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Thiotepa for Infusion

General Notices

Thiotepa for Injection

Details for the public consultation of this monograph are as follows:

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Target Publication Date (subject to change)	BP 2028
Notes	Revised monograph If limits are too restrictive, please provide batch/stability data to demonstrate that an increase is required. Title revised, sub-monograph separated from Thiotepa Injection Definition amended Content upper limit reduced Identification IR replaces tests A and B Related substances quantitative limits and reporting threshold introduced, unspecified impurity limit revised Water new test added Assay resolution requirement and duplication of conditions removed Impurities section added

Action and use

Antineoplastic alkylating agent.

DEFINITION

Thiotepa for Infusion is a sterile material consisting of [Thiotepa](#) with or without excipients. It is intended to be prepared by dissolving the dry ingredients in the specified volume just before issue for use.

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 thiotepa, C₆H₁₂N₃PS

95.0 to 105.0% of the stated amount.

CHARACTERISTICS

A white powder.

IDENTIFICATION

The [infrared absorption spectrum](#), [Appendix II A](#), is concordant with the *reference spectrum* of thiotepa ([RS 337](#)).

TESTS

Acidity or alkalinity

Dissolve a quantity containing 20 mg of Thiotepa in 2 mL of [carbon dioxide-free water](#). The pH of the resulting solution is 5.5 to 7.5, [Appendix V L](#).

Clarity of solution

Dissolve a quantity containing 15 mg of Thiotepa in 4 mL of [water](#). The solution is *clear*, [Appendix IV A](#).

Related substances

Carry out the method for [liquid chromatography](#), [Appendix III D](#), using the following freshly prepared solutions.

- (1) Dissolve, with shaking, a quantity of the contents of the sealed container containing 15 mg of Thiotepa in 4 mL of [water](#), filter and use the filtrate.
- (2) Dilute 1 volume of solution (1) to 100 volumes with [water](#) and further dilute 1 volume to 5 volumes with [water](#).
- (3) Dissolve 10 mg of [thiotepa BPCRS](#) in 2 mL of [methanol](#) in a ground-glass-stoppered tube, add 50 µL of a 0.1% v/v solution of [orthophosphoric acid](#), stopper the tube and heat in a water bath at 65° for 50 seconds (generation of methoxythiotepa). Allow the solution to cool and add 1 mL of [methanol](#).
- (4) Dissolve 15 mg of [thiotepa BPCRS](#) in 10 mL of [water](#), add 1 g of [sodium chloride](#), boil in a water bath for 10 minutes and cool (generation of impurity A).

CHROMATOGRAPHIC CONDITIONS

- (a) Use a stainless steel column (15 cm × 4.6 mm) packed with [end-capped octadecylsilyl silica gel for chromatography](#) (5 µm) (Nucleosil C18 is suitable).
- (b) Use isocratic elution and the mobile phase described below.
- (c) Use a flow rate of 1 mL per minute.
- (d) Use an ambient column temperature.
- (e) Use a detection wavelength of 215 nm.
- (f) Inject 20 µL of each solution.
- (g) For solution (1) allow the chromatography to proceed for 4 times the retention time of the principal peak.

MOBILE PHASE

15 volumes of [acetonitrile](#) and 85 volumes of [0.1M mixed phosphate buffer pH 7.0](#).

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the [resolution](#) between thiotepa and methoxythiotepa is at least 3.0.

CALCULATION OF IMPURITIES

For each impurity, use the concentration of thiotepa in solution (2).

For the reporting threshold, use the concentration of thiotepa in solution (2).

For peak identification, use solution (4).

Thiotepa retention time: about 12 minutes.

Relative retentions: methoxythiotepa, about 1.3; impurity A, about 3.7.

LIMITS

- impurity A: not more than 0.15%;
- unspecified impurities: for each impurity, not more than 0.2%;
- total impurities: not more than 0.4%;
- reporting threshold: 0.1%.

[Water](#)

Not more than 1.0% w/w, Appendix IX C, Method III. Use 0.3 g.

ASSAY

Carry out the method for [liquid chromatography](#), [Appendix III D](#), using the following solutions prepared in [water](#).

- (1) Dissolve the contents of a sealed container to produce a solution containing 0.15% w/v of Thiotepa.
- (2) 0.15% w/v of [thiotepa BPCRS](#).

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Related substances may be used.

DETERMINATION OF CONTENT

Calculate the amount of $C_6H_{12}N_3PS$ in the sealed container from the chromatograms obtained and using the declared content of $C_6H_{12}N_3PS$ in [thiotepa BPCRS](#).

Repeat the procedure with a further nine sealed containers. Calculate the average content of $C_6H_{12}N_3PS$ per container from the 10 individual results thus obtained.

STORAGE

The sealed container should be stored at a temperature of 2° to 8°.

IMPURITIES

The impurities limited by the requirements of this monograph include those listed under [Thiotepa](#).