For the Use of a Registered Medical Practitioner Only

1.0 GENERIC NAME AND BRAND NAME

Ademetionine Tablets 400mg
Heptral®

2.0 QUALITATIVE AND QUANTITATIVE COMPOSITION:

Each Enteric Coated Tablet Contains:
Ademetionine 1,4 – butane disulfonate (SD4) equivalent to Ademetionine Ion…400mg

3.0 DOSAGE FORM AND STRENGTH

Refer section 1 and 2

4.0 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

For the management of intrahepatic cholestasis and liver diseases.

4.2 POSOLOGY AND METHOD OF ADMINISTRATION

Heptral is available as 400mg tablet. The recommended dosing is 10-25 mg/kg/day orally. The usual starting dose is 400-800 mg/day and total daily dose should not exceed 1600mg.

Heptral tablets should be swallowed whole and not chewed. For better absorption of the active ingredient and complete therapeutic effect, Heptral tablets should not be taken with meals.

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

4.3 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 hyperhomocysteinemia (e.g. cystathionine beta-synthase deficiency, Vitamin B_{12} metabolism defect)

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Paediatric 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.

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.

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.

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.

4.5 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.

4.6 USE IN SPECIAL POPULATION

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.

Breastfeeding

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

Use in children

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

Use in the elderly

Clinical studies of ademetionine did not include sufficient numbers of subjects ≥65 years 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.

4.7 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.

4.8 UNDESIRABLE EFFECTS

In clinical trials, more than 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	Ac
Gastrointestinal disorders		
	Common	Abdominal pain, Diarrh
	Uncommon	Dry mouth, Dyspepsia, Gastrointestinal haemo Vomiting, Oesophagiti
	Rare	Abdominal distension
General disorders and administration site conditions		
	Common	Asthenia
	Uncommon	Oedema , Pyrexia, Chil site necrosis*
	Rare	Malaise
Immune System Disorder		
	Uncommon	Hypersensitivity*, Ana reactions (e.g. flushing, chest discomfort, altera hypertension) or pulse
Infections and infestations		
	Uncommon	Urinary tract infection
Musculoskeletal and connective tissue disorders		
	Uncommon	Arthralgia, Muscle spa
Nervous system disorders		
	Common	Headache
	Uncommon	Dizziness, Paraesthesia

*Undesirable effects from spontaneous reporting which 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).

4.9 OVERDOSE

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.

5.0 PHARMACOLOGICAL PROPERTIES

5.1 Mechanism of action

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).

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.

5.2 Pharmacodynamic Properties

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.

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.

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 metaanalysis 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. 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.

5.3 Pharmacokinetic Properties

Absorption

In humans, following intravenous administration, the ademetionine pharmacokinetic profile is biexponential 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 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 ≤ 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 Sadenosyl- homocysteine. S-adenosyl-homocysteine is then hydrolyzed to homocysteine and adenosine by Sadenosyl-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.

6.0 NON-CLINICAL PROPERTIES

6.1 ANIMAL TOXICOLOGY OR PHARMACOLOGY

Toxicological studies were performed in multiple animal species (rat, mouse, dog) of both sexes. Chronic toxicity testing did not identify any significant changes to body organs. Single-dose toxicity, repeated-dose toxicity, reproduction toxicity and mutagenicity studies were performed and did not demonstrate any signs of toxic effects.

When administered throughout pregnancy, no adverse effects were observed in the growth and development of the embryo or fetus.

7.0 DESCRIPTION

HEPTRAL is supplied for oral administration, as an enteric coated tablet of Ademetionine. Each enteric coated tablet of HEPTRAL contains Ademetionine 1,4 – butane disulfonate (SD4) equivalent to Ademetionine Ion 400mg.

8.0 PHARMACEUTICAL PARTICULARS

8.1 INCOMPATIBILITIES
Not applicable

8.2 SHELF LIFE
Refer Pack

8.3 PACKAGING INFORMATION
Refer Pack

8.4 STORAGE AND HANDLING INSTRUCTIONS
Refer Pack

9.0 PATIENT COUNSELING

a. Appropriate treatment

- Each Enteric Coated Tablet Contains Ademetionine 400mg.
- The Dosage is advised as per the Physician Discretion based on individual needs and severity of the disease.
- Instruct the patient that total daily dose should not exceed 1600mg.
- Instruct the patients that Heptral tablets should be swallowed whole and not chewed. Also, Advise the patients that for better absorption of the active ingredient and complete therapeutic effect, Heptral tablets should not be taken with meals.
- Instruct the patient that Heptral Tablets should be extracted from the blister package immediately before use.
- Advice the patient to check the colour of the tablets and if they appear other than white to yellowish in colour (due to presence of holes in the aluminium wrapper), it is advised to not to use that product.
- Advice the patient to reach out to the doctor if these symptoms do not improve after a while, if you develop new symptoms or you are concerned about your symptoms (see Posology and Method of Administration **4.2**)

b. Interactions

- Advice the patients about the risk of Serotonin syndrome who are taking ademetionine and are on clomipramine treatment as well.
- Therefore, caution is advised when administering ademetionine concomitantly with selective serotonin reuptake inhibitors (SSRI), tricyclic antidepressants (such as clomipramine), and over-the-counter and herbal supplements containing tryptophan and
- Advice the patients to seek immediate medical attention in-case of concomitant administration of these drugs and ademetionine.

c. Warning and precautions

- Advise the patient 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.

- Advise the patients about ammonia levels to be monitored in patients with pre-cirrhotic and cirrhotic states of hyperammonemia taking oral ademetionine.
- Advice the patients at risk (anemia, liver disease, pregnancy or potential for vitamin deficiencies due to other illnesses or eating habits eg, vegans) for vitamin B12 and folate deficiencies to have routine blood tests to check the plasma levels of vitamin B12 and folate.
- Advice the patients with depression, especially those who are at risk for suicide and other serious events, to receive continuous psychiatric support during therapy with ademetionine to ensure that the symptoms of depression are adequately addressed and treated. Patients should be encouraged to inform their physicians if their symptoms do not abate or worsen during ademetionine therapy.
- Advice the patients about risk of transient or worsening anxiety in patients treated with ademetionine, but in most cases, interruption of therapy may not be required.
- Advice the patients treated with ademetionine to use non-immunological methods to measure plasma homocysteine.
- Caution is Advised when administering ademetionine to elderly patients. [see Special warnings and Precautions 4.4)

10.0 DETAILS OF MANUFACTURER
Refer Pack for manufacturer details.

Marketed By:
Abbott India Limited
Angel Space, Lifestyle, Bldg. No. D4,
Gala No. 4 to 10, 14 to 20 Ground Floor,
107 to 110 & 117 to 120 1st Floor, 207 to 210
& 217 to 220 2nd Floor, Pimplas, Dist. Thane,
Bhiwandi-421 302, Maharashtra, India.

11.0 DETAILS OF REVISION OR LICENSE NUMBER WITH DATE
10/UA/2004, dated 10th November 2014

12.0 DATE OF REVSION
Version: 9.0, dated 11th March 2025

For Product Complaints/Adverse events or Queries please write to
webmasterindia@abbott.com

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