



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

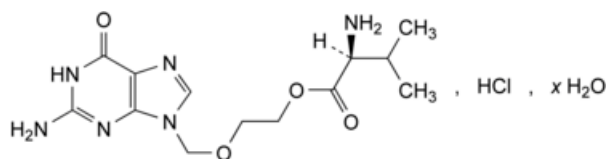
Valaciclovir Hydrochloride Hydrate



[General Notices](#)

Valaciclovir Hydrochloride, Hydrated

(Ph. Eur. monograph 2751)



$C_{13}H_{21}ClN_6O_4 \cdot xH_2O$ 360.8 (anhydrous substance) 1218948-84-5

Action and use

Purine nucleoside analogue; antiviral (herpesviruses).

Preparation

[Valaciclovir Tablets](#)

Ph Eur

DEFINITION

2-[(2-Amino-6-oxo-1,6-dihydro-9H-purin-9-yl)methoxy]ethyl L-valinate hydrochloride hydrate.

Content

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

It contains a variable quantity of water.

CHARACTERS

Appearance

White or almost white powder, hygroscopic.

Solubility

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

It shows polymorphism ([5.9](#)).

IDENTIFICATION

A. Infrared absorption spectrophotometry ([2.2.24](#)).

Preparation Dissolve the substance to be examined in the minimum volume of [water R](#), evaporate to dryness at room temperature and record the spectrum using the residue.

Comparison Repeat the operations using [anhydrous valaciclovir hydrochloride CRS](#).

B. It complies with the limit for impurity R (see test A for related substances).

C. Water (see Tests).

D. It gives reaction (a) of chlorides ([2.3.1](#)).

TESTS

Impurities G and S

Thin-layer chromatography ([2.2.27](#)).

Test solution Dissolve 0.250 g of the substance to be examined in 2 mL of [water R](#) and dilute to 5.0 mL with [ethanol \(96 per cent\) R](#).

Reference solution Dissolve 5.0 mg of [valaciclovir impurity G CRS](#) and 5.0 mg of [valaciclovir impurity S CRS](#) in a mixture of 2 mL of [water R](#) and 6 mL of [ethanol \(96 per cent\) R](#) and dilute to 10.0 mL with [ethanol \(96 per cent\) R](#). Dilute 0.5 mL of the solution to 10.0 mL with [ethanol \(96 per cent\) R](#).

Plate [TLC silica gel F₂₅₄ plate R](#) (2-10 µm).

Pretreatment Wash the plate with [methanol R](#) until the solvent front has migrated over at least 4/5 of the plate; allow to dry in air.

Mobile phase [concentrated ammonia R](#), [tetrahydrofuran R](#), [methanol R](#), [methylene chloride R](#) (3:12:34:54 V/V/V/V); use freshly prepared mobile phase.

Application 4 µL.

Development Over 4/5 of the plate.

Drying In a current of air.

Detection Examine in ultraviolet light at 254 nm.

Retardation factors Valaciclovir = about 0.3; impurity S = about 0.7; impurity G = about 0.8.

System suitability The chromatogram obtained with the reference solution shows 2 clearly separated spots due to impurities S and G.

Limits:

— *impurity G*: any spot due to impurity G is not more intense than the corresponding spot in the chromatogram obtained with the reference solution (0.05 per cent);

— *impurity S*: any spot due to impurity S is not more intense than the corresponding spot in the chromatogram obtained with the reference solution (0.05 per cent).

Related substances

A. Liquid chromatography ([2.2.29](#)): use the normalisation procedure.

Test solution Dissolve 50.0 mg of the substance to be examined in a 0.5 per cent V/V solution of [hydrochloric acid R](#) and dilute to 100.0 mL with the same solution.

Reference solution (a) Dissolve 2.5 mg of [valaciclovir for system suitability CRS](#) (containing impurities A, B, C, D, H, M and R) in a 0.5 per cent V/V solution of [hydrochloric acid R](#) and dilute to 5.0 mL with the same solution.

Reference solution (b) Dissolve 50.0 mg of [anhydrous valaciclovir hydrochloride CRS](#) in a 0.5 per cent V/V solution of [hydrochloric acid R](#) and dilute to 100.0 mL with the same solution.

Reference solution (c) Dilute 3.0 mL of the test solution to 100.0 mL with a 0.5 per cent V/V solution of [hydrochloric acid R](#). Dilute 1.0 mL of this solution to 100.0 mL with a 0.5 per cent V/V solution of [hydrochloric acid R](#).

Column:

- **size:** $l = 0.15$ m, $\varnothing = 4.0$ mm;
- **stationary phase:** crown-ether silica gel for chiral separation R (5 μ m);
- **temperature:** 10 °C.

Mobile phase [perchloric acid R](#), [methanol R](#), [water for chromatography R](#) (0.5:5:95 V/V/V).

Flow rate 0.75 mL/min.

Detection Spectrophotometer at 254 nm.

Injection 10 μ L of the test solution and reference solutions (a) and (c).

Run time 1.5 times the retention time of valaciclovir.

Identification of impurities Use the chromatogram supplied with [valaciclovir for system suitability CRS](#) and the chromatogram obtained with reference solution (a) to identify the peaks due to impurities A + B, C + R, D and M.

Relative retention With reference to valaciclovir (retention time = about 17 min): impurities A and B = about 0.2; impurities C and R = about 0.6; impurity D = about 0.7; impurity M = about 1.3.

System suitability Reference solution (a):

- **peak-to-valley ratio:** minimum 1.5, 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 impurities C and R.

Limits:

- **correction factor:** for the calculation of content, multiply the peak area of impurities A and B by 0.7;
- **impurity R:** maximum 3.0 per cent; for the calculation, subtract the content of impurity C as determined in test B for related substances from the content of the coeluting impurities C and R as determined in this test;
- **sum of impurities A and B:** maximum 2.0 per cent;
- **disregard limit:** the area of the principal peak in the chromatogram obtained with reference solution (c) (0.03 per cent); disregard any peaks due to impurities other than A + B and C + R.

B. Liquid chromatography ([2.2.29](#)): use the normalisation procedure. *Use the solutions within 24 h of preparation.*

Solvent mixture [ethanol \(96 per cent\) R](#), [water R](#) (20:80 V/V).

Test solution Dissolve 80 mg of the substance to be examined in the solvent mixture and dilute to 100.0 mL with the solvent mixture.

Reference solution (a) Dissolve 1.6 mg of [valaciclovir for system suitability CRS](#) (containing impurities A, B, C, D, H, M and R) in the solvent mixture and dilute to 2.0 mL with the solvent mixture.

Reference solution (b) Dilute 1.0 mL of the test solution to 100.0 mL with the solvent mixture. Dilute 1.0 mL of this solution to 20.0 mL with the solvent mixture.

Reference solution (c) Dissolve 2 mg of [valaciclovir impurity P CRS](#) in the solvent mixture and dilute to 25.0 mL with the solvent mixture. Dilute 1.0 mL of the solution to 100.0 mL with the solvent mixture.

Column:

- **size:** $l = 0.25$ m, $\varnothing = 4.6$ mm;
- **stationary phase:** [end-capped phenylhexylsilyl silica gel for chromatography R](#) (5 μ m);
- **temperature:** 15 °C.

Mobile phase:

— mobile phase A: [trifluoroacetic acid R](#), [water for chromatography R](#) (0.2:100 V/V);

— mobile phase B: [trifluoroacetic acid R](#), [methanol R2](#) (0.2:100 V/V);

Time (min)	Mobile phase A (per cent V/V)	Mobile phase B (per cent V/V)
0 - 5	90	10
5 - 35	90 → 60	10 → 40
35 - 45	60	40

Flow rate 0.8 mL/min.

Detection Spectrophotometer at 254 nm.

Injection 10 µL.

Identification of impurities Use the chromatogram supplied with [valaciclovir for system suitability CRS](#) and the chromatogram obtained with reference solution (a) to identify the peaks due to impurities A, B, C, D, H and M; use the chromatogram obtained with reference solution (c) to identify the peak due to impurity P.

Relative retention With reference to valaciclovir (retention time = about 20 min): impurity A = about 0.3; impurity B = about 0.4; impurity H = about 0.5; impurity C = about 1.06; impurity D = about 1.2; impurity M = about 1.6; impurity P = about 2.0.

System suitability Reference solution (a):

— **peak-to-valley ratio**: minimum 2.0, 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 peak due to valaciclovir.

Limits:

- **impurity M**: maximum 0.6 per cent;
- **impurity D**: maximum 0.3 per cent;
- **impurity C**: maximum 0.2 per cent;
- **impurities H, P**: for each impurity, maximum 0.10 per cent;
- **unspecified impurities**: for each impurity, maximum 0.05 per cent;
- **disregard limit**: 0.6 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.03 per cent); disregard the peaks due to impurities A and B.

Limit:

- **total for tests A and B**: maximum 4.0 per cent.

Water (2.5.12)

4.5 per cent to 11.0 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 test A for related substances with the following modification.

Injection Test solution and reference solution (b).

Calculate the percentage content of $C_{13}H_{21}ClN_6O_4$ taking into account the assigned content of [anhydrous valaciclovir hydrochloride CRS](#).

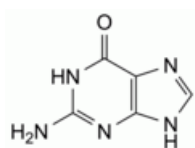
STORAGE

In an airtight container.

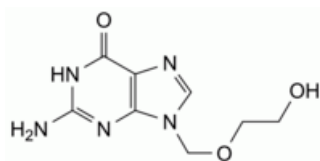
IMPURITIES

Specified impurities A, B, C, D, G, H, M, P, R, S.

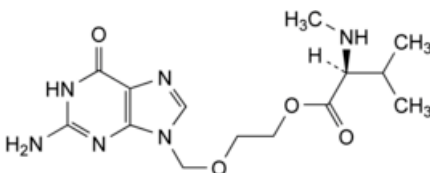
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph [Substances for pharmaceutical 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](#)) I, J, N.



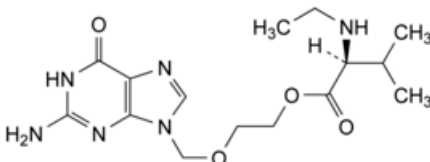
A. 2-amino-1,9-dihydro-6H-purin-6-one (guanine),



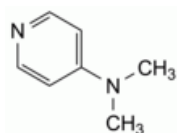
B. 2-amino-9-[(2-hydroxyethoxy)methyl]-1,9-dihydro-6H-purin-6-one (aciclovir),



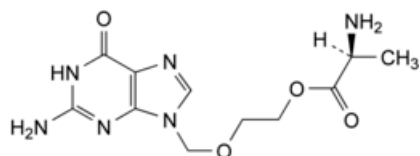
C. 2-[(2-amino-6-oxo-1,6-dihydro-9H-purin-9-yl)methoxy]ethyl N-methyl-L-valinate,



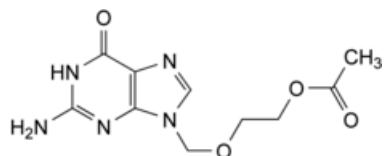
D. 2-[(2-amino-6-oxo-1,6-dihydro-9H-purin-9-yl)methoxy]ethyl N-ethyl-L-valinate,



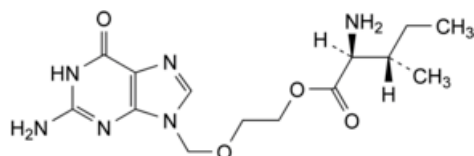
G. N,N-dimethylpyridin-4-amine,



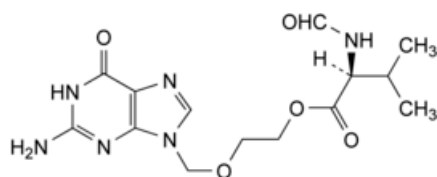
H. 2-[(2-amino-6-oxo-1,6-dihydro-9*H*-purin-9-yl)methoxy]ethyl L-alaninate,



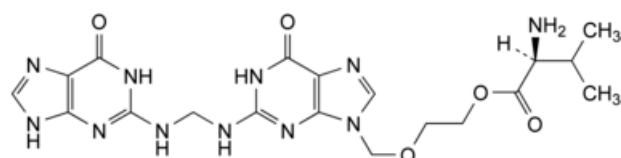
I. 2-[(2-amino-6-oxo-1,6-dihydro-9*H*-purin-9-yl)methoxy]ethyl acetate,



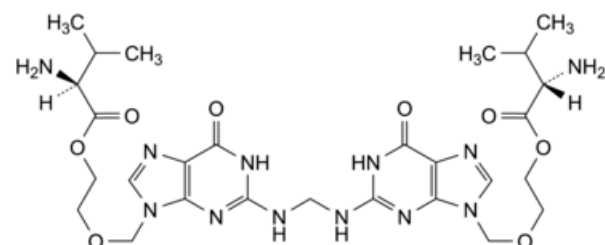
J. 2-[(2-amino-6-oxo-1,6-dihydro-9*H*-purin-9-yl)methoxy]ethyl L-isoleucinate,



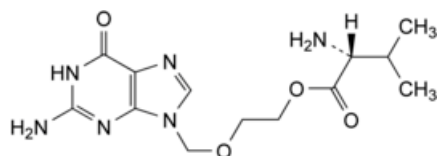
M. 2-[(2-amino-6-oxo-1,6-dihydro-9*H*-purin-9-yl)methoxy]ethyl *N*-formyl-L-valinate,



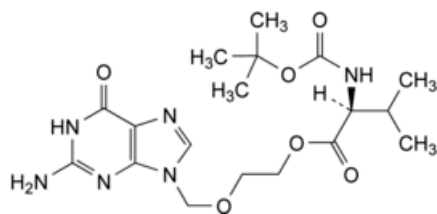
N. 2-[[6-oxo-2-[[[(6-oxo-6,9-dihydro-1*H*-purin-2-yl)amino]methyl]amino]-1,6-dihydro-9*H*-purin-9-yl]methoxy]ethyl L-valinate,



P. [methylenebis[azanediyl(6-oxo-1,6-dihydro-9*H*-purine-2,9-diyl)methyleneoxyethan-2,1-diyl]] di-L-valinate,



R. 2-[(2-amino-6-oxo-1,6-dihydro-9*H*-purin-9-yl)methoxy]ethyl D-valinate,



S. 2-[(2-amino-6-oxo-1,6-dihydro-9*H*-purin-9-yl)methoxy]ethyl *N*-(*tert*-butoxycarbonyl)-L-valinate.

Ph Eur