

## LEVONORGESTREL TABLETS

### Draft proposal for *The International Pharmacopoeia*

(September 2010)

*REVISED DRAFT FOR COMMENT*

This document was provided by a quality control expert and was discussed at the recent WHO consultation on specifications for medicines and quality control laboratory issues. Previous comments received have been incorporated into this revised draft. Should you have any comments, please send these to Dr S. Kopp, Manager, Medicines Quality Assurance Programme, Quality Assurance and Safety: Medicines, World Health Organization, 1211 Geneva 27, Switzerland; fax: (+41 22) 791 4730 or e-mails: [kopps@who.int](mailto:kopps@who.int) with a copy to Ms C. Mendy [mendyc@who.int](mailto:mendyc@who.int) by 26 October 2010.

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**SCHEDULE FOR THE ADOPTION PROCESS OF DOCUMENT QAS/10.371**  
*International Pharmacopoeia monograph on Levonorgestrel tablets*

	<b>Date</b>
Preparation of first draft by laboratory	April-May 2010
Discussion at consultation on specifications for medicines and quality control laboratory issues	10-12 May 2010
Draft monograph mailed out for comments	July 2010
Collation of comments	August 2010
Revised draft discussed during video- and teleconference on specifications for medicines	25 August 2010
Revised draft mailed out for comments	September 2010
Presentation to WHO Expert Committee on Specifications for Pharmaceutical Preparations	18-22 October 2010
Further action as necessary	

## LEVONORGESTREL TABLETS

### Draft proposal for *The International Pharmacopoeia*

(September 2010)

**Category.** Contraceptive.

**Storage.** Levonorgestrel tablets should be kept in a well-closed container, protected from light.

**Additional information.** Strength in the current WHO Model list of essential medicines: 30 µg, 750 µg, 1.5 mg.

### Requirements

Comply with the monograph for “Tablets”.

**Definition.** Levonorgestrel tablets contain Levonorgestrel. They contain not less than 90.0% and not more than 110.0% of the amount of levonorgestrel (C<sub>21</sub>H<sub>28</sub>O<sub>2</sub>) stated on the label.

### Identity tests

- Either tests A and B or tests A and C may be applied
- A. To a quantity of the powdered tablets containing 37.5 mg of Levonorgestrel, add 5 quantities of dichloromethane R, each of 40 ml. After each addition, stir thoroughly and filter through a sintered-glass filter (G4). Wash the residue and the filter with dichloromethane R, combine the filtrates, evaporate to dryness on a water-bath with the aid of a stream of air and allow to cool. Dissolve the residue in 5 ml of dichloromethane R and measure the optical rotation. The optical rotation of the resulting solution is not less than -0.18°.
- B. Carry out test B.1 or, where UV detection is not available, test B.2.
  - B.1 Carry out the test as described under 1.14.1 Thin-layer chromatography, using silica gel R6 as the coating substance and a mixture of 7 volumes of cyclohexane R and 3 volumes of acetone R as the mobile phase. Apply separately to the plate 10 µl of each of the following two solutions in acetonitrile R. For solution (A) shake a quantity of the powdered tablets containing 1.5 mg of Levonorgestrel with 5 ml, filter, and use the clear filtrate. For solution (B) use 0.30 mg of levonorgestrel RS per ml. After removing the plate from the chromatographic chamber, allow it to dry exhaustively in air or in a current of cool air. Examine the chromatogram in ultraviolet light at 254 nm.

The principal spot obtained with solution A corresponds in position, appearance and intensity to that obtained with solution B.

- B.2 Carry out the test as described under 1.14.1 Thin-layer chromatography, using the conditions described under test B.1 but using silica gel R5 as the coating substance. Spray with a mixture of equal volumes of sulfuric acid TS and ethanol (~750 g/l) TS. Heat the plate for a few minutes at 105°C. Examine the chromatogram in daylight.

The principal spot obtained with solution A corresponds in position, appearance and intensity to that obtained with solution B.

- C. See the method described below under the test for Dextronorgestrel. The retention time of the principal peak in the chromatogram obtained with solution (2) is similar to that in the chromatogram obtained with the solution (3).

### **Dissolution**

Carry out the test as described under 5.5 Dissolution test for solid oral dosage forms, using as the dissolution medium, 500 ml of 0.1% solution of sodium dodecyl sulfate R in hydrochloride solution (0.1 mol/l) VS, and rotating the paddle at 75 revolutions per minute. At 30 minutes withdraw a sample of 10 ml of the medium through an in-line filter and use the filtrate. Prepare standard solution as follows: add a suitable volume of ethanol (~750 g/l) TS to dissolve a suitable amount of levonorgestrel RS, then add a suitable volume of the dissolution medium to obtain a concentration of 6 µg per ml.

Carry out the test as described under 1.14.4 High-performance liquid chromatography, using the chromatographic conditions as described under Assay.

For each of the six tablets, calculate the total amount of levonorgestrel (C<sub>21</sub>H<sub>28</sub>O<sub>2</sub>), in the medium. The amount of levonorgestrel in solution for each tablet is not less than 80% of the amount declared on the label. If the amount obtained for one of the six tablets is less than 80%, repeat the test using a further six tablets; the average amount for all 12 tablets tested is not less than 75% and no tablet contains less than 60%.

*[Note from Secretariat: possible alternative dissolution method for the 30 µg tablets, which will not use sodium dodecyl sulfate is under investigation.]*

### **Dextronorgestrel**

Carry out the test as described under 1.14.4 High-performance liquid chromatography, using a stainless steel column (15 cm × 4.6 mm) packed with particles of silica gel, the surface of which has been modified with chemically bonded octadecylsilyl groups (5 µm)<sup>1</sup>. As the mobile phase, use a solution prepared as follows: dissolve 5.0 g of gamma-cyclodextrin R in 500 ml of water R and dilute to 1000.0 ml with methanol R.

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<sup>1</sup> Hypersil ODS is suitable.

Prepare the following solutions in a dissolution solvent prepared by mixing 80 volumes of methanol R and 20 volumes of water R. For solution (1) transfer a quantity of powdered tablets containing about 3.0 mg of Levonorgestrel to a 25-ml volumetric flask. Add about 15 ml of the dissolution solvent, heat in a water-bath at 60°C for 10 minutes, shaking occasionally. Allow to equilibrate to room temperature, dilute to volume with the dissolution solvent and mix. Filter through a 0.45-µm filter. For solution (2), dilute a suitable volume of solution (1) to obtain a concentration of 6 µg of Levonorgestrel per ml. For solution (3) use 6 µg of levonorgestrel RS per ml. For solution (4), use 12 µg of norgestrel RS per ml. For solution (5), use 0.12 µg of Levonorgestrel RS per ml.

Operate with a flow rate of 1.5 ml per minute. As a detector, use an ultraviolet spectrophotometer set at a wavelength of 242 nm.

Inject 20 µl of solution (3). In the chromatogram obtained with solution (3), the test is not valid unless the resolution factor between the peaks due to levonorgestrel and dextronorgestrel is at least 1.5.

Inject separately 20 µl, each of solutions (1), (2), (3), (4) and (5).

In the chromatogram obtained with solution (1) the area of the peak due to dextronorgestrel, is not greater than the area of the principal peak in the chromatogram obtained with solution (5) (0.1%).

#### **Related substances**

Carry out the test as described under 1.14.4 High-performance liquid chromatography, using a stainless steel column (25 cm × 4.6 mm) packed with particles of silica gel, the surface of which has been modified with chemically bonded octadecylsilyl groups (5 µm)<sup>2</sup>. As the mobile phase, use a solution prepared as follows: mix 15 volumes of methanol R, 35 volumes of acetonitrile R and 50 volumes of water R.

Prepare the following solutions in a dissolution solvent prepared by mixing equal volumes of methanol R and water R. For solution (1), transfer a quantity of powdered tablets containing about 0.18 mg of Levonorgestrel, accurately weighed, in 5 ml. Sonicate for 30 minutes, stir vigorously for 15 minutes, centrifuge and use the supernatant liquid. For solution (2), dilute a suitable volume of solution (1) to obtain a concentration of 0.36 µg of Levonorgestrel per ml. For solution (3) use 4 µg of ethinylestradiol RS and 4 µg of levonorgestrel RS per ml.

Operate with a flow rate of 1.2 ml per minute. As a detector use an ultraviolet spectrophotometer set at a wavelength of 220 nm.

Maintain the column temperature at 30°C.

Inject 100 µl of solution (3). Record the chromatogram for twice the retention time of

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<sup>2</sup> Spherisorb ODS 2 is suitable.

levonorgestrel (retention time about 26 minutes ). The test is not valid unless, in the chromatogram obtained with solution (3), the resolution factor between the peaks due to ethinylestradiol and levonorgestrel is at least 12.

Inject separately 100 µl of each of solutions (1) and (2). Record the chromatogram for twice the retention time of levonorgestrel.

In the chromatogram obtained with solution (1) the area of any peak, other than the principal 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 all peaks, other than the principal peak, is not greater than twice the area of the principal peak in the chromatogram obtained with solution (2) (2.0%).

### **Assay**

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

### **Uniformity of content**

The tablets comply with the test for 5.1 Uniformity of content for single-dose preparations, using the following method of analysis.

Carry out the test as described under 1.14.4 High-performance liquid chromatography, using a stainless steel column (15 cm × 4.6 mm) packed with particles of silica gel, the surface of which has been modified with chemically bonded octadecylsilyl groups (5 µm).<sup>2</sup>

As the mobile phase, use a solution prepared by mixing equal volumes of acetonitrile R and water R.

Prepare the following solutions. For solution (1), transfer one powdered tablet to a stoppered test-tubes, add 5.0 ml of the mobile phase, sonicate for 45 minutes, shake for 15 minutes, and centrifuge. Dilute a suitable volume to produce a solution containing 6 µg of Levonorgestrel per ml. For solution (2), accurately weigh 12 mg of levonorgestrel RS, dissolve in sufficient mobile phase to produce 100.0 ml, and mix. Dilute 5.0 ml of this solution to 100.0 ml with the same solvent.

Operate with a flow rate of 1.3 ml per minute. As a detector, use an ultraviolet spectrophotometer set at a wavelength of 220 nm.

Inject 25 µl, each solution (1) and (2). The retention time of levonorgestrel is about 7.9 minutes. The test is not valid unless the column efficiency, determined for the peak due to levonorgestrel using solution (2) is at least 5000. The symmetry factor of the peak due to levonorgestrel is not more than 1.6.

Measure the areas of the peak responses obtained in the chromatograms from solutions (1) and (2) , and calculate the content of levonorgestrel (C<sub>21</sub>H<sub>28</sub>O<sub>2</sub>) in each tablet.

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