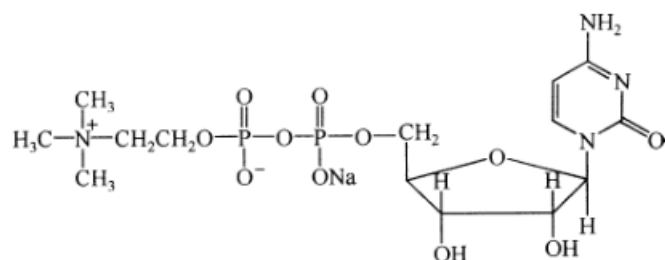


Storage Tightly closed.

Citicoline Sodium



$C_{14}H_{25}N_4NaO_{11}P_2$ 510.31

[33818-15-4]

Citicoline sodium is cytidine-5'-diphosphocholine monosodium salt. It contains not less than 98.0% of $C_{14}H_{25}N_4NaO_{11}P_2$, calculated on the dried basis.

Description White crystals or a crystalline powder; odourless; freely soluble in water, insoluble in ethanol and in acetone.

Identification (1) To about 1 mg add 3 ml of dilute hydrochloric acid TS and 1 ml of **bromine TS**, heat on a water bath for 30 minutes, and remove the bromine with ventilation. Add 0.2 ml of **3,5-dihydroxy-methylbenzene** ethanol solution (1→10) and 3 ml of ammonium ferric sulfate solution in hydrochloric acid (1→1000), and heat on a water bath for 20 minutes, a green colour is produced.

(2) In the Assay, the retention time of the principal peak in the chromatogram obtained with the test solution is identical with that of the principal peak in the chromatogram obtained with the reference solution.

(3) The infrared absorption spectrum <0402> is concordant with the reference spectrum (IR Album No. 1096).

(4) The aqueous solution yields the reaction (1) of sodium salts <0301>.

Acidity or alkalinity Dissolve 0.5 g in 10 ml of water, pH 6.0-7.5 <0631>.

Clarity and colour of solution A solution of 1.0 g in 8 ml of water is clear and colourless <0902 method 1> and <0901 method 1>.

Chlorides Carry out the limit test for chlorides <0801>, using 0.10 g. Any opalescence produced is not more pronounced than that of a reference solution using 5.0 ml of sodium chloride standard solution (0.05%).

Ammonium Carry out the limit test for ammonium <0808>, using 0.20 g. Any opalescence produced is not more pronounced than that of a reference solution using 10.0 ml of ammonium chloride standard solution (0.05%).

Iron Carry out the limit test for iron <0807>, using 0.20 g. Any opalescence produced is not more pronounced than that of a reference solution using 2.0 ml of iron standard solution (0.01%).

Phosphate Dissolve 0.10 g in 10 ml of water, add 1 ml of ammonium molybdate solution (dissolve 1 g of ammonium molybdate in 40 ml of 0.5 mol/L sulfuric acid solution) and 0.5 ml of 1-amino-2-naphthol-4-sulfonic acid TS, allow to stand for 5 minutes. Any colour produced is not more intense than that of a reference solution using 5.0 ml of phosphate standard solution (Place accurately weighed 0.286 g of potassium dihydrogen phosphate

previously dried to constant weight at 105°C, in a 1000 ml volumetric flask, add water to dissolve and dilute to volume with the same solvent, shake well. Before using, transfer accurately measured 10 ml into a 100 ml volumetric flask, dilute to volume with water and shake well. Each ml is equivalent to 20 µg of PO_4^{3-}) prepared in the same manner (0.1%).

Related Substance Dissolve an accurately weighed quantity of the substance being examined in water to produce a solution containing 2.5 mg per ml, and use as the test solution. Transfer accurately measured 1 ml of the test solution into a 500 ml volumetric flask, dilute to volume with water, shake well and use as reference solution (1). Dissolve an accurately weighed quantity of 5'-cytidylate in water to produce a solution containing 7.5 µg per ml, and use as reference solution (2). Using the chromatographic conditions described under Assay, Inject separately 10 µl each of the test solution, reference solution (1) and (2) onto the column, and record the chromatogram for 2.5 times the retention time of the principal peak. In the chromatogram obtained with the test solution, the content of 5'-cytidylate is not more than 0.3%, calculated with respect to the peak area obtained in the chromatogram by the

external standard method; the area of any other single impurity peak is not more than the area of the principal peak in the chromatogram obtained with the reference solution (1) (0.2%); the sum of the areas of all impurity other than 5'-cytidylate is not more than 3.5 times the area of the principal peak in the chromatogram obtained with the reference solution (1) (0.7%).

Residual Solvents *Methanol, Ethanol and Acetone* Dissolve a quantity of *n*-propanol in water to produce a solution containing about 500 µg per ml as the internal standard solution. Dissolve an accurately weighed quantity of methanol, ethanol and acetone, in water to produce a mixture solution containing 450 µg, 750 µg and 750 µg per ml respectively as the stock reference solution. Transfer accurately measured 5 ml of the stock reference solution and 5 ml of the internal standard solution into a 50 ml volumetric flask, dilute to volume with water, shake well and use as the reference solution. Place accurately weighed about 0.75 g of the substance being examined in a 50 ml volumetric flask, add 5 ml of the internal standard solution to dissolve, dilute to volume with water, shake well and use as the test solution. Transfer accurately measured 5 ml of the reference solution and the test solution in a head-space vial separately, close the vial. Carry out the method for determination of residual solvents <0861 method 1>. The gas

chromatography is equipped with a fused-silica capillary column coated with polyethylene glycol (PEG-20M or with similar polarity. Maintain the temperature of the column at 60°C; maintain the temperature of injection port at 200°C and the detector temperature at 250°C. The head-space injection method is used. The equilibration temperature is 80°C and maintained for 45 minutes. Inject head space of the reference solution into the chromatograph and record the chromatogram, the resolution factor between each pair of adjacent principal peaks complies with the requirements. Inject equal volume of the head space of the test solution and the reference solution into the chromatograph and record the chromatogram. Calculate the content of methanol, ethanol and acetone with respect to the peak area obtained in the chromatogram by the internal standard method, respectively. It complies with the requirements.

Loss on drying When dried under reduced pressure over

phosphorous pentoxide at 100°C for 5 hours, loses not more than 6.0% of its weight <0831>.

Heavy metals Carry out the limit test for heavy metals, using 2.0 g <0821 method 1>: not more than 0.0005%.

Arsenic Carry out the limit test for arsenic, using 2.0 g <0822 method 1>: not more than 0.0001%.

Bacterial endotoxin Carry out the limit test for bacterial endotoxin <1143>: less than 0.30 EU per mg.

Sterility Complies with the test for sterility (for parenteral use) <1101>.

Assay Carry out the method for high performance liquid chromatography <0512>, using a column packed with octadecylsilane bonded silica gel and a mixture of phosphate BS [mix equal volumes of 0.1 mol/L potassium dihydrogen phosphate solution and 0.01 mol/L tetrabutylammonium hydroxide solution (adjust pH to 4.5 with phosphorous acid)] -methanol (95 : 5) as the mobile phase. The detection wavelength is 276 nm. Dissolve a quantity of 5'-cytidylate CRS in water to produce a solution containing 0.25 mg per ml, mix well a same amount with citicoline sodium reference solution. Inject 20 µl of the solution onto the column and record the chromatogram, the resolution factor between the peaks due to citicoline sodium and 5'-cytidylate complies with the requirements.

Procedure Dissolve an accurately weighed quantity of the substance being examined in water to produce a solution containing about 0.25 mg per ml as the test solution. Inject 10 µl onto the column and record the chromatogram. Repeat the operation using citicoline sodium CRS instead of the substance being examined. Calculated the content of $C_{14}H_{25}N_4NaO_{11}P_2$ with respect to the peak areas obtained in the chromatogram by the external standard method.

Category Medicines for improving cell metabolism.

Storage Preserve in tightly closed containers, protected from light.

Preparation (1) Citicoline Sodium Tablets
(2) Citicoline Sodium Injection
(3) Citicoline Sodium for Injection
(4) Citicoline Sodium and Inosine for Injection
(5) Citicoline Sodium and Glucose Injection
(6) Citicoline Sodium and Sodium Chloride Injection

Citicoline Sodium Tablets

Citicoline Sodium Tablets contain not less than 90.0% and not more than 110.0% of the labelled amount of citicoline sodium ($C_{14}H_{25}N_4NaO_{11}P_2$).

Description White tablets or film coated tablets with white to slightly white cores.

Identification Weigh a quantity of the powder equivalent to about 1 mg of citicoline sodium. Complies with tests (1) and (2) for Identification described under Citicoline Sodium.

Related Substances Dissolve an accurately weighed quantity of the powder under Assay in water to produce a solution containing 2.5 mg citicoline sodium per ml, filter and use as the test solution. Transfer accurately measured 1 ml of the test solution into a 500 ml volumetric flask, dilute to volume with water, mix well and use as reference solution (1).

Dissolve an accurately weighed quantity of 5'-cytidylate in water to produce a solution containing 7.5 µg per ml, and use as reference solution (2). Carry out the method described in the test for Related substances under citicoline sodium. In the chromatogram obtained with the test solution, the content of 5'-cytidylate is not more than 0.3% of the labelled amount of citicoline sodium, calculated with respect to the peak area obtained in the chromatogram by the external standard method; the area of any other impurity peak is not more than the area of the principal peak in the chromatogram of the reference solution (1) (0.2%); the sum of the areas of all impurity other than 5'-cytidylate is not more than 3.5 times the area of the principal peak in the chromatogram of the reference solution (1) (0.7%).

Dissolution Carry out the dissolution and drug release test <0931 method2>, using 900 ml of water as dissolution medium, adjust the rotational speed of the paddle to 50 rpm. Withdraw the solution at 25 minutes and filter, the successive filtrate as the test solution (Strength 0.1 g); or accurately measured of the successive filtrate, dilute with dissolution medium to produce a solution of 0.11 mg per ml as the test solution (Strength 0.2 g). Dissolve a quantity of citicoline sodium CRS, accurately weighed, in water and dilute to produce a solution of 0.11 mg per ml as the reference solution. Carry out the method described under Assay; Calculate the dissolution of $C_{14}H_{25}N_4NaO_{11}P_2$ from each tablet by the external standard method. Not less than

80% of the labelled amount is dissolved.

Other requirements Comply with the general requirements for tablets <0101>.

Assay Weigh accurately and powder finely 20 tablets. Transfer an accurately weighed quantity of the powdered tablets equivalent to about 125 mg of citicoline sodium into a 100 ml volumetric flask, add a quantity of water, shake to dissolve citicoline sodium, dilute with water to volume, mix well and filter, measured accurately 10 ml of the successive filtrate into a 50 ml volumetric flask, dilute to volume with water, mix well and use as test solution. Carry out the method described under Citicoline Sodium, Calculated the content of $C_{14}H_{25}N_4NaO_{11}P_2$ with respect to the peak areas obtained in the chromatogram by the external standard method.

Category As described under Citicoline Sodium.

Strength (1) 0.1 g (2) 0.2 g

Storage Preserve in tightly closed containers, protected from light.

Citicoline Sodium Injection

Citicoline Sodium Injection is a sterile solution of Citicoline Sodium in Water for Injection. It contains not less than 90.0% and not more than 110.0% of the labelled amount of Citicoline Sodium ($C_{14}H_{25}N_4NaO_{11}P_2$).

Description A clear and colourless liquid.

Identification Complies with tests (1), (2) and (4) for Identification described under Citicoline Sodium.

Acidity or alkalinity pH 6.0-8.0 <0631>.

Related substances Dilute an accurately measured volume of the injection with water to produce a solution containing