HEPTRAL
ADEMETIONINE

Product Description:
Heptral 500mg Gastroresistant Tablets

Quality and Quantity Composition
One tablet contains:
Ademetionine 1,4-butanedisulfonate equivalent to 500 mg ion.

Pharmaceutical forms
White to yellowish, oval tablet

CLINICAL PARTICULARS

Therapeutic Indications
Ademetionine is indicated for treatment of adults with:

- Intrahepatic cholestasis in pre-cirrhotic and cirrhotic states
- Intrahepatic cholestasis in pregnancy
- Relief of fatigue caused by chronic liver disease

POSOLOGY AND METHOD OF ADMINISTRATION
Treatment can be initiated with parenteral administration and continued orally or initiated orally.

Intrahepatic cholestasis/ Fatigue in chronic liver disease
Oral: The recommended dosing is 10-25 mg/kg/day orally. The usual starting dose is 400-800 mg/day, total daily dose not to exceed 1600mg.

Maintenance therapy:
Oral: 800 to 1,600 mg/day.

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

Elderly Population
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
There is limited clinical data in patients with renal impairment. Caution is recommended when administering ademetionine to these patients.

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

Method of Administration
Treatment can be initiated orally.

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**.**

CONTRAINDICATIONS
- hypersensitivity to the active substance or to any of the excipients
- patients with genetic defects affecting the methionine cycle and/or causing homocystinuria and/or hyperhomocysteineimia (e.g cystathionine beta-synthase deficiency, vitamin B_{12} metabolism defect).

SPECIAL WARNINGS AND PRECAUTIONS
To be used under the supervision of a physician.

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

Because vitamin B12 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 B12 and / or folate is recommended prior to or concurrently with administration of ademetionine. (see **PHARMACOLOGIC PROPERTIES** - Metabolism).

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**).

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
In clinical studies no adverse reactions were observed in women in the last three months of pregnancy treated with ademetionine. 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
In clinical trials, approximately 2000 patients were exposed to Ademetionine. The most frequently reported events with Ademetionine treatment were Headache, Diarrhoea and Nausea.

The following undesirable effects have been observed with the frequencies indicated below during clinical trials using Ademetionine (n=1922) and from spontaneous reporting.

Adverse reactions listed by System Organ Class. Frequencies are defined using the following convention: very common (≥1/10), common (≥1/100, <1/10), uncommon (≥1/1000, <1/100), rare (≥1/10000, <1/1000), very rare (<1/10000).

MedDRA System Organ Class	**Frequency**	**Adverse Reactions**
Gastrointestinal disorders		
	Common	Abdominal pain, Diarrhoea, Nausea,
	Uncommon	Dry mouth, Dyspepsia, Flatulence, Gastrointestinal pain, Gastrointestinal haemorrhage, Gastrointestinal disorder, Vomiting, Oesophagitis
	Rare	Abdominal distension,
MedDRA System Organ Class	**Frequency**	**Adverse Reactions**
General disorders and administration site conditions		

	Common	Asthenia
	Uncommon	, Oedema, Pyrexia, Chills*, Injection site reactions*, Injection site necrosis*
	Rare	Malaise
Immune System Disorder		
	Uncommon	Hypersensitivity*, Anaphylactoid reactions* or anaphylactic reactions (e.g. flushing, dyspnoea, bronchospasm, back pain, chest discomfort, alterations in blood pressure (hypotension, hypertension) or pulse rate (tachycardia, bradycardia)) *
Infections and infestations		
	Uncommon	Urinary tract infection
Musculoskeletal and connective tissue disorders		
	Uncommon	Arthralgia, Muscle spasms
Nervous system disorders		
	Common	Headache
	Uncommon	Dizziness, Paraesthesia, Dysgeusia*
Psychiatric disorders		
	Common	Anxiety, Insomnia
	Uncommon	Agitation, Confusional state
Respiratory, thoracic and mediastinal disorders		
	Uncommon	Laryngeal oedema*
Skin and subcutaneous tissue disorders		
	Common	Pruritus
	Uncommon	Hyperhidrosis, Angioedema*, Allergic skin reactions (e.g. rash, pruritus, urticaria, erythema) *
Vascular disorders		
	Uncommon	Hot flush, Hypotension, Phlebitis

* Undesirable effects from spontaneous reporting which have not been reported more frequently in spontaneous reporting or have not been observed in clinical trials have been attributed to the frequency 'uncommon' based on the fact that the upper limit of the 95% confidence interval of the frequency estimate is not higher than 3/X where X =1922 (total number of subjects observed in clinical trials).

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

Pharmacotherapeutic group: Amino acids and derivatives

ATC-Code: A16AA02

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 SD4).

Mechanishm of action and Pharmacodynamics effects

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 B12 are essential co-nutrients in the metabolism and replenishment of ademetionine.

Clinical efficacy

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 2000 were treated with this drug. In most of these trials, ademetionine was compared with placebo due to the almost total absence of alternative therapies at the point in time. 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 orally, improved intrahepatic cholestasis due to chronic liver disease in pregnancy and alcoholic cirrhosis.

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.

Relief of fatigue in chronic liver disease (CLD)
A number of studies have demonstrated the efficacy of Ademetionine in the treatment of fatigue in patients with CLD. Ademetionine has shown an improvement of fatigue in CLD consistently over several studies. An integrated analysis of subjects with fatigue at baseline showed the effect of ademetionine treatment on fatigue response along with a range of other symptoms i.e., depression, jaundice, malaise and pruritus. In subjects with ALD, treatment with ademetionine significantly improved depressed mood in individuals who also responded in terms of fatigue.

Moreover, in subjects with ALD or with NALD, treatment with ademetionine significantly improved jaundice, malaise and pruritus in individuals who also responded in terms of fatigue.

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.

A review of the clinical efficacy of ademetionine for the treatment of depression, and liver disease was published in 2002 by the Agency for Healthcare Research and Quality (AHRQ,USA). The meta- analysis of these studies concludes that ademetionine is more effective than placebo for relief of symptoms of depression, , 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.

Pharmacokinetic Properties
Absorption
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. Oral bioavailability is enhanced when ademetionine is administered under fasting conditions.

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 14C) 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.

PHARMACEUTICAL PARTICULARS

List of excipients
Tablet core
Colloidal anhydrous silica, Microcrystalline cellulose, Sodium starch glycolate (Type A), Magnesium Stearate

Tablet coating
Methacrylic acid - ethyl acrylate copolymer, Macrogol 6000, Polysorbate 80, Simethicone emulsion, Sodium hydroxide, Talc

Incompatibilities
No incompatibility is known so far.

SHELF LIFE
36 months

STORAGE
Do not store above 30°C

Description of Packaging: Each carton contains 1 blister or 2 blisters (aluminium/aluminium) with 10 tablets of 500mg Gastroresistant Tablets.

Product Registration Holder & Importer:
Abbott Laboratories (M) Sdn. Bhd.
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No. 8, Jalan SS 21/37,
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