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

Levonorgestrel and Ethinylestradiol Tablets

General Notices

Action and use

Progestogen.

DEFINITION

Levonorgestrel and Ethinylestradiol Tablets contain Levonorgestrel and Ethinylestradiol.

The tablets comply with the requirements stated under Tablets and with the following requirements. For Levonorgestrel and Ethinylestradiol Tablets presented in 21-day or 28-day calendar packs, apply the requirements separately to tablets of each combination of different proportions, by weight, of the active ingredients. Where applicable, disregard any tablets that contain no active ingredient (placebo tablets).

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

90.0 to 110.0% of the stated amount.

Content of ethinylestradiol, $C_{20}H_{24}O_2$

90.0 to 110.0% of the stated amount.

IDENTIFICATION

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

(1) Extract 15 powdered tablets with 30 mL of *acetone*, filter, evaporate to dryness and dissolve the residue in 1 mL of *chloroform*.
(2) 0.075% w/v of *levonorgestrel BPCRS* in *chloroform*.
(3) 0.045% w/v of *ethinylestradiol BPCRS* in *chloroform*.

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *silica gel* GF_{254}.
(b) Use the mobile phase as described below.
(c) Apply 20 µL of each solution.
(d) Develop the plate to 15 cm. Develop the chromatograms twice, drying the plates between developments.
(e) After removal of the plate, dry in air and examine under *ultraviolet light (254 nm)*.
(f) Spray the plate with a 2% w/v solution of *toluene*-p-*sulfonic acid* in *water* and heat at 105° for 10 minutes and examine under *ultraviolet light (365 nm)*.

MOBILE PHASE

1 volume of *methanol* and 99 volumes of *chloroform*.

CONFIRMATION

By the first method of visualisation:

one of the principal spots in the chromatogram obtained with solution (1) corresponds to that in the chromatogram obtained with solution (2) and the other principal spot corresponds to that in the chromatogram obtained with solution (3).

By the second method of visualisation:

the spots corresponding to levonorgestrel and ethinylestradiol appear as blue spots.

Uniformity of content

Prepare the following stock solutions using a mixture of 40 volumes of *water* and 60 volumes of *acetonitrile*.

Solution A 0.0625% w/v of *levonorgestrel* BPCRS.
Solution B 0.025% of *ethinylestradiol* BPCRS.
Solution C 0.020% w/v of *2-hydroxybiphenyl* (internal standard).
Solution D Dilute 1 mL of solution C to 20 mL with the solvent mixture.

Tablets containing less than 2 mg and/or less than 2% w/w of Levonorgestrel or less than 2 mg and/or less than 2% w/w of Ethinylestradiol 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) Add 4 mL of solution D to one tablet, heat at 60° in an ultrasonic bath for 25 minutes, shake and repeat the ultrasound treatment. Cool, centrifuge and use the clear supernatant liquid.
(2) Mix the volumes of solutions A and B specified in the table with 5 mL of solution C and dilute to 100 mL with a mixture of 40 volumes of *water* and 60 volumes of *acetonitrile*.

Content of		Volume of	
Levonorgestrel µg	Ethinyloestradiol µg	Solution A ml	Solution B ml
250	50	10.0	5.0
250	30	10.0	3.0
150	30	6.0	3.0
125	30	5.0	3.0
75	40	3.0	4.0
50	30	2.0	3.0

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (15 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 an ambient column temperature.
(e) Use a detection wavelength of 215 nm.
(f) Inject 20 µL of each solution.

MOBILE PHASE

49 volumes of *acetonitrile* and 51 volumes of *water*.

DETERMINATION OF CONTENT

Calculate the content of $C_{21}H_{28}O_2$ and of $C_{20}H_{24}O_2$ in each tablet using the declared content of $C_{21}H_{28}O_2$ in *levonorgestrel BPCRS* and the declared content of $C_{20}H_{24}O_2$ in *ethinylestradiol BPCRS*.

ASSAY

For both levonorgestrel and ethinylestradiol use the average of the individual results determined in the test for Uniformity of content.