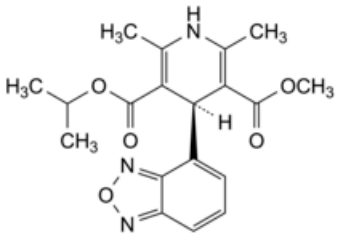
Edition: BP 2025 (Ph. Eur. 11.6 update)

Isradipine

General Notices

(Ph. Eur. monograph 2110)



and enantiomer

$C_{19}H_{21}N_3O_5$ 371.4 *75695-93-1*

Action and use

Calcium channel blocker.

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DEFINITION

3-Methyl 5-(propan-2-yl) (4*RS*)-4-(2,1,3-benzoxadiazol-4-yl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate.

Content

97.0 per cent to 102.0 per cent (dried substance).

CHARACTERS

Appearance

Yellow, crystalline powder.

Solubility

Practically insoluble in water, freely soluble in acetone, soluble in methanol.

mp

About 168 °C.

IDENTIFICATION

Infrared absorption spectrophotometry (2.2.24).

Comparison isradipine CRS.

TESTS

Related substances

Liquid chromatography (2.2.29).

Test solution (a) Dissolve 50 mg of the substance to be examined in 1 mL of methanol R, using an ultrasonic bath if necessary, and dilute to 25.0 mL with the mobile phase.

Test solution (b) Dissolve 50.0 mg of the substance to be examined in 2 mL of methanol R and dilute to 250.0 mL with the mobile phase.

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

Reference solution (b) Dissolve 2 mg of the substance to be examined and 2 mg of isradipine impurity D CRS in the mobile phase and dilute to 10 mL with the mobile phase. Dilute 1 mL of this solution to 10 mL with the mobile phase.

Reference solution (c) Dissolve 10 mg of isradipine for peak identification CRS (containing impurities A and B) in 2 mL of methanol R, using an ultrasonic bath if necessary, and dilute to 5 mL with the mobile phase.

Reference solution (d) Dissolve 50.0 mg of isradipine CRS in 2 mL of methanol R and dilute to 250.0 mL with the mobile phase.

Column:

— *size*: *l* = 0.10 m, Ø = 4.6 mm;

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

Mobile phase acetonitrile for chromatography R, tetrahydrofuran R, water for chromatography R (125:270:625 *V/V/V*).

Flow rate 1.2 mL/min.

Detection Spectrophotometer at 230 nm.

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

Run time 5 times the retention time of isradipine.

Identification of impurities Use the chromatogram obtained with reference solution (b) to identify the peak due to impurity D; use the chromatogram supplied with isradipine for peak identification CRS and the chromatogram obtained with reference solution (c) to identify the peaks due to impurities A and B.

Relative retention With reference to isradipine (retention time = about 7 min): impurity A = about 0.8; impurity D = about 0.9; impurity B = about 1.8.

System suitability Reference solution (b):

— resolution: minimum 2.0 between the peaks due to isradipine and impurity D.

Calculation of percentage contents:

— *correction factor*: multiply the peak area of impurity D by 1.4;

— for each impurity, use the concentration of isradipine in reference solution (a).

Limits:

— *impurity B*: maximum 0.8 per cent;

— *impurity A*: maximum 0.2 per cent;

— *impurity D*: maximum 0.10 per cent;

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

— *total*: maximum 1.0 per cent;

— *reporting threshold*: 0.05 per cent.

Loss on drying (*2.2.32*)

Maximum 0.2 per cent, determined on 1.000 g by drying in an oven at 105 °C for 4 h.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

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

Mobile phase *acetonitrile R*, *tetrahydrofuran R*, *water for chromatography R* (125:270:625 *V/V/V*).

Detection Spectrophotometer at 326 nm.

Injection Test solution (b) and reference solution (d).

Run time Twice the retention time of isradipine.

Calculate the percentage content of isradipine taking into account the assigned content of *isradipine CRS*.

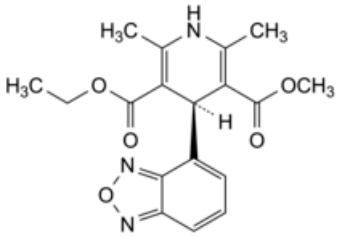
STORAGE

Protected from light.

IMPURITIES

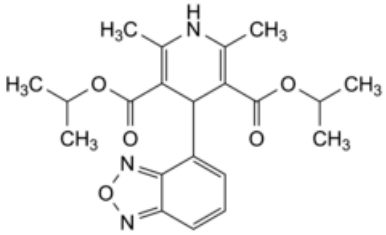
Specified impurities *A, B, D*.

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) *C, E*.

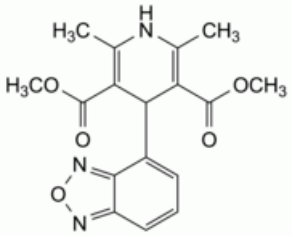


and enantiomer

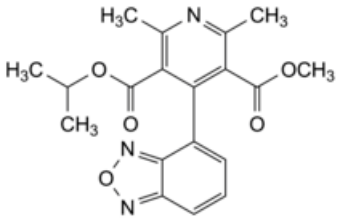
A. 5-ethyl 3-methyl (4*RS*)-4-(2,1,3-benzoxadiazol-4-yl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate,



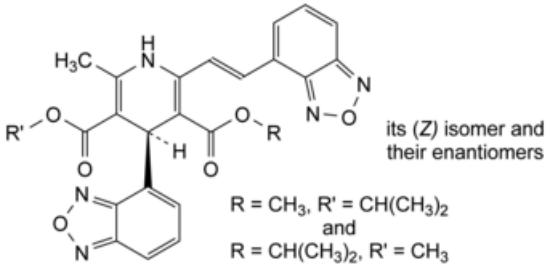
B. di(propan-2-yl) 4-(2,1,3-benzoxadiazol-4-yl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate,



C. dimethyl 4-(2,1,3-benzoxadiazol-4-yl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate,



D. 3-methyl 5-(propan-2-yl) 4-(2,1,3-benzoxadiazol-4-yl)-2,6-dimethylpyridine-3,5-dicarboxylate,



E. mixture of 3-methyl 5-(propan-2-yl) (4*RS*)-4-(2,1,3-benzoxadiazol-4-yl)-2-[(1*EZ*)-2-(2,1,3-benzoxadiazol-4-yl)ethen-1-yl]-6-methyl-1,4-dihydropyridine-3,5-dicarboxylate and 5-methyl 3-(propan-2-yl) (4*RS*)-4-(2,1,3-benzoxadiazol-4-yl)-2-[(1*EZ*)-2-(2,1,3-benzoxadiazol-4-yl)ethen-1-yl]-6-methyl-1,4-dihydropyridine-3,5-dicarboxylate.

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