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 1 vial (400 mg) a day for 15-20 days.
Oral: The recommended dosing is 2 – 3 tablets of 400 mg (800 – 1200 mg/day).

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Maintenance therapy:
Oral: 400-600 mg/day.
The duration of therapy depends on the severity and course of the disease and is determined individually.

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 for 2 weeks. The usual starting dose is 500 mg/day IV or IM, total daily dose not to exceed 800 mg.
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 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 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 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.

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

Lyophilized Powder

The lyophilized powder should be dissolved using the accompanying solvent at the time of use. Discard unused portion.

Heptral 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.

Intravenous Heptral should be administered slowly by IV.

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

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 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.

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-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
The use of high doses of Heptral in women in the last three months of pregnancy did not lead to any adverse effect. It is advisable to administer Heptral 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.

4.8 Undesirable Effects

In clinical trials lasting up to two years, ademetionine was studied in 2434 patients, of which 1983 patients the drug was prescribed for the diseases of the liver, 817 - about depression. The most frequently reported events with Heptral treatment were Headache, Diarrhoea and Nausea.

The table presents information based on the analysis of 1667 patients treated with ademetionine in

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22 clinical trials, of which 121 (7,2%) patients recorded a total of 188 adverse reactions. The most common adverse reactions were: nausea, abdominal pain and diarrhea. To identify the relationship of adverse events with the drug are not always possible.

MedDRA System Organ Class	**Adverse Reactions**
Infections and infestations	Urinary tract infection
Psychiatric disorders	Anxiety Insomnia
Nervous system disorders	Headache Dizziness Paraesthesia
Cardiovascular disorders	Cardiovascular disorders
Vascular disorders	Hot flushes Phlebitis of superficial veins
Gastrointestinal disorders	Abdominal pain, Diarrhea Nausea Dry mouth Dyspepsia Flatulence Gastrointestinal pain Gastrointestinal disorder Gastrointestinal haemorrhage Vomiting Abdominal distension Oesophagitis
Liver function disorders	Hepatic colic Cirrhosis of the liver
Skin and subcutaneous tissue disorders	Sweating Itching Skin reactions
Musculoskeletal and connective tissue disorders	Arthralgia Muscle spasms
General disorders and administration site conditions	Asthenia Oedema Chills* Injection site reactions* Malaise Fever Influenza like

* Adverse reactions observed in the process post-approval use of the drug.

Immune System Disorder
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))

Psychiatric disorders
Anxiety

Respiratory, thoracic and mediastinal disorders
Uncommon Laryngeal oedema

Skin and subcutaneous tissue disorders
Injection site reactions, Injection site necrosis, edema Kvynke, Allergic skin reactions (e.g. rash, pruritus, urticaria, erythema).
In the event of adverse reactions, including not listed in this leaflet, you should stop taking the drug and consult a doctor.

4.9 Overdose

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

MechanismofactionandPharmacodynamicseffects
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.

Heptral 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. Heptral 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 Heptral.

5.2 Pharmacokinetic Properties

Absorption
In humans, following intravenous administration, the Heptral 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 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 ≤ 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 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

500mg/5ml: None
Solvent
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 Distribution in the country of origyn:

With prescription

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
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.

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:
Famar L'Aigle,
BP 103, 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
Famar L'Aigle,
BP 103, 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
Famar L'Aigle,
BP 103, Rue de l'Isle, 28380 Saint-Remy sur Avre, France

6.7. Applicant:

Abbott Laboratories GmbH,
Freundallee 9 A, 30173 Hannover, Germany