



EFAVIRENZ 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 with a copy to Ms C. Mendy mendyc@who.int by 29 October 2010.

If you do not already receive our documents electronically, please let us have your e-mail address (to bonnyw@who.int) which we will add to our electronic mailing list.

© World Health Organization 2010

All rights reserved.

This draft is intended for a restricted audience only, i.e. the individuals and organizations having received this draft. The draft may not be reviewed, abstracted, quoted, reproduced, transmitted, distributed, translated or adapted, in part or in whole, in any form or by any means outside these individuals and organizations (including the organizations' concerned staff and member organizations) without the permission of WHO. The draft should not be displayed on any web site.

Please send any request for permission to:

Dr Sabine Kopp, Quality Assurance Programme, Medicines Quality Assurance Programme, Quality & Safety: Medicines (QSM), Department of Essential Medicines and Pharmaceutical Policies (EMP), World Health Organization, CH-1211 Geneva 27, Switzerland. Fax: (41-22) 791 4730; e-mail: kopps@who.int.

The designations employed and the presentation of the material in this draft do not imply the expression of any opinion whatsoever on the part of the World Health Organization concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted lines on maps represent approximate border lines for which there may not yet be full agreement.

The mention of specific companies or of certain manufacturers' products does not imply that they are endorsed or recommended by the World Health Organization in preference to others of a similar nature that are not mentioned. Errors and omissions excepted, the names of proprietary products are distinguished by initial capital letters.

All reasonable precautions have been taken by the World Health Organization to verify the information contained in this draft. However, the printed material is being distributed without warranty of any kind, either expressed or implied. The responsibility for the interpretation and use of the material lies with the reader. In no event shall the World Health Organization be liable for damages arising from its use.

This draft does not necessarily represent the decisions or the stated policy of the World Health Organization.

SCHEDULE FOR THE ADOPTION PROCESS OF DOCUMENT QAS/10.355
International Pharmacopoeia monograph on Efavirenz tablets

	Date
Preparation of first draft by laboratory	February 2010
Discussion of the draft proposal in the consultation on specifications for medicines and quality control laboratory issues	10-12 May 2010
Mailing of revised draft monograph for comments	July 2010
Collation of comments received	August 2010
Revised draft discussed during tele-/videoconference on specifications for medicines	25 August 2010
Revised draft mailed out for comments	October 2010
Presentation to WHO Expert Committee on Specifications for Pharmaceutical Preparations	18-22 October 2010
Any further action as required	...

Draft proposal for *The International Pharmacopoeia* (September 2010)

EFAVIRENZ TABLETS

Category. Antiretroviral (Non-nucleoside Reverse Transcriptase Inhibitor).

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

Additional information. Strengths in the current WHO Model list of essential medicines: 600 mg. Strengths in the current WHO Model list of essential medicines for children: 600 mg.

Requirements

Comply with the monograph for "Tablets".

Definition. Efavirenz tablets contain Efavirenz. They contain not less than 90.0% and not more than 110.0% of the amount of Efavirenz ($C_{14}H_9ClF_3NO_2$) stated on the label.

Identity tests

- Either test A alone or tests B and D or tests C and D may be applied.
- A. To a quantity of the powdered tablets containing 25 mg of Efavirenz, add 10 ml of methanol R, shake to dissolve and filter. Evaporate the filtrate to dryness. Carry out the examination as described under 1.7 Spectrophotometry in the infrared region. The infrared absorption spectrum is concordant with the spectrum obtained from efavirenz RS or with the *reference spectrum* of efavirenz.

If the spectra thus obtained are not concordant, repeat the test using the test residue and the residue obtained by dissolving efavirenz RS in a small amount of methanol R and evaporating to dryness. The infrared absorption spectrum is concordant with the spectrum obtained from efavirenz RS.
- 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 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 μ l of each of the

following two solutions in methanol R. For solution (A) shake a quantity of the powdered tablets containing 5 mg of Efavirenz with 5 ml, filter and use the clear filtrate. For solution (B) use 1 mg of efavirenz 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 (254 nm).

The principal spot obtained with solution A corresponds in position, appearance and intensity with 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 A.1 but using silica gel R5 as the coating substance. Spray the plate with basic potassium permanganate (~1 g/l) TS. Examine the chromatogram in daylight.

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

- C. See the test described under Assay method A. The retention time of the principal peak in the chromatogram obtained with solution (1) is similar to that in the chromatogram obtained with solution (2).
- D. The absorption spectrum of the final solution prepared for Assay method B, when observed between 210 nm and 300 nm, exhibits one maximum at about 247 nm.

Related substances. Prepare fresh solutions and perform the test without delay.

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 in the dissolution solvent, a mixture of equal volumes of acetonitrile R and water R.

For solution (1) transfer a quantity of the powdered tablets containing about 25 mg of Efavirenz into about 20 ml of the dissolution solvent, sonicate for 5 minutes, allow to cool to room temperature and dilute to 25.0 ml with the same solvent. Filter a portion of this solution through a 0.45- μ m filter, discarding the first few ml of the filtrate. For solution (2) dilute 1.0 ml of solution (1) to 50.0 ml with the dissolution solvent and dilute 5.0 ml of the resulting solution to 100.0 ml with the same solvent. For solution (3) dissolve about 5 mg of efavirenz RS in 5 ml of a solution prepared as follows: dissolve 1 mg of efavirenz impurity B RS in the dissolution solvent and dilute to 10 ml with the same solvent. Dilute 1 ml of the resulting solution to 25 ml with the dissolution solvent.

Inject separately 35 μ l each of solutions (1), (2) and (3) and of the dissolution solvent in the chromatographic system. Examine the blank chromatogram for any extraneous peaks and disregard the corresponding peaks observed in the chromatogram obtained with solution (1).

In the chromatogram obtained with solution (3), the peak due to impurity B is eluted at a relative retention of about 0.9 with reference to Efavirenz (retention time about 20 minutes). The test is not valid unless the resolution factor between the peaks due to impurity B and Efavirenz is at least 3.

In the chromatogram obtained with solution (1) the area of any peak corresponding to impurity B is not greater than four times the area of the principal peak in the chromatogram obtained with solution (2) (0.4%), the area of any other peak, apart from the principal peak, is not greater than twice the area of the principal peak in the chromatogram obtained with solution (2) (0.2%) and the area of not more than three 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 eight times the area of the principal peak in the chromatogram obtained with solution (2) (0.8%). 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%).

[Note from Secretariat: retention times and resolution factor to be confirmed.]

Assay

- Either method A or method B may be applied.
- A. Carry out the assay as described under 1.14.4 High-performance liquid chromatography using a stainless steel column (15 cm x 4.6 mm), packed with cyanopropyltrimethylsilane monolayer (3.5 μm)¹.

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: 90 volumes of a 0.05% solution of trifluoroacetic acid R and 10 volumes of methanol R.

Mobile phase B: 10 volumes of a 0.05% solution of trifluoroacetic acid R and 90 volumes of methanol R.

Time (min)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comments
0 – 16	60 to 50	40 to 50	Linear gradient
16 – 23	50 to 35	50 to 65	Linear gradient
23 – 28	35 to 30	65 to 70	Linear gradient
28 – 29	30 to 20	70 to 80	Linear gradient
29 – 31	20	80	Isocratic
31 – 32	20 to 60	80 to 40	Return to initial composition
32 – 40	60	40	Re-equilibration

¹ Zorbax® SB-CN has been found suitable.

Prepare the following solutions in the dissolution solvent, a mixture of equal volumes of acetonitrile R and water R

For solution (1) weigh and powder 20 tablets. Transfer a quantity of the powdered tablets containing about 25 mg of Efavirenz, accurately weighed, into about 20 ml of the dissolution solvent, sonicate for 5 minutes, allow to cool to room temperature and dilute to 25.0 ml with the same solvent. Filter a portion of this solution through a 0.45- μ m filter, discarding the first few ml of the filtrate. Dilute 1.0 ml of the resulting solution to 100.0 ml with the dissolution solvent. For solution (2) dissolve 25 mg of efavirenz RS in the dissolution solvent and dilute to 25.0 ml with the same solvent. Dilute 1.0 ml of the resulting solution to 100.0 ml with the dissolution solvent. For solution (3) dissolve about 5 mg of efavirenz RS in 5 ml of a solution prepared as follows: dissolve 1 mg of efavirenz impurity B RS in the dissolution solvent and dilute to 10 ml with the same solvent. Dilute 1 ml of the resulting solution to 25 ml with the dissolution solvent.

Operate with a flow rate of 1.5 ml per minute. As a detector use an ultraviolet spectrophotometer set at a wavelength of about 250 nm.

Maintain the column temperature at 40°C.

Inject separately 35 μ l each of solutions (1), (2) and (3). In the chromatogram obtained with solution (3), the peak due to impurity B is eluted at a relative retention of about 0.9 with reference to efavirenz (retention time about 20 minutes). The assay is not valid unless the resolution factor between the peaks due to impurity B and efavirenz is at least 3.

Measure the areas of the peak responses obtained in the chromatograms from solutions (1) and (2), and calculate the content of efavirenz (C₁₄H₉ClF₃NO₂) in the tablets.

[Note from Secretariat: retention times and resolution factor to be confirmed.]

- B. Weigh and powder 20 tablets. Transfer a quantity of the powdered tablets containing about 25 mg of Efavirenz, accurately weighed, to a 50-ml volumetric flask. Add about 25 ml of methanol R, sonicate for about 5 minutes, allow to cool to room temperature and make up to volume using the same solvent. Filter a portion of this solution through a 0.45- μ m filter, discarding the first few ml of the filtrate. Dilute 1.0 ml of this solution to 50.0 ml with methanol R. Measure the absorbance (1.6) of a 1-cm layer of this solution at the maximum at about 247 nm. Calculate the content of efavirenz (C₁₄H₉ClF₃NO₂) in the tablets using an absorptivity value of 55.0

($A_{1\text{cm}}^{1\%} = 550$).

Impurities. The impurities limited by the requirements of this monograph include those listed in the monograph for Efavirenz.
