# COGNOLIN Injection (Citicoline)

*For the use of a Registered Medical Practitioner only or a hospital or laboratory only*

## Qualitative and Quantitative Composition

Each mL contains:

Citicoline Sodium IP equivalent to

Citicoline .....250 mg

Water for Injections IP .....q.s.

## Dosage Form(S) and Strength(S)

Injection for intravenous/intramuscular use

**COGNOLIN** – 2 mL and 4 mL

## Clinical Particulars

### Therapeutic Indications

For the treatment of disturbances of consciousness as resulting from head injuries, brain operation and acute stage of cerebral infraction in adult only.

### Posology and Method of Administration

#### Disturbance of Consciousness resulting from head injury or brain operation

Usually for adults a dose of 500-1000 mg of COGNOLIN Injection is administered once or twice a day, by intravenous drip, infusion, intravenous injection or intramuscular injection. The dose may be adjusted according to the patient's age and condition.

#### Disturbance of Consciousness in the Acute Stage of Cerebral Infarction

Usually, a dose of 1,000 mg of citicoline is administered once a day, by intravenous injection, for 2 consecutive weeks.

The dosage may be adjusted based on the seriousness of the disease. It can be administered intramuscularly, intravenously (3 to 5 minute) injection and in intravenous drop perfusion (dripping speed 40-60 drops/minute). Citicoline is compatible with all intravenous isotonic solutions. It can also be mixed with hypertonic glucose serum.

Method of administration: For I.V. or I.M. or I.V. drip infusion use only.

#### Contraindications

It is contraindicated in patients with a known hypersensitivity to citicoline or any other component of the formulation.

Citicoline must not be administered to patients with hypertonic of the parasympathetic.

## Special Warnings and Precautions for Use

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.

For patients with acute, severe and progressive disturbance of consciousness resulting from a head injury or brain operation, citicoline injection should be administered in conjunction with haemostatics and an intracranial pressure relieving drug, or a treatment such as hypothermia. For patients with disturbance of consciousness in the acute stage of cerebral infarction, it is recommended to start the administration of citicoline injection within 2 weeks after an apoplectic stroke.

In administering citicoline injection intramuscularly, caution should be exercised so as not to affect the tissues, nerves, etc. Intramuscular injection should be given only when indispensable and should be restricted to the minimum to be required. In particular, repeated injection at the same site should be avoided. Care should be exercised to avoid injection at sites along the course of the nerves. In case of intense pain or backflow of blood upon insertion of the injection needle, the needle should be withdrawn immediately and injected at a different site. In intravenous administration, inject as slowly as possible. Since shock may occur, a close observation should be maintained. If any such abnormalities such as drop in blood pressure, distressed feeling of the chest or dyspnoea are observed, citicoline injection should be discontinued and appropriate measures taken.

Persistent Intracranial Haemorrhage

In case of persistent intracranial haemorrhage, it is recommended not to exceed the dose of 1,000mg of citicoline daily, given through very slow intravenous administration (30 drops/minute)

## Drug 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).

## Use in Special Population

**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.

**Patients with Hepatic Impairment**

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

**Pregnant Women**

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

**Lactating Women**

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

**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.

## 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.

## Undesirable Effects

The commonly observed adverse effects (0.1–5%) with intravenous use of citicoline were rash, insomnia, occurrence or intensification of numbness of paralyzed extremities (when used in patients with post-apoplectic hemiplegia), nausea, abnormal laboratory values for function of the liver, and feeling of warmth. The other adverse reactions (<0.1%) were excitation, convulsions, anorexia, transient diplopia, transient blood pressure changes, malaise, shock, distressed feeling of the chest, and dyspnea. In a short-term, placebo-controlled, crossover study, 12 healthy adults took citicoline at daily doses of 600 mg and 1,000 mg or placebo for consecutive 5-day periods. Transient headaches occurred in 4 subjects on the 600 mg dose, 5 on the 1,000 mg dose, and 1 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 aged 60 to 80 years, suffering from senility and cerebral vascular insufficiency. A total of 151incidents 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.

Occasionally, citicoline may exert a stimulating action of the parasympathetic, as well as a fleeting and discrete hypotensive effect.

Citicoline is generally well tolerated. Few adverse effects that are reported with oral citicoline include gastrointestinal disturbances, dizziness and fatigue, Rash, insomnia, nausea, dizziness, convulsions, anorexia, shock, transient blood pressure changes.

**Reporting of Side-effects**

If you experience any side-effects write to drugsafety@cipla.com. You can also report side effects directly via the national pharmacovigilance program of India by calling on 1800 180 3024 or you can report to Cipla Ltd on 18002677779. By reporting side-effects, you can help provide more information on the safety of this product.

## Overdose

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.

# Pharmacological Properties

## Mechanism of Action

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 phospholipidcomponent. 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 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

**Pharmacodynamic Properties**

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.

**Pharmacokinetic Properties**

***Absorption***

Citicoline is well absorbed following intramuscular administration. After intramuscular doses of citicoline 1,000 mg, peak increases in plasma choline levels were seen in 0.4 hours, with levels increasing from 11 micromol/L (baseline) to 25 micromol/L

***Distribution***

Choline derived from citicoline crosses the blood–brain barrier, presumably serving as a source of acetylcholine and phosphatidylcholine (lecithin) synthesis. 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 liver to free choline. The liver is capable of synthesizing lecithin from choline. The half-life of free choline is of 2 hours after intramuscular administration.

***Excretion***

Only small amounts of dose are recovered in the urine and faeces (less than 3% each). Approximately 12% of a dose is eliminated through the lungs as carbon dioxide.

# Nonclinical Properties

## Animal Toxicology or Pharmacology

### 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 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 abnormalities related to drug administration. Intravenous administration of citicoline 300-500mg/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

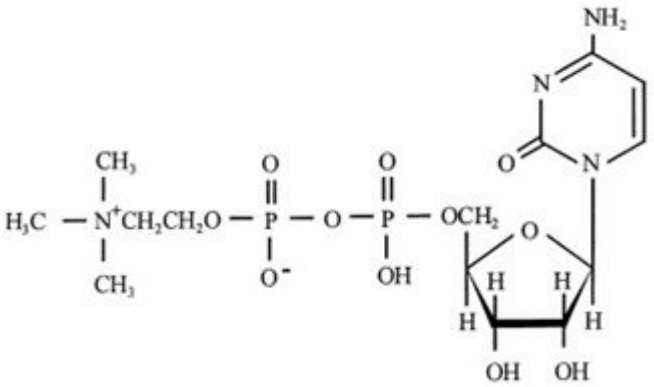
study in rats, 100, 350, and 1000 mg/kg/day oral doses resulted in no mortality. In males, slight significant increases in serum creatinine (350 and 1000 mg/kg/day) and decreases in urine volume (all treated groups) were observed. In females, slight significant increases in total white blood cell and 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.

# Description

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 cytidinediphosphate 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.




# Pharmaceutical Particulars

## Incompatibilities

Not applicable

## Shelf Life

24 months

### Packaging Information

**COGNOLIN Injection:** Ampoule of 2 ml and 4 ml

### Storage and Handling Instructions

Store protected from light at a temperature not exceeding 25°C

Do not freeze

Keep out of reach of children

# Patient Counselling Information

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.

**What COGNOLIN Injection are and what they are used for?**

**COGNOLIN** Injection contains citicoline. They are indicated for the treatment of disturbances of consciousness as resulting from head injuries, brain operation and acute stage of cerebral infraction in adult only.

**What you need to know before you take COGNOLIN Injection?**

*Do not take **COGNOLIN** Injection*

- If you are allergic to citicoline or any of the other ingredients of this medicine
- If you ever had serious kidney problems
- If you are hypertonic
- If you have persistent intracranial haemorrhage

*Warnings and precautions*

Talk to your doctor or pharmacist before taking **COGNOLIN** Injection

- if you think your kidneys may not be working perfectly. (Your doctor may need to start you on a lower dose.)

*Other medicines and **COGNOLIN** Injection*

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:

- Levodopa
- Meclofenoxate
- Centrophenoxine
- Any other medicine, 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 **COGNOLIN** Injection and you think you may be pregnant, consult your doctor immediately.

*Driving and using machines*

Do not to operate heavy machinery or automobiles

**How COGNOLIN Injection is given?**

*For disturbance of Consciousness resulting from head injury or brain operation*

Usually for adults a dose of 500-1000 mg of COGNOLIN Injection is administered once or twice a day, by intravenous drip, infusion, intravenous injection or intramuscular injection. The dose may be adjusted according to the patient's age and condition

*For disturbance of Consciousness in the Acute Stage of Cerebral Infarction*

Usually, a dose of 1,000 mg of citicoline is administered once a day, by intravenous injection, for 2 consecutive weeks.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

**What are the possible side effects of COGNOLIN Injection?**

Like all medicines, this medicine can cause side effects, although not everybody gets them. You may notice the following side effects:

- Rash
- Insomnia
- occurrence or intensification of numbness of paralyzed extremities
- Nausea
- Feeling of warmth
- Convulsions
- Anorexia
- Transient Diplopia
- Malaise
- Shock
- Dyspnea

***Reporting of Side-effects***

If you experience any side-effects write to drugsafety@cipla.com. You can also report side effects directly via the national pharmacovigilance program of India by calling on 1800 180 3024 or you can report to Cipla Ltd on 18002677779. By reporting side-effects, you can help provide more information on the safety of this product.

**How to store COGNOLIN Injection?**

Store protected from light at a temperature not exceeding 25°C.

Do not Freeze

# Details of Manufacturer

Akums Drugs and Pharmaceuticals Ltd.

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### Marketed by

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# Details of Permission or License Number with Date

29/UA/SC/P-2007 on Dated 18/03/2017

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