CETAM INJECTION 200MG/ML

Ingredient(s):
Each ml contains:
Piracetam 200mg

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.

Pharmacodynamics:
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 β 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's phenomenon, compared with pretreatment 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 three times 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 Tmax 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

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.

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.

Non-Clinical Information:
Single doses of piracetam yielded LD 50 values at 26 g/kg in mice but LD 50 values were not reached in rats. In dogs, clinical signs after acute oral dosing were mild and lethality was not observed at the maximum tested dose of 10 g/kg.

Repeated oral treatment for up to 1 year in dogs (10 g/kg) and 6 months in rats (2 g/kg) was very well tolerated: no target organ toxicity or signs of (irreversible) toxicity were clearly demonstrated. Safe dose levels represent a multiple of the maximum intended human daily dose of 0.4 g/kg.

In terms of exposure (Cmax) safe levels obtained in the rat and the dog represent respectively 8 fold and 50 fold of the maximum human therapeutic level. AUC levels obtained in the same animals were a multiple of the human AUC level at the maximum intended daily dose.

The only change which might eventually be attributed to chronic treatment in male, but not in female, rats was an increase of the incidence over control animals of progressive glomerulonephrosis at the dose of 2.4 g/kg/day given for 112 weeks.

Although piracetam crosses the placenta into the foetal circulation, no teratogenic effects were observed at dose levels up to 4.8 g/kg/day (mice, rats) and 2.7 g/kg/day (rabbits). Furthermore, the compound affects neither fertility nor the peri- or postnatal development of the pregnancy at doses up to 2.7 g/kg/day.

Piracetam was found to be devoid of any mutagenic or clastogenic activity and does not represent any genotoxic or carcinogenic risk to man.

Indication(s):
Treatment of the elderly with some degree of cerebral functional impairment such as loss of memory, a lack of concentration or alertness and vertigo.

Dosage and Administration(s):
- The total daily dose can range from 30 to 160 mg/kg/day depending on the indication. This is administered twice daily, but may also be given in three or four separate doses.
- When treating severe symptoms, 12 g daily may need to be administered as an intravenous infusion.
- In the treatment of chronic psycho-organic brain syndrome in the elderly 4.8 g daily is given initially, followed, after a few weeks, by maintenance therapy at 1.2 to 2.4 g per day.

Elderly
Adjustment of the dose is recommended in elderly patients with compromised renal function (see Sections: Precaution(s) / Warnings(s); 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; Precaution(s) / Warnings(s))*. 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 (CL_{cr}) in ml/min is needed. The CL_{cr} in ml/min may be estimated from serum creatinine (mg/dl) determination using the following formula:

$$Cl_{cr} = \frac{([140 - \text{age (years)}] \text{ X weight (kg) (X 0.85 for women)})}{(72 \text{ x serum creatinine (mg/dl)})}$$

Group	Creatinine Clearance (ml/min)	Posology and frequency
Normal	> 80	Usual daily dose, 2 to 4 divided doses
Mild	50 – 79	⅔ 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	Contraindicated
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)*.

Mode of Administration:
Parenteral:
For Intravenous Use.

Contraindication(s):
Piracetam is contraindicated in:

- hypersensitivity to piracetam, other pyrrolidone derivatives or any of the excipients,
- Severe renal disease (renal creatinine clearance of less than 20 ml per minute),
- cerebral haemorrhage.
- Huntington's chorea.

Precaution(s) / Warning(s):
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 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.

Interaction with Other Medicaments:
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 Ki 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, β-thromboglobulin release, levels of fibrinogen and von Willebrand's factors (VIII: C; VIII: vW: Ag; VIII: 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.

Pregnancy and Lactation:
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 breast-feeding or to discontinue piracetam therapy taking into account the benefit of breast-feeding 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 effects, which were observed after the administration of the preparation, there is the possibility of influence on the ability to drive and to operate machinery and this should be taken into consideration.

Side Effect(s):
Clinical studies
Double-blind placebo-controlled clinical or pharmacoclinical trials, of which quantified safety data are available (extracted from the UCB Documentation Data Bank on June 1997), 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 impaired, epilepsy aggravated, headache, insomnia

Ear and labyrinth disorders
Not known: vertigo

Vascular disorders
Rare: thrombophlebitis, hypotension

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, injection site pain

Investigations
Common: weight increased

Symptoms and Treatment for Overdosage, and Antidote(s):
Symptoms and signs
No additional adverse events specifically related to overdose have been reported with piracetam.

Treatment
There is no specific antidote for overdose with piracetam. Treatment for an overdose will be symptomatic treatment and may include haemodialysis. The extraction efficiency of the dialyser is 50 to 60% for piracetam.

Incompatibilities:
There are no known incompatibilities.

Piracetam is compatible (physico-chemical compatibility) with the following IV infusion fluids:
1) Sodium Chloride 0.9%
2) Glucose 5%

The IV solution should be prepared at the time of infusion or stored at below 30°C for no more than 24 hours.

Shelf-Life:
3 years. Discard after opening.

Storage Condition(s):
Store at temperature below 30°C. Protect from light and moisture.

Product Description:
A clear and colorless solution.
Solution remains clear after reconstitution

Excipients:
Hydrochloric Acid, Sodium Phosphate Dibasic, Citric Acid, Water for Injection.

Dosage Forms and Packaging available:
5ml x 10 and 5ml x 50 ampoules.
Not all presentations may be available locally.

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