

Piracetam

Proposed Core Safety Profile

4.2 Posology and method of administration

[This information is applicable if the indication is registered]

Treatment of myoclonus of cortical origin

The daily dosage should begin at 7.2 g increasing by 4.8 g every three to four days up to a maximum of 24 g, in two or three sub-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.

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 and Adams syndrome, in order to prevent the possibility of sudden relapse or withdrawal seizures).

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 vertigo

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

For prophylaxis and remission of sickle cell vaso-occlusive crises

The recommended daily dose for prophylaxis is 160 mg/kg orally.

The recommended daily dose for remission is 300 mg/kg intravenously.

A dose lower than 160 mg/kg/day or irregular intake may result in relapse of crises.

Children

Treatment of dyslexia in combination with speech therapy

In children from 8 years old and adolescents, the recommended daily dose is about 3.2 g, in two sub-doses.

For prophylaxis and remission of sickle cell vaso-occlusive crises

The recommended daily dose for prophylaxis is 160 mg/kg orally.

The recommended daily dose for remission is 300 mg/kg intravenously.

A dose lower than 160 mg/kg/day or irregular intake may result in relapse of crises.

Piracetam can be administered to children from 3 years old onwards suffering from sickle cell anemia at the recommended daily dose regimen (mg/kg). Piracetam has been administered in a limited number of children aged 1 to 3 years old.

Elderly

Adjustment of the dose is recommended in elderly patients with compromised renal function (see 'Dosage adjustment in patients with renal impairment' below). For long term treatment in the elderly, regular evaluation of the creatinine clearance is required to allow dosage adaptation if needed.

Patients with renal impairment

The daily dose must be individualized 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:

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

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

Patients with 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 'Dosage adjustment in patients with renal impairment' above).

Method of administration

Piracetam should be administered orally, and may be taken with or without food. The capsule(s) and/or tablet(s) should be swallowed with liquid. Granules should be dissolved in liquid. It is recommended to take the daily dose in two to four sub-doses.

[This information is applicable if the parenteral formulations are registered]

Parenteral administration

When parenteral administration is needed (e.g. swallowing difficulties, unconsciousness) piracetam can be administered intravenously at the same recommended daily dose.

- The injectable ampoules will be administered intravenously over several minutes.
- The infusion will be administered continuously at the recommended daily dose over a 24-hour period.

4.3 Contra-indications

Hypersensitivity to piracetam or other pyrrolidone derivatives or any of the excipients.

Piracetam is contra-indicated in patients with cerebral haemorrhage.

Piracetam is contra-indicated in End Stage Renal Disease patients.

Piracetam should not be used in patients suffering from Huntington's Chorea.

4.4 Special warnings and special precautions for use

Effects on platelet aggregation

Due to the effect of piracetam on platelet aggregation (see section 5.1), 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 aspirin.

Renal insufficiency

Piracetam is eliminated via the kidneys and care should thus be taken in cases of renal insufficiency (see section 4.2).

Elderly

For long-term treatment in the elderly, regular evaluation of the creatinine clearance is required to allow dosage adaptation if needed (see section 4.2).

[This information is applicable if the indication is registered]

Discontinuation

Abrupt discontinuation of treatment should be avoided in myoclonic patients as this may induce sudden relapse or withdrawal seizures.

[This information is applicable if the indication is registered]

Sickle cell

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

[This information is applicable depending on the registered formulation]

Warnings related to the excipients ¹:

- Sunset Yellow FCF (E110): May cause allergic reactions.
- Mannitol (E421): May have a mild laxative effect from an intake of 6.5g piracetam or more, daily.
- Aspartam (E951): Contains a source of phenylalanine equivalent to 50 mg for a dose of 2.4g piracetam. May be harmful for people with phenylketonuria.
- Methyl parahydroxybenzoate and propylparahydroxybenzoate: May cause allergic reactions (possibly delayed).
- Glycerol: May cause headache, stomach upset and diarrhoea.
- Sorbitol: Patients with rare hereditary problems of fructose intolerance should not take this medicine. Contains 4.8 g sorbitol for a dose of 2.4g piracetam, a source of 1.2 g fructose. May have a mild laxative effect at dose higher than 5 g sorbitol. Calorific value: 2.6 kcal/g sorbitol.
- Sodium:

Piracetam 800 mg and 1200 mg film-coated tablets: This product contains about 2 mmol (or about 46 mg) sodium per 24 g piracetam. To be taken into consideration by patients on a controlled sodium diet.

Piracetam 20% oral solution (bottle and ampoule): This product contains about 3.5 mmol (or about 80.5 mg) sodium per 24 g piracetam. To be taken into consideration by patients on a controlled sodium diet.

Piracetam 33% oral solution (bottle and ampoule): This product contains about 1 mmol (or about 23 mg) sodium per 24 g piracetam. To be taken into consideration by patients on a controlled sodium diet.

Piracetam 1g/5ml, 3g/15ml ampoule: This product contains less than 1 mmol (23mg) sodium per 24 g piracetam.. Piracetam 12g/60ml infusion: This product contains about 19 mmol (or about 445 mg) sodium per 24 g piracetam. To be taken into consideration by patients on a controlled sodium diet.

4.5 Interaction with other medicinal products and other forms of interaction

Pharmacokinetics 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.

¹ To be selected according to pharmaceutical form

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, 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 and alcohol levels were not modified by a 1.6 g oral dose of piracetam.

4.6 Pregnancy and lactation

Pregnancy

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 (see section 5.3).

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

Lactation

Piracetam is excreted in human breast milk. Therefore, 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.

4.7 Effects on ability to drive and use machines

Given the adverse events observed with the drug, an influence on driving and using machines is possible and should be taken into account.

4.8 Undesirable effects

a. Summary of safety profile

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.

b. Tabulated list of adverse reactions

Undesirable effects reported in clinical studies and from post-marketing experience are listed in the following table per System Organ Class and per frequency. The frequency is defined as follows: very common ($\geq 1/10$); common ($\geq 1/100, < 1/10$); uncommon ($\geq 1/1,000, < 1/100$); rare ($\geq 1/10,000, < 1/1,000$); very rare ($< 1/10,000$). Data from post-marketing experience are insufficient to support an estimate of their incidence in the population to be treated.

Blood and Lymphatic 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 (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: injection site pain (only for injectable form), pyrexia (only for injectable form)

Investigations

Common: weight increased

4.9 Overdose

4.9.1 Symptoms

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. Bloody diarrhoea with abdominal pain, was most probably related to the extreme high dose of sorbitol contained in the used formulation.

4.9.2 Management of overdose

In acute, significant overdosage, the stomach may be emptied by gastric lavage or by induction of emesis. There is no specific antidote for overdose with piracetam. Treatment for an overdose will be symptomatic

treatment and may include hemodialysis. The extraction efficiency of the dialyser is 50 to 60% for piracetam.