**SUMMARY OF PRODUCT CHARACTERISTICS**

**Ademetionine**

## 1 NAME OF THE MEDICINAL PRODUCT

Heptral 400 mg/5 ml lyophilized powder and solvent

## 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Heptral 400 mg/5ml lyophilized powder and solvent

One vial of lyophilized powder contains 760 mg ademetionine 1,4-butanedisulfonate equivalent to 400 mg Ademetionine

<For a full list of excipients, see Section 6.1.>

## 3 PHARMACEUTICAL FORM

Heptral 400 mg/5 ml Lyophilized powder and solvent

Lyophilized powder:

White to yellowish lyophilized cake

Solvent:

Clear, colourless to yellow solution

## 4 CLINICAL PARTICULARS

### 4.1 Therapeutic Indications

Heptral is indicated for treatment of adults with:

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

Relief of fatigue caused by chronic liver disease.

### 4.2 Posology and Method of Administration

Treatment is usually started with parenteral administration of the drug and continued using the drug in the form of tablets or immediately with the use of tablets.

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.

The lyophilized powder for IM or IV administration should be dissolved using the accompanying solvent at the time of use. Discard unused portion. The appropriate dose of ademetionine for IV administration should be further diluted in 250 ml saline or 5% dextrose and infused slowly within 1 to 2 hours. Ademetionine should not be mixed with an alkaline or calcium ion-containing solution. If the lyophilized powder appears other than white to yellowish in colour (due to a crack in the vial or exposure to heat), the product should not be used.

*Adults*

*Initial therapy:*

IV or IM: The recommended dosing is 5-12 mg/kg/day IV or IM for 2 weeks. The usual starting dose is 400 mg/day IV or IM, total daily dose not to exceed 800 mg. Duration of initial therapy for depression is 15-20 days and for intrahepatic cholestasis, intrahepatic cholestasis in pre-cirrhotic

and cirrhotic states, intrahepatic cholestasis in pregnancy is 14 days.
Oral: for oral administration the drug should be used Heptral film-coated tablets. The recommended dosing is 10-25 mg/kg/day orally. The usual starting dose is 800 mg/day (2 tablets), total daily dose not to exceed 1600 mg.
*Maintenance therapy:*
Oral: 500 to 1600 mg/day.
*Pediatric Population*
The safety and efficacy of Heptral for the use in children has not been stablished.
*Elderly Population*
Clinical studies of Heptral 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 another drug therapy.
*Renal Impairment*
There is limited clinical data in patients with renal impairment. Caution is recommended when administering Heptral to these patients.
*Hepatic Impairment*
Pharmacokinetic parameters are similar in healthy volunteers and patients with chronic liver disease.

## 4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients (see section 6.1)
- 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

Heptral 400 mg/5, lyophilized powder and solvent contains less than 1 mmol sodium (23 mg) per dose, i.e. essentially ‘sodiumfree’.
Because vitamin $B_{12}$ and folate deficiencies may decrease Heptral 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 Heptral (see section 5.2).
Some patients may experience dizziness with the use of Heptral. Patients should be advised not to drive or operate machinery during treatment until they are reasonably certain that Heptral therapy does not affect their ability to engage in such activities.
Heptral 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. Patients should be encouraged to inform their physicians if their symptoms (depression) do not abate or worsen during Heptral therapy.
Patients with depression are at risk for suicide and other serious events and therefore should receive

continuous psychiatric support during therapy with Heptral 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 Heptral. 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.
Heptral interferes with homocysteine immunoassays, which may show falsely elevated levels of plasma homocysteine in patients treated with Heptral. In patients treated with Heptral, it is therefore recommended to use non-immunological methods to measure plasma homocysteine.
*Hepatic Impairment*
No dosage correction is needed. Ammonia levels should be monitored in patients with hyperammonemia.
*Renal Impairment*
Heptral should be used with caution.
*Pediatric Population*
The safety and efficacy of Heptral for the use in children has not been stablished.

**4.5 Interaction with Other Medicinal Products and Other Forms of Interaction**
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 section 4.4).

**4.6 Fertility, 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 necessary.
Breast- feeding
Ademetionine should be used while breast-feeding only if the potential benefit justifies the potential risk to the infant.

**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**
The following undesirable effects have been observed
*Common (≥1/100, <1/10)*
- Abdominal pain, Diarrhoea, Nausea
- Headache
- Anxiety, Insomnia

- Asthenia
- Pruritus

*Uncommon (≥1/1000, <1/100)*

- Dry mouth, Dyspepsia, Flatulence, Gastrointestinal pain, Gastrointestinal haemorrhage, Gastrointestinal disorder, Vomiting
- Oedema, Pyrexia, Chills, Injection site reactions, Injection site necrosis
- 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))
- Urinary tract infection
- Arthralgia, Muscle spasms
- Dizziness, Paraesthesia, Dysgeusia
- Agitation, Confusional state
- Laryngeal oedema
- Hyperhidrosis, Angioedema, Allergic skin reactions (e.g. rash, pruritus, urticaria, erythema)
- Hot flush, Hypotension, Phlebitis

*Rare (≥1/10000, <1/1000)*

- Abdominal distension
- Malaise

## 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.

## 5.1 Pharmacodynamic Properties

Pharmacotherapeutic group: Amino acids and derivatives. ATC-Code: A16AA02

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.

*Intrahepatic cholestasis*

The experience accumulated with the oral and parenteral use of Ademetionine 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.
*Relief of fatigue in chronic liver disease (CLD)*
Several 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. Ademetionine is compatible with other anti-depressant drugs tricyclic antidepressants and monoamine oxidase inhibitors (see section 4.4 and 4.5).
*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.

## 5.2 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 ≤ 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.

### 5.3 Preclinical 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.

## 6 PHARMACEUTICAL PARTICULARS

### 6.1 List of Excipients

400 mg/5 ml: None

*Solvent*

L-Lysine, Sodium Hydroxide, Water for Injection

### 6.2 Incompatibilities

Not applicable

### 6.3 Shelf Life

Heptral 400 mg/5 ml lyophilized powder and solvent

Lyophilized powder in vials - 3 years

The solvent in ampoule - 3 years

On the secondary packaging (carton) the Manufacturing date is related to lyophilized powder. The

shelf life of the final product is determined with respect to the component (lyophilized powder or solvent), which expiration date is gone earlier

**6.4 Special Precautions for Storage**

Not applicable

Store at temperatures not above 25 ° C away from children.

**6.5 Nature and Contents of Container**

Heptral 400 mg/5 ml lyophilized powder and solvent

5 glass vials with lyophilized powder and 5 ampoules (5 ml) with a solvent for powder in blisters sealed with aluminum foil. 1 blister in a cardboard box.

**6.6 Special Precautions for Disposal <and Other Handling>**

Not applicable

**MANUFACTURER**

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**MARKETING AUTHORIZATION HOLDER**

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