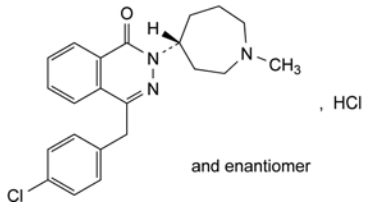
01/2008:1633
corrected 6.0

AZELASTINE HYDROCHLORIDE

Azelastini hydrochloridum



$C_{22}H_{25}Cl_2N_3O$ M_r 418.4
[79307-93-0]

DEFINITION

4-(4-Chlorobenzyl)-2-[(4*RS*)-1-methylhexahydro-1*H*-azepin-4-yl]phthalazin-1(2*H*)-one hydrochloride.

Content: 99.0 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance: white or almost white, crystalline powder.

Solubility: sparingly soluble in water, soluble in ethanol and in methylene chloride.

IDENTIFICATION

A. Infrared absorption spectrophotometry (*2.2.24*).
Comparison: *azelastine hydrochloride CRS*.

B. Solution S (see Tests) gives reaction (a) of chlorides (*2.3.1*).

TESTS

Solution S. Dissolve 1.0 g in *carbon dioxide-free water R* and dilute to 100 mL with the same solvent.

Appearance of solution. Solution S is clear (*2.2.1*) and colourless (*2.2.2, Method II*).

Acidity or alkalinity. To 10 mL of solution S add 0.2 mL of *bromothymol blue solution R1*. Not more than 0.1 mL of *0.01 M hydrochloric acid* or *0.01 M sodium hydroxide* is required to change the colour of the solution.

Related substances. Liquid chromatography (*2.2.29*).

Solvent mixture: *acetonitrile for chromatography R, water R* (45:55 *V/V*).

Test solution. Dissolve 0.125 g of the substance to be examined in the solvent mixture and dilute to 50.0 mL with the solvent mixture.

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

Reference solution (b). Dissolve 1 mg of *azelastine impurity B CRS*, 1 mg of *azelastine impurity D CRS* and 1 mg of *azelastine impurity E CRS* in the test solution and dilute to 20 mL with the test solution.

Column:

– *size*: *l* = 0.25 m, Ø = 4.6 mm,
– *stationary phase*: *nitrile silica gel for chromatography R* (10 µm),
– *temperature*: 30°C.

Mobile phase: dissolve 2.16 g of *sodium octanesulfonate R* and 0.68 g of *potassium dihydrogen phosphate R* in 740 mL of *water for chromatography R*, adjust to pH 3.0-3.1 with *dilute phosphoric acid R*, add 260 mL of *acetonitrile for chromatography R* and mix.

Flow rate: 2.0 mL/min.

Detection: spectrophotometer at 210 nm.

Injection: 10 µL.

Run time: twice the retention time of azelastine.

Relative retention with reference to azelastine (retention time = about 8-9 min): impurity A = about 0.2; impurity B = about 0.3; impurity C = about 0.4; impurity D = about 0.6; impurity E = about 1.4.

System suitability: reference solution (b):

– *resolution*: minimum 4.0 between the peaks due to impurities B and D,
– the peaks due to impurities D and E are baseline separated from the principal peak.

Limits:

– *correction factors*: for the calculation of content, multiply the peak areas of the following impurities by the corresponding correction factor: impurity B = 3.6; impurity D = 0.7; impurity E = 2.1;
– *impurities A, B, C, D, E*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.1 per cent);
– *any other impurity*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.1 per cent);
– *total*: not more than twice the area of the principal peak in the chromatogram obtained with reference solution (a) (0.2 per cent);
– *disregard limit*: 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.05 per cent).

Loss on drying (*2.2.32*): maximum 0.5 per cent, determined on 1.000 g by drying in an oven at 105 °C.

ASSAY

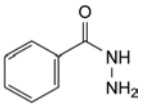
In order to avoid overheating in the reaction medium, mix thoroughly throughout and stop the titration immediately after the end-point has been reached.

Dissolve 0.300 g in 5 mL of *anhydrous formic acid R*. Add 30 mL of *acetic anhydride R*. Titrate quickly with *0.1 M perchloric acid*, determining the end-point potentiometrically (*2.2.20*).

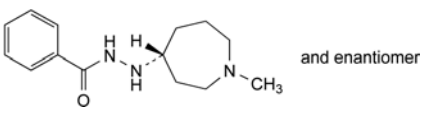
1.0 mL of *0.1 M perchloric acid* is equivalent to 41.84 mg of $C_{22}H_{25}Cl_2N_3O$.

IMPURITIES

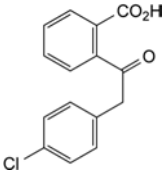
Specified impurities: A, B, C, D, E.



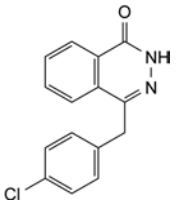
A. benzoyldiazane (benzohydrazide),



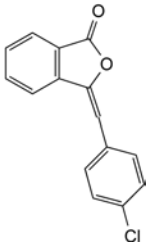
B. 1-benzoyl-2-[(4*RS*)-1-methylhexahydro-1*H*-azepin-4-yl]diazane,



C. 2-[(4-chlorophenyl)acetyl]benzoic acid,



D. 4-(4-chlorobenzyl)phthalazin-1(2*H*)-one,

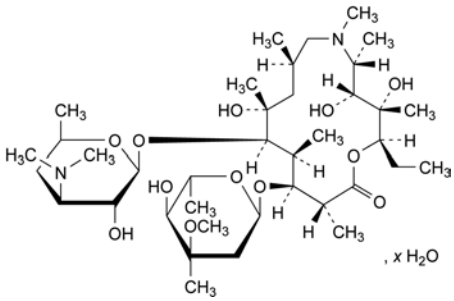


E. 3-(4-chlorobenzylidene)isobenzofuran-1(3*H*)-one.

01/2011:1649

AZITHROMYCIN

Azithromycinum



$C_{38}H_{72}N_2O_{12},xH_2O$ M_r 749 (anhydrous substance)
with x = 1 or 2

Azithromycin monohydrate: [121470-24-4]
Azithromycin dihydrate: [117772-70-0]

DEFINITION

(2*R*,3*S*,4*R*,5*R*,8*R*,10*R*,11*R*,12*S*,13*S*,14*R*)-13-[(2,6-Dideoxy-3-*C*-methyl-3-*O*-methyl-α-L-*ribo*-hexopyranosyl)oxy]-2-ethyl-3,4,10-trihydroxy-3,5,6,8,10,12,14-heptamethyl-11-[[3,4,6-trideoxy-3-(dimethylamino)-β-D-*xylo*-hexopyranosyl]oxy]-1-oxa-6-azacyclopentadecan-15-one. The degree of hydration is 1 or 2.

Semi-synthetic product derived from a fermentation product.

Content: 96.0 per cent to 102.0 per cent (anhydrous substance).

CHARACTERS

Appearance: white or almost white powder.

Solubility: practically insoluble in water, freely soluble in anhydrous ethanol and in methylene chloride.

IDENTIFICATION

Infrared absorption spectrophotometry (*2.2.24*).

Comparison: *azithromycin CRS*.

If the spectra obtained in the solid state show differences, prepare further spectra using 90 g/L solutions in *methylene chloride R*.

TESTS

Solution S. Dissolve 0.500 g in *anhydrous ethanol R* and dilute to 50.0 mL with the same solvent.

Appearance of solution. Solution S is clear (*2.2.1*) and colourless (*2.2.2, Method II*).

pH (*2.2.3*): 9.0 to 11.0.

Dissolve 0.100 g in 25.0 mL of *methanol R* and dilute to 50.0 mL with *carbon dioxide-free water R*.

Specific optical rotation (*2.2.7*): – 45 to – 49 (anhydrous substance), determined on solution S.

Related substances. Liquid chromatography (*2.2.29*).

Solvent mixture. Prepare a 1.73 g/L solution of *ammonium dihydrogen phosphate R* adjusted to pH 10.0 with *ammonia R*. Transfer 350 mL of this solution to a suitable container. Add 300 mL of *acetonitrile R1* and 350 mL of *methanol R1*. Mix well.

Test solution. Dissolve 0.200 g of the substance to be examined in the solvent mixture and dilute to 25.0 mL with the solvent mixture.

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

Reference solution (b). Dissolve the contents of a vial of *azithromycin for system suitability CRS* (containing impurities F, H and J) in 1.0 mL of the solvent mixture and sonicate for 5 min.

Reference solution (c). Dissolve 8.0 mg of *azithromycin for peak identification CRS* (containing impurities A, B, C, E, F, G, I, J, L, M, N, O and P) in 1.0 mL of the solvent mixture.

Column:

– *size*: *l* = 0.25 m, Ø = 4.6 mm;
– *stationary phase*: *end-capped octadecylsilyl amorphous organosilica polymer for mass spectrometry R* (5 µm);
– *temperature*: 60 °C.

Mobile phase:

– *mobile phase A*: 1.80 g/L solution of *anhydrous disodium hydrogen phosphate R* adjusted to pH 8.9 with *dilute phosphoric acid R* or with *dilute sodium hydroxide solution R*;
– *mobile phase B*: *methanol R1, acetonitrile R1* (250:750 *V/V*);

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 25	50 → 45	50 → 55
25 - 30	45 → 40	55 → 60
30 - 80	40 → 25	60 → 75
80 - 81	25 → 50	75 → 50
81 - 93	50	50

Flow rate: 1.0 mL/min.

Detection: spectrophotometer at 210 nm.

Injection: 50 µL.

Identification of impurities: use the chromatogram supplied with *azithromycin for peak identification CRS* and the chromatogram obtained with reference solution (c) to identify the peaks due to impurities A, B, C, E, F, G, I, J, L, M, N, O and P; use the chromatogram supplied with *azithromycin for system suitability CRS* and the chromatogram obtained with reference solution (b) to identify the peak due to impurity H.

Relative retention with reference to azithromycin (retention time = 45-50 min): impurity L = about 0.29; impurity M = about 0.37; impurity E = about 0.43; impurity F = about 0.51; impurity D = about 0.54; impurity J = about 0.54; impurity I = about 0.61; impurity C = about 0.73; impurity N = about 0.76; impurity H = about 0.79; impurity A = about 0.83; impurity P = about 0.92; impurity O = about 1.23; impurity G = about 1.26; impurity B = about 1.31.