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

Ifosfamide Injection

General Notices

Action and use

Cytotoxic alkylating agent.

DEFINITION

Ifosfamide Injection is a sterile solution of Ifosfamide in Water for Injections or a suitable liquid. It is prepared by dissolving Ifosfamide for Injection in the requisite amount of a suitable liquid immediately before use.

The injection complies with the requirements stated under Parenteral Preparations.

STORAGE

Ifosfamide Injection should be used immediately after preparation but, in any case, within the period recommended by the manufacturer when prepared and stored strictly in accordance with the manufacturer's instructions.

IFOSFAMIDE FOR INJECTION

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

CAUTION *Ifosfamide is Cytotoxic. Carry out the procedures described below exercising appropriate precautions.*

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 ifosfamide, $C_7H_{15}Cl_2N_2O_2P$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

The *infrared absorption spectrum*, Appendix II A, is concordant with the *reference spectrum* of ifosfamide (*RS 428*).

TESTS

Solution A

Dissolve 5.0 g in *carbon dioxide-free water* and dilute to 50.0 mL with the same solvent.

Appearance of solution

Solution A is clear, Appendix IV A, and not more intensely coloured than *reference solution* Y_7, Appendix IV B.

Acidity or alkalinity

pH of an 8% w/v solution, 4.0 to 7.0, Appendix V L.

Related substances

A. Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.
(1) Dissolve a sufficient quantity of the contents of the sealed container in a mixture of equal volumes of *methanol* and *water* to produce a solution containing 10.0% w/v of Ifosfamide.
(2) 0.025% w/v of *ifosfamide impurity A EPCRS* and 0.025% w/v of *chloroethylamine hydrochloride* (impurity C) in a mixture of equal volumes of *methanol* and *water*.
(3) 0.015% w/v of *ifosfamide impurity B EPCRS* in a mixture of equal volumes of *methanol* and *water*.
(4) 0.005% w/v of *ethanolamine*, 0.02% w/v of *ifosfamide impurity A EPCRS* and 0.08% w/v of *chloroethylamine hydrochloride* (impurity C) in a mixture of equal volumes of *methanol* and *water*.

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *silica gel G*.
(b) Use the mobile phase as described below.
(c) Apply 10 µL of each solution.
(d) Develop the plate to 15 cm.
(e) After removal of the plate, dry at 115° for 45 minutes. At the bottom of a chromatography tank, place an evaporating dish containing a 0.32% w/v solution of *potassium permanganate* and add an equal volume of *dilute hydrochloric acid*, close the tank and allow to stand for 10 minutes. Place the plate whilst still hot in the tank, avoiding contact of the stationary phase with the solution, and close the tank. Leave the plate in contact with the chlorine vapour for 20 minutes. Withdraw the plate and place it in a current of cold air until the excess of chlorine is removed (about 20 minutes) and an area of coating below the points of application does not give a blue colour with a drop of *potassium iodide and starch solution*. Avoid prolonged exposure to cold air. Immerse the plate in a 0.1% w/v solution of *tetramethylbenzidine* in *ethanol (96%)* for 5 seconds. Allow the plate to dry and examine.

MOBILE PHASE

10 volumes of *water*, 15 volumes of *methanol*, 25 volumes of *acetic acid* and 50 volumes of *dichloromethane*.

SYSTEM SUITABILITY

The test is not valid unless the chromatogram obtained with solution (4) shows three clearly separated spots.

LIMITS

In the chromatogram obtained with solution (1) any spot corresponding to impurity A or impurity C is not more intense than the corresponding spot in the chromatogram obtained with solution (2) (0.25%); any spot corresponding to impurity B is not more intense than the corresponding spot in the chromatogram obtained with solution (3) (0.15 %); any other spot is not more intense than the principal spot in the chromatogram obtained with solution (3) (0.15%).

B. Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.
(1) Dissolve a sufficient quantity of the contents of the sealed container in a mixture of equal volumes of *methanol* and *water* to produce a solution containing 2.0% w/v of Ifosfamide.
(2) 0.005% w/v of *ifosfamide impurity E EPCRS* and 0.005% w/v of *ifosfamide impurity F EPCRS* in a mixture of equal volumes of *methanol* and *water*.
(3) 0.01% w/v of *ifosfamide impurity E EPCRS* and 0.01% w/v of *ifosfamide impurity F EPCRS* in a mixture of equal volumes of *methanol* and *water*.

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *silica gel G*.
(b) Use the mobile phase as described below.
(c) Apply 5 µL of each solution.

(d) Develop the plate to 15 cm.
(e) After removal of the plate dry at 115° for 45 minutes. At the bottom of a chromatography tank, place an evaporating dish containing a 0.32% w/v solution of *potassium permanganate* and add an equal volume of *dilute hydrochloric acid*, close the tank and allow to stand for 10 minutes. Place the plate whilst still hot in the tank, avoiding contact of the stationary phase with the solution, and close the tank. Leave the plate in contact with the chlorine vapour for 20 minutes. Withdraw the plate and place it in a current of cold air until the excess of chlorine is removed (about 20 minutes) and an area of coating below the points of application does not give a blue colour with a drop of *potassium iodide and starch solution*. Avoid prolonged exposure to cold air. Immerse the plate in a 0.1% w/v solution of *tetramethylbenzidine* in *ethanol (96%)* for 5 seconds. Allow the plate to dry and examine.

MOBILE PHASE

1 volume of *dichloromethane* and 10 volumes of *acetone*.

SYSTEM SUITABILITY

The test is not valid unless the chromatogram obtained with solution (3) shows two clearly separated spots.

LIMITS

In the chromatogram obtained with solution (1) any spot corresponding to impurity E or impurity F is not more intense than the corresponding spot in the chromatogram obtained with solution (2) (0.25%).

Water

Not more than 0.5% w/w, Appendix IX C. Use 1g.

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 method for *liquid chromatography*, Appendix III D, using the following solutions in the mobile phase.

(1) Dissolve a sufficient quantity of the contents of the sealed container to produce a solution containing 0.060% w/v of Ifosfamide.
(2) 0.060% w/v of *ifosfamide BPCRS*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Zorbax SB-C18 is suitable).
(b) Use isocratic elution and the mobile phase described below.
(c) Use a flow rate of 1.5 mL per minute.
(d) Use a column temperature of 30°.
(e) Use a detection wavelength of 195 nm.
(f) Inject 20 µL of each solution.

MOBILE PHASE

A mixture of 30 volumes of *acetonitrile R1* and 70 volumes of *carbon dioxide-free water*.

DETERMINATION OF CONTENT

Calculate the content of $C_7H_{15}Cl_2N_2O_2P$ in a container of average content weight using the declared content of $C_7H_{15}Cl_2N_2O_2P$ in *ifosfamide BPCRS*.

STORAGE

The sealed container should be kept protected from light.

IMPURITIES

The impurities limited by the requirements of this monograph include those listed under Ifosfamide. Related substances test A is intended to control degradation impurities and Related substances test B is intended to control synthetic impurities.