Ivermectin tablets (Ivermectini compressi)

Category. Antiparasitic.

Storage. Ivermectin tablets should be kept in well-closed containers, protected from light, and stored at a temperature below 30 °C.

Additional information. Strength in the current WHO Model List of Essential Medicines (EML): 3 mg per tablet. Strength in the current WHO EML for children: 3 mg per tablet. Additional strengths available: 6 mg per tablet. This monograph is applicable for tablets containing 3 mg or 6 mg lvermectin per tablet.

Requirements

Complies with the monograph on Tablets.

Definition. Ivermectin tablets contain not less than 90.0% and not more than 110.0% of the amount of Ivermectin stated on the label, calculated as the sum of the Ivermectin components H_2B_{1a} ($C_{48}H_{74}O_{14}$) and H_2B_{1b} ($C_{47}H_{72}O_{14}$).

Identity tests.

-Either test A or test B may be applied.

A. Carry out the test as described under <u>1.14.1 Chromatography</u>, <u>High-performance liquid chromatography</u> using the conditions given under "Assay", Method A. The retention time of the principal peaks in the chromatogram obtained with solution (1) corresponds to the retention times of the peaks due to ivermectin in the chromatogram obtained with solution (2).

B. Carry out the test as described under <u>1.14.1 Chromatography</u>, Thin-layer chromatography using silica gel R4 or R2 as the coating substance and a mixture of 90 volumes of dichloromethane R, 8 volumes of methanol R and 0.8 volume of ammonia (~260 g/L) TS as the mobile phase. Apply separately to the plate 30 µL of each of the following two solutions in methanol R. For solution (A), transfer a quantity of the powdered tablets used to prepare solution (1) as described under "Assay", method A, containing nominally 25 mg of Ivermectin, into a 25 mL volumetric flask, add 2.5 mL of water R and sonicate for 10 minutes. Add about 15 mL of methanol R, mix, and sonicate for 5 minutes. Allow the solution to cool to room temperature. Dilute with methanol R to volume, mix and filter. For solution (B), dissolve 25 mg of ivermectin RS in methanol R and dilute to 25.0 mL with the same solvent.

Develop the plate. After removing the plate from the chromatographic chamber, allow it to dry in air or in a current of air. Examine the chromatogram under ultraviolet light (254 nm).

The partly separated spots in the chromatogram obtained with solution (A) correspond in position, appearance, and intensity with the two partly separated principal spots due to ivermectin in the chromatogram obtained with solution (B).

Dissolution. Carry out the test as described under <u>5.5 Dissolution test for solid oral dosage forms</u> using as the dissolution medium 900 mL of a solution of 0.5% sodium dodecyl sulfate R in phosphate buffer, pH 7.0 (0.01 mol/L) TS and rotating the paddle at 50 revolutions per minute. At 45 minutes, withdraw a sample of 10 mL of the medium through an in-line filter and use the filtrate as solution (1). For solution (2), dissolve 33.0 mg of ivermectin RS in dissolution medium and dilute to 250.0 mL with the same solvent. For 3 mg tablets, dilute 5.0 mL of solution (2) to 200.0 mL with dissolution medium. Use this solution as solution (3). For 6 mg tablets, dilute 5.0 ml of solution (2) to 100.0 mL with dissolution medium. Use this solution (3).

Carry out the test as described under <u>1.14.1 Chromatography</u>, High-performance liquid chromatography using the chromatographic conditions as described under "Assay", Method A, but injecting alternately 100 µL each of solutions (1) and (3).

Measure the areas of the peaks corresponding to the components H_2B_{1a} and H_2B_{1b} in the chromatogram of solution (1) and the area of the peak corresponding to the component H_2B_{1a} in the chromatogram of solution (3) and calculate the percentage content of ivermectin (component H_2B_{1a} and component H_2B_{1b}) for each of the tablets by comparing the peak areas due to the components H_2B_{1a} and H_2B_{1b} in the chromatogram obtained with solution (1) with the peak area due to the component H_2B_{1a} in the chromatogram of solution (3) and considering the assigned content of component H_2B_{1a} in ivermectin RS.

Evaluate the results as described under <u>5.5 Dissolution test for solid oral dosage forms</u>, Acceptance criteria. The amount of ivermectin (component H_2B_{1a} and component H_2B_{1b}) released is not less than 80% (Q) of the amount declared on the label.

Related substances. Carry out the test as described under <u>1.14.1 Chromatography</u>, High-performance liquid chromatography using a stainless steel column (25 cm × 4.6 mm) packed with particles of silica gel, the surface of which has been modified with chemically-bonded octadecylsilyl groups (5 μ m).

As the mobile phase, use a mixture of 39 volumes of water R, 55 volumes of methanol R and 106 volumes of acetonitrile R. Operate with a flow rate of 1.5 mL per minute. As a detector, use an ultraviolet spectrophotometer set at a wavelength of 245 nm

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and, for impurity D, at 280 nm.

Prepare the following solutions. For solution (1), use the powdered tablets described under "Assay", method A. Transfer a quantity of the powdered tablets, containing nominally 25.0 mg of Ivermectin, into a 100 mL volumetric flask, add 10 mL of water R and sonicate for 10 minutes. Add about 60 mL of methanol R, mix and sonicate for 5 minutes. Allow the solution to cool to room temperature. Dilute with methanol R to volume, mix and filter. For solution (2), dilute 1.0 mL of solution (1) to 100.0 mL with methanol R. For solution (3), dissolve 25.0 mg of ivermectin RS and dilute to 50.0 mL with methanol. For solution (4), dilute 1.0 mL of solution (3) to 100.0 mL with methanol R. Dilute 5.0 mL of this solution to 100.0 mL. For solution (5), use a solution containing 5.0 µg of 3-*tert*-butyl-4-hydroxyanisole R per mL methanol R. For solution (6), weigh about 2.2 mg of the copper (I) bromide R into a 10 mL volumetric flask. Add 5.0 mL of solution (1) and 100 µL of tert-butyl hydroperoxide R and dilute to volume. Mix well and let the solution stand at room temperature for approximately 20 minutes. Use solution (6) within 2 hours after preparation.

Inject 20 μ L each of solutions (3) and (4). The test is not valid unless, in the chromatogram obtained with solution (3), the resolution between the peaks due to ivermectin component H_2B_{1b} (with a relative retention of about 0.74 with reference to the component H_2B_{1a}) and due to component H_2B_{1a} (with a retention time of about 34 minutes) is at least 3.0. In the chromatogram obtained with solution (4), the signal-to-noise ratio of the principal peak is at least 10.

Inject alternately 20 μ L each of solutions (1), (2), (5) and (6). Record the chromatograms for about two times the retention time of the peak due to component H₂B_{1a}.

Use the chromatogram obtained with solution (6) to identify the peak due to impurity D. In the chromatogram obtained with solution (1), the following impurity, if present, is eluted at the following relative retention with reference to component H_2B_{1a} (with a retention time of about 34 minutes): impurity D about 0.69.

In the chromatogram obtained with solution (1):

-the area of any peak corresponding to impurity D is not greater than the area of the principal peak in the chromatogram obtained with solution (5) (2.0%);

-the area of any impurity peak with a relative retention of 1.3 to 1.5 with reference to the principal peak is not greater than 2.7 times the area of the principal peak in the chromatogram obtained with solution (2) (2.7%);

-the area of any other impurity peak is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (1%).

-Determine the sum of the areas of all impurities, other than impurity D, using solution (2) as a reference solution. Disregard any peak with an area less than 0.1 times the area of the principal peak in the chromatogram obtained with solution (2) (0.1%). Calculate the sum of all impurities considering the concentration found for impurity D. The sum of all impurities is not greater than 6%.

Assay

-For 3 mg tablets, either methods A or B may be applied.

-For 6 mg tablets, calculate the percentage content of the declared ivermectin quantity in the total weight of tablets. For tablets where the declared quantity of ivermectin is 5% or less of the total weight of the tablet, either methods A or B may be applied. For tablets where the declared quantity of ivermectin is more than 5%, apply method A.

A. Carry out the test as described under <u>1.14.1 Chromatography</u>, High-performance liquid chromatography, using a stainless steel column (25 cm \times 4.6 mm) packed with particles of silica gel, the surface of which has been modified with chemically-bonded octadecylsilyl groups (5 µm).

As the mobile phase, use a mixture of 12 volumes of water R, 35 volumes of methanol R and 53 volumes of <u>acetonitrile R</u>. Operate with a flow rate of 1.2 mL per minute. As a detector, use an ultraviolet spectrophotometer set at a wavelength of 245 nm.

Prepare the following solutions. For solution (1), weigh and powder 20 tablets. Transfer a quantity of the powdered tablets, containing nominally 25.0 mg of Ivermectin, into a 100.0 mL volumetric flask, add 10 mL of water R and sonicate for 10 minutes. Add about 60 mL of methanol R, mix, and sonicate for 5 minutes. Allow the solution to cool to room temperature. Dilute with methanol R to volume, mix and filter. For solution (2), dissolve 25.0 mg of ivermectin RS in methanol R and dilute to 100.0 mL with the same solvent. For solution (3), dilute 5.0 mL of solution (2) to 100.0 mL.

Inject alternately 10 μ L each of solutions (1), (2) and (3). Record the chromatograms for about two times the retention time of the peak due to component H₂B_{1a}.

The test is not valid unless, in the chromatogram obtained with solution (2), the resolution between the peaks due to component H_2B_{1b} (with a relative retention of about 0.74 with reference to component H_2B_{1a}) and due to

component H_2B_{1a} (retention time about 34 minutes) is at least 3.0.

Measure the areas of the peaks corresponding to the components H_2B_{1a} and H_2B_{1b} in the chromatogram of solution (1) and the areas of the peaks corresponding to the component H_2B_{1a} in the chromatograms of solutions (2) and (3) and calculate the percentage content of ivermectin (component H_2B_{1a} and component H_2B_{1b}) in the tablets by comparing the peak areas due to the component H_2B_{1a} in the chromatograms of solutions (1) and (2) and the peak area due to the component H_2B_{1a} in the chromatograms of solutions (1) and (2) and the peak area due to the component H_2B_{1b} in the chromatogram of solution (1) with the peak area due to the component H_2B_{1a} in chromatogram of solution (3) and considering the assigned content of component H_2B_{1a} in ivermectin RS.

B. Use the average of the 10 individual results obtained in the test for "Uniformity of content".

Uniformity of content. 3 mg tablets comply with the test for <u>5.1 Uniformity of content for single-dose preparations</u> using the following method of analysis; 6 mg tablets comply with the test in case the declared quantity of ivermectin is 5% or less of the total weight of the tablet.

Carry out the test as described under <u>1.14.1 Chromatography</u>, High-performance liquid chromatography using the chromatographic conditions as described under "Assay", Method A.

Prepare the following solutions using mobile phase as diluent. For solution (1), transfer one tablet to a 25 mL volumetric flask, add 5 mL of water R and sonicate for 10 minutes. Add about 15 mL of methanol R, mix and sonicate for 5 minutes. Allow the solution to cool to room temperature. Dilute with methanol R to volume, mix and filter. For 6 mg tablets, dilute 5.0 mL of this solution to 10.0 mL with methanol R. For solution (2), dissolve 30.0 mg of ivermectin RS in methanol R and dilute to 250.0 mL with the same solvent. For solution (3), dilute 5.0 mL of solution (2) to 100.0 mL.

Inject alternately 25 μ L each of solutions (1), (2) and (3). Measure the areas of the peaks corresponding to the components H₂B_{1a} and H₂B_{1b} in the chromatogram of solution (1) and the areas of the peaks corresponding to the component H₂B_{1a} in the chromatograms of solutions (2) and (3) and calculate the percentage content of ivermectin (component H₂B_{1a} and component H₂B_{1b}) in the tablets by comparing the peak areas due to the component H₂B_{1a} in the chromatograms of solutions (1) and (2) and the peak area due to the component H₂B_{1b} in the chromatogram of solutions (1) and (2) and the peak area due to the component H₂B_{1a} in the chromatogram of solutions (3) and considering the assigned content of component H₂B_{1a} in ivermectin RS.

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