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Public Assessment Report

Scientific discussion

Cikappa 1000 mg oral solution (citicoline sodium)

ES/H/0996/001/DC

Date: 16/03/2026

This module reflects the scientific discussion for the approval of Cikappa 1000 mg oral solution. The procedure was finalised at 31/08/2025. For information on changes after this date please refer to the module 'Update'.

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Cikappa 1000 mg oral solution from Pharmacare S.r.l.

The product is indicated for:

- Treatment of neurological and cognitive disorders associated with cerebrovascular accidents,
- Treatment of neurological and cognitive disorders associated with traumatic brain injuries.

A comprehensive description of the indications and posology is given in the SmPC.

The marketing authorisation has been granted pursuant to Article 10.1 of Directive 2001/83/EC.

II. QUALITY ASPECTS

II.1 Introduction

The product is presented as monodose sachets of 10 mL containing 1000 mg of the drug substance Citicoline (as sodium salt).

Other ingredients are Saccharin sodium, Sorbitol, liquid (non-crystallising) (E420), Glycerol (E422), Methyl parahydroxybenzoate (E218), Propyl parahydroxybenzoate (E216), Sodium citrate, Glycerol formal, Potassium sorbate (E202), Strawberry flavour (contains propylene glycol (E1520)), Ponceau 4R red colouring (E124), Citric acid and Water purified.

The primary packaging intended for commercial use is sachets of PET 23µm /White Ext.PE 12gsm /ALU 9µm /Extruded Copolymer 25gsm.

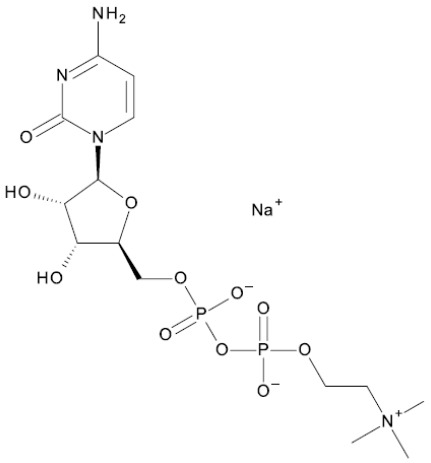
II.2 Drug Substance

Full information of the active substance, Citicoline sodium, is presented in the dossier.

General Information

INN	Citicoline (sodium)
IUPAC name	Sodium [[(2S,3R,4S,5S)-5-(4-amino-2-oxo-pyrimidin-1-yl)-3,4-dihydroxy-tetrahydrofuran-2-yl]methoxy-oxido-phosphoryl] 2-(trimethylammonio)ethyl phosphate
Synonyms	Citydine 5'-diphosphocoline sodium

Structure



Molecular Formula	$C_{14}H_{25}N_4NaO_{11}P_2$
Relative Molecular Mass	Mr 510.31

Citicoline has four chiral centers in the cytidine part of the molecule. It does not show polymorphism.

The drug substance is a white crystalline powder, odourless substance. It is hygroscopic. Citicoline sodium is freely soluble in water, insoluble in ethanol, acetone and chloroform.

Manufacture, process controls and characterisation

The description of the manufacturing process is properly detailed. The specifications of the materials used in the synthesis are sufficient and adequate. The profile of impurities, including residual solvents, of these materials which can influence the quality of the active substance are well defined and controlled. The acceptance criteria for the critical stages and the information on the quality and control of intermediates are adequate.

Specification, analytical procedures, batch analysis

Active substance specifications are considered appropriate and limits justified. Analytical methods are correctly described and validation carried out according to ICH. Batch results support consistent production.

Container closure system

The choice of the container closure system is properly justified. Compliance with the relevant requirements and/or regulations is confirmed.

Stability

Stability studies have been performed in accordance with current guidelines. Protocol, controlled parameters and test methods are considered adequate. The packaging material is similar to that proposed for storage. Proposed re-test period and storage conditions are justified.

II.3 Medicinal Product

Description of the product

The product is presented as a clear, pink solution with strawberry odour packaged in sachets containing 10 mL of citicoline sodium solution. Each sachet contains 1000 mg citicoline (as sodium salt).

Pharmaceutical Development

The development of the product has been described; the choice of excipients is justified and their functions explained. It contains solvents, sweeteners, buffering agents and preservatives. Methyl parahydroxybenzoate, propyl parahydroxybenzoate and potassium sorbate are preservatives of the formulation. Considering the pharmaceutical form, oral solution, the use of preservatives is justified.

The physicochemical characteristics of the active substance that may affect the pharmaceutical form are identified and their control strategy is justified.

Manufacture of the product

The manufacturing process is fully described, and in-process controls are appropriate considering the nature of the product and the manufacturing process. The industrial batch size is well-defined.

Excipients

Excipients used are well known and of appropriate quality.

Product specification, analytical procedures, batch analysis

The finished product specifications are adequate to control the finished product. Provided description and validation data for the analytical methods are adequate. Batch analysis data have been submitted, and the results show that the finished product meets the proposed release specification.

Container closure system

The finished product is packaged in sachets of PET 23µm /White Ext.PE 12gsm /ALU 9µm /Extruded Copolymer 25gsm. The choice of the container closure system is justified considering the nature of the finished product. Compliance with the relevant requirements and/or regulations is confirmed.

Stability

Stability studies have been performed in accordance with current guidelines. The proposed protocol is considered adequate. The packaging material is the same as that intended for marketing. Proposed shelf-life and storage conditions are properly established.

- Shelf-life: 3 years
- Storage conditions: This medicinal product does not require any special storage conditions.

III. NON-CLINICAL ASPECTS

Pharmacodynamic, pharmacokinetic and toxicological properties of citicoline sodium are well known. As citicoline sodium is a widely used, well-known active substance, the applicant has not provided additional studies and further studies are not required.

Environmental Risk Assessment (ERA)
Since Cikappa 1000 mg oral solution is a generic product, it will not lead to an increased exposure to the environment. Additional ERA studies are therefore not deemed necessary.

IV. CLINICAL ASPECTS

IV.1 Introduction

Citicoline sodium is a well-known active substance with established efficacy and safety. A clinical overview has been provided, which is based on scientific literature. The clinical overview justifies that there no need to generate additional clinical data.

Clinical bioequivalence studies are not submitted in view that both the reference and the proposed product are aqueous solutions intended for oral administration and the proposed product contains the same active substance in the same concentration as the currently approved product.

IV.2 Pharmacokinetics

Biowaiver
According to *the Guideline on the investigation of bioequivalence*, if the test product is an aqueous oral solution at time of administration and contains an active substance (citicoline) in the same concentration as an approved oral solution, bioequivalence studies may be waived. However if the excipients may affect gastrointestinal transit (e.g. sorbitol, mannitol, etc.), absorption (e.g. surfactants or excipients that may affect transport proteins), *in vivo* solubility (e.g. co-solvents) or *in vivo* stability of the active substance, a bioequivalence study should be conducted, unless the differences in the amounts of these excipients can be adequately justified by reference to other data.

In this case, the qualitative composition is similar with the exception of sodium citrate (pH adjuster) but this difference is considered acceptable from a bioequivalence perspective. The bioequivalence study can be waived as the difference in the quantitative composition with regard to the sodium citrate for adjusting pH is not considered to affect the bioavailability.

The bioequivalence between the test and the reference product can be assumed.

IV.3 Pharmacodynamics/ Clinical efficacy/ Clinical safety

No new clinical data have been provided and none is required for this type of generic application.

The submitted clinical documentation based on scientific literature is sufficient and acceptable regarding clinical information.

IV.4 Risk Management Plan

The MAH has submitted a risk management plan (version 0.1, 15 July 2024), in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Cikappa 1000 mg oral solution.

There are neither proposed additional pharmacovigilance activities nor proposed additional risk minimisation measures planned for Cikappa 1000 mg oral solution.

IV.5 Discussion on the clinical aspects

For generic applications please refer to section IV.2.

V. USER CONSULTATION

The package leaflet has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The language used for the purpose of user testing the PIL was English.

The results show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

The test consisted of three rounds: a preliminary round with 4 participants, followed by two rounds with 10 participants each. The questions covered the following areas sufficiently: traceability, comprehensibility and applicability.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The quality of the generic product is found adequate. There are no objections to the approval of *Cikappa 1000 mg oral solution* from a non-clinical and clinical point of view. Bioequivalence between the test and reference product has been adequately demonstrated. The product information is acceptable. The benefit/risk is considered positive, and the application is therefore recommended for approval.