

SUMMARY OF PRODUCT CHARACTERISTIC

Ademetionine

1. NAME OF THE MEDICINAL PRODUCT

Heptral 500 mg/5 ml lyophilized powder and solvent

Heptral 500 mg, gastro-resistant tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Heptral 500mg/5ml lyophilized powder and solvent

One vial of lyophilized powder contains 949 mg ademetionine 1,4-butanedisulfonate equivalent to 500 mg Ademetionine

Heptral 500mg gastro-resistant tablets

One tablet contains 949 mg ademetionine 1,4-butanedisulfonate equivalent to 500 mg Ademetionine

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

3. PHARMACEUTICAL FORM

Heptral 500mg/5ml Lyophilized powder and solvent Lyophilized powder:

White to yellowish lyophilized cake Solvent:

Clear, colourless to yellow solution

Heptral 500mg, gastro-resistant tablets White to yellowish, oval tablet

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

4.2. Posology and Method of Administration

Posology

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

Depression

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 1000 mg, for 15-20 days.

Oral: The recommended dosing is 10 - 25 mg/kg/day orally. The usual starting dose is from 400 to 800 mg/day, total daily dose not to exceed 1600mg.

SUMMARY OF PRODUCT CHARACTERISTIC

Ademetionine

Maintenance therapy:

Oral: 500 - 1600 mg/day.

Intrahepatic cholestasis

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

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 1000 mg, for 2 weeks.

Oral: The recommended dosing is 10 - 25 mg/kg/day orally. The usual starting dose is from 400 to 800 mg/day, total daily dose not to exceed 1600mg.

Maintenance therapy:

Oral: 500 - 1600 mg/day.

The duration of therapy depends on the severity and course of the disease and is determined individually.

Pediatric Population

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

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 other 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.

Method of Administration

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

Lyophilized Powder

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

SUMMARY OF PRODUCT CHARACTERISTIC

Ademetionine

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.

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.

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 B12 metabolism defect)

4.4. Special Warnings and Precautions for Use

Intravenous Heptral should be administered slow IV (see section 4.2).

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

Because vitamin B12 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).

Patients with suicidal behavior history or those who have had suicidal thoughts before treatment, should be under constant supervision during treatment. A meta-analysis of clinical trials for the treatment of mental disorders has shown that the use of antidepressants compared with placebo in patients in the age group under 25 years is accompanied by an increased risk of suicidal behavior. In the prescription of antidepressants requires close monitoring of patients, especially in the initial stages of treatment and after dose changes. Patients (and persons caring for patients) should be alerted to the need for ongoing monitoring and the need for immediate informing the physician if they have persisting symptoms of depression do not decrease or become worse during treatment with ademetionine, and in the case of behavior change, the emergence of suicidal thoughts.

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 Heptral. There has been a single literature report of serotonin syndrome in a patient taking Heptral and clomipramine. Although a potential interaction is postulated, caution is recommended when administering Heptral concomitantly with selective serotonin reuptake inhibitors (SSRI), tricyclic antidepressants (such as clomipramine), and over-

SUMMARY OF PRODUCT CHARACTERISTIC

Ademetionine

the-counter and herbal supplements containing tryptophan. (see section 4.5).

The efficacy of Heptral in the treatment of depression was studied in short-term clinical trials (3-6 weeks in duration). The effectiveness of Heptral 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 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.

Interference with homocysteine immunoassays

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.

4.5. Interaction with Other Medicinal Products and Other Forms of Interaction

Serotonin syndrome has been reported in a patient taking Heptral and clomipramine. Therefore, although a potential interaction is postulated, caution is recommended when administering Heptral 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

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.

–Breast-feeding

Heptral 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 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.

SUMMARY OF PRODUCT CHARACTERISTIC

Ademetionine

4.8. Undesirable Effects

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 ($\geq 1/10$), common ($\geq 1/100$, $< 1/10$), uncommon ($\geq 1/1000$, $< 1/100$), rare ($\geq 1/10000$, $< 1/1000$), 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
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,

SUMMARY OF PRODUCT CHARACTERISTIC

Ademetionine

		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 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).

4.9. Overdose

SUMMARY OF PRODUCT CHARACTERISTIC

Ademetionine

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

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic Properties

Pharmacotherapeutic group: Amino acids and derivatives

ATC-Code: A16AA02

Mechanism of action and Pharmacodynamics effects

S-adenosyl-L-methionine (Heptral) is a naturally occurring amino acid present in virtually all body tissues and fluids. Heptral 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. Heptral can penetrate the blood-brain barrier and Heptral-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 Heptral.

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, drug-induced liver injury, viral hepatitis, cholestasis induced by total parenteral nutrition, alcoholic liver disease and non-alcoholic fatty 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 approximately 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

SUMMARY OF PRODUCT CHARACTERISTIC

Ademetionine

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.

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.

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 polar 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, anti-cholinergic reactions.

5.2. Pharmacokinetic Properties

Absorption

In humans, following intravenous administration, the Heptral pharmacokinetic profile is bi-exponential

SUMMARY OF PRODUCT CHARACTERISTIC

Ademetionine

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 Heptral is practically complete (96%); the maximum plasma concentrations of Heptral are reached after approximately 45 minutes. Following oral administration of Heptral, peak plasma concentrations are achieved 3 to 5 hours after ingestion of enteric-coated tablets (400–1000 mg). Oral bioavailability is enhanced when Heptral 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 Heptral, respectively. Binding to plasma proteins is negligible being $\leq 5\%$.

Metabolism

The reactions that produce, consume, and regenerate Heptral are called the Heptral cycle. In the first step of this cycle, Heptral-dependent methylases use Heptral 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 Heptral, completing the cycle.

Excretion

In tracer balance studies using orally administered, radioactive (methyl ^{14}C) SAME in normal volunteers, urinary excretion of radioactivity was $15.5 \pm 1.5\%$ after 48 hours and fecal excretion was $23.5 \pm 3.5\%$ 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

500mg/5ml: None Solvent

SUMMARY OF PRODUCT CHARACTERISTIC

Ademetionine

L-Lysine, Sodium Hydroxide, Water for Injection

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.

6.2. Incompatibilities:

NA

6.3. Shelf Life

Heptral 500 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

Heptral 500 mg, gastro-resistant tablets – 3 years

6.4. Storage conditions

Store at a temperature not above 25°C, keep out of the reach of children.

6.5. Nature and Contents of Container

Heptral 500 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.

Heptral 500 mg, gastro-resistant tablets

10 tablets in a blister. 1 or 2 blisters in a carton box.

6.6. Manufacturer:

Heptral 500 mg, gastro-resistant tablets

AbbVie S.r.l.,

S.R. 148 Pontina KM 52, SNC - Campoverde di Aprilia (loc. Aprilia) – 04011 Aprilia (LT), Italy.

SUMMARY OF PRODUCT CHARACTERISTIC

Ademetionine

Heptral 500 mg/5 ml lyophilized powder and solvent

Solvent Manufacturer:

Famar S.A.,

Alimos Plant, 63 AG. Dimitriou Str, 17456 Alimos Attiki, Greece.

Powder Manufacturer:

Delpharm Saint Remy,

Rue de l'Isle, 28380 Saint-Remy sur Avre, France or

Biologici Italia Laboratories S.R.L.,

Via Filippo Serpero, 2 - 20060 Masate (MI), Italy

Primary Packaging

Delpharm Saint Remy,

Rue de l'Isle, 28380 Saint-Remy sur Avre, France

or

Biologici Italia Laboratories S.R.L.,

Via Filippo Serpero, 2 - 20060 Masate (MI), Italy

Secondary Packaging, Testing and Batch Release

Delpharm Saint Remy,

Rue de l'Isle, 28380 Saint-Remy sur Avre, France

6.7. Applicant:

Abbott Laboratories GmbH,

Freundallee 9 A, 30173 Hannover, Germany