Nevirapine oral suspension (Nevirapini suspensio peroralum)

Category. Antiretroviral (Non-Nucleoside Reverse Transcriptase inhibitor).

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

Labelling. The designation of the container of nevirapine oral suspension should state that the active ingredient is the hemihydrate form and the quantity should be indicated in terms of the equivalent amount of nevirapine.

Additional information. Strength in the current WHO Model list of essential medicines: 50 mg per 5 mL (10 mg per mL). Strength in the current WHO Model list of essential medicines for children: 50 mg per 5 mL (10 mg per mL).

Requirements

Complies with the monograph for "Liquids for oral use".

Definition. Nevirapine oral suspension is a suspension of Nevirapine, as the hemihydrate, in a suitable vehicle; it may be flavoured. It contains 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

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 *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 volume of the oral suspension containing the equivalent of 50 mg of nevirapine with 50 mL. 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).
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> The principal spot obtained with solution A corresponds in position, appearance and intensity with that obtained with solution B.
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> A.2 Carry out the test as described under *1.14.1 Chromatography*, Thin-layer chromatography, 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.
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> The principal spot obtained with solution A corresponds in position, appearance and intensity with that obtained with solution B.

B. See the test described under Assay. The retention time of the principal peak in the chromatogram obtained with solution (1) corresponds to that obtained with solution (2).

Related substances

Prepare fresh solutions and perform the tests without delay. Carry out the test as described under *1.14.1 Chromatography*, High-performance liquid chromatography, using the conditions given under Assay.

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) shake the bottle of the oral suspension vigorously for 2 minutes and mix a weighed quantity of the oral suspension containing the equivalent of 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. 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 3.0 mL of solution A and dilute to 50.0 mL with the mobile phase. For solution (4) dissolve a suitable amount of each of the excipients (other than any parahydroxybenzoates) stated on the label in 10 mL of a suitable solvent and dilute to 100 mL with the mobile phase.

Inject 50 µl of solution (3) and (4). The test is not valid unless the resolution between nevirapine and nevirapine impurity B RS is not less than 5. The test is also not valid if any of the peaks in the chromatogram obtained with solution (4) correspond to any of the peaks in the chromatogram obtained with solution (3) or if interference by excipients has been demonstrated by any other means.

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 10000. The peak symmetry factor of nevirapine should be between 0.8 and 1.2.

Inject separately 50 µl each of solution (1) and of the mobile phase and record the chromatograms for four times the retention time of nevirapine. For preparations containing parahydroxybenzoates record the chromatograms for nine times the retention time of nevirapine in the chromatogram obtained with solution (2) in order to wash these excipients from the column. 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 the same retention time as that of any of the peaks in the chromatogram obtained with solution (4), any peak with a relative retention with reference to nevirapine greater than 3.0 (corresponding to parahydroxybenzoates) and 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

Prepare fresh solutions and perform the tests without delay. 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 hexadecylamidylsilyl groups (5 µm). 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) shake the bottle of the oral suspension vigorously for 2 minutes and mix an accurately weighed quantity of the oral suspension containing the equivalent of 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. 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 3.0 mL of solution A and dilute to 50.0 mL with the mobile phase. For solution (4) dissolve a suitable amount of each of the excipients (other than any parahydroxybenzoates) stated on the label in 10 mL of a suitable solvent and dilute to 100 mL with the mobile phase.

Inject 50 µl of solution (3) and (4). The test is not valid unless the resolution between nevirapine and nevirapine impurity B RS is not less than 5. The test is also not valid if any of the peaks in the chromatogram obtained with solution (4) correspond to the peak due to nevirapine in the chromatogram obtained with solution (3).

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 µl each of solution (1) and of the mobile phase and record the chromatograms for four times the retention time of nevirapine.

Measure the areas of the peak responses obtained in the chromatograms from solutions (1) and (2). Determine the weight per mL (1.3.1) of the oral suspension and calculate the content of nevirapine ($C_{15}H_{14}N_4O$), weight in volume, of the oral suspension.

Impurities

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