



Citicoline

Zynapse®

Cerebroprotective/Neurotropic

FORMULATION:

Each mL of Zynapse adult solution contains: Citicoline 100mg
Each capsule contains: Citicoline 500mg

Citicoline, a naturally occurring endogenous nucleoside, is an intermediate compound in the major pathway for the biosynthesis of the structural phospholipids of cell membranes, including neurons.

PHARMACODYNAMICS

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 phospholipid fraction of the cellular membrane and microsomes.

The concept that administration of exogenous Citicoline can augment the synthesis of neural membrane phospholipid is attractive, because accelerated replacement or repair plays a critical role in maintaining the healthy function of numerous physiological processes. It has shown therapeutic efficacy in a variety of diseases in which membrane disorder, dysfunction, or degeneration result in cellular and tissue ischaemia and necrosis.

PHARMACOKINETICS

Citicoline is a water soluble compound with greater than 90% bioavailability. Pharmacokinetic studies in healthy adults have shown oral doses of citicoline to be rapidly absorbed, with less than 1% excreted in the feces. Plasma levels peak in a biphasic manner, at 1 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. After 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 re-synthesis into citicoline in the brain.

Pharmacokinetic studies using ¹⁴C citicoline show citicoline elimination occurs mainly via respiratory CO₂ and urinary excretion, in two phases, mirroring the biphasic plasma peaks. The initial peak in plasma concentration is followed by a sharp decline, which then slows over the next 4 to 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.

PHARMACOLOGICAL PROPERTIES

Citicoline activates the bio-synthesis of structural phospholipids in the neuronal membrane, increases cerebral metabolism and increases the level of various neurotransmitters, including acetylcholine and dopamine. Citicoline has shown neuroprotective effects in situations of hypoxia and ischaemia, as well as improved learning and memory performance in animal models of the brain aging. Furthermore, it has been demonstrated that citicoline restores the activity of mitochondrial ATPase and of membrane Na⁺/K⁺-ATPase, inhibits the activation of phospholipase A2 and accelerates the re-absorption of cerebral edema in various experimental models.

INDICATIONS

For cerebrovascular accidents, in acute recovery phase, in signs and symptoms of cerebral vascular insufficiency and in cranial traumatism and their sequelae.

- Cerebrovascular diseases- e.g. from ischaemia due to stroke, where Citicoline accelerates the recovery of consciousness and overcoming motor deficit. The clinical testing of Citicoline has challenged the historical concept that one can do nothing for a stroke patient after a certain period of time has transpired after the onset of symptoms. The practicality of a drug that can be administered up to 24 hours after stroke is a key factor in evaluating the potential of Citicoline.

The results of a recent phase 3 clinical trial among patients suffering from ischaemia stroke demonstrated a statistically and clinically significant improvement in the neurological function of patients treated with optimal dose of Citicoline, 500mg daily. The potential of Citicoline as stroke therapy is underscored by other key attributes: its oral dosage for, a 24 hour window of therapeutic opportunity following stroke, an apparent absence of significant side effects. Preliminary evidence suggests that in a small sub-group of patients, Citicoline may reduce the size of the impact caused by stroke.

Treatment of Citicoline within the first 24 hours after onset in patients with moderate to severe stroke increase the probability of complete recovery at 3 months.

- Head Trauma of varying severity: In a clinical trial, Citicoline accelerated the recovery from post-traumatic coma and the recuperation of walking ability, achieved a better final functional result and reduced hospital stay.
- Cognitive disorders of diverse aetiology - e.g. senile cognitive impairment which is secondary to degenerative diseases (e.g. Alzheimer's disease) and to chronic cerebral vascular disease. Citicoline improves scores on cognitive evaluation scales and slowed the progression of Alzheimer's disease.
- Parkinson's disease - Citicoline has also been shown to be effective as co-therapy for Parkinson's disease. Beneficial neuroendocrine, neuroimmunomodulatory, and neurophysiological effects have been described. Considerable experimental evidence of effects of Citicoline on CNS dopaminergic system has accumulated. After treatment with Citicoline, regeneration of cells in rats with substantia nigra lesions has been demonstrated. Citicoline increases striatal dopamine and tyrosine hydroxylase synthesis.

CONTRAINDICATIONS

Must not be administered to patients with hypertonia of the parasympathetic.

USE IN PREGNANCY AND LACTATIONS

There is inadequate evidence of safe use of Zynapse in human pregnancy. Zynapse should be used in pregnancy and lactation only if the potential benefits justify the potential risks.

PRECAUTIONS AND WARNING

In case of persistent intracranial hemorrhage, the very slow administration (30 drops/minute) is recommended, the administration of larger doses could provoke an increase of the cerebral blood flow.

Large doses of citicoline could aggravate increase in cerebral blood flow in episodes of persistent intracranial hemorrhage.

INCOMPATIBILITIES

Zynapse must not be administered in conjunction with medicaments containing meclofenoxate (also known as clophenoxate)

DRUG INTERACTIONS

Zynapse potentiates the effects of L-dopa.

SIDE-EFFECTS

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

OVERDOSE AND TREATMENT

Citicoline exhibits very low toxicity profile in humans. In clinical use it has been observed to be safe at doses up to 2g/day.

The LD₅₀ of a single IV dose of citicoline was 4.6 and 4.15g/kg in mice and rats, respectively. An oral LD₅₀ could not be determined as no deaths occurred at the maximum possible oral dose.

In an unpublished acute toxicity study, free-base citicoline was administered to male and female rats at a dose of 2g/kg body weight for 14 days. No changes in body weight, deaths, clinical symptoms, or gross pathological changes were observed.

CAUTION

Foods, Drugs, Devices and Cosmetics Act prohibits dispensing without prescription.

DOSAGE

Zynapse adults oral drops: 1–2 mL twice or thrice a day

Zynapse capsule: 1 capsule once or twice a day

Zynapse tablet: 1 tablet once or twice a day

AVAILABILITY

Zynapse 100mg/mL adult oral drops – Bottle of 15mL

Zynapse 500mg capsule – 3 blistered strips x 8 capsules

Zynapse 1g tablet – 3 blistered strips x 8 tablets

STORE BELOW 25°C.

For suspected adverse drug reaction, report to the FDA: www.fda.gov

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Manufactured for
Natrpharm, Inc.
The Patriot Building
Km. 18, West Service Road
SLEX, Sucat, Parañaque City
by Hizon Laboratories, Inc.
Assumption Road
Sumulong Highway, Antipolo City

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