Natrapharm

Citicoline
Zynapse® 1000

Nootropic

FORMULATION:
Each mL of Zynapse 1000 contains Citicoline 250mg
(1000mg Citicoline per 4mL ampoule)

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 through out 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 ^{14}C citicoline show citicoline elimination occurs mainly via respiratory CO_2 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 CO_2 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:
Cerebrovascular accident in acute recovery phase, symptoms and signs of cerebral insufficiency, recent cranial traumatisms and their sequelae.

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 LD_{50} of a single IV dose of citicoline was 4.6 and 4.15g/kg in mice and rats, respectively. An oral LD_{50} 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 500 – 125mg/mL Injection: 1 to 2 injections daily
Zynapse 1000 – 250mg/mL Injection: 1 injection daily
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).
Zynapse is compatible with all the intravenous isotonic solutions. It can also be mixed with hypertonic glucose serum. Direct administration in the vein, if it is not made very slow, can produce hypotension.

AVAILABILITY:
Zynapse 1000 - 250mg/mL (1000mg/4mL ampoule): Type I Glass Ampoule x 4mL (box of 5's)

ALSO AVAILABLE:
Zynapse 500 - 125mg/mL (500mg/4mL ampoule): Type I Glass Ampoule x 4mL (box of 5's)
Zynapse 500mg capsule - Box x 24's
Zynapse 100mg/mL adult oral drops - Bottle x 15mL
Zynapse 1g tablet - 3 blistered strips x 8 tablets

STORE AT TEMPERATURES NOT EXCEEDING 25°C

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

Registration Number: DRP-6953
Date of First Authorization: June 2002
Revision Date: May 2017

Manufactured by
Ferrer Internacional, S.A.
Barcelona, Spain
Imported and distributed by
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The Patriot Building
Km. 18, West Service Road
SLEX, Sucat, Parañaque City

Repacked by
Hizon Laboratories, Inc.
Assumption Road, Sumulong Highway,
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NTZPS250001IN1701