SUMMARY OF SAFETY AND EFFECTIVENESS DATA

I. GENERAL INFORMATION

Device Generic Name:	Transurethral Microwave Thermotherapy System
Device Trade Name:	TherMatrx TMx-2000™ BPH Thermotherapy System
Applicant:	TherMatrx, Inc. 3675 Commercial Avenue Northbrook, Illinois 60062
Premarket Approval (PMA) Number:	P000043
Date of Notice of Approval to Applicant:	June 29, 2001

II. INDICATIONS FOR USE

The TMx-2000™ BPH Thermotherapy System is a non-surgical device for the treatment of symptomatic Benign Prostatic Hyperplasia (BPH) in men who have a minimum prostatic urethra length of 30 mm and a total prostate volume between 30 and 100 cc.

III. CONTRAINDICATIONS

The TMx-2000™ System is contraindicated in patients who have one or more of the following conditions:

1. Patients with peripheral arterial disease with intermittent claudication or Leriches syndrome (i.e., claudication of the buttocks and perineum).
2. Patients with severe urethral strictures, preventing easy catheterization.
3. Patients with implanted defibrillators, pacemakers, or any other active implant.
4. Patients with a penile or urinary sphincter implant.
5. Patients with a metallic implant in the prostatic treatment area, pelvis, or hip.
6. Patients with a minimum prostatic urethra length <30mm and a total prostate volume <30 or >100 cc.

7. Patients with clinical or histological evidence of prostatic or bladder cancer.

8. Patients who have undergone prior radiation therapy to the pelvic region.

IV. WARNINGS AND PRECAUTIONS

Warning:

1. The TMx-2000™ System procedure has inherent risks of complications (refer to Adverse Events). The TMx-2000™ System and components should not be used in any way other than the intended and indicated use and according to the instructions for use.

2. Failure to properly position the Rx-200 Applicator could result in heating and severe injuries outside of the treatment area. If applicator placement is in question, verify placement by ultrasound imaging after inflating the balloon. Inflation of the balloon with more than 5 cc of sterile water may position the catheter too high in the urinary channel, which may result in heating outside of the treatment area.

Precautions:

Therapy Related

Before Treatment:

1. The safety and effectiveness of the TherMatrx, Inc. TMx-2000™ System have not been established in patients with the following conditions:

   - Interest in preserving future fertility
   - Coagulation disorders
   - Renal impairment
   - Neurological disorders which may affect bladder function
   - Post void residual volume of > 200 mL
   - Urinary retention requiring indwelling catheter
   - Large median lobe of the prostate protruding into the bladder
   - Active urinary tract infections
   - Bacteriological evidence of bacterial prostatitis
   - Bladder stones
   - Previous pelvic surgery
   - Previous rectal surgery (other than hemorrhoidectomy)
   - Prostatic urethra lengths greater than 57 mm in length

2. The use of the TherMatrx, Inc. TMx-2000™ System must be prescribed and administered under the direct supervision of a qualified and trained physician, after appropriate urological evaluation of the patient.

3. Select the proper Rx-200 Applicator based on the prostatic urethra length (bladder neck to verumontanum). The 2.5 cm coil length is for patients with a prostatic urethra length ≥3.0 but <4.0 cm. The 3.5 cm coil length is for patients with a prostatic urethra length ≥4.0 but <5.0 cm. The 4.5 cm coil length is for patients with a prostatic urethra length ≥5 cm.

4. Do not use the disposable urethral Rx-200 Applicator if it appears damaged or if the package seal has been compromised.

5. Use the disposable Rx-200 Applicator prior to the "Use Before" date specified on the package.

6. Care should be taken in handling all components of the TMx-2000™ System procedure to avoid damage that may lead to subsequent failure of the component or procedure.

Treatment

7. Attention by a qualified physician is required during the use of the TMx-2000™ System. The control unit display must be monitored and controlled during the course of a therapy session to make sure that the Rx-200 Applicator and rectal temperatures are within prescribed treatment parameters. Failure to monitor and deliver the TMx-2000™ System procedure per recommendations by TherMatrx, Inc. may lead to decreased patient safety and/or reduced clinical effectiveness.

8. All components of the TMx-2000™ System (Rx-200 Applicator with temperature sensors and rectal probe with temperature sensor) must be used according to the instructions included in the TMx-2000™ System Operator's Manual. Failure to do so may result in insufficient therapy or increased risk of injury or infection to the patient.

9. The disposable Rx-200 Applicator must only be used with the TMx-2000™ Control System.

10. The disposable Rx-200 Applicator must not, under any circumstances, be connected to the TMx-2000™ Control System before the applicator has been carefully passed into the patient's urethra.

11. Following inflation of the balloon (maximum of 5 cc), the balloon must be positioned at the base of the bladder by gently pulling on the catheter. In order to maintain proper positioning of the radiating antenna within the prostate throughout the treatment, light tension must be maintained on the catheter by gently pulling on the urine drainage tube and securing the drainage tube, under tension, to the patient's leg.

12. Risks of improper placement of the Rx-200 Applicator include procedure failure or heating damage of non-target tissues such as the bladder neck, external sphincter, or penile urethra.

13. It is possible that the balloon can unintentionally deflate during treatment, resulting in applicator migration outside of the treatment area. Closely monitor patient's pain level, temperature fluctuations, urine drainage, and tension of drainage tube. Increased pain, a

sudden drop in temperature >2°C, and decreased tension of drainage tube during treatment may be indications of catheter migration.

14. Do not initiate treatment until the rectal probe is properly placed.

15. The emission of microwaves must be off during placement and removal of the Rx-200 Applicator to avoid stray microwave radiation directed either towards the patient's or the operator's eyes or testes.

16. The patient should be placed in a comfortable supine position during treatment. Elevating the patient's torso more than 30° may cause the rectal and prostatic tissues to be compressed, reducing the distance between the rectal tissues and the radiating antennae, which could result in higher rectal temperatures.

17. BPH treatment using the TMx-2000™ System deposits 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 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.

18. The disposable Rx-200 Applicator is intended for **one time use only. DO NOT** resterilize or reuse the Rx-200 Applicator, as this will likely result in compromised device performance and increased risk of injury or infection to a patient.

Post-Treatment

19. As patient responses to the TMx-2000™ System procedure are variable, the patient should be evaluated by their physician following treatment.

20. Because the TMx-2000™ System procedure elevates intraprostatic tissue temperature, causing tissue damage that may result in acute urinary retention, it is advisable for the patient to be catheterized for 2 to 5 days following treatment (refer to Adverse Events, discussion of 2-5 Days Follow-up Events).

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

22. It is recommended that patients treated with the TMx-2000™ System be followed on an annual basis to assess for prostatic changes.

23. The safety and effectiveness of retreatment with the TMx-2000™ System has not been established.

<u>Device Related - Microwave and AC Power</u>

24. Operate the TMx-2000™ Control System and system components only in clinical environments where the installation is in accordance with international standard DIN VDE

0107; and the national standard ANSI/NFPA 70. The equipment must be connected to a fully tested, hospital grade power outlet that has adequate grounding.

25. The TMx-2000™ Control System must be plugged into the appropriate voltage outlet.
Power Requirements:
Supply: 220/240 V [±10%](8 A) Single phase 50 or 60 Hz or
110/120 V [±10%](15 A) Single phase 50 or 60 Hz or
100 V [±10%](15 A) Single phase 50 or 60 Hz

AC Connection: Hospital Grade Plug

26. Do not use the equipment in an explosive atmosphere.

27. Exposing eyes to microwave energy may damage eyes.

28. Failure to properly maintain the equipment may result in exposure of the patient and/or the operator to excessive microwave energy.

29. The TMx-2000™ System uses voltages that are potentially lethal. Use extreme caution when performing maintenance of the TMx-2000™ System console.

30. TherMatrx, Inc. recommends that all electronic medical devices be kept at a minimum distance of one meter from the TMx-2000™ System when performing a thermotherapy procedure. However, a 1-meter separation of electronic medical devices from the TMx-2000™ System does not guarantee that operation of other medical devices will not be impacted. The operations of all other medical equipment used in proximity to the TMx-2000™ System must be closely monitored, as the functions of electronic equipment may be effected by the energy emitted during operation of the TMx-2000™ System.

31. Do not operate an electronic device or equipment emitting electromagnetic energy in proximity to the TMx-2000™ System during a thermotherapy procedure, as the electronic equipment may interfere with the operation of the TMx-2000™ System.

32. The ANSI/IEEE C95.1992 recommended stray field exposure level for partial body exposure, at 915 MHz, is 20 mW/cm^2, except for eyes and testes. Stray field testing on the Rx-200 Applicator has shown that the maximum stray field level observed at a 5 cm distance from the Rx-200 coaxial cable is 5.2 mW/cm^2. The ANSI/IEEE recommended maximum stray field exposure level for whole body exposure, including the testes and eyes, is 3 mW/cm^2, as averaged for any 6-minute period. In order to comply with these ANSI/IEEE guidelines, TherMatrx, Inc. recommends that a minimum distance of 10 cm be maintained between the Rx-200 Applicator coaxial cable and the operators during a thermotherapy procedure.

V. DEVICE DESCRIPTION

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The TherMatrx, Inc. TMx-2000™ System is a computer-controlled system designed to deliver transurethral microwave thermotherapy treatment to the prostate for the treatment of BPH. The TMx-2000™ System consists of three basic components: a 915-MHz microwave delivery subsystem; a proprietary, thermistor-based, thermometry subsystem; and a computerized monitoring and control subsystem. The heating process is controlled by the computer subsystem, which uses a closed-loop feedback control system connecting the microwave delivery subsystem and the thermometry subsystem. The computerized control system automatically monitors and controls the heating by adjusting the microwave power output based on the measured temperature data from two independent urethral temperature sensors.

The TMx-2000™ System's microwave subsystem includes a 23 watt 915 MHz microwave generator and the disposable Rx-200 Applicator, which is comprised of a silicone urethral Foley urine drainage catheter, a radiating helical coil antenna, and two closed-tip urethane lumens bonded to the outside of the catheter. The disposable Rx-200 Applicator is used for urine drainage, heating of the prostatic tissues, and positioning of the sensors that monitor the temperature of the prostatic tissues. In order to provide thermotherapy treatment to a wide range of prostate sizes, the microwave antenna comes in three heating lengths (2.5 cm, 3.5 cm, and 4.5 cm). The three antennae lengths provide heating targeted to the measured length of the urethra (between the verumontanum and bladder neck) of the patient being treated. Use of a patient-specific heating length antenna targets the thermotherapy treatment to the same area that would be treated by a transurethral prostatectomy (TURP) and prevents heating of non-obstructing tissues. The Rx-200 Applicator is a sterile single-use device.

The TMx-2000™ System's thermometry subsystem includes three, non-sterile, reusable, thermistor, temperature sensors and the associated electronics module. Two of the three sensors are inserted into the two closed-tip lumens of the disposable, sterile, Rx-200 Applicator. These sensors are used to continuously monitor the prostatic urethral temperatures along the length of the catheter and control the heating of the prostate. The third temperature sensor is inserted into a non-sterile, disposable, blind end, catheter that is attached along the anterior length of a reusable, non-sterile, silicone rubber, rectal probe and is used to continuously monitor rectal temperatures. The temperature sensor measures the temperature of the anterior rectal wall directly adjacent to the prostate. The entire rectal probe fixture is covered with a condom (not supplied by TherMatrx, Inc.).

The thermotherapy treatment is applied transurethrally to the prostatic adenoma using the disposable Rx-200 Applicator (treatment catheter). The microwave applicator is a helical coil design antenna which is impedance matched to ensure efficient energy delivery (<10% reflected power). The antenna is positioned 5 mm below the balloon to ensure precise and consistent positioning within the targeted prostatic tissue. The inflated balloon, located at the distal end of the treatment catheter, is seated in the bladder outlet and positions the radiating portion of the antennae within the prostatic urethra. Following inflation of the balloon, the balloon is positioned at the base of the bladder by gently pulling on the treatment catheter and confirming free flow of urine. In order to maintain proper positioning of the radiating antennae within the prostate throughout the treatment, tension is maintained on the catheter by gently pulling on the urine drainage tube and securing the drainage tube, under tension, to the patient's leg. If catheter placement is ever in doubt, verify the Rx-200 Applicator treatment catheter placement using visual, manual, or ultrasound verification techniques.

The standard therapy regimen is delivery of a single treatment at a control temperature of 50°C to 52.5° C for 30 to 60 minutes. After the urethral Rx-200 Applicator, rectal probe, and corresponding temperature sensors have been properly placed, treatment begins by the delivery of microwave power (maximum output of 23 watts) to the urethral Rx-200 Applicator according to a temperature induction algorithm. The system is set to a default urethral control temperature of 50.0°C and a treatment time of 40 minutes. This default temperature and time can be manually changed, but the maximum allowed urethral temperature is 52.5°C and the maximum allowed treatment time is 60 minutes. The maximum allowed rectal temperature of 42.5°C cannot be manually changed. The power output is automatically discontinued after the treatment time (at the operator-selected temperature) has elapsed.

During each patient's treatment, treatment parameters, including microwave energy output, urethral and rectal temperatures, and treatment time, are continuously monitored and controlled by the TMx-2000™ Control System. The power output level is controlled by the computer, based on pre-defined treatment parameters. The application of microwave power output is set to 0 watts if the urethral temperature rises 2°C above the operator selected treatment temperature. If the rectal temperature rises above 42.5°C, the treatment is automatically paused - the power output is set to 0 watts and an alarm is sounded.

The Rx-200 Applicator is designed and manufactured to emit the microwave energy in a reproducible, cylindrically symmetrical pattern that targets the BPH tissues. The rationale behind the use of thermotherapy at temperatures of 50-52.5°C, without urethral cooling, is to limit the heating to the BPH tissues, which provides relief of BPH symptomalogy and reduces the chance of deleterious heating to adjacent structures, including the rectum, ejaculatory ducts, and urinary sphincter. Thus, side effects are minimized and necrosis of the BPH tissue in the transition zone is maximized.

VI. ALTERNATIVE PRACTICES AND PROCEDURES

The treatment of BPH has been predominantly focused on the reduction of patient symptomatology and degree of associated urinary obstruction. The following are the currently available BPH treatment options, listed in order from least to most invasive: observation without treatment (watchful waiting), alpha blocker therapy, finasteride therapy, balloon dilation, heat therapy (i.e., using laser, radiofrequency, microwave, or conduction energy), transurethral incision of the prostate, transurethral resection of the prostate (TURP), and open prostatectomy.

VII. MARKETING HISTORY

Approximately 26 TMx-2000™ Systems have been marketed in Europe, Asia, South America, and Africa since 1989. Approximately 600 patients have been treated with the TMx-2000™ System in the U.S. and outside the U.S. The TMx-2000™ System has not been withdrawn from marketing for any reason relating to its safety or effectiveness.

VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

A total of 188 patients (125 patients in the active group and 63 patients in the sham group) were treated and 114 of the treated patients were available for evaluation at 12 months for adverse events in the clinical study of the TMx-2000™ System. See Table 3 for a complete listing of the adverse events observed in this study.

Listed below are possible side effects of thermotherapy treatment. However, these side effects were not experienced during the clinical study of the TMx-2000™ System.

- Rectal damage/fistula
- Urinary infection
- Changes in ejaculation following treatment (retrograde, painful, or difficult ejaculation; loss of ejaculation; or decreased fluid volume)
- Burns within prostate from the heat treatments, which may lead to temporary bleeding or increased discomfort in the prostate area
- Urethral narrowing from urinary scarring at a later date, leading to restriction of the urinary flow
- Temporary sterility (the therapy's effect on fertility is unknown)

IX. SUMMARY OF PRECLINICAL STUDIES

Biocompatibility Studies:

The only patient contacting component is the disposable Rx-200 Applicator. It is composed of a silicone rubber Foley catheter; two polyurethane temperature catheters bonded to the Foley, a piece of copper ribbon, room-temperature vulcanizing (RTV) silicone rubber adhesive, and a Silastic® silicone tubing used to isolate the microwave coil from patient contact. Both the silicone rubber Foley catheter and the polyurethane temperature catheters have been cleared for marketing under 510(k) clearances for similar or more extensive patient contact applications than those required to deliver thermotherapy treatments to the prostate. The copper ribbon is fixed in place and fully sealed with the RTV silicone adhesive between the silastic silicone tubing and the silicone Foley catheter, hence no patient contact. The RTV adhesive and Silastic silicone tubing have a long-history of safe and effective use. The RTV adhesive has passed USP XXIII Cytotoxicity and Class VI Tests for plastics (70°C). The Silastic tubing used to cover the microwave antenna has been tested for skin sensitization, cytotoxicity, genotoxic, pyrogenic, and thrombogenic potentials, as well as for the ability to elicit a response in USP Class V and 90-day implant tests, and has passed these tests. Testing, approvals, and the long history of safe use indicate that the disposable Rx-200 Applicator is non-toxic and safe for its intended use.

Electrical/Electromagnetic Compatibility (EMC) Testing:

Electrical safety testing (e.g., leakage current, grounding, and isolation) demonstrated that the TMx-2000™ System meets applicable electrical safety requirements specified in the latest version of IEC 60601-1-2. Testing was also 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 TMx-2000™ System meets the EMC standards of IEC 60601-1-2. Testing was also conducted to characterize the strength of the

electromagnetic field being emitted from the TMx-2000™ System during operation. These measurements indicated that it is safe for medical personnel who are around the equipment or in contact with the patient during the treatment based on the recommendations from the American National Standards Institute (ANSI) standard C95.1-1982. Emissions testing has been conducted on the TMx-2000™ System; however, emissions testing between the TMx-2000™ System and other medical devices has not been conducted. Keep all other electronic medical devices at least 1 meter from the antenna.

Spatial Specific Absorption Rate Testing:

Spatial Specific Absorption Rate (SAR) testing was conducted to determine the SAR distributions for the TMx-2000™ System's microwave antenna in longitudinal and transverse planes. The Rx-200 Applicator was tested for quantification of absolute SAR using temperature change measurement of short duration heating of muscle equivalent phantoms that modeled the dielectric characteristics of the tissues of the prostate, urethra, and penis. Relative SAR was measured using an E-field mapping probe scanning system in liquid phantoms. The SAR testing involved both straight insertion and a 90-degree curved insertion to provide worst case testing of the coil. Qualitative SAR tests also were also performed using temperature sensitive liquid crystal plastic sheets in a split phantom.

The SAR testing demonstrated uniform ellipsoid, cylindrically symmetric heating patterns, with maximum heating directly adjacent to the antenna and minimal heating at the applicator tip, which indicates that the TMx-2000™ System delivers microwave energy in a reproducible, uniform, and controlled manner.

Heating Characterization Studies

Heating characterization studies (animal and clinical) were conducted to validate equipment design and performance, verify operational safety and reliability; characterize the heating patterns in the region of the microwave antenna and applicator, and quantify the effects of heating on prostatic and rectal tissues. Heating characterization studies included animal, percutaneous thermometry, and histopathological studies.

Testing demonstrated that maximum temperature elevation occurs immediately adjacent to the Rx-200 Applicator surface, and that the thermal gradient is steep enough to confine heating to the BPH prostatic tissue and still provide adequate penetration for effective heating of the BPH tissue area. The heating zone was reproducible and was not shifted away from the prostate by patient movement. The studies demonstrated that the temperature could be precisely measured and regulated by sensors mounted on the applicator surface. There was no evidence of hazardous heating in either the rectal mucosa or outside the prostatic capsule.

Other Performance Testing:

The TMx-2000™ System and Rx-200 Applicator underwent numerous tests to ensure proper operation. Performance testing addressed the electrical, mechanical, and software properties of the device and included: reflected power levels, system/simulation testing, thermal time delay response, durability/reliability, stress, wear, functional performance in accordance with ASTM F623 (with deviations), and simulated insertion of the Rx-200 Applicator. Additionally, accelerated aging, environmental conditioning, and shelf life studies were conducted.

Testing indicated that the system performed properly, according to design specifications, in all testing conditions, demonstrating the performance of the device for its intended use. Accelerated aging and shelf life testing justified the 2-year shelf life proposed for the disposable Rx-200 Applicator.

X. SUMMARY OF CLINICAL STUDIES

Pilot Clinical Studies

Non-IDE studies were conducted in Europe to optimize equipment design and to demonstrate sufficient improvements in objective and subjective criteria to justify further study. Safety of the treatment was demonstrated and patient benefit was indicated by the results, supporting further studies.

In October 1997, prior to initiation of a large-scale randomized trial, TherMatrx, Inc. conducted a pilot study (IDE #G890050) that was designed to evaluate patient tolerance and the dose response in order to optimize the treatment temperature. The study included 10 patients treated at the University of Utah Medical Center and Urology Associates of DuPage. The dose escalation study used treatment temperatures from 50°C to 55°C delivered for up to 60 minutes. The prostatic transition zone and rectal tissue temperatures were monitored to quantify the results of the heating. Data showed that clinically relevant heating was limited to the periurethral prostate area, with no evidence of excess heating or hazardous hot spots in the rectal mucosa.

Pilot clinical studies demonstrated a sufficient safety margin and sufficient improvements in objective and subjective criteria to justify further study.

Pivotal Clinical Study

Study Design and Methodology

A multi-center, randomized, double blinded, cross-over study comparing the transurethral microwave thermotherapy treatment using the TMx-2000™ System to a sham treatment control group was conducted at seven (7) clinical sites to determine if the delivery of microwave thermotherapy would alleviate symptoms of urinary obstruction in patients suffering from BPH.

The design of the clinical investigation of the TMx-2000™ System was consistent with the recommendations made in the FDA guidance document entitled, "Draft Guidance for the Clinical Investigation of Devices used for the Treatment of Benign Prostatic Hyperplasia (BPH), Nov. 1994."

The primary study endpoint was the change in AUA Symptom Index (AUASI), in both groups, from baseline to 3-months, with continued follow-up to 1 year for the thermotherapy treated group. Treatment success for the study was defined as a reduction of ≥50% in the AUASI, from baseline to 3 months post-treatment. Continued patient follow-up to 1-year following treatment allowed evaluation of duration of response. Additional effectiveness outcome measures included: Bother Index, Quality of Life, Sexual Function, uroflow measurements, PSA, cystoscopy, and pressure-flow studies. The principal safety concern was the number of adverse events and complications that could be attributed to thermotherapy.

The AUASI is a symptom index scoring method that has been validated by the American Urological Association to asses BPH symptoms (Clinical Practice Guideline Number 8 Benign Prostatic Hyperplasia: Diagnosis and Treatment, U.S. Department of Health and Human Services, Public Health Service, Agency for Health Care Policy and Research, AHCPR Publication No.94-0582, 1994). Bother Index and Quality of Life were assessed per Mebust, W.K., Bosch, R., Donovan, J. et al: Symptom Evaluation, Quality of Life and Sexuality. Proceedings of the 2nd International Consultation on Benign Prostatic Hyperplasia (BPH). Edited by A.T.K. Cockett, S. Khoury, Y. Aso et al. Channel Islands: Scientific Communication International, Ltd., Chapter 5, pp.129-147, 1993. Sexual Function was assessed per Rosen, R.C., Riley, A., Wagner, G., Osterloh, I.H., Kirkpatrick, J. and Mishra, A.: The International Index of Erectile Dysfunction (IIEF): A Multidimensional Scale for Assessment of Erectile Dysfunction. Urology 49:822, 1997.).

A total of 207 patients were screened and enrolled. Of these 207 patients, seven patients were treated but were not randomized. The patients treated but not randomized were evaluated as a separate cohort. Therefore, a total of 200 patients were randomized and attempted treatment, using a ratio of 2 to 1, into either an active treatment group (n=134) or a double blinded sham control group (n=66). Of these 200 randomized patients, 12 patients (9 active treatment patients and 3 sham treatment patients) were not evaluated in the statistical analysis due to protocol deviations. Thus, a total of 188 patients were evaluated for the randomized study. Of the 188 patients, 125 were randomized to the active treatment group and 63 were randomized to the sham treatment group.

Table 1 provides the number of randomized patients included in the statistical analyses for each treatment group by center.

Table 1. Study Participants

Study Site	Number of Patients		Total Patients
	Active	Sham	
Urology of DuPage Wheaton, IL[1]	24	17	41
Loyola University Med. Center Maywood, IL	22	12	34
Methodist Urology Indianapolis, IN	5	6	11
Washington University Med. Center St. Louis, MO	15	4	19
Urologic Surgery Associates Overland Park, KS[2]	30	12	42
Scottsbluff Urology Scottsbluff, NE	4	0	4
Devine Tidewater Urology Norfolk, VA	25	12	37
Total # Randomized Patients Included in Statistical Analysis	125	63	188[3]

[1] A subset of 10 patients at this site underwent pressure flow studies prior to treatment and at the 6-month evaluation.

[2] A subset of 30 patients at this site underwent 6-month cystoscopic evaluation.

[3] Twelve out of 200 randomized patients were not included in statistical analysis. Three did not meet study requirements (2 active, 1 sham), four developed non-treatment related medical conditions that would have confounded study results (3 active, 1 sham), one active patient began taking post-treatment medications that would have confounded study results, one active patient did not meet testing requirements, and three did not meet treatment requirements (2 active, 1 sham).

Patient follow-up was scheduled for 2-5 days and at 1, 3, 6, 9, and 12 months post-treatment. At 3 months, patients were unblinded and patients who had received a sham treatment were offered the opportunity to receive a thermotherapy treatment. If the sham patient elected to receive treatment, he returned for follow up visits at 2-5 days and at 1, 3, 6, 9, and 12 months post-treatment.

At screening and follow-up visits, data collection included: physical examination, uroflow measurements, AUASI, Bother Score, Quality of Life Score, Sexual Function Questionnaire, cystoscopy (all patients at screening and 30 patients at 6 months), pressure-flow studies (subset only), digital rectal exam, transrectal ultrasound (screening, 6 and 12 months), PSA, urinalysis, and CBC/creatinine/electrolytes (screening).

Patient Selection

The study population included male patients from 50 to 86 years, with a mean age of 65, who had a diagnosis of symptomatic BPH. Study inclusion criteria included an AUASI $\geq$13 and a bother score $\geq$11; a peak urine flow rate $\leq$12 ml/sec on a voided volume of $\geq$125 ml; a prostate size ranging from 30 to 100 grams (without a significant intravesical middle lobe); and a

prostatic urethral length from bladder neck to verumontanum ≥3.0cm. All patients underwent a screening cystoscopy.

By the date of database closure, 124 of 125 active patients and 62 of 63 sham patients had completed their 3-month visit and 119 of 125 active patients had completed their 12-month follow-up visit. Seven patients (6 active, 1 sham) were lost to follow-up during the clinical study. Of the 7 patients who were lost to follow-up, 2 patients were lost to follow-up prior to their 3-month evaluation (one active patient relocated following his 1-month follow-up and one sham patient never returned for his follow-up evaluations). One active patient began taking post-treatment medications that would have confounded study results prior to his 6-month evaluation. Three active patients were lost to follow-up following their 6-month evaluation (one patient refused further medical testing procedures after the 6-month evaluation; two patients received other BPH treatments, prostatectomy and TURP respectively, after their 6 and 9-month evaluation.). One active patient was unavailable for evaluation after his 9-month evaluation due to a non-treatment related medical condition. In addition, there are missing data for various parameters (e.g., uroflow data, etc.) at all follow-up visits. Some patients were willing to complete questionnaires but were unwilling to participate in the other tests while other patients missed specific follow-up visits.

Baseline Characteristics

The overall mean age of study participants was 65 with a range from 50 to 86. (Two patients who exceeded the age requirement were enrolled in the study based on the opinion of the treating physician that their physical age was much lower than their chronological age.) The mean baseline AUASI for all patients (active and sham) was 22.6±5.2; the mean baseline bother score was 18.2±4.6; the mean quality of life (QOL) score was 11.4±3.3; and the mean sexual function score (total sexual score) was 24.95±11.03. The mean peak flow rate (PFR) was 8.6±1.9 cc/sec; mean average flow rate was 4.9±2.0 cc/sec; mean post void residual (PVR) volume was 53.7±49.4 cc; mean voided volume was 233.5±88.1 cc; and the mean void time was 64.9 ±79.0 sec. The mean baseline prostate size was 49.8±17.5 grams. The mean prostatic urethral length from bladder neck to verumontanum was 3.8 cm with a range from 3 to 6.2 cm.

The evaluated baseline characteristics (AUASI, bother score, QOL score, sexual function score, age, PFR, average flow rate, PVR, and prostate volume and size) were well matched and similar among study groups and treatment sites. Although a marginally significant difference was observed at baseline for post void residual volume (p=0.040 [MANOVA]) by study site, a covariate analysis demonstrated it did not effect the outcome of the study results. Therefore, the data from the clinical sites were pooled for analysis.

Treatment Parameters

All treatments were performed on an outpatient basis in urology offices or clinics. Patients (both active and sham) received both an oral analgesia and an oral sedative prior to treatment. No general or regional anesthesia was required for any patient treatment. The administration of prophylactic antibiotics before and/or after catheterization and following treatment was recommended.

Patients randomized to the treatment group received a single treatment at a minimum temperature of 50°C (maximum of 52.5°C). After the ramp-up was completed and a default control temperature of 50.0°C was obtained, treatment continued for 40 minutes under computer control, or as modified by the physician within the range of 50°C to 52.5°C and 30 to 60 minutes. Patients randomized to the control group were given a simulated (sham) heat treatment using a selected (non-heating) control temperature of 35°C. Sham patients underwent placement of the microwave catheter for the treatment period, without energy delivery, and received the same post-treatment care as the active patients.

The applicator heating length was selected to match the distance from the bladder neck to the verumontanum; i.e., the 2.5cm Rx-200 Applicator for a measured length $\geq$3.0 but <4.0cm; the 3.5cm Rx-200 Applicator for a measured length $\geq$4.0 but <5.0cm; and the 4.5cm Rx-200 Applicator for a measured length $\geq$5.0cm.

Power output levels for the active treatment group patients ranged from 3 to 17 watts with a mean of 6.9±2.3 watts (n=119). The mean maximum urethral temperature was 50.8°C±0.89 (n= 121). The range of values for maximum urethral temperature was 50°C to 55.8°C. [Note: The urethral temperature range for the pivotal study was 50-55° C, therefore a maximum urethral temperature of 57° C (2° C above the maximum allowed temperature) could have been achieved. The maximum urethral temperature of 52.5° C was not implemented until after database closure.] The mean thermal dose for treated patients was 1746.0±799.4 (n=121). Rectal temperatures ranged from 35.6 to 41.9 with a mean of 38.4±1.2 (n=120).

Data Analysis and Results

Effectiveness Endpoints

The evaluation of device effectiveness is based on the results of 125 patients who were treated with the TMx-2000™ BPH Thermotherapy System. Of these 125 active patients, 124 patients and 119 patients were available for evaluation at the 3-month and 12- month follow-up visit, respectively.

The primary study endpoint was the change in AUASI, from baseline to 3 months, with continued follow-up to 1 year. Treatment success was defined as a reduction of ≥50% in the AUASI and treatment failure was defined as a reduction of <30% in the AUASI, from baseline to 3 months post-treatment. Continued patient follow-up to 1-year following treatment allowed evaluation of the durability of the treatment.

The statistical tests used to evaluate the study data included: the independent samples *t*-test [IT], paired samples *t*-test [PT], and Pearson Chi-Square [PCS].

Comparing baseline to 3 months post-treatment for the active group (n=124), the mean AUASI decreased from 22.5±5.0 to 12.4±6.6, a 44.9% improvement ($p<0.001$ [PT]). Comparing baseline to 3 months post-treatment for the sham group (n=62), the mean AUASI decreased from 22.8±5.5 to 17.0±7.4, a 25.4% improvement ($p<0.001$ [PT]).

Table 2 summarizes the primary effectiveness results (success and failure) of the TMx-2000™ System and sham patients at the 3-month follow-up visit. The results demonstrate that a

significantly higher proportion of patients in the active group (45.2%) had a ≥50% reduction in AUASI than did the patients in the sham group (22.6%) (p<0.001 [IT]).

Table 2. AUASI Reduction at the 3-Month Follow-up Visit

	TMx (n=124)	Sham (n=62)	Between Group Difference
Reduction ≥50%	56 (45.2%)	14 (22.6%)	0.003 [PCS]
Reduction 30-49%	29 (23.4%)	16 (25.8%)	
Reduction <30%	39 (31.5%)	32 (51.6%)	

At 1-year follow-up, the AUASI for the active patients (n=119) decreased from 22.5±5.0 to 11.9±7.1, a 47.1% improvement (p<0.001 [PT]). The 1-year follow-up data demonstrated that 75.6% of the TMx-2000™ System treated patients experienced AUASI improvement greater than 25% and that 52.1% experienced improvement greater than 50%, comparing baseline to 1-year follow-up.

The secondary endpoints of device effectiveness were uroflow measurements (PFR, Ave. flow rate, mean void time, and PVR), Bother Score, Quality of Life (QOL) Score, and sexual function. Each of these endpoints was evaluated by patient self-report (except for the uroflow measurements) using standardized surveys at baseline, 3 months, and 1-year. The results of these effectiveness endpoints are described below.

Comparing baseline to 3 months post-treatment for the active group (n=120), the mean PFR increased from 8.6±1.9 to 11.4±5.4, a 32.5% improvement (p<0.001 [PT]). For the sham group (n=61), the mean PFR increased from 8.3±2.0 to 11.1±6.5, a 33.7% improvement (p=0.002 [PT]). There is not a statistically significant difference between the groups at 3 months. Approximately 90% of all patients, active (90.0%) and sham (90.2%), achieved improvements in PFR ≥25% at 3 months and just under 30% of the patients, active (29.2%) and sham (27.8%), achieved improvements in PFR ≥50% at 3 months. At the 1-year follow-up, PFR improvement for the active group (n=111) was maintained (8.6±1.9 to 13.6±8.4, 58.1% improvement) (p<0.001 [PT]).

Comparing baseline to 3 months post-treatment for the active group (n=120), significant improvement in mean average flow rate and mean void time were noted; however, no improvement was noted in PVR. For the sham group at 3 months, a significant improvement was demonstrated only in mean average flow rate (n=60). The results were sustained at the 1-year follow-up visit for the active group (n=111).

Comparing baseline to 3 months post-treatment for the active group (n=124), the QOL score improved from 11.4±3.3 to 6.2±4.2, a 45.6% improvement (p<0.001 [PT]). For the sham group (n=62), the QOL score improved 11.5±3.3 to 8.7±4.3, a 24.3% improvement (p<0.001 [PT]). The results were sustained at the 1-year follow-up visit for the active group (n=119).

Comparing baseline to 3 months post-treatment for both the active (n=122) and sham (n=61) groups, there was no decrease in sexual function reported; and no decrease in sexual function

(particularly with regard to erection and ejaculation in the active group) reported at the 12-month follow-up visit for the active group (n=116).

Safety Endpoints

Safety of the TMx-2000™ System was evaluated using the data collected during treatment and at each follow-up evaluation. In addition, safety was assessed by laboratory measurements, digital rectal exams, and cystoscopy evaluations. There were no unanticipated adverse events or patient deaths reported during the study.

A total of 188 patients (125 active, 63 sham) were evaluated for adverse events in the clinical investigation of the TMx-2000™ BPH Thermotherapy System. Sixty-six (66) (52.8%) active patients and 14 (22.2%) sham patients reported adverse events during treatment and/or through 1-month post-treatment. All adverse events reported in the active group were minor and nearly all were transitory and self-resolving. All adverse events reported in the sham group were minor, transitory, and self-resolving. There were no unanticipated adverse events, severe reactions to thermotherapy treatment, retreatments, or patient deaths reported during the study. In both groups, there was no rectal damage, sphincter damage, decrease in sexual function (particularly with regard to erection and ejaculation in the active group), or urethral strictures noted during the follow-up. The following table identifies the adverse events reported for this protocol. Table 3 provides a description of these adverse events.

Table 3. Adverse Events

	Active		Sham	
	Number	Rate	Number	Rate
At treatment				
Bladder Spasm	26	20.8%	3	4.8%
Bleeding	19	15.2%	3	4.8%
Burning Sensation after catheter insertion	1	0.8%	0	0.0%
2-5 Day Visit				
Hematuria	21	16.8%	0	0.0%
Dysuria[1]	18	14.4%	3	4.9%
Bladder spasm	17	13.6%	7	11.4%
Urgency	8	6.4%	2	3.2%
Bleeding from penis	0	0.0%	1	1.6%
1-Month Visit				
Hematuria	11	9.1%	0	0.0%
Dysuria	8[1]	6.6%	3	4.8%
Bladder spasm	5	4.1%	0	0.0%
Hematospermia	1	0.8%	0	0.0%

[1]One active patient reported dysuria at both the 2-5 day and 1-month visit, which persisted through the 12-month visit.

At Treatment: Of the 125 active patients, 38 (30.4%) reported 46 adverse events. Eight (8) active patients reported more than one adverse event. Of the 63 sham patients, 6 (9.5%) reported 6 adverse events.

2-5 Days Follow-up Events: Of the 125 active patients, 38 (30.4%) reported 64 adverse events. Seventeen (17) active patients reported more than one adverse event. Of the 61 sham patients, 8 (13.1%) reported 13 adverse events. Three (3) sham patients reported more than one adverse event.

All patients were discharged with a Foley catheter, which was left indwelling for 2-5 days. Twenty-three (23) of the 125 active patients (18.4%) required re-catheterization due to continued voiding difficulty. Of these 23 patients, 14 patients required catheterization longer than 5 days. All patients were catheter free within 10 days post-treatment. No sham patients were recatheterized.

1-Month Follow-up Events: Of the 122 active patients, 22 (18.0%) reported 25 adverse events. Three (3) active patients reported more than one adverse event. Of the 62 sham patients, 3 (4.8%) reported 3 adverse events.

The majority of these events resolved by the 3-month follow-up visit. One (1) of the 22 patients who reported an event at 1-month reported a new event at 3 months.

3-Month Follow-up Events: Of the 124 active patients, 2 (1.6%) reported 3 adverse events (two events of dysuria (1.6%) and one event of bladder spasm (0.8%)). None of the 62 sham patients reported an adverse event.

Adverse Events After 3 Months Post-Treatment: Of the active patients who reported adverse events during treatment and at the 2-5 day, 1-month, and 3-month visits, only 3 patients reported adverse events not resolved by the 3-month visit. One patient reported bladder spasm that persisted through the 6-month visit and resolved prior to the 9-month visit. One patient reported dysuria that resolved by the 6-month visit. One patient reported bladder spasm that resolved by the 6-month visit and dysuria that persisted through the 12-month visit.

Two patients reported 2 new adverse events during the 9- and 12-month visits. The newly reported events included dysuria at 9 months (which persisted through 1-year) and hematospermia at 1-year (which resolved immediately).

Cystoscopic examinations on a subset of the active patients (n=32) at the 6-month follow-up visit revealed no evidence that the periurethral thermotherapy treatment caused any deleterious effects and that the spectrum of post therapy observations were consistent with the pre-treatment examinations. Improvement in prostate mass was noted; however, the reduction is not believed to be clinically significant. During the study, 5 patients (4 active, 1 sham) had an abnormal digital rectal exam (i.e., tender/nodular). The abnormalities were not associated with any other significant findings and all but one (1) resolved by 1-year post-treatment. Prostatic specific antigen did not significantly change during the clinical study.

XI. CONCLUSIONS DRAWN FROM THE STUDIES

The laboratory, animal, and clinical data provide reasonable assurance of the safety and effectiveness of the TMx-2000™ System for the treatment of symptomatic BPH, when used as indicated.

The clinical data from patients treated with the TMx-2000™ System demonstrate that the treatment provides patient benefit combined with low morbidity. The 1-year effectiveness results for the thermal therapy treated patients demonstrate the durability of the treatment response with no decrease in sexual function.

Adverse effects were generally transitory, minor, and self-resolving and consisted mainly of bladder spasm, dysuria, urgency, and hematuria. There were few side effects after the 1-month follow-up visit; only 4 active patients reported adverse events past the 1-month evaluation. There were no reports of unanticipated adverse events, severe reactions to thermotherapy treatment, retreatments, or patient deaths. There was no sphincter damage, urethral strictures, rectal damage, or decrease in sexual function in either group.

XII. PANEL RECOMMENDATIONS

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

XIII. CDRH DECISION

Based on the data contained in the PMA, CDRH has determined that the TMx-2000™ BPH Thermotherapy System is safe and effective for the indication of relief of symptoms associated with BPH in men with a minimum prostatic urethra length of 30 mm and a total prostate volume between 30 and 100 cc. Furthermore, the applicant agreed to the postapproval requirement that they collect data on the long-term (5-year) effect of their device.

The applicant's manufacturing facility was inspected on June 29, 2001, and was found to be in compliance with the device Quality Systems regulations.

XIV. APPROVAL SPECIFICATIONS

Directions for Use: See the labeling.

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

Postapproval Requirements and Restrictions: See approval order.