Module 2.5

Clinical Overview

ADAPTOL

500 mg tablets

JSC Olainfarm, Latvia

2016

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2.5.1. PRODUCT DEVELOPMENT RATIONALE

The aim of the underlying Clinical Overview is to support marketing authorisation of medicinal product **Adaptol 500 mg tablets** in well-established use (WEU) category as defined by Article 10a of Directive 2001/83/EC. Adaptol 500 mg tablets contain mebicar as an active substance. Therefore, the Applicant was not required to provide the results of clinical and preclinical tests since he can demonstrate that the active substance of the medicinal product have been in well-established medicinal use within the Community for at least ten years with recognised efficacy and acceptable level of safety.

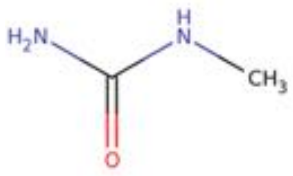
Mebicar structurally has two cyclic methyl urea (Figure 1) molecules; therefore it is chemically inert and similar to endogenic metabolites [1].

Mebicar was proposed by N.D.Zelinskiy Institute of Organic Chemistry of the Academy of Sciences of the USSR (in Moscow) and Kazan S.V.Kurashov Medical Institute. The clinical trials of mebicar were authorized in 1972. Wide application of the drug started already in 1979 [2].

Mebicar exerts moderate anxiolytic effects, it prevents or diminishes anxiety, inner emotional stress, and excitement. Mebicar has no effect on muscle relaxation and movement coordination, mental or physical activity depression, thus it can be used without termination of work or studies. Mebicar has no direct effect on sleep initiation, however it potentiates the effect of other tranquilizing drugs and normalizes sleep disturbances. It is known that mebicar effectively treats alcohol withdrawal. Mebicar does not cause mood changes or euphoria, as well as tolerance, dependence or withdrawal.

Mebicar is used in the treatment of neurosis and neurotic disorders, e.g. anxiety and emotional lability; in the treatment of different origin cardialgies, which are not associated with coronary heart disease. Mebicar is also used to improve neuroleptic and tranquilizing drug tolerance, e.g. to diminish muscle asthenia, excessive tranquilization and emotional depression.

Figure 1: **Structure of N-methylurea.**



This report summarizes the relevant publications (papers published in English and Russian) based on *MedLine/PubMed/Toxnet* search, search extended to other sources of medicinal databases. Publications in Russian were translated by qualified translators to English. The primary keyword “mebicar” have been used, with coupled limitations applying the combinations of secondary keywords. Data were included and collected using pharmacological reference books and electronic document base and databases. This report provides an overview of the published literature regarding clinical pharmacodynamics, pharmacokinetics, efficacy and safety aspects for mebicar.

2.5.2. OVERVIEW OF BIOPHARMACEUTICS

Biopharmaceutic studies (bioavailability, bioequivalence) are not applicable and have therefore not been performed with mebicar since the application is bibliographical. Presented full dossier is based on scientific reviews and research articles.

Mebicar has two cyclic methyl urea molecules and a following chemical structure (Figure 2):

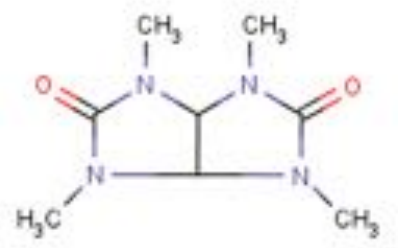


Figure 2. Structure of mebicar [3].

The chemical name for mebicar is 1,3,4,6-tetramethyl-3a,6a-dihydroimidazo[4,5-d]imidazole-2,5-dione. It has a molecular formula of C8-H14-N4-O2, a MW of 198.225.

INN: Mebicarum

Well-established (WEU) product of joint stock company "Olainfarm", 5 Rūpnīcu Str., Olaine, LV-2114, Latvia

ATC code: NO5BX

Drug class: Anxiolytics

CAS number: 10095-06-4

Drug form and composition: tablets, 1 tablet contains 500 mg of mebicar

Storage: Store in dry room

Package: 20 tablets of 500 mg

Synonyms: 2,4,6,8-Tetramethyl-2,4,6,8-tetraazobicyclo(3.3.0)octane-3,7-dione; Tetrahydro-1,3,4,6-tetramethylimidazo(4,5-d)imidazole-2,5(1H,3H)-dione; Mebicar

Composition of product:

- active ingredient – mebicarum 500 mg,
- excipients – methylcelulose, calcium stearate.

Mebicar is colorless powder with bitter taste, a weak amide odour, readily soluble in water and many other organic solvents; chemically inert substance; does not react with acids, alkalis, oxidizers, deoxidizers, medicinal agents ad food components.

Adaptol® is stabile during storage; it stands up to sterilization by any method. Melting temperature is 224-228°C [4; 5].

Mebicar has a wide spectrum of clinical effects, including tranquilizing, nootropic, anti-depressant, bio-correcting, adaptogenic, hypolipidemic and antianginal [6]. Mebicar was introduced to medical practice in 1979.

Mebicar is not metabolized or bounded to plasma proteins and is excreted in unchanged state completely. The structure of mebicar is similar to the metabolites of organism and probably it is a structural analogue of endogenous substances/ regulators [4; 7]. Mebicar is a tranquilizer adaptogen, it has low toxicity and easily crosses blood-brain barrier. Mebicar has GABA-positive, central serotonin-positive and central adrenolytic effects. It does not affect the cholinergic system, but increases sensitivity of the central M-cholinergic effects of arecoline. Electroencephalography studies have showed that mebicar synchronizes bioelectric activity in a wakeful state and normalizes sleep phases III and IV (so called delta-sleep) [7].

In experiments and in patients mebicar improves behavior, functions of the regulatory systems, organs and tissues, as well as at cellular and molecular levels [1]. Mebicar was showed to act on limbic system and reticular formation [1]. Mebicar taken in complex therapy in traumatic shock normalizes psychic, nervous, hormonal and metabolic systems [1]. Mebicar previously has decreased gastric ulcerations, normalized arterial pressure under stressful conditions and changed potassium levels in plasma, skeletal muscles and myocardium [2]. Mebicar together with promedol in traumatic shock had reduced mortality, pulmonary, renal and cardiovascular complications in patients, restoring also hemodynamics, depth and rate of respiration, acid-base equilibrium [7].

Mebicar has shown some benefits in depression treatment, since it exerts tranquilizing properties and increases serotonin levels [6]. Mebicar helps to reduce anxiety, irritability, anxious, hypochondria, indecision and people suffering from emotional instability [6]. Mebicar has anti-asthenic, psycho-stimulating, sedative and vaso-vegetative effects [6]. Moreover, mebicar optimizes thinking processes, thus showing cognition improving results [6].

A wide range of cardioprotecting action of mebicar has been shown. Mebicar increases contractility of myocardium, stroke volume and cardiac output, creates oxygen reserves in

venous and coronary blood. It reduces supertension of cerebral blood vessels. Chronic use of mebicar during heavy physical activity has an adaptive effect, it promotes accumulation of glycogen in cytoplasm of cardiomyocytes, increased granular endoplasmic reticulum and increased number of nucleoli on nuclei. Mebicar normalizes oxygen homeostasis, acid-base balance, electrolytic balance, has antihypoxic action [7]. It treats cardialgias, however in cardialgias caused by extensive spine osteochondrosis the therapeutic effect is low. In rehabilitation of patients with myocardial infarction mebicar positively influences the coronary circulation and the state of mind of patient; improves physical efficiency better than physical rehabilitation only [7].

Mebicar reduces psychopathological disorders in alcoholics, asthenic disorders, affective disorders, mood changes, irritability, drowsiness, reduction of appetite. High doses of mebicar (3.6 g /day) normalizes sleep, together with azaphenum improves also mood and behavior of alcoholic patients, besides, mebicar does not cause addiction like diazepam [7].

Mebicar effectively treats paroxysms after closed craniocerebral injuries. Mebicar in patients with pre-menstrual tension syndrome eliminates tearfulness, anxiety, emotional lability, irritability and depressed mood [7].

The intensity of tranquilizing effect of mebicar is similar to that of diazepam, however mebicar does not have a direct hypnotic effect. Mebicar reduces the intensity of high mental and physical fatigability, weakness, exhaustion, absent-mindness, poor organization, affective lability, irritability, memory dysfunctions, sleep disturbances in patients with vascular and traumatic brain injuries. Mebicar also reduces the deficit disorders of thinking in schizophrenia patients. If compared to other drugs, mebicar promotes restoration of the normal state of thinking processes and intensification of verbal and logic functions while piracetam enhances emotional and figurative brain functions [7].

Mebicar in comparison to other tranquilizers is less toxic, does not cause muscular relaxation, flaccidity, sleepiness [4]. Mebicar is better tolerated than benzodiazepines, and it can restore the adverse effects of neuroleptics and benzodiazepines [6]. Mebicar effectively reduces neuroleptic therapy side effects, such as tremor, muscle hypertonia, hypersalivation, sweating, dysuric events, obsession, hypersedation. Mebicar decreases also the side effects of benzodiazepines, having no effect on reduction of anxiolytic effect of tranquilizers [7].

The maximal daily dose of mebicar in adults should not exceed 10 g [6]. Mebicar is usually administered at a dose of 0.3 – 0.5 g 2-3 times a day. Sometimes a single dose is

enough, but in more severe cases mebicar is used for weeks-months at doses 1.8-10 g /day [6].

Thus there is a wide spectrum of use of mebicar in clinics. Mebicar is used in psychiatry to treat patients with neuroses and to reduce the side effects of benzodiazepines and neuroleptics; in narcology to treat alcohol withdrawal syndrome and to reduce attraction to alcohol; in neuropathology to treat patients with closed craniocerebral injuries; and in prophylaxis of neurotic disorders in stress situations [4].

2.5.3. OVERVIEW OF CLINICAL PHARMACOLOGY

2.5.3.1. Pharmacokinetics

When entering blood-brain barrier, mebicar is concentrated mainly in cortex of hemispheres, where it has stronger effects than in other brain regions [25].

When administered by intramuscular injections, concentration of mebicar increases considerably quicker, but reduces with the same speed [25]. Mebicar after intramuscular injection enters blood as 98-100% of injected, with oral administration as 77-80%, showing that bioavailability degree of mebicar is high [25]. After entering blood, 40% of mebicar is bound by erythrocytes; distribution volume of the drug is 0.9 l/kg for humans [25]. Besides mebicar also penetrates intensively inside the cell [25]. The highest concentration of mebicar is found in blood plasma, and then in the liver, followed by the heart and the brain [26].

In human plasma after single 1.5 g dose mebicar reaches its maximal content in 0.5 hours and decreases till insignificant values in 24 hours, thus mebicar in humans is absorbed quicker and excreted slower than in rats. Administration of the drug 3 times a day with 6 hours interval ensures its blood concentration close to maximal. 55-70% of mebicar is excreted with urine in humans; the significant part is excreted also with faeces [25].

The pharmaceutical filler for tablets is starch or sugar powder. Tablets contain from 0.25 to 0.5 g of active principle. It is prescribed to be taken 3 times a day, per 1.0-1.5 g. Aqueous solutions of the compound are stable against sterilization. Mebicar does not cause cumulative effects, morphological changes of the viscera, and is excreted in 24 h [30; 47].

2.5.3.1.1. Absorption

Mebicar is usually administered *per os* in the form of capsules or tablets. In humans mebicar is absorbed quicker than in rats, reaches maximal plasma concentration in 30 minutes and is maintained for 3-4 hours, then the level decreases gradually and in 24h is excreted [4].

2.5.3.1.2. Distribution and protein binding

In human plasma after single 1.5 g dose of mebicar reaches its maximal content in 0.5 hours and decreases till insignificant values in 24 hours [25]. After entering blood, 40% of mebicar is bound by erythrocytes, distribution volume of the drug is 0.9 l/kg for humans [25].

Besides mebicar also penetrates intensively inside the cell [25]. The highest concentration of mebicar is found in blood plasma, and then in the liver, followed by the heart and the brain [25].

2.5.3.1.3. Metabolism and excretion

In humans mebicar does not metabolize and is excreted unchanged [1].

2.5.3.1.4. Drug interactions

No interactions of Adaptol® with other drugs are noted. Adaptol® can be used simultaneously with neuroleptics, tranquilizers (such as benzodiazepines), drugs for the treatment of insomnia, anti-depressants and psycho-stimulants.

2.5.3.2. Pharmacodynamics

Mebicar is a tranquilizator with wide spectrum of anxiolytic activity. Great role of the functioning of mebicar is its nootropic properties. Mebicar has mimetic effects on GABA-ergic and M-cholinergic systems, which provide its tranquilizing effects. Mebicar can act on neuromediator systems, inhibiting excitatory adrenergic and glutamatergic systems and activating GABA and serotoninergic systems [8; 9].

Thus mebicar regulates interactions of neuromediators of the brain. Mebicar has anti-hypoxic and membrane stabilizing effects, it improves energy providing for cells, glucose exchange and cellular respiration. Mebicar is showed to have central and peripheral effects. It improves cerebral blood flow, increases physical and mental working abilities, it can be used in prophylaxis of stressful conditions. Mebicar is involved in the regulation of vegetative functions, it shows beneficial effects in the treatment of neurocirculatory dystonia. Mebicar is a day tranquilizer, it has vegetative system stabilizing, and analgesic effects. Mebicar has been widely used in menstrual and climacteric disorders, in chronic alcoholism, chronic fatigue. Usual doses are 0.3 g 3 times a day. Single dose should not be more than 3 g and maximal daily dosage is 10 g. Course duration is from few days to 2-3 months [8].

Mebicar has moderate tranquilizing effect with practically no side effects. It is structurally similar to metabolites of the organism, thus mebicar can normalize stress-induced metabolic processes [9].

However more recent experiments showed that mebicar has more influence on cateholaminergic system. Mebicar unites the effects of dopamine positive effects and agonist-antagonist properties of adrenergic system. These properties of mebicar provide its normalizing effects in fear, anxiety, emotional tension and simultaneously activating of neurophysiologic functions in asthenic-neurotic syndrome. Mebicar has also antioxidant effects, by decreasing superoxide radicals, concentration of malondialdehyde *in vitro*. Receptor studies reveal that mebicar might be agonist of GABA-A receptors on post-synaptic or pre-synaptic membrane, and the binding site is different than that of benzodiazepines [9]. Mechanism of action of mebicar probably is due to action on endogenous nonspecific systems of integration, regulation, adaptation of the body, whose influence extends from the highest mental to the cellular level [7].

2.5.4. OVERVIEW OF EFFICACY

Adaptol® is a tranquilizator with wide spectrum of anxiolytic activity. Great role of the functioning of Adaptol® is its nootropic properties. Adaptol® has a wide spectrum of clinical effects, including tranquilizing, nootropic, anti-depressant, bio correcting, adaptogenic, hypolipidemic and antianginal [6].

Therapeutic indications and dosing schedule

Adaptol® is used in the treatment of neurotic states, connected with increased excitement, emotional labiality, anxiety and fear. Adaptol® can be used in combinations with neuroleptics and tranquilizers in order to reduce or prevent their somato-vegetative and neurologic side effects. Adaptol® is effectively used to treat cardialgias [2; 4; 58].

2.5.4.1. Cardiovascular disorders

Adaptol® has showed beneficial effects in many clinical studies of cardiovascular pathologies.

In patients with cardio-vascular disorders Adaptol® reduces anxiety, cardialgy, improves physical performance, normalizes arterial blood pressure and coronary blood flow, reduces some of the arrhythmias, normalizes the ability of myocardium to contract, systolic blood flow, increases blood supply with oxygen, reduces platelet aggregation, normalizes vascular flow, lipid content and blood electrolyte balance [1]. In previous studies Adaptol® normalized cardiac blood flow in patients with climacteric myocardiodystrophy [10].

Adaptol® in previous studies was useful in the treatment of angina pectoris and other cardiovascular pathologies [11]. Anti-anginal properties of Adaptol® allowed it to be prescribed to treat ischemic heart disease. Preferable forms of administration of Adaptol® are tablets or liquids for injections, so that tablet contains 0.3 g of the active principle and 10% solution for injections [5]. In clinical trials in ischemic heart disease patients Adaptol® increased by 74% muscular blood flow, improved microcirculation and decreased intravascular erythrocyte aggregation [12]. Adaptol® in other study of patients with ischemic heart disease was given at daily dose of 1.8-3.6 g for 3-4 weeks. The drug stopped stenocardia degree I attacks, improved also mood and sleep, in patients with more sever stenocardias (degree II and III) the effects were less pronounced [2; 5]. Adaptol® also increased threshold power (by 43-55%), total scope of work (by 73-90%) and time of work

(by 39-67%) in veloergometry test. Besides, on the 2nd-5th day Adaptol® decreased pressure in patients with hypertension [2]. In ischemic heart disease patients Adaptol® also reduced total cholesterol in blood serum (till 6.37 mmol/l), increased potassium level in erythrocytes [2], and corrected impairments in repolarization processes [10]. Thus Adaptol® is effective in the treatment of ischemic heart disease at initial stages.

In ischemic heart disease patients (n=56) in complex with basic therapy patients received Adaptol® at dose of 500 mg/ 3 times a day for 2 months. Adaptol® decreased the number of angina pectoris attacks. Adaptol® reduced by 65.4% extrasystolic arrhythmias. Adaptol® effectively abolished anxiety disorders. There were no significant differences in control group and Adaptol® group in functional activity of platelets. Adaptol® showed positive effect on oxidant and antioxidant systems, decreasing free radicals and increasing antioxidants, thus normalizing cell metabolic processes [13].

Adaptol® was showed also to normalize electrolyte blood balance. Adaptol® at dose 0.5-1.0 g / 3 times a day normalized shifted potassium and sodium levels in patients with neuroses, having no effect on healthy control volunteers [14].

However, Adaptol® had no effect on extrasystoles [10].

Since Adaptol® has tranquilizing and mild analgetic properties, it can be used to treat different cardailgias. Adaptol® administered at dose of 0.9-1.2 g/day abolished heart pains after 2-4 weeks, even on 2nd and 3rd day patients became calmer, their mood improved, tension and fear disappeared [15]. In patients with cardiovascular diseases Adaptol® after 1 month treatment decreased activity of sympathetic and increased the activity of parasympathetic autonomic nervous system. Adaptol® was given at dose of 300 mg/ 3 times a day. Adaptol® decreased anxiety, fear, emotional tension, improved sleep and decreased cardialgias [16].

Intramuscular injections of Adaptol® (at 0.6-10.0 g) alone or together with fentanyl in cardiac infarction patients significantly reduced heart pain [17]. Fentanyl had stronger, but shorter analgesia. Adaptol® also reduced excitement, anxiety and fear in these patients. Besides, Adaptol® did not change vegetovascular reactions, arterial pressure, heart rate or respiratory rate in cardiac infarction patients [17].

In patients with hypertonic disease Adaptol® normalized (decreased) arterial pressure, increased number of erythrocytes, hemoglobin, leucocytes and potassium in erythrocytes. No side effects were noted, as well as any contraindications [5].

60 patients with essential arterial hypertension stage I received Adaptol® at 500 mg/ two times a day together with enalapril or placebo. Adaptol® showed good tolerability, with no side effects. Adaptol® provided additional antihypertensive effects, by lowering average daily blood pressure by 6.4%. The antihypertensive effect of Adaptol® was due to its reducing effects on vegetative disorders. This allowed suggesting Adaptol® as an effective drug in the complex treatment of hypertension [18].

The effects of Adaptol® were studied in early post-infarction period of 61 patients with anxiety disorders. Adaptol® was given in complex therapy for 1 month at the dose of 1000-1500 mg/ daily. Adaptol® showed high anxiotlytic activity, normalization of vegetative functions, reduction of sleep disorders and psychological stress, and reduction of asthenia in patients with anxiety disorders in early post-infarction period. Besides, Adaptol® was well tolerated and safe drug [19].

70 patients with post-infarction cardiosclerosis received Adaptol® at the doses of 500 mg/ twice a day for 30 days. Adaptol® reduced anxiety, inner tension, excitement, emotional tension, improved sleep and increased work ability. Adaptol® increased the indices of physical functioning, bodily pain, general health, emotional role functioning and mental health. Adaptol® reduced the number of angina pectoris, showing anti-anginal effect. Adaptol® increased tolerability to physical load. Adaptol® also positively influenced the blood pressure, lipid spectrum and antioxidant activity. Thus Adaptol® in post-infarction cardiosclerosis patients improves no only psychosomatic disorders, but also decreases incidence of angina pectoris, increases tolerability to physical load and improves metabolic profile [20].

70 patients (40-65 years) with chronic cerebral ischemia received either Adaptol® at dose 500 mg/ twice a day for 14 days or placebo. After treatment, Adaptol® significantly reduced fatigue, improved working abilities and sleep disorders, decreased headache and dizziness, improved memory, decreased anxiety and excitement. No side effects of Adaptol® were detected [21].

77 patients with high cardiovascular risk, which had ischemic heart disease, and hypertension, had complex therapy. 42 patients were given Adaptol® at dose of 500 mg/ twice a day for 2 months. Adaptol® in complex therapy significantly decreased syndrome of vegetative dystonia, depressive disorders and anxiety in petients with cardiovascular complications. Besides, Adaptol® did not change any biochemical markers in blood of the

patients, thus showing no toxic or harmful effects. This suggests effective combination of Adaptol® with cardiovascular drugs in patients with high cardiovascular risk [22].

2.5.4.2. Alcoholic patients

Adaptol® in previous studies has revealed anti-alcoholism properties even better than benzodiazepines.

In ten chronic alcoholic patients Adaptol® was given orally at dose 0.3 g. Already in the first days of treatment with Adaptol®, patients had beneficial effects. Adaptol® in comparison to benzodiazepines did not inhibit fast sleep. In these alcoholic patients Adaptol® normalized bioelectric activity of the brain. It was concluded that integral clinic-pharmacokietic parameter, that is the amount of Adaptol® in plasma during the tranquilizing effect after one dose, can be used to calculate the effective Adaptol® concentration for complex treatment. Individual dosage regime provides effective treatment of psycho-pathologic disorders in chronic alcoholics. Electrophysiological examination could adequately evaluate the condition of the patients during psychotropic therapy [23].

Adaptol® had beneficial effects in the treatment of alcohol withdrawal syndrome; it also removed borderline neuropsychic disorders in chronic alcoholism and reduced or removed attraction to alcohol [2; 24]. For mild alcohol-induced disorders Adaptol® was used at dose 1.8-2.1 g/ day as two administrations. At later stage Adaptol® was used at dose 2.4-3.6 g/ day as two administrations. After 3-5 days of Adaptol® administration alcoholic patients had reduced excitability, inner tension and irritability and normalized behavior. After 6-8 days Adaptol® also improved sleep quality of alcoholics [2; 24]. In more severe phases of alcoholism Adaptol® sole administration did not show effect, however it was combined with azaphenum. Adaptol® in complex therapy was administered at doses of 1.8-3.0 g/day as two administrations. In 3-5 days due to complex therapy anxiety and irritability reduced, after 6-10 days patients became more cheerful, increased their activity and vitality and reduced sleep disturbances [2].

Diazepam in combination with azaphenum acted quicker than Adaptol®, however it caused flaccidity, daytime sleepiness and decreased work capacity. Adaptol® instead removed flaccidity even at the most severe form of alcoholism. Moreover, in the long time treatment of alcoholism (up to 3 months), Adaptol® does not cause addiction. Diazepam does cause one [2].

Adaptol® in previous studies increased the low level of endogenous alcohol more than other tranquilizers, in alcoholics Adaptol® at 1.5 g single dose was showed to enter the blood stream much slower and removed quicker than in healthy volunteers [24]. Adaptol® concentration positively correlated with clinical efficiency of the alcoholism therapy, in electroencephalogram alpha-index value increased from 34% till 47% due to Adaptol® therapy, indicating synchronization of electrobiological brain activity. Adaptol® normalized also the sleep structure of alcoholics and did not inhibit at the same time the fast sleep phase [24]. Concentration of Adaptol® in blood of alcoholic patients after reaching therapeutic effect of the drug was 3-15 mg/ml [24].

2.5.4.3. Psychiatric disorders

Since Adaptol® exerts anxiolytic and tranquilizing effects, it has widely used in the treatment of different psychiatric disorders. In stress situations Adaptol® increases psychic stability and physical endurance. Adaptol® does not cause emotional indifference, in contrary to other tranquilizers [4].

Adaptol® can be used in neuroses and neurotic states with compulsive thoughts for mental insanity patients [2]. Within 2-3 days patients became calmer, anxiety and hypochondria lessened, compulsive thoughts were less acute, Adaptol® improved patient's mood. Although Adaptol® decreased anxiety states; however, it had no effect on depressed mood, guilt and self-humiliation [2; 26]. Previous studies show also that Adaptol® had no effect on neuroses without apparent anxiety, such as hysteric neurosis, pseudoneurotic schizophrenia, neurotic hypochondria and neurotic psychasthenia [2; 26].

Adaptol® was given in patients with psychotic disorders orally at 0.3-1.0 g / 3 times a day or intramuscularly as 10% solution (3-6 ml). Adaptol® was given for 10 days – 1.5 months, it improved patients' mood, reduced motor activity, normalized behaviour, reduced anxiety, fear and agitation. However, Adaptol® had no effects on patients with intensive catatonic, maniacal and epileptic excitation [27].

There were examined eczema patients from psycho emotional aspect. Additional therapy with Adaptol® improved the psycho emotional state of eczema patients, increased tolerability of nervous system and normalized social-psychological rehabilitation [28].

Adaptol® exerted tranquilizing action in patients with neuroses. Even after 2-3 days of treatment, patients became calmer, with less compulsive thoughts, their attention of concentration increased, and mood became more cheerful. Adaptol® does not cause myorelaxation, sleepiness ad flaccidity, and does not interact with intellectual and physical working abilities of everyday life. Therefore it is called the day tranquilizer, it is suitable also for elderly patients. Adaptol® restores disturbed emotions to normal state, but does not change normal state [4].

In 48 patients with duodenal ulcer and signs of psycho-emotional and vegetative dysfunction Adaptol® was given at doses 500 mg/ 2 times a day together with basic therapy. Results showed that Adaptol® significantly reduced anxiety and perplexity, as well as aggressive behaviour [29].

The effects of Adaptol® were assessed in 32 patients (25-45 years) with burn-out syndrome, characterized as neuro-asthenic and psycho-vegetative symptoms. Adaptol® was administered at dose of 1500 mg/ day for 60 days. After the therapy course Adaptol® significantly reduced asthenia, fatigue, anxiety, electroencephalogram results showed also normalization of brain functional activity in these patients [30].

72 patients (18-45 years) with headache of tension received Adaptol® at 1500 mg/ day for 30 days, other group received alprazolam at dose of 0.75 mg/ day. Adaptol® significantly reduced asthenia, increased activity, reduced fatigue and intensity of headache, as well as reduced anxiety. Alprazolam significantly reduced only intensity of headache and anxiety. This allows suggesting Adaptol® as effective in the treatment of headache of tension [31].

68 patients (16-65 years) with gastrointestinal tract disorders and vegetative dysfunctions received Adaptol® at dose 1000 mg / day for 4 weeks. Adaptol® showed high clinical efficacy, by normalizing vegetative system and reducing anxiety. Besides, Adaptol® showed no side effects [32].

38 patients with syndrome of irritated guts had also psycho-neurologic and vegetative complains. Patients had a complex therapy, Adaptol® was included at dose of 500 mg/ 2 times a day for 10 days. Complex therapy with Adaptol® significantly reduced sensation of discomfort, diarea, and symptoms of visceral hypersensitivity. Adaptol® did not cause any significant side effects, in first days in 6 patients increased abdominal pain and meteorism, which disappeared themselves. For more pronounced effects in these patients, Adaptol® has to be administered at higher dose for longer period of time [33].

2.5.4.4. Schizophrenic patients

Positive influence of Adaptol® on schizophrenia patients has been showed in monotherapy, as well as in combination with neuroleptrics.

In paranoid schizophrenia patients Adaptol® at dose 0.6-1.2 g/ 3 times a day after 7-12 day treatment diminished paralogicality, arguing, incoherence of thinking in 54% of patients [34].

Adaptol® is effectively combined with neuroleptics, since it does not change their neuroleptic properties, but reduces their side effects [2]. In patients with paranoid schizophrenia Adaptol® at 1.8-3.6 g/day after 5-7 days reduced neuroleptic-caused sleep disturbances, stupefaction, extrapyramidal tremor, tachycardia, thirst, urinary difficulties and hyperkinetic disorders [35]. Adaptol® treatment in these patients decreased thinking

disturbances, improved working capacity, especially in more severe cases, and normalized attention. The effects of piracetam and Adaptol® were different in cognition disturbances. Adaptol® changed right-hemisphere thinking to the left one, while piracetam increased right-hemisphere thinking [34].

Due to mild tranquilizing activity and nootropic action, Adaptol® can significantly reduce neuroleptic-induced side effects, such as dysarthria, coordination, motor-speed and vegetative disorders, sleep disorders, especially for elderly patients. Piracetam did not show these effects, however it reduced headaches [35].

2.5.4.5. Nootropic effects

The nootropic properties of Adaptol® were characterized as increase in attention, memory and intellectual capacity, when Adaptol® was given at dose 0.6-0.9 g / 3 times a day for two weeks [35]. Adaptol® probably accelerated the identification and decision-making processes, thus it improved patients' behavior order and rationality, ability and labor adaptation and rehabilitation, as well as normalized normal level of thinking in mentally tired persons [34]. However, Adaptol® had no effect on healthy control volunteers [35]. Besides, Adaptol® changed thinking from right-brain, responsible for emotions, pictures, concreteness, to left-brain, responsible for verbal, abstract and logic functions; however piracetam intensified only the right-brain thinking abilities [4; 35].

Adaptol® as a nootropic agent improved logical thinking, consistency, rate of thinking, attention and mental work capacity without simultaneous stimulation of delirium and pathologic emotional activity. Adaptol® also recovered normal level of thinking in healthy but mentally tired persons [4].

2.5.4.6. Combination with BZDs

Another important effect of Adaptol® is that it can reduce the benzodiazepine-induced side effects, not reducing their therapeutic properties.

Adaptol® at dose of 0.6 g/ 3 times a day reduced the benzodiazepine-induced myorelaxation, impairment of coordination functions and slow-down of psychic processes. Therefore Adaptol® can be effectively used together with benzodiazepines, especially for elderly and somatically weak patients [35].

The difference between benzodiazepine tranquilizers and Adaptol® is that diazepam, in contrast to Adaptol®, activates positive emotions and Adaptol® inhibits negative emotions without the effect on positive ones [35].

2.5.4.7. Climacteric disorders

Adaptol® was found to be effective in the treatment of climacteric neuro-psychic disorders for women [2; 38]. Adaptol® showed efficacy in 78% patients, especially primary patients. Adaptol® reduced hot flushes, restored work capacity and ameliorated mood, also reduced cerebral vascular supertension and eliminated cerebral vascular functional asymmetry [38]. Adaptol® effectively relieved hot flushes, headaches, vertigo, anxiety, neurasthenia in patients with climacteric myocardiodystrophy [10].

In 73 women patients with climacteric disorders Adaptol® was given at doses 300-500 mg / 3 times a day for 6 months. Adaptol® decreased headaches, improved sleep quality, decreased emotional tension and anxiety, as well as improved mood. However, these positive effects reduced with cessation of use of Adaptol®. Adaptol® decreased severity of climacteric disorders, mostly the mild ones. Thus Adaptol® decreases climacteric disorders, depression and anxiety in perimenopausal women [39].

Pre-menstrual psychosomatic syndrome, characterized by neuro-psychic, endocrine disorders, is usually treated with benzodiazepines, however they have several unwilling side effects, e.g. sleepiness, ataxia, myorelaxation, and decrease of physical and mental work ability. Adaptol® has vegetative system stabilizing effect, it was administered in 28 women with pre-menstrual syndrome at doses 0.3-0.6 g/ 3 times a day for 15-20 days. 83-100% of patients after Adaptol® therapy had decreased head aching, vertigo, fatigue, weakness, sleep disorders. Positive effect of Adaptol® started already on day 3-5 after beginning of treatment. After the Adaptol® therapy course neuronal-psychic disorders were abolished in 89.3% of patients [47].

2.5.4.8. Psychiatric disturbances in children

In 62 children with neurasthenia (age of 7-14) Adaptol® was administered at 1000 mg/ day for 30 days. Other group received pantogam at 0.75-1.0 g/ day for 30 days. Results showed that Adaptol® and pantogam both reduced asthenia, however the effects of Adaptol® were more significant. Besides, Adaptol® also significantly reduced fatigue and headache,

and anxiety. Thus Adaptol® is highly effective in the treatment of neurasthenia in children [42].

32 children (10-14 years) with school maladaptation, having general anxiety disorders, received Adaptol® at the dose of 1000 mg/ day for 30 days. Adaptol® significantly reduced reactive anxiety in these children. Adaptol® also reduced other signs of anxiety disorders, such as fear, headache, fatigue, Adaptol® reduced also sleep disorders. 2 children (6.3%) faced with temporal sleepiness [43].

60 children (10-14 years) with attention deficit and hyperactivity disorders (ADHD) received either Adaptol® at the dose of 500 mg/ twice a day or piracetam at 1.2 g. day for one month. Adaptol® had temporal side effects in 2 children, 1 patient had hyperactivity and other had day sleepiness, however these side effects disappeared after finishing therapy. Adaptol® significantly reduced hyperactivity and impulsiveness; however piracetam more effectively increased attention. Adaptol® also reduced reactive anxiety [44].

30 children patients (age of 10-15) with motor tick hyperkinesia received Adaptol® at doses 1000 mg/ day for 30 days. Other 30 patients received pantokalcin at 0.75-1.0 g/day. Adaptol® treatment reduced tick hyperkinesia in 70% of patients. 2 patients had insignificant increase in tick hyperkinesia. Adaptol® also reduced anxiety in 73.7 % patients. Pantokalcin had less expressed effects (only in 50% of patients reduced tick hyperkinesia). Thus Adaptol® is effective in the treatment of tick hyperkinesia in children [45].

Adaptol® was used in different pathologies in children psychiatry. Adaptol® was administered at 100-300 mg/ 2-3 times a day for 3 months in 7 neurotic children with organic insufficiency of brain tissue. Adaptol® showed positive effects, decreases walking and talking in the sleep, improved the symptoms [46]. In 5 children with addiction to narcotics (12-14 years old) Adaptol® was given at 300-600 mg/ 2-3 times a day for 3-4 weeks. Adaptol® effectively abolished aggressive behavior and excitement and anxiety. Adaptol® was used effectively also in complex therapy in neuroleptic syndrome in children. Since Adaptol® is a mild day tranquilizer with no or minimal side effects, little toxic and causes no addiction, its use in many cases of children psychiatry would be effective [46].

2.5.4.9. Other uses

Analgesic effects

Adaptol® showed also analgetic effects. In dental clinic Adaptol® at 0.3 g/ 2 times increased the pain threshold by 40-50% and pain tolerance threshold by 70-90 %. Adaptol® did not intensify the effects of amidopyrine and analgin, however it significantly increased the pain-relieving effect of lidocaine paste. Maximal effect of Adaptol® was obtained in 30-60 minutes after administration and lasted for 7 hours [2; 36]. The analgesic effect of Adaptol® on cardialgias, described above, is also relevant.

Effects of Adaptol® on shock

Adaptol® has revealed anti-shock action. Adaptol® (intramuscular 10-20 ml of 10% solution (or 2 x 0.3 g pills)) added to anti-shock treatment normalized quicker gas composition and acid-base state and improved clinical symptoms [2; 37]. Thus Adaptol® is non-specific anti-shock compound.

Effects of Adaptol® in craniocerebral injury

Adaptol® showed beneficial effects in the treatment of patients of medium neuro-vegetative paroxysms after closed craniocerebral injury. Adaptol® at 0.9-1.2 g/day within 10-14 days lessened paroxysms, headache and psychosensory disorders and normalized 17-oxycorticosteroide and 17-ketosteroide levels in 60% of patients. Thus Adaptol® reduced intensity of symptoms of craniocerebral injury and promoted quicker recovery [2; 37].

Effects of Adaptol® in hyperlipidemias

Adaptol® was given in 21 patients with hypercholisteronemia at dose 1.2 g /day for 21 days. On day 14 Adaptol® significantly decreased total cholesterol in plasma by 28%, LDL by 21% and increased HDL by 32%. Experimental data with Adaptol® and diazepam allowed to prove that the anti-hyperlipidemic effect of Adaptol® is not due to psychotropic activity, but due to specific action on lipid level. Thus Adaptol® can be effectively used in complex therapy of dyslipidemias [40].

Effects of Adaptol® on radiation-caused disturbances

Adaptol®, in 21 patients with delayed consequences after radiation, was administrated for two weeks. The doses of Adaptol® were – 300 mg/ first day, 600 mg/ 2nd-3rd days and 900 mg/ for rest of the time. Adaptol® after the end of the therapy course significantly reduced insomnia, fatigue, anxiety, normalized heart rhythm and arterial blood pressure, reduced head ache and cardialgias [41].

2.5.4.10. Dosage and administration

Doses

Adults use 300-500 mg 2-3 times a day. The highest single dose is 3 g, the highest daily dose - 10 g.

The course of treatment - from a few days up to 2-3 months.

Complex therapy to decrease inclination for smoking – 600-1000 mg a day for 5-6 weeks.

Elderly should not adjust the dose.

Patients with liver failure should not diminish the dose.

Dose adjustment is not studied in patients with kidneys failure. These patients should use the medicines with caution.

Paediatric population

The safety and efficacy of Adaptol in children aged to 18 years have not been established yet.

Administration

The medicine is administered orally independently of food intake.

2.5.5. OVERVIEW OF SAFETY

2.5.5.1. Adverse reactions

Adaptol® in patients in psychoneurologic dispensary caused no changes in their somatic state, general clinical and biochemical blood and urine analyses [26].

Side effects of Adaptol® are rare. In high doses Adaptol® can cause allergic reactions (such as skin itch) and dyspeptic disorders, which disappear with the cessation of treatment. No addiction or withdrawal syndrome is found with the use of Adaptol®, as well as no contraindications were found [2; 4].

One of the positive actions of Adaptol® is also that it does not cause myorelaxation, therefore it did not affect patients' physical and intellectual work capacity [26]. Intellectual work capacity even increased after 2-3 week administration of Adaptol® [26]. There was a slight tendency of decreased arterial pressure in 50% of patients in first 5-6 days of administration of Adaptol®, it also caused small infrequency of pulse [26]. Patients taking Adaptol® had no slackness, fatigue or flaccidity apart from diazepam, however Adaptol® caused sense of heaviness in head in one patient [26].

Adaptol® increases physic stability and physical endurance, especially in stressful situations [2].

The following adverse reactions have been reported in adults:

- skin itch,
- dyspeptic disorders,
- slight decrease of arterial blood pressure,
- heaviness in head.

The following adverse reactions have been reported in the children:

- hyperactivity,
- sleepiness.

2.5.5.2. Cautions

No special precautions with the use of mebicar have been noted.

2.5.5.3. Contraindications

Increased individual sensitivity to the drug is said to be the only contraindication of the drug.

2.5.5.4. Pregnancy and breast-feeding

Mebicar distributes in unchanged state in all tissues and fluids. There is not enough experience in use of the drug; therefore it is not suggested to use mebicar during pregnancy and lactation period.

2.5.5.5. Overdose

Mebicar is not toxic compound. In previous studies even extremely high dose of mebicar in humans (100 pills or 30 grams) did not cause any toxic effects. In case of overdosage general detoxification methods have to be used.

Mebicar is very specific in action and no particular problems are expected following overdosage with mebicar formulations.

According to expert point of view information and cited literature data shown in this conclusion are sufficient to evaluate effectiveness and safety of Adaptol as peroral form of 500 mg tablets, produced by joint stock company “Olainfarm”.

2.5.6. BENEFITS AND RISKS CONCLUSIONS

Mebicar as a sedative and tranquilizer (anxiolytic and nootropic agent) has a long history of effective and safe clinical usage within more than three decades in many East Europe countries. The nonclinical and clinical investigations of mebicar were performed in the former USSR and the results were documented in relevant scientific publications and symposia reports. Mebicar is an anxiolytic agent with nootropic properties indicated for the treatment of anxiety, sleep disturbances, neurotic disorders, cardiovascular disorders, pre-menstrual or climacteric syndrome and alcoholism.

It was found that mebicar is superior to other tranquilizers (diazepam and phenazepam) not only to incomparably lower toxicity, but also due to absence of distressing effects such as muscular relaxation, flaccidity and sleepiness. Very important characteristics of mebicar are its harmlessness, safety, absence of potential addiction.

Mebicar tablet formulation were developed for treating anxiety in Russia as Mebicar 300 mg tablets and Mebicar 500 mg tablets by N.D. Zelinsky Institute of Organic Chemistry of the Russian Academy of Sciences and N.A. Semashko Moscow Medical Stomatology Institute. JSC Olainfarm was the first manufacturer of this product since 1978. Since 2003 JSC Olainfarm has manufactured mebicar products with trade name Adaptol.

There are many countries of Eastern Europe, Kosovo, Mongolia and Albania where Adaptol has gained marketing authorisation and has been successfully used in ambulatory practice in treatment of neuroses, psychotic disorders and anxiety. It also can improve tolerance to neuroleptics and benzodiazepines, relieve alcohol withdrawal symptoms.

During the long period of clinical practice Adaptol products have not been withdrawn, nor have restrictions been placed on their use. No severe adverse reactions associated with mebicar use have been reported. In rare cases mebicar can cause allergic reactions, dyspeptic disorders, hypotension, hyperactivity and sleepiness. However, these side effects are not severe and are complete reversible after stopping taking medicine.

Extensive clinical experience with mebicar is considered to have demonstrated the therapeutic value of the compound. Expert is of the opinion that Adaptol 500 mg tablets benefit-risk ratio is positive.

It is also important to note that the capsulated form of mebicar Adaptol 300 mg hard capsules is already authorised in Albania in 09 May 2012 (Reg.No. 6584).

On the basis of a considerable amount of published scientific clinical and medical evidences, also post-marketing data it is concluded that *ADAPTOL 500 mg tablets* produces the claimed pharmacological properties and it can safely administered within the therapeutic indications given, therefore the expert endorses the application for marketing authorisation in category of well-established use.

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Literature references

1. Zimakova IE, Karpov LM, Tagirova TS and al. 1995. **Variety analysis of tranquilizer Mebicar effects in experimental and clinical medicine.** *Kazan Medical Journal. Clinical and Theoretical Medicine* 76(2): 85-87.

2. Zaikonnikova VI, Zimakova IE, Lebedev OV, Khmelnitskiy LI. **Mebicar.** *Practioner's handbook, Soyuzpharmatsiya all-soviet centre for scientific and pharmaceutical information. 30 pages.*

3. **Mebicar**, ChemIDplus Lite, NML. *http://chem.sis.nlm.nih.gov/chemidplus/*

4. **Mebicar – day tranquilizer.** 1990. *Kazan S.V.Kurashov Medical institute, N.D.Zelinskiy institute of organic chemistry.*

5. Zimakova IE, Valimukhametova DA, Zaikonnikova IV et al. 1986. **Antianginal medicated compound**. US 4,571,403.

6. Zimakova IE, Gumerov RH, Karpov AM, Zimakov AY, Galliulina TN. 2000. **Unique combination of therapeutic effects of day tranquilizer Mebicar.** *Terra Medica Nova*, 4. (Summary).

7. Demenkov AN. 1989. **Application of mebicar in clinical practice** (Guidelines). 10 pages.

8. Burchinskiy S.G. **Pharmacotherapeutic aspects of Adaptol.** Gerontology Institute of the Ukraine Akademy of Medical Sciences,Kiev. *http://www.olainfarm.ru/pages/texts/s_adaptol.html*

9. Gromov L, Dudko E. 2003. **"Typical" and "atypical" tranquilizers Bulletin of pharmacology and pharmacy,** *Modern Approaches to the Therapy of Internal Diseases;* No.10: 7-12.

10. Zamotaev IP, Mkrtchyan VR, Venediktova MG. 1987. **Mebicar treatment of climacteric myocardiodystrophy.** *Soviet Medicine*, 8: 57-80.

11. Zimakova IE, Valimuchametova DA, Zaikonnikova IV et al. 1987. **Pharmazautishe Verwendung von 2,4,6,8-Tetramethyl-2,4,6,8-tetraazobicyclo-[3.3.0]-oktandion-3,7**. DE 3306128.

12. *Zaikonnikova VI, Zimakova IE, Lebedev OV, Khmelnitskiy LI.* **Mebicar. Effect on heart and cardiovascular system. Effect on blood supply to heart and tissues. (17p).** Practioner's handbook**,** Soyuzpharmatsiya all-soviet centre for scientific and pharmaceutical information. 30 pages.

13. Volkov VI, Strona VI, Ladny AI. **Role of anxiolytics in complex therapy of patients with coronary artery disease.** *Problems of Current Medical Science and Education*, No. 3, 2009; 20-23.

14. *Zaikonnikova VI, Zimakova IE, Lebedev OV, Khmelnitskiy LI.* **Mebicar. Effect on Electrolyte Balance (17p).** *Practioner's handbook, Soyuzpharmatsiya all-soviet centre for scientific and pharmaceutical information.* 30 pages.

15. *Zaikonnikova VI, Zimakova IE, Lebedev OV, Khmelnitskiy LI.* **Mebicar. Effect on Cardialgias (17p).** Practioner's handbook**,** Soyuzpharmatsiya all-soviet centre for scientific and pharmaceutical information. 30 pages.

16. Kovalenko VN, Nesukay EG, Dmitrichenko EV. 2006. **Heart rate variability as a parameter of function of autonomic nervous system in patients with cardiovascular diseases.** *Ukrainian cardiological journal,* 3: 68-71.

17. *Zaikonnikova VI, Zimakova IE, Lebedev OV, Khmelnitskiy LI.* **Mebicar. Application for cardiac infarction (19-20p).** Practioner's handbook**,** Soyuzpharmatsiya all-soviet centre for scientific and pharmaceutical information. 30 pages.

18. Amosova EN, Konopleva LF, Andreyev EV, Mischenyuk OY. 2010. **Treatment of "soft" arterial hypertension: not only anti-hypertensives.** *Ukrainskiy Terapevtichniy Zhurnal*, 1: 139-142.

19. Statsenko ME, Sporova OE, Kolodyazhnaya OI, Evtereva ED. 2009. **Efficacy of adaptol in complex therapy of anxiety disorders in early postoperative period.** *Kardiol serdecno-sosud hir*, 5: 18-22.

20. Lapshina LA, Kravchuk PG, Shevchenko OS. 2008. **Adaptol correction of psychopathological manifestations and oxidative stress in patients after myocardial infarction.** *Medical practice*, 1(61): 23-30.

21. Mokina TV, Antipenko EA, Gustov AV. 2009. **Administration of Adaptol in treatment of asthenic syndrome in patients with dyscirculatory encephalopathy.** *Zh Nevrol Psichiatr Im Korsakova,* 109(6): 76-77.

22. Girina ON,Skarzhevskaya NA, 2010. **The use of adaptol day tranquilizer in the complex therapy of patients with high cardiovascular risk: adequacy, efficacy and safety.** *Ukrainian Therapeutic Journal*, 1: 125-128.

23. Treskov VG, Berliand AS, Serov NV, Sidorov AA, Knizhnik AZ. 1985. **Clinical pharmacokinetics of Mebikar. Assessment of individual dosage regimes.** *Farmakol Toksikol* 48(1): 46-48.

24. *Zaikonnikova VI, Zimakova IE, Lebedev OV, Khmelnitskiy LI.* **Mebicar. Antialcololic action (13-15p).** Practioner's handbook**,** Soyuzpharmatsiya all-soviet centre for scientific and pharmaceutical information. 30 pages.

25. *Zaikonnikova VI, Zimakova IE, Lebedev OV, Khmelnitskiy LI.* **Mebicar. Penetration thtough Hematoencephalic Barrier. Distribution in the Body and Excretion (11-13p).** Practioner's handbook**,** Soyuzpharmatsiya all-soviet centre for scientific and pharmaceutical information. 30 pages.

26. *Zaikonnikova VI, Zimakova IE, Lebedev OV, Khmelnitskiy LI.* **Mebicar. Psyhotropic Action. Tranquilizing Action (5-6 p).** Practioner's handbook**,** Soyuzpharmatsiya all-soviet centre for scientific and pharmaceutical information. 30 pages.

27. Novikov SS, Khmelnitsky LI, Lebedev OV et al., 1977**. 2,4,6,8-Tetra-methyl-2,4,6,8-tetraazabicyclo-[3.3.0]-octanedi-3,7-one in treating psychic disorders.** US 4,004,013.

28. Kovaleva LN, Khrushch VI. 2006. **Pecularities of the personal psychological status among patients with eczema and atopic dermatitis in southern region of Ukraine.** *Ukrainian journal of dermatology, venereology, cosmetology,*2:13-17.

29. Nykula TD, Moyseyenko VO, Manzhalii EH. 2007. **Heart rate variability in peptic ulcer patients and opportunity of vegetative dysfunction correction with Adaptol.** *Modern Gastroenterology*, 5(37): 89-91.

30. Chutko LS, Surushkina SYu, Nikishena IS, Yakovenko EA, Rozhkova AV, Anisimova TI. 2010. **Clinical and neuropharmacological study of the efficacy of adaptol in the treatment of emotional burn-out.** *Zh Nevrol Psichiatr Im Korsakova,* 110(10): 30-33.

31. Chutko LS, Surushkina SYu, Nikishena IS, Yakovenko EA, Kuzovenkova MP, Anisimova TI, Rozhkova AV, Sergeev AV. 2010. **Headaches of tension: clinical-psychological variants and perspectives of therapy.** *Zh Nevrol Psichiatr Im Korsakova*, 110(4): 53-56.

32. Skrypnik IN, Nevoit AV, Beruk OV. 2007. **The evaluation of Adaptol efficiency in the complex therapy for patients with digestive organs diseases in combination with somatoform vegetative dysfunction.** *Вистник проблем биологии и медицини*, 4: 151-154.

33. Vdovichenko V.I, Bodrevych B.B**. Effectiveness of Treatment of Irritable Bowel Syndrome Patients with Using Adaptol.** *Unpublished data*.

34. Zimakova IE, Makarchikov NS, Karpov AM. 1986**. Evaluation of the nootropic effect of mebicar in clinical practice.** *Farmakol Toksikol*, 49(5): 50-53.

35. *Zaikonnikova VI, Zimakova IE, Lebedev OV, Khmelnitskiy LI.* **Mebicar. Nootropic Action. (8-10p).** Practioner's handbook**,** Soyuzpharmatsiya all-soviet centre for scientific and pharmaceutical information. 30 pages.

36. Zorian EV, Larentsova LI, Sharagin NV. 1984. **The comparison of tranquillizer effects in the experiment and in the clinical practice.** Report in All-USSR Conference: Mebicar and its use in medicine. Moscow.

37. *Zaikonnikova VI, Zimakova IE, Lebedev OV, Khmelnitskiy LI.* **Mebicar. Antishock action. Action on neurovegetative paroxysms after closed craniocerebral injuries (20-21p).** Practioner's handbook**,** Soyuzpharmatsiya all-soviet centre for scientific and pharmaceutical information. 30 pages.

38. Mendelevich DM, Zimakova IE, Mendelevich VD. 1983**. The administration of Mebicar tranquillizer for treatment of climacteric neuropsychic disorders.** *Obstetrics and Gynecology*, 2: 51-53.

39. Dubossarskaya YuA, Goncharenko VN. 2006. **The complex therapy of psychosomatic disorders in perimenopausal period.** *Meditsina*, 12: 56-61.

40. Zimakova I.Ye., Haziakhmetova V.N. **Mebicar Daytime Tranquilizer for Prevention of Ischemic Heart Disease.** State Medical Academy Kazan, Russia . http://www.terra-medica.spb.ru/3_2002/zimakova.htm . (Translated from Russian).

41. Kanazhevskaya Y.V, Naurysbayeva B.N,2005. **Efficacy of mebicar in patients with late effects of ionizing radiation.** *Head of the therapeutics department of the Republican Clinical Hospital for World War II disabled veterans.* Unpublished data.

42. Chutko LS, Surushkina SYu, Nikishena IS, Yakovenko EA, Anisimova TI, Kuzovenkova MP. 2010. **The asthenic disorders in children.** *Zh Nevrol Psichiatr Im Korsakova*, 110(11): 26-29.

43. Chutko LS, Surushkina SYu, Nikishena IS, Yakovenko EA, Anisimova TI, Livinskaya AM, Sidorova YuI, Kuzovenkova MP, Aitbekov KA, Mamaeva YuV. 2010. **The treatment of anxiety disorders by adaptol during the school disadaptation.** *Zh Nevrol Psichiatr Im Korsakova*, 110(2): 45-49.

44. Chutko LS, Surushkina SYu, Nikishena IS, Yakovenko EA, Anisimova TI, Sergeev AV. 2009. **The administration of adaptol in the treatment of attention deficit hyperactivity disorder in children.** *Zh Nevrol Psichiatr Im Korsakova*, 109 (8): 45-48.

45. Chutko LS, Surushkina SYu, Yakovenko EA, Nikishena IS, Anisimova TI, Livinskaya AM, Aitbekov KA. 2009. **The experience of adaptol administration during tic hyperkinesis in children.** *Zh Nevrol Psichiatr Im Korsakova*, 109(10): 65-66.

46. Saduakasova KZ. 2002. **The administration of Mebicar in the child psychiatry.** *Meditsina,* 1: 98-99.

47. Novikov SS, Khmelnitsky LI, Lebedev OV et al. 1976. **Tetra-N-alkyl derivates of bicyclic ureas and method of their production.** US 3,966,472.

48. Svinitsky A.S., Lakatosh V.P. 2003.**Using of Adaptol in treatment of premenstrual syndrome.** *ЛИКИ*, 1-2: 121-127.

49. Zimakova IE. 1977. **Pharmacological effects of the new psychotropic preparation, Mebicar.** *Farmakol Toxicol* 40(6): 684-687.