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

CITILIN P

1.Generic Name

Citicoline and Piracetam Tablets

2. Qualitative and quantitative composition

Each film coated tablet contains:

Citicoline Sodium I.P. equivalent to Citicoline 500mg

Piracetam I.P. 400mg

Excipients q.s

Colour: Sunset Yellow Lake

The excipients used are Starch, Polyvinyl Pyrrolidone, Isopropyl Alcohol, Sodium Methyl Paraben, Sodium Propyl Paraben, Sodium Benzoate, Talcum, Colloidal Silicon Dioxide, Croscarmellose sodium, Sodium Starch Glycolate, Magnesium Stearate, Sodium Lauryl Sulphate, Super Coat, Titanium Dioxide, Colour Red Oxide of Iron Lake.

3. Dosage form and strength

Dosage form: Film Coated Tablet

Strength: Citicoline 500 mg and Piracetam 400 mg

4. Clinical particulars

4.1 Therapeutic indication

CITILIN P Is Indicated for the treatment of acute Ischemic Stroke in adult patients as an adjunct.

4.2 Posology and method of administration

The dose depends on the seventy of 'the symptoms and the response of the Individual patient. The usual recommended dosage is one tablet administered orally three times in a day. The dose may be increased upto four tablets per day administered in divided doses.

Dosage adjustment is required in those with mild to moderate renal impairment and eldar1y patients with diminished renal function.

4.3 Contraindications

CITILIN P is contraindicated in patients with hypersensitivity to Citicoline or Piracetam or any other component of the formulation.

Because of its Piracetam component, CITILIN P is also contraindicated in patients with severe renal impairment (creatinine clearance of < 20 ml/mln), hepatic Impairment, cerebral haemorrhage, Huntington's chorea and in those less than 16 years of age.

4.4 Special warnings and precautions for use

Citicoline

Citicoline may cause hypotension and in such case the hypotensive effect can be treated with corticosteroids or sympathomimetics.

Piracetam

Dosage reduction Is recommended for those with mild to moderate renal Impairment Therapy with Piracetam should not be wi1hdrawn abruptly in myoclonic patients due to the risk of inducing seizures.

4.5 Drugs interactions

Citicoline

Citicoline must not be used with medicines containing meciophenoxates {cantrophenoxine). Citicoline increases the effects of L-dopa.

Piracetam

No known drug Interaction

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

PREGNANCY AND LACTATION:

Citicoline

There are no adequate and well controlled studies of Citicoline during pregnancy and lactation. Citicoline should be used during pregnancy only if the potential benefit justified at the potential risk to the fetus. Caution should be exercised during breast feeding because it is not known whether Citicoline is excreted inhuman breast milk.

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 *I* foetal development parturition on or post-natal development.

Piracetam crosses the placental barrier and is excreted in human breast milk.

The safety of CITILIN P in pregnancy and lactation is not known. A decision must be made whether to discontinue breast-feeding of to discontinue CITILIN P therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

Pediatrics:

Piracetam is contraindicated in children less than 16 years of age.

Geriatrics:

Dosage adjustment Is required in elderly patients with diminished renal function

4.7 Effects on ability to drive and use machines

In clinical studies, at dosages between 1.6 - 15 grams per day, hyperkinesia, somnolence, nervousness and depression were reported more frequently in patients on CITILIN P than on placebo. There is no experience on driving ability in dosages between 15 and 20 grams daily. Caution should therefore be exercised by patients intending to drive or use machinery whilst taking CITILIN P.

4.8 Undesirable effects

Citicoline

Piracetam is generally well tolerated. Few adverse effects that are reported with oral Citicoline include gastrointestinal disturbances, dizziness and fatigue.

Piracetam

Piracetam is reported to produce insomnia or somnolence, weight gain, hyperkinesia, nervousness, end depression.

Other reported adverse effects Include gastrointestinal disorders such as abdominal pain, diarrhoea, nausea and vomiting,

Hypersensitivity reactions, ataxia, vertigo, confusion, hallucinations,angioedema,and rashes**.**

4.9 Overdose

Citicoline

No available data.

Piracetam

Symptoms

No additional adverse events specifically related to overdose OR have been reported with Piracetam.

The highest reported overdose with Piracetam was oral intake of75 g. Bloody diarrhoea with abdominal pain, was most probably related to the extreme high doses of sorbitol contained In the used formulation.

Management of over dose:

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 dialyzer is 50 to 60% for Piracetam**.**

5. Pharmacological properties

5.1 Mechanism of Action

Citicoline

Citicoline ability to increase the synthesis of phosphatidylcholine, the primary neuronal membrane component. It also enhances acetylcholine synthesis, and thus ameliorates symptoms caused by the stroke induced loss of cholinergic neurons. Another mechanism by which Cltlcollne may Influence acute effect on the outcome of stroke patient relates to b ability to reduce free fatty acid accumulation at the site of injury, which prevents further damage.

Piracetam

Piracetam' s mode of action in cortical myoclonus is as yet unknown.

5.2 Pharmacodynamic properties

Citicoline

The extensive damage caused by stroke requires regeneration of axons and synapses of neurons, so new membrane production is essential for repair. The primary mechanism by which Citicoline achieves therapeutic effect in stroke is its ability to increase the synthesis of phosphatidylcholine, the primary neuronal membrane component. It also enhances acetylcholine synthesis, and thus ameliorates symptoms caused by the stroke induced loss of cholinergic neurons. Another mechanism by which Cltlcollne may Influence acute effect on

the outcome of stroke patient relates to b ability to reduce free fatty acid accumulation at the site of injury, which prevents further damage.

Citicoline prevents or reduces the effects of Ischemia and/or hypoxia in major part of animals and cellular models studies and acts in the cranial traumatic forms, reduces and limits the injuries to the membranes of the nerve calls, re-establishes the Sensitivity and the function of the regulatory Intracellular enzymes and accelerates the re-absorption of the cerebral edema. Results of experimental and clinical studies support he use of Citicoline for increasing, maintaining end repairing the membranes and the neuronal function in sl1uatlons such as Ischemia and traumatic lnjur1es. In patents with senile dementia,

Citicoline reduces the further damage**.**

Piracetam

Piracetam’ s mode of action in cortical myoclonus is as yet unknown. Piracetam exerts its haemorrheologioal effects on the platelets, red blood cells, and vassal 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 anemia, Piracetam improves the deformability of the erythrocyte membrane, decreases blood viscosity, and prevents rouleaux formation.

Effects on platelets: In open studies in heathy volunteers and in patients wi1h Reynaud's phenomenon, increasing doses of Piracetam up to 12 g was associated with a dose--dependent reduction in platelet functions compare with pre-treatment values (tests of aggregation induced by ADP, collagen, epinephrine and BTG release), without significant change in platelet count. In these studies, Piracetam prolonged bleeding time.

Effects on blood vessels: In animal studies, Piracetam inhibited vasospasm end counteraction the effects of various spasm genic agents. It lacked any vasodilatory action and did not induce "steal phenomenon, nor low or no 1'9flow, nor hypotensive effect.

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 Wlllebrand's factors (VIII: C; VIII R: AG; VIII R: vW) by30 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 Wille brand's factors (VIII: C; VIII R: AG; VIII R: vW (RCF)) by 30 to 40%, reduced plasma viscosity and increased bleeding time.

5.3Pharmacokinetic properties

Citicoline

Citicoline is well absorbed after oral administration. Citicoline has an absolute bioavailability of a proximately 99%. Citicoline is metabolized in the liver to free choline. The liver Is capable of synthesizing lecithin from choline and resynthesizing Citicoline from cytidine and choline.

Due to difficulties in detecting plasma levels of Citicoline Itself, assays have been performed for free choline or total plasma

radioactivity in terms of Citicoline equivalents. Plasma choline levels are elevated significantly after oral administration. Two peaks of plasma Citicoline equivalents have been reported after oral doses or radiolabeled abled Citicoline (300mg). An Initial Peak Is observed in approximately 1 hour (1.5mcglml), presumably related to a mixture of unchanged Citicoline and its metabolites (choline and cytidine diphosphate). A second peak of approximately 3mcglml is seen 24 hours post dose and may be due to delayed absorption of the drug *or* continued metabolite accumulation over this time. Choline derived from Citicoline crosses the blood brain barrier, presumably serving as a source for acetylcholine and phosphatidylcholine (lecithin) synthesis. The major

part of a dose of Cltlcollne appears to be incorporated into the tissues and or used in blosynthe1iclblodegradatlon pathways, including leclthinl1ipid membrane synthesis. Small quantity of a dose Is recovered in urine (2% to 3%) and in feces {less than 1%).Approximately 12% of a dose Is eliminated as respiratory Carbon dioxide. Elimination half-life of Citicoline is 3.5 hours (first peak concentration) and 125 hours (second peak concentration).

Piracetam is rapidly and extensively absorbed from the gastro intestinal tract; peak plasma concentrations are reached within 1.5 hours after oral doses. The plasma half-life is reported to be 5 hours and it crosses the blood-brain barrier. Piracetam is excreted almost completely in the urine. It crosses the placenta and is distributed into breast milk.

6. Nonclinical properties

6.1 Animal Toxicology or Pharmacology

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) 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 glomerulonephritis 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.

Citicoline,

In The reported study concluded that the excess of renal mineralisation in treated female rats was likely to be due to the increased dietary intake of phosphorus (Citicoline has a 12.69 % phosphorus content). Upon request from the Panel with respect to the absence of use of a functional observational battery, despite the potential neurological effects of the test substance, the applicant answered that careful clinical examination of the rats was carried out once before the first exposure and weekly thereafter for physical signs of toxicity, including changes in general state, external appearance and behaviour. A published study (Romero et al., 1983b) describes the effects of administration of Citicoline to six Beagle dogs by gavage for six months at a dose of 1.5 g/kg bw per day; two additional dogs served as a control group and received the vehicle. The animals were weighed weekly, and blood and urine samples were collected from all animals prior to the start of treatment and at the end of the experimental period. Clinical chemistry and haematology parameters examined were haematocrit, haemoglobin, red blood cell, WBC, leukocyte formula, glucose, aspartate aminotransferase (AST), alanine aminotransferase (ALT), BUN, chloride, protein, globulin, lipid, cholesterol, and bilirubin levels. Urine samples were collected at the same time-points and urobilinogen, blood, bilirubin, ketone, and glucose levels were measured semi-quantitatively, as well as urinary pH, protein content, and density. At the end of the experimental period all animals were subject to necropsy and a gross examination of tissues was made. Liver, kidney, heart, spleen, lung, ovary or testes were weighed, and samples of these plus the mesenteric lymphatic ganglia were preserved for histological examination. Statistical analyses were not conducted by the authors due to the limited number of animals in each group. No deaths were recorded during the experimental period. No differences were observed in the haematology/clinical chemistry results or in relative or absolute organ weights of animals administered Citicoline compared with those in the control group, but the small number of animals and variability in the data makes comparisons very difficult. No histological evidence of Citicoline toxicity was found in any of the organs examined. Some individual histological abnormalities were observed, which are considered to be incidental to treatment; these included but were not limited to hepatic granulomas and inflammatory infiltration, renal cortical granulomas and evidence of septic nephritis, myocardial necrosis and pulmonary granulomatous foci. Based on the reported findings, the authors concluded that Citicoline was not toxic to dogs under the conditions of the study. The Panel notes that the full study report is not available for a full assessment. The incidental pathology suggests that the dogs used in the study were not as healthy as might be expected for experimental animals. The Panel considers that the study is not adequate for establishing a NOAEL for consumer safety assessment.

7. Description

<u>Citicoline Sodium</u>

Citicoline Sodium is Cytidine-5'-diphosphocholine sodium. Its empirical formula is $C_{14}H_{25}N_4NaO_{11}P_2$ and molecular weight is 510.3. Citicoline Sodium is a white crystalline powder which is freely soluble in water and insoluble in methanol.

<u>Piracetam</u>

Piracetam is 2-(2-oxopyrrolidin-1-yl) acetamide. Its empirical formula is $C_6H_{10}N_2O_2$ and molecular weight is 142.2. Piracetam is a white or almost white powder which is freely soluble in water and soluble in ethanol (95 per cent).

Citicoline and Piracetam Tablets are orange coloured elongated, biconvex, scored on both side, film coated tablets. The excipients used are Starch, Polyvinyl Pyrrolidone, Isopropyl Alcohol, Sodium Methyl Paraben, Sodium Propyl Paraben, Sodium Benzoate, Talcum, Colloidal Silicon Dioxide, Croscarmellose sodium, Sodium Starch Glycolate, Magnesium Stearate, Sodium Lauryl Sulphate, Super Coat, Titanium Dioxide, Colour Red Oxide of Iron Lake.

8. Pharmaceutical particulars

8.1 Incompatibilities

Not applicable

8.2 Shelf-life

Do not use later than date of expiry

8.3 Packaging information

CITILIN P is available in pack of 10 tablets

8.4 Storage and handing instructions

Store below 30°C. Protect from light &moisture. Keep all medicines out of reach of children.

9. Patient Counselling Information

Package leaflet: Information for the patient

CITILIN P

Read all of this leaflet carefully before you start taking this medicine because it contains important
information for you.

• Keep this leaflet. You may need to read it again.
• If you have any further questions, ask your doctor or pharmacist.
• This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
• If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet:

1. What *Citilin P* Tablets are and what they are used for

Citilin P is a fixed dose combination of Citicoline as its sodium salt with Piracetam.

Citicoline, also known a cytidine diphosphate-choline (CDP Choline) & cytidine5''-diphosphocholine, Is a psycho stimulant/ Nootropic. It is an intermediate in the generation of phosphatidylcholine from choline. It is claimed to increase blood flow in the brain and has been given in the t of cerebrovascular disorders Including! ischaemic stroke, parkinsonism, and head injury.

Piracetam, a CITILIN Drug, is a cyclic derivative of GABA It is said to protect the cerebral cortex against hypoxia. It is also reported to inhibit platelet aggregation and reduce blood

viscosity at high doses. It has been used in alcoholism, vertigo, cerebrovascular accidents, dyslexia, behavioral disorders in children, and after trauma or surgery.

CITILIN P Is Indicated for the treatment of acute Ischemic Stroke in adult patients as an adjunct.

. What you need to know before you take CITILIN P Tablets

Do not take CITILIN P

• if you are allergic to Piracetam, Citicoline or any of the other ingredients of this medicine
• if you have ever had serious kidney problems
• if you suffer from Huntington ‘s Disease (also known as Huntington ‘s Chorea)
• if you have ever experienced a brain haemorrhage
• if you think your kidneys may not be working perfectly. (Your doctor may need to start you on a lower dose.)
• if you have ever had any kind of bleeding problem.

Other medicines and CITILIN P Tablets

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines.

Tell your doctor if you are taking any of the following medicines:

• Thyroid extract or thyroxine
• Anticoagulants such as warfarin or acenocoumarol
• Low dose aspirin
• Any other medicines, including medicines obtained without a prescription.

Pregnancy and breast-feeding

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine. If you are taking this medicine, use contraception to avoid becoming pregnant. If you are taking CITILIN P Tablets and you think you may be pregnant, consult your doctor immediately.

Driving and using machines

CITILIN P Tablets may cause drowsiness and shakiness. If this happens to you, do not drive or use machinery.

Warning about some of the ingredients in CITILIN P Tablets

This medicine contains sodium. To be taken into consideration by patients on a controlled sodium diet.

3. How to take CITILIN P Tablets

Always take this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

Your doctor will choose the dose that is right for you. Your dose will be shown clearly on the label that your pharmacist puts on your medicine. If it does not, or you are not sure, ask your doctor or pharmacist.

Adults

How much medicine to take and when to take it

Dosage: As directed by the Neurologist/Specialist

If you take more CITILIN P Tablets than you should

If you accidentally take too much, immediately go to the nearest hospital casualty department or your doctor.

If you forget to take CITILIN P Tablets
Do not take a double dose to make up for a forgotten dose. Simply take the next dose as planned.
If you stop taking CITILIN P Tablets
Do not stop taking CITILIN P Tablets without first talking to your doctor. Abruptly stopping your medicine may cause twitching and jerking.
If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.
You may notice the following side effects:
• An allergic reaction and experience difficulty breathing, swelling, fever
• Spontaneous bleeding caused by defects in your blood clotting mechanism
• Worse fits
• Hallucinations
• Difficulty balancing and unsteadiness when standing
• Anxiety and agitation
• Confusion
• Restlessness
• Nervousness
• Sleepiness
• Depression
• Weakness
• Vertigo
• Weight increase
• Stomach pain
• Diarrhoea
• Feeling or being sick
• Headache
• Being unable to sleep
• Swelling of the skin, particularly around the face
• Skin rash and itching.

Reporting of side effects

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via any point of contact of Torrent Pharma available at: http://www.torrentpharma.com/Index.php/site/info/adverse_event_reporting. By reporting side effects, you can help provide more information on the safety of this medicine

5. How to store CITILIN P Tablets

Store below 30^0C. Protect from light and moisture.
Keep all medicines out of the reach of children

.6. Contents of the pack and other information

What CITILIN P Tablets contains

The active substance is Piracetam and Citicoline. Each tablet contains 400 mg Piracetam. and 500mg of Citicoline
The other ingredients are : Starch, Polyvinyl Pyrrolidone, Isopropyl Alcohol, Sodium Methyl Paraben, Sodium Propyl Paraben, Sodium Benzoate, Talcum, Colloidal Silicon Dioxide, Crosscarmellose sodium, Sodium Starch Glycolate, Magnesium Stearate, Sodium Lauryl Sulphate, Super Coat, Titanium Dioxide, Colour Red Oxide of Iron Lake.

10. Details of manufacturer

Manufactured in India by:

Synokem Pharmaceuticals Ltd.

Plot No. 56-57, Sector – 6A, IIE (SIDCUL),

Ranipur (BHEL), Haridwar – 249403, (Uttarakhand).

11. Details of permission or licence number with date

Mfg Lic No. 27/UA/2018 issued on 17.11.2017

12. Date of revision

Not available

MARKETED BY

TORRENT PHARMACEUTICALS LTD.

Indrad-382721, Dist. Mehsana, INDIA.

IN/ CITILIN P 400 and 500 mg/AUG-19/01/PI