



## **DRAFT MONOGRAPH FOR *THE INTERNATIONAL PHARMACOPOEIA***

### **EMTRICITABINE CAPSULES**

**(September 2010)**

***DRAFT FOR COMMENT***

This document was provided by a quality control expert and was discussed during a video-/teleconference on specifications for medicines held on 25 August 2010. Should you have any comments thereon, 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.

**In order to speed up the process for receiving draft monographs and for sending comments, please let us have your e-mail address (to [bonnyw@who.int](mailto:bonnyw@who.int)) and we will add it to our electronic mailing list.**

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**SCHEDULE FOR THE ADOPTION PROCESS OF DOCUMENT QAS/10.390**  
*International Pharmacopoeia monograph on Emtricitabine capsules*

	<b>Date</b>
Preparation of first draft by laboratory	August 2010
Comments discussed during video-/teleconference on specifications for medicines	25 August 2010
Draft monograph mailed out for comment	September 2010
Collation of comments	October 2010
Presentation to WHO Expert Committee on Specifications for Pharmaceutical Preparations	18-22 October 2010
Further action as necessary	

## EMTRICITABINUM CAPSULAE EMTRICITABINE CAPSULES

**Category.** Antiretroviral (Nucleoside Reverse Transcriptase Inhibitor).

**Storage.** Emtricitabine capsules should be kept in a tightly closed container.

**Additional information.** Strength in the current WHO Model list of essential medicines: 200 mg Emtricitabine.

### Requirements

Comply with the monograph for “Capsules”.

**Definition.** Emtricitabine capsules contain Emtricitabine. They contain not less than 90.0% and not more than 110.0% of the amount of emtricitabine ( $C_8H_{10}FN_3O_3S$ ) stated on the label.

### Identity tests

- Either tests A and B or test C may be applied.

A. Carry out test A.1 or, when UV detection is not available, test A.2.

A.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 90 volumes of dichloromethane R, 10 volumes of methanol R and 3 volumes of glacial acetic acid R as the mobile phase. Apply separately to the plate 5  $\mu$ l of each of the following two solutions in methanol R. For solution (A) disperse a quantity of the contents of the capsules to obtain a concentration of 5 mg of Emtricitabine per ml, filter and use the filtrate. For solution (B) use 5 mg of emtricitabine RS per ml. After removing the plate from the chromatographic chamber, allow it to dry exhaustively in air or in a current of air. Examine the chromatogram in ultraviolet light (254 nm).

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

A.2 Carry out the test as described under 1.14.1 Thin-layer chromatography, using the conditions described above under test A.1 but using silica gel R5 as the coating substance. Stain the plate with iodine vapor and examine in daylight.

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

- B. Disperse the quantity of contents of the capsules containing about 50 mg of Emtricitabine with 40 ml of methanol R, dilute to 50 ml and filter. Dilute 1 ml of the filtrate to 50 ml with methanol R. The absorption spectrum (1.6) of the resulting solution, when observed between 220 and 350 nm, exhibits two maxima at about 242 nm and 284 nm.
- C. See the test described under Assay, Method A. The retention time of the principal peak in the chromatogram obtained with the test solution is similar to that in the chromatogram obtained with the reference solution.

**Dissolution.** Carry out the test as described under 5.5 Dissolution test for solid oral dosage forms, using as the dissolution medium, 900 ml of hydrochloric acid (~4 g/l) TS and rotating the paddle at 50 revolutions per minute. At 45 minutes withdraw a sample of 10 ml of the medium through an in-line filter. Allow the filtered sample to cool to room temperature. Measure the absorbance (1.6) of a 1-cm layer of the resulting solution, suitably diluted if necessary, at the maximum at about 280 nm. Determine the content of emtricitabine ( $C_8H_{10}FN_3O_3S$ ) in the medium from the absorbance obtained from a solution of known concentration of emtricitabine RS.

For each of the six capsules tested, calculate the total amount of emtricitabine ( $C_8H_{10}FN_3O_3S$ ) in the medium from the results obtained and from the declared content of  $C_8H_{10}FN_3O_3S$  in emtricitabine RS. The amount in solution for each capsule is not less than 80% of the amount declared on the label. If the amount of emtricitabine obtained for one of the six capsules is less than 80%, repeat the test using a further six capsules; the average amount of emtricitabine for all 12 capsules tested is not less than 75% and no capsule contains less than 60%.

### Related substances

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

Prepare the following solutions using a mixture of 20 volumes of acetonitrile R and 80 volumes of water R as a diluent. For solution (1) weigh and mix the contents of 20

capsules and disperse a quantity containing about 50 mg of Emtricitabine in 80 ml of the diluent, dilute to 100 ml with the diluent, filter and use the filtrate. For solution (2) dilute a suitable volume of solution (1) with the diluent to obtain a concentration of 0.50 µg of Emtricitabine per ml.

For the system suitability test: prepare solution (3) using 5 ml of solution (1) and 2 ml of phosphoric acid (~105 g/l) TS, heat carefully in a boiling water-bath for 15 minutes.

Operate with a flow rate of 1.0 ml per minute. As a detector use an ultraviolet spectrophotometer set at a wavelength of 280 nm.

Maintain the column temperature at 35°C.

Inject 20 µl of solution (3). The test is not valid unless the resolution between the peak due to emtricitabine (retention time about 9 minutes) and the peak with a relative retention of about 1.3 is not less than 6.

Inject separately 20 µl each of solutions (1) and (2).

In the chromatogram obtained with solution (1) the area of any peak eluting before the principal peak is not greater than 5 times the area of the principal peak in the chromatogram obtained with solution (2) (0.5%); the area of not more than two such peaks is greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.1%); the area of any peak eluting after the principal peak is not greater than 7 times the area of the principal peak in the chromatogram obtained with solution (2) (0.7%); the area of not more than two such peaks is greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.1%). The sum of the areas of all peaks, other than the principal peak is not greater than 10 times the area of the principal peak in the chromatogram obtained with solution (2) (1%). Disregard any peak with an area less than 0.5 times the area of the principal peak in the chromatogram obtained with solution (2) (0.05%).

### Assay

- Either test A or test B may be applied.
  - A. Carry out the test as described under 1.14.4 High-performance liquid chromatography, using a stainless steel column (25 cm x 4.6 mm) packed with base-deactivated particles of silica gel the surface of which has been modified with chemically bonded octadecylsilyl groups (5 µm)<sup>1</sup>.

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<sup>1</sup> Hypersil BDS C18 has been found suitable.

The mobile phases for gradient elution consist of a mixture of Mobile phase A and Mobile phase B, using the following conditions:

Mobile phase A: 5 volumes of potassium dihydrogen phosphate (27.2 g/l) TS and 95 volumes of water R.

Mobile phase B: 70 volumes of acetonitrile R, 5 volumes of potassium dihydrogen phosphate (27.2 g/l) TS and 25 volumes of water R.

<b>Time (min)</b>	<b>Mobile phase A (% v/v)</b>	<b>Mobile phase B (% v/v)</b>	<b>Comments</b>
0-9	93	7	Isocratic
9-15	93 to 0	7 to 100	Linear gradient
15-19	0	100	Isocratic
19-19.1	0 to 93	100 to 7	Return to initial composition
19.1-30	93	7	Re-equilibration

Operate with a flow rate of 1.0 ml per minute. As a detector use an ultraviolet spectrophotometer set at a wavelength of 280 nm.

Maintain the column temperature at 35 °C.

Prepare the following solutions using a mixture of 20 volumes of acetonitrile R and 80 volumes of water R as a diluent. For solution (1): weigh and mix the contents of 20 capsules and disperse a quantity containing about 50 mg of Emtricitabine in 80 ml of the diluent, dilute to 100 ml with the diluent, filter and use the filtrate.

For solution (2) use 0.5 mg of emtricitabine RS per ml of the diluent.

For the system suitability test: prepare solution (3) using 5 ml of solution (1) and 2 ml of phosphoric acid (~105 g/l) TS, heat carefully in a boiling water-bath for 15 minutes.

Inject 20 µl of solution (3). The test is not valid unless the resolution between the peak due to emtricitabine (retention time about 9 minutes) and the peak with a relative retention of about 1.3 is not less than 6.

Inject separately 20 µl each of solutions (1) and (2).

Measure the areas of the peak responses obtained in the chromatograms from solutions (1) and (2), and calculate the content of emtricitabine (C<sub>8</sub>H<sub>10</sub>FN<sub>3</sub>O<sub>3</sub>S).

- B. Weigh and mix the contents of 20 capsules and disperse a quantity containing about 50 mg of Emtricitabine in 40 ml of methanol R, dilute to 50 ml with methanol R and filter. Dilute 1 ml of the filtrate to 50 ml with methanol R.

Measure the absorbance (1.6) of the resulting solution in a 1-cm layer at the maximum at about 284 nm.

Calculate the content of emtricitabine ( $C_8H_{10}FN_3O_3S$ ), using the absorptivity value of 33.2 ( $A_{1cm}^{1\%} = 332$ ).

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**New reagent to be added to Ph.Int.**

**Hydrochloric acid (~4 g/l) TS.**

Dilute 10 ml of hydrochloric acid (~420 g/l) TS with sufficient water to produce 1000 ml (approximately 0.1 mol/l).

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Draft for comment