INSTRUCTION
for medical use of medicinal product
LEKPLEX®

Composition:
active ingredients: thiamine hydrochloride, pyridoxine hydrochloride, vitamin B_{12} crystalline H (cyanocobalamin);
1 mL of solution contains thiamine hydrochloride (in recalculation on 100% substance) 50 mg, pyridoxine hydrochloride (in recalculation on 100% substance) 50 mg, vitamin B_{12} crystalline H (cyanocobalamin) (in recalculation on 100% substance) 0.5 mg;
excipients: lidocaine hydrochloride, benzyl alcohol, sodium polyphosphate, potassium ferricyanide, sodium hydroxide, water for injections.

Pharmaceutical form. Solution for injections.
Basic physical and chemical properties: clear red liquid.

Pharmacotherapeutic group. Vitamin B_1 combined with vitamin B_6 and/or B_{12}.
ATC code A11D B.

Pharmacological properties.
Pharmacodynamics.
Neurotropic vitamins B have a positive effect in inflammatory and degenerative nervous and musculoskeletal disorders. They are used to correct deficiency states, and in high doses they have an analgesic effect, improve blood circulation and nervous system function and the process of haematopoiesis.
Vitamin B_1 is an essential active substance. In the body, Vitamin B_1 is phosphorylated to biologically active thiamine diphosphate (cocarboxilase) and thiamine triphosphate (TTP). Thiamine diphosphate as a coenzyme involved in essential processes of carbohydrate metabolism and in the metabolism of nervous tissue, it has influence on the conduction of nerve impulses at synapses. In vitamin B_1 deficit in tissues, metabolites, primarily lactic and pyruvic acids, accumulate leading to various nervous pathological states and disorders.
Vitamin B_6 is in its phosphorylated form (pyridoxal-5'-phosphate, PALP) is a coenzyme of several enzymes interacting in general non-oxidative amino acid metabolism. By decarboxylation they participate in the formation of physiologically active amines (epinephrine, histamine, serotonin, dopamine, tyramine) by transamination in anabolic and catabolic metabolic processes (glutamate oxaloacetate transaminase, glutamate pyruvate transaminase, gamma-aminobutyric acid, α-ketoglutarate transaminase) as well as in various processes of synthesis and cleavage of amino acids. Vitamin B_6 acts on four different stages of tryptophan metabolism. During synthesis of haemoglobin vitamin B_6 catalyzes α-amino-β-ketoadinine acid
Vitamin B_{12} is essential for cell metabolism. It has an effect on haematopoiesis (external anti-anaemia factor), and is involved in the formation of choline, methionine, creatinine, nucleic acids, and is a pain relieving agent.
Pharmacokinetics.
Following parenteral administration thiamine is distributed in the body. Approximately 1 mg of thiamine is metabolized daily. Metabolites are excreted in urine. Dephosphorilation take place in kidneys. The biological elimination half-life is 21 min. Accumulation of thiamine in the body does not occur due to weak solubility in fats.
Vitamin B_6 is phosphorylated and oxidized to pyridoxal-5'-phosphate. In plasma pyridoxal 5'-phosphate and pyridoxal are bound to albumin. Pyridoxal as the only form of transport in blood. Pyridoxal-5-phosphate bound to albumin is hydrolyzed by alkaline phosphatase to pyridoxal to pass through the cell membrane.
Following parenteral administration, Vitamin B_{12} forms transport protein complexes that are rapidly absorbed by the liver, bone marrow and other proliferative organs. Vitamin B_{12} enters the bile and takes part in the enterohepatic circulation. Vitamin B_{12} penetrates through placenta.

Clinical particulars.

Indications.

Neurological manifestations of any origin: neuritis, neuralgias, polyneuropathy (diabetic, alcoholic), radicular syndrome, optic neuritis, facial palsy.

Contraindications.

Hypersensitivity to any drug components, acute cardiac conduction abnormalities, acute decompensated heart failure.

Vitamin B_1 is contraindicated in allergic reactions.

Vitamin B_6 is contraindicated in acute gastric and duodenal ulcer (possible increased gastric juice).

Vitamin B_{12} is contraindicated in erythremia, polycythemia, thromboembolism.

Lidocaine. Increased hypersensitivity to lidocaine, other amide local anaesthetics, a history of epileptiform convulsions with lidocaine, severe bradycardia, severe hypotension, cardiogenic shock, severe chronic heart failure (II-III degree), sick sinus syndrome, Wolff-Parkinson-White syndrome, Adams-Stokes syndrome, II and III degree atrioventricular (AV) block, hypovolemia, severe hepatic/renal impairment, porphyria, myasthenia.

Interactions with other medicinal products and other forms of interaction

Thiamine is inactivated by 5-fluorouracil since the latter competitively inhibits the phosphorylation of thiamine to thiamine pyrophosphate. Loop diuretics, e.g. furosemide that inhibit tubular reabsorption may cause increased excretion of thiamine in long-term therapy and, thus, lowering of the thiamine level.

Concomitant use with levodopa is contraindicated. If taken simultaneously with levodopa, vitamin B_6 can reduce the levodopa effect. The simultaneous administration of pyridoxine antagonists (e.g. isoniazide, hydralazine, penicillamine or cycloserine), oral contraceptives may increase the vitamin B_6 requirement.

Beverages containing sulphite (e.g. wine) enhance thiamine degradation. Lidocaine potentiates inhibitory effect on the respiratory center of anaesthetics (hexobarbital, thiopental sodium intravenously), hypnotics and sedatives and weakens the cardiotonic effect of digitoxin.

Concomitant use with hypnotics and sedatives may increase inhibitory action on the central nervous system. Ethanol increases the inhibitory effect of lidocaine on respiration.

β-adrenoreceptor blocking agents (incl. propranolol, nadolol) may slow down the hepatic metabolism of lidocaine, and enhance the effects of lidocaine (incl. toxic effects) and increase the risk of bradycardia and hypotension.

Curare-like drugs may increase muscle relaxation (possible paralysis of the respiratory muscles).

Norepinephrine, mexiletine may reduce clearance of lidocaine (increased toxicity).

Izadrin and glucagon may increase clearance of lidocaine.

Cimetidine, midazolam may increase lidocaine plasma concentration. Cimetidine displaces from its association with proteins and slows inactivation of lidocaine in the liver increasing the risk of adverse effects of lidocaine. Midazolam may moderately increase lidocaine blood concentration.

Anticonvulsants, barbiturates (incl. phenobarbital) may accelerate hepatic metabolism of lidocaine and decrease blood concentration.

Antiarrhythmics (amiodarone, verapamil, quinidine, ajmaline, disopyramide), anticonvulsants (hydantoin derivatives) potentiate cardiodepressive action; concomitant use with amiodarone can lead to seizures.

Novocaine, novocainamide may excite CNS and cause hallucinations if co-administered with lidocaine.

Monoamine oxidase inhibitors, chlorpromazine, bupivacaine, amitriptyline, nortriptyline, imipramine: the combination with lidocaine may increase the risk of hypotension and prolong local anaesthetic effect of lidocaine.

Narcotic analgesics (morphine, etc.) may enhance analgesic effect of narcotic analgesics, cause respiratory depression if co-administered with lidocaine.

Prenylamine increases the risk of ventricular arrhythmias «torsade de pointes».

Propafenone may increase duration and severity of CNS adverse effects.

Rifampicin may reduce the blood concentration of lidocaine.
Polymyxin B requires respiratory function monitoring.
Procainamide may cause hallucinations.
The effect of cardiac glycosides may weaken if co-administered with lidocaine.
Digitalis glycosides: lidocaine may exacerbate the severity of AV-block in intoxication.
Vasoconstrictors (epinephrine, methoxamine, phenylephrine) reduce absorption and prolong the effects of lidocaine if co-administered with lidocaine.
Guanadrel, guanethidine, mecamylamine, trimethaphan: the risk of severe hypotension and bradycardia increases in this combination for spinal and epidural anaesthesia.
β-adrenoreceptor blocking agents may reduce the hepatic metabolism of lidocaine, enhance the effects of lidocaine (including toxic effects) and increase the risk of bradycardia and hypotension. Lidocaine dose should be reduced in co-administration of β-adrenoreceptor blocking agents and lidocaine.
Acetazolamide, thiazide and loop diuretics reduce the effect of lidocaine due to hypokalaemia if co-administered with lidocaine.
Anticoagulants (incl. ardeparin, dalteparin, danaparoid, enoxaparin, heparin, warfarin, etc.) increase the risk of bleeding if co-administered with lidocaine.
Anticonvulsants, barbiturates (phenytoin) may accelerate hepatic metabolism of lidocaine, decrease blood concentration, potentiate cardiodepressive effect if co-administered with lidocaine.
Neuromuscular-blocking drugs enhance the action of these drugs, as they reduce the conductivity of nerve impulses.

Special warnings and precautions for use.
The product should not be administered by intravenous route.
Parenteral vitamin B_{12} administration may temporarily impair the diagnosis of funicular myelosis or pernicious anaemia.
Long-term administration of vitamin B_6 (over 6-12 months) of daily dosages exceeding 50 mg or 1000 mg per day (more than two months) may cause reversible peripheral sensory neuropathy. If symptoms of peripheral sensory neuropathy (paraesthesia) occur, the dosage should be reviewed and treatment with the medicinal product discontinued, if necessary.
This medicinal product contains sodium compounds. This is to be taken into account in persons under sodium-restricted diet. Each ampoule contains traces of potassium.
Vitamin B_6 is contraindicated in patients with the history of acute gastric and duodenal ulcer with severe renal and hepatic impairment.
Patients with tumours, except cases involving megaloblastic anaemia and vitamin B_{12} deficiency should not use the drug.
The drug should not be used in severe cardiac decompensation and angina.
The product contains lidocaine; therefore the risk of local reactions (pain and swelling) increases if the injection site is treated with disinfectants containing heavy metals.
Since lidocaine has a strong antiarrhythmic action and can itself act as arrhythmogenic factor that may lead to the development of arrhythmias, and the drug should be used with caution in persons with complaints of arrhythmia in the past.
Caution and lower doses should be administered in patients with moderate heart failure, moderate hypotension, incomplete AV-block, intraventricular conduction disorders, moderate hepatic and renal disorders (creatinine clearance not less than 10 mL/min), impaired respiration, epilepsy, heart surgery, genetic predisposition to malignant hyperthermia, debilitated and elderly patients.
ECG monitoring is mandatory during lidocaine administration. The dose should be reduced/the product should be withdrawn in sinus node disorders, interval PQ prolongation, QRS complex or new arrhythmia episode.
Blood potassium level should be normalized before using lidocaine in heart diseases (hypokalaemia reduces effectiveness of lidocaine). Intramuscular administration may increase creatinine concentrations which can interfere with the diagnosis of acute myocardial infarction.

Use during pregnancy and in nursing women.
The daily requirement for vitamin B_6 during pregnancy and/or breastfeeding is up to 25 mg.

The product contains 100 mg of vitamin B_6 per ampoule, thus it shall not be used during pregnancy and/or lactation.

Effects on ability to drive and use machines.
The product does not affect the ability to drive and use machines. Patients with dizziness during drug administration should avoid driving and using machines.

Dosage and administration.
For intramuscular administration.
Sensitivity skin test to lidocaine is required before using the product; sensitivity is evidenced by swelling and redness at the injection site.
In severe (acute) cases, treatment is initiated with 2 mL intramuscularly once daily to remove acute symptoms. For further treatment 2 mL (1 injection) should be administered 2-3 times a week.
Treatment course is at least 1 month.
Intramuscular injections should be performed in the upper outer quadrant of the gluteus area.
The drugs for oral use of the similar pharmacotherapeutic group are recommended to maintain or continue a therapeutic course of injections, or to prevent recurrence.

Paediatric patients.
The product is not used in children.

Overdose.
In case of overdose side effects of the drug may increase.
Vitamin B_1 has a wide therapeutic range. Very high doses (over 10 g) cause curare-like effect suppressing the conductivity of nerve impulses.
Vitamin B_6 has a very low toxicity.
Excessive use of vitamin B_6 at doses greater than 1 g daily for several months can lead to neurotoxic effects.
Neuropathies with ataxia and sensitivity disorders, cerebral convulsions with EEG changes as well as, in individual cases, hypochromic anaemia and seborrhoeic dermatitis have been described after administration of more than 2 g daily.
Vitamin B_{12}: Allergic reactions, eczematous skin alterations and a benign form of acne have been observed after high-dose parenteral administration (in rare cases after oral administration).
Long-term use at high doses may impair the activity of liver enzymes, cause cardiac pain, hypercoagulation.
Treatment: symptomatic treatment.
Lidocaine. Symptoms: psychomotor agitation, dizziness, general weakness, decreased blood pressure, tremor, blurred vision, tonic clonic seizures, coma, collapse, AV block, central nervous system depression, apnoea. The first symptoms of overdose arise in healthy volunteers at lidocaine blood concentration over 0.006 mg/kg, seizures occur at 0.01 mg/kg.
Treatment: termination of the drug administration, oxygen therapy, anticonvulsants, vasoconstrictors (noradrenaline, mesaton), in bradycardia – anticholinergics (0.5-1 mg of atropine) Intubation, artificial lung ventilation and resuscitation can be performed. Dialysis is ineffective.

Undesirable effects.
Long-term treatment (>6-12 months) of a daily dosage >50 mg of vitamin B_6 may, however, cause peripheral sensory neuropathy, nervous excitement, malaise, dizziness, headache.
Gastrointestinal disorders: gastrointestinal complaints such as nausea, vomiting, diarrhoea, abdominal pain, gastric hyperacidity.
Immune system disorders: hypersensitivity reactions including rash, respiratory disorders, anaphylactic shock, angioedema; hyperhidrosis.
Skin disorders: pruritus, rash, acne, generalized exfoliative dermatitis, angioedema.
Cardiac and vascular disorders: tachycardia, arrhythmia, bradycardia, slowing of cardiac conduction, AV heart block, cardiac arrest, peripheral vasodilatation, collapse, increased/decreased blood pressure, heart pain.

Nervous system disorders: excitation of the central nervous system (CNS) (if used in high doses), anxiety, headache, dizziness, sleep disturbances, confusion, drowsiness, loss of consciousness, coma; in patients with hypersensitivity – euphoria, tremor, locked jaw, restlessness, paraesthesia, convulsions.
Eye disorders: nystagmus, reversible blindness, double vision, muscae volitantes, photophobia, conjunctivitis.
Ear disorders: hearing disorders, tinnitus, hyperacusis.
Respiratory system disorders: dyspnoea, rhinitis, depression or respiratory arrest.
Others: fever or cold sensation or numbness of extremities, swelling, weakness, malignant hyperthermia, impaired sensitivity, motor block.
General disorders: reaction at the injection site.
Seizure-like systemic reactions may develop in case of very rapid parenteral administration.

Shelf life. 2 years.

Storage. Keep away from children. Store in original package at temperature from 2 °C to 8 °C.

Incompatibilities.
Pyridoxine is not compatible with levodopa-containing drugs as peripheral decarboxylation of levodopa increase, and its antiparkinsonian action decrease if co-administered with these drugs.
Thiamine is incompatible with oxidising or reducing compounds: mercuric chloride, iodide, carbonate, acetate, tannic acid, ferric ammonium citrate, and sodium phenobarbital, riboflavin, benzylpenicillin, glucose and sodium metabisulphite as it is inactivated in their presence. Copper accelerates the decomposition of thiamine, moreover, thiamine loses its activity at higher pH (greater than 3).
Vitamin B_{12} is not compatible with heavy metal salts.

Nature and contents of container. 2 mL in ampoule; 5 ampoules in a carton or 5 ampoules in a blister, 1 blister in a carton.

Prescription status. By prescription.

Manufacturer. Joint Stock Company «Lekhim-Kharkiv».

Location of the manufacturer and address of carrying out its activities.
Ukraine, 61115, Kharkiv region, Kharkiv, Severyna Pototskoho street, building 36.

Date of the last revision.