CITICOLINE
CHOLINERV®

500 mg FILM-COATED TABLET
1 g FILM-COATED TABLET
100 mg/mL ADULT SOLUTION (ORAL DROPS)
125 mg/mL (500 mg/4 mL) SOLUTION FOR INJECTION
250 mg/mL (1 g/4 mL) SOLUTION FOR INJECTION

CNS STIMULANT / NEUROPROTECTIVE AGENT

FORMULATIONS
Each film-coated tablet contains:
Citicoline (as Sodium) ..... 500 mg or 1g
Each mL adult solution (oral drops) contains:
Citicoline (as Sodium)..... 100 mg
Each mL solution for injection contains:
Citicoline (as Sodium) .....125 mg or 250 mg

PRODUCT DESCRIPTIONS
Citicoline Sodium (Cholinerv®) 500 mg Film-Coated Tablet: Purple, capsule-shaped, film-coated tablet
Citicoline Sodium (Cholinerv®) 1 g Film-Coated Tablet: Purple, elliptical, film-coated tablet
Citicoline Sodium (Cholinerv®) 100 mg/mL Adult Solution (Oral Drops): Clear, light purple-colored fruit-flavored liquid
Citicoline Sodium (Cholinerv®) 125 mg/mL or 250 mg/mL Solution for Injection: Clear, colorless, sterile aqueous solution filled in 5 mL clear Type I glass ampules with a fill volume of 4 mL

CLINICAL PHARMACOLOGY

PHARMACODYNAMICS
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 or 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.

The pharmacologic action of citicoline appears to involve mechanisms that extend beyond phospholipid metabolism. Citicoline metabolites - choline, methionine, betaine, and cytidine-derived nucleotides - enter a number of metabolic pathways.

Biochemical markers of cholinergic nerve transmission are known to be deficient in conditions characterized by degeneration of cholinergic neurons, such as Alzheimer's disease. Citicoline modestly improves cognitive function in Alzheimer's disease by serving as an acetylcholine precursor. The brain uses choline preferentially for acetylcholine synthesis, which can limit the amount of choline available for phosphatidylcholine production.

Citicoline has been investigated as a therapy for stroke patients. Three mechanisms are postulated: (1) repair of the neuronal membrane via increased synthesis of phosphatidylcholine; (2) repair of damaged cholinergic neurons via potentiation of acetylcholine production; and (3) reduction of free fatty acid build-up at the site of stroke-induced nerve damage.

Citicoline protects cholinergic neurons from autocannibalism, a process in which membrane phospholipids are catabolized to provide choline for the synthesis of acetylcholine. This occurs when choline supplies are depleted, necessitating sacrifice of membrane phospholipids to maintain neurotransmission. As an exogenous source of choline for acetylcholine production, citicoline thus spares membrane phospholipids (in particular, phosphatidylcholine) and prevents neuronal cell death.

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.

INDICATIONS
- Acute and recovery phase of cerebral infarction (e.g., ischemia due to stroke)
- Cognitive dysfunction due to degenerative (i.e., Alzheimer's disease) and cerebrovascular disease
- Cerebral insufficiency (e.g., dizziness, memory loss, poor concentration, disorientation) due to head trauma or brain injury
- Parkinson's disease

DOSAGE AND ADMINISTRATION
Dosing must be individualized and adjusted according to disease severity.

Citicoline (Cholinerv) Oral:

ORAL CITICOLINE (Cholinerv) DOSE in ADULTS		
500 mg Tablet	**1 g Tablet**	**100 mg/mL Adult Solution (Oral Drops)**
500 mg (1 tablet) once or twice a day	1g (1 tablet) once a day	100 mg to 200 mg (1 to 2 mL) two or three times a day
Or, as prescribed by a physician		

Citicoline (Cholinerv) Solution for Injection:

SOLUTION FOR INJECTION CITICOLINE (Cholinerv) DOSE in ADULTS	
125 mg/mL (500 mg/4 mL)	**250 mg/mL (1 g/4mL)**
500 mg to 1 g (1 to 2 injections) per day	1 g (1 injection) per day
Or, as prescribed by a physician	

Directions for Intramuscular (IM) or Intravenous (IV) Use:
- Can be administered through IM or IV (3 to 5 minutes) route; and as IV drip (infusion rate of 40 to 60 drops/minute)
- Direct IV administration should be made very slowly to prevent episodes of hypotension.
- Citicoline is compatible with all IV isotonic solutions and hypertonic glucose solution.

CONTRAINDICATIONS
Hypersensitivity to any component of the product
Patients with hypertonia of the parasympathetic nervous system

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

INTERACTIONS WITH OTHER MEDICAMENTS
Citicoline must not be administered with products containing meclofenoxate.
Citicoline potentiates the effects of L-dopa.

STATEMENT ON USAGE FOR HIGH RISK GROUPS
Pregnancy and Lactation: There is not enough evidence on citicoline's safety in pregnant and breastfeeding women. Citicoline should be used in pregnancy and breastfeeding only when benefits justify the potential risks.
Children: No data on use in children.

UNDESIRABLE EFFECTS
Cardiovascular: Bradycardia, tachycardia, hypotension
Gastrointestinal: Diarrhea, epigastric distress, stomach pain
Nervous: Dizziness, headache, fatigue
Skin: Rash

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 2 g/day.
The LD_{50} of a single IV dose of citicoline was 4.6 and 4.15 g/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 2 g/kg body weight for 14 days. No changes in body weight, deaths, clinical symptoms, or gross pathological changes were observed.

STORAGE CONDITION
Store at temperatures not exceeding 30°C.
Keep the product out of sight and reach of children.

ADVERSE DRUG REACTION REPORTING STATEMENT
For suspected adverse drug reaction, seek medical attention immediately and report to the FDA at www.fda.gov.ph **AND** Unilab at (+632) 858-1000 or productsafety@unilab.com.ph. By reporting undesirable effects, you can help provide more information on the safety of this medicine.

AVAILABILITY
* Citicoline Sodium (Cholinerv®) 1 g Film-Coated Tablet in blister pack by 6's (Box of 30's) - DRXY44609
* Citicoline Sodium (Cholinerv®) 500 mg Film-Coated Tablet in blister pack by 10's (Box of 30's) - DRXY33845
* Citicoline Sodium (Cholinerv®) 100 mg/mL Adult Solution (Oral Drops) (Bottle of 15mL) - DRXY33558
** Citicoline Sodium (Cholinerv®) Solution for Injection:
4 mL of 125 mg/mL solution per ampule (Box of 6 ampules) - DRXY33773
4 mL of 250 mg/mL solution per ampule (Box of 6 ampules) - DRXY33774

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

* Manufactured by
AMHERST LABORATORIES, INC.
UNILAB Pharma Campus, Barangay Mamplasan
Biñan, Laguna, Philippines
for **UNILAB, Inc.**
No. 66 United Street, Mandaluyong City
Metro Manila, Philippines

** Manufactured by
AMHERST PARENTERALS, INC.
Sta. Rosa-Tagaytay Road, Don Jose
Sta. Rosa City, Laguna, Philippines
for **UNILAB, Inc.**
No. 66 United Street, Mandaluyong City
Metro Manila, Philippines

Trusted Quality Healthcare

Date of Revision: June 2015

Date of First Authorization:
* Citicoline Sodium (Cholinerv®) 1 g Film-Coated Tablet in blister pack by 6's (Box of 30's) - June 2015
* Citicoline Sodium (Cholinerv®) 500 mg Film-Coated Tablet in blister pack by 10's (Box of 30's) - September 2007
* Citicoline Sodium (Cholinerv®) 100 mg/mL Adult Solution (Oral Drops) (Bottle of 15mL) - July 2007
** Citicoline Sodium (Cholinerv®) Solution for Injection 4 mL of 125 mg/mL solution per ampule (Box of 6 ampules) and 4 mL of 250 mg/mL solution per ampule (Box of 6 ampules) - August 2007

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*Reg. IPOPHIL