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Notes:	

Lorazepam Tablets

Lorazepam Preparations

Action and use
Benzodiazepine.

DEFINITION

Lorazepam Tablets contain Lorazepam.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of lorazepam, $C_{15}H_{10}Cl_2N_2O_2$
95.0 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) Shake a quantity of the powdered tablets containing 5 mg of Lorazepam with 5 mL of *acetone* and centrifuge.

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

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

Dissolution
Carry out the procedure protected from light. Comply with the requirements for Monographs of the British Pharmacopoeia in the *dissolution test for tablets and capsules*, Appendix XII B1.

TEST CONDITIONS

(a) Use Apparatus 1, rotating the basket at 100 revolutions per minute.

(b) Use 900 mL of 0.1M *hydrochloric acid*, at a temperature of 37°, as the medium.

PROCEDURE

(1) After 45 minutes withdraw a 10 mL sample of the medium. Using 2 cm cells measure the *absorbance* of the filtered sample, suitably diluted with the dissolution medium if necessary, to produce a solution expected to contain about 0.00011% w/v of Lorazepam, at the maximum at 232 nm, Appendix II B using 0.1M *hydrochloric acid* in the reference cell.

DETERMINATION OF CONTENT

Calculate the content of $C_{15}H_{10}Cl_2N_2O_2$, in the medium taking 1115 as the value of A(1%, 1cm) at the maximum at 232 nm.

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) Disperse 5 whole tablets with the aid of ultrasound in a suitable volume to produce a 0.1% w/v solution of Lorazepam and filter.

(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 correction factor of 4.95.

In the chromatogram obtained with solution (1):

the area of any peak corresponding to impurity E is not greater than four times the area of the peak in the chromatogram obtained with solution (2) (2.0%);

the area of any other *secondary peaks* is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.5%);

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%).

Uniformity of content

Tablets containing less than 2 mg and/or less than 2% w/w of Lorazepam comply with the requirement stated under Tablets using the following method of analysis.

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) Disperse one tablet with the aid of ultrasound with 5 mL. Allow to cool and dilute to 10 mL. Further dilute, if necessary, to produce a solution expected to contain 0.01% w/v of Lorazepam, filter and use the filtrate.

(2) 0.01% w/v of *lorazepam BPCRS*.

(3) 0.01% 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 each tablet from the chromatograms obtained and using the declared content of $C_{15}H_{10}Cl_2N_2O_2$ in *lorazepam BPCRS*.

ASSAY

For tablets containing the equivalent of less than 2 mg and/or less than 2% w/w of lorazepam

Use the average of the 10 individual results obtained in the test for Uniformity of content.

For tablets containing the equivalent of 2 mg or more and 2% w/w or more of lorazepam

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) Disperse ten whole tablets in sufficient solvent to produce a solution expected to contain 0.01% w/v Lorazepam and filter.

(2) 0.01% w/v of *lorazepam BPCRS.*

(3) 0.01% w/v of *lorazepam BPCRS* and 0.0004% w/v of *6-chloro-4-(2-chlorophenyl)quinazoline-2-carboxaldehyde BPCRS.*

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Uniformity of content may be used.

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

STORAGE

Lorazepam Tablets should be protected from light.

IMPURITIES

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