COGNOLIN 500 Tablets (Citicoline)

Composition

COGNOLIN 500 Tablets
Each film-coated tablet contains:
Citicolone Sodium equivalent to
Citicolone ...................... 500 mg
Excipients ........................... q.s.
Colour: Titanium Dioxide, IP

Dosage Form

Film-coated tablet

Pharmacology

Pharmacodynamics

Citicolone is a complex organic molecule that functions as an intermediate in the biosynthesis of cell membrane phospholipids. Citicolone is also known as CDP-choline and cystidinediphosphate choline (cytidine5'-diphosphocholine). Citicolone is composed of two essential moieties, cystidine and choline, linked by a diphosphate bridge, and serves as the phosphocholine donor to 1, 2-diacylglycerol (DAG) to form phosphatidylcholine. It is a pyrimidine 5'-nucleotide, which serves as an essential precursor in the synthesis of lecithin (phosphatidylcholine) and other phospholipids. The extensive damage caused by stroke requires repair and regeneration of the axons and synapses of neurons, so new membrane production is necessary. Results of various studies have suggested the following actions of citicolone:

Phospholipid Precursor

Evidence of citicolone'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 citicolone, thus, helps preserve the structural and functional integrity of the neuronal membrane. In an in vitro study, citicolone at high concentrations stimulated brain acetylcholinesterase (AChE) along with Na+/K+-ATPase. The postulated mechanism involves the bioconversion of citicolone to phosphatidylcholine.

Neuronal Membrane Repair

Citicolone has been investigated as a therapy for stroke patients. Three mechanisms are postulated: (1) ability to repair 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 build-up at the site of stroke-induced nerve damage.

In addition to phosphatidylcholine, citicolone serves as an intermediate in the synthesis of sphingomyelin,
another neuronal membrane phospholipid component. Citicoline has shown the potential to restore post-
ischaemic sphingomyelin levels.

Citicoline also restores the levels of cardiolipin, a phospholipid component of the inner mitochondrial
membrane. The mechanism for this is unknown, but data suggest that citicoline inhibits enzymatic
hydrolysis of cardiolipin by phospholipase A2. Citicoline avoids, reduces or reverses the effects of ischaemia
and/or hypoxia in the major part of animals and cellular models studied; it also acts in the cranial traumatic
forms, reduces and limits the injuries to the membranes of the nerve cells, re-establishes the sensitivity and
the function of the regulatory intracellular enzymes and accelerates the re-absorption of cerebral oedema.
Thus, considerable evidence accumulated supports the use of citicoline for increasing, maintaining and
repairing the membranes and the neuronal function in situations such as ischaemia and traumatic injuries.

Reduction of Free Fatty Acid Build-Up

Citicoline may benefit patients experiencing ischaemia by decreasing the accumulation of free fatty acids at
the site of the lesion, which occurs as a result of neuronal cell damage and death. Soon after the initiation of
ischaemia, there is a significant increase in pro-inflammatory arachidonic acid, glycerols and free fatty acids
caused by the breakdown of neuronal membranes. Toxic metabolites as well as prostaglandins, thromboxanes
and free radicals can accumulate, leading to further damage. Animal studies have demonstrated evidence in
suppressing free fatty acid build-up. Human data is limited.

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 build-up of beta-amyloid.

Effect on Norepinephrine

Evidence of the ability of citicoline to enhance norepinephrine release in humans was found in a study
showing that citicoline raises 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 7
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.

Activation of the Dopaminergic System

With respect to dopaminergic activation, citicoline has been reported to exert dopaminergic agonist effects in
the corpus striatum, enhanced dopamine synthesis in the striate body (by activation of tyrosinehydroxylase),
inhibit dopamine uptake by synaptosomes, and increase the sensitivity of dopaminergic receptors that have
been down-regulated during prolonged levodopa therapy. The addition of citicoline to therapy with levodopa
(with or without other anti-Parkinsonian agents) has been reported to improve symptoms in patients with
Parkinson’s disease in small open and controlled studies.

Pharmacokinetics

Absorption

Citicoline is a water-soluble compound with an absolute bioavailability of 99%. Pharmacokinetic studies on
healthy adults show that oral doses of citicoline are rapidly absorbed, with less than 1% excreted in
the faeces. Plasma levels peak in a biphasic manner, at 1 hour after ingestion followed by a second larger
peak at 24 hours post-dosing. Two peaks of plasma citicoline equivalents have been reported after oral doses
of radiolabelled citicoline (300 mg). An initial peak is observed in approximately 1 hour (1.5 mcg/mL),
presumably related to a mixture of unchanged citicoline and its metabolites (choline
and cystidinediphosphate). A second peak of approximately 3 mcg/mL is seen 24 hours post-dose, and may be due to delayed absorption of the drug or continued metabolite accumulation over this period.

Brain uptake of citicoline metabolites was demonstrated as early as 30 minutes after administration. When labelled citicoline is administered orally, only about 0.5% of the total radioactivity is incorporated into the brain. Brain uptake increased to about 2% of the total radioactivity when citicoline was administered intravenously. The cerebral levels of citicoline after its administration are unknown. It is not known to what extent brain tissue levels are altered at any given dose.

Distribution

Following absorption, choline and cytidine are dispersed throughout the body; they enter the systemic circulation for utilization in various biosynthetic pathways and cross the blood–brain barrier for re-synthesis into citicoline in the brain. Choline crosses the blood–brain barrier, presumably serving as a source for acetylcholine and phosphatidylcholine. The major portion of a dose of citicoline appears to be incorporated into tissues and/or used in biosynthetic/biodegradation pathways, including lecithin/lipid membrane synthesis.

Metabolism

Citicoline is metabolized in the gut wall and liver. Exogenous citicoline is hydrolysed and absorbed as cytidine and choline. Following absorption, choline and cytidine are re-phosphorylated, and citicoline is synthesized from cytidine triphosphate and choline monophosphate by cytidinetriphosphate phosphocholinecytidyl transferase (PCCT). As the rate-limiting intermediate in phosphatidylcholine biosynthesis, it was believed that citicoline administration would provide benefit in pathological conditions such as central nervous system (CNS) injury where membrane damage contributes to neuronal death. During phosphatidylcholine synthesis, choline monophosphate is incorporated into phosphatidylcholine and cytidine 5'-monophosphate (CMP) is released. CMP can be utilized for the synthesis of RNA, or of DNA as the deoxyribonucleotide. The choline moiety from citicoline is also acetylated to the neurotransmitter, acetylcholine, or metabolized to betaine, which serves as a source of methyl groups in the synthesis of methionine and S-adenosyl-L-methionine. AdoMet is the methyl donor in the methylation of proteins and nucleotides, and the conversion of phosphatidyl-ethanolamine (PtdEtn) to phosphatidylcholine. The product, S-adenosyl-L-homocysteine, can be metabolized further to glutathione (GSH).

Elimination

Pharmacokinetic studies using 14C-citicoline show that citicoline elimination occurs in two phases mirroring the biphasic plasma peaks, mainly via respiratory carbon dioxide (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 initial rapid decline after the 24-hour plasma peak is similarly followed by a slower elimination rate. Small amounts of a dose are recovered in the urine (2–3%) and in the faeces (less than 1%). Approximately 12% of a dose is eliminated as respiratory CO₂. The elimination half-life of citicoline is 3.5 hours (first peak concentration), and 125 hours (second peak concentration).

Indications

COGNOLIN Tablets are indicated in the treatment of patients with serious cerebral injuries of a vascular or traumatic nature, with or without loss of consciousness. They are also indicated for the treatment of degenerative damages and chronic cerebral vascular injuries in senile dementia.

Dosage And Administration

Dosage should be individualized. The usually recommended dose of COGNOLIN Tablet is 500–1,000 mg daily.
No dosage adjustment is required for the elderly population and the usual recommended adult dose can be administered.

**Contraindications**

Hypersensitivity to COGNOLIN Tablets or any other component of the formulation.

**Warnings And Precautions**

- **General**
  
  In case of persistent intracranial haemorrhage, it is recommended not to exceed the dose of 1,000mg of Citicoline daily.

- **Drug Interactions**
  
  Carbidopa, Levodopa and Entacapone
  
  Citicoline may enhance the effects of levodopa, carbidopa and entacapone. The exact mechanism is unknown, but animal model studies 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-sparing effects, whereby the addition of citicoline (500–1,200 mg/day) allowed for lower dosages of levodopa to be used with stable or improved therapeutic efficacy and reduced the side effects in some patients. However, data are limited.
  
  Co-administration with Centrophenoxine
  
  Must not be administered in conjunction with medications containing centrophenoxine.

- **Pregnancy**
  
  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 justifies the potential risk to the foetus.

- **Lactation**
  
  Caution should be exercised during breastfeeding because it is not known whether citicoline is excreted in breast milk.

- **Geriatric Use**
  
  No dosage adjustment is required in this patient population and the usually recommended adult dose can be administered.

**Undesirable Effects**

Citicoline is a safe and effective nutraceutical, and toxicological tests have shown no serious side effects even after prolonged treatment. The most commonly seen undesirable effects on the administration of citicoline are anxiety, leg oedema, agitation, coughing, diarrhea, dizziness, ECG abnormality, fever, auricular fibrillation, headache, haematuria, hypertension, hypokalaemia, hypotension, urinary tract infection, insomnia, joint pain, nausea, vomiting, pain (back/chest/shoulders), rash and restlessness. Citicoline may cause hypotension and, if necessary, the hypotensive effect can be treated with corticosteroids or sympathomimetics. In a short-term, placebo-controlled, crossover study, 12 healthy adults took citicoline at daily doses of 600 and 1,000 mg or placebo for consecutive 5-day periods. Transient headaches occurred in 4 subjects on the 600mg dose, 5 on the 1,000mg dose, and 1 on placebo. No changes or abnormalities were
observed in haematology, clinicalbiochemistry or neurological tests. A large drug surveillance study analysed the results of citicolinetreatment in 2,817 patients aged 60 to 80 years, suffering from senility and cerebral vascular insufficiency. A total of 151 incidents of side effects were recorded, representing 5% of the patient sample. The most common adverse effects were transient in nature and included stomach pain and diarrhoea in 102 cases. Vascular symptoms of hypotension, tachycardia or bradycardia occurred in 16 cases.

### Overdosage

There are no known cases of overdose in humans available for citicoline.

### Storage And Handling Instructions

Store in a cool and dry place. Protect from light and moisture.

### Packaging Information

COGNOLIN 500: Strip of 10 tablets

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