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Abacavir, Zidovudine and Lamivudine Tablets

General Notices

Action and use

Nucleoside reverse transcriptase inhibitor; antiviral (HIV).

DEFINITION

Abacavir, Zidovudine and Lamivudine Tablets contain Abacavir Sulfate, Zidovudine and Lamivudine.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of abacavir, $C_{14}H_{18}N_6O$

95.0 to 105.0% of the stated amount.

Content of zidovudine, $C_{10}H_{13}N_5O_4$

95.0 to 105.0% of the stated amount.

Content of lamivudine, $C_8H_{11}N_3O_3S$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.
(1) Shake a quantity of powdered tablets containing the equivalent of 0.2 g of abacavir with 50 mL of *water*, filter and use the filtrate.
(2) 0.2% w/v of *zidovudine BPCRS* in *water*.
(3) 0.23% w/v of *abacavir sulfate BPCRS* in *water*.
(4) 0.1% w/v of *lamivudine BPCRS* in *water*.

CHROMATOGRAPHIC CONDITIONS

(a) Use precoated *silica gel F_{254}* plates (Merck silica gel 60 F_{254} plates are suitable).
(b) Use the mobile phase described below.
(c) Apply 10 µL of each solution.
(d) Develop the plate to 12 cm.
(e) After removal of the plate, dry it in air and immediately examine under *ultraviolet light (254 nm)*.

MOBILE PHASE

3 volumes of *glacial acetic acid*, 10 volumes of *methanol* and 90 volumes of *dichloromethane*.

SYSTEM SUITABILITY

The test is not valid unless the chromatogram obtained with solution (1) shows three clearly separated spots.

CONFIRMATION

The chromatogram obtained with solution (1) shows three spots corresponding in position, colour and size to the spots in the chromatograms obtained with solutions (2), (3) and (4).

B. In the Assay, the chromatogram obtained with solution (1) shows principal peaks with the same retention time as the principal peaks due to abacavir, zidovudine and lamivudine in the chromatograms obtained with solutions (2), (3) and (4) respectively.

TESTS

Dissolution

Comply with the *dissolution test for tablets and capsules*, Appendix XII B1.

TEST CONDITIONS

(a) Use Apparatus 2 and rotate the paddle at 75 revolutions per minute.
(b) Use 900 mL of 0.1M *hydrochloric acid*, at a temperature of 37°, as the medium.

PROCEDURE

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) After 45 minutes withdraw a 10 mL sample of the medium and filter.
(2) Dissolve suitable quantities of *abacavir sulfate BPCRS*, *zidovudine BPCRS* and *lamivudine BPCRS* in solvent A, described under Related substances, to produce the same concentrations as that expected for solution (1).
(3) 0.075% w/v of *zidovudine and lamivudine impurity standard BPCRS* and 0.025% w/v of *abacavir sulfate BPCRS* in solvent A.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Related substances may be used.

DETERMINATION OF CONTENT

Calculate the total content of abacavir, $C_{14}H_{18}N_6O$, zidovudine, $C_{10}H_{13}N_5O_4$, and lamivudine, $C_8H_{11}N_3O_3S$, in the medium using the declared content of $C_{14}H_{18}N_6O$ *abacavir sulfate BPCRS*, the declared content of $C_{10}H_{13}N_5O_4$ in *zidovudine BPCRS* and the declared content of $C_8H_{11}N_3O_3S$ in *lamivudine BPCRS*.

LIMITS

The amounts of abacavir, zidovudine and lamivudine released are not less than 75% (Q) of the stated amounts.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in solvent A.

SOLVENT A

Dissolve 1.9 g of *ammonium acetate* in 900 mL of *water*, adjust the pH to 3.9 with *glacial acetic acid* and dilute to 1000 mL.

(1) Shake a quantity of the powdered tablets containing the equivalent of 0.1g of abacavir in 60 mL with the aid of ultrasound for 30 minutes, dilute to 100 mL and filter.
(2) Dilute 1 volume of solution (1) to 100 volumes.
(3) Dilute 1 volume of solution (2) to 10 volumes.
(4) 0.002% w/v of *thymine*.

(5) 0.075% w/v of *zidovudine and lamivudine impurity standard BPCRS* and 0.025% w/v of *abacavir sulfate BPCRS* in solvent A.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (YMC ODS-A is suitable).
(b) Use gradient elution and the mobile phase described below.
(c) Use a flow rate of 1 mL per minute.
(d) Use a column temperature of 30°.
(e) Use a detection wavelength of 270 nm.
(f) Inject 10 µL of each solution.

MOBILE PHASE

Mobile phase A 0.025M *ammonium acetate*, the pH adjusted to 3.9 with *glacial acetic acid*.

Mobile phase B *methanol*.

Mobile phase C *acetonitrile*.

Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Mobile phase C (% v/v)	Comment
0-15	95	5	0	isocratic
15-30	95→70	5→30	0	linear gradient
30-38	70	30	0	isocratic
38-60	70→0	30→0	0→100	change of solvent
60-65	0	0	100	washing column
65-66	0→95	0→5	100→0	change in solvent
66-75	95	5	0	re-equilibration

SYSTEM SUITABILITY

The test is not valid unless:

the chromatogram obtained with solution (5) closely resembles the reference chromatogram supplied with *zidovudine and lamivudine impurity standard BPCRS* and the retention of abacavir relative to zidovudine is about 1.2;

the *resolution* between the peaks due to lamivudine impurity B and lamivudine is at least 2.0;

the *resolution* between the peaks due to lamivudine and thymidine is at least 2.0;

the *resolution* between the peaks due to zidovudine and zidovudine impurity B is at least 4.0;

the *resolution* between the peaks due to zidovudine and abacavir is at least 1.5.

LIMITS

Using the chromatogram obtained with solution (5) and the reference chromatogram supplied with *zidovudine and lamivudine impurity standard BPCRS* identify any peaks in solution (1) corresponding to the named lamivudine and zidovudine impurities.

In the chromatogram obtained with solution (1):

the area of any peak corresponding to thymine (zidovudine impurity C) is not greater than the area of the principal peak in the chromatogram obtained with solution (4) (2.0%);

the area of any peak corresponding to zidovudine impurity B is not greater than the area of the peak due to zidovudine in the chromatogram obtained with solution (2) (1.0%);

the area of any peak corresponding to zidovudine impurity G (retention relative to zidovudine about 1.4) is not greater than 0.5 times the area of the peak due to zidovudine in the chromatogram obtained with solution (2) (0.5%);

the area of any peak corresponding to zidovudine impurity 1 (eluting between lamivudine impurity G and zidovudine impurity C) is not greater than 0.4 times the area of the peak due to zidovudine in the chromatogram obtained with solution (2) (0.4%);

the area of any peak corresponding to lamivudine impurity A is not greater than 3 times the area of the peak due to lamivudine in the chromatogram obtained with solution (3) (0.3%);

the area of any peak corresponding to a named lamivudine impurity is not greater than 0.2 times the area of the peak due to lamivudine in the chromatogram obtained with solution (2) (0.2%);

the area of any peak corresponding to a named zidovudine impurity is not greater than 0.2 times the area of the peak due to zidovudine in the chromatogram obtained with solution (2) (0.2%);

the area of any other *secondary peak* is not greater than 0.2 times the area of the peak due to abacavir in the chromatogram obtained with solution (2) (0.2%);

the sum of the areas of all the named zidovudine impurities is not greater than 4 times the area of the peak due to zidovudine in the chromatogram obtained with solution (2) (4.0%);

the sum of the areas of all the named lamivudine impurities is not greater than the area of the peak due to lamivudine in the chromatogram obtained with solution (2) (1.0%);

the sum any other *secondary peaks* is not greater than the area of the peak due to abacavir in the chromatogram obtained with solution (2) (1.0%);

Disregard any peak with an area less than the area of the peak due to abacavir in the chromatogram obtained with solution (3) (0.1%).

ASSAY

Weigh and powder 20 tablets. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions dissolved in solvent A described under Related substances.

(1) Shake a quantity of the powdered tablets containing the equivalent of 0.1 g of abacavir with 50 mL of solvent A in a 100 mL amber volumetric flask for 30 minutes, dilute to 100 mL and filter. Dilute 1 volume to 5 volumes.
(2) 0.023% w/v of *abacavir sulfate BPCRS*
(3) 0.02% w/v of *zidovudine BPCRS*.
(4) 0.01% w/v of *lamivudine BPCRS*.
(5) 0.075% w/v of *zidovudine and lamivudine impurity standard BPCRS* and 0.025% w/v of *abacavir sulfate BPCRS* in solvent A.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Related substances may be used.

SYSTEM SUITABILITY

The test is not valid unless:

the chromatogram obtained with solution (5) closely resembles the reference chromatogram supplied with *zidovudine and lamivudine impurity standard BPCRS* and the retention of abacavir relative to Zidovudine is about 1.2*;*

the *resolution* between the peaks due to lamivudine impurity B and lamivudine is at least 2.0;

the *resolution* between the peaks due to lamivudine and thymidine is at least 2.0;

the *resolution* between the peaks due to zidovudine and zidovudine impurity B is at least 4.0;

the *resolution* between the peaks due to zidovudine and abacavir is at least 1.5.

DETERMINATION OF CONTENT

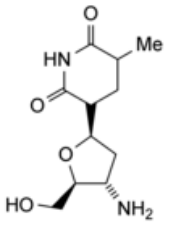
Using solutions (1) and (2), calculate the total content of $C_{14}H_{18}N_6O$ in the tablets from the chromatograms obtained using the declared content of $C_{14}H_{18}N_6O$ in *abacavir sulfate BPCRS*.

Using solutions (1) and (3), calculate the total content of $C_{10}H_{13}N_5O_4$ in the tablets from the chromatograms obtained using the declared content of $C_{10}H_{13}N_5O_4$ in *zidovudine BPCRS*.

Using solutions (1) and (4) calculate the total content $C_8H_{11}N_3O_3S$ in the tablets from the chromatograms obtained using the declared content of $C_8H_{11}N_3O_3S$ in *lamivudine BPCRS*.

IMPURITIES

The impurities limited by the requirements of this monograph include impurities, A, B, C, E, F, G, H and J listed under Lamivudine, impurities B, C, E and G listed under Zidovudine and the following:



1. 1-[(2*R*,4*S*,5*S*)-4-amino-5-(hydroxymethyl)oxolan-2-yl]-5-methylpyrimidin-2,4(1*H*,3*H*)-dione.