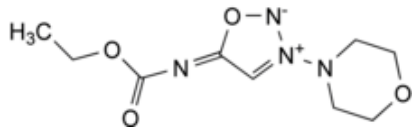
Edition: BP 2025 (Ph. Eur. 11.6 update)

Molsidomine

General Notices

(Ph. Eur. monograph 1701)



$C_9H_{14}N_4O_4$ 242.2 *25717-80-0*

Action and use

Nitric oxide donor; treatment of angina pectoris.

Ph Eur

DEFINITION

N-(Ethoxycarbonyl)-3-(morpholin-4-yl)sydnonimine.

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 anhydrous ethanol and in methylene chloride.

mp

About 142 °C.

IDENTIFICATION

Infrared absorption spectrophotometry (2.2.24).

Comparison molsidomine CRS.

TESTS

Appearance of solution

The solution is clear (2.2.1) and not more intensely coloured than reference solution B_7 (2.2.2, Method II).

Dissolve 1.0 g in anhydrous ethanol R by heating at about 50 °C for about 5 min and dilute to 20.0 mL with the same solvent.

pH (2.2.3)

5.5 to 7.5.

Dissolve 0.50 g in carbon dioxide-free water R and dilute to 50.0 mL with the same solvent.

Impurity B

Liquid chromatography (2.2.29) as described in the test for related substances with the following modifications.

Detection Spectrophotometer at 240 nm.

Injection 20 µL of test solution (a) and reference solution (b).

Relative retention With reference to molsidomine (retention time = about 9 min): impurity B = about 0.43.

System suitability Reference solution (b):

— signal-to-noise ratio: minimum 20 for the principal peak.

Limit:

— *impurity B*: not more than the area of the corresponding peak in the chromatogram obtained with reference solution (b) (3 ppm).

Impurity E

Liquid chromatography (2.2.29).

Test solution Dissolve 0.200 g of the substance to be examined in the mobile phase and dilute to 100.0 mL with the mobile phase.

Reference solution (a) Dissolve 50.0 mg of morpholine for chromatography R in 500.0 mL of water for chromatography R. Dilute 20.0 mL of the solution to 500.0 mL with water for chromatography R. Dilute 5.0 mL of this solution to 100.0 mL with water for chromatography R.

Reference solution (b) Mix 10.0 mL of the test solution with 10.0 mL of reference solution (a).

Column:

— *size*: *l* = 0.25 m, Ø = 4.0 mm;

— *stationary phase*: *resin for reversed-phase ion chromatography R*;

— *temperature*: 25 °C.

Mobile phase Mix 3.0 mL of *methanesulfonic acid R* and 75 mL of *acetonitrile R* in *water for chromatography R* and dilute to 5000 mL with *water for chromatography R*.

Suppressor regenerant *water for chromatography R*.

Flow rate 1.0 mL/min.

Expected background conductivity Less than 0.5 µS.

Detection Conductivity detector at 10 µS.

Injection 50 µL.

Run time 20 min.

Relative retention With reference to molsidomine (retention time = about 3 min): impurity E = about 2.4.

System suitability Reference solution (b):

— *signal-to-noise ratio*: minimum 6 for the peak due to impurity E.

Limit:

— *impurity E*: not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.01 per cent).

Related substances

Liquid chromatography (*2.2.29*). *Protect the solutions from light.*

Solvent mixture *methanol R*, mobile phase A (10:90 *V/V*).

Test solution (a) Dissolve 0.200 g of the substance to be examined in 2.5 mL of *methanol R* and dilute to 5.0 mL with mobile phase A.

Test solution (b) Dilute 1.0 mL of test solution (a) to 20.0 mL with the solvent mixture.

Reference solution (a) Dilute 1.0 mL of test solution (b) 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 2.4 mg of *molsidomine impurity B CRS* in 80 mL of *methanol R* and dilute to 100.0 mL with *methanol R*. Dilute 2.0 mL of the solution to 100.0 mL with the solvent mixture. Dilute 5.0 mL of this solution to 20.0 mL with the solvent mixture.

Reference solution (c) Dissolve 10 mg of *linsidomine hydrochloride R* (impurity A) and 5 mg of *molsidomine impurity D CRS* in 10 mL of *methanol R* and dilute to 50.0 mL with the solvent mixture. Dilute 5.0 mL of this solution to 50.0 mL with the solvent mixture.

Column:

— *size*: *l* = 0.15 m, Ø = 4.6 mm;

— *stationary phase*: *end-capped octadecylsilyl silica gel for chromatography R* (5 µm);

— *temperature*: 30 °C.

Mobile phase:

— *mobile phase A*: dissolve 4.0 g of *potassium dihydrogen phosphate R* in *water for chromatography R* and dilute to 1000 mL with the same solvent;

— *mobile phase B*: *methanol R1*;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 3	90	10
3 - 10	90 → 20	10 → 80
10 - 13	20	80

Flow rate 1.3 mL/min.

Detection Spectrophotometer at 210 nm.

Injection 20 µL of test solution (b) and reference solutions (a) and (c).

Relative retention With reference to molsidomine (retention time = about 9 min): impurity A = about 0.2; impurity D = about 0.3.

System suitability Reference solution (c):

— *resolution*: minimum 3.5 between the peaks due to impurities A and D.

Limits:

— *unspecified impurities*: for each impurity, not more than the area of the peak due to molsidomine in the chromatogram obtained with reference solution (a) (0.10 per cent);

— *total*: not more than 3 times the area of the peak due to molsidomine in the chromatogram obtained with reference solution (a) (0.3 per cent);

— *disregard limit*: 0.5 times the area of the peak due to molsidomine 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.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Dissolve 0.200 g in a mixture of 5 mL of *acetic anhydride R* and 50 mL of *anhydrous 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 24.22 mg of $C_9H_{14}N_4O_4$.

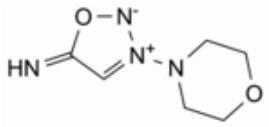
STORAGE

Protected from light.

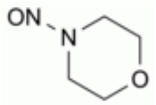
IMPURITIES

Specified impurities *B, E.*

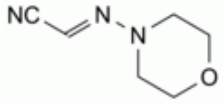
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical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



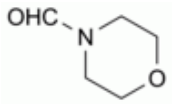
A. 3-(morpholin-4-yl)sydnonimine (linsidomine),



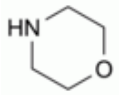
B. 4-nitrosomorpholine,



C. (2*E*)-(morpholin-4-ylimino)acetonitrile,



D. morpholine-4-carbaldehyde,



E. morpholine.