YSP KNOWFUL® INJECTION 200MG/ML

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

Pharmacology (Summary of Pharmacodynamic and Pharmacokinetic):
Pharmacodynamics:
Piracetam is a psychotropic agent which acts directly on the brain to improve the efficacy of the telencephalon in both normal subjects and those suffering from some functional deficit. This area of the brain is involved in cognition and also has a role to play in learning and memory, in alertness and in consciousness. Piracetam does not produce either sedation or stimulation. Piracetam can act on the central nervous system in a variety of ways. It will modify neurotransmission within the brain, and can help to improve the metabolic environment essential for good neuronal function.
It is also a haemorrheological agent and can improve microcirculation without producing vasodilation.
When given as acute or long term treatment for patients suffering from a functional CNS deficit, it will heighten alertness and increase cognitive function. These changes are seen as a significant increase in the alpha and beta activity, with a reduction in delta activity, on an EEG trace.
Piracetam will protect and restore cognitive functional capacity after cerebral trauma such as hypoxia or intoxication, and after electroshock therapy.
Piracetam may be given alone or together with other drugs when treating cortical myoclonia. This product will reduce the duration of vestibular nystagmus. Piracetam will improve regional oxygen and glucose uptake in the brain in patients suffering from dementia subsequent to multiple infarcts, or in those with cerebral ischaemia. Piracetam will inhibit the increased aggregation of activated platelets and, in conditions where there is abnormal rigidity of the red blood cell, it can restore deformability and the ability to pass through the microvasculature.

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 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. 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.

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

2. Indicated for patients suffering from myoclonus of cortical origin, irrespective of aetiology and should be used in combination with other anti-myoclonic therapies.

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, either by mouth or parenterally. The oral route is preferred to parenteral if the patient's condition permits. Should parenteral treatment be discontinued, the contents of any remaining ampoules can be given by mouth.
- 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.
- In the treatment of cortical myoclonias, dosage should commence at 7.2 g/day, increasing by 4.8 g/day every three or four days up to a maximum of 24 g/day, the drug being given twice or three times daily.

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.
Nevertheless, 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, in order to prevent the possibility of sudden relapse.

Mode of Administration:
Parenteral.

Contraindication(s):
Piracetam is contraindicated in:
- hypersensitivity to piracetam, other pyrrolidone derivatives or any of the excipients,
- end stage renal disease (renal creatinine clearance of less than 20 ml per minute),
- cerebral haemorrhage.

Precaution(s) / Warning(s):
As the principal route of elimination for piracetam is via the kidney, special care must be taken when treating patients known to suffer from renal insufficiency. Monitoring of renal function is recommended in such cases. The increase in half-life is directly related to the decrease in renal function and creatinine clearance. This is also true for the older patient in whom creatinine clearance is dependent on age. The daily dose

must be individualized according to renal function. Due to effect of piracetam on platelet aggregation, caution is recommended in patients with underlying disorders of haemostasis, major surgery or severe haemorrhage.

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

Interaction with Other Medicaments:
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.

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.

Incompatibilities:
The compatible solutions that can be mixed are:
i) 5% Glucose
ii) 0.9% Sodium Chloride
The mixture should be prepared the same day the solution is to be used.

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.

Side Effect(s):
The side effects reported in connection with this product include nervousness, agitation, irritability, anxiety and sleep disturbances. In the majority of cases, a dose reduction sufficed to make these symptoms disappear. Some patients may complain of fatigue or drowsiness. Gastrointestinal problems eg, nausea, vomiting, diarrhea and stomach ache have also been reported. Other symptoms eg, vertigo, headaches, trembling and sexual stimulation have occasionally been reported.

There is the possibility of influence on the ability to drive and to operate machinery and this should be taken into consideration.

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, headache, insomnia

Ear and labyrinth disorders
Not known: vertigo

Vascular disorders
Rare: thrombophlebitis (only parenteral formulations), hypotension (only parenteral formulations)

Gastrointestinal disorders
Not known: abdominal pain, abdominal pain upper, diarrhoea, nausea, vomiting

Skin and subcutaneous tissue disorders
Not known: angioedema, dermatitis, pruritus, urticaria

General disorders and administration site conditions
Uncommon: asthenia
Rare: pyrexia (only parenteral formulations), pain at the place of injection (only parenteral formulations)

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.
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
In acute, significant overdosage, the stomach may be emptied by induction of emesis. 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.

Shelf-Life:
3 years. Discard after opening.

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

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

Dosage Forms and Packaging available:
5ml x 10 and 5ml x 50 ampoules.

Y. S. P.®
Manufacturer and Product Registration Holder:
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