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

STROLIN P

1. **Generic Name**

Citicoline And Piracetam Tablets

2. **Qualitative and quantitative 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.

The list of excipients used are Maize Starch, Crospovidone, Croscarmellose Sodium, Polyvinylpyrrolidone, Talcum, Colloidal Silicon Dioxide, Magnesium Stearate, Hydroxy Propyl Methyl Cellulose, Polyethylene Glycol, Titanium Dioxide, Yellow Oxide of Iron Lake Colour, Isopropyl Alcohol and Methylene Chloride.

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.

The list of excipients used are Maize Starch, Crospovidone, Croscarmellose Sodium, Polyvinylpyrrolidone, Microcrystalline Cellulose, Talcum, Colloidal Silicon Dioxide, Magnesium Stearate, Sodium Lauryl Sulphate, Sodium Starch Glycolate, Hydroxy Propyl Methyl Cellulose, Ethyl Cellulose, Diethyl Phthalate, Polyethylene glycol, Lake Brilliant Blue, Titanium Dioxide, Isopropyl Alcohol and Methylene Chloride.

3. **Dosage form and strength**

Dosage form: Film coated tablet.

Strength: 500 mg + 400 mg & 500 mg + 800 mg

4. **Clinical particulars**

4.1. Therapeutic indication

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

4.2. Posology and method of administration

Posology

Dosage should be individualized; it depends on the severity of the symptoms and the response of the individual patient. The usually recommended dose is one tablet three times a day orally or as directed by the physician. The dose may be increased up to four tablets per day.

Elderly

Adjustment of the dose is recommended in elderly patients with compromised renal function. 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.

Table: Dosaage adjustment in patients with renal impairment

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

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.

Method of administration

Piracetam should be administered orally and may be taken with or without food. The tablet(s) should be swallowed with liquid.

4.3. Contraindications

- Must not be administered to patients with hypertonic of the parasympathetic and hypersensitivity to citicoline/piracetam or any other component of the formulation.
- Piracetam is contra-indicated in patients with severe renal impairment (renal creatinine clearance of less than 20 ml per minute). It is also contraindicated in patients with cerebral hemorrhage and in patients suffering from Huntington's Chorea.

4.4. Special warnings and precautions for use

Citicoline

Must not be administered in conjunction, with medications containing centrophenoxine. In case of persistent intracranial haemorrhage, it is recommended not to exceed the dose of 1000 mg daily.

Cholines are generally regarded as safe and appear to be well-tolerated. High intake of cholines may cause low blood pressure, steatorrhea (undigested fat in stool), nausea, vomiting, salivation, diarrhoea, constipation, anorexia, dizziness (vertigo), sweating, insomnia and headache. Cholines can possibly trigger existing epilepsy.

Dosages at the upper limit (UL) intake levels are contraindicated for person suffering from trimethylaminuria, Parkinson's disease, or kidney or liver disease. Skin rash has been reported. A cold and cough were noted in patients taking citicoline in a trial. Choline should be used cautiously by people with kidney or liver disorders. Agitation, paranoia and severe depression have been reported. Use cautiously in patients with a history of depression. Because choline is a product of the breakdown of succinylcholine, it may produce similar side effects as the drug,

like respiratory depression. A "fishy" odour has been associated with choline. Sweating and stunted growth may occur.

Do not consume alcohol while taking citicoline. Make sure doctor is aware of upcoming surgeries that may have scheduled; or will be scheduling while taking this medication.

Piracetam

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 cerebro-vascular accident (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.

Elderly

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

Discontinuation

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

4.5. Drugs interactions

Levodopa

Citicoline may enhance the effects of levodopa. The exact mechanism is unknown, but animal models suggest that citicoline may increase dopamine levels in the brain and/or improve dopaminergic cell survival. In patients with Parkinson's disease, a few studies have demonstrated levodopa-saving effects, whereby the addition of citicoline (500 to 1200 mg/day) allowed for lower dosages of levodopa to be used with stable or improved therapeutic efficacy and reduced side effects in some patients. However, data are limited.

Coadministration with Meclofenoxate

Citicoline must not be administered in conjunction with medication containing meclofenoxate (also known as Clophenoxate).

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.

4.6. Use in special populations (such as pregnant women, lactating women, paediatric patients, geriatric patients etc.)

Patients with Renal Impairment

Adjustment of the dose is recommended in elderly patients with compromised renal function. For long-term treatment in the elderly, regular evaluation of the creatinine clearance is required to allow dosage adaptation if needed. The daily dose must be individualized according to renal function. (see patients with renal impairment above)

Patients with Hepatic Impairment

There are no data concerning the effects of liver insufficiency on the safety profile and pharmacokinetics of citicoline.

No dose adjustment is needed in patients with solely hepatic impairment. In patients with hepatic impairment and renal impairment, adjustment of dose is recommended

Pregnant Women

There are no adequate and well controlled studies od citicoline during pregnancy and lactation. Citicoline should be used in pregnancy only if the potential benefit justifies the potential risk to the foetus.

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. 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

Lactating Women

There are no adequate and well controlled studies od citicoline during pregnancy and lactation. Caution should be exercised during breastfeeding because it is not known whether citicoline is excreted in human breast milk.

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.

Paediatric Patients

The experience in children is limited; therefore, it may only be administered when the expected therapeutically benefit is higher than any possible risk.

Geriatric Patients

No dosage adjustment is required in this patient population and the usually recommended adult dose can be administered. However, adjustment of the dose is recommended in elderly patients with compromised renal function.

4.7. Effects on ability to drive and use machines

Patient are advised not to operate heavy machinery or automobiles until the full effect of citicoline is known.

4.8. Undesirable effects

Citicoline

A study administered citicoline or placebo to 12 healthy volunteers in two oral regimens repeated at short-term intervals (600 mg/day and 1g/day), every day for 5 days. The only adverse effects that appeared were self-limiting headaches in four and five subjects with high and low doses, respectively and in one subject who was given placebo. The results of haematological and clinical analyses did not show any abnormality associated to citicoline administration. No clinically significant ECG and EEG abnormalities were registered. Empirical neurological tests, tendon reflexes, blood pressure and heart rate were not affected by any dose of the drug or placebo.

In addition to an excellent tolerability in healthy individuals, as demonstrated in the above study, all of the authors of clinical trials using citicoline that have been reviewed in this present article, agree in rating the safety of this drug as excellent without serious side effects being reported. In some cases, the appearance of digestive intolerance has been

reported and occasional excitability or restlessness in the first days of treatment. For instance, a study of the efficacy and safety of citicoline in 2,817 patients of all ages, with a predominance of patients between 60 and 80 years, who had different neurological processes, mostly cognitive disorders of diverse origin. The duration of citicoline Treatment ranged from 15 to 60 days and the mean dose administered was 600 mg/day orally. Only 5.01% of the patients had collateral effects associated with citicoline treatment, most often digestive intolerance (3.6%). In no case was it necessary to interrupt treatment for side effects attributable to citicoline use.

In the pooled analysis of citicoline in the treatment of acute ischemic stroke, in the safety

analysis, there were few adverse events that were reported in more than the 5 %. These adverse events are listed in Table 2.

In the South Korean drug surveillance study, the safety of the product was considered as

excellent, with only 37 side effects in 31 cases among the 4191 patients treated, that is a rate of side effects of 0.73%.

Also, in the Cochrane Library review, it was demonstrated a lower rate on the incidence of adverse events related with citicoline in comparison with placebo.

Table: Safety analysis in the pooling data analysis of acute ischaemic stroke patients treated with citicoline. The table shows adverse events that were reported in more than 5% of cases

	Placebo		**Citicoline**	
	n	**%**	**n**	**%**
Adverse events with incidence > 5% in the citicoline group				
Anxiety	58	9.95	***108***	13.69
Leg oedema	38	6.52	77	9.76
Adverse events with incidence > 5%				
Accidental injury	86	14.75	135	17.11
Agitation	78	13.38	113	14.32
Constipation	228	39.11	286	36.25
Coughing	81	13.89	105	13.31
Diarrhoea	81	13.89	117	14.83
Dizziness	47	7.89	72	9.13
ECG abnormally	57	9.78	74	9.38
Fever	182	31.22	241	30.54
Auricular fibrillation	65	11.15	92	11.66
Headache	186	31.90	261	33.08
Haematuria	53	9.09	91	11.53
Hypertension	88	15.09	131	16.60
Hypokalaemia	71	12.18	119	15.08
Hypotension	55	9.43	90	11.41
Urinary tract infection	235	40.31	298	37.77
Insomnia	103	17.67	145	18.38
Joint pain	48	8.23	78	9.89
Nausea	111	19.04	157	19.90
Pain	180	30.87	227	28.77
Back pain	45	7.72	74	9.38
Chest pain	55	9.43	82	10.39
Rash	79	13.55	112	14.20
Restlessness	49	8.40	74	9.38
Shoulder pain	75	12.86	105	13.31
Vomiting	89	15.27	111	14.07
Adverse events with incidence > 5% in the placebo group				
Depression	160	27.44	178	22.56

	Placebo		Citicoline	
	n	**%**	**n**	**%**
Falling Down	109	18.70	99	12.55
Urinary incontinence	82	14.07	83	10.52

In conclusion, the tolerability of citicoline is excellent and the side effects attributable to this drug are infrequent. In any case, side effects are never severe and consist, mainly, in gastrointestinal discomfort and restlessness.

Piracetam

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.

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 (≥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).

Data from post-marketing experience are insufficient to support an estimate of their incidence in the population to be treated.

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

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

Reporting of adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Report suspected adverse reactions via any point of contact available at www.torrentpharma.com or at email: pv@torrentpharma.com or call on 1800-120-3001.

4.9. Overdose

Citicoline

Citicoline exhibits very low toxicity profile in humans. In a short term, placebo controlled, crossover study, 12 healthy adults took citicoline at daily doses of 600 and 1000 mg or placebo consecutive 5-days periods. Transient headaches occurred in 4 subjects on 600 mg dose, 5 on the 1000 mg dose and 1 in placebo. No changes or abnormalities were observed.

Piracetam

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. One case of bloody diarrhoea with abdominal pain, associated with the oral intake of 75 g piracetam daily, was most probably related to the extreme high dose of sorbitol contained in the used formulation.

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 haemodialysis. The extraction efficiency of the dialyser is 50 to 60% for piracetam..

5. Pharmacological properties

5.1. Mechanism of Action

Citicoline

Citicoline acts by various mechanisms as cerebral activator listed below:

Phospholipid Precursor

Evidence of citicoline's role as a phosphatidylcholine precursor has been found in animal studies. The brain uses choline preferentially for acetylcholine synthesis, which can limit the amount of choline available for phosphatidylcholine production. When the demand for acetylcholine increases or choline stores in the brain are low, phospholipids in the neuronal membrane can be catabolized to supply the needed choline. Exogenous citicoline thus helps preserve the structural and functional integrity of the neuronal membrane. In an *in vitro* study, citicoline at high concentrations stimulated brain acetylcholinesterase (AChE) along with Na+/K+-ATPase. The postulated mechanism involves bioconversion of citicoline to phosphatidylcholine.

Neuronal Membrane Repair

Citicoline has been investigated as a therapy for stroke patients. Three mechanisms are postulated: (1) repair of neuronal membranes via increased synthesis of phosphatidylcholine; (2) repair of damaged cholinergic neurons via potentiation of acetylcholine production; and (3) reduction of free fatty acid buildup at the site of stroke-induced nerve damage. In addition to phosphatidylcholine, citicoline serves as an intermediate in the synthesis of sphingomyelin, another neuronal membrane phospholipid component. Citicoline has shown the potential to restore post-ischemic sphingomyelin levels.

Citicoline also restores levels of cardiolipin, a phospholipid component of the inner mitochondrial membrane. The mechanism for this is unknown, but data suggest citicoline inhibits enzymatic hydrolysis of cardiolipin by phospholipase A2.11 In an animal study, citicoline decreased the formation of hydroxyl radicals following ischemia and perfusion, again suggesting citicoline acts to decrease phospholipase stimulation

Effect on Beta-Amyloid

Evidence has surfaced that citicoline counteracts the deposition of beta-amyloid, a neurotoxic protein believed to play a central role in the pathophysiology of Alzheimer's disease (AD). The characteristic lesion in AD is the formation of plaques and neurofibrillary tangles in the hippocampus. The degree of cognitive dysfunction and neurodegeneration in AD is proportional to the buildup of beta-amyloid. Citicoline counteracted neuronal degeneration in the rat hippocampus induced by intrahippocampal injection of beta-amyloid protein. The number of apoptotic cells was also reduced. Memory retention as measured by a passive-avoidance learning task improved in the rats.

Effect on Neurotransmitters

Evidence of citicoline's ability to enhance norepinephrine release in humans was found in a study showing citicoline raised urinary levels of 3-methoxy- 4-hydroxyphenylglycol (MHPG), a norepinephrine metabolite. Citicoline increased brain levels of neurotransmitters in rats at a dose of 100 mg/kg, administered daily for seven days. Norepinephrine increased in the cerebral cortex and hypothalamus; dopamine increased

in the corpus striatum, and serotonin increased in the cerebral cortex, striatum, and hypothalamus. Rat studies have found evidence that citicoline potentiates dopamine release in the brain, presumably by stimulating release of acetylcholine

Piracetam

Piracetam's mode of action is as yet unknown.

5.2. Pharmacodynamic properties

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

Piracetam

Piracetam exerts its hemorheological effects on the platelets, red blood cells, and vessel walls by increasing erythrocyte deformability and by decreasing platelet aggregation, erythrocyte adhesion to vessel walls and 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 ßTG 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 prostacyclin 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.

5.3. Pharmacokinetic properties

Absorption

Citicoline is a water-soluble compound with greater than 90-percent bioavailability. Pharmacokinetic studies on healthy adults show 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.

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.

Distribution

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 resynthesise into citicoline in the brain.

The volume of distribution of piracetam is 0.7 L/kg. Piracetam crosses the blood-brain and the placental barrier and diffuses across membranes used in renal dialysis.

Metabolism

Citicoline is metabolized in the gut wall and liver. The by-products of exogenous citicoline formed by hydrolysis in the intestinal wall are choline and cytidine.

Up to now, no metabolite of piracetam has been found.

Excretion

Pharmacokinetic studies using 14C citicoline show citicoline elimination occurs in two phases mirroring the biphasic plasma peaks, mainly via respiratory CO2 and urinary excretion. 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 CO2 and 71 hours for urinary excretion.

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. The plasma half-life is 5.0 hours, in young adult men. Clearance of the compound is dependent on the renal creatinine clearance and would be expected to diminish with renal insufficiency.

6. Nonclinical properties

6.1. Animal Toxicology or Pharmacology

Citicoline

Acute Toxicity

Acute toxicity from single citicoline administration has been studied in various animal species and using different administration routes. The intravenous LD50 in mice, rats, and rabbits is 4.6, 4.15, and 1.95 g/kg, respectively. Oral LD50 is 27.14 g/kg in mice and 18.5 g/kg in rats. The intravenous LD50 of citicoline is approximately 44 times higher than the LD50 of choline hydrochloride at equivalent doses, and it has been shown that choline doses inducing cholinergic crises do not cause any toxicity sign when equivalent doses of citicoline are administered. This suggests that administration of choline has metabolic implications clearly different from those of exogenous choline administration. The administration of 2000 mg/kg of citicoline p.o. during 14 days was well tolerated.

Subacute Toxicity

Intraperitoneal administration to rats of doses up to 2 g/kg/d of citicoline for 4.5 weeks did not results in clinical toxicity signs or significant changes in the haematological, biochemical, or histological parameters analysed. A slight decrease in intake and weight gain was only seen from 2 weeks of the study. Similar results were seen following subcutaneous administration to male rats of up 1 g/kg for 4 weeks. Oral administration of 1.5 g/kg/d to rats for 30 days did not cause weight, haematological, biochemical, or histological changes.

Chronic Toxicity

Chronic oral (1.5 g/kg/d for 6 months in dogs) and intraperitoneal (1 g/kg/d for 12 weeks in rats) toxicity studies did not reveal either significant abnormality related to drug administration. Intravenous administration of citicoline 300-500 mg/kg/d for 3 months in dogs only caused toxic signs immediately after injection, including vomiting and occasional diarrhoea and sialorrhea. In a 90-day study in rats, 100, 350, and 1000 mg/ kg/day oral doses resulted in no mortality. In males, slight significant increases in serum creatinine (350 and 1000 mg/kg/day) and decreases in urine volume (all treated groups) were observed. In females, slight significant increases in total white blood cell and absolute lymphocyte counts (1000 mg/kg/day), and blood urea nitrogen (BUN) (100 and 350, but not 1000 mg/kg/day) were noted. A dose-related increase in renal tubular mineralization, without degenerative or

inflammatory reaction, was found in females (all treated groups) and two males (1000 mg/kg/day). Renal mineralization in rats (especially females) is influenced by calcium: phosphorus ratios in the diet. A high level of citicoline consumption resulted in increased phosphorus intake in the rats, and likely explains this result.

Teratogenicity

Citicoline was administered to albino rabbits at a dose of 800 mg/kg during the organogenesis phase, *i.e.* from days 7th to 18th of pregnancy. Animals were killed on day 29, and a detailed examination was made of foetuses and their mothers. No signs of maternal or embryofoetal toxicity were seen. Effects on organogenesis were imperceptible, and only a slight delay in cranial osteogenesis was seen in 10% of treated foetuses.

Piracetam

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 (C_{max}) 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/k/day given for 112 weeks.

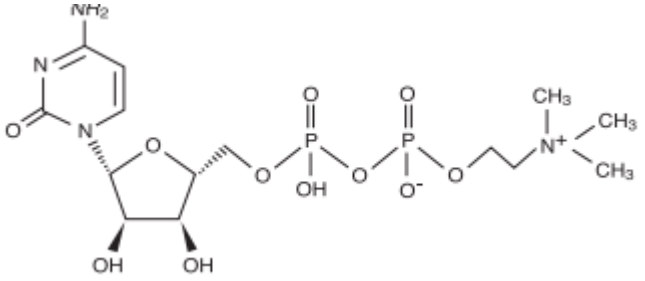
Although piracetam crosses the placenta into the foetal circulation, no teratogenic effects were observed at dose levels up to 4.8 g/kg/day (mice, rats) and 2.7 g/kg/day (rabbits). Furthermore, the compound affects neither fertility nor the peri- or postnatal development of the pregnancy at doses up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

7. Description

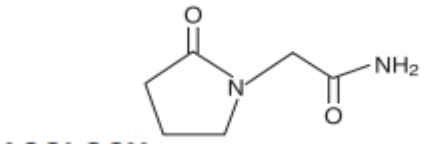
Citicoline

Citicoline is [[(2R,3S,4R,5R)-5-(4-amino-2-oxopyrimidin-1-yl)-3,4-dihydroxyoxolan-2-yl] methoxy-hydroxyphosphoryl] 2-(trimethylazaniumyl)ethyl phosphate. The molecular formula is $C_{14}H_{26}N_4O_{11}P_2$, and its molecular weight is 488.32 g/mol. The chemical structure is:



Piracetam

Paracetam is 2-(2-Oxopyrrolidin-1-yl)acetamide. The molecular formula is $C_6H_{10}N_2O_2$ and its molecular weight is 142.2 g/mol. The chemical structure is:



Strolin P 400

Strolin P 400 is yellow coloured, capsules shaped, biconvex, film coated tablet, having scored on one side.

The list of excipients used are Maize Starch, Crospovidone, Croscarmellose Sodium, Polyvinylpyrrolidone, Talcum, Colloidal Silicon Dioxide, Magnesium Stearate, Hydroxy Propyl Methyl Cellulose, Polyethylene Glycol, Titanium Dioxide, Yellow Oxide of Iron Lake Colour, Isopropyl Alcohol and Methylene Chloride.

Strolin P 800

Strolin P 800 is Light blue coloured, capsule shaped, biconvex, film coated tablet having scored on one side.

The list of excipients used are Maize Starch, Crospovidone, Croscarmellose Sodium, Polyvinylpyrrolidone, Microcrystalline Cellulose, Talcum, Colloidal Silicon Dioxide, Magnesium Stearate, Sodium Lauryl Sulphate, Sodium Starch Glycolate, Hydroxy Propyl Methyl Cellulose, Ethyl Cellulose, Diethyl Phthalate, Polyethylene Glycol, Lake Brilliant Blue, Titanium Dioxide, Isopropyl Alcohol and Methylene Chloride.

8. Pharmaceutical particulars

8.1. Incompatibilities

Not applicable

8.2. Shelf-life

Do not use later than the date of expiry.

8.3. Packaging information

Strolin P 400 and **Strolin P 800** are available in pack of 10 Tablets.

8.4. Storage and handing instructions

Store below 25°C, protected from light and moisture.

Keep out of reach of children.

9. Patient Counselling Information

Ask the patients to inform the treating physicians in case of any of the below:

- Have any allergies
- Have kidney or liver problems
- Are pregnant or plan to become pregnant
- Are breastfeeding or plan to breastfeed
- Have any serious illness

- Are taking any medicines (prescription, over-the-counter, vitamins, or herbal products)

10. Details of manufacturer

Ravenbhel Healthcare Pvt. Ltd.

16-17, EPIP, SIDCO, Kartholi,

Bari-Brahmana, Jammu-181133.

11. Details of permission or licence number with date

STROLIN P 400

Mfg. Lic. No. is JK/01/56. Issue on 15.06.2010.

STROLIN P 800

Mfg. Lic. No. is JK/01/56. Issue on 23.05.2016.

12. Date of revision

NA

MARKETED BY

TORRENT PHARMACEUTICALS LTD.

IN/STROLIN P /MAR-2026/01/PI