*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, Ø = 4.6 mm,
– *stationary phase*: *base-deactivated octadecylsilyl silica gel for chromatography R* (3 µm),
– *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 µl.

*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 $C_{29}H_{33}ClN_2O_3$.

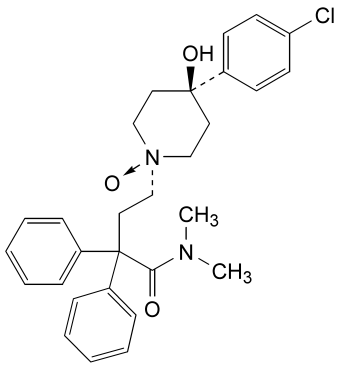
STORAGE

In an airtight container, protected from light.

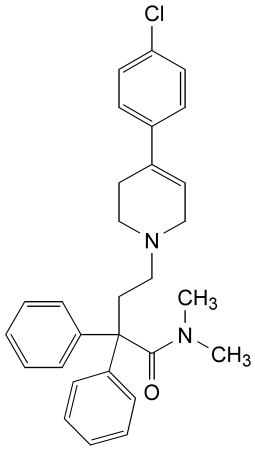
IMPURITIES

*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,

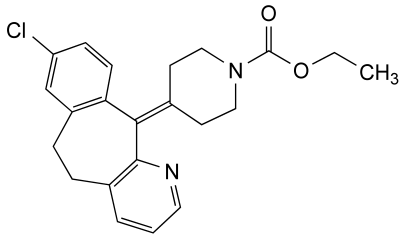


C. 4-[4-(4-chlorophenyl)-3,6-dihydropyridin-1(2*H*)-yl]-*N*,*N*-dimethyl-2,2-diphenylbutanamide.

**01/2008:2124**

# LORATADINE

## Loratadinum



$C_{22}H_{23}ClN_2O_2$ $M_r$ 382.9

[79794-75-5]

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 $BY_5$ (*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, Ø = 0.32 mm;
- *stationary phase*: *poly(dimethyl)siloxane R* (film thickness 0.52 µm).

*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 µl 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, Ø = 4.6 mm;
- *stationary phase*: spherical *end-capped octadecylsilyl silica gel for chromatography R* (5 µm) 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 µl 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

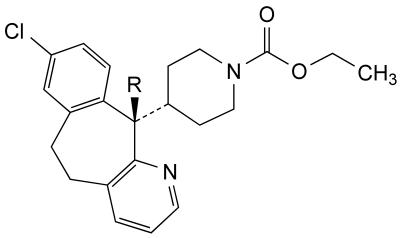
Dissolve 0.300 g in 50 ml of *glacial acetic acid R*. Titrate with *0.1 M perchloric acid*, determining the end-point potentiometrically (*2.2.20*).

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.*

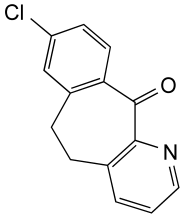
*Other detectable impurities* (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph *Substances for pharmaceutical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



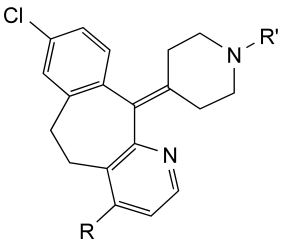
and enantiomer

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,



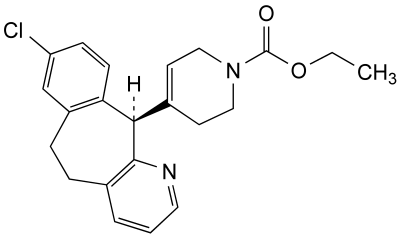

B. 8-chloro-5,6-dihydro-11*H*-benzo[5,6]cyclohepta-[1,2-*b*]pyridin-11-one,




C. R = Cl, R′ = CO-$OC_2H_5$: ethyl 4-(4,8-dichloro-5,6-dihydro-11*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridin-11-ylidene)piperidine-1-carboxylate,

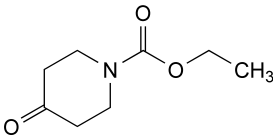
D. R = R′ = H: 8-chloro-11-(piperidin-4-ylidene)-6,11-dihydro-5*H*-benzo[5,6]cycloheptа[1,2-*b*]pyridine,

G. R = H, R′ = $CH_3$: 8-chloro-11-(1-methylpiperidin-4-ylidene)-6,11-dihydro-5*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridine,



and enantiomer

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,

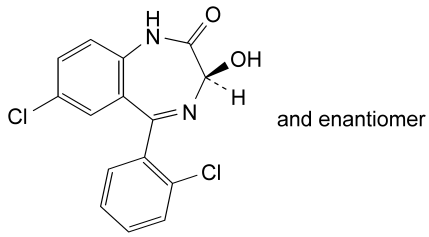



H. ethyl 4-oxopiperidine-1-carboxylate.

**01/2008:1121**
**corrected 6.0**

# LORAZEPAM

## Lorazepamum



and enantiomer

$C_{15}H_{10}Cl_2N_2O_2$ $M_r$ 321.2
[846-49-1]

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.