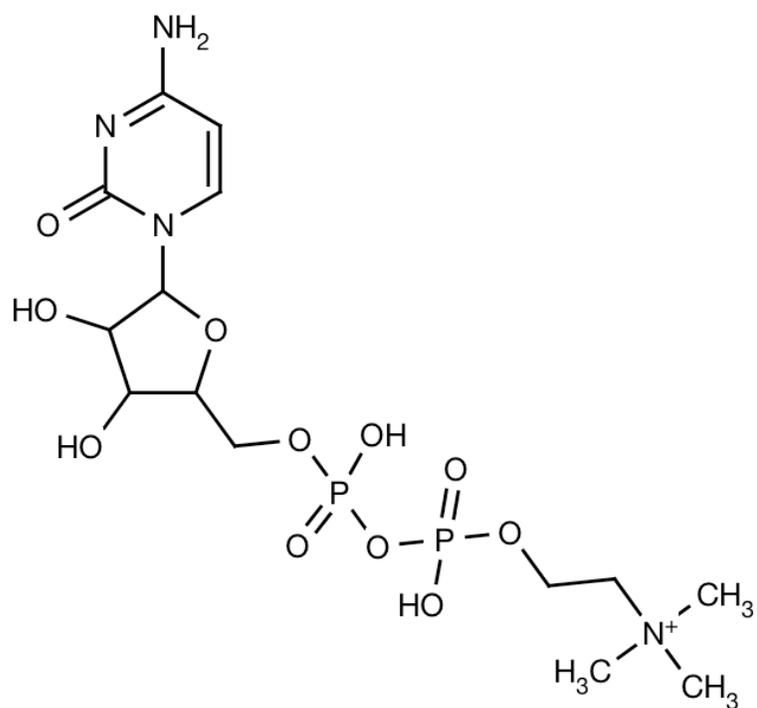


# CINAPS Compound Dossier

## Citicoline



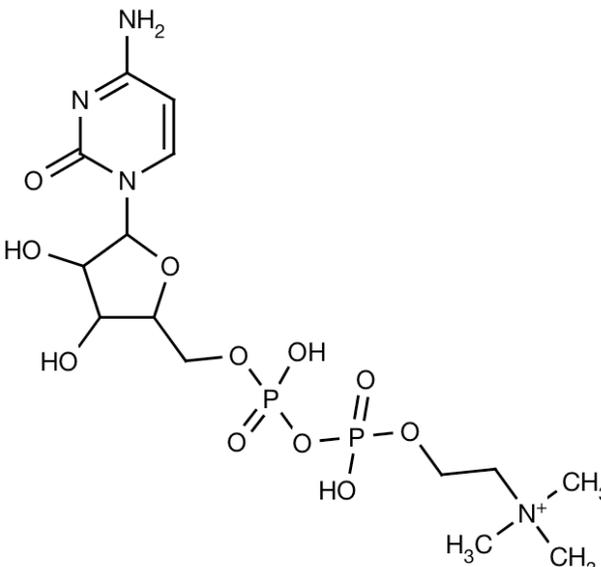
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## I. Compound Information

<b>Common name</b>	Citicoline				
<b>Structure</b>					
<b>PubChem ID</b>	291	<b>MF</b> C14 H27 N4 O11 P2	<b>MW</b> 489.33		
<b>CASRN</b>	987-78-0	<b>Polar surface area</b>	230.29	<b>logP</b>	-4.06
<b>IUPAC name</b>	[[{[5-(4-Amino-2-oxo-1,2-dihydropyrimidin-1-yl)-3,4-dihydroxyoxolan-2-yl]methoxy} (hydroxy)phosphoryl]oxy][2-(trimethylazaniumyl)ethoxy]phosphinic acid				
<b>Other names</b>	CDP choline; cytidine 5'-diphosphocholine; cytidine diphosphate choline				
<b>Drug class</b>	Choline donor in biosynthesis of choline-containing phosphoglycerides				

**Notes** Launched worldwide (outside of the U.S. and Canada only) as a drug for stroke and head injuries. Phase III clinical studies for stroke suspended in the U.S. and Canada (**ADIS, 8961**). Despite some promising indications of clinical efficacy against the effects of head injuries or stroke, large scale clinical studies have failed to reveal a clear dose response.

Citicoline is an ingredient in many over-the-counter “health” drinks and dietary supplements marketed in the U.S.

### Development status

## II. Rationale

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### Ila. Scientific Rationale / Mechanism

Cytidine-(*S*)-diphosphocholine (INN: citicoline) is an endogenous precursor of phospholipids, known for its dopaminomimetic properties and its therapeutic efficacy in Parkinson's disease; it has also been proposed in the treatment of various neurological disorders, such as senile dementia (Alzheimer type), traumatic and apoplectic disorders. The mechanism underlying its therapeutic efficacy remains, however, unclear but chronic treatment has been proved most effective. Its therapeutic efficacy in disturbances of consciousness is attributable to its ability to improve phospholipid metabolism, with a consequent improvement in the deteriorated axonal flow of dopamine (**Saligaut, 1987**).

Citicoline has been shown to act as a dopaminergic agonist, and has a particularly significant effect on levels of dopamine and its metabolites in the striatum. The results obtained suggest that, with citicoline administration, striatal dopamine synthesis is increased, probably through tyrosine hydroxylase activation. Increase in dopamine levels would partly result from inhibition of dopamine reuptake, possibly related to citicoline action upon phospholipid synthesis. In addition, citicoline also has some effects upon the other monoamines, serotonin and norepinephrine, muscarinic receptors, and glutamate and GABA (**Secades, 2006**).

Citicoline stimulates dopamine synthesis in nigrostriatal areas and antagonizes changes in CNS dopamine and norepinephrine levels caused by various toxins. Citicoline stimulates cholinergic neurotransmission. In various brain disease models, citicoline has improved or normalized biochemical and functional parameters of the central nervous system. Citicoline stimulates the synthesis and inhibits catabolism of cerebral phospholipids, and also has a protective effect upon membrane ATPase and enzymes involved in brain energy metabolism, particularly succinyl dehydrogenase and citrate synthetase, as well as protein and nucleic acid metabolism, increasing RNA biosynthesis at certain brain regions (**Secades, 2006**).

Neuroprotection by citicoline has been described since 1978 and several mechanisms of action have been proposed. Ameliorating the effects of free oxygen radicals and reducing the damage of membraneous structures at the cellular level during and after cerebral ischemia are key features (**Overgaard, 2006**).

Chronic administration of citicoline to aged animals promoted a partial recovery of the striatum dopamine receptor function normally reduced with aging. A proposed mechanism is modulation of the fluidity of brain neuronal membranes (**Gimenez, 1991**).

Citicoline cleaved caspase-3, attenuated both expression of pro-caspases and fragmentation of nuclear DNA after focal cerebral ischemia. Citicoline in combination with nimodipine reduced infarction and increased expression of antiapoptotic Bcl-2 after focal cerebral ischemia. Citicoline pre-treatment prevented excitotoxic death caused by excessive glutamate exposure in cerebellar granule neurons and in an *in vivo* focal cerebral ischemia model (**Adibhatla, 2005**).

Citicoline stimulates tyrosine hydroxylase activity and dopamine release, which may be due to increases in brain acetylcholine since choline administration produces the same effects. Citicoline has been tested in treatment of Parkinson's disease because of its ability to increase the availability of dopamine. Combination treatment of Parkinson's patients with citicoline and levodopa allowed significant reduction of the levodopa dose, thus minimizing side effects of L-DOPA therapy (**Adibhatla, 2005**).

A very interesting recent study concluded that citicoline exerts stimulant and neuroprotective actions on cultured dopaminergic neurons. Primary dopaminergic cultures from mouse mesencephala were treated with citicoline to investigate its neuroprotective potential on the survival of dopaminergic neurons exposed

## II. Rationale (cont.)

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to MPP(+) and glutamate. Treatment with citicoline alone significantly increased the survival of dopaminergic neurons compared to controls. MPP(+) or glutamate decreased the total number of dopaminergic neurons whereas citicoline afforded significant protection against either toxicity. In addition, citicoline significantly decreased propidium iodide uptake by cultured cells (an indication that citicoline may block the uptake of MPP(+) into dopaminergic neurons) (**Radad, 2007**).

### IIb. Consistency

n/a

### III. Efficacy (animal models of Parkinson's disease)

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#### IIIa. Animal Models: Rodent

Administration of citicoline to rats in a single dose of 500 mg/kg i.p., caused a significant ( $p < 0.05$ ) increase in striatal dopamine levels one hour after injection. Additionally, citicoline was shown to have a neuroprotective effect in substantia nigra lesioned by (horseradish) peroxydases, achieving an increased number of surviving cells. A trophic or stimulating effect of citicoline upon nigrostriatal dopaminergic neurons in a model of lesion induced by kainic acid has also been reported. Chronic administration of citicoline to aged mice promotes partial recovery of the function of dopaminergic and muscarinic receptors that normally decreases with aging (**Secades, 2006**).

Male Wistar rats were treated on day 21 after 6-hydroxydopamine lesioning with either apomorphine, amphetamine, or L-DOPA. This produced circling behavior in the animals. The rats were then treated with citicoline (1000 mg/kg p.o.) for 3 days. On day 24 (90 min. after the last administration of citicoline) the rats were treated again with apomorphine, amphetamine and L-DOPA and measurement of circling behavior was repeated. Citicoline itself was devoid of any behavioral effects. It potentiated the effects of L-DOPA and amphetamine, but did not interfere with the effects of apomorphine; this suggests that citicoline acts on the presynaptic side of the synapse by: (1) Increasing synthesis of dopamine (DA) or increasing release of DA or (2) increasing release of DA in the lesioned striatum after treatment with L-DOPA. This increase of release could occur in surviving dopaminergic neurones but also in serotonergic neurones or non-aminergic decarboxylase-containing interneurones and could be related to changes in the lipid structure of the axonal membrane (**Saligaut, 1987**).

Citicoline was administered 20 mg/kg/d i.p. for 20 days to 24-month-old male Sprague-Dawley rats that had begun to exhibit cognitive and motor deficits. The drug was also given to rats with behavioral changes induced by a single injection of scopolamine, a cholinergic antagonist. In all cases, citicoline improved learning and memory performance evaluated using active and passive avoidance tests. In an older rat group, improved motor capacity and coordination was also seen. These results suggest that citicoline affects the central mechanisms involved in cognitive behavior, probably through a cholinergic action (**Secades, 2006**).

#### IIIb. Animal Models: Non-human primates

n/a

## IV. Efficacy (Clinical and Epidemiological Evidence)

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### IVa. Clinical studies

As the intermediate in phosphatidylcholine biosynthesis, it was believed that citicoline would rectify membrane damage and provide benefit in CNS disorders and injury. Citicoline has been studied in >11,000 volunteers and patients and showed beneficial effects in cerebral ischemia, traumatic brain injury, hypoxia, Alzheimer's and Parkinson's diseases, learning and memory disorders, alcoholism, drug addiction, amblyopia and glaucoma. Citicoline has been tested in treatment of Parkinson's disease because of its ability to increase the availability of dopamine. Combination treatment of Parkinson's patients with citicoline and L-DOPA allowed significant reduction of the L-DOPA dose, thus minimizing side effects of L-DOPA therapy (**Adibhatla, 2005**).

In a double-blind crossover study conducted on 28 parkinsonian patients comparing citicoline 600 mg/d i.v. to placebo, citicoline was shown to be an effective treatment for these patients, achieving improvements in the assessment of bradykinesia, rigidity, and tremor, and also in the scores of the Webster scale and the Northwestern University Disability Scale (NUDS). Two groups of patients with Parkinson disease were subsequently studied. The first group included 28 patients who had not previously received treatment, while the second group included 30 patients who were already receiving treatment with L-DOPA and carbidopa for at least 2 months, and in whom dosage had been stabilized at the minimum effective level. Treatment was administered for 20 days at a dose of 500 mg/d by the parenteral route. Treatment with citicoline provided statistically significant improvements in Webster scale, NUDS, and assessment of bradykinesia in both patient groups. Rigidity also improved in both groups, although this improvement only reached statistical significance in the previously treated group of patients. Tremor also improved in both groups, but the desired statistical significance was not reached (**Secades, 2006**).

It has been shown that association of citicoline with L-DOPA treatment allows for reducing L-DOPA dose by 50%, thus minimizing the side effects associated to levodopa therapy. In one study, 65 patients were randomized to a group to which citicoline 1 g/d i.v. was added or to a placebo group. Treatment lasted 21 days. All patients continued their underlying treatment with L-DOPA plus mianserin or benserazide for at least 8 weeks. There were significant differences between citicoline and placebo after 14 and 21 days of treatment in all parameters assessed by the Webster and NUDS scales. Patients treated with citicoline experienced a significant worsening 45 days after the medication was discontinued, thus showing the efficacy of citicoline as adjuvant treatment to L-DOPA in patients with Parkinson disease.

In another study, 61 parkinsonian patients were treated with citicoline, of whom 48 patients were already receiving treatment with L-DOPA. Parkinsonian symptoms were assessed using the Webster scale. Among patients receiving L-DOPA, 36% improved when citicoline was added, with the greater percent improvements being obtained in bradykinesia, rigidity, posture, gait, and limb sway. It was found that citicoline treatment allows for delaying the start of L-DOPA therapy in the early disease stages, and for decreasing or maintaining L-DOPA dosage in already treated subjects (**Secades, 2006**).

Citicoline was studied in 30 parkinsonian patients who were already being treated with L-DOPA. The dose administered was 500 mg/d by the intramuscular route for 2 months, and was reduced to a third at the end of the first month of treatment. Changes in parkinsonian symptoms, according to the Yahr scale, showed after the first month of treatment a moderate improvement in facial expression and digital skills, and an obvious improvement in postural stability, motor changes and bradykinesia. A greater stabilization of therapeutic response was also seen, with a decreased incidence of "wearing-off" and "on-off" phenomena, although dyskinesia increased. When L-DOPA dose was decreased during the second study

#### IV. Efficacy (Clinical and Epidemiological Evidence) (cont.)

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month, clinical improvement was maintained and incidence of dyskinesia was decreased (**Secades, 2006**).

The effects of citicoline in 20 parkinsonian patients treated with L-DOPA for more than 2 years was examined. These patients were administered citicoline 1 g/d/15 d i.m., and then continued with half the dose for 15 additional days. A progressive symptom improvement was achieved. Thus, 4.16% and 7.26% overall improvements were achieved in the Columbia University scale at 15 days and at the end of treatment respectively. Partial improvements achieved in ambulation, turning time in bed, and writing time were particularly noteworthy. In assessment conducted by relatives, improvements achieved in agility, ambulation, and general patient status deserved special mention (**Secades, 2006**).

##### **IVb. Epidemiological evidence**

n/a

## V. Relevance to other neurodegenerative diseases

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There have been 13 stroke clinical trials of citicoline since 1980 in Europe (8 trials), Japan (1 trial) and USA (4 trials). Both European and Japanese clinical trials reported an improvement of global and neurological function and an earlier motor and cognitive recovery, whereas USA clinical trials did not clearly demonstrate beneficial effects of citicoline treatment. On post-hoc analysis, citicoline in parenteral administration was effective for long-term treatments (12 week) in a subgroup of moderate-to-severe stroke cases. In view of these discrepancies, further studies are essential before making any conclusions on citicoline activity for stroke treatment (**Parnetti, 2007**)

Cochrane meta-analysis concluded that citicoline has a positive effect on memory and behavior in the medium term primarily in patients suffering from cognitive deficits associated with cerebrovascular disease. Further longer term studies with patients affected by cerebrovascular disease and vascular dementia (VaD) recruited with currently accepted standardized diagnostic criteria are necessary to demonstrate an activity of citicoline in cognitive disorders associated with cerebrovascular disease (**Parnetti, 2007**).

In a study on the effects of citicoline on 25 patients with head trauma and depressed consciousness, the drug was shown to be effective, leading to recovery from neurological clinical symptoms and return to a conscious state in 70% of cases, and was very well tolerated, causing no reported side effects (**Secades, 2006**).

A clinical trial in 101 patients with disorders of consciousness from different causes (30% of traumatic origin), showed the effectiveness of citicoline for improving the General Recovery Rate, closely related to the Principal Component Analysis Score. Citicoline was found to be more effective in items related to the executive factor than in those related to the verbal factor, and that the greatest effect was achieved in patients under 60 years of age and with a stabilized period of impaired consciousness not longer than 3 weeks (**Secades, 2006**).

One hundred patients with head trauma were treated with citicoline starting at doses of 600-1200 mg/d by the parenteral route, switched to 300-900 mg/d by the oral route in the rehabilitation phase. The treatment regimen caused a decrease in duration of post-traumatic coma and rate of both neurological and psychic sequelae, and achieved a better response in recovery from intellectual disorders and motor deficits (**Secades, 2006**).

In 921 cases of severe head trauma, i.e. with an initial score in the Glasgow Coma Scale (GSC) of 8 or less, no significant differences were found in mortality. Citicoline improved quality of survival, allowing for more frequent social and familiar reinsertion as well as return to work or school (**Secades, 2006**).

A study of two hundred and sixteen patients with an initial Glasgow Coma Scale score ranging from 5 to 10 was reported. Of these, 115 patients received treatment with citicoline. Mean citicoline dose administered was 4 g/d. Analysis of the results showed that citicoline decreased hospital stay, promoted the recovery of memory, motor disorders, higher neurological functions, and mood changes, and improved global functional outcome (**Secades, 2006**).

In a double-blind study comparing citicoline (750 mg/d i.v.) versus placebo in 64 patients with cerebral infarction assessment at 3 months showed citicoline to be superior to placebo for improving motor deficit ( $p < 0.05$ ), hypertonia ( $p < 0.03$ ), gait recovery ( $p < 0.02$ ), changes over time in electroencephalographic tracing ( $p < 0.01$ ) and psychometric tests ( $p < 0.05$ ), achieving a higher number of independent states (51.6% with citicoline; 24.24% with placebo). In a similar study, in 52 patients, of whom 27 patients received citicoline (750 mg/d/10 d i.v.) and 25 placebo, an assessment was made at 10 days, and showed that citicoline-treated patients had a better course as regarded consciousness disorders, with recovery of consciousness in 66.7% of cases as compared to 32.0% in the placebo group ( $p < 0.01$ ), and

## V. Relevance to other neurodegenerative diseases (cont.)

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also deficit syndromes (82.6% and 54.5% of patients recovered with citicoline and placebo respectively;  $p < 0.04$ ) and electronencephalographic tracings 83.3% with citicoline versus 35.3% with placebo;  $p < 0.01$ ). In both studies, citicoline tolerability was rated as excellent by investigators (**Secades, 2006**).

A double-blind, prospective, multi-center, placebo-controlled study on the value of citicoline for the treatment of acute cerebral infarction was reported. Sixty-three Japanese academic centers participated in this study, in which a total of 272 patients were enrolled following strict inclusion criteria. Patients were randomized to receive 1 g/d i.v. of citicoline or saline (placebo) for 14 days. At the end of treatment, citicoline was shown to significantly improve consciousness (51% vs. 33% for placebo;  $p < 0.05$ ) and overall improvement 52% vs. 26%;  $p < 0.01$ ) and usefulness rates (47% vs. 24%;  $p < 0.001$ ) (**Secades, 2006**).

The activity of choline alfoscerate was investigated in 789 patients with vascular dementia (VaD). Three homogeneous-case trials evaluated 408 patients and three combined-case trials included 381 patients with VaD. In four trials, choline alfoscerate was administered orally at the dose of 1200 mg/day for 3 or 6 months, while in the other three studies it was administered by intramuscular injection at the dose of 1000 mg/day for 3 months. Of the 431 orally-treated patients, 418 received the drug over 6 months and 13 over 3 months. A total of 358 were treated intramuscularly over 3 months. In these studies, investigators thoroughly assessed cognitive impairment, behavioral disturbances, changes of interpersonal relations, affective disorders and somatic problems. Similarly as observed in degenerative dementia disorders in all trials on VaD, treatment with choline alfoscerate improved memory and attention impairment, as well as affective and somatic symptoms (fatigue, vertigo). Effects of choline alfoscerate were superior to those of placebo and of the same extent or superior to those of reference compounds. Comparison between choline alfoscerate and citicoline gave SCAG scores more favorable to choline alfoscerate (**Parnetti, 2007**).

## VI. Pharmacokinetics

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### Via. General ADME

Exogenous citicoline metabolism in humans differs from that in rodents. In rodents, oral administration of citicoline increased blood plasma levels of cytidine and choline, whereas, in humans, blood plasma levels of uridine but not cytidine were increased. It was observed in human subjects that rapid degradation of citicoline occurs following oral administration and before reaching the systemic circulation (**Wurtman, 2000**).

### Vib. CNS Penetration

In animal studies, brain uptake of citicoline or its metabolites was 0.5% of the oral dose, whereas i.v. administration elevated brain uptake to 2%. Liposome encapsulation of the drug can further increase brain uptake up to 23% and also circumvent CTP:phosphocholine cytidyltransferase, the key rate limiting enzyme in phosphatidylcholine synthesis. Liposome encapsulation suggests a possible strategy to increase the citicoline levels in the CNS and enhance its clinical effectiveness (**Adibhatla, 2002; Adibhatla, 2005; Agut, 1983**).

Studies of transient cerebral ischemia in rats using liposomal citicoline showed that administration of liposomal citicoline is more effective as compared to non-liposomal citicoline (**Secades, 2006**).

Long circulating liposomes with various ligands (including citicoline) have been extensively investigated to deliver therapeutic agents to the brain, circumventing the blood-brain barrier (**Suresh Reddy, 2006**).

Vic. Calculated  $\log([brain]/[blood])$  (Clark Model):

## VII. Safety, Tolerability, and Drug Interaction Potential

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### VIIa. Safety and Tolerability

The intravenous LD<sub>50</sub> in mice, rats, and rabbits is 4.6, 4.15, and 1.05 g/kg, respectively . Oral LD<sub>50</sub> is 27.14 g/kg in mice and 18.5 g/kg in rats (**Secades, 2006**).

Citicoline (600 or 1000 mg/d) or placebo to healthy volunteers did not show any abnormal side effects in terms of hematological or clinical analysis. No clinically significant ECG and EEG abnormalities were noticed. Neurological tests, tendon reflexes, blood pressure and heart rate were not affected by any dose of the drug or placebo. The tolerance of citicoline is excellent and side effects were rare, never severe and consisted mainly of digestive intolerance, gastrointestinal discomfort and restlessness. In no case was it necessary to interrupt the treatment for side effects attributed to citicoline use. Indevus Inc. licensed exclusive North American rights from Ferrer Internacional, S. A. for the manufacture, use and sale of citicoline for the treatment of stroke (**Adibhatla, 2005**).

### VIIb. Drug Interaction Potential

n/a

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