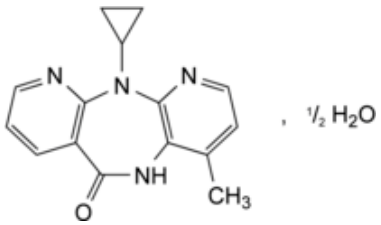
Edition: BP 2025 (Ph. Eur. 11.6 update)

Nevirapine Hemihydrate

General Notices

(Ph. Eur. monograph 2479)



$C_{15}H_{14}N_4O,½H_2O$ 275.3 *220988-26-1*

Action and use

Non-nucleoside reverse transcriptase inhibitor; antiviral (HIV).

Preparation

Nevirapine Oral Suspension

Ph Eur

DEFINITION

11-Cyclopropyl-4-methyl-5,11-dihydro-6*H*-dipyrido[3,2-*b*:2′,3′-*e*][1,4]diazepin-6-one hemihydrate.

Content

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

CHARACTERS

Appearance

White or almost white powder.

Solubility

Practically insoluble in water, slightly soluble in methanol and in methylene chloride.

IDENTIFICATION

A. Infrared absorption spectrophotometry (2.2.24).

Comparison nevirapine hemihydrate CRS.

B. Water (see Tests).

TESTS

Related substances

Liquid chromatography (2.2.29).

Test solution Dissolve 20.0 mg of the substance to be examined in methanol R and sonicate until dissolution is complete. Dilute to 50.0 mL with methanol R.

Reference solution (a) Dilute 1.0 mL of the test solution to 100.0 mL with methanol R. Dilute 1.0 mL of this solution to 10.0 mL with methanol R.

Reference solution (b) Add 1 mL of methanol R to a vial of nevirapine for peak identification CRS (containing impurities A, B and C), mix and sonicate for 1 min.

Reference solution (c) Dissolve 20.0 mg of anhydrous nevirapine CRS in methanol R and sonicate until dissolution is complete. Dilute to 50.0 mL with methanol R.

Column:

— *size*: *l* = 50 mm, Ø = 2.1 mm;

— *stationary phase*: end-capped octadecylsilyl silica gel for chromatography compatible with 100 per cent aqueous mobile phases R (1.8 µm);

— *temperature*: 40 °C.

Mobile phase:

— *mobile phase A*: dissolve 0.77 g of ammonium acetate R in 900 mL of water for chromatography R, adjust to pH 5.6 with acetic acid R and dilute to 1000 mL with water for chromatography R;

— *mobile phase B*: acetonitrile R;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 – 1.35	90	10
1.35 – 3.85	90 → 67	10 → 33
3.85 – 6.70	67 → 60	33 → 40
6.70 – 7.65	60	40

Flow rate 0.7 mL/min.

Detection Spectrophotometer at 282 nm.

Injection 2.0 µL of the test solution and reference solutions (a) and (b).

Identification of impurities Use the chromatogram supplied with *nevirapine for peak identification CRS* and the chromatogram obtained with reference solution (b) to identify the peaks due to impurities A, B and C.

Relative retention With reference to nevirapine (retention time = about 3 min): impurity B = about 0.9; impurity A = about 1.2; impurity C = about 1.3.

System suitability:

— *resolution*: minimum 5.0 between the peaks due to impurity B and nevirapine and minimum 5.0 between the peaks due to nevirapine and impurity A in the chromatogram obtained with reference solution (b);

— *symmetry factor*: maximum 1.7 for the peak due to nevirapine in the chromatogram obtained with reference solution (a).

Calculation of percentage contents:

— for each impurity, use the concentration of nevirapine hemihydrate in reference solution (a).

Limits:

— *impurities A, B, C*: for each impurity, maximum 0.2 per cent;

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

— *total*: maximum 0.6 per cent;

— *reporting threshold*: 0.05 per cent.

Water (*2.5.12*)

3.1 per cent to 3.9 per cent, determined on 0.300 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 modification.

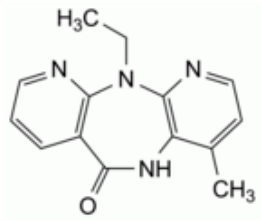
Injection 2.0 µL of the test solution and reference solution (c).

Calculate the percentage content of $C_{15}H_{14}N_4O$ taking into account the assigned content of *anhydrous nevirapine CRS*.

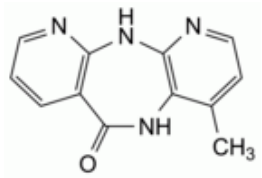
IMPURITIES

Specified impurities *A, B, C.*

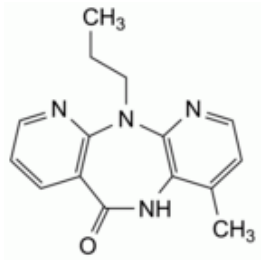
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical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



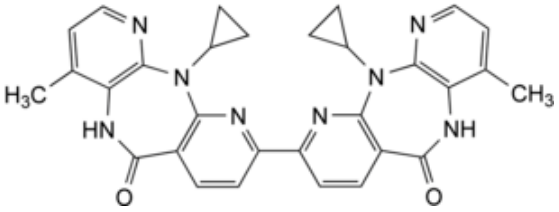
A. 11-ethyl-4-methyl-5,11-dihydro-6*H*-dipyrido[3,2-*b*:2′,3′-*e*][1,4]diazepin-6-one,



B. 4-methyl-5,11-dihydro-6*H*-dipyrido[3,2-*b*:2′,3′-*e*][1,4]diazepin-6-one,



C. 4-methyl-11-propyl-5,11-dihydro-6*H*-dipyrido[3,2-*b*:2′,3′-*e*][1,4]diazepin-6-one,



D. 11,11′-dicyclopropyl-4,4′-dimethyl-5,5′,11,11′-tetrahydro-6*H*,6′*H*-9,9′-bidipyrido[3,2-*b*:2′,3′-*e*][1,4]diazepine-6,6′-dione.

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