ASSAY
Dissolve 0.180 g, heating if necessary, in 5 ml of anhydrous formic acid R. Add 25 ml of anhydrous acetic acid R. Add 25 ml of dioxan R and 0.1 ml of crystal violet solution R. Titrate with 0.1 M perchloric acid, until a green colour is obtained.
1 ml of 0.1 M perchloric acid is equivalent to 19.72 mg of C9H11NO4.

STORAGE
Protected from light.

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

A. R = OH: (2S)-2-amino-3-(2,4,5-trihydroxyphenyl)propanoic acid,

B. R = H: (2S)-2-amino-3-(4-hydroxyphenyl)propanoic acid (tyrosine),

C. (2RS)-2-amino-3-(4-hydroxy-3-methoxyphenyl)propanoic acid (3-methoxy-DL-tyrosine),

D. (2R)-2-amino-3-(3,4-dihydroxyphenyl)propanoic acid (D-dopa).

CHARACTERS
Appearance: white or almost white powder.
Solubility: slightly soluble in water, freely soluble in dilute acetic acid and in methanol, slightly soluble in ethanol (96 per cent).

IDENTIFICATION
A. Specific optical rotation (2.2.7): −30.0 to −33.5 (dried substance).
Dissolve 1.50 g in a 21 g/l solution of hydrochloric acid R and dilute to 50.0 ml with the same acid.
B. Infrared absorption spectrophotometry (2.2.24).
Comparison: levodropropizine CRS.

TESTS
pH (2.2.3): 9.2 to 10.2.
Suspend 2.5 g in carbon dioxide-free water R, heat to dissolve, cool to room temperature and dilute to 100 ml with the same solvent.

Impurity B and related substances. Liquid chromatography (2.2.29).
Test solution. Dissolve 24.0 mg of the substance to be examined in the mobile phase and dilute to 100.0 ml with the mobile phase.
Reference solution (a). Dissolve 12.0 mg of 1-phenylpiperazine R (impurity B) in methanol R and dilute to 100.0 ml with the same solvent. Dilute 1.0 ml of this solution to 100.0 ml with the mobile phase.
Reference solution (b). Mix 2 ml of the test solution with 2 ml of reference solution (a) and dilute to 10 ml with the mobile phase.
Column:
– size: l = 0.15 m, Ø = 4.6 mm;
– stationary phase: base-deactivated octylsilyl silica gel for chromatography R (5 µm).
Mobile phase: mix 12 volumes of methanol R and 88 volumes of a 6.81 g/l solution of potassium dihydrogen phosphate R adjusted to pH 3.0 with phosphoric acid R.
Flow rate: 1.5 ml/min.
Detection: spectrophotometer at 254 nm.
Injection: 20 µl.
System suitability: reference solution (b):
– resolution: minimum 2.0 between the peaks due to levodropropizine and impurity B.

Limits:
– impurity B: not more than the area of the corresponding peak in the chromatogram obtained with reference solution (a) (0.5 per cent);
– unspecified impurities: for each impurity, not more than 0.2 times the area of the peak due to impurity B in the chromatogram obtained with reference solution (a) (0.10 per cent);
– disregard limit: 0.02 times the area of the peak due to impurity B in the chromatogram obtained with reference solution (a) (0.01 per cent).

Impurity C. Gas chromatography (2.2.28). Prepare the solutions immediately before use.
Test solution. Dissolve 0.50 g of the substance to be examined in methylene chloride R and dilute to 2.5 ml with the same solvent.

LEVODROPROPIZINE

Levodropropizinum

C13H20N2O2
[99291-25-5]

DEFINITION
(2S)-3-(4-Phenylpiperazin-1-yl)propane-1,2-diol.
Content: 98.5 per cent to 101.0 per cent (dried substance).
Reference solution (a). Dissolve 0.20 g of glycidol R (impurity C) in methylene chloride R and dilute to 100.0 ml with the same solvent. Dilute 0.5 ml of this solution to 100.0 ml with methylene chloride R.

Reference solution (b). Dissolve 0.50 g of the substance to be examined in methylene chloride R; add 0.5 ml of reference solution (a) and dilute to 2.5 ml with methylene chloride R.

Column:
- material: fused silica
- size: l = 30 m, Ø = 0.53 mm

Carrier gas: helium for chromatography R.

Flow rate: 2.5 ml/min.

Split ratio: 1:8.

Temperature:
- column: 140 °C;
- injection port: 170 °C;
- detector: 250 °C.

Detection: flame ionisation.

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

Use a split-liner consisting of a column about 1 cm long packed with glass wool.

At the end of a series of tests, heat the column at 250 °C for 4-6 h.

Limit:
- impurity C: not more than 0.5 times the area of the corresponding peak in the chromatogram obtained with reference solution (b) (10 ppm).

Enantiomeric purity. Liquid chromatography (2.2.29).

Solvent mixture: anhydrous ethanol R, hexane R (40:60 V/V).

Test solution. Dissolve 10.0 mg of the substance to be examined in 10.0 ml of the solvent mixture. Dilute 1.0 ml of this solution to 50.0 ml with the solvent mixture.

Reference solution (a). Dissolve 10.0 mg of levodropropizine CRS in 10.0 ml of the solvent mixture. Dilute 1.0 ml of this solution to 50.0 ml with the solvent mixture.

Reference solution (b). Dissolve 10.0 mg of levodropropizine impurity A CRS in 10.0 ml of the solvent mixture. Dilute 1.0 ml of this solution to 50.0 ml with the solvent mixture.

Reference solution (c). Dilute 1.0 ml of reference solution (b) to 50.0 ml with the solvent mixture.

Reference solution (d). Dilute 0.5 ml of reference solution (b) to 25 ml with reference solution (a).

Column:
- size: l = 0.25 m, Ø = 4.6 mm;
- stationary phase: silica gel OD for chiral separations R.

Mobile phase: diethylamine R, anhydrous ethanol R, hexane R (0.2:5:95 V/V/V).

Flow rate: 0.8 ml/min.

Detection: spectrophotometer at 254 nm.

Injection: 20 µl of the test solution and reference solutions (a), (c) and (d).

Elution order: impurity A, levodropropizine.

System suitability:
- retention times: the retention times of the principal peaks in the chromatograms obtained with the test solution and reference solution (a) are similar;

- resolution: minimum 1.3 between the peaks due to impurity A and levodropropizine.

Limit:
- impurity A: not more than the area of the corresponding peak in the chromatogram obtained with reference solution (c) (2 per cent).

Loss on drying (2.2.32): maximum 1.0 per cent, determined on 0.500 g by drying in vacuo at 60 °C over diphosphorus pentoxide R at a pressure of 0.15-0.25 kPa for 4 h.

Sulphated ash (2.4.14): maximum 0.2 per cent, determined on 1.0 g.

ASSAY
Dissolve 0.100 g in 50 ml of anhydrous acetic acid R.

Carry out a potentiometric titration (2.2.20), using 0.1 M perchloric acid. Read the volume added at the 2nd point of inflexion.

1 ml of 0.1 M perchloric acid is equivalent to 11.82 mg of C_{10}H_{20}O.

STORAGE
Protected from light.

IMPURITIES
Specified impurities: A, B, C.

A. (2R)-3-(4-phenylpiperazin-1-yl)propane-1,2-diol (dextrodropropizine),

B. 1-phenylpiperazine,

C. [(2RS)-oxiran-2-yl]methanol (glycidol).

01/2008:0619

LEVOMENTHOL
Levomenthol

C_{10}H_{20}O

M_r 156.3

DEFINITION
(1R,2S,5R)-5-Methyl-2-(1-methylethyl)cyclohexanol.

CHARACTERS
Appearance: prismatic or acicular, colourless, shiny crystals.