Edition: BP 2025 (Ph. Eur. 11.6 update)

Calcium Folinate Injection

General Notices

Action and use

Vitamin B component.

DEFINITION

Calcium Folinate Injection is a sterile solution of Calcium Folinate Hydrate. It is either supplied as a ready-to-use solution or it is prepared by dissolving Calcium Folinate for Injection in the requisite amount of Water for Injections immediately before use.

The injection complies with the requirements stated under Parenteral Preparations and, when supplied as a ready-to-use solution, with the following requirements.

Content of folinic acid, $C_{20}H_{23}N_7O_7$

90.0 to 110.0% of the stated amount.

IDENTIFICATION

A. To a volume containing the equivalent of 20 mg of folinic acid add 40 mL of *acetone*, mix, allow to stand and then centrifuge, discarding the solvent. Suspend the residue in 40 mL of *acetone* and centrifuge. Dry the residue in a stream of nitrogen and then at a pressure of 0.7 kPa for 2 hours. The *infrared absorption spectrum* of the residue, Appendix II A, is concordant with the *reference spectrum* of calcium folinate *(RS 368)*.
B. Yields reaction B characteristic of *calcium salts*, Appendix VI.

TESTS

Acidity or alkalinity

pH, 6.5 to 8.5, Appendix V L.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions protected from light.

(1) Dilute with *water*, if necessary, a volume of the injection to produce a solution containing the equivalent of 0.1% w/v of folinic acid.
(2) Dilute 1 volume of solution (1) to 100 volumes with *water*.
(3) 0.1% w/v of *calcium folinate BPCRS* in *water*.
(4) Dilute 1 volume of solution (2) to 10 volumes with *water*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (5 µm) (Hypersil ODS is suitable).
(b) Use isocratic elution and the mobile phase described below.
(c) Use a flow rate of 1 mL per minute.
(d) Use a column temperature of 40°.
(e) Use a detection wavelength of 280 nm.
(f) Inject 20 µL of each solution.
(g) For solution (1) allow the chromatography to proceed for 2.5 times the retention time of folinate.

MOBILE PHASE

220 mL of *methanol* and 780 mL of a solution containing 2.0 mL of *tetrabutylammonium hydroxide solution* and 2.2 g of *disodium hydrogen orthophosphate*, previously adjusted to pH 7.5 with 10% v/v *orthophosphoric acid*.

When the chromatograms are recorded under the prescribed conditions, the retention times of calcium folinate and formyl folic acid are about 12 minutes and 21 minutes respectively.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks corresponding to folinate and formylfolic acid is at least 2.2. If necessary, adjust the methanol content in the mobile phase.

LIMITS

In the chromatogram obtained with solution (1):

the area of any peak corresponding to formylfolic acid is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (1%);

the area of any other *secondary peak* is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (1%);

the sum of the areas of any *secondary peaks*, excluding the peak corresponding to formylfolic acid, is not greater than 2.5 times the area of the principal peak in the chromatogram obtained with solution (2) (2.5%).

Disregard any peak with an area less than that of the principal peak in the chromatogram obtained with solution (4) (0.1%).

ASSAY

Protect the solutions from light. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Dilute a volume of the injection with *water* to produce a solution containing the equivalent of 0.01% w/v of folinic acid.
(2) 0.011% w/v of *calcium folinate BPCRS* in *water*.
(3) 0.1% w/v of *calcium folinate BPCRS* in *water*.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Related substances may be used.

SYSTEM SUITABILITY

The Assay is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks corresponding to folinate and formylfolic acid is at least 2.2. If necessary, adjust the methanol content in the mobile phase.

DETERMINATION OF CONTENT

Calculate the content of $C_{20}H_{23}N_7O_7$ in the injection using the declared content of $C_{20}H_{21}CaN_7O_7$ in *calcium folinate BPCRS*. Each mg of $C_{20}H_{21}CaN_7O_7$ is equivalent to 0.9255 mg of $C_{20}H_{23}N_7O_7$.

STORAGE

When supplied as a ready-to-use solution, Calcium Folinate Injection should be protected from light and stored at a temperature of 2° to 8°.

LABELLING

The quantity of active ingredient is stated in terms of the equivalent amount of folinic acid.

CALCIUM FOLINATE FOR INJECTION

DEFINITION

Calcium Folinate for Injection is a sterile material consisting of Calcium Folinate Hydrate with or without excipients. It is supplied in a sealed container.

The contents of the sealed container comply with the requirements for Powders for Injections or Infusions stated under Parenteral Preparations and with the following requirements.

Content of folinic acid, $C_{20}H_{23}N_7O_7$

90.0 to 110.0% of the stated amount.

IDENTIFICATION

A. The *infrared absorption spectrum*, Appendix II A, is concordant with the *reference spectrum* of calcium folinate *(RS 368)*. If the spectra are not concordant prepare a solution containing 1% w/v of Calcium Folinate and carry out Identification Test A for the ready-to-use solution.
B. Yield reaction B characteristic of *calcium salts*, Appendix VI.

TESTS

Acidity or alkalinity

pH of a solution containing the equivalent of 1.0% w/v of folinic acid, 6.5 to 8.5, Appendix V L.

Related substances

Carry out the test described for the ready-to-use solution but using the following solution as solution (1). Dissolve sufficient of the mixed contents of 10 containers in *water* to produce a solution containing the equivalent of 0.1% w/v of folinic acid.

ASSAY

Determine the weight of the contents of 10 containers as described in the test for *uniformity of weight*, Appendix XII C1, Powders for Parenteral Use.

Carry out the Assay described for the ready-to-use solution but using the following solution as solution (1). Dissolve sufficient of the mixed contents of the 10 containers in *water* to produce a solution containing the equivalent of 0.01% w/v of folinic acid.

Calculate the content of $C_{20}H_{23}N_7O$ in a container of average content weight using the declared content of $C_{20}H_{21}CaN_7O_7$ in *calcium folinate BPCRS*. Each mg of $C_{20}H_{21}CaN_7O_7$ is equivalent to 0.9255 mg of $C_{20}H_{23}N_7O_7$.

LABELLING

The quantity of active ingredient is stated in terms of the equivalent amount of folinic acid.