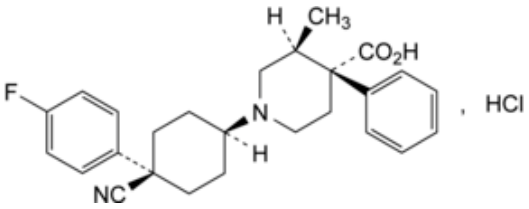
Edition: BP 2025 (Ph. Eur. 11.6 update)

Levocabastine Hydrochloride

General Notices

(Ph. Eur. monograph 1484)



$C_{26}H_{30}ClFN_2O_2$ 457.0 *79547-78-7*

Action and use

Histamine H_1 receptor antagonist; antihistamine.

Ph Eur

DEFINITION

(3*S*,4*R*)-1-[*cis*-4-Cyano-4-(4-fluorophenyl)cyclohexyl]-3-methyl-4-phenylpiperidine-4-carboxylic acid hydrochloride.

Content

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

CHARACTERS

Appearance

White or almost white powder.

Solubility

Practically insoluble in water, sparingly soluble in methanol, slightly soluble in ethanol (96 per cent) and in a 2 g/L solution of sodium hydroxide.

IDENTIFICATION

A. Specific optical rotation (see Tests).
B. Infrared absorption spectrophotometry (2.2.24).

Comparison *levocabastine hydrochloride CRS*.

C. Dissolve 50 mg in a mixture of 0.4 mL of *ammonia R* and 2 mL of *water R*. Mix, allow to stand for 5 min and filter. Acidify the filtrate with *dilute nitric acid R*. It gives reaction (a) of chlorides (2.3.1).

TESTS

Solution S

Dissolve 0.250 g in *methanol R* and dilute to 25.0 mL with the same solvent.

Appearance of solution

Solution S is clear (2.2.1) and not more intensely coloured than reference solution Y_7 (2.2.2, *Method II*).

Specific optical rotation (2.2.7)

-106 to -102 (dried substance), determined on solution S.

Related substances

Liquid chromatography (2.2.29). *Carry out the test protected from light*.

Test solution Dissolve 50 mg of the substance to be examined in *methanol R* and dilute to 10.0 mL with the same solvent.

Reference solution (a) Dissolve the contents of a vial of *levocabastine for system suitability 1 CRS* (containing impurities A, B, E, J and K) in 1 mL of *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 10.0 mL with *methanol R*.

Column:

— *size*: *l* = 0.10 m, Ø = 2.1 mm;

— *stationary phase*: *end-capped ethylene-bridged phenylsilyl silica gel for chromatography (hybrid material) R* (1.7 µm);

— *temperature*: 60 °C.

Mobile phase:

— *mobile phase A*: 17 g/L solution of *tetrabutylammonium hydrogen sulfate R*;

— *mobile phase B*: *acetonitrile R1*;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 0.5	95	5
0.5 - 3.5	95 → 90	5 → 10
3.5 - 6.0	90 → 85	10 → 15
6.0 - 11.0	85 → 70	15 → 30
11.0 - 14.5	70 → 20	30 → 80
14.5 - 15.5	20	80

Flow rate 0.45 mL/min.

Detection Spectrophotometer at 214 nm.

Injection 2.0 µL.

Identification of impurities Use the chromatogram supplied with *levocabastine for system suitability 1 CRS* and the chromatogram obtained with reference solution (a) to identify the peaks due to impurities A, B, E, J and K.

Relative retention With reference to levocabastine (retention time = about 6.5 min): impurity A = about 0.85; impurity J = about 0.86; impurity B = about 0.90; impurity E = about 0.94; impurity K = about 1.07.

System suitability Reference solution (a):

— *peak-to-valley ratio*: minimum 2.9, where H_p = height above the baseline of the peak due to impurity K and H_v = height above the baseline of the lowest point of the curve separating this peak from the peak due to levocabastine; minimum 5.0, where H_p = height above the baseline of the peak due to impurity J and H_v = height above the baseline of the lowest point of the curve separating this peak from the peak due to impurity A.

Calculation of percentage contents:

— for each impurity, use the concentration of levocabastine hydrochloride in reference solution (b).

Limits:

— *impurity E*: maximum 0.4 per cent;

— *impurity A*: maximum 0.2 per cent;

— *impurity B*: maximum 0.15 per cent;

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

— *total*: maximum 0.6 per cent;

— *reporting threshold*: 0.05 per cent.

Impurity C

Liquid chromatography (*2.2.29*). *Carry out the test protected from light.*

Test solution Dissolve 50 mg of the substance to be examined in *methanol R* and dilute to 10.0 mL with the same solvent.

Reference solution (a) Dissolve the contents of a vial of *levocabastine for system suitability 2 CRS* (containing impurity C) in 1 mL of *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 10.0 mL with *methanol R*.

Column:

— *size*: *l* = 0.15 m, 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*: 35 °C.

Mobile phase:

— *mobile phase A*: 17 g/L solution of *tetrabutylammonium hydrogen sulfate R*;

— *mobile phase B*: *acetonitrile R1*;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 0.5	90	10
0.5 - 15.5	90 → 80	10 → 20
15.5 - 20.5	80 → 50	20 → 50

Flow rate 0.30 mL/min.

Detection Spectrophotometer at 214 nm.

Injection 2.0 µL.

Identification of impurities Use the chromatogram supplied with *levocabastine for system suitability 2 CRS* and the chromatogram obtained with reference solution (a) to identify the peak due to impurity C.

Relative retention With reference to levocabastine (retention time = about 16 min): impurity C = about 0.98.

System suitability Reference solution (a):

— *peak-to-valley ratio*: minimum 10.0, 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 levocabastine.

Calculation of percentage content:

— for impurity C, use the concentration of levocabastine hydrochloride in reference solution (b).

Limit:

— *impurity C*: maximum 0.3 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.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g in a platinum crucible.

ASSAY

Dissolve 0.175 g in 50 mL of *ethanol (96 per cent) R*, previously neutralised to *phenol red solution R*, and add 5.0 mL of *water R*. Carry out a potentiometric titration (*2.2.20*), using *0.1 M sodium hydroxide*. Read the volume at the 2nd point of inflexion.

1 mL of *0.1 M sodium hydroxide* is equivalent to 22.85 mg of $C_{26}H_{30}ClFN_2O_2$.

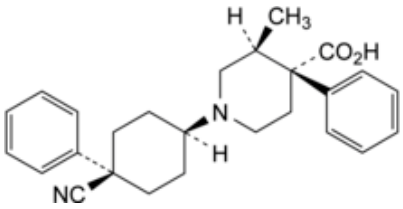
STORAGE

Protected from light.

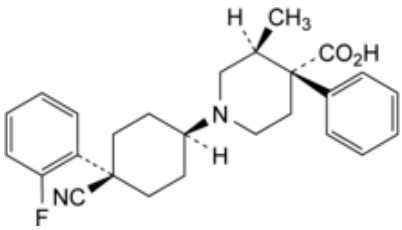
IMPURITIES

Specified impurities *A, B, C, E.*

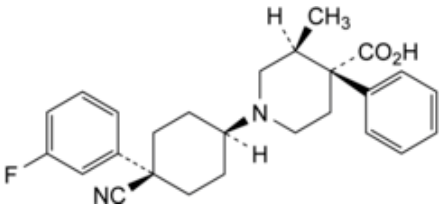
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical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



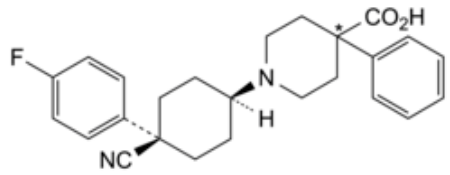
A. (3*S*,4*R*)-1-(*cis*-4-cyano-4-phenylcyclohexyl)-3-methyl-4-phenylpiperidine-4-carboxylic acid,



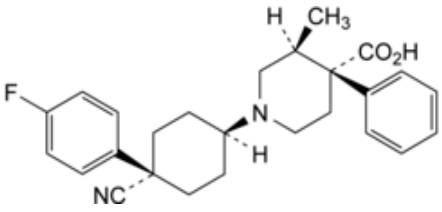
B. (3*S*,4*R*)-1-[*cis*-4-cyano-4-(2-fluorophenyl)cyclohexyl]-3-methyl-4-phenylpiperidine-4-carboxylic acid,



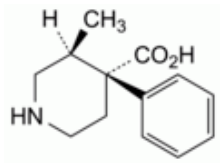
C. (3*S*,4*R*)-1-[*cis*-4-cyano-4-(3-fluorophenyl)cyclohexyl]-3-methyl-4-phenylpiperidine-4-carboxylic acid,



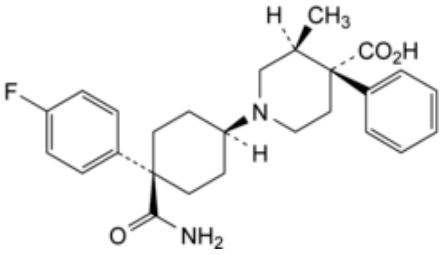
D. 1-[*cis*-4-cyano-4-(4-fluorophenyl)cyclohexyl]-4-phenylpiperidine-4-carboxylic acid,



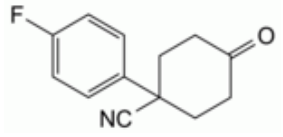
E. (3*S*,4*R*)-1-[*trans*-4-cyano-4-(4-fluorophenyl)cyclohexyl]-3-methyl-4-phenylpiperidine-4-carboxylic acid,



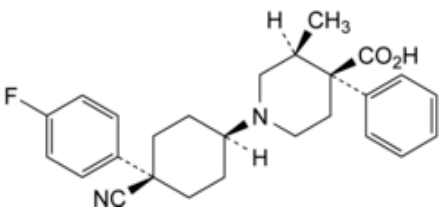
F. (3*S*,4*R*)-3-methyl-4-phenylpiperidine-4-carboxylic acid,



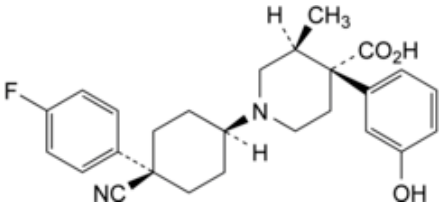
G. (3*S*,4*R*)-1-[*cis*-4-carbamoyl-4-(4-fluorophenyl)cyclohexyl]-3-methyl-4-phenylpiperidine-4-carboxylic acid,



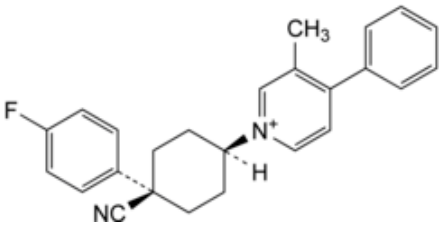
H. 1-(4-fluorophenyl)-4-oxocyclohexanecarbonitrile,



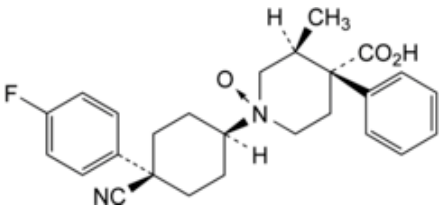
I. (3*S*,4*S*)-1-[*cis*-4-cyano-4-(4-fluorophenyl)cyclohexyl]-3-methyl-4-phenylpiperidine-4-carboxylic acid,



J. (3*S*,4*R*)-1-[*cis*-4-cyano-4-(4-fluorophenyl)cyclohexyl]-4-(3-hydroxyphenyl)-3-methylpiperidine-4-carboxylic acid,



K. 1-[*cis*-4-cyano-4-(4-fluorophenyl)cyclohexyl]-3-methyl-4-phenylpyridinium,



L. (3*S*,4*R*)-1-[*cis*-4-cyano-4-(4-fluorophenyl)cyclohexyl]-3-methyl-4-phenylpiperidine-4-carboxylic acid 1-oxide.

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