Ademetionine butanedisulfonate

Transmetil

FORMULATION

Tablet:
Each enteric-coated tablet contains 949 mg of ademetionine butanedisulfonate equivalent to 500 mg Ademetionine.

Lyophilized Powder for Injection:
Each vial contains:
Ademetionine (Sulfo-Adenosyl-L-Methionine) 1,4-butanedisulfonate 949 mg equivalent to 500 mg Ademetionine

Solution for Injection:
Each ampoule contains:
L-lysine ……..... 428 mg
Sodium hydroxide ……... 14.4 mg
Water for Injection ……..... q.s. 5 mL

DESCRIPTION

Ademetionine or S-adenosyl-L-methionine, is a derivative of the amino acid methionine. Because of structural instability, stable salt forms of ademetionine are required for its use as an oral drug. The active ingredient is the salt, ademetionine 1,4-butanedisulfonate (ademetionine SD_4).

INDICATIONS

Ademetionine is indicated for treatment of adults (≥ 18 years old) with:

- Intrahepatic cholestasis in pre-cirrhotic and cirrhotic states
- Intrahepatic cholestasis in pregnancy

DOSAGE AND ADMINISTRATION

Treatment can be initiated with parenteral administration and continued orally or initiated orally.

Lyophilized Powder

Ademetionine lyophilized powder and solvent (water solution for injection, L-lysine, sodium hydroxide) is available in 500 mg/5 mL vials for intravenous and intramuscular injection. The lyophilized powder should be dissolved using the accompanying solvent at the time of use. Discard unused portion.

Ademetionine should not be mixed with an alkaline or calcium ion-containing solution. If the lyophilized powder appears other than white to yellowish in color (due to a crack in the vial or exposure to heat), the product should not be used**.**

Intravenous ademetionine should be administered slow IV.

Tablets

Ademetionine tablets are available in 500 mg strength. Ademetionine tablets should be swallowed whole and not chewed.
For better absorption of the active ingredient and complete therapeutic effect, ademetionine tablets should not be taken with meals.

Ademetionine tablets should be extracted from the blister package immediately before use. If the tablets appear other than white to yellowish in color (due to presence of holes in the aluminum wrapper), it is recommended the product not be used**.**

Intrahepatic cholestasis

Initial therapy:

IV or IM: The recommended dosing is 5-12 mg/kg/day IV or IM. The usual starting dose is 500 mg/day IV or IM, total daily dose not to exceed 800 mg, for 2 weeks.

Oral: The recommended dosing is 10-25 mg/kg/day orally. The usual starting dose is 800 mg/day, total daily dose not to exceed 1600mg.

Maintenance therapy:

Oral: 800 to 1,600 mg/day.

Pediatric

The safety and efficacy of ademetionine for the use in children has not been established.

Geriatric

Clinical studies of ademetionine did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

Renal Impairment

Studies have not been conducted in patients with renal impairment. Therefore, caution is recommended when administering ademetionine to these patients.

Hepatic Impairment

Pharmacokinetic parameters are similar in healthy volunteers and patients with chronic liver disease.

CONTRAINDICATIONS

Ademetionine is contraindicated in patients with genetic defects affecting the methionine cycle and/or causing homocystinuria and/or hyperhomocysteinemia (e.g. cystathionine beta-synthase deficiency, Vitamin B_{12} metabolism defect).

Ademetionine is contraindicated in patients with a known hypersensitivity to the active substance or to any of the inactive ingredients.

WARNINGS AND PRECAUTIONS

Intravenous ademetionine should be administered slow IV (see **DOSAGE AND ADMINISTRATION**).

Ammonia levels should be monitored in patients with pre-cirrhotic and cirrhotic states of hyperammonemia taking oral ademetionine.

Because vitamin B_{12} and folate deficiencies may decrease ademetionine levels, at risk patients (anemia, liver disease, pregnancy or potential for vitamin deficiencies due to other illnesses or eating habits such as vegans) should have routine blood tests to check the plasma levels. If a deficiency is found, treatment with B_{12} and/or folate is recommended prior to or concurrently with administration of ademetionine. (see PHARMACOLOGIC PROPERTIES - Metabolism).

Some patients may experience dizziness with the use of ademetionine. Patients should be advised not to drive or operate machinery during treatment until they are reasonably certain that ademetionine therapy does not affect their ability to engage in such activities. (see **EFFECTS ON ABILITY TO DRIVE OR USE MACHINES**).

Ademetionine is not recommended for use in patients with bipolar disease. There have been reports of patients switching from depression to hypomania or mania when treated with ademetionine.

There has been a single literature report of serotonin syndrome in a patient taking ademetionine and clomipramine. Although a potential interaction is postulated, caution is recommended when administering ademetionine concomitantly with selective serotonin reuptake inhibitors (SSRI), tricyclic antidepressants (such as clomipramine), and over-the-counter and herbal supplements containing tryptophan. (see **DRUG INTERACTIONS**).

The efficacy of ademetionine in the treatment of depression was studied in short-term clinical trials (3-6 weeks in duration). The effectiveness of ademetionine in the treatment of depression over longer periods is unknown. There are many medications to treat depression, and patients should consult with their physicians to determine optimal therapy. Patients should be encouraged to inform their physicians if their symptoms do not abate or worsen during ademetionine therapy.

Patients with depression are at risk for suicide and other serious events and therefore should receive continuous psychiatric support during therapy with ademetionine to ensure that the symptoms of depression are adequately addressed and treated.

There have been reports of transient or worsening anxiety in patients treated with ademetionine. In most cases, interruption of therapy was not required. In a few cases, the anxiety resolved after a reduction in dosage or discontinuation of therapy.

Interference with homocysteine immunoassays

Ademetionine interferes with homocysteine immunoassays, which may show falsely elevated levels of plasma homocysteine in patients treated with ademetionine. In patients treated with ademetionine, it is therefore recommended to use non-immunological methods to measure plasma homocysteine.

DRUG INTERACTIONS

Serotonin syndrome has been reported in a patient taking ademetionine and clomipramine. Therefore, although a potential interaction is postulated, caution is recommended when administering ademetionine concomitantly with selective serotonin reuptake inhibitors (SSRI), tricyclic antidepressants (such as clomipramine), and over-the-counter and herbal supplements containing tryptophan. (see **WARNINGS AND PRECAUTIONS**).

PREGNANCY AND LACTATION

Pregnancy

The use of high doses of ademetionine in women in the last three months of pregnancy did not lead to any adverse effect. It is advisable to administer ademetionine in the first three months of pregnancy only if it is absolutely necessary.

Lactation
Ademetionine should be used while breast-feeding only if the potential benefit justifies the potential risk to the infant.

EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Some patients may experience dizziness with the use of ademetionine. Patients should be advised not to drive or operate machinery during treatment until they are reasonably certain that ademetionine therapy does not affect their ability to engage in such activities (see **WARNINGS AND PRECAUTIONS**).

ADVERSE REACTIONS

Clinical Trials

Ademetionine was studied in 2434 patients of whom 1983 were exposed to ademetionine with liver disease and 817 patients with depression, in controlled and open trials for up to 2 years.

The table is based on 1667 patients in 22 clinical trials treated with ademetionine, of whom 121 (7.2%) experienced a total of 188 adverse reactions. Nausea, abdominal pain, and diarrhea were the most frequently reported adverse reactions. A causal relationship of the adverse event with the drug was not always assessable.

System Organ Class (SOC)	**Preferred Term**
Infections and infestations	Urinary tract infection
Psychiatric disorders	Confusion Insomnia
Nervous System Disorders	Dizziness Headache Paresthesia
Cardiac disorders	Cardiovascular disorder
Vascular disorders	Hot flush Superficial phlebitis
Gastrointestinal disorders	Abdominal distension Abdominal pain Diarrhea Dry mouth Dyspepsia Esophagitis Flatulence Gastrointestinal pain Gastrointestinal disorder Gastrointestinal hemorrhage Nausea Vomiting
Hepato-biliary disorders	Biliary colic Hepatic cirrhosis
Skin and subcutaneous tissue disorders	Hyperhydrosis Pruritus Skin reactions
Musculoskeletal and connective tissue disorders	Arthralgia Muscle spasms
General disorders and administration site conditions	Asthenia Chills Injection site reactions Influenza like illness Malaise Peripheral edema Pyrexia

Post Marketing Experience

Immune system disorders
Hypersensitivity, Anaphylactoid reactions or anaphylactic reactions (e.g. flushing, dyspnea, bronchospasm, back pain, chest discomfort, alterations in blood pressure [hypotension, hypertension] or pulse rate [tachycardia, bradycardia]).

Psychiatric disorders
Anxiety

Respiratory, thoracic and mediastinal disorders
Laryngeal edema

Skin and subcutaneous tissue disorders
Injection site reaction (very rarely with skin necrosis), angioedema, allergic skin reactions (e.g. rash, pruritus, urticaria, erythema).

OVERDOSAGE

Cases of overdose with ademetionine appear to be rare. Physicians should contact their local poison control centers. In general, patients should be monitored and supportive care provided.

PHARMACOLOGIC PROPERTIES

Pharmacodynamic Properties

S-adenosyl-L-methionine (ademetionine) is a naturally occurring amino acid present in virtually all body tissues and fluids. Ademetionine functions primarily as a coenzyme and donor transfer of the methyl group (transmethylation) is an essential metabolic process in humans and animals. Methyl transfer is also essential to the development of the phospholipid bilayer of cell membranes and contributes to membrane fluidity. Ademetionine can penetrate the blood-brain barrier and ademetionine-mediated transmethylation is critical in the formation of neurotransmitters in the central nervous system including catecholamines (dopamine, noradrenalin, adrenaline), serotonin, melatonin and histamine.

Ademetionine is also a precursor in the formation of physiological sulfurated compounds (cysteine, taurine, glutathione, CoA, etc.) via transsulfuration. Glutathione, the most potent antioxidant in the liver, is important in hepatic detoxification. Ademetionine increases hepatic glutathione levels in alcoholic and non-alcoholic liver disease patients. Both folate and vitamin B_{12} are essential co-nutrients in the metabolism and replenishment of ademetionine.

Pharmacokinetic Properties

Absorption

In humans, following intravenous administration, the ademetionine pharmacokinetic profile is bi-exponential and composed of a rapid apparent distribution phase into the tissues and a terminal elimination phase characterized by a half-life of approximately 1.5 hours. When administered intramuscularly, absorption of ademetionine is practically complete (96%); the maximum plasma concentrations of ademetionine are reached after approximately 45 minutes. Following oral administration of ademetionine, peak plasma concentrations are achieved 3 to 5 hours after ingestion of enteric-coated tablets (400–1000 mg). Oral bioavailability is enhanced when ademetionine is administered under fasting conditions. Peak plasma concentrations obtained after administration of enteric-coated tablets are dose related, with peak plasma concentrations of 0.5 to 1 mg/L achieved 3 to 5 hours after single doses ranging from 400 mg to 1000 mg. Plasma concentrations decline to baseline within 24 hours.

Distribution

Volumes of distribution of 0.41 and 0.44 L/kg have been reported for doses of 100 mg and 500 mg ademetionine, respectively. Binding to plasma proteins is negligible being $\leq$ 5 %.

Metabolism

The reactions that produce, consume, and regenerate ademetionine are called the ademetionine cycle. In the first step of this cycle, ademetionine-dependent methylases use ademetionine as a substrate and produce S-adenosyl-homocysteine. S-adenosyl-homocysteine is then hydrolyzed to homocysteine and adenosine by S- adenosyl-homocysteine hydrolase. The homocysteine is then recycled back to methionine with the transfer of a methyl group from 5-methyltetrahydrofolate. Finally, methionine can be converted back to ademetionine, completing the cycle.

Excretion

In tracer balance studies using orally administered, radioactive (methyl^{14}C) SAMe in normal volunteers, urinary excretion of radioactivity was 15.5 ± 1.5% after 48 hours and fecal excretion was 23.5 ± 3.5% after 72 hours, leaving approximately 60% incorporated into stable pools.

PRE-CLINICAL SAFETY DATA

Toxicology studies were performed as single dose and repeat dose in multiple animal species including mouse, rat, hamster and dog of both sexes by the oral, subcutaneous, intravenous, and intramuscular route.

Repeat dose toxicity testing indicated that the kidney is the target organ in the rat and hamster and to a much lesser extent in the dog. Possibly, the testis is a further target organ in the rat. No other significant changes to body organs were observed. Single dose toxicity, repeated dose toxicity through 104 weeks, reproduction toxicity, and mutagenicity studies did not demonstrate any other notable signs of toxic effects.

DESCRIPTION OF CLINICAL STUDIES

Numerous scientific studies indicate that ademetionine may be useful in the treatment of depression and liver disorders. A review of the clinical efficacy of ademetionine for the treatment of depression, osteoarthritis and liver disease was published in 2002 by the Agency for Healthcare Research and Quality (AHRQ). This report was based on the literature on the use of ademetionine for the treatment of depression, osteoarthritis and liver disease published till 2000. There were 102 relevant studies identified: 47 studies for depression, 14 studies for osteoarthritis, and 41 studies for liver disease. The meta-analysis of these studies concludes that ademetionine is more effective than placebo for relief of symptoms of

depression, pain of osteoarthritis, pruritus in cholestasis of pregnancy, and intrahepatic cholestasis. Ademetionine is more effective than placebo in reducing serum bilirubin for cholestasis of pregnancy and for intrahepatic cholestasis. Treatment with ademetionine was equivalent to standard therapy for depression and osteoarthritis.

Intrahepatic cholestasis

The experience accumulated with the oral and parenteral use of ademetionine for more than 20 years has shown that this drug is effective in the treatment of intrahepatic cholestasis of liver disease and of pregnancy and other chronic liver disorders.

Intrahepatic cholestasis is a complication of chronic liver diseases and other causes of hepatocellular damage. In hepatic disease, normal hepatocyte function such as the regulation and clearance of bile acids is compromised, resulting in cholestasis.

The use of ademetionine has been studied in patients with chronic liver diseases that involve intrahepatic cholestasis, including primary biliary cirrhosis, primary sclerosing cholangitis, drug-induced liver injury, viral hepatitis, cholestasis induced by total parenteral nutrition, alcoholic liver disease and non-alcoholic liver disease.

More than 2,700 patients affected by intrahepatic cholestasis and/or chronic liver diseases have been included into the clinical trials with ademetionine and 1983 were treated with this drug. In most of these trials, ademetionine was compared with placebo due to the almost total absence of alternative therapies. In almost 90% of cases a cholestatic component was associated with chronic liver diseases. The remaining patients were suffering from alcoholic liver disease, acute and chronic hepatitis or intrahepatic cholestasis of pregnancy. The efficacy parameters considered in the clinical studies included the main subjective symptoms of cholestasis (itching, jaundice, fatigue, return to well-being), and biochemical markers of cholestasis and liver damage, such as total and conjugated bilirubin, alkaline phosphatase, bile salts, transaminases, γ-glutamyltransferase. The treatment with ademetionine given IV, IM or orally, improved intrahepatic cholestasis due to chronic liver disease or pregnancy, and alcoholic cirrhosis. The effects of IV or IM treatment are evident after 1-2 weeks of therapy, whereas, oral treatment is suitable for maintenance therapy.

One long-term, double-blind, placebo controlled study of 123 men and women with alcoholic liver cirrhosis found that 1,200 mg/day ademetionine for 2 years may improve survival rates and delay the need for liver transplants more effectively than placebo. The overall mortality/liver transplantation at the end of the trial decreased from 30% in the placebo group to 16% in the ademetionine group, although the difference was not statistically significant. Long-term treatment with ademetionine reduced the overall mortality/liver transplantation, especially in patients with less advanced liver disease.

Depression

Ademetionine has been given orally or parenterally in the management of depression. The results from several review articles on the efficacy of ademetionine in the treatment of depressive disorders and from the meta- analysis of the clinical studies show that ademetionine, at doses of 200-1600 mg/day, possesses a pronounced anti-depressive activity in patients suffering from different types of depression (uni- and bipolar endogenous, neurotic, dysthymic disturbances). Several double-blind studies have found the efficacy of ademetionine in treating depressive disorders superior to placebo and similar to tricyclic antidepressants. The anti-depressive action is rapid and manifests itself within 5 - 7 days of treatment in the absence of side effects, in particular, anti-cholinergic reactions. Ademetionine is compatible with other anti-depressant drugs, in particular, tricyclic antidepressants and monoamine oxidase inhibitors. (see **WARNINGS AND PRECAUTIONS; DRUG INTERACTIONS)**

Intrahepatic cholestasis of pregnancy

The efficacy of treatment with Ademetionine was assessed in 7 clinical trials including 264 women with intrahepatic cholestasis of pregnancy. Of these, 156 were treated with ademetionine, 21 received placebo, 60 an active control (ursodeoxycholic acid) and 27 ademetionine plus ursodeoxycholic acid. The treatment with ademetionine given IV, IM or orally, was effective in treatment of intrahepatic cholestasis of pregnancy with improvement of pruritus and biochemical parameters.

CAUTION

Foods, Drugs, Devices and Cosmetics Act prohibits dispensing without prescription.

STORAGE

Store at temperatures not exceeding 30°C.

SHELF LIFE

24 months

AVAILABILITY

Tablet: Alu/Alu blister pack of 10’s in a box

Solution for injection: One (1) box contains: Type 1 clear glass vial (as active) x 5’s + EP Type 1 clear glass ampoule in 5 mL (net content) (as diluents) x 5’s

Ademetionine butanedisulfonate (Transmetil) 500mg tablet:
Manufactured by:
AbbVie S.r.L.
S.R. 148 Pontina Km. 52 SNC
04011 Campoverde di Aprilia, Aprilia (LT)
Italy

Ademetionine butanedisulfonate (Transmetil) 500mg powder for solution for injection:
Manufactured by:
Famar L'Aigle
Rue de I'Isle
28380 Saint-Remy sur Avre
France

Imported by:
Abbott Laboratories
Venice Corporate Center, 8 Turin St.
Mckinley Town Center, Fort Bonifacio
Taguig City, Philippines

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