Reference solution. Dissolve 56.0 mg of *boric acid R* in *water R* and dilute to 100.0 ml with the same solvent. Dilute 5.0 ml of this solution to 100.0 ml with *water R*. *Keep in a well-closed polyethylene container.*

In 4 polyethylene 25 ml flasks, place separately:

– 1.00 g of the substance to be examined and 1 ml of *water R* (solution A);

– 1.00 g of the substance to be examined and 1 ml of the reference solution (solution B);

– 1 ml of the reference solution and 1 ml of *water R* (solution C);

– 2 ml of *water R* (solution D).

To each flask, add 4.0 ml of *acetate-edetate buffer solution pH 5.5 R*. Mix and add 4.0 ml of freshly prepared *azomethine H solution R*. Mix and allow to stand for 1 h. Measure the absorbance (*2.2.25*) of solutions A, B and C at 420 nm, using solution D as the compensation liquid. The test is not valid unless the absorbance of solution C is at least 0.25. The absorbance of solution B is not less than twice that of solution A.

Lead (*2.4.10*): maximum 0.5 ppm, calculated with reference to the declared content of lactulose.

Sulphated ash (*2.4.14*): maximum 0.2 per cent, determined on 1.5 g and calculated with reference to the declared content of lactulose.

Microbial contamination. Total viable aerobic count (*2.6.12*) not more than 10^2 micro-organisms per gram, determined by plate count. It complies with the test for *Escherichia coli* (*2.6.13*).

ASSAY

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

Injection: the test solution and reference solution (b).

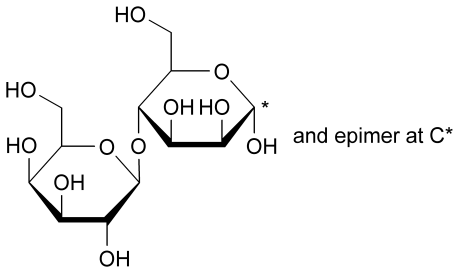
Calculate the percentage content of $C_{12}H_{22}O_{11}$ from the declared content of *lactulose CRS*.

LABELLING

The label states the declared content of lactulose.

IMPURITIES

Specified impurities: *A, B, C, D, E.*

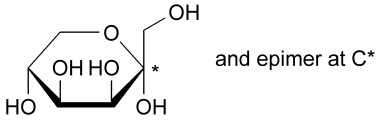


A. 4-*O*-(β-D-galactopyranosyl)-D-mannopyranose (epilactose),

B. galactose,

C. lactose,

D. fructose,



E. D-*lyxo*-hex-2-ulopyranose (tagatose).

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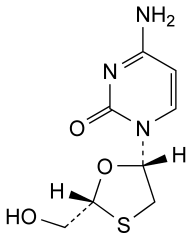
LAMIVUDINE

Lamivudinum



$C_8H_{11}N_3O_3S$ M_r 229.3
[134678-17-4]

DEFINITION

4-Amino-1-[(2*R*,5*S*)-2-(hydroxymethyl)-1,3-oxathiolan-5-yl]pyrimidin-2(1*H*)-one.

Content: 97.5 per cent to 102.0 per cent (dried substance).

CHARACTERS

Appearance: white or almost white powder.

Solubility: soluble in water, sparingly soluble in methanol, slightly soluble in ethanol (96 per cent).

It shows polymorphism (*5.9*).

IDENTIFICATION

First identification: *B, C.*

Second identification: *A, B.*

A. Specific optical rotation (*2.2.7*): – 97 to – 99 (dried substance).

Dissolve 0.250 g in *water R* and dilute to 50.0 ml with the same solvent.

B. Infrared absorption spectrophotometry (*2.2.24*).

Comparison: *lamivudine CRS*.

If the spectra obtained in the solid state show differences, dissolve the substance to be examined and the reference substance separately in *methanol R*, evaporate to dryness and record new spectra using the residues.

C. Enantiomeric purity (see Tests).

TESTS

Absorbance (*2.2.25*): maximum 0.3 at 440 nm, using a path length of 4 cm.

Dissolve 1.00 g in *water R*, using sonication if necessary, and dilute to 20.0 ml with the same solvent.

Related substances. Liquid chromatography (*2.2.29*).

Test solution. Dissolve 50.0 mg of the substance to be examined in the mobile phase and dilute to 100.0 ml with the mobile phase.

Reference solution (a). Dilute 1.0 ml of the test solution to 100.0 ml with the mobile phase. Dilute 1.0 ml of this solution to 10.0 ml with the mobile phase.

Reference solution (b). Dissolve 5 mg of *salicylic acid R* in the mobile phase and dilute to 100.0 ml with the mobile phase. Dilute 1.0 ml of the solution to 100.0 ml with the mobile phase.

Reference solution (c). Dissolve 50.0 mg of *lamivudine CRS* in the mobile phase and dilute to 100.0 ml with the mobile phase.

Reference solution (d). Dissolve 5 mg of *cytosine R* and 5 mg of *uracil R* in the mobile phase and dilute to 100.0 ml with the mobile phase. Dilute 2.0 ml of this solution to 10.0 ml with the mobile phase.

Reference solution (e). Dissolve 5 mg of *lamivudine for system suitability 1 CRS* (containing impurities A and B) in 2 ml of mobile phase. Add 1.0 ml of reference solution (d) and dilute to 10.0 ml with the mobile phase.

Column:

– *size*: *l* = 0.25 m, Ø = 4.6 mm,
– *stationary phase*: *base-deactivated octadecylsilyl silica gel for chromatography R* (5 µm),
– *temperature*: 35 °C.

Mobile phase: mix 5 volumes of *methanol R* and 95 volumes of a 1.9 g/l solution of *ammonium acetate R*, previously adjusted to pH 3.8 with *glacial acetic acid R*.

Flow rate: 1.0 ml/min.

Detection: spectrophotometer at 277 nm.

Injection: 10 µl.

Run time: 3 times the retention time of lamivudine.

Identification of impurities: use the chromatograms obtained with reference solutions (e) and (b) to identify the peaks due to impurities A, B, E, F and C.

Relative retention with reference to lamivudine (retention time = about 9 min): impurity E = about 0.28; impurity F = about 0.32; impurity A = about 0.36; impurity B = about 0.91; impurity J = about 1.45; impurity C = about 2.32.

System suitability: reference solution (e):

– *resolution*: minimum 1.5 between the peaks due to impurity F and impurity A; minimum 1.5 between the peaks due to impurity B and lamivudine.

Limits:

– *correction factors*: for the calculation of content, multiply the peak areas of the following impurities by the corresponding correction factor: impurity E = 0.6; impurity F = 2.2; impurity J = 2.2;
– *impurity A*: not more than 3 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.3 per cent);
– *impurity B*: not more than twice the area of the principal peak in the chromatogram obtained with reference solution (a) (0.2 per cent);
– *impurity C*: not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (0.1 per cent);
– *any other impurity*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.1 per cent);
– *total*: not more than 6 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.6 per cent);
– *disregard limit*: 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.05 per cent).

Enantiomeric purity. Liquid chromatography (*2.2.29*): use the normalisation procedure.

Test solution. Dissolve 25.0 mg of the substance to be examined in *water R* and dilute to 100.0 ml with the same solvent.

Reference solution. Dissolve the contents of a vial of *lamivudine for system suitability 2 CRS* (containing impurity D) in 1.0 ml of *water R*.

Column:

– *size*: *l* = 0.25 m, Ø = 4.6 mm,
– *stationary phase*: *silica gel BC for chiral chromatography R*,
– *temperature*: maintain at constant temperature between 15 °C and 30 °C; the temperature may be adjusted to optimise the resolution between lamivudine and impurity D; a lower temperature favours improved resolution.

Mobile phase: mix 5 volumes of *methanol R* and 95 volumes of a 7.7 g/l solution of *ammonium acetate R*.

Flow rate: 1.0 ml/min.

Detection: spectrophotometer at 270 nm.

Injection: 10 µl.

Run time: twice the retention time of lamivudine.

Relative retention with reference to lamivudine (retention time = about 8 min): impurity D = about 1.2; impurity B and enantiomer = about 1.3 and 1.5.

System suitability: reference solution:

– *peak-to-valley-ratio*: minimum 15, where H_p = height above the baseline of the peak due to impurity D and H_v = height above the baseline of the lowest point of the curve separating this peak from the peak due to lamivudine.

Calculate the sum of the percentage contents of all impurity peaks with a relative retention from 1.2 to 1.5. Subtract the percentage content of impurity B as obtained in the test for related substances.

Limit:

– *impurity D*: maximum 0.3 per cent.

Heavy metals (*2.4.8*): maximum 20 ppm.

1.0 g complies with test F. Prepare the reference solution using 2 ml of *lead standard solution (10 ppm Pb) R*.

Loss on drying (*2.2.32*): maximum 0.5 per cent, determined on 1.000 g by drying in an oven at 105 °C.

Sulphated ash (*2.4.14*): maximum 0.1 per cent, determined on 1.0 g.

ASSAY

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

Injection: test solution and reference solution (c).

Calculate the percentage content of $C_8H_{11}N_3O_3S$ using the chromatograms obtained with the test solution and reference solution (c) and the declared content of $C_8H_{11}N_3O_3S$ in *lamivudine CRS*.

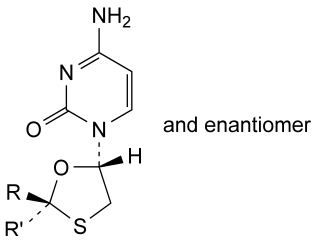
STORAGE

Protected from light.

IMPURITIES

Specified impurities: *A, B, C, D.*

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*): *E, F, G, H, I, J.*

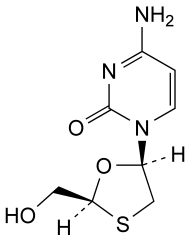


and enantiomer

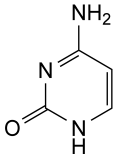
A. R = H, R′ = CO_2H: (2*RS*,5*SR*)-5-(4-amino-2-oxopyrimidin-1(2*H*)-yl)-1,3-oxathiolane-2-carboxylic acid,

B. R = CH_2OH, R′ = H: 4-amino-1-[(2*RS*,5*RS*)-2-(hydroxymethyl)-1,3-oxathiolan-5-yl]pyrimidin-2(1*H*)-one ((±)-*trans*-lamivudine),

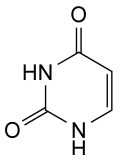
C. salicylic acid,



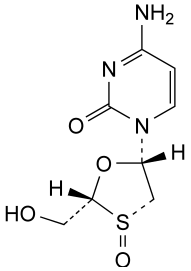
D. 4-amino-1-[(2*S*,5*R*)-2-(hydroxymethyl)-1,3-oxathiolan-5-yl]pyrimidin-2(1*H*)-one,



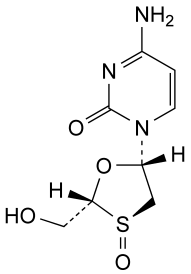
E. 4-aminopyrimidin-2(1*H*)-one (cytosine),



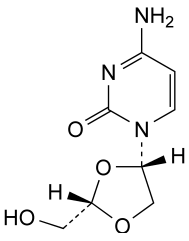
F. pyrimidine-2,4(1*H*,3*H*)-dione (uracil),



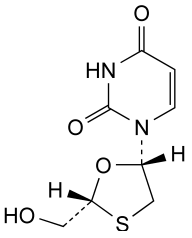
G. 4-amino-1-[(2*R*,3*S*,5*S*)-2-(hydroxymethyl)-1,3-oxathiolan-5-yl]pyrimidin-2(1*H*)-one *S*-oxide,



H. 4-amino-1-[(2*R*,3*R*,5*S*)-2-(hydroxymethyl)-1,3-oxathiolan-5-yl]pyrimidin-2(1*H*)-one *S*-oxide,



I. 4-amino-1-[(2*S*,4*S*)-2-(hydroxymethyl)-1,3-dioxolan-4-yl]pyrimidin-2(1*H*)-one,



J. 1-[(2*R*,5*S*)-2-(hydroxymethyl)-1,3-oxathiolan-5-yl]pyrimidine-2,4(1*H*,3*H*)-dione.

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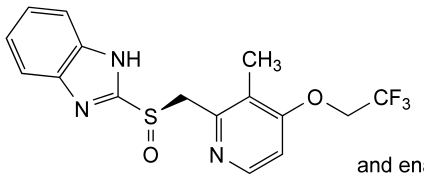
LANSOPRAZOLE

Lansoprazolum



and enantiomer

$C_{16}H_{14}F_3N_3O_2S$ M_r 369.4
[103577-45-3]

DEFINITION

2-[(*RS*)-[[3-Methyl-4-(2,2,2-trifluoroethoxy)pyridin-2-yl]methyl]sulphinyl]-1*H*-benzimidazole.

Content: 99.0 per cent to 101.0 per cent (anhydrous substance).

CHARACTERS

Appearance: white or brownish powder.

Solubility: practically insoluble in water, soluble in anhydrous ethanol, very slightly soluble in acetonitrile.

It shows polymorphism (*5.9*).

IDENTIFICATION

Infrared absorption spectrophotometry (*2.2.24*).

Comparison: *lansoprazole CRS*.

If the spectra obtained in the solid state show differences, dissolve the substance to be examined and the reference substance separately in *anhydrous ethanol R*, evaporate to dryness and record new spectra using the residues.

TESTS

Appearance of solution. The solution is clear (*2.2.1*) and not more intensely coloured than reference solution B_2 or BY_2 (*2.2.2, Method II*).

Dissolve 1.0 g in *dimethylformamide R* and dilute to 20 ml with the same solvent.

Related substances. Liquid chromatography (*2.2.29*). *Prepare the solutions immediately before use and protect them from light.*