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*P920051*

Memorandum

Date FEB 17 1995  
From Director, Office of Device Evaluation (HFZ-400)  
Center for Devices and Radiological Health (CDRH)  
Subject Premarket Approval of Karl Storz Endoscopy-America, Inc.'s  
Storz Modulith™ Lithotripter, Model SL20 - ACTION  
To The Director, CDRH  
ORA \_\_\_\_\_

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

FACTS. Tab A contains a FEDERAL REGISTER notice announcing:

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

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

*Philip J. Philiza*  
for Susan Albert, Ph.D., M.D.

Attachments

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

DECISION

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

Prepared by: John H. Baxley, CDRH, HFZ-472, 02-01-95, 594-2194  
A:\PMA\1995\P920051.ACT

DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

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

KARL STORZ ENDOSCOPY-AMERICA, INC.; PREMARKET APPROVAL OF STORZ MODULITH™  
LITHOTRIPTER, MODEL SL20

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA) is announcing its approval of the application by Karl Storz Endoscopy-America, Inc., Kennesaw, GA, for premarket approval, under section 515 of the Federal Food, Drug, and Cosmetic Act (the act), of the Storz Modulith™ Lithotripter, Model SL20.

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

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

FOR FURTHER INFORMATION CONTACT:

John H. Baxley

Center for Devices and Radiological Health (HFZ-472)

Food and Drug Administration

9200 Corporate Blvd.

Rockville, MD 20850

301-594-2194.

SUPPLEMENTARY INFORMATION: On November 24, 1993, Karl Storz Endoscopy-America, Inc., Kennesaw, GA 30144, submitted to CDRH an application for premarket approval of the Storz Modulith™ Lithotripter, Model SL20. The device is an extracorporeal shock wave lithotripter and is indicated for use in the noninvasive fragmentation of urinary calculi in the kidney and upper ureter.

In accordance with the provisions of section 515(c)(2) of 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.

On February 17, 1995, CDRH approved the application by a letter to the applicant from the Director of the Office of Device Evaluation, CDRH.

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

OPPORTUNITY FOR ADMINISTRATIVE REVIEW

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

Petitioners may, at any time on or before (insert date 30 days after date of publication in the FEDERAL REGISTER), file with the Dockets Management Branch (address above) two copies of each petition and supporting data and information, identified with the name of the device and the docket number found in brackets in the heading of this document. Received petitions may be seen in the office above between 9 a.m. and 4 p.m., Monday through Friday. This notice is issued under the act section 520(h), 90 Stat. 554-555, 571 (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: \_\_\_\_\_.

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

FEB 17 1995

Food and Drug Administration  
9200 Corporate Boulevard  
Rockville MD 20850

Mr. Paul L. Sumner  
Technical Director  
Karl Storz Endoscopy-America, Inc.  
1201 Roberts Boulevard  
Kennesaw, Georgia 30144

Re: P920051  
Storz Modulith™ Lithotripter, Model SL20  
Filed: November 24, 1993  
Amended: August 17 and October 17, 1994,  
and February 17, 1995

Dear Mr. Sumner:

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 Storz Modulith™ Lithotripter, Model SL20. This device is indicated for use in the noninvasive fragmentation of urinary calculi in the kidney and upper ureter. 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 participate in the National Electrical Manufacturers Association's study, "A Controlled Study of the Effect of Extracorporeal Lithotripsy on Blood Pressure Secondary to Nephrolithiasis," 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 Federal Food, Drug, and Cosmetic Act (the act).

Page 2 - Mr. Paul L. Sumner

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

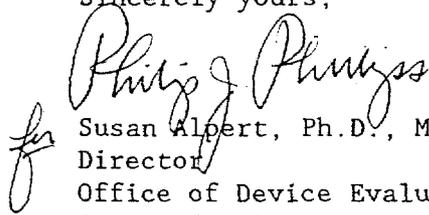
You are reminded that as soon as possible, and before commercial distribution of your device, that you must submit an amendment to this PMA submission with copies of all approved labeling in final printed form.

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

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

If you have any questions concerning this approval order, please contact Mr. John Baxley at (301) 594-2194.

Sincerely yours,

  
Susan Albert, Ph.D., M.D.  
Director  
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 Effectuated" 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 acknowledgement by FDA that the submission is being processed as a "Special PMA Supplement - Changes Being Effectuated." This acknowledgement is in addition to that issued by the PMA Document Mail Center for all PMA supplements submitted. This procedure is not applicable to changes in device design, composition, specifications, circuitry, software or energy source.

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

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

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

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

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

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

- (1) A 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 become 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-544)  
Center for Devices and Radiological Health  
Food and Drug Administration  
1350 Piccard Drive, Room 3083  
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 above address or by telephoning (301) 594-2735.

**SUMMARY OF SAFETY AND EFFECTIVENESS DATA:**

**STORZ MODULITH™ LITHOTRIPTER, MODEL SL20**

**I. GENERAL INFORMATION**

DEVICE GENERIC NAME:	Extracorporeal Shock Wave Lithotripter
DEVICE TRADE NAME:	Storz Modulith™ Lithotripter, Model SL20
APPLICANT:	Karl Storz Endoscopy-America, Inc. Extracorporeal and Laser Lithotripsy Division 1201 Roberts Boulevard Suite #207 Kennesaw, Georgia 30144
PREMARKET APPROVAL APPLICATION (PMA) NUMBER:	P920051
DATE OF NOTICE OF APPROVAL TO THE APPLICANT:	FEB 17 1995

## II. INDICATIONS FOR USE

The Storz Modulith™ Lithotripter, Model SL20 is indicated for use in the noninvasive fragmentation of urinary calculi in the kidney and upper ureter.

## III. DEVICE DESCRIPTION

The Storz Modulith Lithotripter, Model SL20 (hereafter referred to as the Modulith™ Lithotripter) utilizes shock waves generated outside the patient's body to fragment urinary calculi within either the kidney or the upper ureter. The device consists of: (1) a central unit, which incorporates the patient table, the shock wave source, the system control panel, and the x-ray system; (2) an x-ray system cabinet; and (3) an ultrasound system.

### Stone Localization and Patient Positioning

The stone to be treated is located using either the x-ray or the ultrasound system. The x-ray C-arm is integrally connected to the lithotripter, and is capable of fluoroscopy, digital radiography, and film radiography. For x-ray localization of a urinary stone, two displaced x-ray images are acquired. Using these exposures, the patient table is positioned by the operator in the X-, Y-, and Z-axes. Once the stone has been centered, the patient table is unlocked from the x-ray position and manually slid to the treatment position. At this point, ultrasound imaging should verify that the stone is centered at the shock wave focus.

Ultrasound imaging is used for verification of stone localization, as well as for real-time monitoring of stone disintegration during treatment. Two 3.5 MHz linear phased array sector scanning transducers are used with this system. One is mounted coaxially within the shock wave source to provide an inline image of the pressure wave path, and the other is handheld for manual imaging. The inline transducer can be moved 120 mm axially toward the patient, and rotated about this axis  $\pm 110$  degrees. Using the inline transducer while manipulating the position of the patient table, the physician is able to locate and position the stone. Positioning of the calculi at the shock wave focus of the system is accomplished by centering the stone's image on the crosshairs that are displayed on the ultrasound monitor. If an obstruction is noted along the shock wave path, the shock wave generator assembly can be tilted either laterally or caudally while maintaining the shock wave focus at the stone. This adjustment allows the operator to obtain the best acoustic window.

### Shock Wave Generator and Focusing Assembly

The shock waves of the Modulith™ Lithotripter are generated by underwater, electromagnetically driven expansion of a coaxial cylinder that is mounted within a brass parabolic reflector. This action creates a radially expanding, cylindrical pressure wave, which is focused toward the stone by means of the reflector. As the pressure wave front converges toward the focal region, shock waves are created by sound propagation. This focal region is located 165 mm above the reflector rim and measures approximately 3 mm in diameter and 30 mm in height.

The operator controls the intensity of the pressure pulse, the pulse repetition rate, and the method of pulse triggering. Adjustments can be made for these parameters as follows: (1) shock wave intensity ranges from level 1 to 9 (corresponding to electrical pulses of 12 to 20 kV); (2) pulse repetition rate can be set at either 1, 1.5, or 2 Hz; and (3) the triggering of shock waves can be continuous, ECG-gated, or respiration gated.

The patient is coupled to the shock wave generator assembly via a water-filled coupling bag. The lithotripter's water system automatically degasses and warms the water that is used within the shock wave generator.

#### Operator's Control Panels

Three operator's control panels are situated on the right side of the Modulith™ Lithotripter: (1) a stationary control panel for setting the patient coupling and lithotripsy treatment parameters; (2) a hand-held control unit for moving the patient table and the inline ultrasound transducer; and (3) a hand-held control unit for control of the x-ray C-arm. These control panels also serve to inform the user of the operation of the device and the progress of treatment. In addition to the three control panels, the ultrasound and x-ray systems are operated using their respective keypads and control panels.

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

The labeling for the Modulith™ Lithotripter contains the following contraindications, warnings, and precautions:

Contraindications for the Modulith™ Lithotripter are:

- (1) Patients with coagulation abnormalities as indicated by abnormal prothrombin time (PT), partial thromboplastin time (PTT), or bleeding time. This includes patients currently receiving anti-coagulants (including aspirin).
- (2) Patients in whom pregnancy is suspected, as well as patients in whom the use of x-ray is contraindicated.
- (3) Patients with arterial calcification or vascular aneurysms in the therapy wave axis.
- (4) Patients with a history of chronic or acute cholecystitis, cholangitis, or pancreatitis.
- (5) Patients with urinary tract obstructions distal to the stone.
- (6) Patients whose anatomy does not permit focusing of the device into the patient's posterior flank in the area of the kidney stone, including severely obese patients (exceeding 300 pounds) or those suffering from excessive spinal curvature.

Warnings for the Modulith™ Lithotripter are:

- (1) Although patients with infected stones have been successfully treated with shock wave therapy, the experience with the Storz Modulith™ in the treatment of such cases is limited. Therefore, the safety and effectiveness of treatment with the Modulith™ for infected stones has not been demonstrated. Due to the possibility of systemic infection from pathogen-harboring calculus debris, prophylactic administration of antibiotics should be considered prior to treatment whenever the possibility of stone infection exists.
- (2) The safety and effectiveness of the Modulith™ SL20 Lithotripter in the treatment of middle and lower ureteral stones has not been demonstrated and is currently unknown. The treatment of lower ureteral stones should specifically be 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.
- (3) 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 separate treatment sessions for each side. In the event of total urinary obstruction, corrective procedures may be needed to assure drainage of urine from the kidney.
- (4) 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.
- (5) Children have been treated with shock wave therapy for upper urinary tract stones; however, the experience with the Storz Modulith™ for such treatment is limited. Therefore, the safety and effectiveness of the Modulith™ in the treatment of urolithiasis in children has not been demonstrated. Recent 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 is unknown.

Precautions for the Modulith™ Lithotripter are:

- (1) Cardiac monitoring of patients should 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. Although patients with cardiac pacemakers have been treated with shock wave therapy, the safety of using the Storz Modulith™ to treat persons with cardiac pacemakers and other implanted devices, whose function could be affected by pressure waves, has not been established.
- (2) Clinical experience in treating impacted or embedded stones with the Storz Modulith™ extracorporeal lithotripter is limited and effectiveness cannot be assured. Experience with other manufacturer's lithotripters using extracorporeal shock wave lithotripsy monotherapy

for impacted stones has shown limited success. Alternative or auxiliary procedures are recommended.

- (3) It is important to follow patients radiographically until the patient is stone-free or there are no remaining stone fragments, since stone fragments may cause a silent obstruction and loss of renal function.
- (4) In reference to retreatment, it is recommended that patients should be limited to three treatment sessions of 2000 pressure waves each to the same focal region. The two retreatment sessions should not be scheduled sooner than two weeks and six weeks, respectively, from the first lithotripsy treatment.
- (5) 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.
- (6) The effectiveness of extracorporeal shock wave lithotripsy may be lower in patients with either staghorn stones or large diameter stones. In particular, clinical evidence indicates that the Storz Modulith™ is less effective in treating either staghorn stones or stones  $\geq 20$  mm in largest diameter, than in treating stones  $< 19$  mm. The physician may want to consider the use of alternative therapies for patients with staghorn stones or stones  $\geq 20$  mm in largest diameter.

## 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: pain, skin redness, gross hematuria, cardiac arrhythmia, hypertension, nausea and/or vomiting, infection, ecchymosis, obstruction or steinstrasse, perirenal and intrarenal hematoma, renal injury, and radiation exposure.

Pain was reported during or immediately following 37.6% of the 660 treatments that were performed in the clinical study of the Modulith™ Lithotripter, the majority of which were rated as either discomfort or mild (i.e., 26.8% of the 660 treatments). The rate of pain during treatment varied among the study sites, and is related to the level of sedation or anesthesia that each center used. Pain following treatment was apparently secondary to either the passage of stone fragments or due to auxiliary procedures. At last follow-up  $\geq 21$  days post-treatment, 21.8% of kidneys were reported to have pain (rated as either discomfort or mild in 19.0% of cases). Usual treatment for post-lithotripsy pain, if indicated, is with analgesia or antispasmodic drug therapy.

Skin redness at the treatment site was observed in 34.8% of treatments, and usually resolved spontaneously within 48 hours after treatment. Skin redness appeared to be associated with

higher stone volumes, which usually required a greater number of shock waves to achieve adequate fragmentation.

Gross hematuria (i.e., visible blood in the urine) was observed following 30.0% of the treatments with the Modulith™ Lithotripter. Bleeding normally resolves spontaneously within 24 to 48 hours. By 21 days post-treatment, the incidence of gross hematuria was reported in 1.9% of the treated kidneys. Typically, hematuria found at follow-up is secondary to the presence or passage of stone fragments or auxiliary measures.

Cardiac arrhythmia was reported during or immediately after 13.9% of the 660 patient treatments, of which, 79.3% of these arrhythmias were premature ventricular contractions. Arrhythmias were more frequent in treatments in which no anesthesia or sedation was given as well as among patients who had abnormal pretreatment ECGs, and was usually resolved by switching the triggering mode from internal triggering to ECG gating. Cardiac monitoring, therefore, is advised during treatment.

Hypertension, defined as diastolic blood pressure > 95 mmHg, was reported at last follow-up ≥ 21 days post-treatment in 21 (8.5%) of the 247 patients with both pretreatment and follow-up blood pressures. Of these 21 patients, 19 were normotensive at baseline and 2 were hypertensive at baseline. The relationship between hypertension and extracorporeal shock wave lithotripsy and hypertension is not fully understood, and continues to undergo investigation.

Nausea and/or vomiting was reported during or immediately after 2.6% of treatments. This reaction may be related to the use of analgesics and/or anesthetics during the study.

Infection of the urinary tract was noted in 2.2% of patients at last follow-up ≥ 21 days post-treatment. Infections may occur when stone fragments obstruct the urinary tract or as a result of ancillary procedures, and are treated with antibiotic therapy.

Ecchymosis at the treatment site, extravasation of blood into the skin resulting in small purplish patches on the skin, is known to be a minor complication of lithotripsy and was noted immediately following 2.1% of treatments. Ecchymosis requires no treatment and generally resolves spontaneously in several days. No ecchymosis was reported at follow-up 21 days or more after the last treatment.

Obstruction and steinstrasse are due to the passage of stone fragments, and resolve either spontaneously or with the use of auxiliary measures. One case of obstruction and no cases of steinstrasse were reported during or immediately post treatment, while at 21 days or later, there were 6 (1.9%) cases of obstruction and 1 (0.3%) case of steinstrasse.

Perirenal and intrarenal hematomas were reported in a total of 7 patients (approximately 2% of kidneys treated) following treatment with the Modulith™ Lithotripter, all of which were symptomatic. In 6 of these cases, the hematomas resolved following hospitalization.

However, for the other case, the patient died shortly after treatment; although not deemed to be directly attributable to this patient's death, this hematoma was believed to be one of the initiating factors. Strict follow-up is recommended when post-treatment fluid collections are observed or if flank pain develops.

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.

Radiation exposure is minimized through the use of the Modulith™ Lithotripter's pulse progressive fluoroscopic feature. In a sub-study within the clinical trial, the Modulith™ fluoroscopy system was found to expose the patient to an average of 1.88R, while the use of standard radiography resulted in an average exposure of 2.9R. Patient x-ray exposure can be minimized by following the radiation safety guidelines included in the labeling.

## **VI. ALTERNATE PRACTICES OR 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 fluids. 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 ureter by passing instruments 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. Some of the surgical techniques used to remove kidney stones include pyelolithotomy, nephrolithotomy, partial nephrectomy, Gil-Vernet operation, and ureterolithotomy (Jameson et al. 1976). The use of open surgery carries the risks of bleeding, infection, persistent urinary drainage, and urinoma, as well as the risk of loss of the kidney after multiple surgeries. Hematuria is also noted after open surgery.

In recent years, percutaneous stone removal techniques have been developed for use on patients who were poor surgical candidates or who had undergone open surgery in the past (Segura et al. 1983). 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. This procedure involves the placement of a needle or guidewire into the renal pelvis through a small puncture wound in the flank under ultrasound or x-ray guidance. The needle tract is dilated to admit surgical instruments and the stone can either be removed or, if the stone is too large, it can be fragmented using either mechanical, ultrasonic, or electrohydraulic lithotripsy techniques and the resulting fragments can then be removed. Complications reported with this procedure include hematuria, bleeding, pneumothorax, need for open surgery, and loss of kidney (Wickham et al. 1983).

In general, many small kidney stones can be treated without surgery. For small kidney stones there are few complications other than discomfort for the patient. In the case of larger stones, however, the stone may cause severe pain or damage to the kidney or urinary tract.

Other currently marketed extracorporeal shock wave lithotripters that have the same or broader indications for use may also provide an alternative treatment.

## VII. MARKETING HISTORY

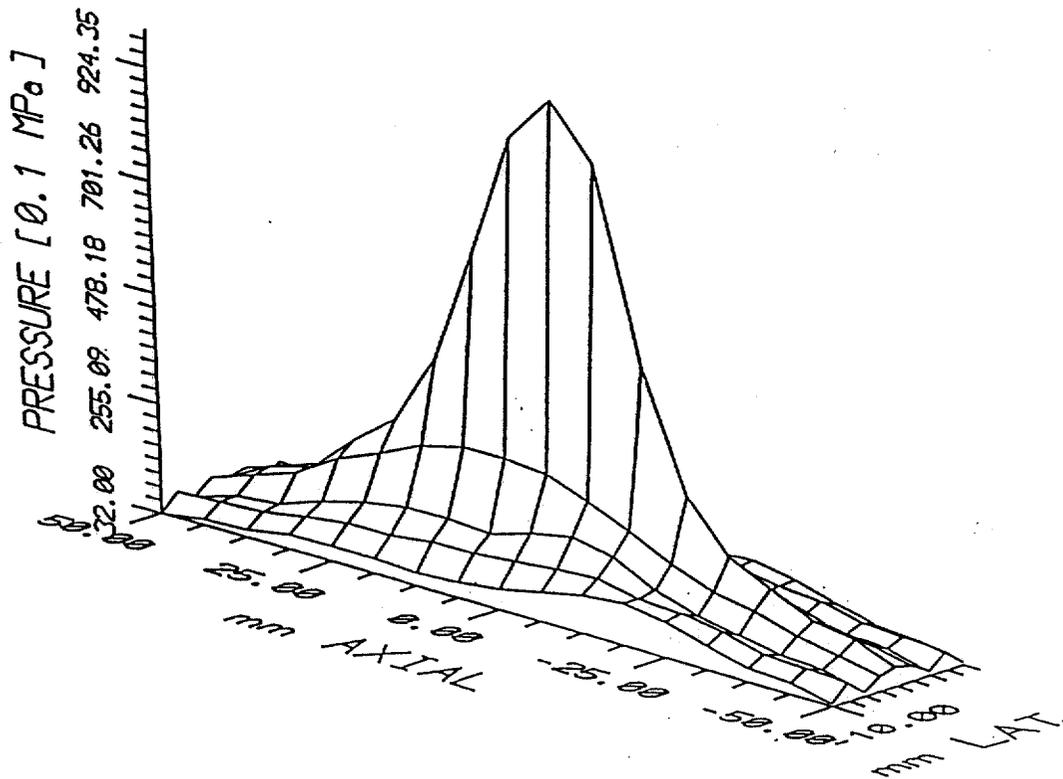
A total of 82 Modulith™ Lithotripters have been sold in 23 countries throughout the world. The device has not been withdrawn from marketing for any reason related to safety or effectiveness of the device.

## VIII. SUMMARY OF STUDIES

### A. LABORATORY STUDIES (NONCLINICAL STUDIES)

#### Characterization of the Shock Wave

Testing was conducted to characterize the shock wave generated by the Modulith™ Lithotripter. The pressure transducers used in this testing were (1) a polyvinylidene fluoride (PVDF) needle hydrophone for the measurement of positive pressure, rise time, pulse width, and waveform; and (2) a PVDF membrane hydrophone for the measurement of negative pressures. For these measurements, each hydrophone was mounted in a computer controlled 3-axis positioning device with a positioning accuracy greater than 0.1 mm. The pressure signals were taken with a digital storage oscilloscope. The measurements were conducted with an analog bandwidth of 100 MHz, a sampling rate of 10 ns, and 8 bits digital resolution. At the maximum power setting of the Modulith™ (i.e., power level = 9; 20 kV), the peak positive and negative pressures were found to be 1,056 bars and -114 bars, respectively. For power setting 7 (i.e., 18 kV), the peak positive pressure measurements obtained were plotted in 3-dimensional form and are illustrated in the figure below.



**3-D Plot of Peak Positive Pressure**  
Power setting = 7 (18 kV)

The recorded amplitude and dimensions at the focal area for the available range of lithotripter power settings are listed in the following table:

**Pressure Measurement Data**

Power Setting	Peak Positive Pressure (bars)	Focal Area	
		Axial (mm)	Lateral (mm)
Level 1 (12 kV)	189	34	4.6
Level 3 (14 kV)	368	27	3.5
Level 5 (16 kV)	750	26	2.6
Level 7 (18 kV)	974	30	2.6
Level 9 (20 kV)	1,056	37	2.8

## Animal Testing

Three animal studies were conducted to evaluate the effects of treatment with the Modulith™ Lithotripter upon target and non-target tissues.

The first study, conducted in Mannheim, Germany, examined the histological effects of lithotripsy shock waves upon the canine kidney. Although laboratory and prototype models of the Modulith™ were used in this study, these early models use identical shock wave generators as the clinical model and, therefore, produce the same pressure fields. Thus, the results of this study are representative of treatment using the Modulith™ model that is the subject of this PMA application.

The first phase of this study consisted of acute studies, which evaluated the effects of lithotripsy at voltages of 11 to 20 kV, with a differing number of pressure waves, from 25 to 2500, on a total of 50 kidneys (i.e., 25 animals). Treatment was performed on both kidneys of the same animal at the same generator voltage, but a different number of waves were applied to each kidney. The animals were sacrificed one hour after treatment following intrarenal perfusion of both kidneys with a 10% solution of barium sulfate. Each kidney was examined both grossly and histologically. The results indicated that the severity of the renal lesion correlated with both the applied number of shock waves and the power level. Low power settings (11-13 kV) did not usually create detectable lesions. A small focal hematoma (1 cm diameter) with traces of peripelvic or subcapsular bleeding was observed in three of eight kidneys treated at the low settings. However, larger sized intraparenchymal lesions occurred at 17-20 kV. In five kidneys treated with the laboratory model at 20 kV, the lesions were associated with significant perirenal hematoma. Similarly, in 12 kidneys treated with the prototype model at power levels of 17-18 kV, parenchymal hematomas ranging from 0.5 to 2.0 cm were observed in 11 kidneys, and perirenal hematomas were observed in three.

In addition to the acute studies described above, chronic animal studies were performed to assess the long term effects of treatment with the Modulith™ Lithotripter. In this investigation, nine kidneys were treated with the laboratory model device at those power settings which caused noticeable parenchymal lesions in the acute study. Each of these dogs were sacrificed 6 weeks following treatment, and subjected to gross and histological examination. In two of the nine kidneys, small scars were observed which correlated to hemosiderin residues and interstitial fibrosis. One wedge shaped scar leading from the cortex to the medulla was seen after 2500 shock waves at 17 kV.

The second animal study, conducted at the University of Tennessee, evaluated the acute and chronic effects of lithotripsy on healthy swine renal and biliary tissues. Sixteen miniswine were randomly assigned to one of three groups: (1) acute group (six pigs), (2) subacute group (four pigs) or (3) chronic group (six pigs). (Although a total of five animals were actually enrolled into the subacute group, one died due to a complication with the anesthesia and is not reported.) All pigs had blood and urinalysis studies and all pigs were sacrificed and necropsied. Each treatment consisted of 3000 shock waves at 20 kV to both the left kidney and the gallbladder.

Acute group pigs underwent one set of lithotripsy treatments to the kidney and gallbladder, and were sacrificed and necropsied within 24 hours. Subacute group pigs underwent a second set of lithotripsy

treatments two weeks after the first treatment. They were sacrificed and necropsied within 24 hours after the second treatment. Chronic group pigs had two sets of lithotripsy treatments like the subacute group, and then received a third set of lithotripsy procedures at 6 weeks (i.e., 4 weeks after the second). They were then maintained for an additional 6 weeks following the third treatment. At week 12, additional blood samples were drawn, and the chronic group pigs were sacrificed and necropsied in the same manner as the other pigs. This retreatment schedule parallels that which was recommended in the clinical protocol.

Eleven biochemical assays, in addition to hemoglobin and white blood cell count, were performed both before and after treatment as described in the protocol. Several of these blood chemistries (i.e., creatine phosphokinase (CPK), lactic dehydrogenase (LDH), and serum glutamic oxaloacetic transaminase (SGOT)) experienced statistically significant changes immediately following lithotripsy. The assay changes, however, are indicative of tissue damage and are expected after lithotripsy. Alkaline phosphatase, blood urea nitrogen (BUN), and serum glutamic pyruvic transaminase (SGPT) also decreased significantly immediately after treatment. Although the etiology of these decreases is not certain, it is possible that hydration state, intramuscular injections, rough handling, or narcotics used for anesthesia could affect these results. By 6 weeks after the third treatment, all of the measured values returned to or below baseline (as demonstrated with the animals in the chronic group). Overall, the blood chemistry results obtained in this study do not differ significantly from those previously reported in the literature.

The visible tissue effects recorded were predominately limited to microscopic hemorrhage, tissue edema, petechiae, and fibrosis. There was no significant injury to any organ other than those that were targeted during treatment (i.e., the left kidney and the gallbladder). The acute effects of treatment consisted of mild perirenal edema and multifocal small perirenal hemorrhages in some kidneys, with localized areas of cortical and/or subcapsular hemorrhage in others. One kidney treated in the subacute group of this study had a clinically significant retroperitoneal hematoma. In the chronic group animals, less than three percent of the parenchyma of each treated kidney was affected by the lithotripter's shock waves. These long term effects are similar to those that have been described by other researchers.

The third animal study was performed at Butterworth Hospital (Michigan State University). In this study, 20 pigs were subjected to biliary extracorporeal shock wave lithotripsy using the Modulith™ to identify the relationship between the acoustic energy delivered and the fragmentation of implanted gallstones. The information gathered from this study suggested that (1) the results of biliary lithotripsy improve with increases in total energy delivered; (2) the amount of acoustic energy delivered should be increased as stone burden increases; and (3) a plateau is reached, at which point the benefits of further treatment may not outweigh the risks. Although this study does not directly pertain to the use of the Modulith™ Lithotripter in the treatment of urinary calculi, it was reported that no complications related to the shock waves were noted.

### Conclusions from Animal Studies

The preclinical information gathered through gross tissue evaluation, histological examination, and physiological and functional testing indicate that shock waves administered to the kidney by the Modulith™ Lithotripter result in non-significant pathologic and transient physiological changes to the kidney. Over time, these changes appear to be limited to minimal areas of fibrosis/scarring, with no discernable functional damage. These results are similar to those reported in the published literature using other lithotripters.

For the purposes of this PMA application, these animal studies were used to determine the safe and appropriate treatment parameters for clinical use, as well as the recommended retreatment schedule.

## B. CLINICAL STUDIES

### Study Design

Clinical investigations were conducted to determine the safety and effectiveness of the Storz Modulith™ Lithotripter in the fragmentation of urinary calculi. These investigations were conducted at four sites in the United States, with a total of 347 patients (387 kidneys) receiving 660 treatments. The first subject was enrolled on October 9, 1990; the last subject was treated on May 7, 1993. All data collected through June 28, 1993 were included in the final database. In these discussions, some variations in the number of patients, kidneys, and treatments occur due to patients lost to follow-up and incomplete reporting. However, the data collected were determined to be adequate to evaluate safety and effectiveness.

The design of the clinical investigation of the Modulith™ Lithotripter 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, each of which have enrolled a minimum of 50 patients who were followed for at least 3 months post-lithotripsy.

Table 1 presents each investigational site and the distribution of patients, kidneys, treatments, and mean number of shock waves delivered per treatment at each site.

**Table 1**  
**Distribution of Patients, Kidneys, Treatments, and**  
**Mean Number of Pressure Waves Per Site**

Principal Investigator Investigational Site	Patients	Kidneys	Treatments	Mean Pressure Waves
Frederick Klein, MD University of Tennessee Medical Center Knoxville, TN	113	131	263	1969.7
Alex Finkbeiner, MD University of Arkansas for Medical Sciences Little Rock, AR	91	107	177	1949.5
Ronald Knobloch, MD Jackson Fowler, MD University of Mississippi Medical Center Jackson, MS	63	66	115	1924.4
Richard Kahnoski, MD West Michigan Stone Center Butterworth Hospital Grand Rapids, MI	80	83	105	1873.4
Totals	347	387	660	1941.1 (mean)

Patient Inclusion and Exclusion Criteria

Male or female patients between 21 and 85 years of age with urinary calculi in the kidney or ureter whose condition indicated the use of lithotripsy were eligible for enrollment in the study. All patients were to have at least one stone greater than 4 mm in size; were to be classified as anesthesia risks ASA I, II, or III; and were to have signed an informed consent form.

The following patients were excluded from study participation: patients whose anatomy did not permit focusing of the device into the posterior flank, including those subjects with excessive spinal curvature or obesity; patients with urinary tract obstructions distal to the stone; pregnant females; patients with calcifications in the major renal arteries in the shock wave axis; patients with vascular aneurysms in the shock wave axis; female subjects of child-bearing potential with stones in the lower ureter; patients with stones that could not be clearly localized; patients whose largest stone is  $\leq 4$  mm in size; patients with coagulation disorders, as well as those on anticoagulants or thrombocyte aggregation inhibitors (unless the medication was discontinued and the patient evidenced a normal coagulation profile before treatment); patients on anti-inflammatory agents (unless discontinued for two weeks prior to treatment or the bleeding time was normal); patients with a history of chronic and/or acute cholecystitis, cholangitis, pancreatitis, or obstructions in the biliary duct system; patients in ASA class IV or V; and patients with pacemaker implants.

## Study Population

Of the 347 patients enrolled, 211 (60.8%) were males and 136 (39.2%) were females. This ratio of males to females is similar to that reported in prior studies of lithotripters, and is representative of the fact that approximately 75% of stone disease patients are males (Gillenwater et al. 1991).

Patient age ranged from 19 years to 84 years, with a mean of 47.0 years. Overall, the majority of patients (275; 79.3%) were treated on an outpatient basis. However, the proportion of patients who received outpatient treatment varied significantly across the study centers: 100% at Tennessee (113 patients), 93.4% at Arkansas (85 patients), 96.3% at Butterworth (77 patients), and 0% at Mississippi (i.e., all 63 patients at the Mississippi site were treated as inpatients).

Twenty-six patients (30 kidneys) were enrolled who did not meet the inclusion or exclusion criteria. These deviations from the protocol, with two exceptions, were of types that would be expected to present a worst-case evaluation of the device (as these cases are at higher risk of experiencing an adverse event or less successful outcome); therefore, all data collected from these 28 kidneys were used in the data analyses for the evaluation of safety and effectiveness. The reasons for these protocol deviations were as follows: abnormal, but not clinically significant, coagulation profiles at the time of enrollment (21 kidneys); histories of pancreatitis or cholecystitis (three kidneys); treatment below the minimum age requirement of 21 years (two kidneys); informed consent not obtained (one kidney); and ASA class IV at the time of enrollment (one kidney). Regarding the two protocol deviations which do not represent worst-case scenarios, both involved the treatment of patients who had largest stone sizes of 4 mm, which are already in the range of post-treatment success ( $\leq 4$  mm). These two cases, therefore, were included in the safety analysis, but excluded from the analysis of device effectiveness.

Eleven patients (twelve kidneys) received treatment parameters outside of those specified in the protocol. Specifically, these protocol deviations consisted of nine kidneys that received greater than 2000 shocks per treatment, and three kidneys that each received more than three treatments. Three of the nine kidneys that received more than 2000 shocks per treatment only exceeded this limit by  $\leq 10$  shocks, and, therefore, were included in the analyses of device safety and effectiveness. However, the remaining kidneys were included in the safety analyses only.

Table 2 presents the distribution of kidneys by study completion status. As of June 28, 1993, the majority of cases (313/387 kidneys; 80.9%) had completed follow-up. Of these 313 kidneys, 235 were evaluated at or before 3 months, while 78 were evaluated after 3 months. Of the 74 kidneys that did not receive complete follow-up, 44 were past due for follow-up, 18 were ongoing in the study, and twelve were discontinued.

The reasons for study discontinuation were as follows: four had discontinued at the option of the patient, three had discontinued because the patient moved or was unable to be located, three were discontinued because of death, and two were discontinued for medical reasons that were unrelated to lithotripsy. Of the two patients discontinuing for medical reasons, one was dying of lung cancer and

the second had suffered a myocardial infarction after the discharge evaluation; in both cases, the investigator felt that further treatment was clinically contraindicated.

Two of the three patient deaths were attributed to circumstances unrelated to the lithotripsy procedure, and were attributed to aspiration of blood secondary to bleeding gastritis in one patient and a myocardial infarction in the second. The third death resulted from a cardiac arrest caused by a consumptive coagulopathy, which occurred following a lithotripsy treatment. Although this death was determined not to be directly caused by lithotripsy, the primary investigator believed that a perinephric hematoma was an initiating factor in the diffuse intravascular coagulopathy.

**Table 2**  
**Distribution of Kidneys by Study Completion Status**

Study Completion Status	Tennessee		Arkansas		Mississippi		Butterworth		Total Kidneys	
	N	%	N	%	N	%	N	%	N	%
<b>Incomplete Follow-up</b>										
Chose not to continue	0	0.0	2	1.9	1	1.5	1	1.2	4	1.0
Discontinued for medical reasons	0	0.0	0	0.0	0	0.0	2	2.4	2	0.5
Unable to locate/patient moved	0	0.0	2	1.9	1	1.5	0	0.0	3	0.8
Deceased	1	0.8	0	0.0	0	0.0	2	2.4	3	0.8
Follow-up past due	4	3.0	18	16.8	9	13.7	13	15.7	44	11.4
Study ongoing	6	4.6	9	8.4	0	0.0	3	3.6	18	4.6
<b>Complete Follow-up</b>										
Seen at or before 3 months	96	73.3	63	58.9	33	50.0	43	51.8	235	60.7
Seen after 3 months	24	18.3	13	12.1	22	33.3	19	22.9	78	20.2
<b>Total Kidneys</b>	<b>131</b>	<b>100.0</b>	<b>107</b>	<b>100.0</b>	<b>66</b>	<b>100.0</b>	<b>83</b>	<b>100.0</b>	<b>387</b>	<b>100.0</b>

### Stone Characteristics

Of the 387 treated kidneys, the majority (258; 66.7%) had one stone at pretreatment. Sixty-five kidneys (16.8%) had two stones, 42 (10.8%) had three stones, 10 (2.6%) had four stones, and 12 (3.1%) had five or more stones. Bilateral treatments occurred in 40 (11.5%) patients. Tables 3, 4, and 5, respectively, present the distribution of kidneys by largest stone diameter, location of largest stone, and total stone volume at pretreatment at each study site. The stones treated ranged from 4 to 37 mm in largest diameter, and the mean stone size was 10.6 mm (this value excludes staghorn stones, whose size was not recorded). Of the 387 kidneys treated, most (43.7%) had largest stones which were 4.5 to 9 mm in size. For the other kidneys, 0.5% had largest stones which were  $\leq 4$  mm, 31.5% had largest stones which were 10 to 14 mm, 12.2% had largest stones which were 15 to 19 mm, 6.2% had largest stones which were  $\geq 20$  mm, and 5.9% had staghorn stones.

The majority of kidneys had the largest stone located in the lower calyx (26.9%) and renal pelvis (27.6%). Additionally, the largest stone was located in the middle and upper calyces 9.6 and 9.0% of kidneys, respectively. The largest stone was located in the ureter in 16.6% of cases, and of these, most were situated in the upper ureter (43/387; 11.1%). The remaining stone positions were either listed as staghorn (5.9%) or "multiple locations" (4.4%).

Pretreatment stone volume was calculated by summing the volumes of the individual stones. The majority of kidneys (207/387; 53.5%) had pretreatment stone volumes  $\geq 0.5$  cc (Table 5). The treated kidneys had a mean total pretreatment stone volume of 1.32 cc, ranging from 0.03 cc to 26.9 cc.

**Table 3**  
**Distribution of Kidneys by Diameter of Largest Stone at Pretreatment According to Study Site**

Largest Stone at Pretreatment	Study Site								Total	
	Tennessee		Arkansas		Mississippi		Butterworth			
	N	%	N	%	N	%	N	%	N	%
Diameter (mm):										
4 or less	0	0.0	1	0.9	0	0.0	1	1.2	2	0.5
4.5 - 9	65	49.6	40	37.4	28	42.4	36	43.4	169	43.7
10 - 14	42	32.1	27	25.2	22	33.3	31	37.3	122	31.5
15 - 19	11	8.4	20	18.7	6	9.1	10	12.1	47	12.2
20 or more	4	3.0	11	10.3	6	9.1	3	3.6	24	6.2
Staghorn	9	6.9	8	7.5	4	6.1	2	2.4	23	5.9
Total Kidneys	131	100.0	107	100.0	66	100.0	83	100.0	387	100.0

Note: Cases with staghorn stones and stone  $\geq 20$  mm in largest diameter are limited, and safety and effectiveness have not been established. Data are included for completeness.

**Table 4**  
**Distribution of Kidneys by Location of Largest Stone at Pretreatment According to Study Site**

Largest Stone at Pretreatment	Study Site								Total	
	Tennessee		Arkansas		Mississippi		Butterworth			
	N	%	N	%	N	%	N	%	N	%
Location:										
Upper Calyx	9	6.9	10	9.4	3	4.6	13	15.7	35	9.0
Middle Calyx	11	8.4	12	11.2	8	12.1	6	7.2	37	9.6
Lower Calyx	36	27.5	26	24.3	22	33.3	20	24.1	104	26.9
Pelvis	40	30.5	28	26.2	21	31.8	18	21.7	107	27.6
Upper Ureter	15	11.4	7	6.5	6	9.1	15	18.1	43	11.1
Middle Ureter	8	6.1	1	0.9	2	3.0	4	4.8	15	3.9
Lower Ureter	0	0.0	1	0.9	0	0.0	5	6.0	6	1.6
Staghorn	9	6.9	8	7.5	4	6.1	2	2.4	23	5.9
Multiple Locations	3	2.3	14	13.1	0	0.0	0	0.0	17	4.4
Total Kidneys	131	100.0	107	100.0	66	100.0	83	100.0	387	100.0

Note: Cases with middle and lower ureteral stones are limited, and safety and effectiveness have not been established. Data are included for completeness.

**Table 5**  
**Distribution of Kidneys by Total Pretreatment Stone Volume**  
**According to Study Site**

	Study Site								Total	
	Tennessee		Arkansas		Mississippi		Butterworth			
	N	%	N	%	N	%	N	%	N	%
Total Stone Volume (cc)										
< 0.2	36	27.5	23	21.5	16	24.2	17	20.5	92	23.8
0.2 - 0.49	25	19.1	13	12.1	8	12.1	19	22.9	65	16.8
0.5 - 1.0	36	27.5	28	26.2	20	30.3	25	30.1	109	28.2
> 1.0	25	19.1	35	32.7	18	27.3	20	24.1	98	25.3
Staghorn	9	6.8	8	7.5	4	6.1	2	2.4	23	5.9
Total Kidneys	131	100.0	107	100.0	66	100.0	83	100.0	387	100.0

### Treatment Parameters

The 387 treated kidneys received a total of 660 treatments: 204 kidneys (52.7%) received one treatment; 96 kidneys (24.8%) received two treatments; 84 kidneys (21.7%) received three treatments; and three kidneys (0.8%) received four treatments.

The majority of the 660 treatments were delivered without anesthesia (559/660; 84.7%). Four hundred four (61.2%) treatments were administered with premedication, and conscious sedation or analgesia was administered during 604 (91.5%) treatments. For the treatments where anesthesia was administered, 6.4% received general (42/660 treatments), 7.4% received epidural (49/660 treatments), and 0.8% received spinal (5/660 treatments) anesthesia. Data on anesthesia administration was not available for 5 treatments.

An average of 1941.1 pressure waves was delivered per treatment. In the majority of treatments (595/660; 90.2%), 1501 to 2000 pressure waves were delivered. The weighted average energy level (i.e., average energy level weighted by the number of pressure waves) per treatment session ranged from 4.0 to 9.0, with a mean of 8.4. Maximum energy level per treatment session ranged from 5 to 9, with a mean of 8.8. Shock waves were delivered using internal triggering exclusively (i.e., 1, 1.5, or 2 Hz) in 37.4% of cases, ECG triggering exclusively in 36.0% of the treatments, and a combination of internal and ECG triggering in 26.6% of cases.

Sixteen treatments were incomplete, seven due to device failure, one because of operator reasons, and eight for other reasons. Reasons for the latter incomplete treatments included the following: pain intolerance (two cases), high blood pressure (two cases), poor stone visualization (two cases), respiratory arrest secondary to anesthesia (one case), and nausea and vomiting (one case).

### Retreatment

The criteria for retreatment was the presence of fragments > 4 mm in diameter. The protocol limited patients to a maximum of three treatment sessions per kidney. Of 387 cases enrolled, 204 (52.7%)

received a single treatment, 96 (24.8%) received two treatments, 84 (21.7%) received three treatments, and three (0.8%) received four treatments. Thus a total 660 treatments were administered to 387 kidneys. The average interval between first and second treatments was 54.8 days, and the average interval between second and third treatments was 46.0 days.

### Radiation Exposure

Average patient x-ray exposure during treatment was assessed in the first 35 patients (41 treatments) at the University of Arkansas. Radiographic exposure mode for these 41 treatments averaged 2.9R. During six treatments, digital exposure mode averaged 2.2R. The use of continuous fluoroscopy mode in 18 treatments resulted in an average of 16.4R, whereas pulsed fluoroscopy mode used in 29 treatments resulted in an average exposure of 1.88R. (Some of these patients were imaged using more than one exposure mode during a single treatment session.) The majority of subsequent treatments were performed using the pulsed fluoroscopy mode which significantly lowers the output rate of radiation, resulting in less exposure to the patient and operator.

### RESULTS

The evaluation of effectiveness of treatment with the Modulith™ Lithotripter was based upon the presence and size of retained kidney stones or stone fragments 3 months post-lithotripsy. For this analysis, the success rate was defined as the proportion of kidneys either stone-free or having fragmented stones  $\leq 4$  mm (considered to pass spontaneously), as evidenced on x-ray. The two cases that were entered into the study with 4 mm stones, and which would have been considered successes based upon these success criteria, were excluded from the efficacy analysis.

Although 387 kidneys were treated during this study, device effectiveness was primarily based upon the results of a cohort of 228 kidneys, all of which were either examined at an appropriately timed 3 month evaluation (i.e., 75 to 120 days post-treatment) or found to be stone-free or failures at an earlier evaluation. Of these 228 kidneys, 170 (74.6%) were deemed to be treatment successes. Table 6, which presents these effectiveness results both by site as well as overall, shows that this success rate is based upon 145/228 (63.6%) kidneys becoming stone-free, and an additional 25/228 (11.0%) kidneys having retained fragments  $\leq 4$  mm. Of all of the treated kidneys for which data are available (excluding those kidneys with pretreatment stone sizes of  $\leq 4$  mm and those with significant treatment deviations), 65.0% (230/354) were judged to have been treated successfully at the time of last follow-up.

**Table 6**  
**Distribution of Kidneys by Fragmentation Results**  
**According to Study Site**

	Study Site								Total	
	Tennessee		Arkansas		Mississippi		Butterworth			
	N	%	N	%	N	%	N	%	N	%
<b>Largest Remaining Fragment</b>										
<b>Stone-Free</b>	58	60.4	39	67.2	16	50.0	32	76.2	145	63.6
<b>4 mm or Smaller Fragment</b>	7	7.3	9	15.5	4	12.5	5	11.9	25	11.0
<b>LITHOTRIPSY SUCCESS</b>	65	67.7	48	82.7	20	62.5	37	88.1	170	74.6
<b>Greater than 4 mm Fragment</b>	15	15.6	8	13.8	9	28.1	4	9.5	36	15.8
<b>Failure - Additional Procedure</b>	16	16.7	2	3.5	3	9.4	1	2.4	22	9.6
<b>TOTAL</b>	96	100.0	58	100.0	32	100.0	42	100.0	228	100.0

Among the 228 kidneys, the success rate varied across study sites from 62.5% at Mississippi to 88.1% at Butterworth, which was determined to be statistically significant ( $p=0.012$ ). The differences in the stone-free rates across study sites, however, were not statistically significant ( $p=0.103$ ). The study sites did not differ significantly with regard to the mean diameter of the largest stone (excluding staghorns), or the proportion of kidneys with largest stones  $\geq 20$  mm in diameter including staghorns. The study sites were found to differ significantly with respect to proportion of kidneys retreated, the mean number of treatments per kidney, the mean number of pressure waves per kidney, and the mean weighted average energy level per treatment. After controlling for retreatments (single versus multiple), the difference in success rates across study sites was no longer statistically significant ( $p=0.093$ ). Table 7, listed below, presents the success rates at each site according to whether or not patients received retreatment. Because of apparent differences in the manner in which treatments using the Modulith™ Lithotripter were delivered between the investigational sites, the data recorded from this study are presented and analyzed both by site and overall.

**Table 7**  
**Distribution of Kidneys by Treatment Effectiveness**  
**According to Number of Treatments**

	Number of Treatments			
	1		≥ 2	
	N	%	N	%
<b>Tennessee</b>				
Success	33	86.8	32	55.2
Failure	5	13.2	26	44.8
Total	38	100.0	58	100.0
<b>Arkansas</b>				
Success	33	97.1	15	62.5
Failure	1	2.9	9	37.5
Total	34	100.0	24	100.0
<b>Mississippi</b>				
Success	13	76.5	7	46.7
Failure	4	23.5	8	53.3
Total	17	100.0	15	100.0
<b>Butterworth</b>				
Success	28	90.3	9	81.8
Failure	3	9.7	2	18.2
Total	31	100.0	11	100.0
<b>Overall</b>				
Success	107	89.2	63	58.3
Failure	13	10.8	45	41.7
Total	120	100.0	108	100.0

Adjuvant therapies that were performed during the study included ureteral stent placement and removal, ureteroscopy, cystoscopy, fragment extraction, percutaneous nephrolithotomy, percutaneous nephrostomy, open surgery, and treatment with other extracorporeal lithotripsy devices. Kidneys treated with any of the following post-lithotripsy procedures were considered lithotripsy failures: percutaneous nephrolithotomy, extracorporeal lithotripsy treatment using another lithotripter, open surgery, laser lithotripsy, electrohydraulic lithotripsy with or without stone manipulation, percutaneous ultrasonic lithotripsy, or lithopaxy.

As expected, analyses of the stone-free and success rates in the cohort of 228 kidneys showed the device to be less effective on patients with large stone sizes, large stone volumes, and multiple stones (i.e.,  $\geq 3$ ) at pretreatment. In particular, stone-free and success rates were significantly lower for staghorn stones and stones  $\geq 20$  mm, as compared to stones  $< 19$  mm in diameter ( $p < 0.0001$ ). Additionally, decreases in treatment success rates were seen with patients with more than one treatment and those who received greater total numbers of shock waves. Other pretreatment characteristics, however, such as stone location, gender, age, body mass index, and lithotripsy treatment prior to study enrollment, were not found to influence treatment success. In particular, the data were specifically analyzed to assess whether the effectiveness results were gender-related. Analyses revealed that treatment was slightly more effective among males than females (77.0% and

71.6%, respectively); however, this difference is not statistically significant, even after controlling for the differences noted between the investigational sites. Treatment with the Modulith™ Lithotripter, therefore, does not appear to be gender-specific.

Tables 8, 9, and 10 present the effectiveness results by pretreatment stone size, stone volume, and stone number for the cohort of 228 kidneys.

**Table 8**  
**Distribution of Kidneys by Treatment Effectiveness**  
**According to Pretreatment Stone Size**

	Pretreatment Stone Size					
	< 10 mm		10 - 19 mm		≥ 20 mm or Staghorn	
	N	%	N	%	N	%
<b>Tennessee</b>						
<b>Success</b>	37	77.1	26	66.7	2	22.2
<b>Failure</b>	11	22.9	13	33.3	7	77.8
<b>Total</b>	48	100.0	39	100.0	9	100.0
<b>Arkansas</b>						
<b>Success</b>	21	87.5	22	88.0	5	55.6
<b>Failure</b>	3	12.5	3	12.0	4	44.4
<b>Total</b>	24	100.0	25	100.0	9	100.0
<b>Mississippi</b>						
<b>Success</b>	13	86.7	6	46.2	1	25.0
<b>Failure</b>	2	13.3	7	53.8	3	75.0
<b>Total</b>	15	100.0	13	100.0	4	100.0
<b>Butterworth</b>						
<b>Success</b>	16	94.1	20	83.3	1	100.0
<b>Failure</b>	1	5.9	4	16.7	0	0
<b>Total</b>	17	100.0	24	100.0	1	100.0
<b>Overall</b>						
<b>Success</b>	87	83.7	74	73.3	9	39.1
<b>Failure</b>	17	16.3	27	26.7	14	60.9
<b>Total</b>	104	100.0	101	100.0	23	100.0

**Table 9**  
**Distribution of Kidneys by Fragmentation Results**  
**According to Total Pretreatment Stone Burden**

	Pretreatment Stone Volume (cc)											
	< 0.2		0.2 - 0.49		0.5 - 1.0		> 1.0		Staghorn		Total	
	N	%	N	%	N	%	N	%	N	%	N	%
<b>Tennessee</b>												
Success	24	92.3	13	65.0	15	62.5	11	55.0	2	33.3	65	67.7
Failure	2	7.7	7	35.0	9	37.5	9	45.0	4	66.7	31	32.3
<b>Total</b>	<b>26</b>	<b>100.0</b>	<b>20</b>	<b>100.0</b>	<b>24</b>	<b>100.0</b>	<b>20</b>	<b>100.0</b>	<b>6</b>	<b>100.0</b>	<b>96</b>	<b>100.0</b>
<b>Arkansas</b>												
Success	12	92.3	6	75.0	14	100.0	13	68.4	3	75.0	48	82.7
Failure	1	7.7	2	25.0	0	0	6	31.6	1	25.0	10	17.3
<b>Total</b>	<b>13</b>	<b>100.0</b>	<b>8</b>	<b>100.0</b>	<b>14</b>	<b>100.0</b>	<b>19</b>	<b>100.0</b>	<b>4</b>	<b>100.0</b>	<b>58</b>	<b>100.0</b>
<b>Mississippi</b>												
Success	11	91.7	2	66.7	3	50.0	4	40.0	0	0	20	62.5
Failure	1	8.3	1	33.3	3	50.0	6	60.0	1	100.0	12	37.5
<b>Total</b>	<b>12</b>	<b>100.0</b>	<b>3</b>	<b>100.0</b>	<b>3</b>	<b>100.0</b>	<b>10</b>	<b>100.0</b>	<b>1</b>	<b>100.0</b>	<b>32</b>	<b>100.0</b>
<b>Butterworth</b>												
Success	8	100.0	8	88.9	11	91.6	10	76.9	0	0	37	88.1
Failure	0	0	1	11.1	1	8.3	3	23.1	0	0	5	11.9
<b>Total</b>	<b>8</b>	<b>100.0</b>	<b>9</b>	<b>100.0</b>	<b>12</b>	<b>100.0</b>	<b>13</b>	<b>100.0</b>	<b>0</b>	<b>0</b>	<b>42</b>	<b>100.0</b>
<b>Overall</b>												
Success	55	93.2	29	72.5	43	76.8	38	61.3	5	45.5	170	74.6
Failure	4	6.8	11	27.5	13	23.2	24	38.7	6	54.5	58	25.4
<b>Total</b>	<b>59</b>	<b>100.0</b>	<b>40</b>	<b>100.0</b>	<b>56</b>	<b>100.0</b>	<b>62</b>	<b>100.0</b>	<b>11</b>	<b>100.0</b>	<b>228</b>	<b>100.0</b>

**Table 10**  
**Distribution of Kidneys by Treatment Effectiveness**  
**According to Pretreatment Stone Number**

	Pretreatment Stone Number					
	1		≥ 2		Total	
	N	%	N	%	N	%
<b>Tennessee</b>						
<b>Success</b>	47	71.2	18	60.0	65	67.7
<b>Failure</b>	19	28.8	12	40.0	31	32.3
<b>Total</b>	66	100.0	30	100.0	96	100.0
<b>Arkansas</b>						
<b>Success</b>	31	77.5	17	85.0	48	82.8
<b>Failure</b>	7	17.5	3	15.0	10	17.2
<b>Total</b>	40	100.0	20	100.0	58	100.0
<b>Mississippi</b>						
<b>Success</b>	16	61.5	4	66.7	20	62.5
<b>Failure</b>	10	38.5	2	33.3	12	37.5
<b>Total</b>	26	100.0	6	100.0	32	100.0
<b>Butterworth</b>						
<b>Success</b>	29	90.6	8	80.0	37	88.1
<b>Failure</b>	3	9.4	2	20.0	5	11.9
<b>Total</b>	32	100.0	10	100.0	42	100.0
<b>Overall</b>						
<b>Success</b>	123	75.9	47	71.2	170	74.6
<b>Failure</b>	39	24.1	19	28.8	58	25.4
<b>Total</b>	162	100.0	66	100.0	228	100.0

**ADVERSE EFFECTS**

Tables 11 and 12 present the complication rates, overall as well as separately for each site, for the following time periods: (1) during and immediately post-treatment, and (2) at last evaluation at least 21 days after the last treatment. These results are presented for all subjects treated (for which data are available). Each table presents only those complications which occurred during the applicable reporting interval.

**Table 11**  
**Distribution of Treatments by Complications Reported**  
**During or Immediately Post-treatment According to Study Site**

Complication	Study Site								Total (n=660)	
	Tennessee (n=263)		Arkansas (n=177)		Mississippi (n=115)		Butterworth (n=105)		N	%
	N	%	N	%	N	%	N	%		
Redness at Treatment Site	6	2.3	114	64.4	62	53.9	48	45.7	230	34.8
Ecchymosis at Treatment Site	0	0.0	7	4.0	1	0.9	6	5.7	14	2.1
Pain										
Discomfort	21	8.0	45	25.4	13	11.3	4	3.8	83	12.6
Mild	16	6.1	16	9.0	54	47.0	8	7.6	94	14.2
Moderate	7	2.7	9	5.1	37	32.2	0	0.0	53	8.0
Severe	5	1.9	6	3.4	0	0.0	0	0.0	11	1.7
Severity Unknown	7	2.7	0	0.0	0	0.0	0	0.0	7	1.1
Total	56	21.3	76	42.9	104	90.4	12	11.4	248	37.6
Gross Hematuria	28	10.6	134	75.7	2	1.7	34	32.4	198	30.0
Arrhythmia	39	14.8	10	5.6	41	35.7	2	1.9	92	13.9
Obstruction	0	0.0	1	0.6	0	0.0	0	0.0	1	0.2
Other	16	6.1	17	9.6	11	9.6	0	0.0	44	6.7

**Table 12**  
**Distribution of Kidneys with Complications Reported at**  
**Last Follow-up 21 Days or More After Last Treatment**  
**According to Study Site**

Complication	Study Site								Total (n=316)	
	Tennessee (n=124)		Arkansas (n=75)		Mississippi (n=54)		Butterworth (n=63)		N	%
	N	%	N	%	N	%	N	%		
Ecchymosis at Treatment Site	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Pain										
Discomfort	15	12.1	3	4.0	13	24.1	6	9.5	37	11.7
Mild	7	5.6	5	6.7	8	14.8	3	4.8	23	7.3
Moderate	2	1.6	0	0.0	5	9.3	0	0.0	7	2.2
Severe	1	0.8	0	0.0	1	1.8	0	0.0	2	0.6
Total	25	20.2	8	10.7	27	50.0	9	14.3	69	21.8
Gross Hematuria	1	0.8	0	0.0	3	5.6	2	3.2	6	1.9
Infection	3	2.4	4	5.3	0	0.0	0	0.0	7	2.2
Steinstrasse	0	0.0	0	0.0	1	1.9	0	0.0	1	0.3
Obstruction	0	0.0	1	1.3	5	9.3	0	0.0	6	1.9
Perirenal Hematoma	0	0.0	1	1.3	0	0.0	0	0.0	1	0.3
Intrarenal Hematoma	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Other	1	0.8	0	0.0	3	5.6	0	0.0	4	1.3

Some differences in the rates of complications were noted between the investigational sites. While some of these differences can be accounted for based upon significant differences between the sites regarding the use of anesthesia (both pain and arrhythmia were higher at Mississippi, where no sedation or anesthesia was administered), definitive explanations for other differences (i.e., skin redness and gross hematuria) are less obvious and may be due to differences in the criteria used to judge the presence of certain adverse events.

The incidence of adverse events was also evaluated according to the number of treatments administered. The data do not indicate increased risk associated with retreatment over that experienced with the initial treatment. Similarly, analysis by gender revealed that equivalent outcomes were experienced by both males and females with regard to the following endpoints: incidence of complications, changes in hematology and blood chemistry values, changes in blood pressure, and changes in renal scan values.

### Pain

Pain during or immediately post-treatment was reported to be associated with 37.6% of the 660 treatments administered, the majority of which were rated as either discomfort or mild. Pain is often associated with either the passage of lithotripsy shock waves into the body or the passage of stone fragments, and may be treated with analgesic or antispasmodic drug therapy. The incidence of pain during or immediately after treatment was highest at Mississippi (90.4%) where sedation and anesthesia were not used; at the other sites, the rate of pain ranged from 11.4% to 42.9%. At last follow-up 21 or more days after the last treatment, the overall rate of pain was 21.8%, ranging from 10.7% at Arkansas to 50.0% at Mississippi. While pain was reported twice as often among failures or for kidneys with residual fragments greater than 4 mm, the rate of this complication did not appear to be related to treatment number, number of pressure waves, or pretreatment stone volume.

### Skin Redness

Skin redness at the treatment site was reported for 34.8% of treatments during or immediately post-treatment. This condition usually resolved spontaneously within 48 hours after treatment.

### Gross Hematuria

Gross hematuria has occurred in a high percentage of patients in prior studies (Drach et al. 1986). Furthermore, this adverse event is often seen with open surgery of the kidney, percutaneous procedures, and ureteroscopy. In this study, gross hematuria was reported for 30.0% of treatments during or immediately post-treatment. The incidence ranged from 1.7% at Mississippi to 75.7% at Arkansas, and was observed to be higher among treatments where ancillary procedures were performed. By the last follow-up 21 or more days after the last treatment, 1.9% kidneys treated had reports of gross hematuria. Hematuria at follow-up is often secondary to the passage of stone fragments, auxiliary measures, or the presence of stones themselves.

### Cardiac Arrhythmia

Cardiac arrhythmias developed during the course of 92 treatments (13.9%), ranging from 1.9% at Butterworth to 35.7% at Mississippi. Cardiac rhythms usually returned to normal either by switching the triggering mode from internal triggering to ECG gating, or spontaneously. Most of the arrhythmias reported were premature ventricular contractions (79.3%); only one (1.1%) of the patients was symptomatic. While arrhythmias did not appear to be related to the treatment number, number of pressure waves, pretreatment stone volume, or use of ancillary procedures, they were reported more frequently for treatments in which no anesthesia or sedation was given (9.4% with anesthesia/sedation versus 35.7% without). Cardiac monitoring is advised during treatment.

### Other

Other complications were reported during or immediately after 44 treatments, and were most commonly listed as nausea (17/44 reports). At the last follow-up 21 or more days after the last treatment, four cases were associated with other complications--two patients exhibited hypertensive blood pressures, one patient complained of dysuria, and one patient developed an encrusted ureteral stent.

### Infection

Seven kidneys (2.2%) were noted to have urinary tract infections at last follow-up greater than 21 days post-treatment. This adverse event is typically treated with antibiotic therapy.

### Ecchymosis

Ecchymosis was reported immediately following 14 treatments (2.1%), and usually resolved spontaneously within several days. No ecchymosis was reported at follow-up greater than 21 days post-treatment.

### Obstruction and Steinstrasse

Obstructions were reported immediately following treatment in 1 kidney, and in 6 kidneys at follow-up 21 days or greater after treatment. Steinstrasse was noted in 1 kidney at last follow-up 21 days or greater post-treatment. Obstructions and steinstrasse occur due to the passage of stone fragments, and usually resolve spontaneously or with the use of auxiliary measures.

### Perirenal and intrarenal hematoma

Hematomas were reported in a total of seven kidneys following treatment with the Modulith™ Lithotripter, of which one was noted at last follow-up greater than 21 days post-treatment. Of these seven hematomas, six resolved following conservative therapy and continued patient monitoring. The other hematoma occurred in one of the patients that subsequently died; this case is described above.

## Hypertension

Elevated blood pressure (diastolic blood pressure > 95 mmHg) was reported in 21 patients at last follow-up greater than 21 days after treatment (out of 247 patients with pre- and post-treatment blood pressures recorded). Nineteen of these 21 patients were normotensive prior to treatment and two were hypertensive prior to treatment. Furthermore, eleven had a prior history of hypertension. Overall, a mean decrease (statistically significant;  $p=0.0191$ ) in systolic blood pressure of 2.98 mmHg was observed. Additionally, a mean increase (not statistically significant) in diastolic blood pressure of 0.37 mmHg was recorded. None of the mean changes that occurred, however, were found to be clinically significant. The relationship between hypertension and extracorporeal lithotripsy is not fully understood and continues to undergo investigation.

## LABORATORY VALUES

Table 13 presents the mean values for each laboratory test performed at pretreatment, within 3 days of treatment, and at the last follow-up visit 21 days or more after the last treatment.

**Table 13**  
**Mean Laboratory Values**

Test		Pretreatment		Within 3 Days		Last 3-month follow-up		Reference Range <sup>1</sup>
		N	Mean	N	Mean	N	Mean	
<b>Hematocrit</b>	Tennessee	113	41.12	223	38.92	98	41.67	35-54%
	Arkansas	91	42.17	120	39.85	57	42.04	34-52%
	Mississippi	63	40.48	109	39.07	44	41.92	37-52%
	Butterworth	73	42.75	72	41.19	58	42.72	36-54%
	Overall	340	41.63	524	39.48	257	42.03	38-54%
<b>Creatinine</b>	Tennessee	113	1.10	219	1.07	98	1.05	0.5-1.7 mg/dl
	Arkansas	91	0.99	121	0.97	56	1.05	0.5-1.4 mg/dl
	Mississippi	63	1.00	111	1.11	48	1.07	0.5-1.4 mg/dl
	Butterworth	72	0.99	69	1.03	57	1.01	0.4-1.8 mg/dl
	Overall	339	1.03	520	1.05	259	1.04	0.6-1.2 mg/dl
<b>BUN</b>	Tennessee	113	13.25	219	12.36	98	14.47	5-26 mg/dl
	Arkansas	89	13.52	123	12.18	55	14.18	6-20 mg/dl
	Mississippi	63	14.98	111	14.82	48	15.54	5-25 mg/dl
	Butterworth	72	15.44	69	15.23	56	15.71	6-26 mg/dl
	Overall	337	14.11	522	13.22	257	14.88	8-23 mg/dl
<b>LDH</b>	Tennessee	112	481.03	217	505.58	97	456.79	313-618 mu/ml 0-240 U/L
	Arkansas	89	137.83	120	156.43	48	140.33	313-618 U/L 90-190 U/L
	Mississippi	59	153.93	108	159.82	44	158.80	91-190 U/L
	Butterworth	72	171.01	69	162.88	57	166.88	300-618 U/L 80-240 U/L
	Overall <sup>2</sup>	220	153.00	297	159.16	149	155.94	313-618 mu/ml 100-190 U/L
<b>Amylase</b>	Tennessee	113	52.01	218	49.93	96	56.32	11-170 U/L
	Arkansas	88	66.81	121	58.05	52	70.40	23-115 U/L
	Mississippi	61	74.51	108	69.86	45	74.18	30-140 U/L
	Butterworth	73	84.49	70	72.40	54	80.85	0-220 U/L
	Overall	335	67.07	517	59.03	247	67.90	60-160 U/L
<b>SGOT</b>	Tennessee	112	33.84	217	36.91	97	33.07	0-60 U/ml
	Arkansas	90	24.76	121	25.55	52	27.02	5-45 U/ml
	Mississippi	63	30.37	110	29.57	47	28.79	10-47 U/ml
	Butterworth	73	26.79	69	26.00	57	24.86	0-45 U/ml
	Overall	338	29.25	517	31.24	253	29.18	16-60 U/ml

Notes (for Table 13):

<sup>1</sup> Todd J. Sanford H, Davidson I, Henry J. Clinical Diagnosis and Management by Laboratory Method. Philadelphia: 1979, WE Saunders.

<sup>2</sup> Tennessee is excluded from overall totals and means, because of LDH reporting differences.

Of these mean blood chemistry values, statistically significant changes from baseline values were noted for hematocrit, BUN, LDH, and amylase at 0-3 days post-treatment, all of which returned to normal by the last 3-month follow-up. These changes were within the normal ranges and were not clinically significant.

### Bleeding

Hematocrit was obtained both pre- and post-treatment to evaluate blood loss. Mean hematocrit decreased following treatment and returned to pretreatment level at the last follow-up greater than or equal to 21 days. This slight downward trend likely reflects transient hematuria or some degree of blood cell hemolysis. These changes are consistent with published data.

### Renal function

Creatinine and BUN levels were obtained before and following treatment to evaluate renal function. Mean creatinine values were fairly constant pretreatment to post-treatment. Mean BUN values decreased at 0-3 days post-treatment, but returned to pretreatment values at last follow-up  $\geq 21$  days. Constant creatinine levels and a slight decrease in BUN following lithotripsy represent a trend that is consistent with published data. This pattern may be attributable to relief of a partial obstruction.

### Hepatic Trauma

LDH and SGOT levels were obtained pre- and post-treatment to evaluate for possible liver damage. The mean LDH level was higher within 3 days post-treatment than pretreatment, and decreased somewhat at last follow-up  $\geq 21$  days. However, at last follow-up  $\geq 21$  days, the LDH mean was still slightly higher than the pretreatment value. Mean SGOT levels were elevated slightly within 3 days compared with pretreatment, and returned to pretreatment levels by the last follow-up  $\geq 21$  days. Both values indicated no liver damage following treatment.

### Pancreatic Trauma

Serum amylase levels were monitored to evaluate the potential for pancreatic damage. The mean amylase level was somewhat lower at 0-3 days post-treatment than at pretreatment, but returned to the pretreatment level at last follow-up  $\geq 21$  days. These values remained within the typical normal range of 60 to 160 U/L throughout follow-up.

## RENAL SCAN STUDY

The effects of treatment with the Modulith™ Lithotripter upon renal function were evaluated in 84 patients using Mag III/Tech 99 (Technesium 99 / Mercaptoacetyltriglycine) renal scans. The study protocol required pre- and post-treatment renal scans on the first 50 patients enrolled into the trial, and additional subjects were monitored using renal scans if they were allergic to the IVP dye. Of the 84 subjects who received renal scans, pre- and post-treatment scans were obtained in a cohort of 69 patients. These renal scan results are presented as split renal function values, and the analysis of these data consists of comparisons between the pre- and post-treatment values. For this analysis, the normal range of split renal function was considered to be 45-55%, and pre- to post-treatment changes of  $\geq 5\%$  were considered to be clinically significant. Additionally, the creatinine and BUN values of these subjects were included in the analysis as another measure of renal function.

Overall, the average split renal functions of the treated kidneys did not show a significant change from pre- to post-treatment (i.e., the mean values experienced a decrease of 1.1%, from 47.9% at baseline to 46.8% at follow-up). In nine (13%) of the kidneys, there was no difference between the pretreatment and follow-up split renal function. Thirty-eight (55%) of the kidneys treated showed a decrease in split renal function, of which 20 (29%) experienced clinically significant decreases of 5% or more. The remaining 22 (32%) kidneys had an increase, with eleven (15.9%) indicating increased split renal function of 5% or greater. No relationship was found between the renal scan results and either the number of treatments or the presence of obstruction (either pre- or post-treatment). Furthermore, changes in split renal function were not found to correlate with changes in either serum creatinine or BUN.

Out of the 69 renal scan subjects, eleven (15.9%) had normal renal scans at pretreatment (i.e., 45-55%) which decreased into the abnormal range at post-treatment. Of these eleven cases, information regarding the causes and/or methods of resolution are as follows: two had clinically insignificant drops of  $< 5\%$ ; one developed a perinephric hematoma which resolved with treatment (but had a direct influence on the post-treatment renal scan value); one had a retained fragment at the time of the follow-up scan (the split renal function of this subject was likely to return to normal following fragment passage); six demonstrated normal bilateral kidney function on a later IVP; and one refused to return for either a second post-treatment scan or IVP.

Based upon these renal scan data, some patients experienced reductions in renal function. In the majority of cases, however, these changes either resolved spontaneously, were clinically insignificant, or were associated with some other underlying medical condition that was treated (i.e., hematoma or retained fragment).

## DEVICE FAILURES

Eight patient treatments had to be interrupted during the clinical trials for device related reasons. Seven of these were due to device malfunctions and one because of operator reasons. No patient injury occurred due to device malfunction.

### Therapy Wave Generator

Three of the treatment interruptions were caused by difficulties with the therapy wave generator. In two of these cases, a circuit breaker tripped prior to system start-up. In the third case, the Pulse Current Source inhibited the release of therapy waves above energy level 5. An engineering change added a current limiting resistor and an inductor to reduce the Thyatron Tube filament current and voltage, and these problems have not recurred.

### X-ray Localization

Four of the treatment interruptions were due to difficulties with the x-ray localization system. In one instance, an intermittent loss of x-ray exposure was caused by a failure of a component in the x-ray generator power supply. The faulty component was replaced and the problem has not recurred. In another instance, C-arm or image intensifier motion was not possible; however, this problem could not be duplicated by the service engineer and has not recurred. Two failures at one site were linked to failures within the high voltage generator power supply. It was determined that arcing in the high voltage transformer had occurred, and was corrected by replacement of the transformer. These were determined to be random failures and required no design changes to this device.

### Operational

The operator discontinued a patient treatment when the audible pitch of the shock wave varied. This change in sound level was later determined to be caused by the normal water degassing cycling, as well as changes in patient coupling surface area.

## **IX. CONCLUSIONS DRAWN FROM THE STUDIES**

Laboratory tests were performed to determine the pressure and spatial configuration of the shock wave at the focal point. At the highest energy setting (i.e., level 9, which corresponds to 20 kV), the maximum pressure was 1056 bars and the dimensions of the focal area at -6dB were 37 mm (axial) by 2.8 mm (lateral). These tests demonstrated that the Modulith™ Lithotripter produced consistent shock wave pressures at the focal point of the device.

Animal studies were conducted on dogs and pigs to determine the effect of shock waves on the kidney (without implanted stones). In the dog study, animals were subjected to various shock wave levels and numbers, and were sacrificed either immediately or 6 weeks post-treatment. The pig study assessed the effect of varying numbers of treatments on the kidney and gallbladder, and also analyzed the effects of treatment upon relevant blood chemistry values. Both studies demonstrated that treatment with the Modulith™ Lithotripter was associated with non-significant pathological transformations and transient physiological changes to the kidney. Over time, these changes appear to be limited to minimal areas of fibrosis/scarring, with no discernable functional damage.

Clinical investigations were conducted at four centers in the United States to determine the safety and effectiveness of the Modulith™ Lithotripter in the fragmentation of urinary calculi. Clinical data

were collected on 347 patients (387 kidneys) who received 660 treatments, each of whom were limited to 2000 pressure waves per treatment and a maximum of three treatments. The mean diameter of the largest stone at pretreatment, excluding staghorns, was 10.6 mm, with a range of 4.0 to 37.0 mm. The largest stone was located in either the lower renal calyx or renal pelvis in the majority of patients; however, a significant number of subjects were treated with stones in the upper ureter, upper calyx, and middle calyx. Complications reported following treatment included pain (37.6% total--discomfort or mild pain in 26.8% and moderate or severe pain in 9.7%), skin redness (34.8%), gross hematuria (30.0%), infection (2.2%), obstruction (1.9%), intrarenal or perirenal hematoma (1.8%), steinstrasse (0.3%), and hypertension (8.5%). Successful treatments, defined as patients either being stone-free or having fragments  $\leq 4$  mm by 3 months following lithotripsy, were recorded for 74.6% of kidneys. Since the success rate varied significantly among the study sites (from 62.5% to 88.1%), data have been presented and analyzed by institution.

A cohort of 69 of the study patients were evaluated with pre- and post-treatment renal scans, to further assess the potential for renal damage. The average renal function of the treated kidney post-treatment was 46.8%, which is clinically equivalent to the pretreatment value of 47.9% based upon the uncertainty inherent in this diagnostic measure. This subgroup of patients demonstrates that the Modulith™ Lithotripter is capable of treating urinary calculi without impairment of renal function.

The results of the laboratory, animal, and clinical studies conducted with the Storz Modulith™ SL20 Lithotripter provide reasonable assurance of the safety and effectiveness of the device for the noninvasive fragmentation of urinary calculi in the kidneys and upper ureter.

## **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 Karl Storz Endoscopy-America, Inc., manufacturing facility was completed in October, 1993, 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 Modulith™ Lithotripter is safe and effective for the indications of fragmentation of urinary calculi in the kidney and upper ureter. Furthermore, the applicant agreed to participate in the postapproval study "A Controlled Study of the Effect of Extracorporeal Lithotripsy on Blood Pressure Secondary to Nephrolithiasis" to determine whether a relationship exists between lithotripsy and hypertension.

CDRH issued an approval order for the stated indication for the applicant's PMA for the Storz Modulith™ Model SL20 Lithotripter on FEB 17 1995.

## XII. REFERENCES AND OTHER RELEVANT PUBLICATIONS

1. Jameson RM, Burrows K, Large B. Management of the Urological Patient. Churchill Livingstone, New York, 142-145. 1976.
2. Segura JW, Patterson DE, LeRoy AJ, May GR, Smith LH. "Percutaneous Lithotripsy." *J. Urol.* 130: 1051-1054. December 1983.
3. Wickham JEA, Kellet MJ, Miller RA. "Elective Percutaneous Nephrolithotomy in 50 Patients: An Analysis of the Technique, Results and Complications." *J. Urol.* 129: 904-905. May 1983.
4. Gillenwater J, Grayhack J, Howards S, Duckett J, editors. Adult and Pediatric Urology (2nd Edition). Mosby-Year Book, Inc., St. Louis, 408-409. 1991.
5. Drach GW, Dretler S, Fair W, Finlayson B, Gillenwater J, Griffith D, Lingeman J, Newman D. "Report of the United States Cooperative Study of Extracorporeal Shock Wave Lithotripsy." *J. Urol.* 135: 1127-1133. June 1986.

## 1.1 Medical Fundamentals

The application of extracorporeally generated therapy waves is a non-invasive method. It results in the disintegration of stones of different compositions and can be used for urinary stones.

### 1.1.1 Range of Application

A basic requirement for the treatment of stones using extracorporeal lithotripsy is their ability to be located. With the Modulith™ SL 20, an inline ultrasound locating system and x-ray locating system are implemented.

### 1.1.2 Indications and Contraindications

#### Indications

The Storz Modulith™ Lithotripter is indicated for use in the noninvasive fragmentation of urinary calculi in the kidney and upper ureter.

#### Contraindications

The Storz Modulith™ is contraindicated for:

- Patients with coagulation abnormalities as indicated by abnormal prothrombin time (PT), partial thromboplastin time (PTT), or bleeding time. This includes patients currently receiving anti-coagulants (including aspirin).
- Patients in whom pregnancy is suspected, as well as patients in whom the use of x-ray is contraindicated.
- Patients with arterial calcification or vascular aneurysms in the therapy wave axis.
- Patients with a history of chronic or acute cholecystitis, cholangitis, or pancreatitis.
- Patients with urinary tract obstructions distal to the stone.
- Patients whose anatomy does not permit focusing of the device into the patient's posterior flank in the area of the kidney stone, including severely obese patients (exceeding 300 pounds) or those suffering from excessive spinal curvature.



**Precautions:**

Cardiac monitoring of patients should 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. Although patients with cardiac pacemakers have been treated with shock wave therapy, the safety of using the Storz Modulith™ to treat persons with cardiac pacemakers and other implanted devices, whose function could be affected by pressure waves, has not been established.

Clinical experience in treating impacted or embedded stones with the Storz Modulith™ extracorporeal lithotripter is limited and effectiveness cannot be assured. Experience with other manufacturer's lithotripters using extracorporeal shock wave lithotripsy monotherapy for impacted stones has shown limited success. Alternative or auxiliary procedures are recommended.

It is important to follow patients radiographically until the patient is stone-free or there are no remaining stone fragments, since stone fragments may cause a silent obstruction and loss of renal function.

In reference to retreatment, it is recommended that patients should be limited to three treatment sessions of 2000 pressure waves each to the same focal region. The two retreatment sessions should not be scheduled sooner than two weeks and six weeks, respectively, from the first lithotripsy treatment.

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.

The effectiveness of extracorporeal shock wave lithotripsy may be lower in patients with either staghorn stones or large diameter stones. In particular, clinical evidence indicates that the Storz Modulith™ is less effective in treating either staghorn stones or stones  $\geq 20$  mm in largest diameter, than in treating stones  $< 19$  mm. The physician may want to consider the use of alternative therapies for patients with staghorn stone or stone  $\geq 20$  mm in largest diameter.

**Warnings:**

Although patients with infected stones have been successfully treated with shock wave therapy, the experience with the Storz Modulith™ in the treatment of such cases is limited. Therefore, the safety and effectiveness of treatment with the Modulith™ for infected stones has not been demonstrated. Due to the possibility of systemic infection from pathogen-harboring calculus debris, prophylactic administration of antibiotics should be considered prior to treatment whenever the possibility of stone infection exists.



The safety and effectiveness of the Storz Modulith™ SL 20 Lithotripter in the treatment of middle and lower ureteral stones has not been demonstrated and is currently unknown. The treatment of lower ureteral stones should specifically be 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.

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 separate treatment sessions 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.

Children have been treated with shock wave therapy for upper urinary tract stones; however, the experience with the Storz Modulith™ is limited. Therefore, the safety and effectiveness of the Modulith™ in the treatment of urolithiasis in children has not been demonstrated. Recent 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 is unknown.

#### 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: pain, skin redness, gross hematuria, cardiac arrhythmia, hypertension, nausea and/or vomiting, infection, echymosis, obstruction or steinstrasse, perirenal and intrarenal hematoma, renal injury, and radiation exposure.

- Pain was reported during or immediately following 37.6% of the 660 treatments that were performed in the clinical study of the Modulith™ Lithotripter, the majority of which were rated as either discomfort or mild (i.e., 26.8% of the 660 treatments). The rate of pain during treatment varied among the study sites, and is related to the level of sedation or anesthesia that each center used. Pain following treatment was apparently secondary to either the passage of stone fragments or due to auxiliary procedures. At last follow-up  $\geq 21$  days post-treatment, 21.8% of kidneys were reported to have pain (rated as either discomfort or mild in 19.0% of cases). Usual treatment for post-lithotripsy pain, if indicated, is with analgesia or antispasmodic drug therapy.
- Skin redness at the treatment site was observed in 34.8% of treatments, and usually resolved spontaneously within 48 hours after treatment. Skin redness appeared to be associated with higher stone volumes, which usually required a greater number of shock waves to achieve adequate fragmentation.

- Gross hematuria (i.e., visible blood in the urine) was observed following 30.0% of the treatments with the Modulith™ Lithotripter. Bleeding normally resolves spontaneously within 24 to 48 hours. By 21 days post-treatment, the incidence of gross hematuria was reported in 1.9% of the treated kidneys. Typically, hematuria found at follow-up is secondary to the presence or passage of stone fragments or auxiliary measures.
- Cardiac arrhythmia was reported during or immediately after 13.9% of the 660 patient treatments, of which, 79.3% of these arrhythmias were premature ventricular contractions. Arrhythmias were more frequent in treatments in which no anesthesia or sedation was given as well as among patients who had abnormal pretreatment ECGs, and was usually resolved by switching the triggering mode from internal triggering to ECG gating. Cardiac monitoring, therefore, is advised during treatment.
- Hypertension, defined as diastolic blood pressure > 95 mmHg, was reported at last follow-up ≥21 days post-treatment in 21 (8.5%) of the 247 patients with both pretreatment and follow-up blood pressures. Of these 21 patients, 19 were normotensive at baseline and 2 were hypertensive at baseline. The relationship between hypertension and extracorporeal shock wave lithotripsy is not fully understood, and continues to undergo investigation.
- Nausea and/or vomiting was reported during or immediately after 2.6% of treatments. This reaction may be related to the use of analgesics and/or anesthetics during the study.
- Infection of the urinary tract was noted in 2.2% of patients at last follow-up ≥21 days post-treatment. Infections may occur when stone fragments obstruct the urinary tract or as a result of ancillary procedures, and are treated with antibiotic therapy.
- Ecchymosis at the treatment site, extravasation of blood into the skin resulting in small purplish patches on the skin, is known to be a minor complication of lithotripsy and was noted immediately following 2.1% of treatments. Ecchymosis requires no treatment and generally resolves spontaneously in several days. No ecchymosis was reported at follow-up 21 days or more after the last treatment.
- Obstruction and steinstrasse are due to the passage of stone fragments, and resolve either spontaneously or with the use of auxiliary measures. One case of obstruction and no cases of steinstrasse were reported during or immediately post treatment, while 21 days or later, there were 6 (1.9%) cases of obstruction and 1 (0.3%) case of steinstrasse.
- Perirenal and intrarenal hematomas were reported in a total of 7 patients (approximately 2% of kidneys treated) following treatment with the Modulith™ Lithotripter, all of which were symptomatic. In 6 of these cases, the hematomas resolved following hospitalization. However, for the other case, the patient died shortly after treatment; although not deemed to be directly attributable to this patient's death, this hematoma was believed to be one of the initiating factors. Strict follow-up is recommended when post-treatment fluid collections are observed or if flank pain develops.

- 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.
- Radiation exposure is minimized through the use of the Modulith™ Lithotripter's pulse progressive fluoroscopic feature. In a sub-study within the clinical trial, the Modulith™ fluoroscopy system was found to expose the patient to an average of 1.88R, while the use of standard radiography resulted in an average exposure of 2.9R. Patient x-ray exposure can be minimized by following the radiation safety guidelines included in the labeling.

### 1.1.3 Accompanying Medical Measures

As a rule, the Modulith™ SL 20, enables a treatment without anesthesia. The decision whether an anesthetic or analgesia is to be administered depends on how sensitive the patient is to pain, which is to be determined by the attending physician.

During treatment with therapy waves, the patient is to be treated and observed with the usual medical care.

We recommend ECG monitoring for all patients.

Furthermore, the disintegration process should be checked often, the patient observed (and monitored), and the anesthesia observed throughout the entire course of treatment.

Following the therapy-wave treatment, it is recommended to perform a concluding examination by ultrasound or x-ray, to check, and if necessary, document the result of treatment.