INSTRUCTION ON DRUG ADMINISTRATION FOR SPECIALISTS

ADEMTA

TRADE NAME
Ademta

INTERNATIONAL NONPROPRIETARY NAME
Ademetionine

CHEMICAL NAME
(3S)-5'-[(3-amino-carboxypropyl)methylsulfonio]-5'-deoxy-adenosine 1,4-Butanedisulfonate

PHARMACEUTICAL FORM
Enteric coated tablets.
Description: orange-pink colored, oval, biconvex, enteric coated tablets.

COMPOSITION
Enteric coated tablet contains
Active substance: ademetionine (as ademetionine 1,4-butanedisulfonate) 400 mg.
Excipients: microcrystalline cellulose, sodium starch glycolate, silica colloidal anhydrous, magnesium stearate.
Coating materials: iron oxide yellow, iron oxide red, eudragit L-100-55, macrogol 6000, polysorbate 80, simethicone, sodium hydroxide, talc.

ATC CODE A16AA02

PHARMACOTHERAPEUTIC GROUP
Hepatoprotector.

PHARMACOLOGICAL PROPERTIES
PHARMACODYNAMICS
Ademta belongs to the group of hepatoprotectors, also has antidepressant activity. It has choleretic and cholekinetic action and detoxifying, regenerating, antioxidant, antifibrosing and neuroprotective properties. It fills deficit of S-adenosyl-L-methionine (ademetionine) and stimulates its production in the body, it is found in all internal environments. The highest concentration of ademetionine has been noted in liver and brain. Ademetionine plays a key role in metabolic processes of the body, it is involved in important biochemical reactions: transmethylation, transsulfuration, transamination. In reactions of transmethylation ademetionine donates a methyl group for synthesis of cell membranes phospholipids, neurotransmitters, nucleic acids, proteins, hormones, and others. In reactions of transsulfuration ademetionine is a precursor of cysteine, taurine, glutathione (providing redox mechanism of cell detoxification), coenzyme A (is included to biochemical reactions of citric acid cycle and replenishes energy potential of cells). **Ademta** increases the content of glutamine in liver, cysteine and taurine in plasma; lowers level of methionine in serum, normalizing metabolic reactions in liver. After decarboxylation it participates in reactions of aminopropylation, as a precursor of polyamines - putrescine (a stimulator of cell regeneration and proliferation of hepatocytes), spermidine and spermine, included into structure of ribosomes, which reduces the risk of fibrosis. It has choleretic action. Ademetionine normalizes endogenous phosphatidylcholine synthesis in hepatocytes, which increases membrane fluidity and polarization. This improves the function of membranes-associated hepatocytes of bile acid transport systems and facilitates passage of bile acids to bile duct. It is effective with intralobular version of cholestasis (impaired synthesis and

bile flow). Ademetionine reduces toxicity of bile acids in hepatocyte, exercising their sulfation and conjugation. Conjugation with taurine increases solubility of bile acids and removes them from hepatocyte. The process of sulfation of bile acids contributes to the possibility of their elimination by kidneys, facilitating the passage through membrane of hepatocytes and excretion with bile. In addition, the sulfated bile acids themselves further protect the membranes of liver cells from the toxic effect of non-sulfated bile acids (presented in high concentrations in hepatocytes at intrahepatic cholestasis). In patients with diffuse liver diseases (cirrhosis, hepatitis) with intrahepatic cholestasis syndrome ademetionine reduces the severity of itching and changes in biochemical indicators, including the level of direct bilirubin, alkaline phosphatase, aminotransferases and other. Choleretic and hepatoprotective effects last up to 3 months after treatment cessation. The efficiency at hepatopathy caused by different hepatotoxic drugs has been proved. Appointment in patients of opioid addiction accompanied by liver disease leads to regression of clinical manifestations of abstinence, improves liver function and processes of microsomal oxidation. The antidepressant activity is manifesting gradually, starting from the first week of treatment and stabilizing during 2 weeks of treatment. It is effective with recurrent endogenous and neurotic depression resistant to amitriptyline. It has an ability to interrupt recurrences of depression. Prescription reduces expression in osteoarthritis pain, increases synthesis of proteoglycans and leads to partial regeneration of cartilage tissue.

PHARMACOKINETICS

Absorption

Enteric coated tablets dissolve only in the intestine, thereby ademetionine is released in duodenum.

Oral bioavailability is 5% increase in fasting state. Maximum concentrations (C_{max}) in plasma of ademetionine are dose-dependent and are 0.5-1 ml/L in 3-5 hours after single oral dose from 400 mg to 1000 mg. C_{max} of ademetionine in plasma are reduced to initial level within 24 hours.

Distribution

Plasma protein binding is insignificant, which is ≤ 5%. It penetrates through blood-brain barrier. Significant increase in concentration of ademetionine in cerebrospinal fluid is noted.

Metabolism

It is metabolized in liver. The process of building-up, consumption and rebuilding-up of ademetionine is called ademetionine cycle. In the first phase of this cycle ademetionine-dependent methylases use ademetionine as a substrate for S-adenosylhomocysteine production, which is then hydrolyzed to adenosine and homocysteine via S-adenosylhomocysteine hydrolase. Homocysteine in its turn undergoes inverse transformation to methionine by transferring methyl group from 5-methyltetrahydrofolate. As a result, methionine can be converted into ademetionine, completing the cycle.

Elimination

The half-life ($T_{1/2}$) is 1.5 hours. It is excreted renally.

THERAPEUTIC INDICATIONS

Intrahepatic cholestasis at pre-cirrhotic and cirrhotic conditions can be observed in the following diseases:

- hepatic steatosis;
- chronic hepatitis;
- toxic hepatic injuries of various etiology, including alcohol, virus, drug-induced (antibiotics, anti-cancer, anti-tuberculosis and anti-viral drugs, tricyclic antidepressants, oral contraceptives);
- chronic noncalculolis cholecystitis;
- cholangitis;
- hepatic cirrhosis;
- encephalopathy of secondary genesis, including associated with hepatic decompensation (alcohol, etc.).

Intrahepatic cholestasis in pregnancy.

Depression.
Combined treatment of osteoarthritis.

DOSAGE AND ADMINISTRATION
Enteric coated tablets are administered orally, as a single piece, without chewing, preferably in the morning hours between meals. Tablets must be removed from blister immediately before oral administration. If the tablets have a color different from that described in the patient information leaflet, the drug is not recommended for use.
Recommended daily dose is 2-4 tablets (from 800 mg to 1600 mg per day).
The duration of therapy is determined by a doctor.
Elderly patients (over 65 years)
Clinical trials of the drug did not show any difference in its effectiveness in elderly patients and younger patients. However, given the high probability of liver function abnormalities, kidneys or heart disease or other cormobidity or combined therapy with other drugs, the dose of the drug in elderly patients should be selected with caution, starting the drug administration from lower limit of dose range (1-2 tablets per day)
Patients with renal failure
Studies in patients with renal failure have been not conducted, as a result it is recommended to be careful when using the drug in these patients.
Patients with hepatic decompensation
Parameters of ademetionine pharmacokinetics are similar in healthy volunteers and patients with chronic hepatic disorders.

CONTRAINDICATIONS
- hypersensitivity to ademetionine and/or other drug components;
- genetic defects affecting methionine cycle, and/or causing homocystinuria and/or hyperhomocysteinemia (deficit of CBS, violation of vitamin B_{12} metabolism).

SIDE EFFECTS
The most common adverse reactions are: nausea, abdominal pain and diarrhea. Summarized data on adverse reactions have been identified during clinical trials and post-marketing use of ademetionine as follows.
Immune system disorders: hypersensitivity, anaphylactoid or anaphylactic reactions (including skin flushing, dyspnea, bronchospasm, back pain, discomfort in the chest, lower blood pressure, increased blood pressure, tachycardia, bradycardia).
Respiratory disorders: laryngeal edema.
Skin disorders: angioedema, increased hidrosis, dermal reactions, including pruritus, skin rash.
Infections and infestations: urinary tract infections.
Central nervous system disorders: dizziness, headache, paresthesia, anxiety, confused consciousness, insomnia.
Cardiac disorders: hot flashes, phlebitis of superficial veins, vascular disorders.
Gastrointestinal disorders: bloating, abdominal pain, diarrhea, dry mouth, dyspepsia, esophagitis, flatulence, gastrointestinal distress, gastrointestinal bleeding, nausea, vomiting, hepatic colic, hepatic cirrhosis.
Musculoskeletal and connective tissue disorders: arthralgia, muscle spasms.
Other: asthenia, shivers, flu-like syndrome, ailment, peripheral edema, fever.

SPECIAL INDICATIONS
Considering tonic effect, ademetionine is not recommended before bedtime.
In patients with hepatic cirrhosis on the background of hyperasotemia it is required systematic monitoring of residual nitrogen. During long-term therapy it is necessary to determine the content of urea and creatinine in blood serum.

It is not recommended to prescribe ademetionine to *patients with bipolar disorder*. There are reports on transition of depression to hypomania or mania in patients having taking ademetionine.
There are also reports of sudden appearance or unease in patients taking ademetionine. In most cases, therapy cessation is not required, in some cases anxiety was resolved after dose reduction or discontinuation of therapy.
Patients with depression have an increased risk of suicide and other serious adverse events, so during drug treatment, these patients should be under the constant supervision of a psychiatrist.
Since deficiency of vitamin B12 and folic acid can reduce the level ademetionine in *patients at risk* (with anemia, liver disease during pregnancy or with probability of vitamin deficiency, due other diseases or diet, for example in vegetarians) it is necessary to monitor the level of vitamins. If deficiency is detected, the concomitant use of the drug with vitamin B_{12} and folic acid is recommended.
Ademetionine affects the result of homocysteine immunoassay, which may cause falsely high levels of homocysteine in plasma. For patients taking ademetionine it is recommended to use non-immunological methods of analysis for determining the level of homocysteine.
The drug should be prescribed with caution to elderly patients and patients with renal failure.

INFLUENCE ON ABILITY TO DRIVE AND OPERATE OTHER MECHANISMS
Due to possible dizziness arising, it is recommended not to drive vehicle and operate potentially dangerous mechanisms until complete disappearance of symptoms, which may affect reaction rate at indicated types of activities.

ADMINISTRATION DURING PREGNANCY AND LACTATION
The use of high doses of ademetionine in III trimester of pregnancy does not cause any adverse reactions. The use of the drug in I trimester of pregnancy and lactation is possible only if potential benefit to the mother outweighs any potential risk to the fetus.

PEDIATRIC USE
Safety and efficacy of the medicine has not been studied when used for children under 18 years old.

DRUG INTERACTIONS
Known interactions with other drugs have been observed.
Ademetionine should be used with caution with selective serotonin reuptake inhibitors, tricyclic antidepressants (such as clomipramine), as well as herbal medicinal products and drugs containing tryptophan.

OVERDOSE
Drug overdose is unlikely. In case of overdose patient control and symptomatic therapy is recommended.

PACKAGING
Enteric coated tablets.
10 tablets in a blister.
2 blisters with the enclosed leaflet in a carton box.

STORAGE CONDITIONS
Store at temperature not exceeding 25°C.
Keep out of reach of children!

SHELF LIFE
3 years from the manufacture date.
Do not use after expiry date.

SALES TERM
Sold under prescription.

MANUFACTURER
The holder of trade mark and Marketing Authorization is
“DR SERTUS İLAÇ SANAYİ VE TİCARET LİMİTED ŞİRKETİ”, TURKEY.
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