Lopinavir and ritonavir tablets (Lopinaviri et ritonaviri compressi)

Category. Antiretroviral (Protease Inhibitor).

Storage. Lopinavir and ritonavir tabletsshould be kept in a tightly closed container.

Additional information. Strengths in the current WHO Model list of essential medicines:

100 mg Lopinavir and 25 mg Ritonavir

200 mg Lopinavir and 50 mg Ritonavir.

Strengths in the current WHO Model list of essential medicines for children:

100 mg Lopinavir and 25 mg Ritonavir

200 mg Lopinavir and 50 mg Ritonavir.

Requirements

Comply with the monograph for "Tablets".

Definition. Lopinavir and ritonavir tablets contain Lopinavir and Ritonavir. They contain not less than 90.0% and not more than 110.0% of the amounts of lopinavir ($C_{37}H_{48}N_4O_5$) and ritonavir ($C_{37}H_{48}N_6O_5S_2$) stated on the label.

Manufacture. Lopinavir and ritonavir tablets are manufactured using Lopinavir and Ritonavir in the amorphous form in order to ensure suitable solubility properties.

Identity tests

• Either test A or test B 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 *1.14.1 Chromatography*, Thin-layer chromatography, using silica gel R6 as the coating substance and a mixture of 70 volumes of toluene R, 20 volumes of ethyl acetate R, 5 volumes of methanol R and 5 volumes of glacial acetic acid R as the mobile phase. Apply separately to the plate 10 µl of each of the following solutions in methanol R. (A) Shake a quantity of the powdered tablets containing about 40 mg of lopinavir with 5 mL, filter and use the clear filtrate. For solution (B) use 8.0 mg of lopinavir RS per mL. For solution (C) use 2.0 mg of ritonavir RS per mL. If necessary, adapt the concentration of solution C according to the ratio of Lopinavir and Ritonavir in the tablets. 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).

One of the two principal spots obtained with solution A corresponds in position, appearance and intensity with that obtained with solution B and the other one corresponds with that obtained with solution C.

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. Stain the plate with iodine vapour for 1 hour and examine in daylight.

One of the two principal spots obtained with solution A corresponds in position, appearance and intensity with that obtained with solution B and the other one corresponds with that obtained with solution C.

B. See the test described under Assay. The retention times of the principal peaks in the chromatogram obtained with the test solution are similar to those 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 a solution prepared by dissolving 15.7 g of decaethylene glycol monodocecyl ether R in 1000 mL of a 0.85% v/v solution of hydrochloric acid (~0.1 mol/l) VS. Rotate the paddle at 75 revolutions per minute. At 120 minutes withdraw a sample of 10 mL of the medium through an in-line filter.

Carry out the test as described under *1.14.1 Chromatography*, High-performance liquid chromatography, using the conditions given under Assay.

Prepare the following solutions. For solution (1) use the filtrate as described above and dilute, if necessary, with the dissolution medium. For solution (2) use 2.2 mg of lopinavir RS and 0.55 mg of ritonavir RS per mL of methanol R. If necessary, adapt the

concentration of solution (2) according to the ratio of Lopinavir and Ritonavir in the tablets. Dilute 5 mL of this solution to 50 mL with the dissolution medium.

Inject alternatively 20 µl of 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 lopinavir ($C_{37}H_{48}N_4O_5$) and ritonavir ($C_{37}H_{48}N_6O_5S_2$).

The amounts in solution for each tablet are not less than 80% of the amounts of lopinavir ($C_{37}H_{48}N_4O_5$) and ritonavir ($C_{37}H_{48}N_6O_5S_2$) stated on the label. If the amount of lopinavir and/or ritonavir obtained for one of the six tablets is less than 80%, repeat the test using a further six tablets; the average amount of lopinavir and ritonavir for all 12 tablets tested is not less than 75% and the amount obtained for no tablet is less than 60%.

Assay

Carry out the test as described under *1.14.1 Chromatography*, 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) and a mixture of 80 volumes of methanol R and 20 volumes of a phosphoric acid solution at pH 3.5 as the mobile phase.

Prepare the phosphoric acid solution pH 3.5 by adding phosphoric acid (~105 g/l) TS to 1000 mL of water R.

Prepare the following solutions using methanol R as diluent. For solution (1) weigh and powder 20 tablets, transfer a quantity of the powder containing about 100 mg of Lopinavir, accurately weighed, in a 100-mL volumetric flask. Add about 80 mL of methanol R, sonicate, 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. For solution (2) use 1 mg of lopinavir RS and 0.25 mg of ritonavir RS per mL. If necessary, adapt the concentration of solution (2) according to the ratio of Lopinavir and Ritonavir in the tablets.

Operate with a flow rate of 1.0 mL per minute. As a detector use an ultraviolet spectrophotometer set at a wavelength of 240 nm.

Maintain the column temperature at 30 °C.

Inject alternatively 20 µl of each of solutions (1) and (2) and record the chromatogram for 10 minutes. The test is not valid unless the resolution factor between the peaks due to lopivanir (retention time about 5 minutes) and to ritonavir (retention time about 6 minutes) is at least 2.0.

Measure the areas of the peak responses obtained in the chromatograms from solutions (1) and (2), and calculate the content of lopinavir ($C_{37}H_{48}N_4O_5$) and ritonavir ($C_{37}H_{48}N_6O_5S_2$) in the tablets.