

Reference solution (a). Dissolve 5.0 mg of *loperamide hydrochloride CRS* in *methanol R*, add 0.5 ml of the test solution and dilute to 100.0 ml with *methanol R*.

Reference solution (b). Dilute 1.0 ml of the test solution to 20.0 ml with *methanol R*. Dilute 1.0 ml of this solution to 25.0 ml with *methanol R*.

Column:

- size: $l = 0.10$ m, $\varnothing = 4.6$ mm,
- stationary phase: base-deactivated octadecylsilyl silica gel for chromatography R (3 μ m),
- temperature: 35 °C.

Mobile phase:

- mobile phase A: 17.0 g/l solution of *tetrabutylammonium hydrogen sulphate R1*,
- mobile phase B: *acetonitrile R*,

Time (min)	Mobile phase A (per cent V/V)	Mobile phase B (per cent V/V)
0 - 15	90 → 30	10 → 70
15 - 17	30	70
17 - 19	30 → 90	70 → 10
19 - 24	90	10

Flow rate: 1.5 ml/min.

Detection: spectrophotometer at 220 nm.

Injection: 10 μ l.

Relative retention with reference to *loperamide oxide* (retention time = about 7 min): impurity A = about 0.9; impurity B = about 1.11; impurity C = about 1.13.

System suitability: reference solution (a):

- resolution: minimum 3.8 between the peaks due to *loperamide oxide* and impurity A.

Limits:

- impurities A, B, C: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (0.2 per cent),
- any other impurity: not more than 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.1 per cent),
- total: not more than 1.5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.3 per cent),
- disregard limit: 0.25 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.05 per cent).

Water (2.5.12): 3.4 per cent to 4.2 per cent, determined on 0.500 g.

Sulphated ash (2.4.14): maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Dissolve 0.350 g in 50 ml of a mixture of 1 volume of *anhydrous acetic acid R* and 7 volumes of *methyl ethyl ketone R*. Titrate with 0.1 M *perchloric acid* using 0.2 ml of *naphtholbenzein solution R* as indicator.

1 ml of 0.1 M *perchloric acid* is equivalent to 49.30 mg of $C_{29}H_{33}ClN_2O_2$.

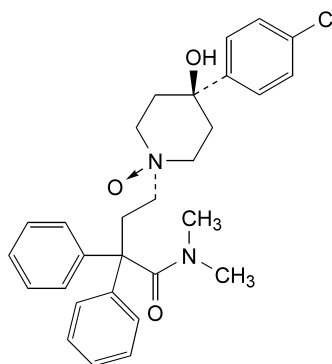
STORAGE

In an airtight container, protected from light.

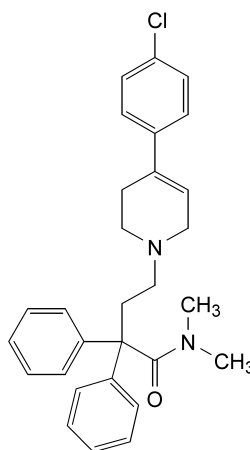
IMPURITIES

Specified impurities: A, B, C.

A. *loperamide*,



B. 4-[*cis*-4-(4-chlorophenyl)-4-hydroxy-1-oxidopiperidin-1-yl]-*N,N*-dimethyl-2,2-diphenylbutanamide,

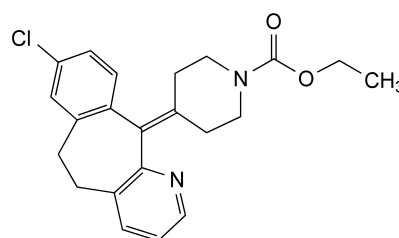


C. 4-[4-(4-chlorophenyl)-3,6-dihydropyridin-1(2*H*)-yl]-*N,N*-dimethyl-2,2-diphenylbutanamide.

01/2008:2124

LORATADINE

Loratadinum



$C_{22}H_{23}ClN_2O_2$
[79794-75-5]

M_r 382.9

DEFINITION

Ethyl 4-(8-chloro-5,6-dihydro-11*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridin-11-ylidene)piperidine-1-carboxylate.

Content: 98.5 per cent to 101.5 per cent (dried substance).

CHARACTERS

Appearance: white or almost white, crystalline powder.

Solubility: practically insoluble in water, freely soluble in acetone and in methanol.

It shows polymorphism (5.9).

IDENTIFICATION

Infrared absorption spectrophotometry (2.2.24).

Comparison: *loratadine CRS*.

If the spectra obtained in the solid state show differences, dissolve the substance to be examined and the reference substance separately in *acetone R*, evaporate to dryness and record new spectra using the residues.

TESTS

Appearance of solution. The solution is clear (2.2.1) and not more intensely coloured than reference solution BY₅ (2.2.2, Method II).

Dissolve 1.0 g in *methanol R* and dilute to 20.0 ml with the same solvent.

Impurity H. Gas chromatography (2.2.28).

Internal standard solution. Dissolve 25 mg of *isoamyl benzoate R* in *methylene chloride R* and dilute to 100 ml with the same solvent. Dilute 5.0 ml of this solution to 50 ml with *methylene chloride R*.

Test solution. Dissolve 25.0 mg of the substance to be examined in *methylene chloride R*, add 1.0 ml of reference solution (a) and 1.0 ml of the internal standard solution and dilute to 5.0 ml with *methylene chloride R*.

Reference solution (a). Dissolve 25.0 mg of *loratadine impurity H CRS* in *methylene chloride R* and dilute to 100.0 ml with the same solvent. Dilute 5.0 ml of this solution to 50.0 ml with *methylene chloride R*.

Reference solution (b). To 1.0 ml of reference solution (a) add 1.0 ml of the internal standard solution and dilute to 5.0 ml with *methylene chloride R*.

Column:

- **material:** fused silica;
- **size:** $l = 25$ m, $\emptyset = 0.32$ mm;
- **stationary phase:** *poly(dimethyl)siloxane R* (film thickness 0.52 μ m).

Carrier gas: *helium for chromatography R*.

Flow rate: 1.0 ml/min.

Split ratio: 1:30.

Temperature:

	Time (min)	Temperature (°C)
Column	0 - 1	80
	1 - 23	80 → 300
	23 - 33	300
Injection port		260
Detector		300

Detection: flame ionisation.

Injection: 1 μ l of the test solution and reference solution (b).

Relative retention with reference to loratadine (retention time = about 32 min): impurity H = about 0.33; isoamyl benzoate = about 0.37.

System suitability: reference solution (b):

- **resolution:** minimum 2.0 between the peaks due to impurity H and isoamyl benzoate;
- **signal-to-noise ratio:** minimum 10 for the peak due to impurity H.

Limit:

- **impurity H:** calculate the ratio (R) of the area of the peak due to impurity H to the area of the peak due to isoamyl benzoate from the chromatogram obtained with reference solution (b); from the chromatogram obtained with the test solution, calculate the ratio of the area of the peak due to impurity H to the area of the peak due to isoamyl benzoate: this ratio is not greater than twice R (0.1 per cent).

Related substances. Liquid chromatography (2.2.29).

Test solution. Dissolve 25.0 mg of the substance to be examined in the mobile phase and dilute to 25.0 ml with the mobile phase.

Reference solution (a). Dissolve 5 mg of *loratadine impurity F CRS* in the mobile phase and dilute to 25 ml with the mobile phase. Dilute 1 ml of this solution to 10 ml with the mobile phase.

Reference solution (b). Dissolve 5 mg of *loratadine for system suitability CRS* (containing impurities A and E) in the mobile phase, add 0.5 ml of reference solution (a) and dilute to 5 ml with the mobile phase.

Reference solution (c). Dilute 1.0 ml of the test solution to 100.0 ml with the mobile phase. Dilute 1.0 ml of this solution to 10.0 ml with the mobile phase.

Column:

- **size:** $l = 0.25$ m, $\emptyset = 4.6$ mm;
- **stationary phase:** spherical *end-capped octadecylsilyl silica gel for chromatography R* (5 μ m) with very low silanol activity;
- **temperature:** 40 °C.

Mobile phase: mix 30 volumes of *methanol R*, 35 volumes of a 6.8 g/l solution of *potassium dihydrogen phosphate R* previously adjusted to pH 2.80 ± 0.05 with *phosphoric acid R* and 40 volumes of *acetonitrile R*.

Flow rate: 1.5 ml/min.

Detection: spectrophotometer at 220 nm.

Injection: 20 μ l of the test solution and reference solutions (b) and (c).

Run time: 5 times the retention time of loratadine.

Identification of impurities: use the chromatogram supplied with *loratadine for system suitability CRS* and the chromatogram obtained with reference solution (b) to identify the peaks due to impurities A and E.

Relative retention with reference to loratadine (retention time = about 12 min): impurity D = about 0.2; impurity B = about 0.4; impurity F = about 0.9; impurity E = about 1.1; impurity A = about 2.4; impurity C = about 2.7.

System suitability: reference solution (b):

- **peak-to-valley ratio:** minimum 2.5, where H_p = height above the baseline of the peak due to impurity E and H_v = height above the baseline of the lowest point of the curve separating this peak from the peak due to loratadine.

Limits:

- **correction factors:** for the calculation of content, multiply the peak areas of the following impurities by the corresponding correction factor: impurity A = 1.7; impurity E = 3.4; impurity F = 1.6;
- **impurity F:** not more than twice the area of the principal peak in the chromatogram obtained with reference solution (c) (0.2 per cent);
- **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 (c) (0.1 per cent);
- **unspecified impurities:** for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (c) (0.10 per cent);
- **total:** not more than 5 times the area of the principal peak in the chromatogram obtained with reference solution (c) (0.5 per cent);

– *disregard limit*: 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (c) (0.05 per cent).

Sulphates (2.4.13): maximum 150 ppm.

Ignite 1.33 g at 800 ± 25 °C and take up the residue with 20 ml of *distilled water R*. Filter, if necessary, through paper free from sulphates. Repeat the filtration with new paper filters until the filtrate is no longer turbid.

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

Sulphated ash (2.4.14): maximum 0.1 per cent, determined on 1.0 g.

ASSAY

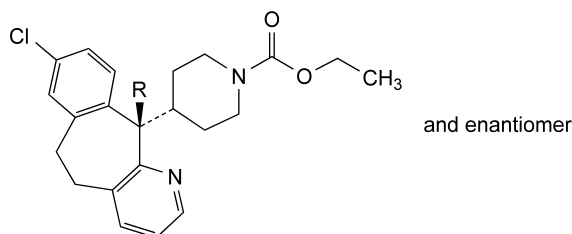
Dissolve 0.300 g in 50 ml of *glacial acetic acid R*. Titrate with 0.1 M *perchloric acid*, determining the end-point potentiometrically (2.2.20).

1 ml of 0.1 M *perchloric acid* is equivalent to 38.29 mg of $C_{22}H_{23}ClN_2O_2$.

IMPURITIES

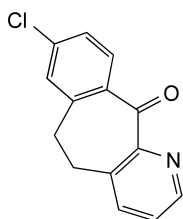
Specified impurities: A, B, C, D, E, F, H.

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*): G.

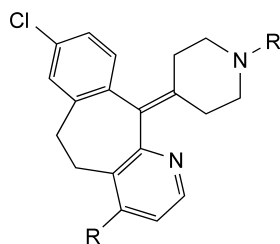


A. R = OH: ethyl 4-[(11*RS*)-8-chloro-11-hydroxy-6,11-dihydro-5*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridin-11-yl]piperidine-1-carboxylate,

F. R = F: ethyl 4-[(11*RS*)-8-chloro-11-fluoro-6,11-dihydro-5*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridin-11-yl]piperidine-1-carboxylate,



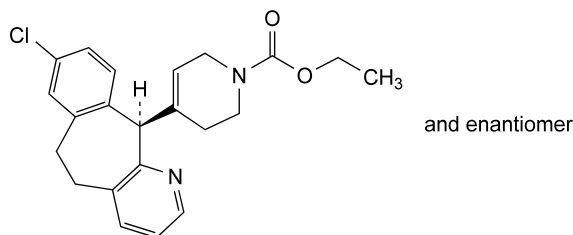
B. 8-chloro-5,6-dihydro-11*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridin-11-one,



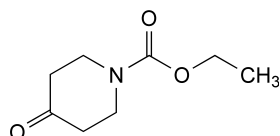
C. R = Cl, R' = CO-OC₂H₅: ethyl 4-(4,8-dichloro-5,6-dihydro-11*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridin-11-ylidene)piperidine-1-carboxylate,

D. R = R' = H: 8-chloro-11-(piperidin-4-ylidene)-6,11-dihydro-5*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridine,

G. R = H, R' = CH₃: 8-chloro-11-(1-methylpiperidin-4-ylidene)-6,11-dihydro-5*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridine,



E. ethyl 4-[(11*RS*)-8-chloro-6,11-dihydro-5*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridin-11-yl]-3,6-dihydropyridine-1(2*H*)-carboxylate,

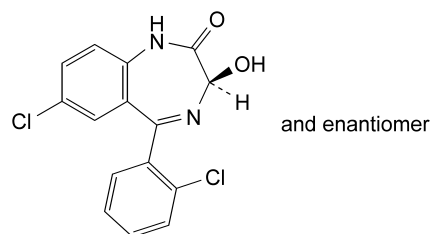


H. ethyl 4-oxopiperidine-1-carboxylate.

01/2008:1121
corrected 6.0

LORAZEPAM

Lorazepamum



$C_{15}H_{10}Cl_2N_2O_2$
[846-49-1]

M_r 321.2

DEFINITION

(3*RS*)-7-Chloro-5-(2-chlorophenyl)-3-hydroxy-1,3-dihydro-2*H*-1,4-benzodiazepin-2-one.

Content: 98.5 per cent to 102.0 per cent (dried substance).

CHARACTERS

Appearance: white or almost white, crystalline powder.