Edition: BP 2025 (Ph. Eur. 11.6 update)

Levonorgestrel Tablets

General Notices

Action and use

Progestogen.

DEFINITION

Levonorgestrel Tablets contain Levonorgestrel.

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

Content of levonorgestrel, $C_{21}H_{28}O_2$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in *methanol (80%)*.
(1) To a quantity of the powdered tablets containing 0.15 mg of Levonorgestrel add 25 mL of *methanol (80%)*, heat in a water bath at 60° for 10 minutes, allow to cool and filter through a 0.45-µm filter.
(2) 0.0006% w/v of *levonorgestrel BPCRS*.
(3) 0.0012% w/v of *norgestrel BPCRS*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (12.5 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Hypersil ODS is suitable).
(b) Use isocratic elution and the mobile phase described below.
(c) Use a flow rate of 1.5 mL per minute.
(d) Use a column temperature of 30°.
(e) Use a detection wavelength of 242 nm.
(f) Inject 20 µL of each solution.

MOBILE PHASE

50 volumes of *methanol* and 50 volumes of a 1% w/v solution of *gamma-cyclodextrin*.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to dextronorgestrel and levonorgestrel and is at least 1.0.

CONFIRMATION

The principal peak in the chromatogram obtained with solution (1) has the same retention time as the peak due to levonorgestrel in the chromatogram obtained with solution (2).

B. In the test for Uniformity of content, the principal peak in the chromatogram obtained with solution (1) has the same retention time as the principal peak in the chromatogram obtained with solution (2).

TESTS

Dissolution

For tablets containing less than 100 µg of levonorgestrel

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 2, rotating the paddle at 75 revolutions per minute.
(b) Use 500 mL of 0.01M *hydrochloric acid*, at a temperature of 37°, as the medium.

PROCEDURE

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

(1) After 30 minutes withdraw a sample of the medium and filter. Dilute the filtrate, with 0.01M *hydrochloric acid* if necessary, to produce a solution expected to contain 0.000006% w/v of Levonorgestrel.
(2) 0.000006% w/v of *levonorgestrel BPCRS* in dissolution medium.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (15 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Spherisorb ODS 2 is suitable).
(b) Use isocratic elution and the mobile phase described below.
(c) Use a flow rate of 1.3 mL per minute.
(d) Use an ambient column temperature.
(e) Use a detection wavelength of 220 nm.
(f) Inject 500 µL of each solution.

MOBILE PHASE

50 volumes of *acetonitrile* and 50 volumes of *water*.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (2), the *column efficiency,* determined on the peak due to levonorgestrel is at least 5000 theoretical plates per metre.

DETERMINATION OF CONTENT

Calculate the total content of $C_{21}H_{28}O_2$ in the medium from the chromatograms obtained and using the declared content of $C_{21}H_{28}O_2$ in *levonorgestrel BPCRS*.

LIMITS

The amount of levonorgestrel released is not less than 75% (Q) of the stated amount.

For tablets containing 100 µg or more of levonorgestrel

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 2, rotating the paddle at 75 revolutions per minute.
(b) Use 500 mL of a 0.1% w/v solution of *sodium dodecylsulfate* in *0.1M hydrochloric acid*, at a temperature of 37°, as the medium.

PROCEDURE

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

(1) After 30 minutes withdraw a sample of the medium and filter. Dilute the filtrate, with a 0.1% w/v solution of *sodium dodecylsulfate* in *0.1M hydrochloric acid* if necessary, to produce a solution expected to contain 0.00015% w/v of Levonorgestrel.
(2) 0.00015% w/v of *levonorgestrel BPCRS* in dissolution medium.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Dissolution (For tablets containing less than 100 µg of levonorgestrel) may be used with an injection volume of 25 µL.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (2), the *column efficiency,* determined on the peak due to levonorgestrel is at least 5000 theoretical plates per metre.

DETERMINATION OF CONTENT

Calculate the total content of $C_{21}H_{28}O_2$ in the medium from the chromatograms obtained and using the declared content of $C_{21}H_{28}O_2$ in *levonorgestrel BPCRS*.

LIMITS

The amount of levonorgestrel released is not less than 75% (Q) of the stated amount.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in *methanol (50%)*.

(1) Add 5 mL of *methanol (50%)* to a quantity of the powdered tablets containing 0.18 mg of Levonorgestrel, mix with the aid of ultrasound for 30 minutes, stir vigorously for 15 minutes, centrifuge and use the supernatant liquid.
(2) Dilute 1 volume of solution (1) to 100 volumes.
(3) 0.004% w/v each of *ethinylestradiol BPCRS* and *levonorgestrel BPCRS*.
(4) Dilute 1 volume of solution (2) to 10 volumes.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Spherisorb ODS 2 is suitable).
(b) Use isocratic elution and the mobile phase described below.
(c) Use a flow rate of 1.2 mL per minute.
(d) Use a column temperature of 30°.
(e) Use a detection wavelength of 220 nm.
(f) Inject 200 µL of each solution.
(g) Allow the chromatography to proceed for twice the retention time of levonorgestrel.

MOBILE PHASE

100 volumes of *methanol*, 240 volumes of *acetonitrile* and 500 volumes of *water*.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to ethinylestradiol and levonorgestrel is at least 12.0.

LIMITS

In the chromatogram obtained with solution (1):

the area of any *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 such peaks is not greater than twice the area of the principal peak in the chromatogram obtained with solution (2) (2%).

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 Levonorgestrel comply with the requirements stated under Tablets using the following method of analysis. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) To 1 tablet add 5 mL of the mobile phase, disperse with the aid of ultrasound for 45 minutes, shaking every 15 minutes, centrifuge and dilute the clear supernatant liquid with the mobile phase, if necessary, to produce a solution expected to contain 0.0006% w/v of levonorgestrel.
(2) 0.0006% w/v of *levonorgestrel BPCRS* in the mobile phase.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Dissolution (For tablets containing less than 100 µg of levonorgestrel) may be used with an injection volume of 25 µL.

MOBILE PHASE

50 volumes of *acetonitrile* and 50 volumes of *water*.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (2), the *column efficiency,* determined on the peak due to levonorgestrel is at least 5000 theoretical plates per metre.

DETERMINATION OF CONTENT

Calculate the content of $C_{21}H_{28}O_2$ in each tablet using the declared content of $C_{21}H_{28}O_2$ in *levonorgestrel BPCRS*.

ASSAY

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

IMPURITIES

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