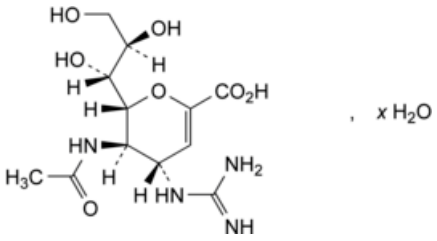
Edition: BP 2025 (Ph. Eur. 11.6 update)

Zanamivir Hydrate

General Notices

(Ph. Eur. monograph 2611)



$C_{12}H_{20}N_4O_7,xH_2O$ 332.3 (anhydrous substance) *551942-41-7*

Action and use

Neuraminidase inhibitor; treatment and prophylaxis of influenza.

Preparation

Zanamivir Inhalation Powder, pre-metered

Ph Eur

DEFINITION

(2*R*,3*R*,4*S*)-3-Acetamido-4-carbamimidamido-2-[(1*R*,2*R*)-1,2,3-trihydroxypropyl]-3,4-dihydro-2*H*-pyran-6-carboxylic acid hydrate.

Content

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

It contains a variable quantity of water.

CHARACTERS

Appearance

White or almost white, slightly hygroscopic powder.

Solubility

Slightly soluble in water, practically insoluble in ethanol (96 per cent) and in methylene chloride.

IDENTIFICATION

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

Comparison *zanamivir hydrate CRS*.

TESTS

Specific optical rotation (2.2.7)

+ 36.0 to + 38.5 (dried substance).

Dissolve 0.250 g in 25.0 mL of *water R*; sonicate until dissolution is complete.

Related substances

Liquid chromatography (2.2.29).

Test solution (a) Dissolve 23.0 mg of the substance to be examined in 20 mL of *water R* and dilute to 50.0 mL with *acetonitrile R1*.

Test solution (b) Dilute 5.0 mL of test solution (a) to 50.0 mL with the mobile phase.

Reference solution (a) Dissolve 23.0 mg of *zanamivir for assay CRS* in 20 mL of *water R* and dilute to 50.0 mL with *acetonitrile R1*. Dilute 5.0 mL of the solution to 50.0 mL with the mobile phase.

Reference solution (b) Dissolve 5 mg of *zanamivir for system suitability CRS* (containing impurities A, B, C and E) in 6 mL of *water R* and dilute to 10 mL with *acetonitrile R1*.

Reference solution (c) Dilute 1.0 mL of test solution (a) 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 (d) Dissolve 3.0 mg of *zanamivir impurity F CRS* in the mobile phase and dilute to 100.0 mL with the mobile phase.

Reference solution (e) Dilute 1.0 mL of reference solution (d) to 100.0 mL with the mobile phase. Dilute 3.0 mL of this solution to 20.0 mL with the mobile phase.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *amino alkyl vinyl polymer for chromatography R* (5 µm);

— *temperature*: 30 °C.

Mobile phase 0.7 g/L solution of *sulfuric acid R* previously adjusted to pH 5.5 with *dilute ammonia R3*, *acetonitrile R1* (40:60 *V/V*).

Flow rate 1.5 mL/min.

Detection Spectrophotometer at 234 nm.

Preconditioning of the column Prior to first use, rinse with a 0.7 g/L solution of *ammonium sulfate R* at 1.5 mL/min at 30 °C for about 1 h; prior to each use, rinse with the mobile phase for at least 8 h.

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

Run time 3 times the retention time of zanamivir.

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

Relative retention With reference to zanamivir (retention time = about 9 min): impurity F = about 0.3; impurity B = about 0.6; impurity C = about 0.75; impurity E = about 0.8; impurity A = about 2.6.

System suitability:

— *signal-to-noise ratio*: minimum 10 for the principal peak in the chromatogram obtained with reference solution (e);

— *peak-to-valley ratio*: minimum 2.5, where H_p = height above the baseline of the peak due to impurity E and H_v = height above the baseline of the lowest point of the curve separating this peak from the peak due to impurity C in the chromatogram obtained with reference solution (b).

Calculation of percentage contents:

— for impurity F, use the concentration of impurity F in reference solution (e);

— for impurities other than F, use the concentration of zanamivir hydrate in reference solution (c).

Limits:

— *impurity A*: maximum 0.5 per cent;

— *impurity B*: maximum 0.3 per cent;

— *impurity C*: maximum 0.2 per cent;

— *impurity F*: maximum 0.01 per cent;

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

— *total*: maximum 1.2 per cent;

— *reporting threshold*: 0.05 per cent, except for impurity F.

Loss on drying (*2.2.32*)

4.0 per cent to 9.0 per cent, determined on 1.000 g by drying *in vacuo* 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 the test for related substances with the following modification.

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

Calculate the percentage content of $C_{12}H_{20}N_4O_7$ taking into account the assigned content of *zanamivir for assay CRS*.

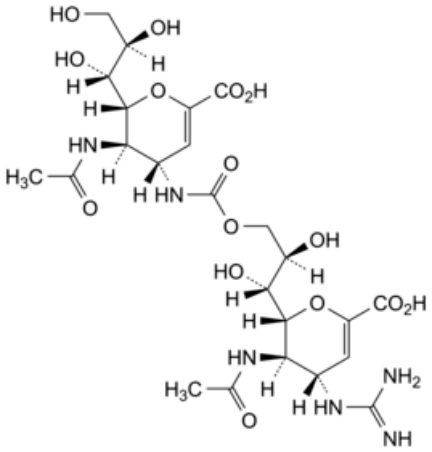
STORAGE

In an airtight container, protected from light.

IMPURITIES

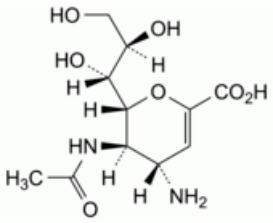
Specified impurities *A, B, C, F.*

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) *D, E, H.*

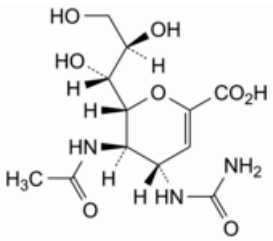


A. (2*R*,3*R*,4*S*)-3-acetamido-2-[(1*R*,2*R*)-3-[[[(2*R*,3*R*,4*S*)-3-acetamido-6-carboxy-2-[(1*R*,2*R*)-1,2,3-trihydroxypropyl]-3,4-dihydro-2*H*-pyran-4-yl]carbamoyl]oxy]-1,2-dihydroxypropyl]-4-carbamimidamido-3,4-dihydro-2*H*-pyran-6-carboxylic acid,

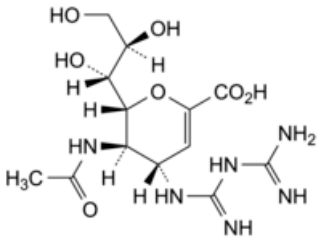
B. unknown structure,



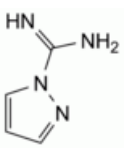
C. (2*R*,3*R*,4*S*)-3-acetamido-4-amino-2-[(1*R*,2*R*)-1,2,3-trihydroxypropyl]-3,4-dihydro-2*H*-pyran-6-carboxylic acid,



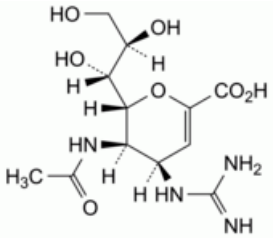
D. (2*R*,3*R*,4*S*)-3-acetamido-4-(carbamoylamino)-2-[(1*R*,2*R*)-1,2,3-trihydroxypropyl]-3,4-dihydro-2*H*-pyran-6-carboxylic acid,



E. (2*R*,3*R*,4*S*)-3-acetamido-4-(*N*′-carbamimidoylcarbamimidamido)-2-[(1*R*,2*R*)-1,2,3-trihydroxypropyl]-3,4-dihydro-2*H*-pyran-6-carboxylic acid,



F. 1*H*-pyrazole-1-carboximidamide,



H. (2*R*,3*R*,4*R*)-3-acetamido-4-carbamimidamido-2-[(1*R*,2*R*)-1,2,3-trihydroxypropyl]-3,4-dihydro-2*H*-pyran-6-carboxylic acid.

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