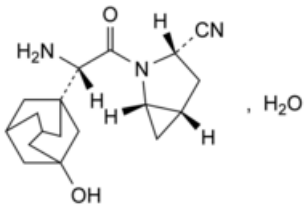
Edition: BP 2025 (Ph. Eur. 11.6 update)

Saxagliptin Monohydrate

General Notices

(Ph. Eur. monograph 3136)



$C_{18}H_{25}N_3O_2,H_2O$ 333.4 *945667-22-1*

Action and use

Dipeptidylpeptidase-4 inhibitor; treatment of type 2 diabetes mellitus.

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DEFINITION

(1*S*,3*S*,5*S*)-2-[(*S*)-Amino(3-hydroxyadamantan-1-yl)acetyl]-2-azabicyclo[3.1.0]hexane-3-carbonitrile monohydrate.

Content

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

PRODUCTION

It is produced by highly stereoselective methods of manufacture; consideration must be given to the formation of potential stereoisomeric impurities during the manufacturing process, and procedures must be implemented for the appropriate control of these impurities.

CHARACTERS

Appearance

White or almost white powder.

Solubility

Sparingly soluble in water, soluble in anhydrous ethanol, very slightly soluble in heptane.

IDENTIFICATION

Infrared absorption spectrophotometry (2.2.24).

Comparison saxagliptin monohydrate CRS.

TESTS

Related substances

Liquid chromatography (2.2.29): use the normalisation procedure.

Test solution Dissolve 54.0 mg of the substance to be examined in mobile phase A and dilute to 50.0 mL with mobile phase A.

Reference solution (a) Dissolve 54.0 mg of saxagliptin monohydrate CRS in mobile phase A and dilute to 50.0 mL with mobile phase A.

Reference solution (b) Dilute 1.0 mL of the test solution to 100.0 mL with mobile phase A. Dilute 1.0 mL of this solution to 20.0 mL with mobile phase A.

Reference solution (c) Dissolve the contents of a vial of saxagliptin impurity mixture CRS (containing impurities A and B) in 1.0 mL of mobile phase A.

Reference solution (d) Dissolve the contents of a vial of saxagliptin for system suitability CRS (containing impurity C) in 1.0 mL of mobile phase A.

Column:

— *size*: *l* = 0.15 m, Ø = 3.0 mm;

— *stationary phase*: end-capped extra-dense bonded octadecylsilyl silica gel for chromatography R (3.5 µm);

— *temperature*: 40 °C.

Mobile phase:

— *mobile phase A*: trifluoroacetic acid R, methanol R2, water for chromatography R (1:100:900 *V/V/V*);

— *mobile phase B*: trifluoroacetic acid R, water for chromatography R, methanol R2 (1:100:900 *V/V/V*);

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 2	100	0
2 - 22	100 → 80	0 → 20
22 - 42	80 → 0	20 → 100

Flow rate 0.6 mL/min.

Detection Spectrophotometer at 215 nm.

Injection 15 µL of the test solution and reference solutions (b), (c) and (d).

Identification of impurities Use the chromatogram obtained with reference solution (c) to identify the peaks due to impurities A and B; use the chromatogram supplied with saxagliptin for system suitability CRS and the chromatogram obtained with reference solution (d) to identify the peak due to impurity C.

Relative retention With reference to saxagliptin (retention time = about 21 min): impurity A = about 0.73; impurity B = about 0.75; impurity C = about 1.1.

System suitability:

— *peak-to-valley ratio*: minimum 1.4, 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 saxagliptin in the chromatogram obtained with reference solution (d); minimum 2.0, where H_p = height above the baseline of the peak due to impurity B and H_v = height above the baseline of the lowest point of the curve separating this peak from the peak due to impurity A in the chromatogram obtained with reference solution (c).

Calculation of percentage content:

— *correction factor*: multiply the peak area of impurity A by 0.7.

Limits:

— *impurities A, B, C*: for each impurity, maximum 0.15 per cent;

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

— *total*: maximum 0.50 per cent;

— *reporting threshold*: 0.05 per cent (reference solution (b)).

Water (*2.5.12*)

5.2 per cent to 6.1 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 Test solution and reference solution (a).

System suitability Reference solution (a):

— *symmetry factor*: maximum 6.0.

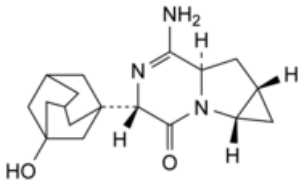
Calculate the percentage content of $C_{18}H_{25}N_3O_2$ taking into account the assigned content of *saxagliptin monohydrate CRS*.

STORAGE

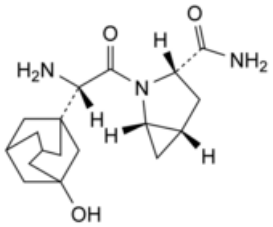
At a temperature of 2 °C to 8 °C.

IMPURITIES

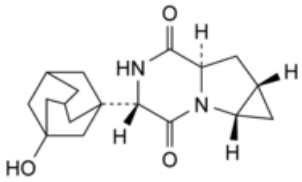
Specified impurities *A, B, C*.



A. (1a*S*,4*S*,6a*R*,7a*S*)-6-amino-4-(3-hydroxyadamantan-1-yl)-1,1a,4,6a,7,7a-hexahydro-3*H*-cyclopropa[4,5]pyrrolo[1,2-*a*]pyrazin-3-one,



B. (1*S*,3*S*,5*S*)-2-[(*S*)-amino(3-hydroxyadamantan-1-yl)acetyl]-2-azabicyclo[3.1.0]hexane-3-carboxamide,



C. (1a*S*,4*S*,6a*R*,7a*S*)-4-(3-hydroxyadamantan-1-yl)hexahydro-1*H*-cyclopropa[4,5]pyrrolo[1,2-*a*]pyrazine-3,6-dione.

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