8027342-9093

For the use of a Registered Medical Practitioner
or a Hospital or a Laboratory only

STROLIN P

(Citicoline And Piracetam Tablets)

COMPOSITION :

STROLIN P 400

Each film coated tablet contains :
Citicoline Sodium I.P. equivalent to
Citicoline 500 mg
Piracetam I.P. 400 mg
Colours : Yellow Oxide of Iron & Titanium Dioxide I.P.

STROLIN P 800

Each film coated tablet contains :
Citicoline Sodium I.P. equivalent to
Citicoline 500 mg
Piracetam I.P. 800 mg
Colours : Brilliant Blue FCF &Titanium Dioxide I.P.

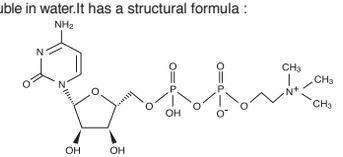
DOSAGE FORM

Tablet for oral use

DESCRIPITION

Citicoline

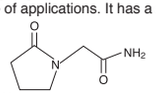
A naturally occurring endogenous nucleoside, is an intermediate compound in the major pathway for the biosynthesis of the structural phospholipids of cell membranes, including neurons. This pathway is termed the Kennedy pathway. It has chemical formula *cytidine 5'-(trihydrogen diphosphate)p'-[2-trimethylammonio)ethyl] ester.* Citicoline is a polarized molecule with molecular formula is $C_{14}H_{26}N_4O_{11}P_2$ and molecular weight is 488.33. It is a white crystalline, very hygroscopic powder which is soluble in water.It has a structural formula :



Piracetam

Piracetam is a nootropic. It is a drug which is claimed to enhance cognition and memory, slow down brain aging, increase blood flow and oxygen to the brain, aid stroke recovery, and improve Alzheimer's, Down syndrome, dementia, and dyslexia, among others. Piracetam's chemical name is 2-(2-oxopyrrolidin-1-yl) acetamide; with a molecular formula is $C_6H_{10}N_2O_2$ and molecular weight is 142.2. it shares the same 2-oxo-pyrrolidone base structure with 2-oxo-pyrrolidine carboxylic acid (pyroglutamate).

Piracetam is a cyclic derivative of GABA. It is one of the racetams. Piracetam is prescribed by doctors for some conditions, mainly myoclonus, but is used off-label for a much wider range of applications. It has a structural formula :



PHARMACOLOGY

Pharmacokinetics :

Citicoline is a water-soluble compound with greater than 90-percent bioavailability. Pharmacokinetic studies on healthy adults have shown oral doses of Citicoline are rapidly absorbed, with less than one percent excreted in feces. Plasma levels peak in a biphasic manner, at one hour after ingestion followed by a second larger peak at 24 hours post-dosing. Citicoline is metabolized in the gut wall and liver. The byproducts of exogenous Citicoline formed by hydrolysis in the intestinal wall are choline and cytidine. Following absorption, choline and cytidine are dispersed throughout the body, enter systemic circulation for utilization in various biosynthetic pathways, and cross the blood-brain barrier for re-synthesis into citicoline in the brain.

Pharmacokinetic studies using ^{14}C citi-coline show citicoline elimination occurs mainly via respiratory CO_2 and urinary excretion, in two phases mirroring the biphasic plasma peaks. The initial peak in plasma concentration is followed by a sharp decline, which then slows over the next 4-10 hours. In the second phase, an initially rapid decline after the 24-hour plasma peak is similarly followed by a slower elimination rate. The elimination half-life is 56 hours for CO_2 and 71 hours for urinary excretion.

Piracetam is rapidly and almost completely absorbed. Peak plasma levels are reached within 1.5 hours after administration. The extent of oral bioavailability, assessed from the Area Under Curve (AUC), is close to 100 % for capsules, tablets and solution. Peak levels and AUC are proportional to the dose given. The volume of distribution of piracetam is 0.7 L/kg, and the plasma half-life is 5.0 hours, in young adult men. Piracetam crosses the blood-brain and the placental barrier and diffuses across membranes used in renal dialysis.

Up to now, no metabolite of piracetam has been found. Piracetam is excreted almost completely in urine and the fraction of the dose excreted in urine is independent of the dose given. Excretion half-life values are consistent with those calculated from plasma/blood data. Clearance of the compound is dependent on the renal creatinine clearance and would be expected to diminish with renal insufficiency.

Pharmacodynamics

Citicoline

When administered orally, it is absorbed almost completely, and its bioavailability is approximately the same when administered intravenously. Once absorbed, the cytidine and choline disperse widely throughout the body, cross the blood-brain barrier, and reach the central nervous system (CNS), where they are incorporated into the phospholipid fraction of the cellular membrane and microsomes.

The concept that administration of exogenous Citicoline might augment the synthesis of neural membrane phospholipid is attractive, because accelerated replacement or repair plays a critical role in maintaining the healthy function of numerous physiological processes. It has shown therapeutic efficacy in a variety of diseases in which memebrane disorder, dysfunction, or degeneration result in cellular and tissue ischaemia and necrosis.

Piracetam

The mechanism of action of piracetam is not known, although it is hypothesized to act on ion channels or ion carriers, thus leading to non-specific increased neuron excitability, while explaining its lack of agonistic or inhibitory effect on synaptic action (quite unlike most neurotransmitters), and its low toxicity. It has been found to increase blood flow and oxygen consumption in parts of the brain but this may be a side-effect of increased brain activity rather than a primary effect or mechanism of action for the drug. Piracetam improves the function of the neurotransmitter acetylcholine via muscarinic cholinergic (ACh) receptors which are implicated in memory processes. Furthermore, Piracetam may have an effect on NMDA glutamate receptors which are involved with learning and memory processes. Piracetam is thought to increase cell membrane permeability.

Piracetam may exert its global effect on brain neuro transmission via modulation of ion channels (i.e., Na^+, K^+). It has been found to increase oxygen consumption in the brain, apparently in connection to ATP metabolism, and increases the activity of adenylate kinase in rat brain. Piracetam appears to increase the synthesis of cytochrome B_5, which is a part of the electron transport mechanism in mitochondria. It also increases the permeability of the mitochondria of some intermediaries of the Krebs cycle.

INDICATIONS

Fixed-dose combination of Citicoline and Piracetam is indicated in the management of acute stroke.

DOSAGE AND ADMINISTRATION

One tablet 2 times daily

CONTRAINDICATIONS

Fixed-dose combination of Citicoline and Piracetam is contra-indicated in patients with severe renal impairment (renal creatinine clearance of less than 20 ml per minute), hepatic impairment and to those under 16 years of age. It is also contraindicated in patients with cerebral haemorrhage, suffering from Huntington's Chorea and in those with hypersensitivity to any of the ingredients, other pyrrolidone derivatives or any of the excipients.

ADVERSE EFFECTS

Citicoline

The most frequent adverse events included minor nervous system-related complaints (numbness, headache, tingling sensations) followed by gastrointestinal symptoms (abdominal discomfort, diarrhea).

Piracetam

Undesirable effects reported in clinical studies and from post-marketing experience are listed as per System Organ Class and per frequency. The frequency is defined as follows: very common (1/10); common (1/100,<1/10); uncommon (1/1,000, <1/100); rare (1/10,000, <1/1,000); very rare (<1/10,000).

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
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
Investigations
Common: weight increased

WARNINGS AND PRECAUTIONS

Fixed-dose combination of Citicoline and Piracetam has two components; a Citicoline and Piracetam. 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 aspirin. Piracetam is eliminated via the kidneys and care should thus be taken in cases of renal insufficiency. For long-term treatment in the elderly, regular evaluation of the creatinine clearance is required to allow dosage adaptation if needed. Abrupt discontinuation of treatment should be avoided as this may induce myoclonic or generalised seizures in some myoclonic patients.

PREGNANCY AND LACTATION

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. Hence Fixed-dose combination of Citicoline and 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. Piracetam is excreted in human breast milk. Therefore, Fixed-dose combination of Citicoline and 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 Fixed-dose combination of Citicoline and Piracetam therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

OVERDOSE

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.

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.

INTERACTIONS

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

EXPIRY DATE

Do not use later than the date of expiry.

STORAGE

Store below 25^{o}C, protected from light and moisture.
Keep out of reach of children

PRESENTATION

Strolin P 400 and Strolin P 800 are available as blister strip of 4 tablets.

torrent

Marketed by :
TORRENT PHARMACEUTICALS LTD.
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