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Mitoxantrone Sterile Concentrate

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

EAG/Panel/Working Party	Medicinal Chemicals 2
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Deadline for Comment	30th September 2021
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Notes	Revised monograph If limits are too restrictive, please provide batch/stability data to demonstrate that an increase is required. **Acidity** pH requirement revised **Related substances** Relative retention times for impurities A, B, C and D added

Action and use

Cytotoxic.

DEFINITION

Mitoxantrone Sterile Concentrate is a sterile solution of Mitoxantrone Hydrochloride in Water for Injections.

The concentrate complies with the requirements for Concentrates for Injections or Infusions stated under Parenteral Preparations and with the following requirements.

Content of mitoxantrone, $C_{22}H_{28}N_4O_6$

90.0 to 105.0% of the stated amount.

CHARACTERISTICS

A dark blue solution.

IDENTIFICATION

A. Dilute a volume of the concentrate containing the equivalent of 2 mg of mitoxantrone to about 100 mL with *water* and add 20 mL of 1M *hydrochloric acid* and sufficient *water* to produce 200 mL. The *light absorption* of the solution, Appendix II B, in the range 220 nm to 350 nm shows a maximum at about 240 nm and a shoulder at 274 nm.

B. In the Assay, the chromatogram obtained with solution (1) shows a peak with the same retention time as the principal peak in the chromatogram obtained with solution (2).

TESTS

Acidity

pH of a solution diluted, if necessary, with *water* to contain the equivalent of 0.2% w/v of mitoxantrone, 2.5 to 4.5, Appendix V L.

Related substances

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

(1) Dilute a volume of the concentrate containing the equivalent of 20 mg of mitoxantrone to 50 mL with the mobile phase.

(2) Dilute 1 volume of solution (1) to 100 volumes with the mobile phase.

(3) 0.2% w/v of *mitoxantrone impurity A EPCRS* and 0.04% w/v of *mitoxantrone hydrochloride EPCRS* in the mobile phase.

(4) Dilute 1 volume of solution (2) to 10 volumes with the mobile phase.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (30 cm × 3.9 mm) packed with *phenyl silica gel for chromatography* (10 µm) (µBondapak Phenyl is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 3 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 254 nm.

(f) Inject 50 µL of each solution.

(g) For solution (1) allow the chromatography to proceed for 3 times the retention time of the principal peak.

MOBILE PHASE

25 volumes of a solution prepared by dissolving 22 g of *sodium heptanesulfonate* in about 150 mL of *water*, filtering through a 0.45-µm filter, washing the filter with *water*, adding 32 mL of *glacial acetic acid* to the combined filtrate and washings and diluting to 250 mL with *water*, 250 volumes of *acetonitrile* and 750 volumes of *water*.

When the chromatograms are recorded under the prescribed conditions, the relative retentions with reference to mitoxantrone are: impurity B, about 0.9; impurity A, about 1.5; impurity D, about 1.7 and impurity C, about 2.1.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the two principal peaks is at least 3.0.

LIMITS

In the chromatogram obtained with solution (1):

the area of any peak corresponding to impurity D is not greater than 3 times the area of the principal peak in the chromatogram obtained with solution (2) (3%);

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* other than any peak corresponding to impurity D is not greater than 5 times the area of the principal peak in the chromatogram obtained with solution (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

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

(1) Dilute a volume of the concentrate containing the equivalent of 20 mg of mitoxantrone to 50 mL with the mobile phase.

(2) 0.047% w/v of *mitoxantrone hydrochloride EPCRS* in the mobile phase.

(3) 0.2% w/v of *mitoxantrone impurity A EPCRS* in solution (2).

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 two principal peaks is at least 3.0.

DETERMINATION OF CONTENT

Calculate the content of $C_{22}H_{28}N_4O_6$ in the concentrate using the declared content of $C_{22}H_{30}Cl_2N_4O_6$ in *mitoxantrone hydrochloride EPCRS*. Each mg of $C_{22}H_{30}Cl_2N_4O_6$ to be equivalent to 0.8591 mg of $C_{22}H_{28}N_4O_6$.

LABELLING

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

IMPURITIES

The impurities limited by the requirements of this monograph include those listed under Mitoxantrone Hydrochloride.