SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

NEUROSETAM 1g/5ml I.V. solution for infusion
Sterile

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active ingredient:
In each vial :

Piracetam	1 g

Excipients:

Sodium acetate trihydrate	0.005 g

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Vial.
Clear, colorless solution

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

In adults

- Symptomatic treatment of psycho-organic syndromes with memory loss, lack of attention and loss of ability to drive,
- Treatment of cortical-induced myoclonus (alone or in combination with other drugs),
- It is indicated for vertigo and related balance disorders (except vasomotor or psychic origin).

In children

- It is indicated for the treatment of dyslexia with appropriate approaches such as speech therapy in children aged 8 and older.

4.2 Posology and method of administration

Posology / frequency and duration of application:
It is recommended that the daily dose is taken in two to four equal doses.
When parenteral (intravenous) administration is required (eg swallowing difficulty, unconsciousness), NEUROSETAM may be administered I.V. at the same dose as recommended daily.

- Injectable vials shall be administered I.V. for several minutes.

Below are the recommended daily doses for each indication

Symptomatic treatment of psycho-organic syndromes

The recommended daily dose; 2.4 g to 4.8 g and the daily dose is divided into 2 or 3 equal doses.

Treatment of cortical myoclonus

The daily dose should be started with 7.2 g, and the dose should be divided into 2 or 3 equal doses in 4.8 g increments every three to four days until a maximum dose of 24 g obtained.

Other anti-myoclonic drugs used in treatment should be given at the same dose; According to the clinical benefit obtained, the dose of the related drugs should, if possible, be reduced.

Once a NEUROSETAM is started, treatment should be continued for the actual cerebral disease period.

Patients with acute seizures may spontaneously recover over time; therefore, every 6 months, an attempt should be made to reduce the dose of the drug or to stop taking the drug.

In doing so, the NEUROSETAM dose should be reduced by 1.2 g every two days (every three or four days in Lance Adams syndrome) to prevent sudden relapse or withdrawal seizures.

Vertigo treatment

The recommended daily dose; It is between 2.4 g and 4.8 g and the daily dose is divided into 2 or 3 equal doses.

Treatment of dyslexia in combination with speech therapy

In children aged 8 years and older, the recommended daily dose is approximately 3.2 g and is divided into 2 equal doses.

Method of administration:

NEUROSETAM is used intravenously.

Additional information on special populations:

Renal/Hepatic failure:

Renal Failure

The daily dose should be individualized according to the kidney function. The dose should be adjusted as shown in the table below. In order to use this dose table, the patient's creatinine clearance (CLcr) should be calculated in ml/min. Using the following formula, CLcr can be calculated ml/min, from the serum creatinine (mg / dl) value:

$$\text{CLcr (mL/min)} = \frac{[140 - \text{age(year)}] \times \text{weight (kg)}}{72 \times \text{serum creatinine (mg/dl)}} \quad (\times 0{,}85 \text{ for women})$$

Group	Creatinine clearance	Posology and frequency
Normal	>80	General daily dose divided by 2-4 equal doses
Mild	50-79	2/3 of the general daily dose is divided into 2 or 3 equal doses.
Moderate	30-49	1/3 of the general daily dose divided by 2 equal doses
Severe	<30	1 / 6 of the general daily dose, 1 single application
End Stage Renal Disease	-	Contraindicated

Hepatic failure
Only patients with hepatic impairment do not need to adjust the dose. Dosage adjustment is recommended in patients with liver and renal impairment (see section "Kidney failure").

Elderly population:
Dose adjustment is recommended in elderly patients with renal dysfunction (see section "Kidney failure"). In the long-term treatment of elderly patients, creatinine clearance needs to be evaluated regularly in order to make a dose adjustment.

Pediatric population:
NEUROSETAM is not recommended for children under 8 years of age because of lack of safety and efficacy data.

4.3 Contraindications

- Hypersensitivity to piracetam or other pyrrolidone derivatives or any of the excipients it contains,
- In patients with cerebral hemorrhage,
- In those with end-stage renal disease,
- Contraindicated in patients with Huntington's chord is disease.

4.4 Special warnings and precautions for use

Due to the platelet antiaggregant effect of NEUROSETAM (see section 5.1 “Pharmacodynamic properties”), in patients with severe hemorrhage, in patients who has risk of bleeding such as patient with gastrointestinal ulcer, in patients with hemostasis induced disorders, in patients with hemorrhagic stroke history, in patients patients with major surgical interventions including dental surgery and those using anticoagulant or platelet antiaggregant drugs, including low-dose asprin, it is recommended that should be used with caution.

Care should be taken in renal failure as NEUROSETAM is excreted through the kidneys (see section 4.2 "Posology and method of administration").

In the long-term treatment of the elderly, creatinine clearance should be evaluated regularly in order to make a dose adjustment.

In patients with myoclonus, discontinuation of treatment may cause sudden relapse or withdrawal seizures, which should be avoided.

Warnings on excipients
Sodium:
Each vial of this medicinal product contains less than 1 mmol (23 mg) of sodium per vial; that is, it does not actually contain sodium.

4.5 Interaction with other medicinal products and other forms of interaction

During concurrent treatment with thyroid extracts (T3 + T4), confusion, irritability, and sleep disturbance have been reported.
In a published single-blind study showed that piracetam at a dose of 9.6 g/day in patients with severe recurrent venous thrombosis does not change the dose of acenocumarol required to raise JNR from 2.5 to 3.5 . However, compared to the effects of acenocoumarol alone; piracetam added at a dose of 9.6 g/day significantly decreased, platelet aggregation; P-thromboglobulin release; the levels of fibrinogen and von Willebrand factors (VIII: C; VIII: vW: Ag; VIII: vW: RCo) and blood and plasma viscosity.

It is expected that the potential for drug interaction that causes a change in the pharmacokinetics of NEUROSETAM is low because about 90% of the dose of NEUROSETAM is excreted in the urine as unchanged medicine.

In vitro, NEUROSETAM at concentrations of 142, 426 and 1422 mcg/ml does not inhibit of human liver cytochrome P450 CYP 1A2, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1 and 4A9 / 11 isoforms.

Minor inhibitory effects of piracetam at 1422 mcg/mL concentration on CYP 2A6 (21%) and 3A4/5 (11%) were observed. However, the Ki values for the inhibition of these two CYP isoforms are probably much higher than 1422 mcg/ml. Therefore, the metabolic interaction of piracetam with other drugs is not expected.

Piracetam, taken at a dose of 20 g daily for 4 weeks, did not alter the peak and baseline serum levels of antiepileptic drugs (carbamazepine, phenytoin, phenobarbitone, sodium valproate) taken at fixed doses in epilepsy patients.

Concurrent alcohol use did not show any effect on piracetam serum levels and piracetam administered in 1.6 g oral dose did not change alcohol levels.

4.6 Pregnancy and lactation

General advice

Pregnancy Category: C.

Women with childbearing potential / Contraception

For NEUROSETAM there is no interaction data defined by oral contraceptives.

Pregnancy

There is insufficient data on the use of NEUROSETAM in pregnant women. NEUROSETAM passes the placental barrier. Drug levels in the newborn are between 70% and 90% of the maternal levels.

NEUROSETAM should not be used unless it is necessary in pregnancy. Only if the mother's clinical condition requires treatment with NEUROSETAM and the benefit of NEUROSETAM for the mother is higher than her risk.

Lactation period

NEUROSETAM passes into breast milk; therefore, it should be avoided during breast-feeding or breast-feeding should be discontinued during treatment.

Fertility

Animal studies; have no direct or indirect adverse effects on pregnancy, embryo / fetus development, birth or post-natal development.

4.7 Effects on ability to drive and use machines

When the adverse effects observed with drug intake are evaluated, it is possible that the effect of NEUROSETAM on ability to drive and use machine is possible and this should be taken into consideration when using the drug.

4.8 Undesirable effects

Adverse effects are very common (≥1 / 10); common (≥1 / 100 to <1/10); uncommon (≥1 / 1.000 to <1/100); infrequent (≥1 / 10,000 to <1 / 1,000); very rare (<1 / 10,000); unknown (not predicted from the available data).

Clinical studies

Safety data available double-blind, placebo-controlled, clinical or pharmacokinetical studies (Obtained from UCB Documentation Database in June 1997); covers more than 3000 subjects taking piracetam regardless of the indication, dosage form, daily dose or population characteristics.

When the adverse events were grouped according to WHO System Organ Class, the following classes were statistically significant in piracetam treatment:

- Psychiatric disorders
- Central and peripheral nervous system disorders
- Metabolism and nutritional disorders
- General disorders in the whole body

The following adverse events were reported to be significantly higher with piracetam than with placebo. Frequency values for patients treated with placebo (n = 2850) versus with (n = 3017) are given below.

WHO System Organ Class	Common (≥1 / 100, <1/10)	Uncommon (≥ 1/1000, <1/100)
Nervous system disorders	Hyperkinetic	
Metabolism and nutritional disorders	Weight gain	
Psychiatric disorders	Irritability	Somnolence, depression
General disorders and diseases related to the administration site		Asthenia

Post-marketing experience

Additional adverse drug reactions listed below are reported from the post-marketing experience (listed by MedDRA System Organ Classes). The data are insufficient to predict the incidence of these adverse drug reactions in the treated population.

Blood and lymphatic system disorders: Hemorrhagic disorder
Ear and Labyrinth disorders: Vertigo
Gastrointestinal disorders: Abdominal pain, upper abdominal pain, diarrhea, nausea, vomiting
Immune system disorders: Anaphylactoid reaction, hypersensitivity
Nervous system disorders: Ataxia, balance disorder, aggravation of epilepsy, headache, insomnia
Psychiatric disorders: agitation, anxiety, confusion, hallucination

Skin and subcutaneous tissue disorders: Angioneurotic edema, dermatitis, pruritus, urticaria.

Following intravenous administration, cases of pain, thrombophlebitis, fever, or hypotension have been rarely reported at the administration site.

Reporting of suspected adverse reactions
Reporting any suspected adverse reactions of drugs is very important after the authorization. Reporting enables tracking the benefit/risk balance of the medicinal product. Health professionals should report any suspected adverse reaction to Turkish Pharmacovigilance Center (TÜFAM) (www.titck.gov.tr; e-mail: tufam@titck.gov.tr; phone: 0 800 314 00 08; fax: 0312 218 35 99).

4.9 Overdose and therapy

Symptoms:
Bloody diarrhea with abdominal pain is caused by taking 75 g of piracetam daily and is most likely associated with an excessively high dose of sorbitol (contained in the syrup containing piracetam). No other case has been reported to indicate an additional adverse event specific to overdose.

Treatment:
In acute overdose, the stomach can be emptied by gastric lavage or by induction of vomiting. Piracetam has no specific antidote for overdose. Treatment of overdose is symptomatic and may include hemodialysis. The extraction efficiency of the dialysis is 50-60% for NEUROSETAM.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Nootrophic
ATC Code: N06BX03
The active substance piracetam is a pyrrolidone (2-oxo-1-pyrrolidine-acetamide) which is a cyclic derivative of gammaaminobutyric acid (GABA).

Effect Mechanism and Pharmacodynamic Effects
Current data suggest that Piracetam's basic mechanism of action is neither cell nor organ specific. Piracetam physically binds to the polar ends of phospholipid membrane models in a dose-dependent manner, inducing the restoration of the membrane lameller structure characterized by the formation of the mobile drug phospholipid complex. This allows the membrane and transmembrane proteins functions to maintain or recover the required folding or three-dimensional structures for demonstrating their function, which is likely to provide better membrane stability.

Piracetam has neuronal and vascular effects.

Neuronal Effects
At the neuronal level, Piracetam shows its effect on the membrane in various ways.
In animals. Piracetam improves various types of neurotransmission, mainly through postsynaptic regulation of receptor concentration and activity. It improves cognitive functions such as learning, memory, attention, and consciousness in both animal and human subjects, both in inadequate conditions and in normal subjects without causing sedative or psychostimulant effects. Piracetam preserves and corrects cognitive abilities after various cerebral events, such as hypoxia, intoxications and electroconvulsive therapy in animals and humans. It protects brain function and performance against hypoxia-induced changes, as determined by EEG (electroencephalography) and psychometric evaluations.

Vascular Effects
Piracetam shows the hemorheological effects on platelets, erythrocytes and vessel walls by increasing the erythrocyte deformability, reducing platelet aggregation, erythrocyte adhesion to vessel walls and capillary vasospasm.

Effects on platelets
In clear studies of healthy volunteers and patients with Raynaud's phenomena, up to 12 g of increasing doses of piracetam were compared with pre-treatment values (aggregation tests induced by ADP, collagen, epinephrine and ßTG release). cause a dosage depended drop without causing any significant change in platelet functions. In these studies, piracetam prolonged bleeding time.

Effects on blood vessels
Piracetam in animal studies inhibited vasospasm and was effective against the effects of various spasmogenic agents. There is no vasodilator effect and it did not induce "steal" phenomenon, did not cause decrease in blood flow, no repeat blood flow, or hypotensive effect. In healthy volunteers, piracetam reduced the adhesion of RBCs to vascular endothelium and possessed also a direct stimulant effect on prostacycline synthesis in healthy endothelium.

Effects on coagulation factors
In healthy volunteers, the increased piracetam dose up to 9.6 g reduces the plasma levels of fibrinogen and von Willebrand factors (VIII: C; VIII R: AG; VIII R: vW) by 30-40% compared with pretreatment values and prolongs bleeding time . Piracetam at a dose of 8 g/day for 6 months in both primary and secondary Raynaud phenomena compared to pre-treatment values showed that it reduces the plasma levels of fibrinogen and von Willebrand factors (VIII: C; VIII R: AG; VIII R: vW (RCF)) at 30-40%, reduces plasma viscosity and prolongs bleeding time.
In another study conducted in healthy volunteers; There was no statistically significant difference between piracetam (up to 12 g, twice a day) and placebo in terms of hemostasis parameters and the time of bleeding.

5.2 Pharmacokinetic properties

General properties
The pharmacokinetic profile of piracetam is linear and time independent; a large dose

inter-subject variability is low. This is consistent with high permeability, high solubility and minimum metabolism of piracetam properties. The plasma half-life of piracetam is 5 hours. This time is the same in adult volunteers and patients. It increases in the elderly (due to the deterioration of kidney clearance) and in subjects with renal failure. Steady-state plasma concentrations are reached within 3 days after dosing.

Distribution:
Piracetam does not bind to plasma proteins and the dispersion volume is about 0.6 l / kg. Following intravenous administration, it can be measured in cerebrospinal fluid. Piracetam passes the blood-brain barrier. The cerebrospinal fluid is reached approximately 5 hours after administration to tmax and the half-life is approximately 8.5 hours.
In animals, the highest concentrations of piracetam in the brain are in the cerebral cortex (frontal, parietal, occipital lobes), cerebellar cortex and basal ganglia.
Piracetam is spread to all tissues except fat tissue; passes through the placental barrier and penetrates through the membranes of isolated erythrocytes.

Biotransformation:
It is not known that NEUROSETAM is metabolized in the human body. This non-metabolisation is supported by the plasma half-life in anuric patients and a high rate of urine in the main component.

Elimination:
IV or after oral administration, the plasma half-life of piracetam is approximately 5 hours in adults. Visible total body clearance is 80-90 ml/min. The main excretion pathway is urine and corresponds to 80-100% of the dose. Piracetam is removed by glomerular filtration.

Linearity / non-linearity:
The pharmacokinetics of piracetam are linear in the range of 0.8-12 g. Pharmacokinetic variables, such as half life and clearance, do not change with dose and duration of treatment.

Characteristic of patients
Gender
In a bioequivalence study comparing formulations at a dose of 2.4 g, Cmax and EAA were about 30% higher in women (N = 6) than men (N = 6). However, the clearances adjusted for body weight are similar.

Race
No official pharmacokinetic studies have been conducted on race effects. Cross-comparative studies included white race and Asians, indicating that the pharmacokinetics of piracetam were similar between the two races. Since piracetam is mainly excreted in the urine and there are no major racial differences in creatinine clearance, race-related pharmacokinetic differences are not expected.

Geriatric population
In the elderly, the half-life of piracetam increases and this increase is associated with reduced renal function in this population (see section 4.2 "Posology and method of administration").

Pediatric population
No pharmacokinetic study was performed in children.

Kidney failure
The clearance of piracetam is associated with creatinine clearance. Therefore, it is recommended that the daily dose of piracetam be adjusted based on creatinine clearance in patients with renal insufficiency (see section 4.2 "Posology and method of administration"). In the patients with anuric end-stage renal disease, the half-life of piracetam increased to 59 hours. During a typical 4-hour dialysis circuit, the removal fraction of piracetam is between 50 and 60%.

Liver failure
The effect of hepatic insufficiency on the pharmacokinetics of piracetam was not evaluated.
Since 80-100% of the dose are excreted as unchanged drugs in urine, liver failure alone is not expected to have a significant effect on piracetam elimination.

5.3 Preclinical safety data
Preclinical data obtained with piracetam indicate that piracetam has low toxicity potential. Single dose studies in mice, rats and dogs showed no irreversible toxicity following oral doses of 10 g/kg. In recurrent dose chronic toxicity studies, no target organ was observed for toxicity in mice (doses up to 4.8 g/kg/day) and in rats (up to 2.4 g/kg/day). In dogs, Piracetam was administered orally at a dose of 1g/kg/day to 10g/kg/day for one year, while mild gastrointestinal effects (vomiting, change in fecal consistency, increased water consumption) were observed.

Similarly, in rats and dogs, up to 1 g/kg/day I.V administration did not generate toxicity for 4-5 weeks.

Genotoxicity and carcinogenicity have not been demonstrated in *in vitro* and *in vivo* studies.

6 PHARMACEUTICAL PROPERTIES
6.1 List of excipients
Sodium acetate trihydrate
Acetic acid

Water for injection

6.2 Incompatibilities

Not available.

5% glucose, 10% glucose, 20% glucose, 5% fructose, 10% fructose, 20% fructose, 0.9% NaCl, Dextran 40 (10% in 0.9% NaCl solution), Ringer, 20% Mannitol, 6% HEPP (hydroxyethyl starch) is physically, chemically and microbiologically compatible for a period of 24 hours provided that 10% HH (hydroxyethyl starch) solutions are stored at room temperature below 25 °C.

Effects on diagnostic examinations: There is no known incompatibility.

6.3 Shelf life

24 month.

6.4 Special precautions for storage

It should be store at room temperature below 25 °C.

6.5 Nature and contents of package

One box contains 12 vials of 5 ml (amber colored Type I glass).

6.6 Special precautions for disposal and the residue from medicinal products

Unused products or waste materials must be disposed of in accordance with the "Medical Wastes Control Regulation" and the "Packaging and Packaging Wastes Control Regulations".

7- MARKETING AUTHORISATION HOLDER

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8- MARKETING AUTHORISATION NUMBER

2019/166

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Date of first authorisation: 27.03.2019
Date of latest renewal :

10- DATE OF REVISION OF THE SPC

19.11.2019