



947009

Memorandum

JUL 21 1997

Date .
From Deputy Director, Clinical and Review Policy,
Office of Device Evaluation (HFZ-400)
Center for Devices and Radiological Health (CDRH)
Subject Premarket Approval of HealthTronics, Inc.'s,
LithoTron™ Lithotripsy System
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.

Kimber Richter

Kimber Richter, M.D.

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

DECISION

Approved Disapproved _____ Date _____

Prepared by Russell P. Pagano, Ph.D., CDRH, HFZ-472, 6-10-97, 594-2194

/

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[DOCKET NO. _____]

HealthTronics, Inc.; Premarket Approval of Lithotron™

Lithotripsy System

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA) is announcing its approval of the application by HealthTronics, Inc., Marietta, GA, for premarket approval, under the Federal Food, Drug, and Cosmetic Act (the act), of the LithoTron™ Lithotripsy System. FDA's Center for Devices and Radiological Health (CDRH) notified the applicant, by letter of July 21, 1997, of the approval of the application.

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

ADDRESSES: 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, 12420 Parklawn Dr., rm. 1-23, Rockville, MD 20857.

FOR FURTHER INFORMATION CONTACT:

Russell P. Pagano,
Center for Devices and Radiological Health (HFZ-470),
Food and Drug Administration,
9200 Corporate Blvd.,
Rockville, MD 20850,
301-594-2194.

SUPPLEMENTARY INFORMATION: On May 16, 1997, HealthTronic, Inc., Marietta, GA 30060, submitted to CDRH an application for premarket approval of the LithoTron™ Lithotripsy System. The device is an extracorporeal shockwave lithotripter and is indicated for use in patients with renal and upper ureteral calculi between 4 and 20 millimeters in size.

In accordance with the provisions of section 515(c)(2) of the the act (21 U.S.C. 360e(c)(2)) as amended by the Safe Medical Devices Act of 1990, this PMA was not referred to the Gastroenterology and Urology Devices Panel of the Medical Devices Advisory Committee, an FDA advisory committee, for review and recommendation because the information in the PMA substantially duplicates information previously reviewed by this panel.

On July 21, 1997, CDRH approved the application by a letter to the applicant from the Deputy Director of Clinical and Review Policy 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, for administrative review of CDRH's decision to approve this application. A petitioner may request either a formal hearing under 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 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

JUL 21 1997

Ms. Marie E. Marlow
Vice President, Clinical and Regulatory Affairs
HealthTronics, Inc.
425 Franklin Road, Suite 545
Marietta, Georgia 30067

Re: P970019
LithoTron™ Lithotripsy System
Filed: May 16, 1997
Amended: June 10, 1997

Dear Ms. Marlow:

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 LithoTron™ Lithotripsy System. This device is indicated for use in patients with renal and upper ureteral calculi between 4 and 20 mm in size. 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, you have agreed to develop a protocol to collect long-term data to study the effect of your device on hypertension to fulfill the postapproval study requirements. The postapproval reports shall include a summary of your progress regarding the completion of the postapproval study requirements, including any available results.

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.

Page 2 - Ms. Marie E. Marlow

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 Boulevard
Rockville, Maryland 20850

If you have any questions concerning this approval order, please contact Russell P. Pagano, Ph.D., at (301) 594-2194.

Sincerely yours,

Kimber C. Richter

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

Enclosure

CONDITIONS OF APPROVAL

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

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

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

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

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

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

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

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

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

- (1) Identification of changes described in 21 CFR 814.39(a) and changes required to be reported to FDA under 21 CFR 814.39(b).
- (2) Bibliography and summary of the following information not previously submitted as part of the PMA and that is known to or reasonably should be known to the applicant:
 - (a) unpublished reports of data from any clinical investigations or nonclinical laboratory studies involving the device or related devices ("related" devices include devices which are the same or substantially similar to the applicant's device); and
 - (b) reports in the scientific literature concerning the device.

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

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

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

REPORTING UNDER THE MEDICAL DEVICE REPORTING (MDR) REGULATION. The Medical Device Reporting (MDR) Regulation became effective on December 13, 1984, and requires that all manufacturers and importers of medical devices, including in vitro diagnostic devices, report to FDA whenever they receive or otherwise became aware of information that reasonably suggests that one of its marketed devices

- (1) may have caused or contributed to a death or serious injury or
- (2) has malfunctioned and that the device or any other device marketed by the manufacturer or importer would be likely to cause or contribute to a death or serious injury if the malfunction were to recur.

The same events subject to reporting under the MDR Regulation may also be subject to the above "Adverse Reaction and Device Defect Reporting" requirements in the "Conditions of Approval" for this PMA. FDA has determined that such duplicative reporting is unnecessary. Whenever an event involving a device is subject to reporting under both the MDR Regulation and the "Conditions of Approval" for this PMA, you shall submit the appropriate reports required by the MDR Regulation and identified with the PMA reference number to the following office:

Division of Surveillance Systems (HFZ-531)
Center for Devices and Radiological Health
Food and Drug Administration
1350 Piccard Drive, 340
Rockville, Maryland 20850
Telephone (301) 594-2735

Events included in periodic reports to the PMA that have also been reported under the MDR Regulation must be so identified in the periodic report to the PMA to prevent duplicative entry into FDA information systems.

Copies of the MDR Regulation and an FDA publication entitled, "An Overview of the Medical Device Reporting Regulation," are available by written request to the address below or by telephoning 1-800-638-2041.

Division of Small Manufacturers Assistance (HFZ-220)
Center for Devices and Radiological Health
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

**SUMMARY OF SAFETY AND EFFECTIVENESS DATA:
HealthTronics, Inc.'s, LithoTron™ Lithotripsy System**

I. GENERAL INFORMATION

DEVICE GENERIC NAME: Extracorporeal Shock Wave Lithotripter

DEVICE TRADE NAME: LithoTron™ Lithotripsy System

APPLICANT: HealthTronics, Inc.
425 Franklin Road, Suite 545
Marietta, Georgia 30067

PREMARKET APPROVAL APPLICATION

(PMA) NUMBER: P970019

DATE OF NOTICE OF APPROVAL
TO THE APPLICANT: JUL 21 1997

II. INDICATIONS FOR USE

The HealthTronics, Inc.'s, LithoTron™ Lithotripsy System is indicated for use in patients with renal and upper ureteral calculi between 4 and 20 mm in size.

III. DEVICE DESCRIPTION/USE

The HealthTronics, Inc.'s, LithoTron™ Lithotripsy System (hereafter referred to as the LithoTron) utilizes spark gap technology to generate shock waves outside the patient's body to fragment urinary calculi within either the kidney or upper ureter. The device consists of (1) the shock wave unit; (2) the C-arm fluoroscopy unit; (3) the patient table; and (4) the ECG recorder.

Shock Wave Unit

The shock wave unit includes the therapy head and the control cabinet. Shock waves in the LithoTron are generated by an underwater electrode mounted within the brass ellipsoid reflector in the therapy head. These shock waves are generated when applied high voltage electrical energy produces a spark across the gap of an electrode positioned at one focus of a water-filled semi-ellipsoid reflector. Vaporization of the water occurs at the location of the spark which produces spherical shockwaves. The shock waves generated then refocus at the second focal point of the ellipse (inside the patient's body at the stone).

The therapy head integrates (1) the shock wave generator, which stores the energy that is discharged across the electrode tips; (2) the brass ellipsoid reflector, which houses the electrode; (3) the NewTrode™ electrode; and (4) the control desk, including a control panel with LED controls, and a handheld electrohydraulic shock wave (ESW) lithotripsy release switch button. The therapy head is coupled to the patient via a water-filled bellows cushion on the top of the therapy head, and is connected via cables and hoses to the control cabinet.

The control cabinet supplies water to the ellipsoid reflector in the therapy head, and automatically de-gasses and warms the water used within the therapy head. It also supplies the electric current required to operate the device. The control cabinet incorporates five compartments: (1) the charging unit, which delivers the high voltage to the shock wave generator; (2) the control unit, which contains a microprocessor which controls the shock wave release and timing, the valves, the charging unit, and the water pumps; (3) the electric module which controls the voltages for the keyboard and contains the power connections; (4) the water drawer unit, which contains a water tank, a safety thermostat, a desalination unit, and a small circulation pump; and (5) the water valve unit, which is connected to the inlet and outlet water hose and contains the vacuum pump, circulation pump, evacuation pump and valves.

C-Arm Fluoroscopy Unit

The stone to be treated is located by fluoroscopic visualization. The LithoTron is designed for use with the Philips BV 25 or the Philips BV 25 Gold x-ray fluoroscopy unit, either of which may be mechanically coupled to the base of the LithoTron. The fluoroscopy unit consists of a C-arm connected to a dual monitor, and is capable of fluoroscopy as well as film radiography.

Patient Table

The patient table is a motorized 3-way radiolucent table top which allows for movement in the x, y and z planes. The patient table is independent of the shock wave unit, except for the anti-collision cable. The anti-collision connection interrupts power to the table if a collision becomes possible between the table and therapy head. The table is operated by a hand-held switch, with two step-on foot brakes for locking in place prior to placing the patient on the table. The table top is radiolucent, as are the mats supplied with the table, with a cutout on one side which allows for the therapy head to be positioned correctly against the patient. The table is supplied with options including stirrups and a urine basin to allow additional procedures routinely performed at the time of lithotripsy to be easily accomplished.

ECG Monitor

The LithoTron is intended for use only with ECG gating, with one shock released during the "R" wave of the ECG trigger pulse. The Hellige ECG recorder Model SMS 181 (premarket clearance K832018A) is supplied with the LithoTron to provide the waveforms for triggering the shock waves; this ECG recorder is not intended for use as a diagnostic device.

For stone localization, an anteroposterior (AP) view is taken for localization in the x and y axes, and an angular (CC) view is taken for localization in the z axis. Guided by these two views, the operator positions the patient table so that the stone is centered within the cross hairs of the x-ray monitors. Correct positioning of the stone within the shock wave focus (f2) is thus assured.

IV. CONTRAINDICATIONS, WARNINGS AND PRECAUTIONS

The labeling for the LithoTron contains the following contraindications, warnings, and precautions:

Contraindications for the LithoTron are:

1. Patients with coagulation abnormality as indicated by abnormal prothrombin time (PT), partial prothrombin time (PTT), or bleeding time, including patients receiving an anti-coagulant (e.g., aspirin);
2. Patients with urinary tract obstructions distal to the target stone;
3. Patients in whom pregnancy is suspected;
4. Patients whose anatomy precludes focusing of the device in the area of the target stone, including obesity or severe curvature of the spine;
5. Patients with arterial calcification or vascular aneurysms in the lithotripter shock wave path;
6. Patients with a history of chronic or acute pancreatitis or gall bladder disease;
7. Patients whose weight exceeds 300 pounds;
8. Patients in whom general, spinal, or epidural anesthesia is contraindicated and for whom IV

sedation is contraindicated; and

9. Patients in whom the use of x-ray is contraindicated.

Warnings for the LithoTron are:

1. Although patients with infected stones and/or acute urinary tract infections have been successfully treated with shock wave therapy, the experience with the LithoTron in such cases is limited. Therefore, the safety and effectiveness of treatment of infected stones with the LithoTron have not been demonstrated. Due to the possibility of systemic infection from pathogen-harboring calculus debris, use of prophylactic antibiotics should be considered prior to treatment whenever the possibility of stone infection exists.
2. Bilateral treatment of renal stones should not be performed in a single treatment session because total urinary tract obstruction by stone fragments may result. Patients with bilateral renal stones should be treated using a separate treatment session for each side. In the event of total urinary obstruction, corrective procedures may be needed to assure drainage of urine from the kidney.
3. Care should be taken to ensure that shock waves are not applied to air-filled areas, i.e., intestines or lungs. Shock waves are rapidly dispersed by passage through an air-filled interface, which can cause harmful side effects.
4. Although children have been treated with shock wave therapy for upper urinary tract stones, experience with the LithoTron in such cases is limited. Therefore, the safety and effectiveness of the LithoTron in the treatment of urolithiasis in children have not been demonstrated. Studies indicate that there are growth plate disturbances in the epiphyses of developing long bones in rats subjected to shock waves. The significance of this finding to human experience, however, is unknown.
5. The safety and effectiveness of the LithoTron in the treatment of middle and lower ureteral stones is currently under study; therefore, the safety and effectiveness of the LithoTron for treating these stones is currently unknown. The treatment of lower ureteral stones should be particularly avoided in women of childbearing age, because treatment of this patient population could possibly result in irreversible damage to the female reproductive system and to the unborn fetus in the undiagnosed pregnancy.

Precautions for the LithoTron are:

1. Lithotripsy procedures performed with the LithoTron should only be performed with ECG gating of shock waves, and cardiac monitoring of patients should also be performed during treatment. This is especially important for patients who may be at risk for cardiac arrhythmia due to a history of cardiac irregularities, because the use of extracorporeal shock wave lithotripsy is known to cause ventricular cardiac arrhythmias in some patients and limited information is available on the effect of the LithoTron on cardiac rhythm.
2. Extreme caution should be used in the treatment of patients at high risk for heart failure, those with cardiac pacemakers or pneumonia, and patients with very low diaphragms. Although

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patients with implanted cardiac pacemakers have been treated with extracorporeal shock wave lithotripters¹, the safety of using the LithoTron to treat patients with cardiac pacemakers and other implanted devices, whose function could be affected by shock waves, has not been studied.

3. Extracorporeal shock wave lithotripsy procedures have been known to cause damage to the treated kidney. The potential for injury, its long term significance, and its duration are unknown. However, lithotripsy is believed to be less damaging than the persistence of the disease or alternative methods of treatment.
4. Treated patients should be followed radiographically until the patient is stone-free or there are no remaining stone fragments which are likely to cause a silent obstruction and loss of renal function.
5. While fluoroscopy must be used during the procedure, caution should be used to minimize the exposure.
6. No safety and effectiveness data are available regarding the treatment of patients with staghorn calculi.
7. Experience treating impacted or embedded stones with the LithoTron lithotripter is limited and safety and effectiveness cannot be assured. Experience by other manufacturers and investigators using extracorporeal shock wave lithotripters for impacted stones has shown limited success. Alternative procedures are recommended.
8. It is recommended that there be no less than a 1 month interval between treatments of the same kidney or focal area, and no more than three treatments to the same kidney. The number of shock waves should be minimized and limited to 3,000 in a single treatment session.
9. Due to noise associated with shock wave generation, both the patients and staff should wear ear protection during treatment.

V. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

Adverse events reported in association with the use of extracorporeal shock wave lithotripsy of upper urinary tract calculi include severe pain or renal colic; steinstrasse or post-treatment obstruction; nausea and/or vomiting; ecchymosis; infection or sepsis; urinary retention; gross hematuria; localized redness or petechiae at the treatment site; cardiac arrhythmia; hypertension; and renal injury or perirenal and intrarenal hematoma. More detailed information on these events can be found on page 11 of this document.

VI. ALTERNATE PRACTICES AND PROCEDURES

Urinary tract stone treatment has been based predominantly on the symptomatology and location of the stone. Treatment varies with the type and size of stone and the condition of the patient. The most common treatment for kidney stones is dietary restriction and consumption of large amounts of fluid. Soft ammonium-magnesium phosphate and uric-acid calculi may be dissolved in some instances by irrigation through ureteral catheters. Calculi of small size may be removed from the

lower ureter by means of instruments passed through the urethra into the ureter to snare the stone.

Patients with stones in the kidney and the proximal ureter with persistent and significant symptoms have historically been treated with open surgery, including partial nephrectomy and ureterolithotomy².

In recent years, percutaneous stone removal techniques have been developed for use on patients who were poor surgical candidates or had undergone open surgery in the past³. Percutaneous stone removal is now being used on patients who have not had previous operations because it is felt to be less invasive than open surgery and, in general, requires shorter hospitalization.

Other currently marketed extracorporeal shock wave lithotripters that have the same or broader indications for use offer another alternative.

VII. MARKETING HISTORY

HealthTronics is the exclusive United States distributor for the LithoTron, which is manufactured in Europe by High Medical Technologies (HMT) AG. No LithoTron devices have been distributed commercially by HealthTronics.

HMT supplies the same lithotripsy system to Philips Medical Systems for distribution as the Philips LDM-E. Approximately 15 Philips LDM-E devices are in distribution outside of the United States. The device has not been withdrawn from marketing for any reason related to safety or effectiveness of the device.

VIII. SUMMARY OF STUDIES

1. NONCLINICAL STUDIES

a. Characterization of the Shock Wave

Testing was conducted by an independent test facility to characterize the shock wave generated by the LithoTron lithotripter. A disposable PVDF Reference Shock Wave HydrophoneTM was used to measure the frequency domain, peak compressional (positive) and refractive (negative) pressures, rise time, and pulse width of the waveform. The following data were collected.

Pressure Measurement Data		
Power Setting	Peak Positive Pressure (MPa)	Peak Negative Pressure (MPa)
14 kV	29.7	-12.7
28 kV	52.3	-12.0

In addition, the rise time was determined to be 145.2 ± 29 ns and the pulse width (at 20kV) was measured as 268 ns.

b. Animal Study

A study was conducted at the Institute of Surgical Research of the University of Munich to evaluate the effects of shock waves generated with two different types of lithotripsy electrodes. One of the electrodes tested was a conventional electrode presently used in a commercially available spark gap lithotripsy system, and the other was the encapsulated electrode that is used in the HealthTronics LithoTron system. A canine model was used for this study.

The experimental design provided for five beagle dogs to be exposed to 3000 shocks from the conventional electrode to one kidney and 3000 shocks from the encapsulated electrode to the other kidney. For unstated reasons, one of the dogs was treated at a lower energy level than the other dogs and cannot be considered in the data evaluation. The kidney pelvis was positioned with x-rays at the focal point of the shock waves. The dogs were observed for gross shock damage to the skin, abdominal cavity, (e.g., intestines, pancreas outer capsule of kidney), and other organs that might be in the shock wave path. In addition, histological evaluation was performed to evaluate the incidence of hemorrhage, hematomas, and other post-treatment occurrences.

The findings indicated that qualitatively, the type of tissue damage is the same for each type of electrode. It was not possible to quantitatively determine whether these observations had any significance.

2. CLINICAL STUDIES

A prospective multicenter study was conducted to demonstrate the safety and effectiveness of the LithoTron when used as indicated for performing ESW lithotripsy in subjects with upper urinary tract (renal pelvis, renal calyx, and upper ureteral) calculi. The design of the clinical investigation is consistent with the recommendations that were made by the Gastroenterology and Urology Devices Panel members at their October 20, 1989, meeting. Specifically, the panel recommended that PMAs for renal extracorporeal shock wave lithotripters be based on a clinical study involving at least three investigational sites and 150 patients.

The investigation was conducted at four investigational sites in the United States, with the first study subject enrolled on July 18, 1996. Two hundred and fifteen study subjects underwent 221 lithotripsy procedures as of March 3, 1997, and 166 subjects had completed all follow up requirements on or by March 3, 1997. Therefore, data for 166 subjects are included in the effectiveness analysis, with data from all 215 subjects included in the safety analyses. The following table presents information regarding study participation status for all subjects enrolled in this clinical study.

Study Participation Status

Study Participation Status	RLS Portland, OR		Nebraska Methodist		Arlington Memorial, TX		Cape Girardeau, MO		TOTAL	
	N	%	N	%	N	%	N	%	N	%
Total Subjects Treated	52	100	50	96.2	90	100	23	95.8	215	98.6
• Total subjects enrolled	52	100	52	100	90	100	24	100	218	100.0
• Enrolled; excluded, not treated	0	0.0	2	3.8	0	0.0	1	4.2	3	1.4
Total Subjects Included in Both Safety and Effectiveness Analyses	43	82.7	48	92.3	60	66.6	15	62.5	166	76.1
Total Subjects Included in Safety Analyses Only:	9	17.3	2	3.8	30	33.3	8	33.3	49	22.5
• Not yet eligible for 1 month follow up	8	15.4	0	0.0	20	22.2	6	25.0	34	15.6
• Study participation ongoing to 3 months	0	0.0	1	1.9	4	4.4	1	4.2	6	2.7
• Noncompliant / Lost to follow up	0	0.0	1	1.9	5	5.5	1	4.2	7	3.2
• Withdrawn	1	1.9	0	0.0	1	1.1	0	0.0	2	0.9

RLS = Regional Lithotripter Services

a. Subject Selection and Inclusion / Exclusion Criteria

Male or female patients at least 21 years of age with urinary calculi in the kidney or upper ureter who were also appropriate candidates for lithotripsy were eligible for study enrollment. All patients must have undergone radiographic evaluation to confirm the presence of at least one stone greater than 4 mm and less than 20 mm in size. A signed informed consent form was obtained from all study participants.

Patients were excluded from study participation for any of the following reasons: urinary tract obstructions distal to the calculi, precluding passage of stone fragments; impaction of the stone(s) to be treated; calcifications in the aorta or the major renal arteries, or vascular aneurysms in the therapy wave axis; acute or unresolved cholecystitis, cholangitis, pancreatitis, or obstruction of the biliary duct system; coagulation abnormalities or anticoagulation therapy associated with abnormal prothrombin time (PT), partial thromboplastin time (PTT), or bleeding time; aspirin taken within 2 weeks prior to treatment or nonsteroidal anti-inflammatory drugs taken within 3 days of treatment; patients in ASA Class V; pregnancy; cardiac pacemaker in place; patients with congenital renal abnormalities; patients who were undergoing retreatment due to a previously failed lithotripsy procedure with another lithotripsy device; patients who could not be positioned correctly for fluoroscopic imaging or for focusing of the shock waves due to such conditions as obesity or physical deformity; and patients for whom radiography or all forms of anesthesia or analgesia were contraindicated. Patients with calculi in the middle or lower ureter were also excluded from participation in this study.

b. Study Population

Of the total 215 patients enrolled in the study, 147(68.4%) were male and 68 (31.6%) were female.

Patient age ranged from 17 to 89 years, with a mean of 48.6 years. The ratio of males to females in this study is similar to that reported in prior lithotripter studies.

c. Stone Characteristics

Total Stone Burden Measured: Each study subject was required to undergo either a radiographic assessment of the kidneys, ureter, and bladder (KUB) with ultrasound examination or an intravenous pyelogram (IVP) prior to the procedure to determine the total number and size of the stone on the side to be treated. Mean total stone burden pretreatment was 11.8 mm (range: 60.0 mm to 4.0 mm).

Total Stone Burden Treated: The total stone burden treated exceeded the maximum size described by the study protocol in three subjects; in all other cases, the stone burden treated fell within the 4 to 20 mm range described by the study protocol. The total stone burden treated was 10 mm or greater in 53.5% of the 215 study subjects.

Stone Location: The majority of stones to be treated (44.6%) were located in the renal calyx, with relatively similar distribution of the remaining stones located in the renal pelvis (22.3%), the ureteropelvic junction (16.7%), and the upper ureter (20.9%). Note that the total number of stones identified treated (n=245) exceeds the total number of subjects treated (n=215). For various reasons (e.g., < 4 mm, total burden > 20 mm, etc.), all stones were not targeted for treatment.

Number of Stones: For 163 of the 215 subjects treated (75.8%), a single stone comprised the total stone burden treated, 27 (12.6%) had two stones, 16 (7.4%) had three stones, 6 (2.8%) had four stones, 2 (0.9%) had five stones and 1 (0.5%) had six stones.

d. Compliance with Protocol Requirements

Fifteen study subjects (6.9%) of the 215 treated did not meet all of the inclusion/exclusion criteria described in the study protocol. Seven subjects (3.2%) with renal or ureteral abnormalities were enrolled in the study; four subjects (1.9%) who had taken aspirin within 2 weeks of treatment were enrolled; three subjects (1.4%) were enrolled with stones to be treated greater than 20 mm; and one subject was enrolled (0.4%) who was underage. In all cases, these deviations from the protocol represented either an increased risk to the subject of post-treatment complications (e.g., aspirin taken within 2 weeks of treatment increased the risk of gross hematuria post-treatment), or the potential for an unsuccessful outcome following the study procedure (e.g., treatment of a stone greater than 20 mm). However, none of these deviations from the study enrollment criteria required subsequent variations in the evaluation, treatment, or follow up of a subject. Therefore, all subjects enrolled with deviations from the study protocol remained in the PMA study cohort and data from these subjects are included in the safety and effectiveness analyses.

e. Number of LithoTron Procedures

A total of 224 lithotripsy procedures have been performed on the 215 subjects enrolled in the study. Two hundred and seven (207) study subjects (96.2%) were treated with a single lithotripsy procedure; seven subjects (3.3%) each were treated with two procedures and one subject (0.5%) was treated with the maximum three procedures allowed by the study protocol. The retreatment rate for the study subjects was 4.1%.

Eleven (5%) of the 215 subjects in the study represent bilateral treatments for stone in both kidneys, or staged, sequential treatment of stones in two distinct anatomic locations within the ipsilateral kidney and/or ureter. In these cases, the subject was assigned a study number and underwent the study procedure for the initial stones or cluster of stones to be treated. All protocol requirements were completed, and the subject was assigned a final status and released from study participation. The subject was then re-enrolled in the study, assigned a second study number, underwent treatment of the contralateral kidney or sequential treatment of the ipsilateral kidney, and again completed all protocol requirements. Therefore, each subject number indicates the treatment of one kidney, rather than represents a patient enrolled in the study. These subjects completed study requirements for one treatment, were assigned a final study status, and then were re-enrolled in the study under a new study subject number.

Of the 224 lithotripsy procedures performed, information regarding the lithotripsy procedure is available for 221 procedures. Three of the repeat procedures were scheduled or performed too close to the date of database closure for these data to be available.

f. Treatment Parameters

Number of Shock Waves: An average of 2482.7 shocks were delivered per treatment session, with 186 of 221 procedures (84.1%) performed with 2000-3000 shocks. No procedure exceeded the 3000 shock maximum mandated by the study protocol. All procedures were performed with ECG gated shock wave delivery, with the exception of one case that deviated from the protocol requirements for gated delivery. In this case, the operator inadvertently disabled ECG gating and approximately 1500 shocks were delivered in a non-gated mode before the error was detected and ECG gating resumed. The study subject sustained no adverse effects as a result of non-gated shock wave delivery.

Power Level Used: The maximum kV setting per treatment ranged from 16 kV to 26 kV, with an average maximum power setting of 23.6 kV used per procedure. The majority of cases (n=110, 51.1%) were performed with a maximum power setting of 24 kV; two procedures (0.9%) were performed with a maximum power setting of 16 kV; five (2.3%) were performed at a maximum of 18 kV; 27 (15.5%) at a maximum of 20 kV; 54 (25.1%) were performed at a maximum of 22 kV; and 17 (7.9%) at a maximum of 26 kV.

Fluoroscopy Time: The average fluoroscopy time for the 221 LithoTron procedures for which data are available is 6.5 minutes. The relative radiation exposure associated with fluoroscopy time for the LithoTron can be estimated by using the röntgen equivalent man (rem) value calculated for a 5'10" 180 pound male, which is 1.53 rem/min. Therefore, a total fluoroscopy time of 6.5 minutes during a LithoTron procedure would result in a total radiation exposure of 9.94 rem.

Anesthesia Use: The majority of the 221 lithotripsy procedures for which data are available were performed without anesthesia and with the use of conscious IV sedation only (n=168, 76.0%). One subject received neither anesthesia nor analgesia. One investigational site performed the majority of procedures conducted under general anesthesia; 66% of the procedures performed at this site were conducted under general anesthesia.

In one case, the lithotripsy procedure was initiated with IV sedation, but the subject's excessive movement during the procedure required general anesthesia to be administered. In a second case,

the lithotripsy procedure was terminated at 2200 shocks due to the subject's discomfort, despite heavy IV sedation. The subject's post-treatment KUB showed that the stone appeared completely disintegrated. In all other cases, there were no reports of inadequate or inappropriate anesthesia or analgesia during the lithotripsy procedure.

g. Effectiveness Results

The evaluation of effectiveness of treatment with the LithoTron was based upon two criteria: 1) the presence and size of stone fragments retained at final assessment and 2) the need for any additional procedures required to achieve stone-free status. "Success" was defined as radiographic evidence of stone-free status or the presence of stone fragments small enough to pass spontaneously (less than or equal to 4 mm), and no additional surgical procedure(s) or treatment(s) with another approved ESW lithotripter or intracorporeal lithotripter performed following the lithotripsy treatment to achieve stone-free status. The study protocol called for patients to be followed for up to 3 months following treatment; however, a final status could be assigned for any patient demonstrating a stone-free status or treatment failure at the 1 month follow up provided there were no unresolved adverse events.

Of the 215 study subjects participating in the study, 166 subjects had completed all protocol requirements and were assigned a final status at the time the database was closed for analysis. Of the remaining subjects, 40 were still participating in the study, 7 were lost to follow up, and 2 subjects were withdrawn from the study.

Of the 166 subjects who completed final follow up requirements, 143 (86.1%) were stone free, or retained stone fragments 4 mm or less in size. These subjects were assigned a final status of "Success". Twenty three (13.9%) subjects had either undergone an additional procedure for the treatment of the stones, or had retained stone fragments larger than 4 mm. These subjects were assigned a final status of "Failure".

Final Status: Effectiveness Results, by Study Site

	RLS, Portland, OR	Nebraska Methodist	Arlington Memorial, TX	Cape Girardeau, MO	TOTAL
FINAL STATUS	N (%)	N (%)	N (%)	N (%)	N (%)
SUCCESS	34 (79.1)	37 (77.1)	57 (95.0)	15 (100.0)	143 (86.1)
• Stone-free	30	23	44	12	109
• Fragments 4 mm or less	4	14	13	3	34
FAILURE	9 (20.9)	11 (22.9)	3 (5.0)	0 (0.0)	23 (13.9)
• Fragments > 4 mm	5	4	2	0	11
• Additional procedure	4	7	1	0	12
TOTAL	43	48	60	15	166 (100.0)

Among the 166 subjects included in the study cohort analyzed for effectiveness parameters, the success rate varied across study sites, ranging from a success rate of 77.1% to 100.0%. This difference was found to be statistically significant, although all of the sites had effectiveness rates in an acceptable range. The following table shows the success rates by site.

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Summary of Overall Success Rate by Site

Site	Total subjects	Total successes	Success Rate (%)	Confidence Bounds for Success	
				Lower Limit	Upper Limit
All sites combined	166	143	86.1	80.9	91.4
RLS, Portland, OR	43	34	79.1	66.9	91.2
Nebraska Methodist	48	37	77.1	65.2	89.0
Arlington Memorial	60	57	95.0	89.5	100.5
Cape Girardeau, MO	15	15	100.0		

Analyses of stone-free status and success rates in the cohort of 166 subjects followed to final assessment showed no statistical difference based on stone size, burden, or number of stones. A non-statistical trend toward reduced effectiveness as stone size/burden increased was noted.

Other pretreatment characteristics including gender, race, age, weight, pretreatment stone location, and history of prior lithotripsy treatment were shown not to affect the outcome of treatment.

h. Safety Results

There were no unanticipated adverse events reported during the course of the study for any of the 215 subjects in the PMA study cohort. No subject required prolonged follow up due to a complication, and all complications resolved without permanent effects or serious clinical sequelae. Twenty three of the 215 subjects experienced a total of 35 complications (16.3%), and an additional 3 complications were reported unrelated to the study procedure (1.4%). All complications and adverse events reported during the course of the study included those known and expected to be associated with ESW lithotripsy.

Adverse events reported in association with the use of extracorporeal shock wave lithotripsy of upper urinary tract calculi have been reported in the literature to include severe pain or renal colic; steinstrasse or post-treatment obstruction; nausea and/or vomiting; ecchymosis; infection or sepsis; urinary retention; gross hematuria; localized redness or petechiae at the treatment site; cardiac arrhythmia; hypertension; and renal injury or perirenal and intrarenal hematoma. Following is a summary of the complications occurring during the clinical study of the LithoTron.

Complication Summary for all 215 Study Subjects in the PMA Cohort

Event	Post-treatment Interval at Onset	Number of Occurrences
Complications / Adverse Events related to lithotripsy procedure:		36 (16.7%)
Severe pain, renal colic	1 day to 2 weeks	11 (5.1%)
Steinstrasse or post-treatment obstruction	1 day to 3 months	8 (3.7%)
Nausea, vomiting	1 day to 2 weeks	6 (2.8%)
Mild / slight ecchymosis	Immediately post-treatment	5 (2.3%)
Infection or sepsis	3 days to 3.5 months	3 (1.4%)
Urinary retention not associated with obstruction; resolved with bladder catheterization	Immediately post-treatment	3 (1.4%)

Severe pain or renal colic: Severe pain or renal colic was considered a complication of the lithotripsy procedure, and this complication was reported for 11 study subjects. It was expected that most subjects would experience mild to moderate pain post-procedure, usually associated with the passage of small stone fragments. Most subjects were prescribed oral analgesics or antispasmodics to be taken as needed following discharge from the lithotripsy facility. If additional intervention was required (e.g., narcotic analgesics), to control the pain, the event was classified as "severe pain".

Steinstrasse or obstruction: The post-procedure course was complicated by steinstrasse or upper urinary tract obstruction associated with the passage of stone fragments for eight study subjects. Steinstrasse or obstruction was commonly accompanied by additional complications including severe pain and renal colic, or severe nausea and vomiting. The steinstrasse or obstruction resolved with stenting or ureteroscopic manipulation in all but one subject, who required repeat ESW lithotripsy.

Nausea and vomiting: Although nausea and vomiting frequently are associated with the administration of general anesthesia, in all six cases reported in this series these symptoms appeared associated with the passage of the crushed stone or retained fragments. This complication occurred within the 2 days immediately following treatment in four subjects, and in two subjects at 10 and 14 days, respectively, post-treatment.

Ecchymosis at the treatment site: Mild ecchymosis (bruising) at the treatment site was reported as a complication immediately post-treatment for five (2.3%) of the study subjects. The size of the involved area was characteristically 1 to 3 inches and localized at the treatment site. In only one subject was any treatment or intervention (i.e., application of an ice pack) required. In all cases, this occurrence had resolved spontaneously by the time the subject was seen at the 1 month post-treatment visit.

Infection or sepsis: Infection or sepsis of the urinary tract occurred following three procedures (1.4%). In two cases, infection was associated with a retained stone fragment and was detected at

72 hours and 11 days, respectively, post-procedure. In the third case, the exact etiology of an episode of pyelonephritis occurring at 3.5 months following the lithotripsy procedure is unclear.

Urinary retention: Urinary retention was reported immediately following three lithotripsy procedures. Of note is the fact that all three subjects received general anesthesia for the lithotripsy procedure. In all cases, urinary retention resolved with bladder catheterization.

Gross hematuria (visible blood in the urine): Mild to moderate gross hematuria (pink or red-tinged urine) commonly occurs following lithotripsy, and normally resolves spontaneously within the first few days following treatment without clinical sequelae. Bleeding immediately following lithotripsy is usually associated with trauma to the kidney, with the presence or passage of stone fragments, or with instrumentation for secondary procedures (e.g., stent placement), and normally resolves spontaneously within the first few days following treatment. Severe hematuria (dark red urine, possibly with the passage of blood clots) should be considered a complication of lithotripsy and potentially indicative of more serious underlying causes. Because mild and moderate hematuria is an expected event, it was not rigorously tracked.

For no study subject was severe hematuria reported as a complication. The presence of mild or moderate hematuria was noted as a finding at clinical exam in some subjects at the immediate post-treatment evaluation (within 72 hours). At the 1 month follow up visit, no subjects were reported to have hematuria. Typically, hematuria found at this follow up interval is secondary to the presence or passage of stone fragments or to auxiliary measures.

Localized reaction including skin redness and petechiae: Skin redness or mild, diffuse petechiae at the treatment site are commonly found following ESW delivery. Some investigators reported the occurrence of skin redness or petechiae as an incidental finding at clinical exam immediately post-procedure for some of the study subjects; however, this event was expected and not routinely tracked.

Cardiac arrhythmia: No occurrences of cardiac arrhythmia were reported during or immediately after any of the lithotripsy procedures performed. The LithoTron requires use of the patient's ECG waveform to trigger shock release, and continuous cardiac monitoring is advised during treatment.

Hypertension: Hypertension was defined as a diastolic blood pressure greater than 95 mm/Hg and an increase in baseline diastolic pressure of greater than 20 mm/Hg. Three subjects received IV antihypertensive agents during the lithotripsy for elevations in blood pressure during the lithotripsy procedure. Although several subjects experienced episodes of hypertension during study participation, no subject experienced sustained hypertension following the lithotripsy procedure. The relationship between hypertension and extracorporeal shock wave lithotripsy is not fully understood, and continues to undergo investigation.

Renal injury; perirenal or intrarenal hematomas: Renal injury to the treated kidney has been known to occur with extracorporeal shock wave lithotripsy, although the potential for injury, its long-term significance, and its duration are unknown. Neither renal injury nor perirenal or intrarenal hematomas were reported to be associated with any of the LithoTron procedures performed in this study.

i. Laboratory Values

Laboratory tests (including hemoglobin, hematocrit, BUN and creatinine) were taken for each patient at enrollment and at all follow up visits. The only case of significance involved a patient whose hemoglobin/hematocrit levels went from 14.4/43.0 at pretreatment to 8.8/25.6 at 72 hours. By the 1 month visit this patient's levels returned to baseline values (14.0/39.5).

j. Renal Scan

Pre and post-treatment renal scans and function assessments were performed on a subgroup of 24 patients at three of the four sites. One subject experienced a deficit in the treated kidney after the procedure. This patient was also a lithotripsy effectiveness failure and is scheduled to receive a percutaneous nephrolithotomy to remove the remaining calculi. This case was not considered serious, and since the rest of the scanned patients did not experience problems post-treatment, the results of the substudy indicate that the device does not have a serious adverse affect on kidney function.

k. Device Failures

The only device failure during the study occurred when the investigator accidentally overrode the software and began a procedure without ECG gating. This case is discussed in section VIII.f Treatment Parameters on page 9 of this document. The software has now been modified so that it is no longer possible to override the ECG gating.

IX. CONCLUSIONS FROM THE STUDIES

The laboratory, animal, and clinical data provide reasonable assurance of the safety and effectiveness of the LithoTron™ Lithotripsy system for use in patients with renal and upper ureteral calculi between 4 and 20 mm in size.

X. PANEL RECOMMENDATION

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.

XI. CDRH DECISION

An FDA inspection of the HealthTronics, Inc., manufacturing facility was completed on June 30, 1997, and determined that the manufacturer was in compliance with the device Good Manufacturing Practices Regulation.

Based upon a review of the data contained in the PMA, CDRH determined that the LithoTron™ Lithotripsy System is safe and effective when indicated for use in patients with renal and upper ureteral calculi between 4 and 20 mm in size. Furthermore, the applicant agreed to the postapproval requirement that they design a study to collect data on the long-term effect of their

device on hypertension.

CDRH issued an approval order for the stated indication for the applicant's PMA for the HealthTronics, Inc., LithoTron™ Lithotripsy System on July 21, 1997.

XII. REFERENCES

1. Goldsmith M.F., "ESWL Now Possible for Patients with Pacemakers", JAMA, 258: pg. 1284, September 11, 1987.
2. Jameson R.M., Burrows K., Large B., Management of the Urological Patient, Churchill Livingstone, New York: pp. 142-145, 1976.
3. Segura J.W, Patterson D.A., LeRoy A.J., May G.R., Smith L.H., "Percutaneous Lithotripsy," J. Urol., 130: pp. 1051-1054, 1983.

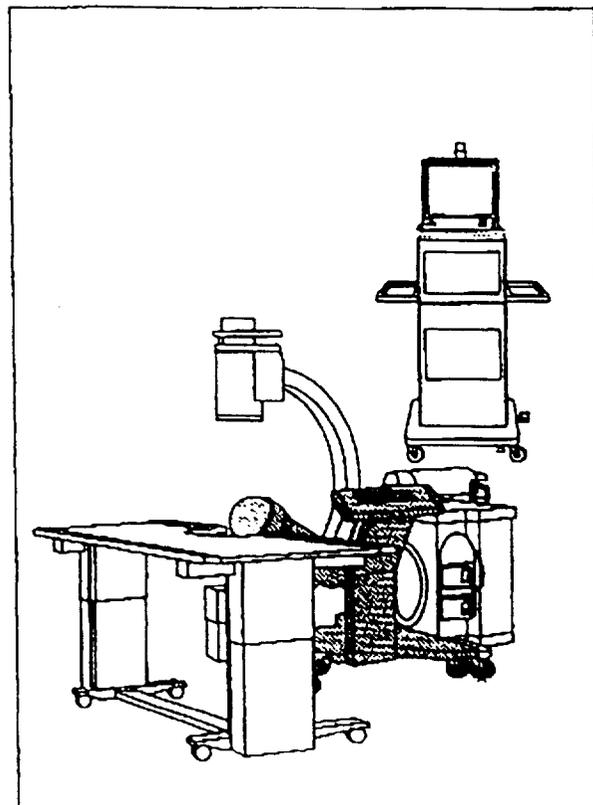
XIII. APPROVAL SPECIFICATIONS

1. Instructions for Use: See labeling;
2. Hazards to Health from Use: See indications, contraindications, warnings, precautions, and adverse events sections of labeling;
3. Postapproval Requirements and Restrictions: See approval order.

LithoTron

Shock wave unit LSH 161

Draft Operator's Manual



! CAUTION - Federal law restricts this device to sale by or on the order of a physician.

Distributor:

HealthTronics, Inc.
425 Franklin Road, Suite 545
Marietta, GA 30067
Tel.: 770-419-0691
Fax: 770-419-9490
USA

Revision
HTI 1.1

Date
6/09/97

Changes

Manufacturer:

HMT AG
Bachstrasse 8
CH - 8280 Kreuzlingen, Switzerland
Tel.: 01141 71 6779177
Fax: 01141 71 6779178

Manufacturer's responsibility

HMT AG and its authorized distributors are responsible for the safe operation, reliability and performance of the device only when:

- installation, adjustment, maintenance and modification of the device are carried out only by persons authorized by HMT
- the electrical installation of the relevant room complies with national standards
- the device is operated according to this instruction manual.

This manual: HTI-Order-# 1000

Technical features are subject to change without notice.

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Indication for Use

The LithoTron System is indicated for use in patients with renal and upper ureteral calculi between 4mm and 20mm in size.

Contraindications, Warnings and Precautions**Contraindications:**

Contraindications for the LithoTron System are:

- patients with coagulation abnormality as indicated by abnormal prothrombin time (PT), partial prothrombin time (PTT), or bleeding time, including patients receiving an anti-coagulant (e.g., aspirin);
- patients with urinary tract obstructions distal to the target stone;
- patients in whom pregnancy is suspected;
- patients whose anatomy precludes focusing of the device in the area of the target stone, including obesity or severe curvature of the spine;
- patients with arterial calcification or vascular aneurysms in the lithotripter shock wave path;
- patients with a history of chronic or acute pancreatitis or gall bladder disease;
- patients whose weight exceeds 300 pounds;
- patients in whom general, spinal, or epidural anesthesia is contraindicated and for whom IV sedation is contraindicated; and
- patients in whom the use of x-ray is contraindicated.

Warnings:

Warnings for the LithoTron System are:

Although patients with infected stones and / or acute urinary tract infections have been successfully treated with shock wave therapy, the experience with the LithoTron in such cases is limited. Therefore, the safety and effectiveness of treatment of infected stones with the LithoTron has not been demonstrated. Due to the possibility of systemic infection from pathogen-harboring calculus debris, use of prophylactic antibiotics should be considered prior to treatment whenever the possibility of stone infection exists.

Bilateral treatment of renal stones should not be performed in a single treatment session because

total urinary tract obstruction by stone fragments may result. Patients with bilateral renal stones should be treated using a separate treatment session for each side. In the event of total urinary obstruction, corrective procedures may be needed to assure drainage of urine from the kidney.

Care should be taken to ensure that shock waves are not applied to air-filled areas, i.e., intestines or lungs. Shock waves are rapidly dispersed by passage through an air-filled interface, which can cause harmful side effects.

Although children have been treated with shock wave therapy for upper urinary tract stones, experience with the LithoTron in such cases is limited. Therefore, the safety and effectiveness of the LithoTron in the treatment of urolithiasis in children has not been demonstrated. Studies indicate that there are growth plate disturbances in the epiphyses of developing long bones in rats subjected to shock waves. The significance of this finding to human experience, however, is unknown.

The safety and effectiveness of the LithoTron in the treatment of middle and lower ureteral stones is currently under study; therefore, the safety and effectiveness of the LithoTron for treating these stones is currently unknown. The treatment of lower ureteral stones should be particularly avoided in women of childbearing age, because treatment of this patient population could possibly result in irreversible damage to the female reproductive system and to the unborn fetus in the undiagnosed pregnancy.

Precautions:

Precautions for the LithoTron are:

Lithotripsy procedures performed with the LithoTron should only be performed with ECG gating of shock waves, and cardiac monitoring of patients should also be performed during treatment. This is especially important for patients who may be at risk for cardiac arrhythmia due to a history of cardiac irregularities, because the use of extracorporeal shock wave lithotripsy is known to cause ventricular cardiac arrhythmias in some patients and limited information is available on the effect of the LithoTron on cardiac rhythm.

Medical Application**DRAFT****HTI**

Extreme caution should be used in the treatment of patients at high risk for heart failure, those with cardiac pacemakers or pneumonia, and patients with very low diaphragms. Although patients with implanted cardiac pacemakers have been treated with extracorporeal shock wave lithotripters, the safety of using the LithoTron to treat patients with cardiac pacemakers and other implanted devices, whose function could be affected by shock waves, has not been studied.

Extracorporeal shock wave lithotripsy procedures have been known to cause damage to the treated kidney. The potential for injury, its long term significance, and its duration are unknown. However, lithotripsy is believed to be less damaging than the persistence of the disease or alternative methods of treatment.

Treated patients should be followed radiographically until the patient is stone-free or there are no remaining stone fragments which are likely to cause a silent obstruction and loss of renal function.

While fluoroscopy must be used during the procedure, caution should be used to minimize the exposure.

No safety and effectiveness data is available regarding the treatment of patients with staghorn calculi.

Experience treating impacted or embedded stones with the LithoTron lithotripter is limited and safety and effectiveness cannot be assured. Experience by other manufacturers and investigators using extracorporeal shock wave lithotripters for impacted stones has shown limited success. Alternative procedures are recommended.

It is recommended that there be no less than a 1 month interval between treatments of the same kidney or focal area, and no more than three treatments to the same kidney. The number of shock waves should be minimized and limited to 3,000 in a single treatment session.

Due to noise associated with shock wave generation, both the patients and staff should wear ear protection during treatment.

Study Design:

A clinical study of the LithoTron System for this indication for use included 221 lithotripsy procedures performed in 215 study subjects; 166 subjects had completed all final follow up requirements at the time of database closure. The study was conducted from July, 1996 to March, 1997 at four clinical sites.

Male or female patients at least 21 years of age with urinary calculi in the kidney or upper ureter who were also appropriate candidates for lithotripsy were eligible for study enrollment. All patients must have undergone radiographic evaluation to confirm the presence of at least one stone greater than 4 mm and less than 20 mm in size. A signed informed consent form was obtained from all study participants.

Patients were excluded from study participation for any of the following reasons: urinary tract obstructions distal to the calculi, precluding passage of stone fragments; impaction of the stone(s) to be treated; calcifications in the aorta or the major renal arteries, or vascular aneurysms in the therapy wave axis; acute or unresolved cholecystitis, cholangitis, pancreatitis, or obstruction of the biliary duct system; coagulation abnormalities or anticoagulation therapy associated with abnormal prothrombin time (PT), partial thromboplastin time (PTT), or bleeding time; aspirin taken within 2 weeks prior to treatment or nonsteroidal anti-inflammatory drugs taken within 3 days of treatment; patients in ASA Class V; pregnancy; cardiac pacemaker in place; patients with congenital renal abnormalities; patients who were undergoing retreatment due to a previously failed lithotripsy procedure with another lithotripsy device; patients who could not be positioned correctly for fluoroscopic imaging or for focusing of the shock waves due to such conditions as obesity or physical deformity; and patients for whom radiography or all forms of anesthesia or analgesia were contraindicated. Patients with calculi in the middle or lower ureter were excluded from participation in this study; this indication for use was studied under a separate protocol.

The study design allowed for investigator choice of type of anesthesia. In the study, 76% of the subjects received IV sedation, 23% received general anesthesia, and less than 1% received spinal or no anesthesia.

Medical Application**DRAFT****HTI**

Of the total 215 patients enrolled in the study, 147 (68.4%) were male and 68 (31.6%) were female. This ratio of males to females is similar to that reported in prior studies of lithotripters, and is representative of previous findings that approximately 75% of stone disease patients are males. Patient age ranged from 17 to 89 years, with a mean of 48.6 years.

Potential Adverse Effects of the Device on Health:

Adverse events reported in association with the use of extracorporeal shock wave lithotripsy of upper urinary tract calculi have been reported in the literature to include severe pain or renal colic; steinstrasse or post-treatment obstruction; nausea and / or vomiting; ecchymosis; infection or sepsis; urinary retention; gross hematuria; localized redness or petechiae at the treatment site; cardiac

arrhythmia; hypertension; and renal injury or perirenal and intrarenal hematoma. Following is a summary of the complications occurring during the clinical study of the LithoTron System

Complications:

There were no unanticipated adverse events reported during the course of the study for any of the 215 subjects in the study cohort, nor did any subject require prolonged follow up due to a complication. All complications resolved without permanent effects or serious clinical sequelae. Twenty three of the 215 subjects experienced a total of 36 complications related to the lithotripsy procedure (16.7%), and an additional 3 complications were reported unrelated to the lithotripsy procedure (1.4%).

Complications Summary for All 215 Subjects in PMA Cohort

Event	Post-treatment Interval at Onset	Number of Occurrences
Complications / Adverse Events related to Lithotripsy procedure:		36 (16.7%)*
Severe pain, renal colic	1 day to 2 weeks	11 (5.1%)
Steinstrasse or post-treatment obstruction	1 day to 3 months	8 (3.7%)
Nausea, vomiting	1 day to 2 weeks	6 (2.8%)
Mild / slight ecchymosis	Immediately post-treatment	5 (2.3%)
Infection or sepsis	3 days to 3.5 months	3 (1.4%)
Urinary retention not associated with obstruction; resolved with bladder catheterization	Immediately post-treatment	3 (1.4%)

*percentages for individual complications do not total exactly due to rounding to the nearest one-tenth of one percent

Severe pain or renal colic: Severe pain or renal colic was considered a complication of the lithotripsy procedure, and this complication was reported for 11 study subjects. It was expected that most subjects would experience mild to moderate pain post-procedure, usually associated with the passage of small stone fragments. Most subjects were prescribed oral analgesics or antispasmodics to be taken as needed following discharge from the lithotripsy facility. If additional intervention was required (e.g., narcotic analgesics), to control the pain, the event was classified as "severe pain".

Steinstrasse or Obstruction: The post-procedure course was complicated by steinstrasse or upper urinary tract obstruction associated with the passage of stone fragments for 8 study subjects. Steinstrasse or obstruction was commonly accompanied by additional complications including severe pain and renal colic, or severe nausea and vomiting. The steinstrasse or obstruction resolved with stenting or ureteroscopic manipulation in all but 1 subject, who required repeat ESW lithotripsy.

Nausea and vomiting: Although nausea and vomiting frequently is associated with the administration of general anesthesia, in all 6 cases reported in this series these symptoms appeared associated with the passage of the crushed calculus or retained fragments. This complication occurred within the 2 days immediately following treatment in 4 subjects, and in 2 subjects at 10 and 14 days, respectively, post-treatment.

Ecchymosis at the treatment site: Mild ecchymosis (bruising) at the treatment site was reported as a complication immediately post-treatment for 5 (2.3%) of the study subjects. The size of the involved area was characteristically 1 to 3 inches and localized at the treatment site. In only one subject was any treatment or intervention (i.e., application of an ice pack) required. In all cases, this occurrence had resolved spontaneously by the time the subject was seen at the one month post-treatment visit.

Infection or sepsis: Infection or sepsis of the urinary tract occurred following three procedures (1.4%). In two cases, infection was associated with a retained stone fragment and was detected at 72 hours and 11 days, respectively, post procedure. In the third case, the exact etiology of an episode of pyelonephritis occurring at 3.5 months following the lithotripsy procedure is unclear.

Urinary retention: Urinary retention was reported immediately following three lithotripsy procedures. Of note is the fact that all three subjects received general anesthesia for the lithotripsy procedure. In all cases, urinary retention resolved with bladder catheterization.

Gross hematuria (visible blood in the urine): Mild to moderate gross hematuria (pink or red-tinged urine) commonly occurs following lithotripsy, and normally resolves spontaneously within the first few days following treatment without clinical sequelae. Bleeding immediately following lithotripsy is usually associated with trauma to the kidney, with the presence or passage of stone fragments, or with instrumentation for secondary procedures (e.g., stent placement), and normally resolves spontaneously within the first few days following treatment. Severe hematuria (dark red urine, possibly with the passage of blood clots) should be considered a complication of lithotripsy and potentially indicative of more serious underlying causes. Because mild and moderate hematuria is an expected event, it was not rigorously tracked. *new 7/15/97*

severe
For no study subject was ^{severe} hematuria reported as a complication. The presence of mild or moderate hematuria was noted as a finding at clinical exam in some subjects at the immediate post-treatment evaluation (within 72 hours). At the one month follow up visit, no subjects were reported to have hematuria. Typically, hematuria found at this follow up interval is secondary to the presence or passage of stone fragments or to auxiliary measures.

Localized reaction including skin redness and petechiae: Skin redness or mild, diffuse petechiae at the treatment site are commonly found following ESW delivery. Some investigators reported the occurrence of skin redness or

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petechiae as an incidental finding at clinical exam immediately post-procedure for some of the study subjects; however, this event was expected and not routinely tracked.

Cardiac arrhythmia: No occurrences of cardiac arrhythmia were reported during or immediately after any of the lithotripsy procedures performed. The LithoTron requires use of the patient's ECG waveform to trigger shock release, and continuous cardiac monitoring is advised during treatment.

Hypertension: Hypertension was defined as a diastolic blood pressure greater than 95 mm/Hg and an increase in baseline diastolic pressure of greater than 20 mm/Hg. Three subjects received IV antihypertensive agents during the lithotripsy for elevations in blood pressure during the lithotripsy procedure. Although several subjects experienced episodes of hypertension during study participation, no subject experienced sustained hypertension following the lithotripsy procedure. The relationship between hypertension and extracorporeal shock wave lithotripsy is not fully understood, and continues to undergo investigation.

Renal injury; perirenal or intrarenal hematomas: Renal injury to the treated kidney has been known to occur with extracorporeal shock wave lithotripsy, although the potential for injury, its long-term significance, and its duration are unknown. Neither renal injury nor perirenal or intrarenal hematomas were reported associated with any of the LithoTron procedures performed in this study.

Radiation exposure: Fluoroscopy time averaged 6.5 minutes per procedure. The relative radiation exposure associated with fluoroscopy time for the LithoTron can be estimated by using the rem value (roentgen equivalent, man; 1 rem = 1 rad x relative biological effectiveness) calculated for a 5'10" 180 pound male, which is 1.53 rem/min. Total fluoroscopy time of 6.5 minutes during a LithoTron procedure would result in a total radiation exposure of 9.94 rem for a 5'10" 180 pound male. Patient radiation exposure can be minimized by following the radiation safety guideline included in the labeling.

Effectiveness

The evaluation of effectiveness of treatment with the HeathTronics LithoTron was based upon two criteria: 1) the presence and size of stone fragments retained at final assessment and 2) the need for any additional procedures required to achieve stone-free status. "Success" was defined as radiographic evidence of stone-free status or the presence of stone fragments small enough to pass spontaneously (less than or equal to 4 mm), and no additional surgical procedure(s) or treatment(s) with another approved ESW lithotripter or intracorporeal lithotripter performed following the lithotripsy treatment to achieve stone-free status.

Of the 166 study subjects who completed final follow up requirements, 143 (86.1%) were stone free, or retained stone fragments 4 mm or less in size, and were assigned a final status of "Success". Twenty three (13.9%) had either undergone an additional procedure for the treatment of the calculi, or had retained fragments larger than 4 mm, and were assigned a final status, "Failure". The success rate varied from 77.1% to 100.0% over the four study sites. Analyses of covariates including gender, race, age, weight, number of stones treated, total stone burden, maximum stone size, stone density, and stone location revealed no other variables affecting outcome. A slight trend towards a decrease in effectiveness was seen in increasing stone size / burden; however, this trend was not statistically significant.

	RLS, Portland, OR	Nebraska Methodist	Arlington Memorial, TX	Cape Girardeau, MO	TOTAL
FINAL STATUS	N (%)	N (%)	N (%)	N (%)	N (%)
SUCCESS	34 (79.1)	37 (77.1)	57 (95.0)	15 (100.0)	143 (88.1)
• Stone-free	30	23	44	12	109
• Fragments 4 mm or less	4	14	13	3	34
FAILURE	9 (20.9)	11 (22.9)	3 (5.0)	0 (0.0)	23 (13.9)
• Fragments > 4 mm	5	4	2	0	11
• Additional procedure	4	7	1	0	12
TOTAL	43	48	60	15	166 (100.0)

For all subjects enrolled in the study, 96.2% were treated with a single lithotripsy procedure, 3.3% were treated with a total of two procedures, and 0.5% were treated with a total of three procedures. The retreatment rate for the LithoTron study overall was therefore 4.1%.