Nootropil®

International Non-Proprietary Name (INN): Piracetam

Dosage Form: solution for intravenous and intramuscular injections

Structure: 1 ml of the solution contains:
Active ingredient: Piracetam 200mg;
Excipients: sodium acetate, glacial acetic acid, water.

Description: transparent colorless liquid

Pharmacological classification: nootropic

ATC code: N06BX03

Pharmacological action: nootropic, antihypoxic, cerebroprotective

Pharmacodynamics:
The active ingredient is Piracetam, a cyclic derivative of gamma-aminobutyric acid (GABA). Available data indicates that the main mechanism of action of Piracetam is not cell-specific or organ-specific. Piracetam binds to polar heads of phospholipids and creates mobile complexes of Piracetam-phospholipids. As a result, the two-layer structure of the cell membrane and its stability are restored, which in turn leads to the restoration of the three-dimensional structure of membrane and transmembrane proteins and the restoration of their function. At the neuronal level, Piracetam facilitates various types of synaptic transmission, with a predominant effect on the density and activity of postsynaptic receptors.

Improves cognitive processes, such as learning ability, memory, attention and mental performance, without having a sedative or psychostimulating effect. The hemorheological effects of piracetam are connected to its effect on erythrocytes, platelets and the vessel wall.
In patients with sickle-cell anemia, piracetam increases the ability of erythrocytes to deform; it reduces the blood viscosity and prevents the formation of "rouleaux". In addition, it reduces aggregation of platelets without significantly affecting their number.
Piracetam inhibits vasospasm and counteracts various vasospastic substances.
Piracetam reduces the adhesion of erythrocytes to the vascular endothelium and stimulates the production of prostacyclins by the healthy endothelium.

Pharmacokinetics:
Absorption: The pharmacokinetic profile of Piracetam is linear and does not depend on time. It is characterized by low variability within the large range of doses. Constant concentration in the plasma is achieved after 3 days from the beginning of the treatment.
Distribution: Does not bind with blood plasma proteins. Distribution volume is about 0.6 l/kg. Piracetam penetrates through the blood-brain barrier and placental barrier. Animal studies showed that Piracetam accumulates selectively in tissues of the cerebral cortex, mainly in the frontal, parietal and occipital lobes, in the cerebellum and in basal nuclei.
Metabolism: Does not metabolize in the body.
Excretion: The half-life is 4-5 hours from the blood plasma and 8.5 hours from the cerebrospinal fluid. The half-life does not depend on the route of administration. 80-100% of Piracetam is excreted in the unchanged form by the kidneys through the glomerular filtration. The total clearance of Piracetam for healthy volunteers is 80-90 ml/min. The half-life is prolonged in case of kidney failure (in case of terminal chronic kidney failure - up to 59

hours). The pharmacokinetics of Piracetam for patients with liver failure does not change.

Intended uses:

- symptomatic treatment of the psycho-organic syndrome (including elderly patients with memory loss, dizziness, reduced ability to concentrate, mood changes, behavioral disorder, gait disorder, as well as patients with Alzheimer's disease and senile Alzheimer-type dementia);
- treatment of consequences of an ischemic stroke, such as speech disorders, emotional disorders, treatment for increasing motor and mental activity;
- treatment of withdrawal syndrome and psycho-organic syndrome in case of chronic alcohol addiction;
- comatose conditions (including the recovery period), including ones after injuries and intoxications of the brain;
- treatment of dizziness and related equilibrium disorders (excluding cases of dizziness of vasomotor and psychogenic origin);
- (as a part of complex therapy) treating of low learning ability in children with psycho-organic syndrome;
- treatment of cortical myoclonia (both in the form of the monotherapy, and as part of the complex therapy);
- preventive treatment of the sickle cell vaso-occlusive crisis (as part of the complex therapy).

Contraindications:

- hypersensitivity to the drug ingredients;
- psychomotor agitation at the time of prescribing;
- Huntington's chorea;
- acute cerebrovascular disorder (haemorrhagic stroke);
- terminal stage of kidney failure (CC < 20 ml/min);
- children under 3 years old;
- pregnancy and lactation.

With caution: hemostasis disorder, extensive surgical interventions, severe bleeding.

Dosage and administration:

Intravenous and intramuscular injections.

Parenteral injection is prescribed when oral administration is not possible (unconsciousness, swallowing problem). Intravenous way is preferable. Intravenous infusion of the daily dose is taken through a catheter at a constant speed during 24 hours (for example, at the initial stage of the severe myoclonus).

The drug is diluted in one of the matching infusion solutions: dextrose 5%, 10% or 20%; fructose 5%, 10%, 20%; sodium chloride 0.9%; dextran 40 10% (in a sodium chloride solution 0.9%); Ringer's solution; mannitol solution 20%. The total volume of a solution intended for administration is determined by the clinical indications and the patient's condition.

Intravenous bolus injection (for example, emergency treatment of the crisis in sickle cell anemia) is performed during at least 2 minutes, the daily dose is divided into several injections (2-4) at the regular intervals so that the dose per injection would not exceed 3 g. The drug is administered intramuscularly, if the administration through the vein is difficult. The volume of the solution administered intramuscularly cannot exceed 5 ml. The frequency of administration of the drug is similar to that of its intravenous or oral administration. When the opportunity arises, there should be a transfer to oral administration of the drug (see instructions for the medical use of the respective forms of the drug). The duration of the treatment is determined by the doctor, depending on the disease and taking into account the dynamics of the symptoms.

Treatment of the chronic psycho-organic syndrome: 2.4-4.8 g/day (2 or 3 sub doses).

Treatment of cerebrovascular disorders (stroke): 4.8-12 g/day (2 or 3 sub doses).

Treatment of coma, as well as difficulties in perception in people with brain trauma: the initial dosage is 9-12 g/day, supporting dosage is 2 g/day (2 or 3 sub doses). Treatment continues for at least 3 weeks.

Alcohol withdrawal syndrome: 12 g/day (2 or 3 sub doses). Supportive dosage is 2.4 g/day.
Treatment of dizziness and related equilibrium disorders: 2.4-4.8 g/day (2 or 3 sub doses).
Treatment of cortical myoclonia: the treatment starts with 7.2 g/day, every 3-4 days the dose is increased by 4.8 g/day (2 or 3 sub doses) until the maximum dose of 24 g/day is reached. The treatment continues throughout the whole period of the disease. Every 6 months attempts should be made to reduce the dose or discontinue the drug, gradually reducing the dose by 1.2 g/day every 2 days. Unless there is a required therapeutic effect, treatment is discontinued.
Treatment of sickle cell anemia: during the crisis the dose is 300 mg/kg intravenous divided into 4 equal injections. The daily preventive dose is 160 mg/kg of the body weight divided into 4 equal doses.

Special Groups of Patients

Kidney disorder: The dose should be adjusted depending on the amount of creatinine clearance (see the table below).
The creatinine clearance for men can be calculated based on the serum creatinine concentration, according to the following formula:
Creatinine clearance, ml/min = [(140 - age, years) × body weight, kg] / (72 × serum creatinine concentration, mg/dL)

The creatinine clearance for women can be calculated by multiplying the obtained value by a factor of 0.85.

Kidney failure	Creatinine clearance, ml/min	Dose regimen
Missing (norm)	> 80	Usual Dose
Light	50-79	2/3 of the usual dose in 2-3 intakes
Average	30-49	1/3 of the usual dose in 2 intakes
Severe	<30	1/6 of the usual dose in a single intake
End-stage	—	Contraindicated

The dose for elderly patients is adjusted in case of kidney failure. The monitoring of the functional state of the kidneys is necessary in case of the long-term therapy.

Liver disorder: Dose adjustment is not required for patients with the liver failure. For patients with both kidney and liver disorders, the dosing is prescribed according to the scheme (see ‘’Kidney disorder”).

Side effects (rare):
Blood and lymphatic system: haemorrhagic disorders.
Immune system disorders: anaphylactoid reactions, hypersensitivity.
Metabolism disorders: increase in the body weight (1.29%).
Central nervous system disorders: hyperkinesia (1.72%), nervousness (1.13%), drowsiness (0.96%), depression (0.83%), asthenia (0.23%), dizziness, headache, ataxia, balance disorder, and acute condition of epilepsy, insomnia, confusion, agitation, anxiety, hallucinations.
Digestive system disorders: in some cases - nausea, vomiting, diarrhea, abdominal pains.
Dermatological reactions: dermatitis, itching, rash, swelling.
Hearing disorders: vertigo.
Other: rarely - pain in the area of injection, thrombophlebitis, hyperthermia, hypotension (after intravenous administration).

Overdose:
Piracetam is a low toxic drug. When it is taken at a dose of 75 g, dyspeptic disorders such as diarrhea with blood and abdominal pains can be reported. In such cases symptomatic treatment which may include hemodialysis, is recommended. No specific antidote exists. The efficiency of hemodialysis is 50-60%.

Interaction with other drugs:

The possibility of changing the pharmacodynamics of piracetam under the influence of other drugs is low because 90% of its dose is excreted in the urine in the unchanged form.

Confusion, irritation and sleep disturbance are reported when the drug is used simultaneously with thyroid hormones.

According to the published study of patients with recurrent venous thrombosis, Piracetam at a dose of 9.6 g/day does not change the dose of Acenocumarol necessary to achieve INR (international normalized ratio) of 2.5-3.5, but compared to the effects of Acenocoumarol alone, the addition of Piracetam at a dose of 9.6 g/day significantly reduces platelet aggregation, the release of β-thromboglobin, the concentration of fibrinogen and von Willebrand factor (VIII: C; VIII: vW: Ag; VIII: vW: RCo), and the viscosity of blood and serum.

At concentrations of 142, 426 and 1422 μg/ml Piracetam does not inhibit the activity of cytochrome P450 isoenzymes.

At a concentration of 1422 μg/ml, slight inhibition of the activity of the isoenzymes CYP 2A6 (21%) and 3A4/5 (11%) is reported. However, the normal indicators of the inhibition constant (Ki) can probably be achieved at a higher concentration. Therefore, metabolic interaction with other drugs is unlikely.

Admission of Piracetam at a dose of 20 g/day for 4 weeks in patients with epilepsy who received stable doses of antiepileptic drugs did not change the maximum serum concentration and AUC (area under the curve) of antiepileptic drugs (carbamazepine, phenytoin, phenobarbital and valproate). When piracetam was taken with alcohol, the concentrations of piracetam and ethanol in the serum remained unchanged.

Pregnancy and lactation:

Adequate and strictly controlled studies of the safety of the use of Nootropil during pregnancy have not been conducted. Therefore the drug should not be prescribed during pregnancy, except cases of emergency. Piracetam penetrates through the placental barrier, and is excreted in breast milk. The concentration of Piracetam in newborns reaches 70-90% of its concentration in the blood of the mother. If taking of the drug is required during lactation, breastfeeding should be discontinued.

Influence on the ability to drive vehicles and operate mechanisms:

Taking into account possible undesirable effects, the patient should be careful when operating mechanisms and driving vehicles.

Special precaution:

Nootropil should be taken no later than 5 pm to prevent sleep disturbances.

Due to the antiaggregant effect (see "Pharmacodynamics"), piracetam should be prescribed with caution to patients with severe haemorrhagic disorders, risk of bleeding (for example, in case of the stomach ulcer), hemostasis disorders, haemorrhagic cerebrovascular disorders in anamnesis, to patients with surgical interference, including dental interference, to patients receiving anticoagulants and antiplatelet agents, including low-doses of acetylsalicylic acid.

When treating patients with cortical myoclonia, abrupt discontinuation of the therapy should be avoided. This can cause episode relapse.

When treating the sickle cell anemia, a dose of less than 160 mg/kg or an irregular intake of the drug may cause an acute condition.

When treating patients on the hyposodium diet, it should be noted that Piracetam pills at a dose of 24 g contain 46 mg of sodium.

Because Piracetam is excreted through the kidneys, special caution should be taken when prescribing the drug to patients with kidney decease.

In case of a long-term therapy of elderly patients, regular monitoring of kidney function indicators is recommended; if

necessary, the dose is adjusted depending on the results of the creatinine clearance study.
Nootropil penetrates through the filtration membranes of hemodialysis apparatus.

Terms of release from pharmacy: on prescription

Storage conditions: store at temperatures no higher than 30°C. Keep out of reach of children.

Shelf life: 5 years. Do not use beyond the expiration date.

Country of manufacture: Belgium