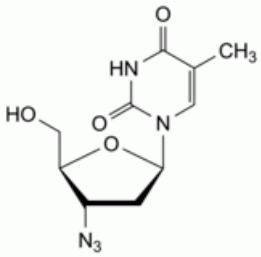
Edition: BP 2025 (Ph. Eur. 11.6 update)

Zidovudine

General Notices

(Ph. Eur. monograph 1059)



$C_{10}H_{13}N_5O_4$ 267.2 *30516-87-1*

Action and use

Nucleoside reverse transcriptase inhibitor; antiviral (HIV).

Preparations

Zidovudine Capsules

Zidovudine Tablets

Zidovudine and Lamivudine Tablets

Zidovudine Infusion

Abacavir, Zidovudine and Lamivudine Tablets

Ph Eur

DEFINITION

3′-Azido-3′-deoxythymidine.

Content

97.0 per cent to 102.0 per cent (dried substance).

CHARACTERS

Appearance

White or slightly brownish powder.

Solubility

Sparingly soluble in water, soluble in anhydrous ethanol, practically insoluble in heptane.

It shows polymorphism (*5.9*).

IDENTIFICATION

A. Specific optical rotation (see Tests).
B. Infrared absorption spectrophotometry (*2.2.24*).

Comparison *zidovudine CRS*.

If the spectra obtained in the solid state show differences, dissolve the substance to be examined and the reference substance separately in the minimum volume of *water R*, evaporate to dryness in a desiccator, under high vacuum over *diphosphorus pentoxide R* and record new spectra using the residues.

TESTS

Appearance of solution

The solution is not more opalescent than reference suspension I (*2.2.1*) and not more intensely coloured than reference solution BY_5 (*2.2.2, Method II*).

Dissolve 0.5 g in 50 mL of *water R*, heating if necessary.

Specific optical rotation (*2.2.7*)

+ 60.5 to + 63.0 (dried substance), measured at 25 °C.

Dissolve 0.50 g in *anhydrous ethanol R* and dilute to 50.0 mL with the same solvent.

Related substances

A. Liquid chromatography (*2.2.29*).

Solvent mixture Mix 4 volumes of *acetonitrile R*, 20 volumes of *methanol R* and 76 volumes of a 2 g/L solution of *ammonium acetate R* previously adjusted to pH 6.8 with *dilute acetic acid R*.

Test solution (a) Dissolve 20.0 mg of the substance to be examined in the solvent mixture and dilute to 20.0 mL with the solvent mixture.

Test solution (b) Dilute 10.0 mL of test solution (a) to 50.0 mL with the solvent mixture.

Reference solution (a) Dissolve 2 mg of *zidovudine impurity B CRS* in the solvent mixture and dilute to 50 mL with the solvent mixture. Dilute 1 mL of the solution to 20 mL with the solvent mixture.

Reference solution (b) Dissolve 5 mg of *zidovudine for system suitability A CRS* (containing impurity G) in reference solution (a) and dilute to 5 mL with reference solution (a).

Reference solution (c) Dilute 1.0 mL of test solution (a) to 100.0 mL with the solvent mixture. Dilute 1.0 mL of this solution to 10.0 mL with the solvent mixture.

Reference solution (d) Dissolve 20.0 mg of *zidovudine CRS* in the solvent mixture and dilute to 20.0 mL with the solvent mixture. Dilute 10.0 mL of the solution to 50.0 mL with the solvent mixture.

Reference solution (e) Dissolve 1 mg of *zidovudine impurity D CRS* in a mixture of 4 volumes of *acetonitrile R*, 40 volumes of *methanol R* and 56 volumes of a 2 g/L solution of *ammonium acetate R* previously adjusted to pH 6.8 with *dilute acetic acid R* and dilute to 50 mL with the same mixture of solvents. Dilute 5 mL of the solution to 10 mL with the same mixture of solvents.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *base-deactivated end-capped octadecylsilyl silica gel for chromatography R* (5 µm).

Mobile phase:

— *mobile phase A*: 2 g/L solution of *ammonium acetate R* adjusted to pH 6.8 with *dilute acetic acid R*;

— *mobile phase B*: *acetonitrile R*;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 3	95	5
3 - 18	95 → 85	5 → 15
18 - 28	85 → 30	15 → 70
28 - 43	30	70

Flow rate 1.5 mL/min.

Detection Spectrophotometer at 265 nm.

Injection 20 µL of test solution (a) and reference solutions (b), (c) and (e).

Identification of impurities Use the chromatogram supplied with *zidovudine for system suitability A CRS* and the chromatogram obtained with reference solution (b) to identify the peaks due to impurities B, and G; use the chromatogram obtained with reference solution (e) to identify the peak due to impurity D.

Relative retention With reference to zidovudine (retention time = about 16 min): impurity B = about 1.05; impurity G = about 1.5; impurity D = about 2.0.

System suitability Reference solution (b):

— *resolution*: minimum 2.0 between the peaks due to zidovudine and impurity B.

Calculation of percentage contents:

— for each impurity, use the concentration of zidovudine in reference solution (c).

Limits:

— *impurity G*: maximum 0.2 per cent;

— *unspecified impurities*: for each impurity, maximum 0.10 per cent;

— *reporting threshold*: 0.05 per cent; disregard any peak due to impurity D and any peak eluting after this impurity.

B. Liquid chromatography (*2.2.29*).

Test solution Dissolve 0.5 g of the substance to be examined in 10 mL of *acetonitrile R* and dilute to 100.0 mL with the mobile phase.

Reference solution (a) Dissolve 5.0 mg of *zidovudine impurity D CRS* in *acetonitrile R* and dilute to 10.0 mL with the same solvent.

Reference solution (b) Dilute 1.0 mL of reference solution (a) to 100.0 mL with the mobile phase.

Reference solution (c) Dilute 1 mL of reference solution (a) to 50 mL with the test solution.

Column:

— *size*: *l* = 0.15 m, Ø = 4.6 mm;

— *stationary phase*: *base-deactivated end-capped octadecylsilyl silica gel for chromatography R* (5 µm).

Mobile phase *water for chromatography R*, *acetonitrile R1* (30:70 *V/V*).

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 210 nm.

Injection 20 µL of the test solution and reference solutions (b) and (c).

Run time 10 times the retention time of zidovudine.

Identification of impurities Use the chromatogram obtained with reference solution (b) to identify the peak due to impurity D.

Relative retention With reference to zidovudine (retention time = about 1.5 min): impurity D = about 2.5.

System suitability Reference solution (c):

— *resolution*: minimum 5.0 between the peaks due to zidovudine and impurity D.

Calculation of percentage contents:

— for each impurity, use the concentration of impurity D in reference solution (b).

Limits:

— *unspecified impurities*: for each impurity, maximum 0.10 per cent;

— *reporting threshold*: 0.05 per cent; disregard any peak eluting before impurity D.

Limit:

— *total for tests A and B*: maximum 1.0 per cent.

Loss on drying (*2.2.32*)

Maximum 1.0 per cent, determined on 1.000 g by drying in an oven at 105 °C.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Liquid chromatography (*2.2.29*) as described in test A for related substances with the following modification.

Injection Test solution (b) and reference solution (d).

Calculate the percentage content of $C_{10}H_{13}N_5O_4$ taking into account the assigned content of *zidovudine CRS*.

STORAGE

Protected from light.

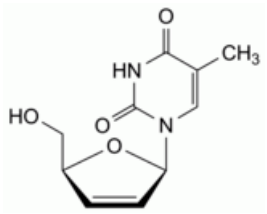
IMPURITIES

Test A for related substances: A, B, C, E, F, G.

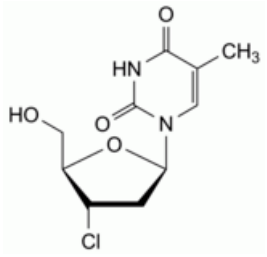
Test B for related substances: D, J, K.

Specified impurities *G.*

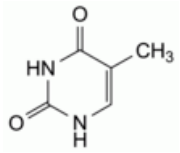
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *A, B, C, D, E, F, J, K.*



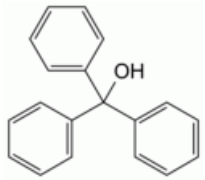
A. 3′-deoxy-2′,3′-didehydrothymidine,



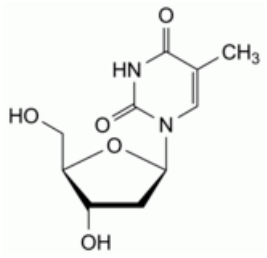
B. 3′-chloro-3′-deoxythymidine,



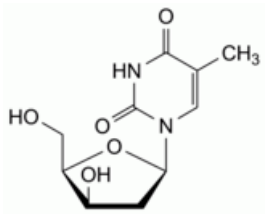
C. 5-methylpyrimidine-2,4(1*H*,3*H*)-dione (thymine),



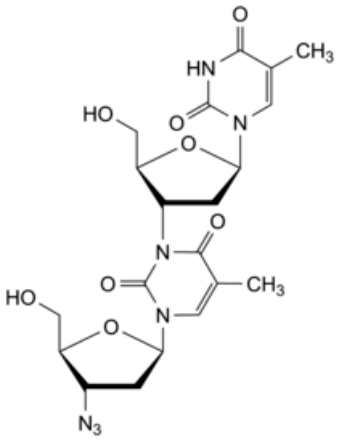
D. triphenylmethanol,



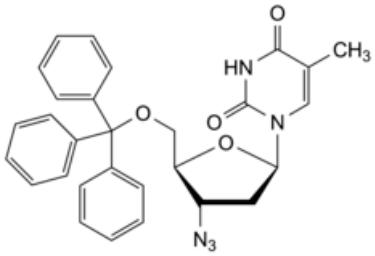
E. thymidine,



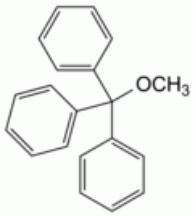
F. 3′-*epi*-thymidine,



G. 3′-(3′-azido-3′-deoxythymidin-3-yl)-3′-deoxythymidine,



J. 3′-azido-3′-deoxy-5′-*O*-(triphenylmethyl)thymidine (trityl-zidovudine),



K. 1,1′,1″-(methoxymethanetriyl)tribenzene (methyl trityl ether).

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