



## MARKETING ANALYSIS OF ADEMETHIONINE IN THE PHARMACEUTICAL MARKET OF UKRAINE

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**Abstract.** *The article presents the results of the marketing analysis of Ademethionine presented on the pharmaceutical market of Ukraine. A review of literature sources on preclinical and clinical studies was conducted, the main areas of application of the drug were characterized, and an analysis of the assortment by dosage forms and producing countries was carried out. A relatively small assortment of dosage forms of the drug ademethionine has been established, despite its significant use in the treatment of hepatobiliary pathology and a wide range of pleiotropic pharmacological properties.*

**Key words:** *Ademethionine, hepatoprotector, marketing analysis, assortment.*

### **Introduction.**

The effectiveness of the treatment of the hepatobiliary system, as before, remains an actual and unsolved problem of practising medicine, as well as the search for drugs with pronounced hepatoprotective properties. The leading role of oxidative stress in the pathogenesis of liver damage provides grounds for a targeted search for drugs for the prevention and treatment of these pathologies [1, 2]. Hepatoprotectors are a heterogeneous group of drugs that, through various mechanisms, protect liver cells from damage and thereby activate their functions. The classification of hepatoprotectors is not finally agreed upon, and scientific discussions continue on this issue, and the pharmacological activity of hepatoprotectors is realized through their common mechanisms of action: inhibition of lipid peroxidation and binding of excess



oxidation products; increasing the activity of enzymes involved in oxidation, repair (restoration) of hepatocyte cell membranes; increase in reserves of glutathione, taurine and sulfates, which increases the antitoxic activity of hepatocytes; reduction of the synthesis of pro-inflammatory cytokines and stabilization of the hepatocyte membrane (anti-inflammatory effect); reduction of hepatocyte necrosis, stimulation of collagenase activity and blockade of connective tissue synthesis enzymes (antifibrotic effect) [3].

Among hepatoprotectors, our attention was drawn to ademetionine - an amino acid derivative, which today in clinical practice, in addition to the treatment of liver diseases (chronic hepatitis, intrahepatic cholestasis, liver cirrhosis, hepatic encephalopathy), is also used in cases of the depressive syndrome. According to the pharmacological group, it belongs to "Agents affecting the digestive system and metabolic processes", ATC code: A 16A A 02 [4, 5].

**The aim of the work** is to conduct a marketing analysis of the use and assortment of Ademetionine drugs registered in the pharmaceutical market of Ukraine and to determine the prospects for their further use in medicine.

#### **Materials and methods.**

The object of the study was the nomenclature of medicines with the active ingredient Ademetionine, which are presented in the pharmaceutical market of Ukraine. The research used the methods of marketing analysis of the assortment of medicines based on Ademetionine according to the state register of pharmaceuticals in Ukraine and the analysis of the international scientific base of preclinical and clinical trials of this active substance.

**The results and discussion.** Numerous experimental and clinical studies have established that the metabolism of exogenous ademetionine occurs in the same way as endogenous [6, 7].

Endogenous ademetionine is an active sulfur-containing metabolite of methionine, a natural antioxidant that is synthesized in the liver from methionine and adenosine in an average amount (8 g/day), present in all living cells of the body, but mostly in the liver and brain. Ademetionine was discovered in 1952, its chemical structure was first presented by G.L. Cantoni [8]. It is a precursor of compounds such as choline, cysteine, taurine, glutathione, coenzyme A, etc., and is involved in three main reactions: transmethylation, transsulfuration, and aminopropylation [9, 10].

The activity of the Ademetionine drug is ensured by the presence of an active sulfur atom and CH<sub>3</sub> group in its chemical structure. The transmethylation reaction contributes to the synthesis of phospholipids, namely phosphatidylcholine of cell membranes, ensuring their fluidity and polarization, which plays an important role in the synthesis of bile [11]. Since various pathogenetic factors cause damage primarily to cell membranes, leading to disruption of intracellular metabolism, ademetionin is a universal cytoprotector, and accordingly, a hepatoprotector [12]. Due to its cyto- and membrane protective properties, ademetionine can prevent the development of mitochondrial dysfunction and bioenergetic stress, which play an important role in the etiology of alcoholic liver disease, and liver cirrhosis [13].

The choleric effect of ademetionine is also ensured by increasing the energy potential of cells, due to an increase in the activity of Na<sup>+</sup>/K<sup>+</sup> -ATPase, normalization



of the permeability of cell membranes, which contributes to a better capture of bile components from the blood, its intracellular transport and excretion [10-13 Recommendations]. These properties of the drug allow it to be used for the treatment of intrahepatic cholestasis, and hepatic encephalopathy [14].

As a result of the transsulfuration reaction, glutathione, sulfates and taurine are synthesized - integral components of the detoxification function of the liver, since damage and necrosis of hepatocytes is a consequence of oxidative stress followed by the formation of free radicals. As a precursor of glutathione and a donor of methyl groups, Ademetionine can prevent and reduce the risk of fatty hepatosis and steatohepatitis [15]. An equally important role in the antitoxic function of the liver is played by the next product of transsulfuration of Ademetionine - taurine, which promotes the conjugation of bile acids and increases their solubility and excretion of bile components.

The transfer of the aminopropyl group from ademetionine to polyamines (putrescine, spermidine and spermine), which play an important role in the structure of ribosomes and protein synthesis, leads to the stimulation of hepatocyte proliferation, promoting liver regeneration [16, 17].

In addition to the main pharmacological activity, the neuroprotective effect of ademetionine is also proven. The methylation process is an important step in the synthesis of neurotransmitters in nerve cells, which explains its central antidepressant effects [18]. Ademetionine belongs to atypical antidepressants, possessing anti-neurotoxic activity due to participation in the synthesis of brain neurotransmitters (norepinephrine, dopamine, serotonin, histamine) and polyamines, which contribute to the transmission of neurohumoral signals and the regeneration of nervous tissue [19].

The relevance of studying the pleiotropic properties of Ademetionine has been confirmed by many preclinical researches. The antiepileptic effect of ademetionine was proven in the pentylenetetrazol-induced seizure model, while the drug improved memory and showed antioxidant properties [20]. Due to the effect of ademetionine on physiological processes in the nervous system, the data of the literature testify to the hypotensive, dose-dependent activation of the amino acid, which is realized by reducing the activation of the autonomic nervous system [21].

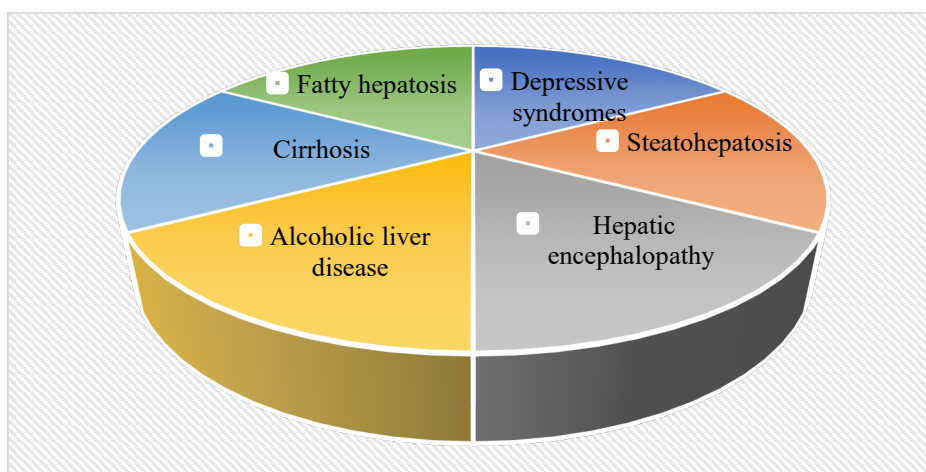
The anti-stress and anti-radiation activity of ademetionine was also established when used in chronically irradiated rats and was realized by increasing the functional capacity of all links of the glutathione redox system against the background of a decrease in the intensity of POL processes [17].

The positive effect of the use of the drug was demonstrated in the modelling of chronic bronchial asthma in rats, where the drug promoted the production of anti-inflammatory cytokines and reduced airway fibrosis by reducing oxidative stress and fibronectin expression. The results of the study suggest a potential role of ademetionine as a new therapeutic agent in chronic bronchial asthma [22].

The nephroprotective potential of ademetionine on kidney tissue cells was shown by the results of experimental studies on models of rhabdomyolytic, ischemic-reperfusion acute kidney injury and the model of gentamicin nephropathy, which was realized both by restoring the functional state of the kidneys and by normalizing the oxidant-antioxidant balance [23].



The multiple pharmacological effects of the drug and the multifaceted use of ademethionine in medical practice are shown in Fig. 1



**Fig. 1. Spectrum of use of ademethionine in medicine**

The above-mentioned effects of the drug, proven at various levels of scientific research (preclinical and clinical), indicate the prospects for the use of ademethionine not only as a hepatoprotective agent, but a drug with pronounced hepatoprotective, antidepressant, antioxidant, detoxifying, regenerating and antifibrotic properties. Therefore, it is relevant to carry out a marketing analysis of the assortment of ademethionine preparations registered on the pharmaceutical market.

According to the results of the marketing research, it was established that 14 names of medicinal products with the active ingredient - Ademethionine are registered on the pharmaceutical market of Ukraine (Table 1).

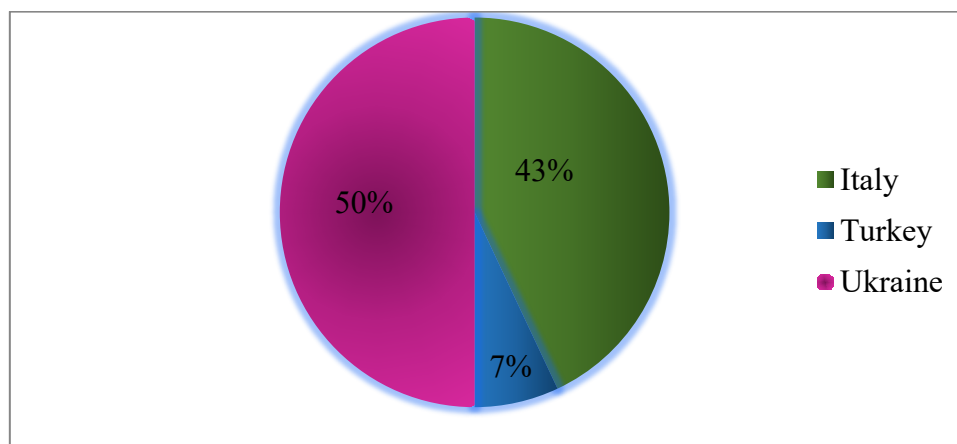
**Table 1 - Medicines registered in Ukraine, which include Ademethionine**

№п/п	Name/	Dosage form	Pharmaceutical company manufacturer
1.	HEPAMETHION ® 500 mg	lyophilisate for solution for injections	PRJSC «HALYCHPHARM», Ukraine PJSC «KIEVMEDPREPARAT», Ukraine
2.	HEP-ART ® 400 mg	lyophilisate for solution for injections	JSC FARMAK, Ukraine
3.	HEPSAM 500 mg	lyophilisate for solution for injections	LABORATORIO ITALIANO BIOCHIMICO FARMACEUTICO LISAFARMA S.P.A., Italy
4.	HEPTRAL ® 400 mg	lyophilisate for solution for injections	Biologici Italia Laboratories S.R.L., Italy
5.	HEPTRAL ® 500 mg	lyophilisate for solution for injections	Biologici Italia Laboratories S.R.L., Italy
6.	RECHOL 400 mg	enteric-soluble tablets	"MICROCHEM" NVF LLC, Ukraine
7.	HEPTRAL ® 500mg	enteric-soluble tablets	AbbVie S r.l., Italy.
8.	HEPTRAL ® 400 mg	enteric-soluble tablets	AbbVie S r.l., Italy.
9.	HEPAMETHION ® 500 mg	enteric-soluble tablets	PJSC «KIEVMEDPREPARAT», Ukraine
10.	ADECYCLOL 400 mg	lyophilisate for solution for injections	Biomedica Foscoma - Industria Chimico-Farmaceutica S.p.A., Italy
11.	ГЕПІАМЕТІОН® 400 mg	lyophilisate for solution for injections	PJSC «KIEVMEDPREPARAT», Ukraine
12.	HEP-ART ® 400 mg	enteric-soluble tablets	JSC FARMAK, Ukraine
13.	HEPAMETIN 400 mg	lyophilisate for solution for injections	LLC «PHARMAX GROUP», Ukraine
14.	ADEMTA 400 mg	lyophilisate for solution for injections	Mefar Ilach San. A.Sh., Turkey



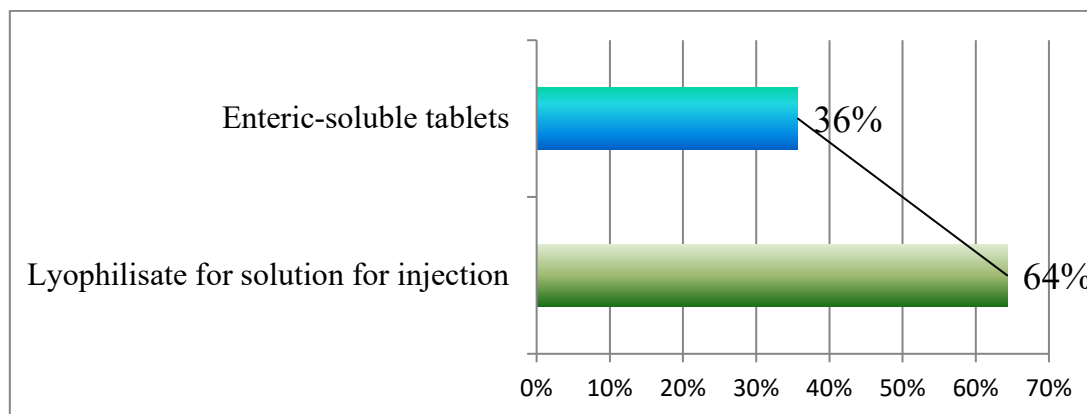
An analysis of the structure of the drug market by producing countries showed that 50% (7 items) of consumers are supplied with domestic drugs and 50% (7 items) with imported products.

Among the drugs manufactured abroad, the leading place is occupied by drugs manufactured in Italy (43%), and Turkey produces only 12% of ademethionine products (Fig. 2).



**Fig. 2. The structure of the domestic pharmaceutical market of the drug – Ademethionine**

Research of the pharmaceutical market in terms of the contribution of different medicinal forms of release showed that ademethionine drugs are presented in 2 medicinal forms - lyophilisate for solution for injections and enteric tablets (Fig. 3)



**Fig. 3. A variety of medicinal forms of Ademethioinin on the pharmaceutical market of Ukraine**

Taking into account the wide range of use of ademethionine in medical practice and the powerful pharmacological activity of the drug, the presence of an antioxidant, choleric, cholekinetic, detoxifying, regenerating, neuroprotective, and antidepressant effects, indicates the promising use of the drug in both in liver pathology of various genesis and in other fields of medicine. According to the results of a comprehensive marketing analysis of the assortment of the domestic market, it should be noted that they have a significant share among other drugs, however, when prescribing drugs, it is important to evaluate the ratio of effectiveness/safety and price/quality, which is important for the patient.





## Conclusions.

The results of the marketing research indicate a relatively small assortment of dosage forms of the drug ademethionine, despite its significant use in the treatment of hepatobiliary pathology and a wide range of pharmacological properties.

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