SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

REGUCOLINE-1000

2. QUALITATIVE AND QUANTATIVE COMPOSITIONS

Each film coated tablet contains:

Citicoline Sodium

Eq. to Citicoline 1000 mg

Colors: Red Oxide of Iron & Titanium Dioxide BP

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film coated tablets (Reddish Brown coloured, elongated, biconvex, scored on one side, plain on other side & film coated tablets)

4. CLINICAL PARTICULARS

4.1 Therapeutic 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.

4.2 Posology and method of administration

Recommended dose is 500 - 2000 mg per day (1–4 tablets).

Doses of the preparation and treatment course duration depend on severity of cerebral lesion; they are adjusted by a doctor.

Elderly patients do not need the dose adjustment

4.3 Contraindications

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

4.4 Special warnings and precautions for use

Must not be administered in conjunction with medications containing centrophenoxine. Do not Citicoline in pregnancy or breast-feeding.

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

Peculiarities in usage:

Citicoline preparation should be administered with caution to patients who suffer from trimethylaminuria, Parkinson's disease and patients with depression in anamnesis.

4.5 Interaction with other medicinal products

Citicoline must not be administered with products containing meclophenoxate Citicoline enhances effects of L-dihydroxyphenylalanine and levodopa.

4.6 Pregnancy and lactation

Category D: There is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience or studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks.

Use in children: No data on use in children

4.7 Effects on ability to drive and use machines

Patients are advised not to operate heavy machinery or automobiles until the full effect of Citicoline are known. Do not consume alcohol while taking Citicoline.

4.8 Undesirable effects

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

Adverse reactions occur very rarely (< 1/10000), including single cases. Mentality: hallucinations, excitement, insomnia.

CNS: headache, dizziness, tremor.

Cardio-vascular system: arterial hypertension or hypotension. Respiratory system: dyspnea.

Digestive tract: nausea, vomiting, gastric pain, hyper salivation, insignificant change of hepatic function indexes, diarrhea.

Skin: redness, urticaria, exanthem.

General disorders: increase of body temperature, fever sensation, trembling, and edema.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the PvERS at www.pharmacyboardkenya.org

4.9 Overdose

Citicoline exhibits very low toxicity profile in humans. In a short term, placebo- controlled, cross-over study, 12 healthy adults took citicoline at daily doses of 600 and 1000 mg or placebo for consecutive five-day periods. Transient headaches occurred in four subjects on 600-mg dose, five on the 1000-mg dose, and one in placebo. No changes or abnormalities were observed in hematology, clinical biochemistry or neurological test. The LD50 of a single IV dose of citicoline was 4,600 mg/kg and 4,150 mg/kg in mice and rats, respectively. In an unpublished acute toxicity study, free-base citicoline was administered to male and female rats at a dose of 2,000 mg/kg BW for 14 days. No changes in BW, deaths, clinical symptoms or gross pathological changes were observed.

5. PHARMACOLOGICAL PROPERTIES

5.1 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 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.

5.2 Pharmacokinetic properties

Citicoline is a water-soluble compound with greater than 90% bioavailability. PK 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 hr after ingestion followed by a second larger peak at 24 hrs 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. Following 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 hrs. In the second phase, an initially rapid decline after the 24-hr plasma peak is similarly followed by a slower elimination rate. The elimination t½ is 56 hrs for CO_2 and 71 hrs for urinary excretion.

5.3 Preclinical safety data

Acute Toxicity Studies

For oral administration, the LD50 has been established to be 27.14 g/kg bw for mice and 18.5 g/kg bw for rats (Kanabayashi et al., 1980).

A study conducted with 99.9 % pure Citicoline base, according to GLP and OECD test guideline No 423, showed no adverse effects following a single gavage dose of 2 g/kg bw to groups of 10 male and female Crl:CD BR Sprague Dawley rats11 (Schauss et al., 2009).

Subchronic/Chronic Toxicity Studies

A 90-day study on Citicoline was performed in compliance with GLP, and claimed to be conducted according to OECD test guideline No 408 (Schauss et al., 2004; Schauss et al., 2009). Groups of 20 Crl: CD: BR Sprague Dawley rats of each sex were given 0, 100, 350 or 1 000 mg/kg bw per day Citicoline by gavage. The test substance was stated to be
99.8 % pure and was dissolved in distilled water prior to administration. Rats were caged in pairs during the study and were allowed ad libitum access to feed and drinking water. The clinical condition of all animals was checked twice daily and each was given a detailed examination once each week. Body weight, feed and water intake were monitored throughout the study. Ophthalmoscopy was performed on the animals from the control group and the high-dose group prior to treatment, and on the same animals during the last three weeks of the

study. Blood and serum analyses were performed on samples obtained from all animals immediately prior to necropsy. Urine was examined after a single collection from 10 rats of each sex per group, during the last week of treatment. At necropsy, a gross examination was made and a range of organs weighed (liver, heart, kidneys, spleen, brain, testes, epididymides, uterus, ovaries, thymus, adrenals) with a wide

range of tissues being preserved for histological examination. Slides were prepared and examined for all tissues from the control and high dose groups; examination of kidneys was extended to all groups following the initial examination.

Genotoxicity

In a bacterial reverse mutation assay (Ames test) conducted at concentrations of 50, 150, 500, 1 500 and 5 000 g/plate, in accordance with OECD test guideline No 471, Citicoline (sodium salt) was reported to be non-mutagenic in Salmonella typhimurium strains TA100, TA98, TA1535 and TA1537, and in E. coli WP2uvrA, in the presence and absence of metabolic activation (unpublished study report by Kyowa Safety Research Laboratories (1993)).

In an in vitro chromosome aberration test conducted in accordance with OECD test guideline No 473, Chinese hamster ovary cells were exposed to Citicoline and its sodium salt at concentrations of 2.5, 5 and 10 mM in the presence and absence of metabolic activation (unpublished study report by Kyowa Safety Research Laboratories (1993)). The NI was not genotoxic in this assay. In a mammalian erythrocyte micronucleus test conducted in accordance with OECD test guideline No 474, negative results were reported in mice administered single doses of Citicoline and its sodium salt of 500, 1 000 or 2 000 mg/kg body weight via intraperitoneal injection (unpublished study report by Kyowa Safety Research Laboratories (1993)).

Citicoline and its sodium salt showed no evidence of genotoxicity in any of these tests. The Panel concludes that there are no safety concerns related to genotoxicity.

Developmental and Reproductive Toxicity Studies

No published studies examining the possible reproductive toxicity of Citicoline were identified by the applicant. Secades and Frontera (1995) cited unpublished data pertaining to an assessment of the potential teratogenic effects of Citicoline. In this assessment, albino rabbits (strain and number of animals not reported) were administered 0 (control) or 800 mg Citicoline/kg bw per day (route of administration not specified) on Gestation Days 7 to 18. The animals were then killed on gestation day 29, and the fetuses were removed for examination. No signs of maternal or foetal toxicity were reported. Approximately 10 % of the fetuses exposed to Citicoline were reported to display a slight delay in cranial ontogenesis. This difference was not considered by

the authors to represent an adverse effect of Citicoline on organogenesis since such delays in ossification can occur

through dietary imbalances such as altered Ca:P ratio.

The applicant indicates that there have been no adverse effects on male and female reproductive organs reported in repeated-dose oral toxicity studies conducted in rats and dogs. The Panel considers that the

Subchronic and developmental studies provide some evidence on the safety of Citicoline, but that on their own are not sufficient to assess the safety of the NFI.

6. PHARMACEUTICAL PARTICULARS

6.1 List of Excipients

Microcrystalline Cellulose, Starch (Maize), Sodium Starch Gycolate, Hydroxy propyl cellulose (Klucel EXF), Magnesium Stearate, Colloidal Anhydrous Silica, Croscarmellose Sodium, Hypromellose, Polyethylene Glycol (PEG-6000), Titanium Dioxide, Purified Talc, Col. Iron Oxide (Ferric oxide USNF) Red.

6.2 Incompatibilities

No effect noted to date.

6.3 Shelf Life

24 mon th s

6.4 Special Precautions for Storage

Store below 30°C, protected from light & moisture. Keep all medicines out of reach of children.

6.5 Nature and Contents of Container

1 x 10 Tablets Packed in Alu-Alu blister.

6.6 Special Precautions for Disposal

There is no special instructions.

7. MARKETING AUTHORIZATION HOLDER:

UNOSOURCE PHARMA LTD.
503-504, 5th Floor,
Hubtown Solaris, N.S.
Phadke Marg, Andheri
(East), Mumbai 400069,
India.

Manufacturing Site

Akums Drugs & Pharmaceuticals Limited Plot No. 19,20 & 21 Sector 6A, IIE, SIDCUL, Ranipur, Haridwar-249403, Uttarakhand, India

8. MARKETING AUTHORIZATION NUMBERS

H2016/ CTD 2753/181

9. DATE OF FIRST REGISTRATION

14.10.2015

10. DATE OF THE REVISION OF THE TEXT

27.02.2026