PHYSICIAN GUIDE

FOR THE

MEDSTONE STS™ SHOCKWAVE THERAPY SYSTEM

GALLSTONE INDICATION

INDICATIONS FOR USE, CONTRAINDICATIONS, PRECAUTIONS, ADVERSE EVENTS, CLINICAL STUDY SUMMARY RESULTS AND SAFETY AND EFFECTIVENESS

MEDSTONE STS™ PHYSICIAN GUIDE

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SAFETY AND EFFECTIVENESS
"GALLSTONE INDICATION"

PREFACE

This information provides Physicians with a brief summary of the indications for use, Contraindications, Adverse Events. The Operations Manual for the STS™ Lithotripter contains full and complete information regarding this safety and effectiveness data and operational safety details. This Guide does not replace the need to read thoroughly the Operations Manual for the STS™ Lithotripter for a complete understanding of the safe operation of the device.

Please pass this Guide to your colleagues and ask for more copies if you need them.

INDICATIONS - GALLBLADDER STONES

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.

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.

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.

CAUTION: Federal law restricts this device to use by or on the order of a physician.

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.

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 actively refuse 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®.

SAFETY DATA

Safety data are derived from three clinical trials with a total enrollment of 260 patients with solitary gallstones, which 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.

Serious Adverse Events

A total of 19 patients out of 260 (7.3%) experienced Serious Adverse Events (clinical event that required medical intervention or hospitalization) in the single stone study population. There were two deaths reported, due to unrelated causes. 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. A listing of the reported Serious Adverse Events for this limited patient population is given in Table 1. The category of "Other" included hospitalizations for a pre-existing respiratory condition, a renal lithotripsy procedure, muscle soreness, and an unknown cause. 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 3.

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

Total Adverse Events

Any patient-reported adverse events during the follow-up period after study enrollment, whether or not they were treatment related, were recorded. A total of 398 different events were documented in the 260 patients. A display of the number of patients reporting specific events is shown in Table 2. Adverse Events affecting less than 1% of subjects were combined into the category listed as "Other."

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%)

Biliary colic

Biliary colic, reported by all patients at some time prior to treatment, was reported by 42% of patients following lithotripsy as abdominal pain, biliary pain, back pain, or gallbladder attack. This may have been related to passage of sludge or stone fragments, or may represent symptoms of cholelithiasis due to stones or fragments remaining in the gallbladder.

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 of 260 patients (45.8%) 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 (119/260, or 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, represents initial stone free rates.

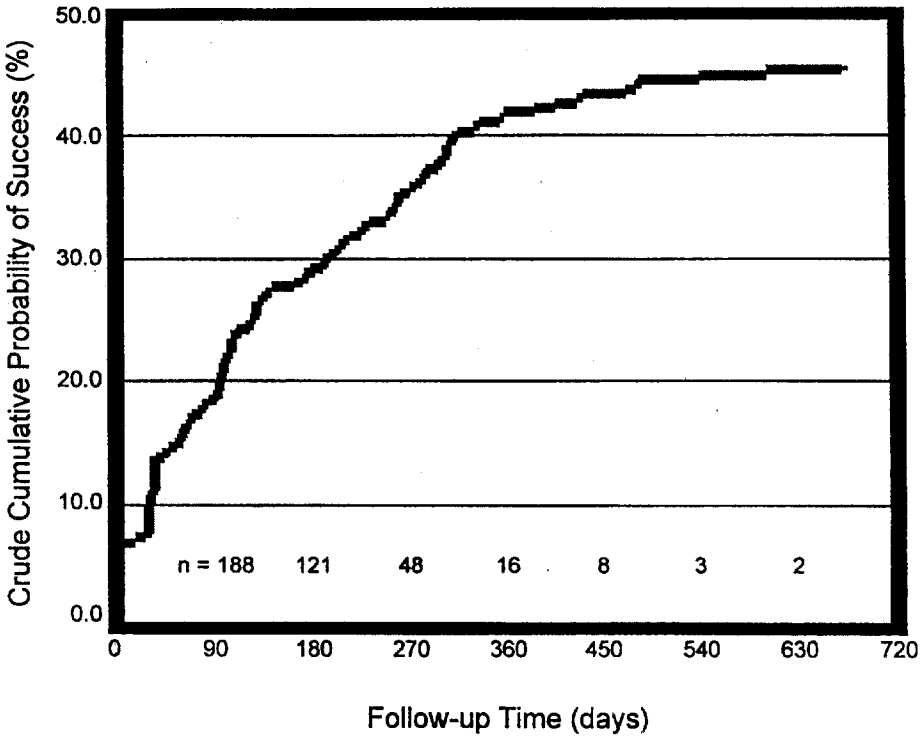

Figure 1: Crude Cumulative Probability of Success by Follow-up Time

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 3. 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 3: Final Reported Study Outcomes

Outcomes	**Frequency (%)**
Stone Free < 15 mm > 15 mm	119 (45.8%) 65/127 (51.2%) 54/133 (40.6%)
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%)

Biliary Lithotripsy

A non-surgical treatment for Gallstones

Cholesterol Gallstone Disease

Gallstones have plagued mankind for many centuries. This year alone, over one million people will be diagnosed with gallstones. The true prevalence of gallstones – it is estimated that 25 million Americans have gallstones.

Although anyone can develop gallstones in their lifetime – there are several groups of individuals who are at higher risk than others. They include:

- Individuals with a family history of gallstones.
- Gallstones are about two times more common in females than males.
- Women who are overweight had multiple pregnancies, or exposure to oral menopausal estrogen therapy or oral contraceptives.
- Individuals on rapid weight loss diet who have recently lost weight.
- Certain ethnic groups, such as Native Americans, have an increased risk of developing gallstones.

Gallstones are more common in females at a younger age, but by age 60 almost 10% of all men will also suffer from gallstones.

What is the gallbladder?

The gallbladder is a small pear-shaped organ located under the liver and connected to the liver and intestine by tubes called bile ducts. The gal bladder stores bile that is produced in the gallbladder and aids in digestion.

What are gallstones?

Gallstones are clumps of solid material that form in the gallbladder and may be small specks or in some cases large lumps. Most are small and less than 20 mm or 1 inch in size.

There are two types of stones that can form in the gallbladder:

- Cholesterol gallstones, which are composed primarily of cholesterol, account for about 80% of all gallbladder stones.
- Pigment gallstones are primarily calcium salts of bile pigments and other compounds which account for only 20% of diagnosed gallstones.

What are the symptoms of gallstones?

Many people have gallstones and have no symptoms related to the gallstones . Gallstones only cause problems and symptoms when they cause blockage which can progress from gradual or occasional blockage of the outlet of the gallbladder causing inflammation and pain to total obstruction which cause severe inflammation which requires surgical treatment. Symptoms include:

- A steady and severe pain in the upper abdominal area which can spread to the chest, shoulder or back and may be mistaken for a heart attack.
- If gallstones block the passage of bile, jaundice, chills and fever may occur.
- If the gallbladder becomes inflamed abdominal pain and tenderness of the right side may occur.
- Stomach upset, vomiting or nausea.

How is gallstone disease treated?

SURGICAL ALTERNATIVES

Open Surgical Removal (Cholecystectomy)
Though the gallbladder plays an important role in the digestive process, it is not essential for life. Many patients with gallstones that suffer from severe symptoms chose to have their gallbladder surgically removed. In an open procedure an incision is made in the abdominal area to gain access to the gallbladder. There were 128,000 surgeries for the removal of the gallbladder in 1997.

Laparoscopic Cholecystectomy
This procedure, unlike an open surgical procedure, requires 3 or 4 small incisions into which tubes are placed. The abdomen is distended with gas and a scope with camera is passed through one of the tubes. Using these tubes as portals — instruments can be passed through them to perform the removal of the gallbladder. This procedure usually requires general anesthesia and is done on an outpatient basis. There were 314,000 procedures done laparoscopically instead of an open incision in 1997.

After removal of the gallbladder – some patients may need to modify their diets. Occasionally individuals may notice a change in their ability to digest certain foods or experience lose stools. Five to 10% of laparoscopic procedures convert to open due to complications experienced during surgery. Infection rates and overall complication rates remain low.

Cholecystectomy, either laparascopic or open results in permanent cure of gallbladder disease for >95% of patients.

NON SURGICAL ALTERNATIVES

Watchful Waiting

Some patients may have minor symptoms that do not cause disruption to their lifestyles and stones small enough that obstruction of the gallbladder is not an immediate risk. These patients may be followed on a regular basis without any type of intervention other than dietary.

Drug Therapy

An oral medication, ursodiol (Actigall®), has provided a safe and effective alternative to gallbladder surgery for selected patients. This medication dissolves cholesterol gallstones by lowering the amount of cholesterol in the bile and slowly dissolving the gallstones within six to 24 months – depending on the size of the stones.

Drug Therapy with Lithotripsy

Shock wave lithotripsy in conjunction with Actigall® can now be offered to patients who are poor surgical candidateswith a solitary cholesterol stone measuring 4 to 20 mm in size, and a functioning gallbladder. Shock wave lithotripsy uses external high-energy shock waves to fragment the gallstone into smaller pieces, which allows the oral medication Actigall® to dissolve the stone fragments more quickly. Some stone fragments may well pass spontaneously after the procedure.

Gallstone Lithotripsy

Lithotripsy technology, since the early eighties, has replaced open surgery for most kidney stones. The procedure uses high-energy shock waves produced outside the body to break stones into small fragments, which in the case of gallstones, allows the Actigall® to dissolve the fragments that do not expel after the procedure, more quickly than drug therapy alone.

Clinical, radiographic, ultrasound and laboratory data are collected prior to shock wave treatment. After reviewing the information your doctor will advise you whether you are a candidate for this procedure.

Candidates are individuals with a solitary, cholesterol (radiolucent) stone, measuring 4 to 20 mm and a functioning gallbladder, who are not good surgical candidates. You must also have been prescribed and taken Actigall® prior to the lithotripsy procedure. You will be prescribed a daily dose of Actigall® two weeks before lithotripsy and until the stone is dissolved.

You will be anesthetized with general anesthesia or intravenous sedation and you will be placed on a treatment table that contains the equipment to generate the shock wave and transmit the shock wave energy to your gallstone. Ultrasound will then be used to visualize the gallstone so that the treatment table can be moved to align the stone with the focal point of the shock wave energy that will be generated. Localization of the gallstone will be routinely performed during the procedure using real time ultrasound.

Shock waves will then be administered to the area of your body where the stone is located. Ultrasound is used during the course of the procedure to monitor stone destruction and to assure that the stone remains in the focus point of the shock wave energy. No incision is made into the skin.

The procedure generally lasts between 45 minutes and one hour, although it may last longer. When the treatment is completed, you will be sent to a recovery room.

You should be able to resume normal activities in just a few days.

Risks of gallstone lithotripsy.
It should be expected that stone fragmentation might cause pain in the gallbladder region. Complications such as inflammation of the gallbladder and/or bile ducts and inflammation of the pancreas and liver are uncommon but may occur.

In cases where your gallstone has been incompletely fragmented, you may require a second treatment. In the uncommon event that a stone fragment lodges in the duct draining the gallbladder, an endoscopic procedure may be necessary to manually remove fragments or surgery could become necessary if the fragments do not expel properly and they obstruct bile ducts.

Skin bruising, some blood in the urine, nausea, constipation or diarrhea, vomiting and/or fever may occur post procedure. Some patients may also experience abdominal pain, pain at the treatment site, weakness, dizziness, headache, muscle ache or upset stomach. Any procedure involving anesthesia may produce sore throat, runny nose, or in rare cases more serious complications, including death.

Contraindications
Patients are excluded from having the treatment if any of the following conditions exist:

- Blood clotting disorders or on blood thinning medication,

- Inability to tolerate anesthesia,
- Pregnancy or another condition for which x-rays are not allowed,
- Inability to image or position stones,
- Cardiac pacemaker or arrhythmia
- Known bile-duct stones
- Calcified stone
- Liver abnormalities
- Aortic aneurysm
- Non-functioning gallbladder,
- Inability or unwillingness to take Actigall for the prescribed period of time.

Effectiveness

Proper patient selection is extremely important to ensure the best chance for success. Oral medication, Actigall®, is required prior to and after the procedure. Stone fragments may expel in a few days – or take months to finally clear the gallbladder completely. In the clinical studies, the effectiveness rates around 45% were observed approximately 18 months after the procedures.

It is important to remember – unlike surgical removal of the gallbladder – Actigall® and lithotripsy combination treatment leaves your gallbladder in place. There is a chance a gallstone could reoccur. Data show that some patients remain stone free for 5 years after the procedure but stone(s) may reoccur earlier and become symptomatic.

What procedure is best for me?

It is important to speak to your doctor about all the options you have in treating your gallstone disease. Many options exist and new therapies may emerge. It is important to ask your doctor about the risks, advantages and expected outcome of each type of treatment.

Lithotripsy and Actigall® combined therapy offers you a new alternative in the treatment of gallstone disease which allows you an access to a less invasive method of treating your stone disease without removal of the gallbladder.