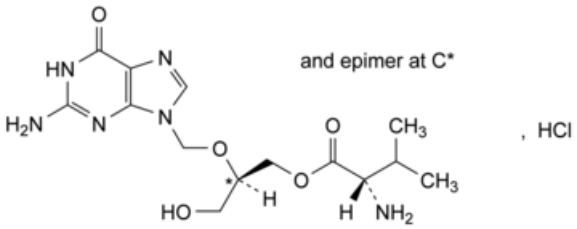
Edition: BP 2025 (Ph. Eur. 11.6 update)

Valganciclovir Hydrochloride

General Notices

(Ph. Eur. monograph 2930)



$C_{14}H_{23}ClN_6O_5$ 390.8 *175865-59-5*

Ph Eur

DEFINITION

(2*RS*)-2-[(2-amino-6-oxo-1,6-dihydro-9*H*-purin-9-yl)methoxy]-3-hydroxypropyl L-valinate hydrochloride.

Content

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

CHARACTERS

Appearance

White or almost white, hygroscopic powder.

Solubility

Freely soluble in water and in methanol, practically insoluble in heptane.

It shows polymorphism (5.9).

IDENTIFICATION

A. Infrared absorption spectrophotometry (2.2.24).

Comparison *valganciclovir hydrochloride CRS*.

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

B. Impurity T (see Tests).
C. It gives reaction (a) of chlorides (*2.3.1*).

TESTS

Impurity T

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

Test solution Dissolve 10.0 mg of the substance to be examined in a 0.103 g/L solution of *hydrochloric acid R* and dilute to 50.0 mL with the same solution.

Reference solution Dissolve 5 mg of *valganciclovir containing impurity T CRS* in a 0.103 g/L solution of *hydrochloric acid R* and dilute to 25 mL with the same solution.

Column:

— *size*: *l* = 0.15 m, Ø = 4.0 mm;

— *stationary phase*: *crown-ether silica gel for chiral separation R* (5 µm).

Mobile phase A 16.2 g/L solution of *perchloric acid R*.

Flow rate 0.8 mL/min.

Detection Spectrophotometer at 254 nm.

Autosampler Set at 5 °C.

Injection 10 µL.

Run time Twice the retention time of the 1st peak due to valganciclovir ((*R*)-ester).

Identification of impurities Use the chromatogram supplied with *valganciclovir containing impurity T CRS* and the chromatogram obtained with the reference solution to identify the peaks due to impurity T (isomers 1 and 2).

Relative retention With reference to valganciclovir (retention time of the 1st peak ((*R*)-ester) = about 11 min): impurity T (isomer 1) = about 0.64; impurity T (isomer 2) = about 0.67; 2nd peak due to valganciclovir ((*S*)-ester) = about 1.1.

System suitability Reference solution:

— *resolution*: minimum 3.5 between the 2nd peak due to impurity T (isomer 2) and the 1st peak due to valganciclovir ((*R*)-ester).

Limit:

— *impurity T*: maximum 3.0 per cent for the sum of the 2 isomers; disregard any peak other than the peaks due to impurity T (isomers 1 and 2) and valganciclovir ((*R*)-ester and (*S*)-ester).

Related substances

Liquid chromatography (*2.2.29*). *Prepare the solutions immediately before use*.

Test solution Dissolve 10.0 mg of the substance to be examined in a 0.103 g/L solution of *hydrochloric acid R* and dilute to 50.0 mL with the same solution.

Reference solution (a) Dissolve the contents of a vial of *valganciclovir for system suitability CRS* (containing impurities A, B, C, D and N) in 1 mL of a 0.103 g/L solution of *hydrochloric acid R*.

Reference solution (b) Dilute 1.0 mL of the test solution to 100.0 mL with a 0.103 g/L solution of *hydrochloric acid R*. Dilute 1.0 mL of this solution to 10.0 mL with a 0.103 g/L solution of *hydrochloric acid R*.

Reference solution (c) Dissolve 10.0 mg of *valganciclovir hydrochloride CRS* in a 0.103 g/L solution of *hydrochloric acid R* and dilute to 50.0 mL with the same solution.

Column:

— *size*: *l* = 0.15 m, Ø = 4.6 mm;

— *stationary phase*: *octadecylsilyl silica gel for chromatography R* (3.5 µm).

Mobile phase:

— *mobile phase A*: a 11.5 g/L solution of *ammonium dihydrogen phosphate R*, adjusted to pH 2.8 with *phosphoric acid R*;

— *mobile phase B*: *methanol R*;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 5	92	8
5 - 15	92 → 80	8 → 20
15 - 30	80 → 30	20 → 70

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 254 nm.

Autosampler Set at 5 °C.

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

Identification of impurities Use the chromatogram supplied with *valganciclovir for system suitability CRS* and the chromatogram obtained with reference solution (a) to identify the peaks due to impurities A, B, C and D.

Relative retention With reference to valganciclovir (retention time of the 1st peak ((*R*)-ester) = about 7 min): impurity B = about 0.3; impurity A = about 0.4; impurity C = about 0.9; impurity D = about 1.3 (impurity D may be eluted as 1 or 2 peaks).

System suitability Reference solution (a):

— *resolution*: minimum 2.5 between the peaks due to the 2 isomers of valganciclovir;

— *peak-to-valley ratio*: minimum 5.0, where H_p = height above the baseline of the peak due to impurity C and H_v = height above the baseline of the lowest point of the curve separating this peak from the 1st peak due to valganciclovir ((*R*)-ester).

Calculation of percentage contents:

— *correction factors*: multiply the peak areas of the following impurities by the corresponding correction factor: impurity A = 0.7; impurity B = 0.5;

— for each impurity, use the concentration of valganciclovir hydrochloride in reference solution (b) and the areas of the peaks due to valganciclovir ((*R*)-ester and (*S*)-ester).

Limits:

— *impurity A*: maximum 1.5 per cent;

— *impurity D*: maximum 0.5 per cent, for the sum of the areas of the 2 peaks;

— *impurity B*: maximum 0.2 per cent;

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

— *total (including impurity N)*: maximum 2.0 per cent;

— *reporting threshold*: 0.05 per cent.

Diastereoisomer ratio

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

Limit Test solution:

— the ratio of the area of the peak due to the (*R*)-ester of valganciclovir to the sum of the areas of the peaks due to the (*R*)-ester and (*S*)-ester of valganciclovir is between 0.45 and 0.55.

Impurity N

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

Column:

— *size*: *l* = 0.15 m, Ø = 4.6 mm;

— *stationary phase*: phenylsilyl silica gel for chromatography R (3.5 µm);

— *temperature*: 30 °C.

Mobile phase:

— *mobile phase A*: dilute 2.5 mL of triethylamine R in 1000 mL of water for chromatography R and adjust to pH 3.0 with trifluoroacetic acid R;

— *mobile phase B*: methanol R;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 10	93	7
10 - 20	93 → 70	7 → 30

Identification of impurities Use the chromatogram supplied with valganciclovir for system suitability CRS and the chromatogram obtained with reference solution (a) to identify the peak due to impurity N.

Relative retention With reference to valganciclovir (retention time of the 1st peak ((*R*)-ester) = about 7 min): impurity N (isomer 1) = about 1.2; impurity N (isomer 2) = about 1.3.

System suitability Reference solution (a):

— resolution: minimum 1.5 between the 2nd peak due to valganciclovir ((*S*)-ester) and the 1st peak due to impurity N (isomer 1).

Calculation of percentage contents:

— for impurity N, use the concentration of valganciclovir hydrochloride in reference solution (b) and the areas of the peaks due to valganciclovir (*R*)-ester and (*S*)-ester.

Limit:

— *impurity N*: maximum 0.2 per cent for the sum of the 2 isomers.

Water (2.5.12)

Maximum 8.0 per cent, determined on 0.100 g.

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 modifications.

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

Calculate the percentage content of $C_{14}H_{23}ClN_6O_5$ (sum of the 2 isomers of valganciclovir hydrochloride) taking into account the assigned content of *valganciclovir hydrochloride CRS*.

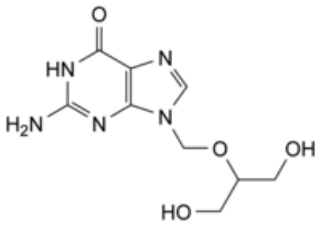
STORAGE

In an airtight container.

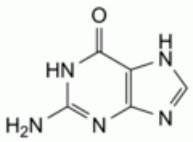
IMPURITIES

Specified impurities *A, B, D, N, T*.

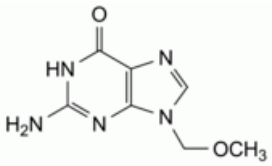
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical 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) *C, E, F, H, I, J, K, L, M, O, P, Q, R, S*.



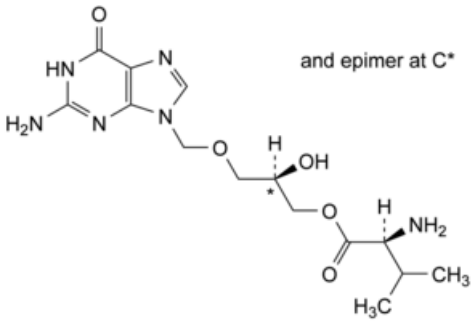
A. 2-amino-9-[[(1,3-dihydroxypropan-2-yl)oxy]methyl]-1,9-dihydro-6*H*-purin-6-one (ganciclovir),



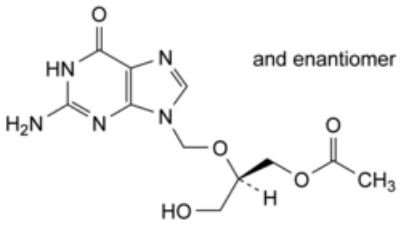
B. 2-amino-1,7-dihydro-6*H*-purin-6-one (guanine),



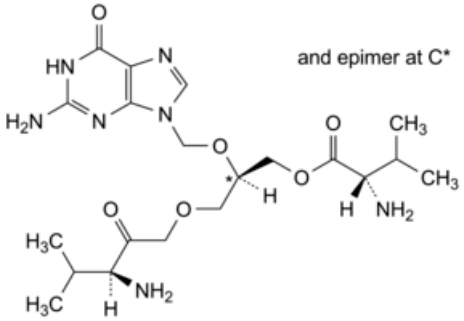
C. 2-amino-9-(methoxymethyl)-1,9-dihydro-6*H*-purin-6-one,



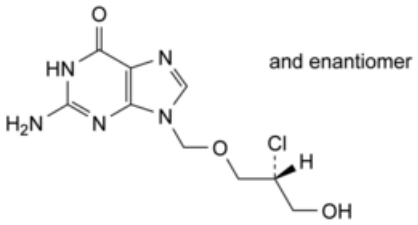
D. (2*RS*)-3-[(2-amino-6-oxo-1,6-dihydro-9*H*-purin-9-yl)methoxy]-2-hydroxypropyl L-valinate,



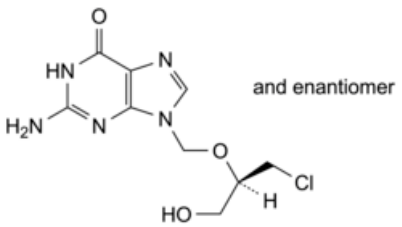
E. (2*RS*)-2-[(2-amino-6-oxo-1,6-dihydro-9*H*-purin-9-yl)methoxy]-3-hydroxypropyl acetate,



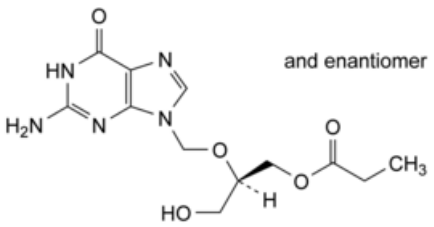
F. (2*RS*)-3-[[(3*S*)-3-amino-4-methyl-2-oxopentyl]oxy]-2-[(2-amino-6-oxo-1,6-dihydro-9*H*-purin-9-yl)methoxy]propyl L-valinate,



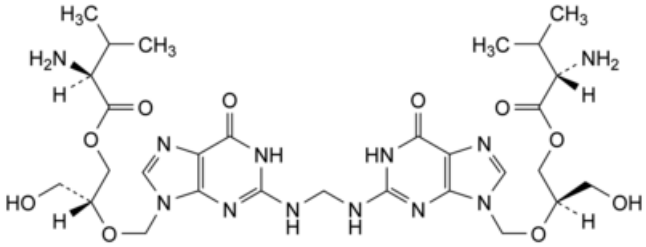
H. 2-amino-9-[[(2*RS*)-2-chloro-3-hydroxypropoxy]methyl]-1,9-dihydro-6*H*-purin-6-one,



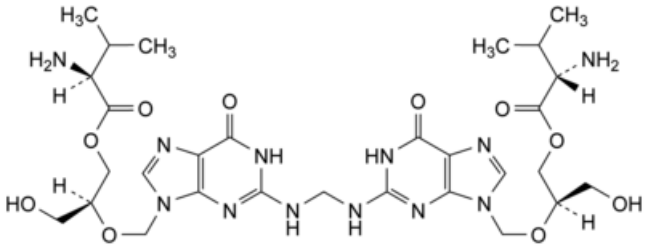
I. 2-amino-9-[[[(2*RS*)-1-chloro-3-hydroxypropan-2-yl]oxy]methyl]-1,9-dihydro-6*H*-purin-6-one,



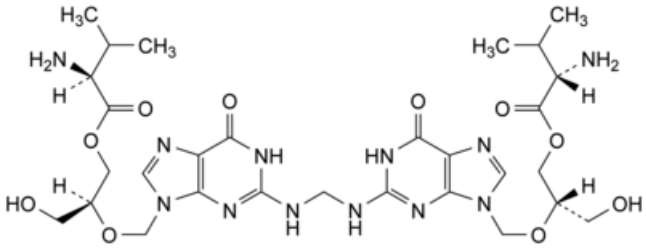
J. (2*RS*)-2-[(2-amino-6-oxo-1,6-dihydro-9*H*-purin-9-yl)methoxy]-3-hydroxypropyl propanoate,



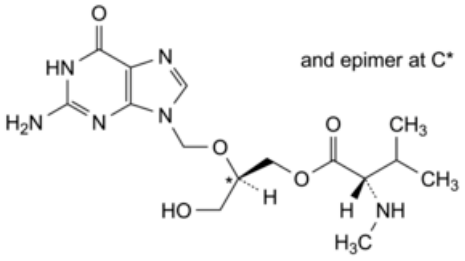
K. [methylenebis[azanediyl(6-oxo-1,6-dihydro-9*H*-purine-2,9-diyl)methyleneoxy[(2*R*)-3-hydroxypropane-2,1-diyl]]] di-L-valinate,



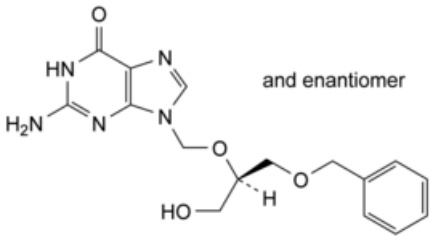
L. (2*R*)-3-hydroxy-2-[[2-[[[[9-[[[(2*S*)-1-hydroxy-3-(L-valyloxy)propan-2-yl]oxy]methyl]-6-oxo-1,6-dihydro-9*H*-purin-2-yl]amino]methyl]amino]-6-oxo-1,6-dihydro-9*H*-purin-9-yl]methoxy]propyl L-valinate,



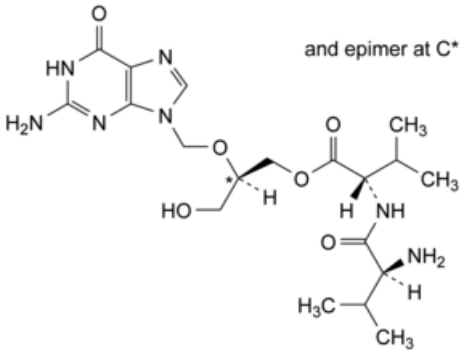
M. [methylenebis[azanediyl(6-oxo-1,6-dihydro-9*H*-purine-2,9-diyl)methyleneoxy[(2*S*)-3-hydroxypropane-2,1-diyl]]] di-L-valinate,



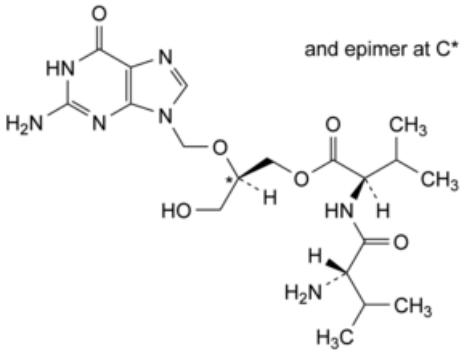
N. (2*RS*)-2-[(2-amino-6-oxo-1,6-dihydro-9*H*-purin-9-yl)methoxy]-3-hydroxypropyl *N*-methyl-L-valinate,



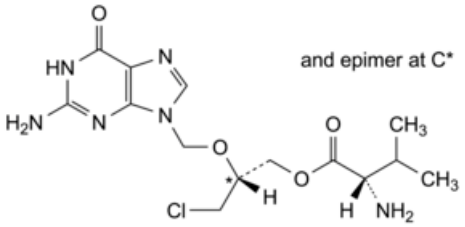
O. 2-amino-9-[[[(2*RS*)-1-(benzyloxy)-3-hydroxypropan-2-yl]oxy]methyl]-1,9-dihydro-6*H*-purin-6-one,



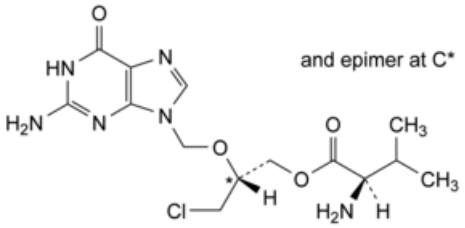
P. (2*RS*)-2-[(2-amino-6-oxo-1,6-dihydro-9*H*-purin-9-yl)methoxy]-3-hydroxypropyl L-valyl-L-valinate,



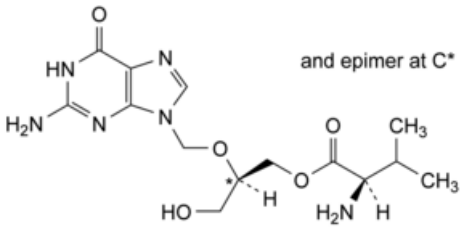
Q. (2*RS*)-2-[(2-amino-6-oxo-1,6-dihydro-9*H*-purin-9-yl)methoxy]-3-hydroxypropyl D-valyl-D-valinate,



R. (2*RS*)-2-[(2-amino-6-oxo-1,6-dihydro-9*H*-purin-9-yl)methoxy]-3-chloropropyl L-valinate,



S. (2*RS*)-2-[(2-amino-6-oxo-1,6-dihydro-9*H*-purin-9-yl)methoxy]-3-chloropropyl D-valinate,



T. (2*RS*)-2-[(2-amino-6-oxo-1,6-dihydro-9*H*-purin-9-yl)methoxy]-3-hydroxypropyl D-valinate.