INDICATIONS AND USAGE: Acetohydroxamic acid is indicated as adjunctive therapy in patients with chronic urea-splitting urinary infection. AHA is intended to decrease urinary ammonia and alkalinity, but it should not be used in lieu of curative surgical treatment (for patients with stones) or antimicrobial treatment. Long-term treatment with AHA may be warranted to maintain urine alkalization as long as urea-splitting infection is present. Experience with AHA does not go beyond 7 years. A patient package insert should be distributed to each patient who receives AHA.

CONTRAINDICATIONS: Acetohydroxamic acid should not be used in:

a. patients whose physical state and disease are amenable to definitive surgery and appropriate antimicrobial agents
b. patients whose urine is infected by non-urease producing organisms
c. patients whose urinary infections can be controlled by culture-specific oral antimicrobial agents
d. patients whose renal function is poor (i.e., serum creatinine more than 2.5 mg/dl and/or creatinine clearance less than 20 ml/min)
e. female patients who do not evidence a satisfactory method of contraception
f. patients who are pregnant

Acetohydroxamic acid may cause fetal harm when administered to a pregnant woman. AHA was teratogenic (retarded and/or clubbed rear leg at 750 mg/kg and above and exencephaly and encephalocele at 1,500 mg/kg) when given intraperitoneally to rats. AHA is contraindicated in women who are or may become pregnant. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be informed of the potential hazard to the fetus.

WARNINGS: A Gooberts negative hemolytic anemia has occurred in patients receiving AHA. Gastrointestinal upset characterized by nausea, vomiting, anorexia, and generalized malaise have accompanied the most severe forms of hemolytic anemia. Approximately 15% of patients receiving AHA have had only laboratory findings of anemia. However, most patients developed a mild reticulocytosis. The untoward reactions have reverted to normal following cessation of treatment. A complete blood count, including a reticulocyte count, is recommended after two weeks of treatment. If the reticulocyte count exceeds 6%, a reduced dosage should be entertained. A CBC and reticulocyte count are recommended at 3-month intervals for the duration of treatment.

PRECAUTIONS:

GENERAL: Hematologic Effects: Bone marrow depression (leukopenia, anemia, and thrombocytopenia) has occurred in experimental animals receiving large doses of AHA, but has not been seen in man to date. AHA is a known inhibitor of DNA synthesis and also chelates metals—notably iron. Its bone marrow suppressant effect is probably related to its ability to inhibit DNA synthesis, but anemia could also be related to depletion of iron stores. To date, the only clinical effect noted has been hemolytic, with a decrease in the circulating red blood cells, hemoglobin and hematocrit. Abnormalities in platelet or white blood cell count have not been noted. However, clinical monitoring of the platelet and white cell count is recommended.

Monitoring Liver Function: Abnormalities of liver function have not been reported to date. However, a chloro-benzoic derivative of acetohydroxamic acid caused significant liver dysfunction in an unrelated study. Therefore, close monitoring of liver function is recommended. (See Carcinogenesis for discussion of possible hepatic carcinogenesis.)

Use In Patients With Renal Impairment: Since AHA is eliminated primarily by the kidneys, patients with significantly impaired renal function should be closely monitored, and a reduction of daily dose may be needed to avoid excessive drug accumulation. (See Dosage and Administration.)

DRUG INTERACTIONS: AHA has been used concomitantly with insulin, oral and parenteral antibiotics, and prognostational agents. No clinically significant interactions have been noted, but until wider clinical experience is obtained, AHA should be used with caution in patients receiving other therapeutic agents.

AHA taken in association with alcoholic beverages has resulted in a rash. (See Adverse Reactions.)

AHA chelates heavy metals—notably iron. The absorption of iron and AHA from the intestinal lumen may be reduced when both drugs are taken concomitantly. When iron administration is indicated, intramuscular iron is probably the product of choice.

CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY: Well controlled, long-term animal studies that identify the carcinogenic potential of AHA treatment have not been conducted. Acetamide, a metabolite of AHA, has been shown to cause hepatocellular carcinoma in rats at oral doses 1,500 times the human dose. AHA is cytotoxic and was positive for mutagenicity in the Ames test.

PREGNANCY: Pregnancy Category X. (See Contraindications.)

NURSING MOTHERS: It is not known whether AHA is secreted in human milk. Because many drugs are excreted in human milk, and because of the potential for serious adverse reactions in nursing infants from AHA, a decision should be made to discontinue nursing the drug, taking into account the significance of the drug to the mother’s well being.

ADVERSE REACTIONS: Experience with AHA is limited. About 150 patients have been treated, most for periods of more than a year. Adverse reactions have occurred in up to thirty percent (30%) of the patients receiving AHA. In some instances the reactions were symptomatic; in others only changes in laboratory parameters were noted. Adverse reactions seem to be more prevalent in patients with preceding thrombophlebitis or phlebothrombosis and/or in patients with advanced degrees of renal insufficiency. The risk of adverse reactions is highest during the first year of treatment. Chronic treatment does not seem to increase the risk nor the severity of adverse reactions.

The following reactions have been reported:

NEUROLOGICAL: Mild headaches are commonly reported (about 30%) during the first 48 hours of treatment. These headaches are mild, responsive to oral salicylate-type analgesics, and usually disappear spontaneously. The headaches have not been associated with vertigo, tinnitus, or visual or auditory abnormalities. Tremulousness and nervousness have also been reported.

GASTROINTESTINAL: Gastrointestinal symptoms, nausea, vomiting, anorexia, and malaise have occurred in 20-25% of patients. In most instances the patients were mild, transitory, and did not result in interruption of treatment. Approximately 3% of patients developed a hemolytic anemia of sufficient magnitude to warrant interruption in treatment; several of these patients also had symptoms of gastrointestinal upset.

HEMATOLOGICAL: Approximately 15% of patients have had laboratory findings characteristic of a hemolytic anemia. A mild reticulocytosis (5-6%) without anemia, is even more prevalent. The hematological abnormalities are more prevalent in patients with advanced renal failure.
The dosage should be reduced in patients with reduced renal function or body weight. Vomiting may be alleviated by administration of an antacid, but it would be expected to induce the following symptoms: anorexia, nausea, vomiting, and diarrhea. Laboratory findings are likely to include an elevated reticulocyte count and a severe hypochromic reaction requiring hospitalization, symptomatic treatment, and possibly blood transfusions. Concomitant reduction in platelets and/or white blood cell counts is likely to be more effective after large stones or obstructing stones have continued treatment, avoiding alcohol or using smaller quantities of it. Alopexia has also been reported in patients taking AHA.

Cardiovascular: Superficial phlebitis involving the lower extremities has occurred in several patients on AHA during the early (Phase II) clinical trials. Several of the affected patients had had phlebitic episodes prior to treatment. One patient developed deep vein thrombosis of the lower extremities. The patient with phlebothrombosis had an associated traumatic injury to the groin. It is unclear whether the phlebitis was related to or exacerbated by treatment with AHA. No patient in the three (3) year controlled (Phase III) clinical trial developed phlebitis. In all instances these vascular abnormalities returned to normal following appropriate medical therapy. Embolic phenomena have also been reported in three patients taking AHA in the Phase II trial. The phlebitis and embolism resolved following discontinuation of AHA and implementation of appropriate medical therapy. Several patients have resumed treatment with AHA without ill effect. Palpitations have also been reported in patients taking AHA.

Respiratory: No symptoms have been reported. Radiographic evidence of small pulmonary emboli has been seen in three patients with phlebitis in their lower legs.

Psychiatric: Depression, anxiety, nervousness, and tremulousness have been observed in approximately 20% of patients taking AHA. In most patients the symptoms were mild and transitory, but in about 6% of patients the symptoms were sufficiently distressing to warrant interruption or discontinuation of treatment.

OVERDOSE: Acute deliberate overdose in man has not occurred, but would be expected to induce the following symptoms: anorexia, malaise, lethargy, diminished sense of well being, tremulousness, anxiety, nausea and vomiting. Laboratory findings are likely to include an elevated reticulocyte count and a severe hypochromic reaction requiring hospitalization, symptomatic treatment, and possibly blood transfusions. Concomitant reduction in platelets and/or white blood cells should be anticipated.

Milder overdoses resulting in hemolysis have occurred in an occasional patient with reduced renal function after several weeks or months of continuous treatment.

The acute LD 50 of AHA in animals (rats) is 4.8 gm/kg.

Recommended treatment for an overdose reaction consists of (1) cessation of treatment, (2) close monitoring of hematologic status, (3) symptomatic treatment, and (4) blood transfusions as required by the clinical circumstances. The drug is probably dialyzable, but this property has not been tested clinically.

Dosage and Administration: AHA should be administered orally, one tablet 3-4 times a day in a total daily dose of 10-15 mg/kg/day. The recommended starting dose is 12 mg/kg/day administered at 6-8 hour intervals at a time when the stomach is empty. The maximum daily dose should be no more than 1.5 grams, regardless of body weight.

The dosage should be reduced in patients with reduced renal function. Patients whose serum creatinine is greater than 1.8 mg/dl should take no more than 1.0 gm/day; such patients should be dosed at q-12-hour intervals. Further reductions in dosage to prevent the accumulation of toxic concentrations in the blood may also be desirable. Insufficient data exists to accurately characterize the optimum dose and/or dose interval in patients with moderate degrees of renal insufficiency.

Patients with advanced renal insufficiency (i.e., serum creatinine more than 2.5 mg/dl) should not be treated with AHA. The risk of accumulation of toxic blood levels of AHA seems to be greater than the chances for a beneficial effect in such patients.

In children an initial dose of 10 mg/kg/day is recommended. Close monitoring of the patient’s clinical condition and hematologic status is required. Titrating of the dose to higher or lower levels may be required to obtain an optimum therapeutic effect and/or to reduce the risk of side effects.

How supplied: LITHOSTAT® tablet, NDC 0178-0500-01, is available for oral administration as 250 mg white, round tablets, in unit of use packages of 100 tablets. Each LITHOSTAT® tablet is debossed MPC 500 on one side and blank on the other side. LITHOSTAT® should be stored in a dry place at room temperature, 15°-30°C (59°-86°F). Container should be closed tightly.

Patient Information

Please read this information before using this drug.

General Information: It has been known for many years that urinary infection may cause the formation of urinary stones. As these stones form, bacteria are trapped within the stones. The trapped bacteria cause the stones to grow, and the stones protect the bacteria from antibiotics. Surgical removal of the stone attempts to break this vicious cycle - many times successfully. However, if infection persists or if a small stone fragment persists, then there is an increased risk of stone recurrence. Multiple attempts to remove kidney stones may result in damage and scarring of the kidney. In some situations removal of the kidney may be necessary.

Drugs that contain iron should not be taken at the same time as LITHOSTAT®, (acetohydroxamic acid). LITHOSTAT® reacts with iron, and may not be absorbed into the bloodstream. Both the iron you take and the LITHOSTAT® you take may be ineffective if both drugs are taken together.

How is LITHOSTAT® used? LITHOSTAT® is a drug which prevents the formation of urinary stones. As these stones form, bacteria are trapped within the stones. The trapped bacteria cause the stones to grow, and the stones protect the bacteria from antibiotics. Surgical removal of the stone attempts to break this vicious cycle - many times successfully. However, if infection persists or if a small stone fragment persists, then there is an increased risk of stone recurrence. Multiple attempts to remove kidney stones may result in damage and scarring of the kidney. In some situations removal of the kidney may be necessary.

In some instances stones may form initially as a result of non-infectious (i.e., metabolic) causes. If a metabolic stone becomes infected, then an “infection stone” may grow onto the “metabolic stone.” Stone analysis and/or biochemical tests will usually determine which factors are present.

Experimental investigations have identified an enzyme called uropep which is made by some (but not all) bacteria. Urease reacts with urine to make ammonia. Ammonia changes the acidity of the urine and the change in acidity encourages stone formation. LITHOSTAT® (acetohydroxamic acid) inhibits urease and thereby reduces urinary ammonia. In some instances, LITHOSTAT® enhances the effectiveness of antibiotics and thereby makes urinary infection easier to control.

What is LITHOSTAT®? LITHOSTAT® is a drug which prevents the excessive buildup of ammonia in your urine, which controls the acidity and alkalinity (pH) of your urine. The cause of excessive ammonia and alkalinity in your urine is a bacterial infection.

What can LITHOSTAT® Do? Treatment with LITHOSTAT® is prescribed to decrease urinary ammonia. This may increase the chance of controlling your infection with antibiotics and may help the treatment of your kidney stones. Dissolution of existing stones is unlikely.

LITHOSTAT® should not be used in place of surgical treatment. Surgical removal of all stones and elimination of all infection with antibiotics offers the possibility of curative treatment. LITHOSTAT® is likely to be more effective after large stones or obstructing stones have been removed.

What are the problems or side effects with LITHOSTAT®? The complete spectrum of side effects induced by LITHOSTAT® (acetohydroxamic acid) is unknown. However, some side effects which have been reported to date have been headaches, abdominal discomfort, nausea, loss of hair, shakiness, and anemia. Life-threatening problems (blood clots in the legs) occurred in several patients with advanced disease in early investigation. In more extensive later investigations, this problem has not occurred. No patient has died as a consequence of taking LITHOSTAT®. The most serious side effects seem to occur in patients with poor kidney function and/or in patients with a previous history of these conditions.

Problems related to LITHOSTAT® have disappeared following cessation of the drug and initiation of appropriate medical treatment. Most patients have resumed treatment without ill effect. A flushing skin reaction (i.e., redness, warmth, and tingling) has occurred in several patients who consumed alcohol during treatment with LITHOSTAT®. The reaction persisted approximately 30 minutes and disappeared without treatment. The cause and significance of this reaction are unknown. Consequently, patients are encouraged to abstain from consumption of alcoholic beverages while being treated with LITHOSTAT®.

In animal studies doses of LITHOSTAT® about 20 times the maximum human dose have caused fetal abnormalities (birth defects) indicating a potential for such an adverse effect in an exposed human fetus. Therefore, LITHOSTAT® should not be given to pregnant women or to any sexually active woman of child-bearing age, not using a highly effective method of contraception (oral contraceptive or IUD).

An acceptable long-term study of the cancer causing potential of LITHOSTAT® has not been conducted, but a known metabolite of LITHOSTAT®, acetamide, is carcinogenic (cancer-causing) to the liver in rats at doses about 80 times the maximum human dose of LITHOSTAT®. LITHOSTAT® thus must be considered a potential human carcinogen. LITHOSTAT® kills tissue cells grown in tissue culture and alters genetic material in cells grown in culture.

LITHOSTAT® may induce other adverse reactions which have not yet been recognized.

Unusual symptoms should be reported to your physician. Mild symptoms usually do not warrant discontinuation of treatment. Severe symptoms may necessitate temporary cessation of treatment and/or alteration of dosage.

What about taking other drugs with LITHOSTAT®? Only take those drugs prescribed by your physician. Do not take prescription drugs or over the counter preparations without your physician’s specific prescription or recommendation.

Drugs that contain iron should not be taken at the same time as LITHOSTAT®, (acetohydroxamic acid).

LITHOSTAT® reacts with iron, and may not be absorbed into the bloodstream. Both the iron you take and the LITHOSTAT® you take may be ineffective if both drugs are taken together.

How important is my daily dosage of LITHOSTAT®? If you fail to follow your daily dosage schedule with LITHOSTAT® you will probably suffer a setback in treatment effectiveness and new kidney stone formation is likely. LITHOSTAT® plus antibiotic therapy must be taken exactly as your physician prescribes it for optimum effectiveness.

In conclusion: Your daily dosage of LITHOSTAT® (acetohydroxamic acid) is important to the proper treatment of your condition. Any unusual side effects should be reported to your physician at once. Rx Only.