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Notes:	

Lorazepam Injection

Lorazepam Preparations

Action and use
Benzodiazepine.

DEFINITION

Lorazepam Injection is a sterile solution of Lorazepam in a suitable solvent.

The injection complies with the requirements stated under Parenteral Preparations and with the following requirements.

Content of lorazepam, $C_{15}H_{10}Cl_2N_2O_2$
92.5 to 105.0% of the stated amount.

IDENTIFICATION

A. Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions protected from light.

(1) Dilute a quantity of the injection with *water* to obtain a 0.1% w/v solution of Lorazepam and extract with 10 mL *dichloromethane*.

(2) 0.1% w/v solution of *lorazepam BPCRS* in *dichloromethane*.

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *silica gel* F_{254} (Merck silica gel 60 plates are suitable).

(b) Use the mobile phase as described below.

(c) Before use, stand the plate in *methanol*, allowing the solvent front to ascend 17 cm, heat the plate at 100° to 105° for 1 hour. Use with the flow of mobile phase in the same direction as that used for the prewash.

(c) Apply 5 µL of each solution.

(d) Develop the plate to 17 cm.

(e) After removal of the plate, dry in air and examine under ultraviolet light (254 nm).

MOBILE PHASE

10 volumes of *methanol* and 100 volumes of *dichloromethane*.

CONFIRMATION

The principal spot in the chromatogram obtained with solution (1) corresponds in position and colour to that in the chromatogram obtained with solution (2).

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

TESTS

Related substances
Carry out the method for *liquid chromatography*, Appendix III D, protected from light using the following solutions in a mixture of equal volumes of *acetonitrile* and *water*.

(1) Dilute a quantity of the injection to produce a solution containing 0.08% w/v of Lorazepam.

(2) Dilute 1 volume of solution (1) to 200 volumes.

(3) 0.0004% w/v of *6-chloro-4-(2-chlorophenyl)quinazoline-2-carboxaldehyde BPCRS* (Ph. Eur. impurity E) and 0.1% w/v of *lorazepam for system suitability EPCRS*.

(4) Dilute 1 volume of solution (2) to 5 volumes.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (5 µm) resistant to bases up to pH 11.5 (Zorbax Extend C18 is suitable).

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

(c) Use a flow rate of 1.0 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 235 nm.

(f) Inject 5 µL of each solution.

Mobile phase A 3.48 g of *dipotassium hydrogen orthophosphate* in a mixture of 50 mL of *acetonitrile* and 850 mL of *water*; adjust the pH to 10.5 with a 4.0% w/v solution of *sodium hydroxide* and dilute to 1000 mL with *water*.

Mobile phase B *acetonitrile*.

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NOT FOR PUBLICATION

Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
0-5	80	20	isocratic
5-35	80→30	20→70	linear

			gradient
35-50	30	70	isocratic
50-60	30→80	70→20	linear gradient
60-75	80	20	re-equilibration

When the chromatograms are recorded under the prescribed conditions the retention times relative to lorazepam (retention time about 17.5 minutes) are; impurity D, about 0.9; impurity B, about 1.2 and impurity E, about 1.4.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3):

the resolution between impurity D and lorazepam is at least 4.5;

the peak to valley ratio between lorazepam and impurity B is at least 5.0.

LIMITS

Identify any peak in the chromatogram obtained with solution (1) due to impurity D using the chromatogram obtained with solution (3). Multiply the area of any peak corresponding to impurity D by the following correction factor: 4.95.

In the chromatogram obtained with solution (1):

the area of any peak corresponding to impurity E is not greater than twice the area of the peak in the chromatogram obtained with solution (2) (5.0%);

the area of any other *secondary peaks* is not greater than half the area of the principal peak in the chromatogram obtained with solution (2) (0.25%);

the sum of the areas of any other *secondary peaks* is not greater than twice the area of the principal peak in the chromatogram obtained with solution (2) (1.0%).

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

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, protected from light using the following solutions in a mixture of equal volumes of *acetonitrile* and *water*.

(1) Dilute a quantity of the injection to produce a solution containing 0.008% w/v of Lorazepam.

(2) 0.008% w/v of *lorazepam BPCRS.*

(3) 0.008% w/v of *lorazepam BPCRS* and 0.0004% w/v of *6-chloro-4-(2-chlorophenyl)quinazoline-2-carboxaldehyde BPCRS.*

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (5 µm) resistant to bases up to pH 11.5 (Zorbax Extend C18 is suitable).

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

(c) Use a flow rate of 1.0 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 235 nm.

(f) Inject 5 µL of each solution.

MOBILE PHASE

450 volumes of *acetonitrile* and 550 volumes of a solution of 3.48 g of *dipotassium hydrogen orthophosphate* in a mixture of 50 mL of *acetonitrile* and 850 mL of *water*; adjust the pH to 10.5 with a 4.0% w/v solution of *sodium hydroxide* and dilute to 1000 mL with *water*.

When the chromatograms are recorded under the prescribed conditions the retention time of lorazepam is about 4 minutes.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between lorazepam and impurity E is at least 8.0.

DETERMINATION OF CONTENT

Calculate the content of $C_{15}H_{10}Cl_2N_2O_2$ in the injection using the declared content of $C_{15}H_{10}Cl_2N_2O_2$ in *lorazepam BPCRS*.

STORAGE

Lorazepam Injection should be protected from light and stored at a temperature of 2° to 8°.

IMPURITIES

The impurities limited by the requirements of this monograph those listed under Lorazepam.