SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

NOOTROVER 1 g/5 mL ampoule containing solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active substance:
In 5 ml ampoule:
Piracetam…….1 g

Excipients:
Sodium acetate 3.H2O…….. 5.00 mg
Glacial acetic acid
Water for injection

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Ampoule
Clear, colorless solution

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

In adults

It is indicated in:

- Symptomatic treatment of psycho-organic syndromes with symptoms such as memory loss, attention deficit and loss of driving ability,
- Cortical originated myoclonus treatment (alone or in combination with other drugs),
- Vertigo and related balance disorders (except dizziness of vasomotor or psychic origin).

In children

- Dyslexia in children aged 8 years and above with appropriate approaches such as speech therapy.

4.2. Posology and method of administration

Posology /administrationfrequency and duration

It is recommended to take the daily dose in two to four equal doses.

When parenteral (intravenous) administration is required (eg difficulty in swallowing, unconsciousness), piracetam can be administered I.V. at the same dose recommended daily.

Injectable ampoules will be administered I.V. for a few minutes.

Below are the recommended daily doses for each indication:

Symptomatic treatment of psycho-organic syndromes

The recommended daily dose is from 2.4 g to 4.8 g and the daily dose is administered in 2 or 3 equal doses.

Cortical originated myoclonus treatment

The daily dose should be started with 7.2 g and administered in 2 or 3 equal doses in increments of 4.8 g every three or four days until the maximum dose of 24 g is reached.

Other anti-myoclonic drugs used in treatment should be given at the same dose; the dose of the drugs in question should be reduced, if possible, based on the clinical benefit achieved.

Once NOOTROVER is initiated, treatment should continue throughout the actual cerebral disease.

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

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

Vertigo treatment

The recommended daily dose is between 2.4 g and 4.8 g and the daily dose is administered in 2 or 3 equal doses.

Dyslexia treatment in combination with talk therapy

For children and adolescents aged 8 years and older, the recommended daily dose is approximately 3.2 g and administered in 2 equal doses.

Method of administration:

NOOTROVER Ampoule is administered intravenously.

Additional information on special populations:

Renal failure:

The daily dose should be individualized according to renal function. The dose should be adjusted as shown in the table below. To use this dosing table, measure the patient's creatinine clearance (CLcr) must be calculated as ml/min. The CLcr in ml/min can be calculated from serum creatinine (mg/dl) using the following formula:

$$\mathrm{CLcr}\left(\frac{\mathrm{mL}}{\mathrm{min}}\right) = \frac{[140 - \mathrm{age(year)x\ weight(kg)}}{72\ \mathrm{x\ serum\ creatinine}\left(\frac{}{}\right)}$$

Group	Creatinine clearance (mL/min)	Posology and frequency
Normal	>80	General daily dose, divided into 2 to 4 equal doses
Mild	50-79	2/3 of the usual daily dose, divided into 2 or 3 equal doses
Medium	30-49	1/3 of the usual daily dose, divided into 2 equal doses
Severe	<30	1/6 of the usual daily dose, 1 single administration
Last period Renal Disease	-	Contraindicated

Hepatic failure:

No dose adjustment is required in patients with only hepatic impairment. Dose adjustment is recommended in patients with hepatic and renal impairment *(see Section "Renal failure").*

Geriatric population:

Dose adjustment is recommended in elderly patients with impaired renal function *(see Section "Renal failure").*In the long-term treatment of elderly patients, regular assessment of creatinine clearance is required so that dose adjustment can be made when necessary.

Pediatric population:

Piracetam is not recommended for use in children under 8 years of age due to insufficient data on safety and efficacy.

4.3. Contraindications

It is contraindicated:

- In hypersensitivity to piracetam or other pyrrolidone derivatives or any of the excipients it contains,
- In patients with cerebral haemorrhage,
- In end-stage renal disease
- In those with Huntington's Chorea disease.

4.4. Special warnings and special precautions for use

Due to the platelet antiaggregant effect of NOOTROVER (see Section 5.1 *"Pharmacodynamic properties"*), it is recommended to be used with caution in patients with severe bleeding, in patients at risk of bleeding such as gastrointestinal ulcer, in patients with underlying hemostasis disorders, in patients with a history of haemorrhagic stroke, in patients with major surgery including dental surgery, and anticoagulants including low dose asprine or patients using platelet antiaggregant drugs.

As NOOTROVER is excreted through the kidneys, caution should be exercised in renal failure (see section 4.2 "Posology and method of administration").

In the long-term treatment of the elderly, regular assessment of creatinine clearance is required so that dose adjustment can be made when necessary.

Abrupt discontinuation of treatment in patients with myoclonus should be avoided as it may cause sudden relapse or withdrawal seizures.

Warnings about excipients

Sodium: This drug contains less than 1 mmol (23 mg) sodium per ampoule; it is not expected to show any side effects at this dose.

4.5 Interaction with other medicinal products and other forms of interaction

Confusion, irritability, and sleep disturbance have been reported during concomitant treatment with thyroid extracts (T3 + T4).

In a published single-blind study, it was shown that NOOTROVER at a dose of 9.6 g/day in patients with severe recurrent venous thrombosis did not change the dose of acenocoumarol required to increase the INR from 2.5 to 3.5. However, when compared to the effects of acenocoumarol alone; NOOTROVER added at a dose of 9.6 g/day, platelet aggregation; P-thromboglobulin release; significantly reduced levels of fibrinogen and von Willebrand factors (VIII: C; VIII: vW: Ag; VIII: vW: RCo) and whole blood and plasma viscosity.

The potential for drug interaction, leading to changes in the pharmacokinetics of NOOTROVER, is expected to be low, since approximately 90% of the NOOTROVER dose is excreted in the urine as unchanged drug.

In vitro, NOOTROVER at concentrations of 142, 426 and 1422 μg/mL does not inhibit human liver cytochrome P450 CYP 1A2, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1 and 4A9/11 isoforms. Minor inhibitory effects of NOOTROVER on CYP 2A6 (21%) and 3A4/5 (11%) were observed at a concentration of 1422 μg/mL. However, Ki values for inhibition of these two CYP isoforms are likely well above 1422 μg/mL. Therefore, no metabolic interaction of NOOTROVER with other drugs is expected.

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

Simultaneous alcohol use had no effect on piracetam serum levels, and piracetam administered at an oral dose of 1.6 g did not change alcohol levels.

4.6 Pregnancy and lactation

General advice

Pregnancy category: C

Women with childbearing potential / Contraception

There are no identified interaction data for NOOTROVER with oral contraceptives.

Pregnancy

There are insufficient data on the use of NOOTROVER in pregnant women.

NOOTROVER crosses the placental barrier. Drug levels in the newborn are approximately 70% -90% of the maternal levels.

NOOTROVER should not be used during pregnancy unless absolutely necessary. It should only be administered if the clinical condition of the mother requires treatment with NOOTROVER and if the benefit of NOOTROVER for the mother is more than the risk in question.

Lactation

NOOTROVER passes into breast milk; therefore, its use should be avoided during breastfeeding or breastfeeding should be discontinued during treatment**.**

Fertility

Animal studies did not show direct or indirect harmful effects in terms of 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, the effect of NOOTROVER on driving and using machine is possible and this should be taken into account while using the drug.

4.8 Undesirable effects

Clinical studies

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

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

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

The following adverse events were reported with a statistically significant higher frequency with piracetam compared to placebo. The frequency values for patients treated with placebo (n = 2850) versus (n = 3017) are given below.

WHO System Organ Class	**Common (≥1 / 100, <1/10)**	**Uncommon (≥ 1/1000, <1/100)**
Nervous system disorders	Hyperkinesis	
Metabolism and nutrition disorders	Weight gain	
Psychiatric disorders	Irritability	Somnolence Depression
General disorders and administration site disease		Asthenia

Post-marketing experience

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

Blood and lymphatic system disorders: Hemorrhagic disorder

Ear and labyrinth diseases: Vertigo

Gastrointestinal disorders: Abdominal pain, upper abdominal pain, diarrhea, nausea, vomiting

Immune system disorders: Anaphylactoid reaction, hypersensitivity

Nervous system disorders: Ataxia, balance disorder, exacerbation of epilepsy, headache, insomnia

Psychiatric disorders: Agitation, anxiety, confusion, hallucinations

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

After intravenous administration, infrequently; injection site pain, thrombophlebitis, fever, or cases of hypotension have been reported.

Reporting of suspected adverse reactions
If you get any side effects not listed in this leaflet, talk to your doctor or pharmacist. You can also report side effects directly to your doctor or pharmacist. You can also report side effects directly to your country’s related health authority. By reporting side effects, you can help provide more information on the safety of this medicine.

4.9 Overdose

Symptoms

The phenomenon of bloody diarrhea with abdominal pain occurs with the daily intake of 75g of piracetam and is most likely related to an excessively high dose of sorbitol (contained in the syrup containing piracetam). No other case reported to indicate a specific additional adverse event related to overdose.

Treatment

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Nootropics

ATC code: N06B X03

The active substance piracetam is a pyrrolidone (2-oxo-1-pyrrolidine-acetamide), a cyclic derivative of gammaaminobutyric acid (GABA).

Mechanism of Action 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 the phospholipid membrane models in a dose-dependent manner, inducing the restoration of the membrane lamellar structure characterized by the formation of the mobile drug phospholipid complex. This allows the membrane and transmembrane proteins to maintain or restore the folding or three-dimensional structure required to demonstrate their function, which is a possible reason for better membrane stability.

Piracetam has neuronal and vascular effects.

Neuronal Effects

At the neuronal level, Piracetam shows its effects on the membrane in various ways.

In animals. Piracetam enhances various types of neurotransmission, mainly by postsynaptic regulation of receptor density and activity. It increases the functions related to cognitive events such as learning, memory, attention, consciousness in both animals and humans, without causing sedative or psychostimulant effects, both in their deficient state and in normal subjects. Piracetam maintains and restores cognitive abilities in animals and humans after various cerebral

events such as hypoxia, intoxications and electroconvulsive therapy. It protects brain function and performance against hypoxia-induced changes, as determined by EEG (electroencephalography) and psychometric assessments.

Vascular Effects

Piracetam shows its hemorrhological effects on thrombocytes, erythrocytes and vessel walls by increasing erythrocyte deformability, decreasing thrombocyte aggregation, erythrocyte adhesion to vessel walls, and capillary vasospasm.

Effects on platelets: In open trials in healthy volunteers and patients with Raynaud's phenomenon, increasing doses of piracetam up to 12 g were associated with no significant change in platelet counts compared to pre-treatment values (ADP, collagen, epinephrine, and ßTG release-induced aggregation tests) causes a dose-dependent decrease. In these studies, piracetam prolonged the bleeding time.

Effects on blood vessels: In animal studies, Piracetam inhibits vasospasm and was effective against the effects of various spasmogenic agents. It did not have any vasodilatory effect and did not induce the "steal" phenomenon, did not result in reduced blood flow, reflux or hypotasmative effect. Piracetam in healthy volunteers reduced the adhesion of red blood cells to the vascular endothelium and also has a direct stimulating effect on prostacyclin synthesis in the healthy endothelium.

Effects on coagulation factors: In healthy volunteers, increasing piracetam dose up to 9.6g reduces plasma levels of fibrinogen and von Willebrand factors (VIII: C; VIII R: AG; VIII R: vW) by 30-40% compared with pre-treatment values and extends bleeding time. Piracetam at a dose of 8g/day taken for 6 months in patients with both primary and secondary Raynaud's phenomenon increased plasma levels of fibrinogen and von Willebrand factors (VIII: C; VIII R: AG; VIII R: vW (RCF)) by 30-40% compared with pre-treatment values, reduces plasma viscosity and prolongs bleeding time.

In another study conducted with healthy volunteers; There was no statistically significant difference between piracetam (up to 12g twice daily) and placebo in terms of hemostasis parameters and its effect on bleeding time.

5.2 Pharmacokinetic properties

General properties:

The pharmacokinetic profile of Piracetam is linear and time independent; Inter-subject variability over a wide dose range is low. This is in line with piracetam's high permeability, high solubility and minimal metabolism properties.

The plasma half-life of piracetam is 5 hours. This period is the same in adult volunteers and patients. It is increased in the elderly (due to impaired renal clearance) and subjects with renal insufficiency. Steady state plasma concentrations are reached within 3 days after dosing.

Distribution:

Piracetam is not bound to plasma proteins and its volume of distribution is about 0.6 l/kg. It can be measured in cerebrospinal fluid following intravenous administration. Piracetam crosses the blood-brain barrier. In cerebrospinal fluid, t_{max} is reached approximately 5 hours after administration and its 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 spreads to all tissues except adipose tissue; It crosses the placental barrier and penetrates the membranes of isolated erythrocytes.

Biotransformation:

Piracetam is not known to be metabolized in the human body. This lack of metabolism is supported by the long plasma half-life in anuric patients and the high detection of parent compound in urine.

Elimination:

After I.V. or oral administration, piracetam has a plasma half-life of approximately 5 hours in adults. Apparent total body clearance is 80-90 mL/min. The main route of excretion is urine and it accounts for 80-100% of the dose. Piracetam is removed by glomerular filtration.

Linearity / nonlinear case

The pharmacokinetics of piracetam are linear over the 0.8-12 g dose range. Pharmacokinetic variables such as half-life and clearance do not change with dose and duration of treatment.

Characteristics in patients

Gender

In a bioequivalence study comparing formulations at a dose of 2.4 g, C_{max} and AUC were approximately 30% higher in women (N = 6) compared to men (N = 6).

However, the clearances adjusted for body weight are similar.

Race

No formal pharmacokinetic studies on the effects of race have been conducted. Cross-comparative studies involving Caucasians and Asians have shown that piracetam pharmacokinetics is similar between the two races. Since piracetam is mainly excreted in the urine and there are no significant racial differences in creatinine clearance, no race-related pharmacokinetic differences are to be expected.

Geriatric population

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

Pediatric population

No formal pharmacokinetic studies have been conducted in children.

Renal failure

Piracetam clearance is linked to creatinine clearance. It is therefore recommended that the daily dose of piracetam be adjusted based on creatinine clearance in patients with renal impairment *(see section 4.2 "Posology and method of administration").* In subjects with anuric end-stage renal disease, the half-life of piracetam increased to 59 hours. The fraction of piracetam removed during a typical 4-hour dialysis cycle is between 50-60%.

Hepatic failure

Effect of hepatic insufficiency on the pharmacokinetics of piracetam is not evaluated. Since 80-100% of the dose is excreted as unchanged drug in the urine, no significant effect of liver failure on piracetam elimination alone is expected.

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 after oral doses of 10g/kg. In repeated dose chronic toxicity studies, no target organ for toxicity was observed in mice (up to 4.8 g/kg /day) and rats (up to 2.4 g/ kg/day).

Mild gastrointestinal effects (vomiting, change in stool consistency, increased water consumption) were observed when Piracetam was administered orally in increasing doses from 1g/ kg/day to 10g/kg/day for one year in dogs.

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

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium acetate 3.H2O

Glacial acetic acid

Water for injection q.s.

6.2 Incompatibilities

Not available.

Piracetam is compatible with the perfusion solutions listed below (physico-chemical compatibility);

- 5%, 10%, 20% Glucose
- 5%, 10%, 20% Fructose
- 0.9% Sodium chloride
- Dextran 40 (10% in 0.9% NaCl solution)
- Ringer
- 20% Mannitol
- 6% and 10% HES (Hydroxy Ethyl Starch) solution

When diluted with the above mentioned solutions, it is stable for 24 hours at room temperature below 25ºC.

Effects on diagnostic examinations: There is no known incompatibility.

6.3 Shelf life

24 months

6.4 Special precautions for storage

Store at room temperature below 25°C.

6.5 Nature and contents of container

A box contains 12 ampoules of 5 mL (amber colored Type I glass).

6.6 Special precautions for disposal

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

7. MARKETING AUTHORISATION HOLDER

HAVER FARMA İlaç A.Ş.

Akbaba Mahallesi Maraş Cad. No:52/2/1

Beykoz / İstanbul/TURKEY

8. MARKETING AUTHORISATION NUMBER

2016/538

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

First authorisation date: 12.07.2016

Renewal date of authorisation:-

10. DATE OF REVISION OF THE TEXT