

Package Insert

Re Cognix[®]

Product Summary

1. Name of the medicinal product

Re Cognix[®]

2. Qualitative and quantitative composition

Each film coated tablet contains

Citicoline Sodium equivalent to Citicoline 500 mg

3. Pharmaceutical form

Film coated tablet

4. Clinical particulars

4.1 Therapeutic indications

- Age-related memory problems: Taking citicoline seems to help memory loss in people aged 50 to 85 years.
- Long-term blood circulation problems in the brain (cerebrovascular diseases): There is some evidence that taking citicoline by mouth or injecting citicoline into the vein or muscle might improve memory and behavior in patients with long-term cerebrovascular diseases, such as stroke.
- Stroke recovery: Stroke patients who take citicoline by mouth within 24 hours of having the kind of stroke that is caused by a clot (ischemic stroke) are more likely than other ischemic stroke patients to have a complete recovery within 3 months. Stroke patients who receive intravenous (IV) citicoline within 12 hours of having an ischemic stroke and daily thereafter for 7 days also have improved recovery.

More evidence is needed to rate the effectiveness of citicoline for these uses.

- Alzheimer's disease and other types of dementia: Some evidence suggests that taking citicoline by mouth might improve learning, memory and information

processing (cognitive function) in people with mild to moderate Alzheimer's disease.

- Lazy eye (amblyopia): Early research suggests that giving citicoline as a shot for 15 days might improve vision in people with a lazy eye.
- Bipolar disorder: Early research suggests that taking citicoline does not improve depression or manic symptoms in people with bipolar disorder and cocaine addiction.
- Cocaine addiction: Early research suggests that taking citicoline might reduce cocaine use in people with bipolar disorder and cocaine addiction.
- Glaucoma: Developing evidence suggests that citicoline might improve vision in some people with glaucoma.
- Vision loss due to blockage of the optic nerve (ischemic optic neuropathy): Early research suggests that taking a specific citicoline product (Cebrolux-Tubilux) for 60 days might improve vision in people with ischemic optic neuropathy.
- Memory: Early research suggests that taking citicoline might improve memory, learning, and speaking ability in people with brain injury due to trauma. Other research suggests that citicoline might improve some aspects of memory in elderly people.
- Muscle strength: Early research suggests that injecting citicoline intravenously (by IV) might improve muscle strength in people recovering from a type of stroke called a cerebral hemorrhage that was not caused by trauma.
- Parkinson's disease: Some research shows that giving citicoline as a shot along with usual treatment might improve some of the symptoms of Parkinson's disease, but not shaking (tremor).
- Recovery after surgery: Early research suggests that taking citicoline 24 hours before surgery and for 4 days after surgery might reduce symptoms of delirium after surgery in elderly people.
- Vascular dementia: Taking citicoline does not seem to improve symptoms in people with vascular dementia.
- Attention deficit-hyperactive disorder (ADHD).
- Head trauma.
- Other conditions.

4.2 Posology and method of administration

Re Cognix[®] should be used as prescribed by the physician. The following doses have been studied in scientific research:

BY MOUTH:

- For decline in thinking skills due to age: 1000-2000 mg of citicoline per day.
- For ongoing disease of the blood vessels that serve the brain (chronic cerebrovascular disease): 600 mg of citicoline per day.
- For immediate treatment of stroke due to a clot (ischemic stroke): 500 – 2000 mg of citicoline per day starting within 24 hours of stroke.

4.3 Contraindications

Hypersensitivity to any of the active ingredients or excipients.

4.4 Special warnings and precautions for use

Refer to section 4.6.

4.5 Interaction with other medicinal products and other forms of interaction

Currently there is no information on the interactions of citicoline with other medicines.

4.6 Fertility, pregnancy and lactation

There is not enough reliable information about the safety of taking citicoline during pregnancy or breast-feeding. Not recommended for use in these two situations.

4.7 Effects on ability to drive and use machines

Currently there is no information on the effects on ability to drive and use machines with the use of citicoline.

4.8 Undesirable effects

Citicoline is possibly safe when taken by mouth short-term (up to 90 days). The safety of long-term use is not known. Most people who take citicoline don't experience problematic side effects. But some people can have side effects such as trouble sleeping (insomnia), headache, diarrhea, low or high blood pressure, nausea, blurred vision, chest pains, and others.

Citicoline exhibits a 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 1,000 mg or placebo for consecutive five-day periods. Transient headaches occurred in four subjects on the 600-mg dose, five on the 1,000-mg dose, and one on placebo. No changes or abnormalities were observed in hematology, clinical biochemistry, or neurological tests. A large drug surveillance study analyzed the results of citicoline treatment in 2,817 patients ages 60-80 suffering from senility and cerebral vascular insufficiency. A total of 151 incidents of side effects were recorded, representing five percent of the patient sample. The most common adverse effects were transient in nature and included stomach pain and diarrhea in 102 cases. Vascular symptoms of hypotension, tachycardia, or bradycardia occurred in 16 cases.

4.9 Overdose

Currently there is no information on overdosage with the use of citicoline. However, if suspected, immediate medical advice and care should be sought.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Citicoline is a complex organic molecule that functions as an intermediate in the biosynthesis of cell membrane phospholipids. Citicoline is also known as CDP-choline and cytidine diphosphate choline (cytidine 5'-diphosphocholine). CDP-choline belongs to the group of biomolecules in living systems known as "nucleotides" that play important roles in cellular metabolism. CDP-choline is composed of ribose, pyrophosphate, cytosine (a nitrogenous base), and choline. Exogenous citicoline research in animal experiments and human clinical trials provides evidence of its cholinergic and neuroprotective actions. As a dietary supplement, citicoline appears useful for improving both the structural integrity and functionality of the neuronal membrane that may assist in membrane repair. Animal and clinical studies indicate the potential of citicoline to improve cognitive deficits, stroke rehabilitation, brain and spinal cord injuries, neurological diseases, and eye conditions.

Grouped with the B vitamins, choline is a trimethylated nitrogenous base that enters three major metabolic pathways:

- (1) phospholipid synthesis via phosphorylcholine;
- (2) acetylcholine synthesis; and
- (3) oxidation to betaine, which serves as a methyl donor.

Endogenously, formation of citicoline from choline is the rate-limiting step in the synthesis of phosphatidylcholine, a key membrane phospholipid. Cytidine, a major component of RNA, undergoes cytoplasmic conversion to cytidine triphosphate (CTP). In the citicoline metabolic pathway, choline is phosphorylated by the enzyme choline kinase; the resulting phosphorylcholine combines with CTP to form citicoline. Citicoline then combines with diacylglycerol (DAG), forming phosphatidylcholine, with choline phosphotransferase serving as the enzyme catalyst in this reaction. Exogenous citicoline, hydrolyzed in the small intestine and readily absorbed as choline and cytidine, enters the various biosynthetic pathways that utilize citicoline as an intermediate. Citicoline thus has a sparing effect on systemic choline reserves, as well as inhibiting the breakdown of membrane phospholipids.

Mechanisms of Action

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. 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 intra-hippocampal 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.

5.2 Pharmacokinetic properties

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. 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 resynthesis into citicoline in the brain.

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.

5.3 Preclinical safety data

The LD₅₀ of a single intravenous dose of citicoline is 4,600 mg/kg and 4,150 mg/kg in mice and rats, respectively. An oral LD₅₀ could not be determined as no deaths occurred at the maximum possible oral dose.

No toxic effects were observed in 30-day subacute toxicity studies of oral citicoline to two groups of rats at doses of 100 mg/kg and 150 mg/kg. No changes occurred in blood chemistry, organ histology, or urinary parameters. The effect of chronic oral consumption of citicoline was studied in dogs fed a single 1.5-g/kg dose daily for six months. No toxic effects were seen nor did any physiological, biochemical, neurological, or morphological abnormalities occur.

6. Pharmaceutical particulars

6.1 List of excipients

Red Oxide of Iron

Titanium dioxide I.P

6.2 Incompatibilities

Not known

6.3 Shelf life

24 months

6.4 Special precautions for storage

Store in a cool, dry place. Protect from light.

Administrative data

7. Marketing authorisation holder

Strides Shasun Limited

Strides House, Bilekahalli,

Bannerghatta Road,

Bengaluru – 560 076, India

8. Toll free number for reporting

1800 4190601

9. Date of text

16th May 2016

10. References

-<http://www.webmd.com/vitamins-supplements/ingredientmono-1090-citicoline.aspx?activeingredientid=1090&activeingredientname=citicoline>

-<http://www.altmedrev.com/publications/13/1/50.pdf>