Summary of Product Characteristics for Pharmaceutical Products

1. Name of the medicinal product:
Ceregard® Plus
Cerebroprotein Hydrolysate 60mg and Citicoline 750mg Tablets.

2. Qualitative and quantitative composition

Each film coated Tablet contains:
Cerebroprotein hydrolysate 60 mg
Citicoline Sodium
Eq.to Citicoline..... 750mg
Excipients... ..... q.s
Colour: Ferric Oxide of red USP and Titanium Dioxide. (for the full list of excipients, see section 6.1)

3. Pharmaceutical form:

Film coated tablet

A brown colored, capsule shaped, biconvex, film coated tablet having break line on one side.

4. Clinical particulars
4.1 Therapeutic indications
Tablet is indicated for the treatment of patients with serious cerebral injuries of vascular traumatic nature with or without loss of consciousness and for treatment of degenerative changes and chronic cerebral vascular injuries in senile dementia.

4.2 Posology and method of administration Posology
The recommended dose is one tablet daily after meal or as directed by physician.

Method of administration
For Oral use

4.3 Contraindications
Cerebroprotein hydrolysate
•Hypersensitivity to any of the product constituents.
•Status epilepticus.
•Major epilepsia: usage of this product may increase attack frequency.
•Severe renal dysfunction.

Citicoline
Must not be administered to patients with hypertonic of the parasympathetic and hypersensitivity to citicoline or any other component of the formulation.

4.4 Special warnings and precautions for use Cerebroprotein hydrolysate

Special care is indicated in following cases:
•Allergic diathesis.
•Epileptic conditions and grand mal convulsions; cerebroprotein Hydrolysate
treatment may result in an increase in the frequency of seizures
•Although there are no Indications that cerebroprotein hydrolysate causes renal stress, the product should not be administered in the presence of existing severe renal insufficiency
•Patients who take cerebroprotein hydrolysate treatment should not drive vehicles or operate machines to avoid any possible risk, though no medical evidence shows that cerebroprotein hydrolysate can reduce one's reactions to these activities.

4.5 Fertility, pregnancy and lactation

Cerebroprotein hydrolysate

Animal studies did not show any indication of reproductive toxicity. However, no data is available for humans. Therefore, during pregnancy and lactation, cerebroprotein hydrolysate should only be used after careful risk/benefit considerations.

Citicoline

There are no adequate and well controlled studies of citicoline during pregnancy and lactation. Citicoline should be used in pregnancy only if the potential benefit justifies the potential risk to the foetus. There are no adequate and well controlled studies of citicoline during pregnancy and lactation. Caution should be exercised during breastfeeding because it is not known whether citicoline is excreted in human breastmilk.

4.6 Effects on ability to drive and use machines

Patients who take cerebroprotein hydrolysate treatment should not drive vehicles or operate machines to avoid any possible risk, though no medical evidence shows that cerebroprotein hydrolysate can reduce one's reactions to these activities.

4.8 Undesirable effects

Most common side effects include headache, nausea, vertigo, increased sweating, agitation, fever, hallucinations, confusion, and flulike syndrome. In rare cases, hyperventilation, hypertension, fatigue, tremor, depression, indifference, numbness and even flu-like symptoms (for example colds, cough and respiratory infection) may show.

A major and extremely rare adverse effect reported is convulsion. Rare cases may have gastrointestinal reactions with deranged appetite, digestive disorders, diarrhea, constipation, vomiting and nausea. In case of a quick injection, moderate fever, sweating, or even vertigo may occur. A most rarebit severe adverse effect is arrhythmia or palpitation. In few cases, local skin hypersensitivity at injection points such as focal skin redness, itching and heat sensation, was reported. Allergic reaction was reported in rare cases, such as itching, focal skin vascular reaction, pains in head, neck

and extremities, fever, mild back pain, shortness of breath, tremor or shock-like appearances.
Since cerebroprotein hydrolysate is used in elderly patients, the above symptoms are, for the most part, typical for this age group and frequently occur without medication.

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 pharmacy and poisons board, Pharmacovigilance Electronic ReportingSystem (PvERS) https://pv.pharmacyboardkenya.org.

4.9 Overdose
As in any case of overdose, treatment should be symptomatic and general supportive measures should be utilized.

5. Pharmacological properties
5.1 Pharmacodynamic properties
Cerebroprotein hydrolysate
Mode of Action
It is reported that cerebroprotein hydrolysate is a unique nutriment for the brain. It helps the central nervous system (CNS)in multiple ways, regulating and improving nerve cell metabolism, promoting synapse generation, inducing nerve cell differentiation, protecting nerve cells against damages by ischaemia and neurotoxins, etc. Animal experiments testified that cerebroprotein hydrolysate promotes cerebral development in chicks, which can also enhance protein synthesis, potentiate functions of the respiratory chain and stimulate the related hormone production in neural cells. Pre- injection of cerebroprotein hydrolysate improves hypoxia tolerability in rats, which depends on the nucleotide concentration in the brain. After administration of cerebroprotein hydrolysate, a pronounced acceleration in maturation in the brain of several day-old rats was demonstrated by electro- optical means and adult rats exhibited enhanced learning ability in labyrinth tests. Compared with a control group, glucose transporter-1 (GLUT-1) in the blood-brain barrier accelerates significantly in rats that were administered cerebroprotein hydrolysate injection.
Cerebroprotein hydrolysate-augmented proliferation, differentiation and migration of adult sub ventricular zone (SVZ) neural progenitor cells results in an increased number of neural progenitor cells and neuroblasts to contribute to neurogenesis.
This may be the mechanism for a beneficial effect in acute ischaemic stroke and traumatic brain injury. Enhancement of neuronal survival is produced through an effect on calpain. The hyper-activation of calpain is implicated in a number of neurodegenerative disorders. Calpain is inhibited by cerebroprotein hydrolysate.
A neuromodulatory effect is produced by increasing GLUT-1expression, which is responsible for more than 90% of glucose transport to the brain. Neuronal

plasticity is produced by the reduction of amyloid-beta accumulation, increased MAP-2 and synaptophysin synthesis. Neuro-immunotrophic activity is produced by inhibition of microglial activation and expression of IL- 1-beta. This results in reduction of inflammation. Other neurotrophic drugs and nootropics do not have such a broad spectrum of action as possessed by cerebroprotein hydrolysate. Patients with neurodegenerative disorders can now be managed in a better way with the use of cerebroprotein hydrolysate.

Citicoline

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

5.2 Pharmacokinetic properties:

Cerebroprotein hydrolysate

The animal brain-derived proteolytic peptide fraction consists of short biological peptides similar or identical to those produced endogenously. Direct measurement of pharmacokinetic properties has not successfully been performed.

Indirect pharmacokinetic data has been established but it is based on the cerebroprotein hydrolysate pharmacodynamic profile. Accordingly, the neurotrophic activity of cerebroprotein hydrolysate can be detected in blood plasma up to 24 hours after a single application.

Furthermore, the components of cerebroprotein hydrolysate can cross the blood brain barrier. Preclinical in vivo experiments revealed identical pharmacodynamic actions on the CNS following intra-cerebroventricular or peripheral application.

Thus, indirect evidence for the passage of components of the drug across the blood-brain barrier has been established.

Citicoline

Absorption

Citicoline is a water-soluble compound with greater than 90-percent bioavailability.

Pharmacokinetic studies on healthy adults show oral doses of citicoline are rapidly absorbed, with less than one percent excreted in feces. Plasma levels peak in a biphasic manner, at one hour after ingestion followed by a second larger peak at 24 hours post-dosing.

Distribution

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 resynthesise into citicoline in the brain *Metabolism*
Citicoline is metabolized in the gut wall and liver. The by-products of exogenous citicoline formed by hydrolysis in the intestinal wall are choline and cytidine
Excretion
Pharmacokinetic studies using 14C citicoline show citicoline elimination occurs in two phases mirroring the biphasic plasma peaks, mainly via respiratory C02 and urinary excretion. The initial peak in plasma concentration is followed by a sharp decline, which then slows over the next 4-10hours. 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 C02 and 71 hours for urinary excretion.

5.3 Preclinical safety data

Not applicable

6. Pharmaceutical particulars
6.1 List of Excipients:
Lactose
Microcrystalline cellulose
Kyron T-314
Sodium starch
glycolate Povidone
K-30 Isopropyl
alcohol Magnesium
stearate Talcum
Colloidal silicon dioxide
Sodium Starch glycolate
Ready mix iron oxide red
Methylene chloride

6.2 Incompatibilities
Not applicable

6.3 Shelf life
36 months.

6.4 Special precautions for storage
Store below 30°C, protect from direct sunlight, heat & moisture.

6.5 Nature and contents of container
Ceregard® Plus is available in 1 x 10 tablets pack.

6.6 Special precautions for disposal and other handling
Any unused medicine product or waste material should be disposed of in accordance with the local requirements.

7. Marketing authorization holder and manufacturing site

addresses Manufactured in India by:
Relax Biotech Pvt. Ltd.
862/1, G.I.D.C. Makarpura
Vadodara - 390 010(Gujarat)
INDIA

Manufactured for & Marketed by:
KRISHNA CHEMISTS LTD.
P.O. BOX 3328-00506
NAIROBI, KENYA.

8. Marketing Authorization Number
H2020/CTD7821/14974

9. Date of first authorization/renewal of the authorization
Date of first authorization: 20/05/2020

10. Date of revision of the text
11/11/2025