SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

1.1 Product Name

Syschol-500

1.2 Strength

500 mg

2. QUALITATIVE AND QUANTITAVE COMPOSITION

Each film-coated tablet contains:

Citicoline Sodium equivalent to

Citicoline 500 mg

3. PHARMACEUTICAL FORM

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.

Method of administration

Orally administer

4.3 Contraindications :

Patients with hypertonia of the parasympathetic nervous system

4.4 Special warnings and precautions for use:

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 and other forms of interaction.

Citicoline must not be administered with products containing meclophenoxate

Citicoline enhances effects of L-dihydroxyphenylalanine and levodopa.

4.6 Pregnancy and lactation

Use in pregnancy & lactation: There is not enough evidence on Citicoline safety in pregnant and breastfeeding women. Citicoline should be used in pregnancy and lactation only when benefits justify the 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.

4.9 Overdose:

Citicoline exhibits very low toxicity profile in humans. In a short-term, placebo-controlled, crossover study, 12 healthy adults took Citicoline at daily doses of 600 and 1000 mg or placebo for consecutive 5-day periods. Transient headaches occurred in 4 subjects on 600-mg dose, 5 on the 1000-mg dose and 1 in placebo. No changes or abnormalities were observed in hematology, clinical biochemistry or neurological test.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties:

It is a nootropic preparation. Citicoline as a predecessor of key ultra structural component of cell membrane (mainly phospholipids) has a wide spectrum of action: it promotes a restoration of damaged cell membranes, inhibits an action of phospholipase, preventing a formation of free radicals and prevents cell death by acting on mechanisms of apoptosis.

It is a source of choline; it increases a synthesis of acetylcholine and stimulates biosynthesis of structural (foot) phospholipids in neuron membrane.

It improves the transmission of nerve impulses in cholinergic neurons; it has a positive effect on plasticity of neuronal membranes and receptor function. It improves cerebral blood flow, enhances cerebral metabolic processes and activates the structure of cerebral reticular formation. In acute phase of a stroke it reduces the volume of damaged tissue and improves cholinergic transmission.

Citicoline alleviates symptoms, which occur during hypoxia and cerebral ischemia, including memory impairment, emotional liability, lack of initiative, difficulty during daily activities and self-service.

In craniocerebral injury it reduces the duration of post-traumatic coma and the severity of neurological symptoms.

Citicoline has anti-edema properties and reduces cerebral edema due to its stabilizing effect on neuronal membrane.

It accelerates the recovery and reduces the duration and intensity of post-traumatic syndrome.

Citicoline is effective in the treatment of cognitive, sensory and motor neurological disorders of degenerative and vascular etiology.

5.2 **Pharmacokinetic properties*:***

Citicoline is well absorbed in oral, intramuscular and intravenous introduction. After the preparation introduction it is observed a significant increase of choline in plasma. The preparation is almost completely absorbed in oral administration. Studies have shown that the bioavailability in per oral and parenteral routes of introduction was similar.

The preparation is metabolized in intestine and liver with the formation of choline and cytidine. After Citicoline introduction it is assimilated by cerebral tissues, while cholines act on phospholipids, cytidine – on cytidine nucleoids and nucleic acids. Citicoline quickly reaches cerebral tissues and actively integrates into cell membrane, cytoplasm and mitochondria, activating an activity of phospholipids.

Only a minor part of introduced dose is excreted with urine and feces (less than 3%). Approximately 12% of introduced dose are excreted via respiratory tract. The preparation excretion via urine and respiratory tract has two phases: first phase – rapid excretion (with urine – within the first 36 hours, via airways – within the first 15 hours), the second phase – slow excretion. Major part of the dose is included into the process of metabolism.

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

Sl. No.	Ingredients	Specifications
1	Colloidal anhydrous silica (Aerosil-200)	BP
2	Microcrystalline Cellulose	BP
3	Lactose (Monohydrate)	BP
4	Maize Starch	BP
5	Crospovidone (Polyplasdone XL-10)	BP
6	Povidone (K 30)	BP
7	Purified Water	BP
8	Crospovidone (Polyplasdone XL-10)	BP
9	Microcrystalline Cellulose (RANQ) PH 102	BP
10	Colloidal Anhydrous Silica (Aerosil-200)	BP
11	Magnesium Stearate	BP
12	Hypromellose (HPMC 15 CPS)	BP
13	Propylene Glycol	BP
14	Titanium Dioxide	BP
15	Talc	BP
16	Isopropyl Alcohol	BP
17	Dichloromethane (Methylene Chloride)	BP

6.2 Incompatibilities

Not applicable

6.3 Shelf life

36 months from the date of manufacturing.

6.4 Special precautions for storage

Store below 30 °C. Protect from light. Keep out from the reach of children.

6.5 Nature and contents of container

Alu - Alu Strip pack of 10 tablets, 3 such blisters in a carton along with pack Insert.

7. Marketing Authorization Holder

Manufactured by:

MICRO LABS LIMITED

92, SIPCOT INDUSTRIAL COMPLEX,

HOSUR, TAMIL NADU – 635126, INDIA

8. Marketing Authorization Number

Not applicable

9. Date of first authorization/renewal of authorization

Not applicable

10. Date of revision of text

June 2017