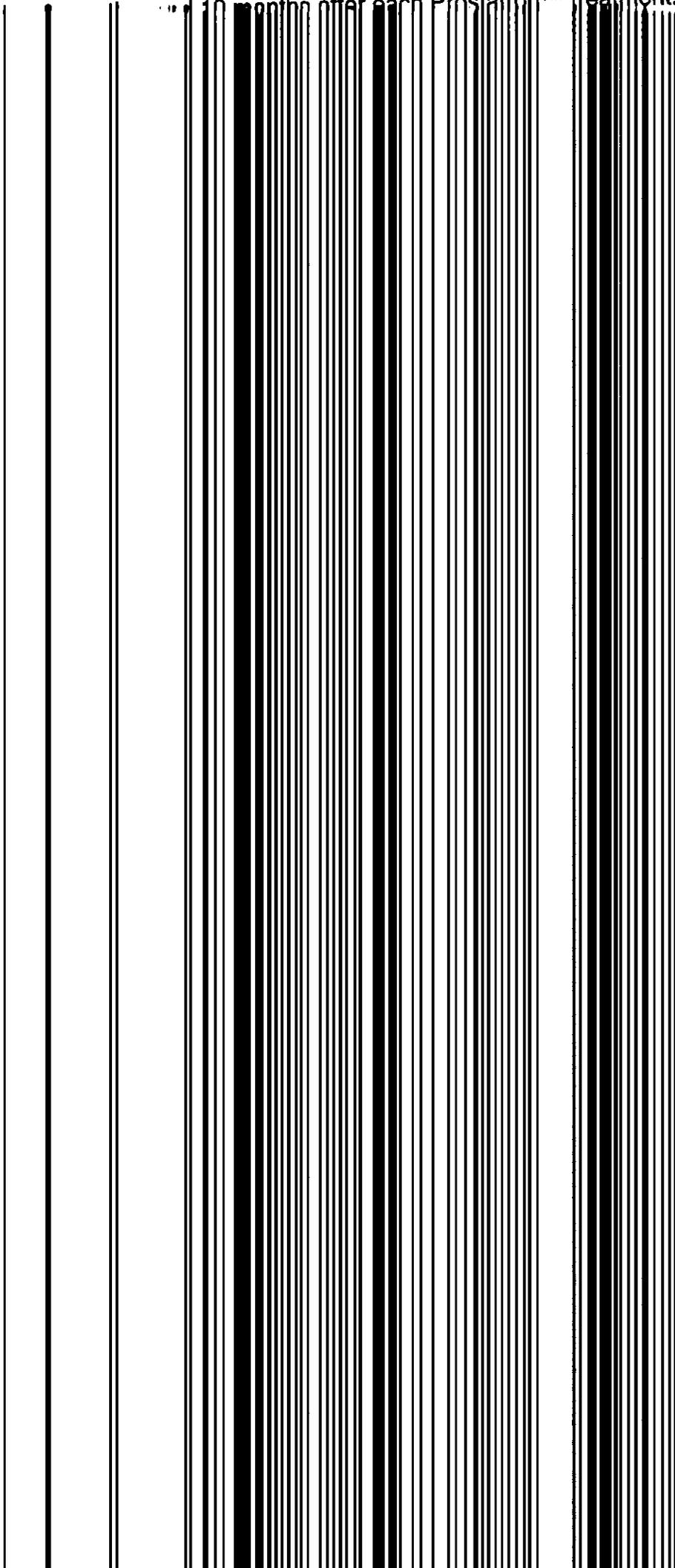
The Interstitial Thermometry Study was performed to evaluate the temperature distribution achieved during thermotherapy, and to examine the association between the intraprostatic temperatures achieved using the Prostatron™ treatment parameters and patient improvement. Intraprostatic temperatures during TUMT were measured in 43 patients using thermosensors inserted into the prostate. The primary endpoint for effectiveness was the evaluation of peak urine flow rate and the Madsen Symptom Score at 3 months post-treatment, stratified by the recorded intraprostatic temperatures. This study was performed in the United Kingdom.

2. Patient Inclusion and Exclusion Criteria

The inclusion and exclusion criteria were comprehensive, well-defined, and consistent with the draft FDA guidance document entitled "Draft Guidance for the Clinical Investigation of Hyperthermia Devices Used for the Treatment of Benign Prostatic Hyperplasia."

3. Follow-up Schedule/Methodology

The protocol included pre-treatment testing and follow-up visits at 1 week, 6 weeks, 10 months after each Prostatron™ treatment. Pre-treatment



the retreated patient cohort is largely self-selected, they were analyzed for effectiveness separately from those who received only a single treatment. Safety data, however, included adverse events that were reported after all treatments.

## Sham/TUMT Study

### 1. Introduction

The Sham/TUMT Study was a randomized study to compare the safety and effectiveness of TUMT treatment with the Prostatron™ to that of sham TUMT treatment (i.e., a simulated treatment without microwave delivery). This study was designed to assess the differences in the effects of microwave heating of the prostate from those due to instrumentation alone. This study was conducted at two of the U.S. investigational sites--Mayo Clinic, Rochester, MN, and Mayo Clinic, Jacksonville, FL.

Patients were randomized 2:1 between sham and TUMT. Patients and evaluating physicians were blinded to treatment group assignment. (Device operators, however, could not be blinded.) After the 3-month evaluation the treatment groups were unblinded, at which time sham patients who still met the study's entry criteria were offered an actual treatment. Although investigators continued to follow patients after the 3-month exam, the effectiveness evaluation of this study is limited to the 3-month follow-up results. The evaluation of complications, however, included those that occurred at any time during the study. The 3-month evaluation period used in this investigation is consistent with several placebo-controlled BPH studies reported in the literature.

### 2. Study Population

In this study, 116 males with BPH were enrolled and randomized, of which 115 received treatment--one patient (randomized to sham) had prior rectal surgery, and, therefore, did not meet the study's entry criteria. Of these 115 subjects, 78 were in the TUMT group and 37 were in the sham group. Enrollment was evenly divided among the two sites. Patient mean age was 66.9 years in both cohorts.

Two patients (both in the sham group) were treated despite being deviations from the protocol. One of these patients had only one baseline urine flow rate, rather than two as required by the protocol. The other sham patient was determined to have intentionally produced low flow rates to meet the enrollment; this patient was excluded from the analysis of device effectiveness due to potential bias.

By the date of database closure, the majority of patients in this study completed their 3-month follow-up according to the protocol (i.e., 75/78 TUMT patients, and 37/37 sham patients). Of the three subjects who were not available for the 3-month follow-up, two

TUMT patients missed their visits (but returned for later evaluations), and one TUMT patient discontinued the study. Furthermore, two sham patients were excluded from the effectiveness analysis--one due to inaccurate baseline flow rates and one due to the temporary use of medication for the treatment of BPH. As a result, effectiveness data are available for 75/78 TUMT patients and 35/37 sham patients. The mean times to the 3-month exam for these two cohorts were 95.5 days (TUMT) and 89.9 days (sham).

### 3. Baseline Characteristics

The 115 treated patients had the following baseline characteristics: mean duration of BPH symptoms of 47.9 months in the TUMT group and 47.6 months in the sham group; mean PFR of 7.3 mL/s in the TUMT group and 7.4 mL/s in the sham group; mean MSS of 13.9 in the TUMT group and 14.9 in the sham group; and mean prostate volume of 38 cm<sup>3</sup> in the TUMT group and 37 cm<sup>3</sup> in the sham group. Based on these comparisons, it appears that these two randomized arms were well-matched. Although statistically significant differences between the two sites were observed in prostate volume and baseline post-void residual urine volume, these differences were not clinically significant.

### 4. Treatment Parameters

Treatment in the TUMT group was performed according to the Prostatron™ algorithm. In 2/78 treatments, the procedure was interrupted prior to the completion of 60 minutes of heating; these two treatments were successfully continued later for a total of 80 treatment sessions. None of the 37 sham treatment sessions were interrupted. During all treatments, the Prostatron™ safety features functioned as intended.

The mean maximum urethral and rectal temperatures obtained during the 80 TUMT treatment sessions were 44.3°C and 42.5°C, respectively. The average maximum power delivered during these treatments was 46.1 watts, and the mean total energy delivered to the prostate was 97.8 kJ. Although sizeable (but not statistically significant) differences were noted between the total microwave energies delivered between these two sites (i.e., 89.5 versus 105.7 kJ), all comparisons between TUMT and sham groups included site effects in the statistical model (i.e., ANCOVA or ANOVA) for completeness.

Other than topical Lidocaine, the only anesthesia used during any of the treatment sessions was IV sedation, which was used in 9/80 (11%) of TUMT treatments (no anesthesia was administered to any of the sham patients). All treatments were administered on an outpatient basis.

In order to assess the success of patient blinding, all subjects were asked at their 1-week exam what treatment they believed they received. The results of this survey indicate that approximately half of the subjects in each study arm guessed correctly (i.e., 51% TUMT and 44% sham). The others were either uncertain, gave no response, or believed that they received the opposite treatment.

## 5. Effectiveness Results

The evaluation of effectiveness of treatment with the Prostatron™ was primarily based upon improvements in symptomatology and PFR, as compared between the two treatment arms, at 3 months. Other effectiveness parameters that were measured were quality of life, PVR, prostate volume, PSA levels, and global patient and physician opinions.

Table 2 presents the changes in symptomatology and quality of life recorded among the two treatment groups at 3 months. The overall Madsen Symptom Score (MSS) decreased from 13.9 to 6.3 (55% improvement) in the TUMT cohort, and from 14.9 to 10.8 (28% improvement) in the sham cohort. This difference between the two groups was statistically significant ( $p < 0.0001$ ). In the TUMT group, 75% of subjects had MSS improvements of  $\geq 30\%$  and 53% had improvements of  $\geq 8$  points. In the sham group, the corresponding proportions are 46% and 26%, respectively. These differences were statistically significant ( $p < 0.01$ ).

Similarly, the TUMT patients demonstrated significantly greater improvement ( $p < 0.01$ ) in the obstructive and irritative components of the MSS as compared to those in the sham group. Furthermore, patient reports of nocturia decreased more among TUMT patients than sham patients ( $p < 0.05$ ).

The mean changes in each of the five quality of life scales only indicate differences between the two groups with respect to "Perception of Urinary Difficulty" and "Activities of Daily Living," both of which were significantly improved among the TUMT subjects ( $p < 0.01$ ). This information also indicates that neither treatment group experienced a decrease in the "Sexual Function" scale.

Table 2. Symptomatology Results at 3 Months Post-Treatment for TUMT and Sham Groups

|                                    | TUMT GROUP | SHAM GROUP |
|------------------------------------|------------|------------|
| <b>MADSEN SYMPTOM SCORE</b>        |            |            |
| Overall Score                      | -55%       | -28%       |
| Obstructive Components             | -61%       | -30%       |
| Irritative Components              | -41%       | -21%       |
| Nocturia                           | -43%       | -27%       |
| % Improved $\geq 30\%$             | 75%        | 46%        |
| % Improved $\geq 8$ points         | 53%        | 26%        |
| <b>QUALITY OF LIFE IMPROVEMENT</b> |            |            |
| Perception of Urinary Difficulties | 79%        | 58%        |
| Sexual Function                    | 12%        | 11%        |
| Activities of Daily Living         | 34%        | 15%        |
| General Well Being                 | 7%         | 2.3%       |
| Social Activities                  | -2.7%      | 0.6%       |

The changes in PFR and PVR observed between baseline and 3 months for each treatment arm are summarized in table 3. In the TUMT group, PFR increased from 7.2 mL/s to 11.5 mL/s (58%). In the sham group, however, PFR increased from 7.4 mL/s to 9.4 mL/s (27%). This difference was statistically significant ( $p < 0.01$ ). Sixty-six percent of the TUMT patients had increases in PFR of  $\geq 30\%$  from baseline, and 54% experienced increases of  $\geq 3$  mL/s. In the sham group, 53% of patients had increases in their PFR of  $\geq 30\%$  and 35% had increases of  $\geq 3$  mL/s. These differences were not statistically significant. As seen in table 3, however, PVR did not change significantly in either of the two treatment arms.

Table 3. Change in Peak Flow Rate and Post-Void Residual Urine Volume at 3 Months Post-treatment for TUMT and Sham Groups

|                          | TUMT GROUP | SHAM GROUP |
|--------------------------|------------|------------|
| Peak Flow Rate           | 58%        | 27%        |
| % Improved $\geq 30\%$   | 66%        | 53%        |
| % Improved $\geq 3$ mL/s | 54%        | 35%        |
| PVR By Catheter          | 3.2%       | 3.7%       |
| PVR By Ultrasound        | -1.3%      | 21%        |

Prostate volume was measured by transrectal ultrasound at baseline and at 3 months in 72 TUMT patients and 35 sham patients. Prior to treatment, prostate volume averaged 38 cm<sup>3</sup> in the TUMT group and 37 cm<sup>3</sup> in the sham group. At the 3-month follow-up exam, the mean prostate volume was 39 cm<sup>3</sup> for both cohorts, indicating that TUMT did not significantly change prostate volume as compared to sham.

PSA was evaluated to determine if there was a differential effect on this diagnostic parameter due to microwave heating of the prostate as compared to instrumentation alone. This blood chemistry was measured in 72 TUMT patients and 32 sham patients at baseline and at the 1-week follow-up evaluation. In addition, PSA levels were available on 56 of the TUMT patients at 6 months post-treatment. The results that were obtained demonstrated that the 1-week PSA levels were 470% greater than baseline in the TUMT patients, while only 28% greater than baseline in the sham group. This difference between these two cohorts was highly statistically significant ( $p < 0.0001$ ). At 6 months follow-up, however, the average PSA levels in the 56 TUMT patients had decreased to baseline levels, indicating that the change in PSA is transitory.

Prior to unblinding, patients and physicians were asked whether they thought the treatment received had improved the patient's condition. Responses were categorized as yes (a lot, some, or a little), no, or uncertain. For the TUMT cohort, 80% of patients and 84% physicians reported a positive change in the patient's condition. Conversely, in the sham group, 30% of patients and 35% of physicians reported a positive change. The differences between the TUMT and the sham groups were statistically significant for both the patient and physician responses ( $p < 0.0001$ ).

## 6. Safety Results

The evaluation of the safety of the Prostatron™ was primarily based upon the rate of adverse events reported by the patient or found during follow-up. Additionally, safety was assessed through the following methods: proctoscopy/anoscopy evaluations, cystoscopy evaluations, laboratory measurements, and questions regarding the incidences of sexual dysfunction and incontinence.

Table 4 summarizes the adverse events which were determined to be related (or possibly related) to treatment for the TUMT and sham groups prior to unblinding. These adverse events were reported in two categories--those events that occurred during or immediately following treatment, and those events that occurred at any follow-up exam until 3 months. Some patients experienced more than one adverse event. Other than the one reaction to medication during treatment (this patient recovered without difficulty), none of the adverse events were considered to be serious in either group. Furthermore, most of the complications that were reported can be attributed to the instrumentation associated with treatment alone. Few complications occurred after the 3-month follow-up exam, none of which were judged to be serious.

Table 4. Adverse Events Reported During Sham/TUMT Study Prior to Unblinding Which are Related to, or Possibly Related to, Treatment

| Event  | # Patients (%)  |                 |
|--|-----------------|-----------------|
|  | TUMT            | Sham            |
| <b>EVENTS DURING TREATMENT OR IMMEDIATE POST-TREATMENT</b> |                 |                 |
| Urethral Trauma Due to Instrumentation                     | 3 (3.8%)        | 0 (0%)          |
| Elevated BP During Treatment                               | 1 (1.3%)        | 1 (2.7%)        |
| Serious Reaction to Anesthesia                             | 1 (1.3%)        | 0 (0%)          |
| <b>Total Patients with Adverse Events</b>                  | <b>3 (3.8%)</b> | <b>1 (2.7%)</b> |
| <b>FINDINGS AT DISCHARGE/FOLLOW-UP</b>                     |                 |                 |
| <b>Urinary Tract Findings</b>                              |                 |                 |
| Hematuria  | 54 (69%)        | 19 (51%)        |
| Urinary Retention  | 20 (26%)        | 0 (0%)          |
| Urethral Bleeding  | 16 (21%)        | 5 (14%)         |
| Urinary Discomfort w/o Infection                           | 6 (8%)          | 4 (11%)         |
| Complications of Retention/Cath.                           | 3 (4%)          | 0 (0%)          |
| Urethral Discharge   | 2 (2.6%)        | 0 (0%)          |
| Urinary Tract Infection                                    | 1 (1%)          | 0 (0%)          |
| Transient Incontinence                                     | 1 (1%)          | 0 (0%)          |
| Abnormalities Identified by Cysto.                         | 1 (1%)          | 0 (0%)          |
| <b>Reproductive Tract Findings</b>                         |                 |                 |
| Inflammation/pain  | 3 (3.8%)        | 0 (0%)          |
| Ejaculatory Changes  | 3 (3.8%)        | 0 (0%)          |
| Decrease in Sexual Functioning                             | 2 (2.6%)        | 0 (0%)          |
| <b>Rectal Findings</b>                                     |                 |                 |
| Rectal Discomfort  | 2 (2.6%)        | 4 (11%)         |
| Hemorrhoid Inflammation                                    | 1 (1.3%)        | 0 (0%)          |
| Abnormalities by Proctoscopy                               | 1 (1.3%)        | 0 (0%)          |
| <b>Other Findings</b>                                      |                 |                 |
| Syncope/Lightheadedness                                    | 2 (2.6%)        | 0 (0%)          |
| Fatigue/Lethargy   | 1 (1.3%)        | 0 (0%)          |
| Fever  | 1 (1.3%)        | 0 (0%)          |
| Nausea/Vomiting  | 1 (1.3%)        | 0 (0%)          |
| Diarrhea   | 1 (1.3%)        | 0 (0%)          |
| General Stomach Discomfort                                 | 1 (1.3%)        | 0 (0%)          |
| Flank Pain   | 1 (1.3%)        | 1 (2.7%)        |
| <b>Total Patients Reporting Adverse Events</b>             | <b>68 (88%)</b> | <b>22 (60%)</b> |

Analysis of measurements of hemoglobin, hematocrit, CBC, platelets, creatinine, and BUN indicated no significant differences between the two groups at any of the follow-up exams.

## General Study

### 1. Introduction

The General Study was conducted to establish the overall safety and effectiveness rates of TUMT treatment with the Prostatron™. This study was designed (i) to demonstrate safety and effectiveness in a large, multicenter population, and (ii) to demonstrate the durability of results over a period of 12 months. This study was conducted at five U.S. investigational sites--Mayo Clinic, Rochester, MN; Mayo Clinic, Jacksonville, FL; the Rush Presbyterian Hospital, Chicago, IL; the Rocky Mountain Kidney Stone Center, Denver, CO; and Georgetown University Hospital, Washington, D.C.

### 2. Study Population

In this study, 217 males with BPH were enrolled, of which 216 received treatment--one patient voluntarily withdrew prior to treatment. These 216 patients had a mean age of 63.5 years, which ranged from 46 to 83. As summarized in table 1, the number of patients treated at each site ranged from 30 at each of the Mayo Clinics to 53 at Georgetown University Hospital.

Twenty-one patients were treated despite being deviations from the protocol's eligibility criteria. However, none of these deviations was believed to justify excluding these patients from the analyses of device safety and effectiveness.

By the date of database closure, the majority of patients in this study completed their 12-month follow-up according to the protocol. Overall, 181/216 patients were included in the effectiveness analysis. This number consists of 149/181 who had both baseline and 12-month follow-up data, and 32/181 who were classified as treatment failures (i.e., subjects who had retreatment, had an alternative BPH treatment, or exited the study because of no improvement). The remaining 35/216 patients either exited the study for medical reasons or were lost-to-follow-up. The mean times to the 12-month exam for this cohort was 372.1 days.

One of the patients discontinued because of death, which was attributed to circumstances unrelated to the Prostatron™ treatment procedure. Specifically, this patient died 10 months post-treatment of complications of AIDS.

### 3. Baseline Characteristics

The 216 treated patients had the following baseline characteristics: mean duration of BPH symptoms of 48.5 months; mean PFR of 7.9 mL/s; mean MSS of 14.0; mean PVR of 129 mL; and mean prostate volume of 38.6 cm<sup>3</sup>. Although statistically significant differences among the five sites were observed in age, mean MSS, mean PVR, prostate volume, these differences were not considered clinically significant.

### 4. Treatment Parameters

Treatment in the TUMT group was performed according to the Prostatron™ algorithm. In 6/216 initial treatment attempts, the procedure was interrupted prior to the completion of 60 minutes of heating; these six treatments were successfully resumed later for a total of 222 initial treatment sessions. Additionally, a total of 21 patients elected to have a second TUMT prior to their 12-month exam, resulting in a total of 243 treatments being delivered during the study period. During all treatments, the Prostatron™ safety features functioned as intended.

The mean maximum urethral and rectal temperatures obtained during the 222 initial TUMT treatment sessions were 44.4°C and 42.4°C, respectively. The average maximum power delivered during these treatments was 46.5 watts, and the mean total energy delivered to the prostate was 102.5 kJ. Although sizeable (and statistically significant) differences were noted between the total microwave energies delivered between these clinical sites (i.e., range from 78.1 to 131.1 kJ), all comparisons included site effects in the statistical model (i.e., ANCOVA or ANOVA) for completeness.

Other than topical Lidocaine, the only anesthetic medications used during any of the treatment sessions were oral or IV sedation. The use of anesthesia was based upon physician and patient preference, and was used in only 79/250 (32%) of cases. All treatments were performed on an outpatient basis.

### 5. Effectiveness Results

The evaluation of effectiveness of treatment with the Prostatron™ was primarily based upon symptomatology and PFR at 12 months post-treatment, as compared to baseline values. Other effectiveness parameters that were measured were quality of life, PVR, and prostate volume.

Table 5 presents the changes in symptomatology (i.e., MSS) and quality of life recorded among the study subjects between baseline and 3 and 12 months. Among the 149 patients with complete effectiveness data, the overall MSS decreased from a baseline of 13.9 to 5.6 at 3 months (60% improvement), and from a baseline of 13.9 to 5.7 at 12 months (59% improvement). This difference between the two groups was

statistically significant ( $p < 0.0001$ ). Including the 32 patients considered treatment failures (i.e.,  $n = 181$ ), 67% of subjects had MSS improvements of  $\geq 30\%$  and 46% had improvements of  $\geq 8$  points. The obstructive components of the MSS decreased more than the irritative components; however, the magnitude of the decreases of both components were statistically significant at both 3 and 12 months. With regard to the rate of nocturia, which is one of the items assessed by the MSS, the study subjects exhibited statistically significant decreases in the frequency of this symptom (from baseline) of 43% and 40% at 3 and 12 months, respectively.

The mean changes in each of the five quality of life scales only indicate differences from baseline in "Perception of Urinary Difficulty" and "Activities of Daily Living," both of which were significantly improved ( $p < 0.0001$ ). Although the "Sexual Function" scale noted significant improvement at 3 months (as compared to baseline), the level at 12 months was not statistically improved. However, this information demonstrates that these patients did not experience a decrease in the "Sexual Function" scale.

Table 5. Symptomatology Results at 3 Months and 12 Months for General Study

|                                     | 3 MONTHS | 12 MONTHS |
|-------------------------------------|----------|-----------|
| <b>MADSEN SYMPTOM SCORE</b>         |          |           |
| Overall Score                       | -60%     | -59%      |
| Obstructive Components              | -67%     | -66%      |
| Irritative Components               | -46%     | -43%      |
| Nocturia                            | -43%     | -40%      |
| % Improved $\geq 30\%$              | 85%      | 67%       |
| % Improved $\geq 8$ points          | 57%      | 46%       |
| <b>QUALITY OF LIFE IMPROVEMENTS</b> |          |           |
| Perception of Urinary Difficulties  | 69%      | 61%       |
| Sexual Function                     | 15%      | 6%        |
| Activities of Daily Living          | 28%      | 29%       |
| General Well Being                  | <1%      | 5%        |
| Social Activities                   | 2%       | 3%        |

The changes in PFR and PVR observed between baseline, 3 months, and 12 months are summarized in table 6. In the General Study, PFR increased from 7.9 mL/s at baseline to 11.0 mL/s at 3 months (39%,  $p < 0.0001$ ). At 12 months post-treatment, PFR increased from 8.3 mL/s at baseline to 11.2 mL/s (35%,  $p < 0.0001$ ). Including the

32 treatment failures, 44% of patients had increases in PFR of  $\geq 30\%$  at 12 months, and 37% had absolute increases of  $\geq 3$  mL/s.

Post-void residual urine volume was evaluated by catheterization at baseline, 6 months, and 12 months post-treatment. As seen in table 6, PVR was not significantly changed from baseline at either 6 or 12 months. However, PVR evaluated by ultrasound showed statistically significant decreases from baseline of 19% at 3 months and 21% at 12 months ( $p < 0.0001$ ).

Table 6. Change in Peak Flow Rate and Post-Void Residual Urine Volume at 3 Months and 12 Months Post-treatment for General Study

|                              | 3 MONTHS       | 12 MONTHS |
|------------------------------|----------------|-----------|
| Peak Flow Rate               | 39%            | 35%       |
| % PFR Improved $\geq 30\%$   | 52%            | 44%       |
| % PFR Improved $\geq 3$ mL/s | 47%            | 37%       |
| Post-Void Residual Urine     |                |           |
| By Catheter                  | -7% (6 Months) | -7%       |
| By Ultrasound                | -19%           | -21%      |

Prostate volume was measured by transrectal ultrasound at baseline ( $n=210$ ), at 6 months ( $n=186$ ), and at 12 months ( $n=141$ ). Prior to treatment, prostate volume averaged  $38.5 \text{ cm}^3$ . At 6 and 12 months, the mean prostate volume was  $36.3 \text{ cm}^3$  and  $38.0 \text{ cm}^3$ , indicating that TUMT did not significantly affect prostate volume within this cohort.

To further examine the stability of the clinical outcome of TUMT, the cohorts of patients who were identified as having clinically significant improvements at 3 months in MSS and PFR were analyzed at 6 and 12 months to determine the percentage who sustained this level of improvement. For MSS, this analysis revealed that of the 154 subjects identified as being clinically improved at 3 months (i.e., MSS improved  $\geq 30\%$  or  $\geq 8$  points), 113 (73%) patients still met these criteria. Likewise, of the 87 subjects identified as being clinically improved at 3 months in PFR (i.e., flow rate improved  $\geq 30\%$  or  $\geq 3$  mL/s), 53 (61%) maintained this level of improvement.

To examine whether there were any prognostic variables predictive of successful outcome, patients who demonstrated improvements in MSS and PFR were separately analyzed for differences in the following baseline/treatment characteristics: age, duration of symptoms, prostate length, prostate volume, MSS, PFR, PVR,

investigational site, and energy delivered during treatment. This analysis revealed that there was a statistically significant association ( $p < 0.01$ ) between improvements in MSS and higher baseline MSS, investigational site, and higher energy delivered. The strongest of these associations was with energy delivered, which indicated that patients who were treated with energy levels higher than 100 kJ were more likely to meet the MSS success criteria of improvement. The association of investigational site and outcome is likely related to the fact that there were significant site differences in baseline MSS scores and energy delivered among these cohorts. There was no statistically significant association between the tested characteristics and PFR.

A total of 21/216 (9.7%) patients had a repeat TUMT treatment prior to their 12-month follow-up exam. An additional seven patients were retreated with the Prostatron™ after their 12-month evaluation. A review was performed of the 28 patients who had TUMT retreatments to identify the factors that could explain the failure of the original TUMT treatment. This analysis compared retreated patients with those patients who did not have retreatments by the following characteristics: patient age, duration of symptoms, baseline MSS, baseline PFR, baseline PVR, baseline prostate volume, maximum power delivered, total energy received, and maximum urethral and rectal temperatures. Retreated patients had significantly lower total energy levels ( $p = 0.0009$ ) and maximum power levels ( $p = 0.003$ ) during their original treatment than did those who were not retreated. These results are consistent with the finding in this study that improvement in MSS is strongly associated with energy delivered.

Five patients in the General Study dropped out prior to their 12-month follow-up exam to have an alternative treatment for their BPH (i.e., either TURP, TUIP, or drug therapy).

## 6. Safety Results

The evaluation of the safety of the Prostatron™ was primarily based upon the rate of adverse events reported by the patient or found during follow-up. Additionally, safety was assessed through the following methods: proctoscopy/anoscopy evaluations, cystoscopy evaluations, laboratory measurements, and questions regarding the incidences of sexual dysfunction and incontinence.

Table 7 summarizes the adverse events which were determined to be related (or possibly related) to treatment during all treatments ( $n = 244$ ; first column) and for all patients ( $n = 216$ ; second column). These adverse events were reported in two categories--those events that occurred during or immediately following treatment, and those events that occurred at any follow-up exam until 12 months.

Table 7. Summary of Adverse Events Related To, or Possibly Related To, Prostatron™ Treatment for General Study

|  | # Events<br>(n=244 Treatments) | # Patients<br>(n=216) |
|--|--------------------------------|-----------------------|
| <b>EVENTS DURING TREATMENT OR IMMEDIATE POST-TREATMENT</b> |                                |                       |
| Elevated BP during Treatment                               | 7 (2.9%)                       | 7 (3.2%)              |
| Urethral Trauma Related Instrumentation                    | 5 (2.0%)                       | 5 (2.3%)              |
| Treatment Discomfort                                       | 2 (1.0%)                       | 2 (1.0%)              |
| Chills/Flu Symptoms  | 1 (<1%)                        | 1 (<1%)               |
| <b>Total Patients with Adverse Events</b>                  |                                | <b>15</b>             |

| <b>FINDINGS AT DISCHARGE AND FOLLOW-UP</b> |             |                  |
|--|-------------|------------------|
| <b>Urinary Tract Findings</b>              |             |                  |
| Hematuria                                  | 100 (41.0%) | 97 (45.0%)       |
| Urinary Retention                          | 69 (28.0%)  | 68 (31.5%)       |
| Urethral Bleeding                          | 25 (10.0%)  | 24 (11.0%)       |
| Urinary Discomfort w/o Infection           | 20 (8.2%)   | 22 (10.0%)       |
| Urinary Tract Infection                    | 18 (7.4%)   | 15 (6.9%)        |
| Urethral Discharge                         | 10 (4.0%)   | 10 (4.6%)        |
| Complications of Retention/Catheterization | 2 (<1.0%)   | 2 (1.0%)         |
| Abnormalities Identified by Cystoscopy     | 3 (1.2%)    | 3 (1.4%)         |
| Other Urinary Tract Events                 | 6 (2.5%)    | 6 (2.8%)         |
| <b>Reproductive Tract Findings</b>         |             |                  |
| Ejaculatory Changes                        | 26 (10.7%)  | 14 (6.5%)        |
| Inflammation/Pain                          | 13 (5.3%)   | 13 (6.0%)        |
| Decrease in Sexual Functioning             | 2 (<1.0%)   | 2 (1.0%)         |
| Other                                      | 3 (1.0%)    | 3 (1.0%)         |
| <b>Rectal Findings</b>                     |             |                  |
| Abnormalities Noted by Proctoscopy         | 9 (3.7%)    | 8 (3.7%)         |
| Rectal Discomfort                          | 6 (2.5%)    | 6 (2.8%)         |
| Exacerbation of Rectal Prolapse            | 1 (<1.0%)   | 1 (<1.0%)        |
| <b>Other Adverse Events</b>                |             |                  |
| Constipation                               | 3 (1.0%)    | 2 (1.0%)         |
| Cold/Flu Symptoms; Chills                  | 2 (1.0%)    | 2 (1.0%)         |
| Vasovagal Reaction                         | 1 (<1.0%)   | 1 (<1.0%)        |
| Low Hematocrit                             | 1 (<1.0%)   | 1 (<1.0%)        |
| Nausea/Vomiting                            | 1 (<1.0%)   | 1 (<1.0%)        |
| General GI Discomfort                      | 1 (<1.0%)   | 1 (<1.0%)        |
| <b>Total Patients with Adverse Events</b>  |             | <b>159 (74%)</b> |

The majority of adverse events were typical of those seen with urethral instrumentation, such as hematuria, urethral bleeding, urethral discharge, urinary discomfort, and urinary tract infection. The main complication unique to TUMT was urinary retention requiring catheterization, which was noted in 68/216 (31.5%) patients. Most of the 68 patients with urinary retention requiring catheterization had their catheter removed at

their 1-week follow-up exam (average of 9.6 days). Statistical analysis revealed that the occurrence of post-treatment urinary retention was most common among patients with larger prostates, patients with higher baseline PVR, and patients who received higher levels of energy during treatment.

Adverse events of the reproductive tract were generally minor. Inflammation/pain was reported by 13/216 (6.0%) patients. This pain was due to epididymitis, prostatitis, swollen penis or scrotum, and pelvic/suprapubic pain. There were 26 reports in 9 patients of ejaculatory changes (i.e., transient hematospermia, dry ejaculate, or decrease in ejaculate volume), none of which were considered to be serious. There were no reports of retrograde ejaculation. The two cases of decreased sexual function refer to one patient who reported a decreased libido and another who reported a decreased ability to have an erection.

The three abnormalities identified by cystoscopy were two cases of Prostate Probe balloon fragments in the bladder, and one case of bladder stones.

The reports of adverse events involving abnormalities by proctoscopy were primarily rectal irritation and discomfort due to the rectal manipulation and instrumentation during treatment and examination, and were transient.

Few complications occurred after the 12-month follow-up exam, none of which were judged to be serious. Additionally, the incidence of complications was not different for those who received a second TUMT treatment.

Analysis of measurements of hemoglobin, hematocrit, CBC, platelets, creatinine, and BUN indicated no significant differences between the baseline and any of the follow-up exams.

## 7. Long-term Follow-up Results

Long-term data on the General Study patients were collected by telephone follow-up to further evaluate the need for retreatment, the level and duration of symptom score improvement, and the occurrence of adverse events beyond the 12-month exam up to 4 years post-treatment.

Of the 216 General Study patients, long-term data were obtained on 169, with a mean follow-up time of 46 months. Out of those patients whose long-term status is known, 48% (81/169) received further treatment for their BPH. The type of alternative treatment sought by these patients was either medical therapy (61/81 patients) or surgery (20/81 patients).

The durability of symptom improvement was assessed among those patients who (i) did not receive any additional therapy for their BPH, and (ii) who had complete data recorded during their initial 12 months of follow-up (n=57). The results from this highly selected patient group demonstrated that the average MSS increased from approximately 4.5 at 12 months to 7.0 at 4 years; however, this average symptom score at 4 years was still significantly less than the baseline value of 14 for these 57 patients.

Few adverse events related to the Prostatron™ were noted at long-term follow-up. Overall, a total of 20/169 patients reported urological adverse events; however, there is no evidence that these complications were directly related to treatment with the Prostatron™.

### TUMT/TURP Study

#### 1. Introduction

The TUMT/TURP Study was a randomized study designed to compare the safety and effectiveness of TUMT treatment with the Prostatron™ to that of TURP, which is the "gold standard" for the treatment of BPH. This study was designed to assess the differences in the outcomes of these two therapies over 12 months, with emphasis on the reduced morbidity associated with TUMT as compared to surgery. This study was conducted at the Sahlgrenska Hospital in Goteberg, Sweden.

Patients were randomized 1:1 between TUMT and TURP. The evaluation of

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By the date of database closure, the majority of patients in this study completed their 12-month follow-up according to the protocol (i.e., 34/38 TUMT patients, and 30/32 TURP patients). Six patients were not available for 12-month follow-up (i.e., five patients discontinued from the study (one TUMT and two TURP patients due to medical reasons, one TUMT patient for surgical treatment for his BPH, and one TUMT patient due to voluntary withdraw), and one TURP patient died). Furthermore, two patients (one TUMT and one TURP) were excluded from the effectiveness analysis due to excessive prostatic length. As a result, effectiveness data are available for 33/38 TUMT patients and 29/32 TURP patients. The mean times to the 12-month exam for these two cohorts were 369 days (TUMT) and 365 days (TURP).

The patient death was attributed to circumstances unrelated to the Prostatron™ treatment procedure. This subject, who was treated in the TURP arm, died of a brain tumor shortly after his 6-month exam.

### 3. Baseline Characteristics

The 70 treated patients had the following baseline characteristics: mean duration of BPH symptoms of 30.9 months in the TUMT group and 32.9 months in the TURP group; mean PFR of 9.1 mL/s in the TUMT group and 8.8 mL/s in the TURP group; mean MSS of 11.9 in the TUMT group and 13.4 in the TURP group; and mean prostate volume of 30.6 cm<sup>3</sup> in the TUMT group and 34.4 cm<sup>3</sup> in the TURP group. Based on these comparisons, it appears that these two randomized arms were well-matched.

Analyses were performed to evaluate whether these Swedish patients were comparable to those in the U.S. investigational sites. This comparison revealed statistically significant differences in patient age, duration of symptoms, prostate volume, and microwave energy delivered. However, since the magnitudes of each of these differences were within the range seen among the individual U.S. sites, these foreign patients were judged to be comparable to the U.S. population.

### 4. Treatment Parameters

Treatment in the TUMT group was performed according to the Prostatron™ algorithm. In 1/38 treatments, the procedure was interrupted prior to the completion of 60 minutes of heating due to a cooling system alarm. This treatment was not resumed, since the patient had received 80% of a complete treatment. During all treatments, the Prostatron™ safety features functioned as intended.

The mean maximum urethral and rectal temperatures obtained during the 38 TUMT treatment sessions were 44.4°C and 42.5°C, respectively. The average maximum power delivered during these treatments was 42.8 watts, and the mean total energy

delivered to the prostate was 86 kJ. None of the TUMT patients required anesthesia of any kind (except for topical Lidocaine), and all were treated as outpatients.

All of the 32 TURP surgeries performed were treated using spinal anesthesia, and all were hospitalized.

#### 5. Effectiveness Results

The evaluation of effectiveness of treatment with the Prostatron™ was primarily based upon improvements in symptomatology and PFR, as compared between the two treatment arms, at 3 months. Other effectiveness parameters measured were quality of life, PVR, prostate volume, and global patient and physician opinions.

Table 8 presents the changes in symptomatology and quality of life recorded among the two treatment groups at 3 months. As expected, the improvements observed among the TURP subjects exceeded those recorded for the TUMT group. The overall MSS decreased 82% in the TUMT cohort, and 96% in the TURP cohort. This difference was not statistically significant between the two groups.

The obstructive and irritative components also showed significant decreases in both groups. The differences between the TUMT and TURP groups were not statistically significant for the obstructive score, but were for the irritative score ( $p=0.01$ ). The difference in the frequency of nocturia was also statistically significant ( $p=0.05$ ).

The mean changes in each of the five quality of life scales demonstrated that both groups had increases in the "Perception of Urinary Difficulty" and "Activities of Daily Living" scales; however, the magnitude of improvement in each these two scales was greater among the TURP patients. The quality of life information also indicates that while the TUMT group experienced a slight improvement in the "Sexual Function" scale, the TURP group demonstrated a slight decrease.

Table 8. Symptomatology Results at 12 Months Post-Treatment for TUMT and TURP Groups

|                                     | TUMT GROUP | TURP GROUP |
|-------------------------------------|------------|------------|
| <b>MADSEN SYMPTOM SCORE</b>         |            |            |
| Overall Score                       | -82%       | -96%       |
| Obstructive Components              | -89%       | -97%       |
| Irritative Components               | -66%       | -93%       |
| Nocturia                            | -39%       | -74%       |
| % Improved $\geq$ 30%               | 97%        | 100%       |
| % Improved $\geq$ 8 points          | 73%        | 97%        |
| <b>QUALITY OF LIFE IMPROVEMENTS</b> |            |            |
| Perception of Urinary Difficulties  | 51%        | 105%       |
| Sexual Function                     | 14%        | -18%       |
| Activities of Daily Living          | 27%        | 53%        |
| General Well Being                  | 2%         | 10%        |
| Social Activities                   | 0%         | 12%        |

The changes in PFR and PVR observed between baseline and 12 months for each treatment arm are summarized in table 9. In the TUMT group, PFR increased from 9.4 mL/s to 12.1 mL/s (29%). In the TURP group, however, PFR increased from 8.4 mL/s to 18.2 mL/s (112%). As expected, this difference was statistically significant.

Table 9 also summarizes the PVR results. PVR was measured by catheter at baseline and the 6-month follow-up, and by ultrasound at baseline and the 12-month follow-up. In both comparisons, the decreases in PVR favored the TURP arm.

Table 9. Change in Peak Flow Rate and Post-Void Residual Urine Volume at 12 Months Post-treatment for TUMT and TURP Groups

|                              | TUMT GROUP | TURP GROUP |
|------------------------------|------------|------------|
| Peak Flow Rate               | 29%        | 112%       |
| % PFR Improved $\geq$ 30%    | 42%        | 86%        |
| % PFR Improved $\geq$ 3 mL/s | 39%        | 90%        |
| Post-Void Residual Urine     |            |            |
| By Catheter                  | 20%        | 56%        |
| By Ultrasound                | 43%        | 79%        |

Prostate volume was measured in both groups using transrectal ultrasound at baseline and at 12 months. At 12 months, prostate volume decreased by 9% in the TUMT group, and 51% in the TURP group.

Similar to the Sham/TUMT Study, patients and physicians were asked their opinion of whether the treatment that was administered had improved the patient's condition. In both groups, 100 percent of the patients stated that they experienced a positive change in their condition. Likewise, the physicians indicated that 94% of the TUMT patients and 100% of the TURP had a positive response.

## 6. Safety Results

The evaluation of the safety of the Prostatron™ was primarily based upon a comparison of the rate of adverse events between the TUMT and TURP treatment arms, as reported by patients or found during follow-up examinations. Additionally, safety was assessed through the following methods: proctoscopy/anoscopy evaluations, cystoscopy evaluations, laboratory measurements, and questions regarding the incidences of sexual dysfunction and incontinence.

Table 10 summarizes the adverse events which were determined to be related (or possibly related) to treatment for the TUMT and TURP groups. These adverse events were reported in two categories--those events that occurred during or immediately following treatment, and those events that occurred at any follow-up exam until 12 months. These results indicate that TUMT is associated with fewer, less serious complications than TURP.

Table 10. Adverse Events Related to, or Possibly Related to, TUMT/TURP Treatment.

| Events   | # Patients (%)  |                              |
|--|-----------------|------------------------------|
|  | TUMT (38)       | TURP (32)                    |
| <b>EVENTS DURING TREATMENT OR POST-TREATMENT</b> |                 |                              |
| Urethral Bleeding Requiring Intervention         | 0 (0%)          | 3 (9.4%)                     |
| Capsular Perforation                             | 0 (0%)          | 2 (6.3%)                     |
| Serious Reaction to Anesthesia                   | 0 (0%)          | 1 (3.2%)                     |
| Treatment Discomfort                             | 2 (5%)          | 0 (0%)                       |
| <b>Total Patients with Adverse Events</b>        | <b>2 (5.0%)</b> | <b>6 (19%)</b>               |
| <b>FINDINGS AT DISCHARGE OR FOLLOW-UP</b>        |                 |                              |
| <b>Urinary Tract Findings</b>                    |                 |                              |
| Urinary Retention/Need for Cath.                 | 9 (24%)         | 32 (100%)                    |
| Hematuria at Week 6                              | 3/27 (11%)      | 18/21 (86%)                  |
| Stricture  | 0 (0.0%)        | 7 (22%)                      |
| Urinary Discomfort w/o Infection                 | 5 (13%)         | 4 (13%)                      |
| Urinary Tract Infection                          | 7 (18%)         | 3 (9.4%)                     |
| Transient Incontinence                           | 0 (0.0%)        | 1 (3.0%)                     |
| Other Urinary                                    | 1 (3.0%)        | 2 (6.0%)                     |
| <b>Reproductive Tract Findings</b>               |                 |                              |
| Retrograde Ejaculation                           | 0 (0.0%)        | 14 repts in 5 patients (16%) |
| Inflammation/Pain                                | 2 (5.0%)        | 2 (6.0%)                     |

## Interstitial Thermometry Study

### 1. Introduction

The Interstitial Thermometry Study was conducted (i) to determine when TUMT achieves its goal of maximizing intraprostatic temperatures, (ii) to quantitatively evaluate the temperature distribution in the region of the microwave antenna, and (iii) to examine the relationship between intraprostatic temperatures and therapeutic outcome. This study was conducted at the Charing Cross Hospital, in London, England.

All patients in this study underwent transperineal, needle thermometry (two probes, one in each lateral lobe) while receiving TUMT treatment. Additionally, a subgroup of 22 patients in this study had voiding cystometrograms (CMG) at baseline and at 6 months post-treatment. With the exception of the CMG data, all safety and effectiveness data were compared between baseline and 3 months; the CMG results were analyzed at 6 months.

### 2. Study Population

In this study, 44 males with BPH were enrolled, of which 43 received treatment--one patient was removed from the study prior to being treated when it was learned that he had Parkinson's disease. These 43 patients had a mean age of 65.7 years.

All of the patients treated in the Interstitial Thermometry Study met the protocol's entry criteria. By the date of database closure, the majority of patients in this study completed their 3-month follow-up according to the protocol. Overall, 41/43 patients were included in the effectiveness analysis. This number consists of 37/43 patients who had both baseline and 3-month follow-up data, and 4/43 patients who missed their 3-month exam, but were evaluated at 6 months. Patients from these two follow-up exams were pooled for analysis since the prior studies demonstrated that the results are stable over this time. Of the remaining 2/43 patients, one patient was discontinued after taking a medication that could confound his therapeutic outcome, and one patient died 2 months after treatment. The mean time to the follow-up exam (either 3 or 6 months) for these 41 patients was 109 days.

One of the patients discontinued because of death, which was attributed to circumstances unrelated to the Prostatron™ treatment procedure. Specifically, this patient died 2 months post-treatment of multiple system failure.

### 3. Baseline Characteristics

The 43 treated patients had the following baseline characteristics: mean duration of BPH symptoms of 23.3 months; mean PFR of 7.4 mL/s; and mean MSS of 14.5.

Analyses were performed to evaluate whether these English patients were comparable to those treated at the U.S. investigational sites. This comparison revealed statistically significant differences in duration of symptoms, PVR, and microwave energy delivered. However, since the magnitudes of each of these differences were within the range seen among the individual U.S. sites, these foreign patients were judged to be comparable to the U.S. population.

#### 4. Treatment Parameters

Treatment in the TUMT group was performed according to the Prostatron™ algorithm. In 13/43 initial treatment attempts the procedure was interrupted. In all but four of these cases, treatment was resumed to complete the 60 minute heating session--in the other four treatments, patients received significantly less than 60 minutes of exposure. The inclusion of the data from these four subjects was judged to be appropriate, since the goal of this study is to stratify patient outcome by treatment parameters. No patients in this study had a retreatment. During all treatments, the Prostatron™ safety features functioned as intended.

The mean maximum urethral and rectal temperatures obtained during the 43 initial TUMT treatment sessions were 44.6°C and 42.1°C, respectively. The average maximum power delivered during these treatments was 54.1 watts, and the mean total energy delivered to the prostate was 135.1 kJ.

Other than topical Lidocaine, which was used both transurethrally and perineally, no anesthetic medications were used during any of the treatment sessions. All treatments were performed on an outpatient basis.

#### 5. Effectiveness Results

The evaluation of effectiveness of treatment with the Prostatron™ in the Interstitial Thermometry Study was based primarily upon symptomatology and PFR at 3 months post-treatment, as compared to baseline values. Additionally, a subgroup of 22 patients underwent pressure-flow urodynamic studies at baseline and at 6 months, to determine whether TUMT had an effect upon this objective measure of urinary obstruction.

Table 11 presents the changes in symptomatology (i.e., MSS) and PFR recorded among the study subjects between baseline and 3 months. Among the 41 patients with complete effectiveness data, the overall MSS decreased from a baseline of 14.4 to 3.3 at 3 months (77% improvement). PFR increased from 7.4 mL/s at baseline to 11.1 mL/s at 3 months (50%).

Table 11. Effectiveness Results at 3 Months Post-treatment for Interstitial Thermometry Study

|                             | 3-Month Improvement |
|-----------------------------|---------------------|
| <b>MADSEN SYMPTOM SCORE</b> |                     |
| Overall Score               | -77%                |
| Obstructive Components      | -81%                |
| Irritative Components       | -68%                |
| % Improved $\geq 30\%$      | 93%                 |
| % Improved $\geq 8$ points  | 76%                 |
| <b>PEAK FLOW RATE</b>       | 50%                 |
| % Improved $\geq 30\%$      | 63%                 |
| % Improved $\geq 3$ mL/s    | 47%                 |

A subset of 22 patients had pressure-flow studies (i.e., CMG) at baseline and at 6 months post-treatment. In these patients, the mean detrusor pressure at urethral opening was 78.1 cm H<sub>2</sub>O at baseline, and 79.1 cm H<sub>2</sub>O at follow-up. The detrusor pressure at maximum flow rate was 81.9 cm H<sub>2</sub>O at baseline, and 84.1 cm H<sub>2</sub>O at 6 months. Among these patients, the mean PFR was 8.9 mL/s at baseline and 9.9 mL/s at follow-up. Based on these results, treatment with the Prostatron™ did not significantly relieve patients' urinary obstruction.

#### 6. Safety Results

The evaluation of the safety of the Prostatron™ was primarily based upon the rate of adverse events reported by the patient or found during follow-up. Additionally, safety was assessed through the following methods: proctoscopy/anoscopy evaluations, cystoscopy evaluations, laboratory measurements, and questions regarding the incidences of sexual dysfunction and incontinence.

Table 12 summarizes the adverse events which were determined to be related (or possibly related) to treatment. These adverse events were reported in two categories-- those events that occurred during or immediately following treatment, and those events that occurred at any follow-up exam until 3 months.

Table 12. Summary of Adverse Events During Interstitial Study Related To, OR Possibly Related To, Prostatron™ Treatment

|  | Number Events | Number Patients<br>N=43 |
|--|---------------|-------------------------|
| <b>Events During Treatment OR Immediate Post-Treatment</b> |               |                         |
| Treatment Discomfort                                       | 6             | 4 (9%)                  |
| Urethral Trauma Related to Instrumentation                 | 1             | 1 (2%)                  |
| <b>Total Patients Reporting Adverse Events</b>             |               | <b>5 (11%)</b>          |
| <b>Events at Discharge and Follow-Up</b>                   |               |                         |
| Urinary Tract Findings                                     | 41            | 41 (95%)                |
| Hematuria  | 24            | 23 (54%)                |
| Urinary Retention  | 10            | 10 (23%)                |
| Urethral Bleeding  | 11            | 9 (21%)                 |
| Urinary Tract Infection                                    | 8             | 8 (19%)                 |
| Urethral Discharge   | 4             | 4 (9%)                  |
| Urinary Discomfort w/o Infection                           | 2             | 2 (5%)                  |
| Complications of Retention/Cath.                           | 1             | 1 (2%)                  |
| Particles in Urine/Debris                                  |               |                         |
| Reproductive Tract Findings                                | 8             | 8 (19%)                 |
| Ejaculatory Changes  | 7             | 5 (12%)                 |
| Inflammation/Pain  | 3             | 2 (5%)                  |
| Decrease in Sexual Functioning                             |               |                         |
| Rectal Findings  |               |                         |
| Abnormalities Identified by Proctoscopy                    | 1             | 1 (2%)                  |
| <b>Total Patients Reporting Adverse Events</b>             |               | <b>42 (98%)</b>         |

The overall rates of hematuria, urethral bleeding, urethral discharge, urinary retention requiring catheterization, and urinary tract infection post-treatment were higher than those reported in the other studies. This finding was likely due to the interstitial needle thermometry procedures performed on all 43 patients, as well as the CMG testing performed on a 22-patient subgroup.

#### 7. Interstitial Temperature Measurements

The protocol for this study instructed physicians to place two percutaneous temperature sensors in each patient, i.e., a sensor was to be placed in each lobe of the prostate, at the site of maximal heating. The objective of these thermometry studies was to determine the relationship between the level of prostatic heating and patient outcome.

A total of 80 interstitial temperature measurements were obtained and analyzed in 41/43 patients. The mean maximum intraprostatic temperatures recorded ranged from 39.7 to 65.2°C. The mean time-averaged temperature recorded ranged from 37.7°C to 54.3°C.

The location of each thermosensor within the prostate was mapped using ultrasound. With this information, it was noted that temperatures exceeding 44°C were achieved at distances ranging from 5 to 18 mm lateral to the urethra. In the axial direction (i.e., along the urethra), heating was found to be uniform along the height of the prostate.

The relationship between therapeutic outcome (i.e., improvements in MSS and PFR) and intraprostatic temperature levels was examined by analyzing the association between the change in MSS and PFR at 3 months with the relative change in maximum and time-averaged temperatures measured during treatment. Specifically, these relative temperature changes were compared between patients who had significant improvements in MSS and PFR (defined as those who improved  $\geq 8$  points or  $\geq 3$  mL/s, respectively) and those who were not improved. This analysis indicated that PFR-improved patients experienced a greater rise in average temperature ( $p < 0.05$ ) than those who were unimproved, and that MSS-improved patients experienced a greater rise in both average temperature ( $p < 0.05$ ) and maximum temperature ( $p < 0.05$ ). The results of this analysis are summarized in table 13.

Table 13. Improvement of Outcome in Relation to Intra-Prostatic Temperature

|                      | Not Improved      | Improved           | P Value |
|----------------------|-------------------|--------------------|---------|
| Peak Flow Rate       |                   |                    |         |
| Number Patients      | 20 (54%)          | 17 (46%)           |         |
| DT Max (°C)          | 9.5 ( $\pm 3.9$ ) | 11.2 ( $\pm 3.7$ ) | N.S.*   |
| DT Avg (°C)          | 5.4 ( $\pm 2.1$ ) | 7.3 ( $\pm 2.5$ )  | p<.05   |
| Madsen Symptom Score |                   |                    |         |
| Number Patients      | 9 (22.5%)         | 31 (78%)           |         |
| DT Max (°C)          | 7.8 ( $\pm 2.2$ ) | 11.1 ( $\pm 3.8$ ) | p<.05   |
| DT Avg (°C)          | 4.7 ( $\pm 1.5$ ) | 6.8 ( $\pm 2.4$ )  | p<.05   |

\* N.S.=Not statistically significant

Furthermore, patients were stratified into three groups based upon the maximum intraprostatic temperature measured during treatment: (1)  $\leq 44^\circ\text{C}$ , (2) between 44 and 48°C, and (3)  $> 48^\circ\text{C}$ . For each of these temperature stratifications, the following parameters were compared: maximum and average power delivered, the mean changes observed in MSS and PFR, and distance from the temperature sensor to the urethra. The results of this analysis are presented in table 14.

The mean maximum and average powers showed a trend, with higher powers being associated with higher temperatures. Also, there appeared to be a relationship between the distance from the thermosensor to the urethra and the temperature measured--as expected, the positions of the higher temperature thermosensors were closer to the urethral applicator than those that measured lower temperatures.

There was a positive trend in the PFR increases for the three groups, although not statistically significant. Specifically, higher maximum temperatures were associated with higher mean changes in PFR. Similarly, there was a trend demonstrating greater improvement with MSS with higher temperatures, which also was not statistically significant.

Table 14. Stratification of Treatment Parameter and Outcome by Maximum Intra-Prostatic Temperature

|                              | Low T Max $\leq 44^{\circ}\text{C}$ | Medium T Max $44^{\circ}-48^{\circ}\text{C}$ | High T Max $>48^{\circ}\text{C}$ |
|------------------------------|-------------------------------------|--|----------------------------------|
| Number Patients              | 8                                   | 16   | 16                               |
| <u>Treatment Parameters:</u> |                                     |  |                                  |
| P Max (W)                    | 46.8 ( $\pm 11.8$ )                 | 54.0 ( $\pm 9.6$ )                           | 58.7 ( $\pm 4.7$ )               |
| P Avg (W)                    | 33.8 ( $\pm 14.5$ )                 | 36.8 ( $\pm 9.8$ )                           | 41.9 ( $\pm 7.3$ )               |
| Dist. to Urethra (mm)        | 12.1 ( $\pm 3.6$ )                  | 10.2 ( $\pm 3.7$ )                           | 8.9 ( $\pm 2.2$ )                |
| <u>Outcome Measurements:</u> |                                     |  |                                  |
| Number Patients              | 8                                   | 14   | 15                               |
| Mean Change in PFR           | 2.0 ( $\pm 2.1$ )                   | 3.7 ( $\pm 2.9$ )                            | 4.9 ( $\pm 3.7$ )                |
| Number Patients              | 8                                   | 16   | 15                               |
| Mean Change in MSS           | 9.1 ( $\pm 5.1$ )                   | 10.4 ( $\pm 4.8$ )                           | 13.0 ( $\pm 3.0$ )               |

#### Device Failures

Throughout the four clinical investigations of the Prostatron™, 38 device-related problems occurred prior to treatment (i.e., were due to device malfunctions or alarms). During treatment, 68 treatment interruptions occurred, of which 48 were due to device-related problems. No patient injury occurred as a result of any device-related problem. The specific device-related problems noted during the study were as follows:

Poor optical link connection was noted in 47 cases, and was generally due to difficulties in adequately connecting the Prostatron to the treatment module. This problem was corrected through the use of another Prostatron.

Coolant water leakage occurred in 17 cases, and was due to either the use of defective Prostatrons or damage from interstitial thermometry (which punctured the catheter). This problem was corrected through the use of a new Prostatron.

Coolant system alarm was noted in nine cases, and may have been related to the incidences of coolant leakage. In all cases, the device functioned as designed.

Balloon breakage was recorded in eight cases, and was corrected through the use of a new Prostatron.

Power oscillator alarm occurred in three cases, and may have been related to poor Prostatron connection. In all cases, the device functioned as designed.

Stopcock malfunction occurred in two cases, and was corrected through the use of a new Prostatron.

## X. CONCLUSIONS DRAWN FROM THE STUDIES

The laboratory, animal, and clinical data provide reasonable assurance of the safety and effectiveness of the Prostatron™ for the treatment of symptomatic BPH, when used as indicated.

## XI. PANEL RECOMMENDATION

The Gastroenterology and Urology Devices Advisory Panel met to discuss the application on October 20, 1995. The Panel recommended that the application be approved subject to submission to, and approval by, the Center for Devices and Radiological Health (CDRH) of modifications to the device's labeling and the inclusion of plans for a postapproval study. The Panel recommended that the labeling be modified to state that the use of the Prostatron™ must be prescribed and administered under the direct supervision of a qualified and trained physician, after appropriate urologic evaluation of the patient.

The Panel also recommended that a postapproval study be conducted to evaluate the long-term effects of treatment on 100 patients, followed for 5 years post-treatment. This study should be designed to record the adverse events among these subjects, as well as to quantify the rates of repeat and alternative treatments during this follow-up period.

## **XII. CDRH DECISION**

CDRH agreed with the Panel's recommendations that the PMA be approved subject to conditions, and concurred with each of the conditions recommended by the Panel. In addition to the Panel's recommended conditions, CDRH also required other information, some of which reflects information discussed during the panel meeting but not included in the final recommendations. These additional conditions included modifications to the labeling's "Warnings," "Adverse Events," and "Effectiveness" sections and submission of the draft training program. Furthermore, the following items were raised during CDRH review of the PMA and were requested of the sponsor: (i) additional data and clarification regarding the electromagnetic compatibility (EMC) testing that was performed; (ii) additional descriptive information regarding the device's software testing and sterilization process; and (iii) information addressing the potential, long-term bioeffects of microwave exposure.

FDA issued a status letter, dated November 6, 1995, to the EDAP Technomed Group (U.S.A.), and another letter dated, November 22, 1995, advising that the PMA was approvable subject to the conditions listed above as recommended by the Panel and required by FDA. In amendments received by FDA on November 16, 1995, and January 17, 1996, the EDAP Technomed Group (U.S.A.) submitted the required information.

The company addressed the labeling, EMC, device description, and microwave safety issues discussed in the approvable letter. To fulfill the conditions of approval, the sponsor will conduct a study to address FDA's and the Panel's concerns. This study will assess the long-term safety of the treatment and the retreatment rate in 100 of the patients currently enrolled in the study, followed for 5 years.

CDRH determined that, based on the modified labeling, additional device description information, and postapproval studies, the applicant's response was adequate.

Early in March of 1996 the agency became aware that clinical data may have been omitted from the PMA. On March 26, 1996, FDA issued a letter requesting that the company submit (i) any clinical data not previously submitted in the PMA, and, if applicable, (ii) the reason(s) why such data were omitted. In an amendment received by FDA on April 8, 1996, the applicant reported the results of several additional foreign clinical studies, and stated that these data were omitted from the PMA for reasons other than poor safety or effectiveness results, such as inadequate study design, multiple protocol deviations, poor follow-up compliance, and the use of different software versions.

CDRH determined that, based on the review of the supplemental clinical data reported in the amendment, the applicant's response was adequate and these data are similar to the results previously reported in the PMA.

Following an FDA inspection on January 25-30, 1996, the manufacturing facilities were determined to be in compliance with the Good Manufacturing Practices (GMP) regulation.

CDRH issued an approval order for the application on May 3, 1996.

### **XIII. REFERENCES AND OTHER RELEVANT PUBLICATIONS**

"Benign Prostatic Hyperplasia: Diagnosis and Treatment," Agency for Health Care Policy and Research (AHCPR) Clinical Practice Guideline Number 8, AHCPR Publication No. 94-0582, U.S. Department of Health and Human Services, 1994.

## 2. CLINICAL INFORMATION

### 2.1. Indications for Use

The PROSTATRON is a non-surgical treatment alternative to TransUrethral Resection of the Prostate (TURP) for the treatment of symptomatic Benign Prostatic Hyperplasia (BPH). The PROSTATRON is indicated for patients with prostatic lengths of 35 to 50 mm. It is intended that the PROSTATRON deliver a complete thermal therapy treatment during a single treatment session.

### 2.2. Contraindications

- Peripheral arterial disease with intermittent claudication or Leriche's syndrome (*i.e.*, claudication of the buttocks and perineum).
- Clinical or histological evidence of prostatic cancer or bladder cancer.
- Severe urethral stricture preventing easy catheterization.
- Presence of a cardiac pacemaker, an implantable defibrillator, or a metallic implant in the region of the hip, pelvis, or femur.

### 2.3. Warnings

Studies have not been conducted on patients with evidence of latex sensitivity, and therefore patients with this condition must be treated with caution.

In the PROSTATRON clinical study, patients with a pre-treatment post-void residual urine of greater than 150 ml and a prostate volume of greater than 40 ml had a higher incidence of transient urinary retention after TUMT than other patients. The retention is likely to be due to a degree of detrusor failure in these men. Prior to discharge, such patients should be carefully assessed to determine their risk of experiencing post-treatment retention. A reasonable period of catheterization may be prudent to avoid the occurrence of acute urinary retention post-discharge.

### 2.4. Precautions

The safety and effectiveness of treatment with the PROSTATRON have not been established in patients with the following conditions:

- Interest in the preservation of future fertility.
- Disorders of coagulation.
- Renal impairment.
- Neurological disorders which might affect bladder function.

- Post-void residual urine volumes greater than 350 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).

The use of the PROSTATRON must be prescribed and administered under the direct supervision of a qualified and trained physician, after appropriate urologic evaluation of the patient. The treating physician should be present at all times during the treatment, and the following additional warnings should be observed with respect to the patient's safety:

- The treatment catheter must be cleaned and high-level disinfected prior to use according to the procedures outlined in the user's manual.
- Do not use a treatment catheter if it appears to be damaged.
- Ensure that the treatment catheter is correctly seated within its connection plate on the PROSTATRON. Never attempt to turn microwave power on without the treatment catheter connected.
- The Prostate probe must not, under any circumstances, be connected to the treatment module before the treatment applicator has been carefully passed into the patient's urethra. The correct positioning of the treatment applicator must always be checked by ultrasound imaging prior to commencing treatment.
- The treatment must not be commenced until the rectal probe is introduced into the patient's rectum after removal of the ultrasound probe. The probe's orientation must be verified, and its position secured using adhesive tape.
- Do not start microwave emission until all jewelry or metallic elements on the patient's clothes are removed.
- The emission of microwaves must be switched off during treatment applicator positioning or premature removal to avoid stray microwave radiation, directed either towards the patient's eyes or testes, or the operator.

- Operators must remain at a distance of at least 15 cm from the patient during microwave emission in order to avoid excessive exposure to electromagnetic fields.
- Substantial changes in prostate specific antigen (PSA) levels—up to 470 percent after 1 week—may be seen in the first few weeks after TUMT. The use of PSA testing during this period will be unreliable. Physicians are cautioned to measure the serum PSA level before treatment for future comparisons. PSA levels should return to baseline by 6 months following TUMT and may once again be used as a diagnostic test.
- It is recommended that TUMT-treated patients be followed on an annual basis to assess for any prostatic changes since treatment with the PROSTATRON does not result in removal or total destruction of the prostate.
- The electrical equipment inside the PROSTATRON uses voltages which are capable of causing serious injury or death from electric shock. To avoid this hazard, operators must never remove any of the PROSTATRON's cabinet covers.
- To minimize the risk of electromagnetic interference between the PROSTATRON and any nearby electrical equipment, any electrical devices should be placed at least 3.25 m (10.6 ft.) from the PROSTATRON's microwave antenna while the PROSTATRON is in operation. Since some medical equipment may not meet the 3 V/m standard and could potentially be affected at distances greater than 3.25 m (10.6 ft.), periodic monitoring of the equipment for erratic operation is recommended. Similarly, since the emissions of some medical equipment may be high enough to affect the operation of the PROSTATRON at distances greater than 3.25 m (10.6 ft.), periodic monitoring of the PROSTATRON for erratic operation is also recommended. If it is necessary to operate an electrical device closer than 3.25 m (10.6 ft.) while the PROSTATRON is in operation, the device and the PROSTATRON should be completely tested for proper simultaneous operation prior to its clinical use.

Since microwave energy can travel through walls, ceilings, and floors to affect other devices, it is important to understand that the 3.25 m safety distance applies not only to the treatment room, but also to all adjacent rooms in the building, including the rooms above and below the treatment room.

- Use of the PROSTATRON results in the deposition of microwave energy within the patient's prostate and in 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.

## 2.5. Adverse Events

A total of 375 patients were evaluated for adverse events in the clinical investigation of the PROSTATRON. The studies conducted indicated the following adverse events:

### *HEMATURIA*

Transient hematuria was noted in 195 (52%) of the cases and is believed to be due to the instrumentation effect. There was no significant bleeding requiring transfusion.

### *URINARY RETENTION REQUIRING CATHETERIZATION*

120 (32%) of patients underwent catheterization for urinary retention. The catheter was removed in most cases at one week which was consistent with the patients return visit.

### *URETHRAL BLEEDING*

50 (13.3%) of the patients reported urethral bleeding, defined as bleeding from the penis not associated with urination. Study investigators attributed this bleeding to the urethral instrumentation, and did not consider any case to be serious or to require intervention.

### *URINARY/RECTAL DISCOMFORT*

Discomfort of the urinary tract (37 patients (9.9%)) and rectum (8 patients (2.1%)) was transitory and did not require hospitalization.

### *URINARY TRACT INFECTION*

32 (8.5%) cases of urinary tract infection were reported in the clinical investigation.

### *MINOR EJACULATORY DISTURBANCES*

25 (6.7%) of the patients reported minor ejaculatory disturbances. These abnormalities were of semen character including hematospermia, dry ejaculate and reduction in ejaculate volume. There was no incidence of retrograde ejaculation.

### *INFLAMMATION/PAIN IN THE REPRODUCTIVE TRACT*

23 (6.1%) of the patients reported inflammation/pain in the reproductive tract.

#### **URETHRAL DISCHARGE**

20 (5.3%) of the patients reported urethral discharge, defined as fluid leaking from the penis which was not blood.

#### **ABNORMALITIES BY PROCTOSCOPY**

Abnormalities by proctoscopy, including small (*i.e.*,  $\leq 4$  mm) nodules/ulcerations/abrasions on the anterior rectal wall, minimal friable anterior mucosa, rectal edema, and bleeding due to irritated hemorrhoids, were noted in 10 (2.7%) of the patients. Study investigators attributed these abnormalities to the rectal instrumentation, rather than to heating of the rectal mucosa. All of the abnormalities were considered minor and were resolved by the 6 week post-treatment examination.

#### **URETHRAL TRAUMA**

During treatment minor urethral trauma (*e.g.*, false passage) was reported in 9 (2.4%) of the patients.

#### **ELEVATED BLOOD PRESSURE**

8 (2.1%) patients were treated for elevated blood pressure during treatment due to anxiety.

#### **DISCOMFORT DURING TREATMENT**

Discomfort during treatment was reported by 8 (2.1%) of the patients.

#### **DECREASED SEXUAL FUNCTION AND IMPOTENCE**

7 (1.9%) of the patients reported a decrease in sexual function which was limited to either transient or partial difficulty with their erections. The rate of impotence after TUMT is probably no more than what is expected to naturally occur with age.

## 2.6. Clinical Trials

Four prospective clinical studies were conducted to assess the safety and effectiveness of the PROSTATRON in the treatment of BPH. A total of 444 patients were treated in these studies, 375 of whom received Transurethral Microwave Thermotherapy (TUMT). Specifically, these studies were as follows:

1. A randomized double-blind study compared patients receiving Transurethral Microwave Thermotherapy (TUMT) to those receiving a simulated sham treatment. The purpose of this study was to evaluate the therapeutic effect and adverse events attributable to instrumentation alone. A total of 115 patients were treated in this study, 78 in the TUMT group and 37 in the sham group.
2. A multi-center study was designed to assess the therapeutic benefit of TUMT in a larger population than the Sham *versus* TUMT study and over a long term (12 months) follow-up period. A total of 216 patients were treated at five U.S. investigational sites.
3. A second randomized study was designed to compare the overall morbidity of patients treated with the PROSTATRON to patients treated with transurethral resection of the prostate (TURP). A total of 70 patients were treated in this study, 38 in the TUMT group and 32 in the TURP group.
4. An Interstitial Thermometry Study was performed at one clinical site to evaluate the temperature distribution achieved during TUMT and to examine the association of intraprostatic temperatures with PROSTATRON treatment parameters and patient improvement. Forty-three patients were treated in this study.

In the study comparing the morbidity of the PROSTATRON to the instrumentation effect (Sham Study), the incidence of hematuria, urethral bleeding, and other urinary tract findings were essentially equivalent.

In all four studies, the primary endpoints for efficacy were improvements in the Madsen Symptom Score and in peak urine flow rates. The results of these studies show that the improvements in these efficacy variables were highly significant across all clinical sites.

### Absolute Levels in Madsen Symptom Score

| Study        | Pre-Treatment | Follow-Up             | p-value |
|--------------|---------------|-----------------------|---------|
| GENERAL      | 13.9 ± 3.6    | 5.7 ± 4.0 (12 months) | 0.0001  |
| SHAM         | 14.9 ± 3.2    | 10.8 ± 4.4 (3 months) | 0.0001  |
| TUMT         | 13.9 ± 3.5    | 6.3 ± 5.0 (3 months)  | 0.0001  |
| TURP         | 13.2 ± 3.7    | 0.5 ± 1.2 (12 months) | 0.0001  |
| TUMT         | 11.8 ± 3.1    | 2.1 ± 2.3 (12 months) | 0.0001  |
| INTERSTITIAL | 14.5 ± 3.3    | 3.3 ± 2.7 (3 months)  | 0.0001  |

### Absolute Levels in Peak Flow Rate (ml/s)

| Study        | Pre-Treatment | Follow-Up              | p-value |
|--------------|---------------|------------------------|---------|
| GENERAL      | 8.3 ± 2.8     | 11.2 ± 4.1 (12 months) | 0.0001  |
| SHAM         | 7.4 ± 1.6     | 9.4 ± 3.7 (3 months)   | 0.001   |
| TUMT         | 7.2 ± 1.6     | 11.5 ± 4.0 (3 months)  | 0.0001  |
| TURP         | 8.6 ± 3.5     | 18.2 ± 5.8 (12 months) | 0.0001  |
| TUMT         | 9.4 ± 2.4     | 12.1 ± 3.6 (12 months) | 0.0001  |
| INTERSTITIAL | 7.4 ± 1.5     | 11.1 ± 3.4 (3 months)  | 0.0001  |

In the General Study population, a statistically significant improvement in the post-void residual urine volume of 21% was observed, decreasing from 176 ml before treatment to 139 ml at 12 months. However, the improvements observed were generally modest and not believed to be clinically significant.

Of the 375 patients in these clinical studies who were treated with the PROSTATRON, 42 (11.2%) of these patients underwent further treatment for BPH during the 1-year period following their initial course of TUMT. Twenty-nine (7.7%) patients were retreated with the PROSTATRON, seven (1.9%) patients received surgical treatment for BPH, and six (1.6%) patients received medications for treatment of BPH.

These data demonstrate that thermotherapy with the PROSTATRON results in sustained, highly significant improvement in BPH symptoms and is a safe and effective treatment for men with symptomatic BPH and prostates of lengths 35 to 50 mm.