Nevirapine tablets (Nevirapini compressi)

Category. Antiretroviral.

Storage. Nevirapine tablets should be kept in a well-closed container.

Labelling. The designation of the container of nevirapine tablets should state that the active ingredient is the anhydrous form.

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

Requirements

Comply with the monograph for "Tablets".

Definition. Nevirapine tablets contain Nevirapine in the anhydrous form. They contain not less than 90.0% and not more than 110.0% of the amount of nevirapine ($C_{15}H_{14}N_4O$) stated on the label.

Identity tests

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

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

A.1 Carry out the test as described under <u>1.14.1 Chromatography</u>, 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 25 mg of nevirapine with 5 mL, filter and use the clear filtrate. For solution (B) use 5 mg of nevirapine 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.

A.2 Carry out the test as described under <u>1.14.1 Chromatography</u>, <u>Thin-layer chromatography</u>, using the conditions described above under test A.1 but using silica gel R5 as the coating substance. Spray the plate with dilute 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.

B. The absorption spectrum of the final solution prepared for Assay method B, when observed between 220 nm and 350 nm, exhibits a maximum at about 283 nm.

C. To a quantity of the powdered tablets containing 50 mg of nevirapine 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 nevirapine RS or with the reference spectrum of nevirapine.

If the spectra thus obtained are not concordant repeat the test using the test residue and the residue obtained by dissolving nevirapine RS in methanol R and evaporating to dryness. The infrared absorption spectrum is concordant with the spectrum obtained from nevirapine RS.

Related substances

Prepare fresh solutions and perform the tests without delay. Carry out the test as described under <u>1.14.1 Chromatography</u>, Highperformance liquid chromatography, using the conditions given under Assay, method A.

Prepare solution A as follows: dissolve 12 mg of nevirapine RS in 2 mL of acetonitrile R, add 40 mL of the mobile phase and sonicate. Dilute to 50.0 mL with the mobile phase. Prepare the following solutions. For solution (1) mix a quantity of the powdered tablets containing about 24 mg of nevirapine with 4 mL of acetonitrile R, add 80 mL of the mobile phase and sonicate. Dilute to 100.0 mL with the mobile phase and filter. For solution (2) dilute 5.0 mL of solution (1) to 50.0 mL with the mobile phase. Dilute 5.0 mL of this solution to 50.0 mL with the same solvent. For solution (3) dissolve 6 mg of nevirapine impurity B RS in a mixture of 25 mL of acetonitrile R and 55 mL of the mobile phase, sonicate for 15 minutes and dilute to 100.0 mL with the mobile phase. Mix 6.0 mL of this solution with 3 mL of solution A and dilute to 50.0 mL with the mobile phase.

Inject 50 µl of solution (3). The test is not valid unless the resolution between nevirapine and nevirapine impurity B RS is not less

than 5. In the chromatogram obtained with solution (3) the peak due to impurity B is eluted at a relative retention of about 0.7 with reference to nevirapine (retention time about 7.6 minutes).

Inject separately 50 μ l of solution (2). The test is not valid unless the column efficiency determined for nevirapine using solution (2) is not less than 10 000. The peak symmetry factor of nevirapine should be between 0.8 and 1.2.

Inject separately 50 μ l each of solution (1) and of the mobile phase and record the chromatograms for six times the retention time of nevirapine. 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 (1) the area of any individual peak corresponding to impurity B, when multiplied by a correction factor of 0.77, is not greater than 0.2 times the area of the principal peak in the chromatogram obtained with solution (2) (0.2%). The area of any other impurity peak is not greater than 0.2 times the area of the principal peak in the chromatogram obtained with solution (2) (0.2%) and the area of not more than two such peaks is greater than 0.1 times 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 0.6 times the area of the principal peak in the chromatogram obtained with solution (2) (0.6%). Disregard any peak with an area less than 0.05 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 <u>1.14.1 Chromatography</u>, 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 hexadecylamidylsilyl groups (5 μ m). As the mobile phase use a filtered and degassed mixture of 20 volumes of acetonitrile R and 80 volumes of a 3.6 g/l solution of ammonium dihydrogen phosphate R previously adjusted to pH 5.0 using ammonia (~260 g/l) TS.

Operate with a flow rate of 1.0 mL per minute. As a detector use an ultraviolet spectrophotometer set at a wavelength of about 220 nm.

Maintain the column temperature at 35 °C.

Prepare solution A as follows: dissolve 12 mg of nevirapine RS in 2 mL of acetonitrile R, add 40 mL of the mobile phase and sonicate. Dilute to 50.0 mL with the mobile phase.

Prepare the following solutions. For solution (1) weigh and powder 20 tablets and mix a quantity of the powder containing about 24 mg of nevirapine, accurately weighed, with 4 mL of acetonitrile R, add 80 mL of the mobile phase and sonicate. Dilute to 100.0 mL with the mobile phase and filter. Dilute 3.0 mL of this solution to 50.0 mL with the mobile phase. For solution (2) dilute 3.0 mL of solution A to 50.0 mL with the mobile phase. For solution (3) dissolve 6 mg of nevirapine impurity B RS in a mixture of 25 mL of acetonitrile R and 55 mL of the mobile phase, sonicate for 15 minutes and dilute to 100.0 mL with the mobile phase. Mix 6.0 mL of this solution with 3 mL of solution A and dilute to 50.0 mL with the mobile phase.

Inject 50 µl of solution (3). The test is not valid unless the resolution between nevirapine and nevirapine impurity B RS is not less than 5. In the chromatogram obtained with solution (3), the peak due to impurity B is eluted at a relative retention of about 0.7 with reference to nevirapine (retention time about 7.6 minutes).

Inject separately 50 µl of solution (2). The test is not valid unless the column efficiency determined for nevirapine using solution (2) is not less than 10 000. The peak symmetry factor of nevirapine should be between 0.8 and 1.2.

Inject separately 50 μ l each of solution (1) and of the mobile phase and record the chromatograms for six times the retention time of nevirapine.

Measure the areas of the peak responses obtained in the chromatograms from solutions (1) and (2) and calculate the content of nevirapine ($C_{15}H_{14}N_4O$) in the tablets.

B. Weigh and powder 20 tablets. Transfer a quantity of the powder containing about 20 mg of nevirapine, accurately weighed, to a 100 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 5.0 mL of the filtrate to 50.0 mL with methanol R. Measure the absorbance of this solution in a 1 cm layer at the maximum at about 283 nm against a solvent cell containing methanol R.

Calculate the content of nevirapine ($C_{15}H_{14}N_4O$) in the tablets using an absorptivity value of 26.7 ($H_{10}m = 267$).

Impurities

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