Efavirenz tablets (Efavirenzi compressi)

2015-01

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 (EML): 600 mg. Strengths in the current WHO EML 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 Chromatography*, 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 µL 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 Chromatography*, 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 *1.14.1 Chromatography*, 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 µm 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 1 mg of efavirenz RS in 10 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 same solvent.

Inject separately 35 µL 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 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%).

Assay

-Either method A or method B may be applied.

A. Carry out the assay as described under *1.14.1 Chromatography*, High-performance liquid chromatography using a stainless steel column (15 cm x 4.6 mm), packed with particles of silica gel, the surface of which has been modified with chemically-bonded cyanopropyl groups (3.5 µm).

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

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 µm 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 1 mg of efavirenz RS in 10 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 same 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 µL 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 ($C_{14}H_9ClF_3NO_2$) in the tablets using the declared content of $C_{14}H_9ClF_3NO_2$ in efavirenz RS.

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 µm 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 ($C_{14}H_9ClF_3NO_2$) in the tablets using an absorptivity value of 55.0 ($A^{1\%}_{1cm}$ = 550).

Impurities

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