Nootropyl

Piracetam

film-coated tablet

NAME OF THE MEDICINAL PRODUCT

Nootropyl 800 mg, film-coated tablet

QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 800 mg of piracetam

Excipients

Macrogol 6000, colloidal anhydrous silica, magnesium stearate, sodium croscarmellose, hydroxypropylmethylcellulose, titanium dioxyde (E171), macrogol 400.

PHARMACEUTICAL FORM

White, oblong, film-coated tablet, with a bisect line, marked N/N on one side and plain on the other side.

CLINICAL INFORMATION

Indications

Adults

Piracetam is indicated for:

- symptomatic treatment of the psycho-organic syndrome whose features, improved by treatment, are memory loss, attention disorders and lack of drive,
- treatment of cortical myoclonus, alone or in combination,
- treatment of vertigo and associated disorders of balance, with the exception of dizziness of vasomotor or psychic origin,
- prophylaxis and remission of sickle cell vaso-occlusive crises.

Children

Piracetam is indicated for:

- treatment of dyslexia, in combination with appropriate measures such as speech therapy,
- prophylaxis and remission of sickle cell vaso-occlusive crises.

Dosage and Administration

Piracetam may be taken with or without food. The film-coated tablets should be swallowed with liquid. It is recommended to take the daily dose in two to four sub-doses.

Route of Administration

For oral use.

Adults

Symptomatic treatment of psycho-organic syndromes

The recommended daily dose ranges from 2.4 g up to 4.8 g, in two or three sub-doses.

Treatment of myoclonus of cortical origin

The daily dosage should begin at 7.2 g, increasing by 4.8 g every three or four days up to a maximum of 24 g, in two or three divided doses. Treatment with other anti-myoclonic medicinal products should be maintained at the same dosage. Depending on the clinical benefit obtained, the dosage of other such medicinal products should be reduced, if possible. The dosage must be set individually for each patient by a therapeutic trial.

Once started, treatment with piracetam should be continued for as long as the original cerebral disease persists. In patients with an acute episode, spontaneous evolution may occur over time and an attempt should be made every 6 months to decrease or discontinue the medicinal treatment. This should be done by reducing the dose of piracetam by 1.2 g every two days (every three or four days in the case of a Lance- Adams syndrome, in order to prevent the possibility of sudden relapse or withdrawal seizures).

Treatment of vertigo

The recommended daily dose ranges from 2.4 g to 4.8 g, in two or three divided doses.

Prophylaxis and remission of sickle cell vaso-occlusive crises

The recommended daily dose for prophylaxis is 160 mg/kg, orally, in four divided doses.

The recommended daily dose for remission is 300 mg/kg intravenously, in four divided doses. For sickle cell anaemia the prophylactic dosage must be permanent. A dose lower than 160 mg/kg/day or irregular intake may result in relapse of crises.

Children

Dyslexia in combination with appropriate measures such as speech therapy

The recommended dosage for school age children (from 8 years old) and adolescents is 3.2 g per day, that means 8 ml of 20% solution twice per day or 2 tablets of 800 mg in the morning and in the evening, usually during the whole period of the school year.

Prophylaxis and remission of sickle cell vaso-occlusive crises

For children from 3 years old onwards the prophylactic dosage is 160 mg/kg/per day divided into 4 divided doses. In case of remission a dose of 300 mg/kg/day is administered intravenously, divided into 4 divided doses. The prophylactic administration in sickle cell anaemia must be permanent.

A dose lower than 160/mg/kg/per day or an irregular intake may cause a relapse of the illness. Piracetam is administered to children with sickle cell anaemia indication in recommended daily doses (mg/kg – see above). Piracetam has been administered only to a limited number of children in the age range of 1-3 years.

Elderly

Adjustment of the dose is recommended in elderly patients with compromised renal function *(see Section Warnings and Precautions; Renal impairment below)*.

For long term treatment in the elderly, regular evaluation of the creatinine clearance is required to allow dosage adaptation if needed.

Renal impairment

Piracetam is contraindicated in severe renal impairment (renal creatinine clearance of less than 20 ml per minute) *(see Sections: Contraindications; Warnings and Precautions)*.

The daily dose must be individualised according to renal function. Refer to the following table and adjust the dose as indicated. To use this dosing table, an estimate of the patient's creatinine clearance (Clcr) in ml/min is needed. The Clcr in ml/min may be estimated from serum creatinine (mg/dl) determination using the following formula:

$$Clcr = \frac{[140 - age\ (years)] \times weight\ (kg)}{72 \times serum\ creatinine (mg/dl)} (\times 0.85\ for\ women)$$

Group	Creatinine Clearance (ml/min)	Posology and frequency
Normal	>80	usual daily dose, 2 to 4 divided doses
Mild	50-79	2/3 usual daily dose, 2 or 3 divided doses
Moderate	30-49	1/3 usual daily dose, 2 divided doses
Severe	20-29	1/6 usual daily dose, 1 single intake
	<20	contre-indiqué
End-stage renal disease	-	contraindicated

Hepatic impairment

No dose adjustment is needed in patients with solely hepatic impairment. In patients with hepatic impairment and renal impairment, adjustment of dose is recommended *(see dose adjustment in Renal impairment above)*.

Contraindications

Piracetam is contraindicated in:

- hypersensitivity to piracetam, other pyrrolidone derivatives or any of the excipients,
- severe renal impairment (renal creatinine clearance of less than 20 ml per minute),
- cerebral haemorrhage,
- patients suffering from Huntington's Chorea.

Warnings and Precautions

Effects on platelet aggregation

Due to the effect of piracetam on platelet aggregation, caution is recommended in patients with severe haemorrhage, patients at risk of bleeding such as gastrointestinal ulcer, patients with underlying disorders of haemostasis, patients with a history of haemorrhagic CVA, patients undergoing major surgery including dental surgery, and patients using anticoagulants or platelet antiaggregant drugs including low dose acetylsalicylic acid.

Renal insufficiency

Piracetam is eliminated via the kidneys and care should thus be taken in cases of renal insufficiency *(see Section Dosage and Administration)*.

Elderly

For long-term treatment in the elderly, regular evaluation of the creatinine clearance is required to allow dosage adaptation if needed *(see Section Dosage and Administration)*

Discontinuation

Abrupt discontinuation of treatment should be avoided as this may induce myoclonic or generalised seizures in some myoclonic patients.

Sickle cell vaso-occlusive crises

For sickle cell indication, a dose lower than 160 mg/kg/day or irregular intake may result in relapse of crises.

Interactions

Pharmacokinetic interactions

The drug interaction potential resulting in changes of piracetam pharmacokinetics is expected to be low because approximately 90% of the dose of piracetam is excreted in the urine as unchanged drug.

In vitro, piracetam does not inhibit the human liver cytochrome P450 isoforms CYP 1A2, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1 and 4A9/11 at concentrations of 142, 426 and 1422 µg/ml. At 1422 µg/ml, minor inhibitory effects on CYP 2A6 (21%) and 3A4/5 (11%) were observed. However, the K_i values for inhibition of these two CYP isoforms are likely to be well in excess of 1422 µg/ml.

Therefore, metabolic interaction of piracetam with other drugs is unlikely.

Thyroid hormones

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

Acenocoumarol

In a published single-blind study on patients with severe recurrent venous thrombosis, piracetam 9.6 g/d did not modify the doses of acenocoumarol necessary to reach INR 2.5 to 3.5, but compared with the effects of acenocoumarol alone, the addition of piracetam 9.6 g/d significantly decreased platelet aggregation, ß-thromboglobulin release, levels of fibrinogen and von Willebrand's factors (VIII: C; VII: vW: Ag; VII: vW: RCo) and whole blood and plasma viscosity.

Antiepileptic drugs

A 20 g daily dose of piracetam over 4 weeks did not modify the peak and trough serum levels of antiepileptic drugs (carbamazepine, phenytoin, phenobarbitone, valproate) in epileptic patients who were receiving stable doses.

Alcohol

Concomitant administration of alcohol had no effect on piracetam serum levels and alcohol levels were not modified by a 1.6 g oral dose of piracetam.

Pregnancy and Lactation

Fertility

There are no relevant data available.

Pregnancy

Piracetam should not be used during pregnancy unless clearly necessary, when benefit exceeds the risks and the clinical condition of the pregnant mother requires treatment with piracetam.

There are no adequate data from the use of piracetam in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/foetal development, parturition or post-natal development.

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

Lactation

Piracetam should not be used during breastfeeding or breastfeeding should be discontinued, while receiving treatment with piracetam. A decision must be made whether to discontinue breastfeeding or to discontinue piracetam therapy taking into account the benefit of breastfeeding for the child and the benefit of therapy for the woman.

Piracetam is excreted in human breast milk.

Ability to perform tasks that require judgement, motor or cognitive skills

In view of the undesirable side effects, which were observed after the administration of the prepartion, there is the possibility of influence on the ability to drive and to operate machinery and this should be taken into consideration.

Adverse Reactions

Clinical Trial and Post Marketing Data

Double-blind placebo-controlled clinical or pharmaco-clinical trials, of which quantified safety data are available, included more than 3000 subjects receiving piracetam, regardless of indication, dosage form, daily dosage or population characteristics.

Adverse drug reactions (ADRs) are listed below by MedDRA system organ class and by frequency.

Frequencies are defined as:

Very common ≥1/10

Common ≥1/100 to <1/10

Uncommon ≥1/1000 to <1/100

Rare ≥1/10000 to <1/1000

Very rare <1/10000

Not known (cannot be estimated from the available data).

Blood and lymphatic system disorders

Not known: haemorrhagic disorder

Immune system disorders

Not known: anaphylactoid reaction, hypersensitivity

Psychiatric disorders

Common: nervousness

Uncommon: depression

Not known: agitation, anxiety, confusion, hallucination

Nervous system disorders

Common: hyperkinesia

Uncommon: somnolence

Not known: ataxia, balance disorder, epilepsy aggravated, headache, insomnia

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Ear and labyrinth disorders
Not known: vertigo
Vascular disorders
Rare: thrombophlebitis (only for injectable form), hypotension (only for injectable form)
Gastrointestinal disorders
Not known: abdominal pain, abdominal pain upper, diarrhoea, nausea, vomiting
Skin and subcutaneous tissue disorders
Not known: angioneurotic oedema, dermatitis, pruritus, urticaria
General disorders and administration site conditions
Uncommon: asthenia
Rare: pyrexia (only for injectable form), injection site pain (only for injectable form)
Investigations
Common: weight increased

Overdosage

Symptoms and signs
No additional adverse events specifically related to overdose have been reported with piracetam.
The highest reported overdose with piracetam was oral intake of 75 g wherein bloody diarrhoea with abdominal pain, was most probably related to the extreme high dose of sorbitol contained in the used formulation.

Treatment
There is no specific antidote for overdose with piracetam. Treatment for an overdose should be symptomatic and may include haemodialysis. The extraction efficiency of the dialyser is 50 to 60% for piracetam.
Further management should be as clinically indicated or as recommended by the national poisons centre, where available.

Clinical Pharmacology

Pharmacodynamics

Pharmacotherapeutic group
Psychostimulants, agents used for ADHD and nootropics

ATC Code
N06BX03

Mechanism of Action
Available data suggest that piracetam basic mechanism of action is neither cell- nor organ-specific. Piracetam binds physically in a dose-dependent manner to the polar head of phospholipids membrane models, inducing the restoration of the membrane lamellar structure characterised by the formation of mobile drug-phospholipid complexes. This probably accounts for an improved membrane stability, allowing the membrane and transmembrane proteins to maintain or recover the three-dimensional structure or folding essential to exert their function. Piracetam has neuronal and vascular effects.

Pharmacodynamic effects
Neuronal effect
At the neuronal level, piracetam exerts its membrane activity in various ways. In animals, piracetam enhances a variety of types of neurotransmission, primarily through postsynaptic modulation of receptor density and activity. In both animals and man, the functions involved in cognitive processes such as learning, memory, attention and consciousness were enhanced, in the normal subject as well as in deficiency states, without the development of sedative or psychostimulant effects. Piracetam protects and restores cognitive abilities in animals and man after various cerebral insults such as hypoxia, intoxications and electroconvulsive therapy. It protects against hypoxia-induced changes in brain function and performance as assessed by electroencephalograph (EEG) and psychometric evaluations.
Vascular effects
Piracetam applies its haemorrhagic effect to thrombocytes, erythrocytes and the walls of the blood vessels by increasing the deformability of erythrocytes, reducing the aggregability of thrombocytes, reduces the adhesion of erythrocytes to the walls of vessels and reduces capillary vasospasm.
Effects on the red blood cells
In patients with sickle cell anaemia, piracetam improves the deformability of the erythrocyte membrane, decreases blood viscosity, and prevents rouleaux formation.
Effects on platelets
In open studies in healthy volunteers and in patients with Raynaud's phenomenon, increasing doses of piracetam up to 12 g was associated with a dose-dependent reduction in platelet functions compared with pre-treatment values (tests of aggregation induced by ADP, collagen, epinephrine and ß TG release), without significant change in platelet count. In these studies, piracetam prolonged bleeding time.
Effects on blood vessels
In animal studies, piracetam inhibited vasospasm and counteracted the effects of various spasmogenic agents. It lacked any vasodilatory action and did not induce "steal" phenomenon, nor low or no reflow, nor hypotensive effects.
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, compared with pre-treatment values, piracetam up to 9.6 g reduced plasma levels of fibrinogen and von Willebrand's factors (VIII: C; VIII R: AG; VIII R: vW) by 30 to 40 %, and increased bleeding time.
In patients with both primary and secondary Raynaud phenomenon, compared with pre-treatment values, piracetam 8 g/d during 6 months reduced plasma levels of fibrinogen and von Willebrand's factors (VIII: C; VIII R: AG; VIII R: vW (RCF)) by 30 to 40 %, reduced plasma viscosity, and increased bleeding time.

Pharmacokinetics
The pharmacokinetic profile of piracetam is linear and time-independent with low intersubject variability over a large range of doses. This is consistent with the high permeability, high solubility, and minimal metabolism of piracetam. Plasma half-life of piracetam is 5 hours. It is similar in adult volunteers and in patients. It is increased in the elderly (primarily due to impaired renal clearance) and in subjects with renal impairment. Steady state plasma concentrations are achieved within 3 days of dosing.

Absorption
Piracetam is rapidly and extensively absorbed following oral administration. In fasted subjects, the peak plasma concentrations are achieved 1 hour after dosing. The absolute bioavailability of piracetam oral formulations is close to 100%. Food does not affect the extent of absorption of piracetam but it decreases C_{max} by 17% and increases T_{max} from 1 to 1.5 hours. Peak concentrations are typically 84 µg/ml and 115 µg/ml following a single oral dose of 3.2 g and repeat dose of 3.2 g twice daily, respectively.

Distribution
Piracetam is not bound to plasma proteins and its volume of distribution is approximately 0.6 l/kg. Piracetam crosses the blood brain barrier as it has been measured in cerebrospinal fluid following intravenous administration. In cerebrospinal fluid, the T_{max} was achieved about 5 hours post-dose and the half-life was about 8.5 hours. In animals, piracetam highest concentrations in the brain were in the cerebral cortex (frontal, parietal and occipital lobes), in the cerebellar cortex and in the basal ganglia. Piracetam diffuses to all tissues except adipose tissues, crosses placental barrier, and penetrates the membranes of isolated red blood cells.

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

Elimination
The plasma half-life of piracetam in adults is about 5 hours following either intravenous or oral administration. The apparent total body clearance is 80-90 ml/min. The major route of excretion is via urine, accounting for 80 to 100% of the dose. Piracetam is excreted by glomerular filtration.

Linearity
The pharmacokinetics of piracetam are linear over the dose range of 0.8 to 12 g. Pharmacokinetic variables like half-life and clearance are not changed with respect to the dose and the duration of treatment.

Special patient populations
Children
No formal pharmacokinetic study has been conducted in children.
Elderly
In the elderly, the half-life of piracetam is increased and the increase is related to the decrease in renal function in this population *(see Section Dosage and Administration)*.
Renal impairment
Piracetam clearance is correlated to creatinine clearance. It is therefore recommended to adjust the daily dose of piracetam based on creatinine clearance in patients with renal impairment *(see Section Dosage and Administration)*. In anuric End Stage Renal Disease subjects, the half-life of piracetam is increased up to 59 hours. The fractional removal of piracetam was 50 to 60% during a typical 4-hour dialysis session.
Hepatic impairment
The influence of hepatic impairment on the pharmacokinetics of piracetam has not been evaluated. Because 80 to 100% of the dose is excreted in the urine as unchanged drug, hepatic impairment solely would not be expected to have a significant effect on piracetam elimination.
Other patient characteristics
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, clearances adjusted for body weight were comparable.
Race
Formal pharmacokinetic studies of the effects of race have not been conducted. Cross study comparisons invalving Caucasians and Asians, however, show that pharmacokinetics of piracetam were comparable between the two races. Because piracetam is primarily renally excreted and there are no important racial differences in creatinine clearance, pharmacokinetic differences due to race are not expected.

Clinical Studies
see Section Pharmacodynamic effects

NON-CLINICAL INFORMATION
The preclinical data indicate that piracetam has a low toxicity potential. Single dose studies showed no irreversible toxicity after oral doses of 10 g/kg in mice, rats and dogs. No target organ for toxicity was observed in repeated dose, chronic toxicity studies in mice (up to 4.8 g/kg/day) and in rats (up to 2.4 g/kg/day). Mild gastrointestinal effects (emesis, change in stool consistency, increased water consumption) were observed in dogs when piracetam was administered orally for one year at a dose increasing from 1 to 10 g/kg/day. Similarly, i.v. administration of up to 1 g/kg/day for 4-5 weeks in rats and dogs did not produce toxicity. *In vitro* and *in vivo* studies have shown no potential for genotoxicity and carcinogenicity.

PHARMACEUTICAL INFORMATION

Shelf-Life
48 months

Storage
Store below 30°C.

Nature and Contents of Container
film-coated tablet in PVC Blister . Box of 45.

Incompatibilities
None known

Use and Handling
There are no special requirements for use or handling of this product.

Manufacturer:
UCB Pharma SA
Chemin du Foriest
1420 Braine-l'Alleud
Belgium

Marketing authorization holder:
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Total Colours & Varnishes: 1

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Total Special Finishes: 0

Body Text Size: 7.0pt	
Smallest Text Size: 7.0pt	
Leading: 7.5pt	
Horizontal Scale: 85%	
Microtext: N	
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200 mm Measuring Bar

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GSK Market is responsible to advise SDC when changes required impact the following:

Formulation
Tablet embossing
Storage conditions
Shelf Life

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