EAG/Panel/Working Party	Antibiotics
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Notes: Revised Monograph. Changes made to the related substances, assay and identification methods.	

Griseofulvin Premix

Griseofulvin Preparations

Action and use
Antifungal.

DEFINITION
Griseofulvin Premix contains Griseofulvin. The particles of Griseofulvin are generally up to 5 µm in maximum dimension, although larger particles, which may occasionally exceed 30 µm, may be present.

The premix complies with the requirements stated under Premixes and with the following requirements.

Content of griseofulvin, $C_{17}H_{17}ClO_6$
90.0 to 110.0% of the stated amount.

IDENTIFICATION
Shake a quantity of the premix containing 0.1 g of Griseofulvin with 10 mL of *dichloromethane*. Centrifuge and decant the supernatant liquid, dry with *anhydrous sodium sulfate* and evaporate the *dichloromethane*. The *infrared absorption spectrum* of the residue, Appendix II A, is concordant with the *reference spectrum* of griseofulvin *(RSV 24)*.

Related substances
Carry out the method for liquid chromatography, Appendix III D, using the following solutions in mobile phase B.

(1) Disperse a quantity of premix containing 250 mg of griseofulvin in mobile phase B and dilute to 500 mL.

(2) Dilute 1 volume of solution (1) to 100 volumes.

(3) 0.05% w/v of *griseofulvin for LC assay and identification EPCRS*.

(4) 0.05% w/v of *griseofulvin for system suitability EPCRS*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (5 µm) (Discovery 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 a column temperature of 30°.

(e) Use a detection wavelength of 290 nm.

(f) Inject 10 µL of each solution.

MOBILE PHASE

Mobile Phase A

Time D_1 (dwell volume used for development of the method) = 1.6 mL (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 3	50	50
3 - 13	50 → 40	50 → 60
13 - 16	40 → 10	60 → 90
16 - 24	10	90

20 volumes of 0.1 % v/v *anhydrous formic acid* adjusted to pH 4.5 with dilute *ammonia R2* and 80 volumes of *water*.

Mobile Phase B

15 volumes of *water*, 20 volumes of 0.1 % v/v *anhydrous formic acid* adjusted to pH 4.5 with *dilute ammonia R2* and 65 volumes of *acetonitrile R*.

When the chromatograms are recorded under the prescribed conditions the retention time relative to griseofulvin (retention time about 16 minutes) are: Impurity A, about 0.4, Impurity B, about 0.7, and impurity C, about 1.1.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (4), the *peak-to-valley ratio* is at least 3.0 where Hp is the height above the baseline of the peak due to impurity C and Hv is the height above the baseline of the lowest point of the curve separating this peak from the peak due to griseofulvin.

LIMITS

In the chromatogram obtained with solution (1):

Identify any peaks corresponding to impurity A and multiply the area of this peak by a correction factor of 0.6.

The area of any peak corresponding to impurity B is not greater than 3 times the area of the principal peak obtained with solution (2) (3%).

The area of any peak corresponding to impurity A is not greater than twice the area of the principal peak obtained with solution (2) (2%).

the area of any other secondary peak is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (1.0%);

the sum of the areas of any such peaks is not greater than 4 times the area of the principal peak in the chromatogram obtained with solution (2) (5%).

Disregard any peaks due to excipients and any peak with an area less than 0.3 times the area of the principal peak in the chromatogram obtained with solution (2) (0.3%).

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ASSAY

Carry out the method for liquid chromatography, Appendix III D, using the following solutions prepared immediately before use.

(1) Disperse a quantity of the premix containing 250 mg of griseofulvin in mobile phase B and dilute to 500 mL.

(2) 0.05% w/v of *griseofulvin for LC assay and identification EPCRS*.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Related substances may be used.

DETERMINATION OF CONTENT

Calculate the content of $C_{17}H_{17}ClO_6$ in the premix using the declared content of $C_{17}H_{17}ClO_6$ in *griseofulvin for LC assay and identification EPCRS*.

IMPURITIES

The impurities limited by the requirements of this monograph include A, B and C listed under Griseofulvin.

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