Summary of Safety and Effectiveness Data

I. General Information

Device Generic Name: Lithotripsy device

Device Trade Name: Medstone STS™ Lithotripter

Applicant: Medstone International, Inc.
100 Columbia, Suite 100
Aliso Viejo, California 92656

Date of Panel Recommendation: April 30, 1998

PMA Number: P970042

Date of Notice of Approval to Applicant: September 5, 2000

II. Indications for Use

Combination therapy with the Medstone STS™ lithotripter and Actigall® is indicated in symptomatic adult patients for whom surgical removal of the gallbladder is medically contraindicated and in symptomatic high-risk patients who have actively refused surgery. The Medstone STS™ fragments and clears the functioning gallbladder of solitary, radiolucent, non-calcified stones between 4 and 20 mm in maximum diameter. Combination therapy consists of lithotripsy treatments of up to 2000 24 kV shocks and Actigall® administration of 8 – 10 mg/kg/day for at least two weeks pre-lithotripsy and until a stone-free state is achieved.

III. Contraindications

The Medstone STS™ Lithotripter is contraindicated where there are:

- Patients with cardiac arrhythmias or pacemakers;
- Coagulation abnormalities as indicated by abnormal prothrombin time (PT), partial thromboplastin time (PTT), or bleeding time – including patients currently receiving anti-coagulants (including aspirin);
- Evidence of non-functioning gallbladder; bile duct obstruction, including non-patent cystic duct; cholangitis; pancreatitis; cholecystitis; active biliary colic; or significant liver disease;
- Inability to tolerate general, intravenous or spinal anesthesia or analgesia;
- Pregnancy or any other condition for which the use of x-rays is contraindicated;
- Inability to image or position the stone;
- Patients with calcified gallstones;
- Patients unable or unwilling to take Actigall® for the prescribed period of time;
- Any condition listed as a contraindication for Actigall® should also be considered as a contraindication for the combination therapy. Actigall®'s labeling should be consulted for a complete list of all contraindications.

IV. Warnings and Precautions

- Combination therapy is not to be used as first-line-therapy for the treatment of gallstones in patients who are reasonable surgical candidates, except for those patients who have actively refused surgery, since its effectiveness is inferior to laparoscopic or open cholecystectomy.

- The long-term effectiveness of the combination therapy, including the dissolution and the risk of recurrence of stones, has not been demonstrated.

- The resolution of symptoms has not been demonstrated through the use of pain scores or quality of life questionnaires. Effectiveness has only been demonstrated through stone-free rates.

- The safety and effectiveness of the Medstone STS™ Lithotripter in the treatment of gallbladder stones in children have not been demonstrated. Recent studies have indicated that there are growth plate disturbances in the epiphysis of developing long bones in rats subjected to shockwaves. The significance of this finding to use of lithotripsy in humans is unknown.

- Care should be taken to ensure that minimal bowel gas is in the blast path. Patients with excessive bowel gas should be prepared with an appropriate non-gaseous cathartic or other treatment prior to lithotripsy.

- It is important to verify that there are no air pockets or bubbles between the various coupling interfaces, including the interface between the coupling bag and the patient's skin. Mineral oil should be applied to the patient's skin and all other coupling surfaces.

- The Medstone STS™'s software will allow a patient to be treated with up to 2400 shockwaves, even though the maximum number of shockwaves indicated for biliary use is 2000. Treatment will terminate only if this upper limit is reached during the course of a session. Physicians are responsible for monitoring this parameter during use to ensure that patients do not receive more shocks than necessary.

- It is important to follow patients with serial gallbladder ultrasound studies until the patient is either stone free or there are no remaining stone fragments, which are likely to cause an obstruction in the biliary tract.

- The Medstone STS™ is to be used only by personnel fully trained in the operation of the device. Prior to operating the machine, personnel must become thoroughly familiar with all aspects of the operation of the lithotripter as described in the Operations Manual. In addition, all personnel must participate in the training program provided by Medstone International, Inc.

- Prior to initiation of treatment with the combination therapy, physicians and patients should consult the labeling for Actigall®.

V. Device Description

A. Medstone STS™ Lithotripter

The Medstone STS™ Lithotripter system includes components for patient positioning, gallstone localization, shock wave generation, and electrocardiographic monitoring.

Electrical energy in the form of a spark is generated between the tips of a spark gap electrode within a fluid-filled semi-ellipsoidal reflector. Vaporization of the fluid surrounding the spark gap apparatus produces the shock wave mechanical energy. When the unit is in operation, the electrical discharge is synchronized with the R-wave of the patient's QRS complex from an EKG lead.

The shock waves that are produced can be focused at the site of a targeted gallstone to create compressive, tensile, and cavitation stresses within the stone. These repeated stresses on gallstones can, depending on the composition of the stones, lead to a progressive disintegration of the outer layers of the stone body. The number of shocks per treatment session is limited to a maximum of 2000, with an average delivery of approximately one shock per second.

The patient table in the Medstone STS™ Lithotripter system can be adjusted to position subjects in three dimensions (X-Y-Z) so as to place the target gallstone within the focal target zone of the device (within 5 centimeters). The STS™ Lithotripter contains both radiographic and ultrasound imaging capabilities. Radiographs are used to obtain approximate stone locations, and can be used to document the results of therapy. An ultrasound image visualizing the exact position of the gallstone within a patient can be digitized and entered into the computer control system of the device for targeting purposes.

It is important to note that the Medstone STS™ Lithotripter system, for use in the treatment of gallstones, has not been modified from the system currently used for the treatment of kidney stones. That device was reviewed by FDA under P870015.

B. The Drug Actigall®

Actigall® is ursodiol USP (ursodeoxycholic acid), a naturally occurring bile acid which has been shown in clinical studies to dissolve gallbladder stones of cholesterol origin. It is suitable for oral administration, and is available in 300-mg capsules. Approximately 90% of a therapeutic dose of Actigall® is absorbed in the small bowel when taken orally, after which it enters the portal vein and is extracted from portal blood by the liver.

Ursodiol in bile is concentrated in the gallbladder and is expelled into the duodenum in gallbladder bile via the cystic and common ducts.

Ursodiol suppresses hepatic synthesis and secretion of cholesterol, and also inhibits intestinal absorption of cholesterol. With repeated dosing, bile concentration reaches a steady state in about 3 weeks. The various actions of ursodiol combine to change the bile of patients with gallstones from cholesterol-precipitating to cholesterol-solubilizing, thus resulting in bile conducive to cholesterol stone dissolution.

VI. Alternative Practices and Procedures

The current standard of care for subjects with symptomatic, documented gallbladder stone disease is cholecystectomy. Between 400,000 and 500,000 of these surgical procedures are performed each year in the United States, with the trend being to utilize new laparoscopic techniques in place of the previous standard of open cholecystectomy.

For some patients with mildly symptomatic gallstone disease, an initial non-invasive course of therapy is used, utilizing one of the two approved oral dissolution agents, ursodiol and chenodiol.

VII. Marketing History

The Medstone STS™ Lithotripter device is commercially marketed for the treatment of kidney stones in the U.S. and elsewhere in the world. The device has not been subject of regulatory action in any country for safety or effectiveness-related issues. There is no marketing history of the STS™ Lithotripter for the treatment of gallstones.

VIII. Potential Adverse Effects of the Drug and Device on Health

The safety profile of Actigall® is well-established. To date, as described in FDA-approved labeling for the drug, for a daily dose of 8-10 mg/kg/day, diarrhea appears to be the only clearly associated adverse event (an incidence of 27.1% vs. a placebo incidence of 21.4% in a randomized, placebo-controlled trial involving 155 patients treated with Actigall® and 159 with placebo).

The patients enrolled in clinical trials for the combination therapy were all to have had symptomatic cholesterol gallstone disease and to have been candidates for gallbladder surgery. The risk for complications of gallstone disease (e.g. cholecystitis, cholangitis, pancreatitis, liver injury) in such patients as part of the natural history of their disease is not inconsequential. Further, the incidence of asymptomatic abnormalities in liver tests in such patients is relatively high.
The majority of the adverse events encountered with use of the Medstone STS™ Lithotripter were related either to 1) lithotripsy-associated trauma of the gallbladder or

other organs or structures in the blast path (e.g. the liver, upper pole of the right kidney, and possibly, the base of the right lung), or 2) to events caused by acute or chronic partial or complete obstruction of the cystic, common bile or pancreatic ducts (by gallstones perhaps mobilized by increased bile flow and/or size reduction caused by Actigall®, or gallstone fragments or sludge created by lithotripsy).

Among the single stone patients studied (n = 260), there were two patient deaths reported due to unrelated causes (1-Parkinson's Disease, 1 – myocardial infarction). A total of 19 (7.3%) patients were reported to have serious adverse events (events that required medical intervention or hospitalization). Of these, 5 patients (1.9%) were hospitalized for reported symptoms of abdominal pain, 5 patients (1.9%) for general gastrointestinal distress, 3 patients (1.2%) for biliary symptoms, and 4 (1.5%) for other pre-existing or unknown causes. These serious adverse events have been summarized in Table 1.

Table 1: Patients with Serious Adverse Events by Category

Category	**Number**
Death	2 (0.8%)*
Abdominal Pain	5 (1.9%)
General GI Distress	5 (1.9%)
Biliary Symptoms	3 (1.2%)
Other	4 (1.5%)
Total	19 (7.3%)

* See comments above

Also among single stone patients, a total of 398 adverse events were recorded, with the most common being abdominal pain (28.5% of patients), followed by general pain (20.4%), gallbladder attack (18.5%), diarrhea (11.9%), application site reaction (11.5%), and biliary pain (8.1%). These adverse events have been summarized in Table 2.

Table 2: Reported Adverse Events

Description	Frequency (%)
Abdominal Pain	74 (28.5%)
Pain	53 (20.4%)
Gallbladder Attack	48 (18.5%)
Diarrhea	31 (11.9%)
Application Site Reaction	30 (11.5%)
Biliary Pain	21 (8.1%)
Back Pain	13 (5.0%)
Asthenia	12 (4.6%)
Nausea	12 (4.6%)
Dyspepsia	9 (3.5%)
Nausea and Vomiting	7 (2.7%)
Dizziness	7 (2.7%)
Headache	7 (2.7%)
Chest Pain	6 (2.3%)
Hematuria	6 (2.3%)
Constipation	6 (2.3%)
Eructation	5 (1.9%)
Pharyngitis	4 (1.5%)
Urinary Frequency	4 (1.5%)
Ecchymosis	3 (1.2%)
Myalgia	3 (1.2%)
Rhinitis	3 (1.2%)
Other	34 (13.1%)

IX. Summary of Non-clinical Studies

Bench and *in vitro* tests were conducted to characterize and validate the mechanical and electrical performance of the Medstone STS™ Lithotripter device at both the component and system level. Many of these data were reported as part of Medstone's PMA for the Medstone STS™ Lithotripter for kidney stones, P870015. A summary of these data can be found in that PMA's Summary of Safety and Effectiveness Data (SSED).

An *in vitro* study was conducted for the current PMA in an effort to demonstrate the device's effectiveness in fragmenting human gallstones. Stones averaging 9.8 mm were used for this test. The data show that after the application of 2000 shocks, 82% of lithotripsy fragments were less than 2.0 mm. The remaining fragments, which measured more than 2 mm, resulted from stones ranging in size from 10-13 mm.

Results from the various tests performed demonstrated that the device is capable of the reliable delivery of lithotripsy therapy within the stated specifications, when used according to its written instructions for use.

Animal (*In Vivo*) Studies

A series of animal studies were conducted to assess the ability of the Medstone STS™ Lithotripter to shatter cholesterol gallstones and the potential for the device to cause injury to the gallbladder or other viscera or structures in the lithotripter blast path. These experiments involved delivery of 1,500 - 10,000 24kV shocks in dogs and pigs. The findings from these studies included:

- One dog had four 6-7 mm gallstones implanted, which were fragmented to less than 0.5 mm (24 hours after treatment) after exposure to 2000 shocks. Stones were not used in any other animals.

- All dogs treated (total of 8) experienced some hemorrhage in the lungs, primarily the right lung.

- Pig studies showed that animals treated with 6000 and 10000 shocks developed hemorrhages in the gallbladder and often in the liver. These injuries, however, were resolved by 35 days post-treatment. Hemorrhages were not reported for pigs treated with 2000 shocks.

- Two pigs treated with 2000 shocks/day for 3 days, for a total of 6000 shocks, developed fewer hemorrhages than the 8 pigs subjected to a one-time treatment of 6000 shocks. This finding seems to indicate that fractionation of shock dosage may reduce tissue damage.

X. Clinical Studies

Three clinical trials evaluated the combination therapy of lithotripsy with the Medstone STS™ Lithotripter and the bile acid drug Actigall® for the treatment of gallstones in symptomatic patients with single and multiple, non-calcified gallstones between 4 and 20 mm in diameter. The trials under protocol numbers GS001, GS002, and GS004 took place from January 1988 through November 1990 and had a total enrollment of 769 patients. All three trials were open label, nonrandomized evaluations of the use of both lithotripsy and Actigall®. The largest trial (GS002, 83% of total population) had a 1:1 randomization of patients to either an active Actigall® pre-treatment or placebo pre-treatment. A total of 46 patients withdrew from the three studies before the lithotripsy procedure was performed. Of the remaining 723 patients, 393 patients (54.4%) were reported to have a single gallstone, with the remaining having multiple stones (314 patients, 43.4%) or an unknown number of stones (16 patients, 2.2%).
There was no significant difference ($p = 0.190$) in the primary efficacy endpoint of stone free status between the three studies, or between stone free status in the two arms of the GS002 study ($p = 1.000$). The PMA data indicated a greater effectiveness in patients with solitary stones. The summary data presented below represent the combined results from the three studies in a total evaluable population of 260 single stone patients.

Patient Selection

The patient population consisted of male or non-pregnant female patients between 18 and 75 years of age with symptomatic cholelithiasis. Patients had to have a history of biliary colic, ultrasound evidence of a gallstone between 4 and 20 mm inclusive, and a documented functioning gallbladder. Each patient had to be an acceptable candidate for cholecystectomy but to have refused the surgical procedure. All patients had to be able to understand and accept the protocol requirements, and provide written informed consent.

Exclusion criteria were any evidence of gallstone calcification, allergies to contrast dyes or bile acid drugs, implantable pacemakers, bleeding abnormalities, and liver disease or other medical conditions that posed an unacceptable risk to either the use of Actigall® or the lithotripsy procedure.

At the time of patient screening a medical history was taken and a physical exam performed, which included blood and urine analyses and ECG recordings. The size, location, and composition of the gallstone present were evaluated using ultrasound and X-ray. The functioning of the gallbladder was determined with an oral cholecystogram.

Study Population

The limited study population of 260 patients with solitary gallstones were enrolled at a total of 12 geographically diverse clinical centers in the United States (average per center, 22). Females (179, 69%) made up approximately two-thirds of the patients (males 81, 31%). The average age of the patients was 48.1 years (SD 14.3, range 19 – 82), with an average body mass index (BMI) of 27.1 (SD 5.3, range 15.8 – 45.2). The majority of the patients identified themselves as *Caucasian* (236, 91%), followed by *Hispanic* (13, 5%), *African-American* (7, 3%), and *Other* (4, 2%).

The stones had a mean diameter of 13.8 mm (SD 4.3, range 4 – 20, median 15.0), with an associated mean volume of 654.8 cu. mm. (SD 356.4, range 50.1 – 1256.6, median 706.9). The mean duration of symptomatic pain associated with the gallstone disease was 17.6 months (SD 23.2, range 1 – 119). The distributions of reported pain intensity (current and most severe recently experienced) are shown in Table 3.

Table 3: Reported Pain Intensity (n = 260)

Pain Intensity	**Current**	**Most Severe**
None	56.9% (149)	0.4% (1)
Mild	30.8% (80)	21.5% (56)
Moderate	9.6% (25)	43.8% (114)
Severe	2.3% (6)	34.2% (89)

In the review of biliary function it was noted that a total of 66 patients (25.4%) had a history of cholecystitis, 1 had cholangitis (0.4%), and none had had complete bile duct obstruction.

Gender Bias Analysis

The higher percentage of female patients enrolled in the study (69% female vs. 31% male) reflects the gender distribution in the population at large, in which a higher percentage of females seek treatment for gallbladder stone disease.

Treatment

Enrolled patients underwent a 1-2 week pre-treatment regimen of Actigall® drug or placebo before the scheduled lithotripsy procedure. Prior to lithotripsy, patients were given intravenous, epidural or general anesthesia. The lithotripsy treatment was performed in conformance with the operating instructions contained in the product manual for the Medstone STS™ Lithotripter. The therapy was limited to a total of no more than 2000 shocks at a setting of 24 kilo-Volts.

Patients continued post-lithotripsy use of Actigall® for a period determined by the attending physician, and dependent on the patient's progress in the dissolution and clearance of the gallstone fragments. Depending on the patient's symptoms and at the physician's discretion, some patients underwent a second lithotripsy treatment, or withdrew from the study to have a cholecystectomy.

A total of 193 patients (74%) had a single lithotripsy treatment, with 67 patients (26%) receiving two treatments, for a total number of 327 procedures. The mean time between the first and second treatment sessions was 137 days (SD 96, range 36 – 554, median 119).

During the course of the studies it was found that the use of general anesthesia was not required in all cases, and that intravenous anesthesia with lithotripsy as an outpatient procedure was feasible for some patients. A total of 143 procedures (44%) reported the use of general anesthesia, with 170 (52%) using intravenous sedation, with details not available on the remaining 14 procedures (4%).

Lithotripsy Parameters

The mean time between the start and completion times of lithotripsy shock delivery was 57.3 minutes (SD 41.4, range 9 – 635, median 50). The mean number of shock delivered was 1798 (SD 426, range 0 – 2000, median 2000). In a total of 320 procedures (97.9%) the treatment sessions were completed as scheduled, with 7 procedures (2.1%) classified as incomplete. The upper allowable limit of 2000 shocks was reached in a total of 239 procedures (73.1%). In all 327 procedures the recommended setting of 24 kV was used. The mean total procedure time in the treatment delivery room was 109.1 minutes (SD 35.5, range 30 – 305, median 105).

Safety Data

All adverse events were documented, whether drug or lithotripsy related, unrelated, or of unknown relationship to the study treatments. As noted earlier, There were two reported deaths in the study, which were from unrelated medical conditions. A listing of the reported serious adverse events (events that required medical intervention or hospitalization) recorded during the clinical evaluations is given in Table 1 above. The list does not include cholecystectomy procedures, since this surgical intervention was considered a standard of care for gallstone management and was reported under outcomes in Table 4.

A total of 19 patients out of 260 (7.3%) experienced serious adverse events in the study population. Most reported events were of the type expected with gallbladder disease (Abdominal Pain, General Gastrointestinal Distress, or Biliary Symptoms) or were expected transient outcomes associated with the prescribed therapy. The category of Other Adverse Events included hospitalizations for a pre-existing respiratory condition, a renal lithotripsy procedure, muscle soreness, and an unknown cause.

In addition to the serious adverse events, a total of 398 different events were documented in the 260 patients. A display of the number of patients reporting specific adverse events is shown in Table 2 above. Events affecting less than 1% of subjects were combined into the category listed as "Other."

Laboratory evaluations to assess renal and liver function and were periodically performed. Blood clinical chemistries were performed at baseline (Screening and Pre-Treatment) and at regularly scheduled follow-up visits after each lithotripsy treatment. These laboratory tests evaluated whether there was evidence of changes in renal or liver function as a result of the lithotripsy treatment. Test values were compared to the normal ranges expected for each parameter.

In comparison with baseline readings at Screening and Pre-Treatment, the percentages of readings out of the normal range at Pre-Discharge (24 hours post-procedure) were observed to be somewhat higher for selected parameters: HCT, HGB, WBC, Total Bilirubin, SGPT, and CPK. These percentages returned to or near baseline levels at one month, except for WBC, which remained slightly elevated out to 6 months post-lithotripsy. Other parameters (Platelets, SGOT, BUN, Alkaline phosphatase, Creatinine, and Amylase) showed no changes from baseline levels.

Effectiveness Data

The progress in the dissolution and clearance of gallstones in patients was evaluated with the use of ultrasound scans at scheduled follow-up visits. The mean follow-up was 169.2 days (SD 121.2, range 1 – 671, median 172.5). A patient was determined to be free of the original gallstone when no fragments could be visualized. A stone free status was achieved in 119 (45.8%) of patients during the follow-up period of observation, with an associated 95% confidence interval of (39.6%, 52.0%). The observed success rate was

dependent on the original stone size. The stone free rate was 51.2% (65/127) in patients with stones less than the median diameter size of 15.0 mm, and 40.6% (54/133) in patients with diameter sizes of 15.0 mm or greater. This difference, however, did not reach statistical significance (p = 0.106).

The mean time until stone free status in these 119 patients was 154.5 days (SD 146.9, range 1 – 671, median 104.0) from the time of the first lithotripsy session. A total of 48 patients (48/260, or 18.5%) became stone-free within the first 3 months after the initial lithotripsy procedure, 76 patients (76/260, or 29.2%) within 6 months, 109 patients (109/260, or 41.9%) within 12 months, 117 patients (117/260, or 45.0%) within 18 months, and the total of 119 patients (45.8%) within 22 months.

A graphical display of the crude cumulative probability of success (stone-free status not based on survival curves) is shown in Figure 1 below. The numbers (n) of patients remaining in the study (i.e., had not achieved stone-free status and continued to be evaluated) are shown at 3-Month follow-up intervals.

The incidence of recurrence of stones in patients treated with the combination therapy could not be determined from the collected data. The data presented here, therefore, represent initial stone free rates.

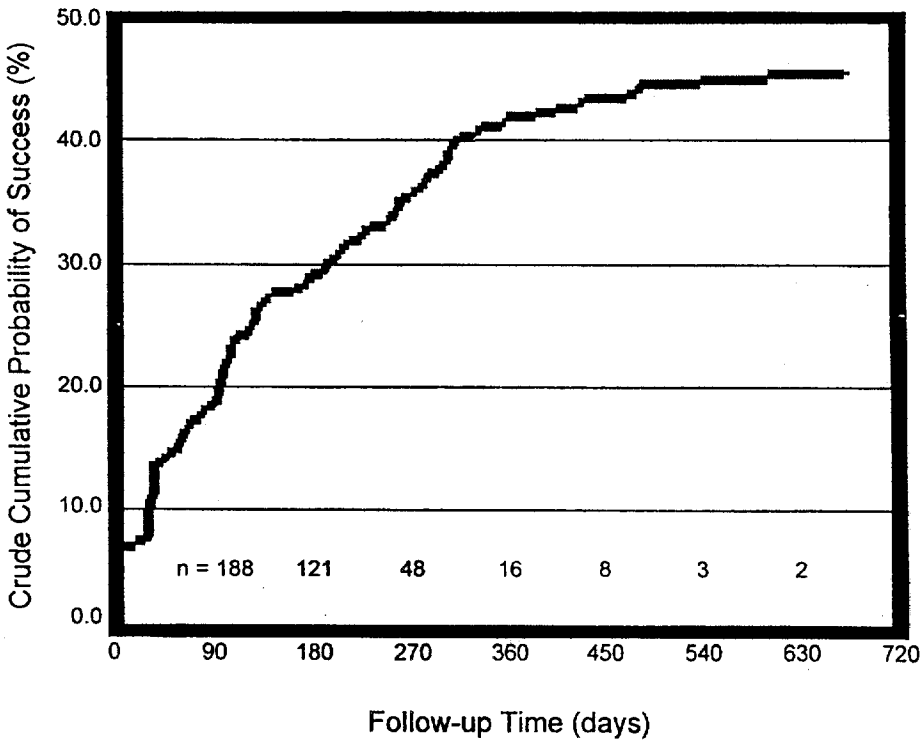

Figure 1: Crude Cumulative Probability of Success by Follow-up Time

Of the 119 patients who became stone free, 100 (84.0%) received only one lithotripsy treatment. The mean time between the first and second treatments for the remaining 19 patients (16.0%) was 150.6 days (SD 108.9, range 36 – 399, median 140.0).

A total of 23 patients (8.8%) went on to cholecystectomy because of either lack of progress in the reduction of the gallstone or because of associated symptoms. The classifications of the final outcomes associated with treatment for all patients over the entire follow-up period are presented in Table 4. These classifications reflect that success was defined to be a completely stone free condition, and do not consider possible reductions in stone size or amelioration of symptoms.

Table 4: Final Reported Study Outcomes

Outcomes	**Frequency (%)**
Stone Free	119 (45.8%)
Completed Study Without Success	88 (33.8%)
Cholecystectomy	23 (8.8%)
Withdrew Without Success	20 (7.7%)
Administratively Censored	8 (3.1%)
No Follow-up after Lithotripsy	2 (0.8%)
Total	260 (100.0%)

The classification of biliary pain (*None*, *Mild*, *Moderate*, and *Severe*) reported by patients after the lithotripsy procedures was recorded at Pre-Discharge (24 hours post-lithotripsy), and at schedule follow-up examinations. The follow-up visits were determined from the time of the second lithotripsy session, if two treatments were given. The distribution of these pain classifications is displayed in Table 5. The numbers may add to greater than the total of patients followed, because of two lithotripsy sessions received by some individuals.

Table 5: Reported Pain Intensity by Follow-up Visit

Visit	**None**	**Mild**	**Moderate**	**Severe**	**Total**
Pre-Discharge	88.6% (226)	10.7% (28)	2.3% (6)	0.4% (1)	100.0% (262)
1 Month	68.1% (171)	22.7% (57)	7.6% (19)	1.6% (4)	100.0% (251)
3 Months	79.8% (99)	10.5% (13)	6.5% (8)	3.2% (4)	100.0% (124)
6 Months	82.1% (46)	14.3% (8)	1.8% (1)	1.8% (1)	100.0% (56)
All Visits	78.8% (917)	15.5% (181)	3.9% (45)	1.8% (21)	100.0% (1164)

The pain classifications in Table 5 were influenced by several factors. These include the underlying biliary pain associated with the gallstone disease, and any pain caused by the lithotripsy procedure or the subsequent clearing of stone fragments. Because some

symptomatic patients went on to cholecystectomy or withdrew from the study, pain assessments at later follow-up visits were collected for only those that remained.

XI. Conclusions drawn from Studies

Results of laboratory testing, animal studies, and clinical investigations have provided evidence that the combination therapy of lithotripsy with the Medstone STS™ Lithotripter and the bile acid drug Actigall® was shown to be safe and effective in the treatment of selected types of gallstones in selected patients, when the device is operated in accordance with its labeling.

XII. Panel Recommendation

The Gastroenterology and Urology Devices Advisory Panel met on April 30, 1998, to discuss the Medstone STS™ Lithotripter for the treatment of gallstones. This panel recommended that the Medstone STS™ Lithotripter be considered approvable with conditions.

The following issues were identified for resolution at that meeting.

1. Long-term follow up data should be provided on all patients treated with the combination therapy.

2. The Indications for Use statement should be revised to specify that the proposed device should only be used for symptomatic non-surgical candidates, or symptomatic high-risk patients who have actively refused surgery. In addition, these patients must have a functioning gallbladder with a patent cystic duct, and must only have a single, radiolucent, non-calcified stone less than 20 mm in maximum diameter.

3. The proposed Contraindications should be revised to include patients with calcified stones, non-functioning gallbladder, non-patent cystic duct, active biliary colic, cholestatic liver disease, cardiac arrhythmias, and pacemakers. Additionally, the contraindication dealing with the inability to tolerate general anesthesia should be removed.

4. The physician labeling should be revised to include a warning or precaution statement which alerts users that the long-term (beyond 18 months) effectiveness, including the dissolution of primary stones and the risk of recurrence of stones, of the proposed combination therapy has not been demonstrated. A warning or precaution should also be included to state that patients unable or unwilling to take Actigall® for the indicated period of time should not be considered for this therapy. Also, the physician labeling should indicate that the proposed

combination therapy is not to be used as first-line-therapy for the treatment of gallstones, since its effectiveness is inferior to that of laparoscopic cholecystectomy, and the resolution of symptoms has not been demonstrated through the use of pain scores or quality of life questionnaires.

5. Patient labeling, in the form of a brochure to inform patients of procedures, risks, and expected outcomes, should be developed for the proposed device. This patient brochure should be given to patients **prior** to any lithotripsy procedures, and should contain the same information as the physician labeling, as discussed above, and be written in a manner comprehensible to a lay person. In addition, the brochure should clearly outline the risks of the proposed combination therapy, and compare these risks to those of laparoscopic cholecystectomy.

6. A post-market study should be developed to further evaluate the safety and effectiveness of the proposed lithotripsy/Actigall® treatments. This study should evaluate the proposed combination therapy's safety and effectiveness by using endpoints including the relief of pain and other symptoms, quality of life, number and occurrence of cholecystectomies, the recurrence of stones, and the incidence of gallstone complications, including acute cholecystitis, pancreatitis, and common bile duct obstructions, as well as other adverse events. Data collected from such a post-market study should be submitted to FDA in the PMA's annual reports. FDA will in turn, provide the Gastroenterology and Urology Devices Panel with periodic updates on this post-market study.

7. A physician training program should be developed similar to that currently used for renal lithotripters.

XIII. CDRH Decision

Throughout the review of this PMA, CDRH has expressed concerns over the safety and efficacy of the Medstone STS™ Lithotripter for the treatment of gallstones, particularly stemming from the lack of long-term follow-up and the number of adverse events. Of significant concern was the use of the combination therapy in patients considered to be reasonable surgical candidates and those with multiple stones.

After the April 30, 1998, advisory panel meeting, CDRH agreed with the panel's recommendation that additional long-term data be collected. However, unlike the panel, CDRH determined that these data would be necessary prior to approving the device. As a result, a non-approvable letter was issued on July 31, 1998.

On March 10, 2000, after several conversations between CDRH and Medstone, the non-approvable determination was reconsidered. CDRH now believes that, with appropriate labeling and with a well-designed and well-executed post-market study, the remaining safety and effectiveness concerns can be overcome. CDRH believes that this option will enable physicians to appropriately use the device to treat a limited patient population (as

restricted in the indications for use and contraindications of the device) while additional data are collected.

Medstone has agreed to the following specifics regarding a post-market study for the Medstone STS™ Lithotripter for the treatment of gallstones. This study will enroll at least 184 adult patients diagnosed with a solitary, non-calcified, radiolucent gallstone. These will be symptomatic adult patients for whom surgical removal of the gallbladder is medically contraindicated or symptomatic high-risk patients who have actively refused surgery. The study's objectives will be to

1. Provide additional information on the use of the Medstone STS™ Lithotripter system in combination with the orally administered drug Actigall® when evaluated with an Actigall® monotherapy concurrent control, for the treatment of single, non-calcified, radiolucent gallstones (from 4-20 mm in maximum diameter).

2. Demonstrate the long-term (24 month) safety of the Medstone STS™ Lithotripsy system.

The study will be a randomized, single-masked, controlled trial in which the combination therapy of lithotripsy and Actigall® will be compared to therapy with Actigall® alone (when used per its drug labeling). The primary safety endpoint will be based on the incidence and severity of any adverse events over the entire 24-month study period. The primary effectiveness endpoint will be the percentage of patients who are stone-free six months after randomization. Secondary effectiveness endpoints will be time to stone-free status, reduction in stone burden, recurrence of stones, delivery of lithotripsy therapy, incidence and severity of pain, and drug compliance. Although the primary endpoints will be evaluated six months after randomization, patients will be followed for a total of 24 months (from baseline). Evaluations will be made on a monthly basis for the first six months, and every three months thereafter for an additional 18 months. At the six-month evaluation, patients initially randomized to the Actigall® monotherapy arm, who are found to have a gallstone qualifying for lithotripsy by study entry criteria, will have the option to cross-over to lithotripsy.

Information on the progress of this study is to be included in post-approval PMA reports to be submitted every six months. The results of the long-term data must be reflected in the labeling (via a PMA supplement) when the post-approval study is completed.

A good manufacturing practices (GMP) inspection was not performed as part of the review of this PMA. Instead, CDRH determined that, since the Medstone STS™ Lithotripter is currently marketed for use in kidney stones, its manufacturing plant can be considered to be in good standing with regards to GMP procedures. Similarly, CDRH determined that Bioresearch Monitoring (BIMO) audits are not necessary in this case.

XIV. Approval Specifications

Directions for Use: See the labeling

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

Post Approval Requirements and Restrictions: see the Approval Order.