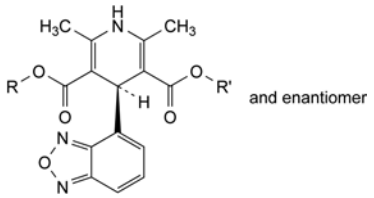
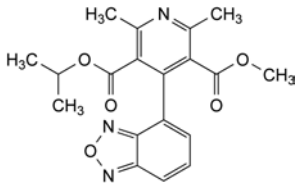
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph *Substances for pharmaceutical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



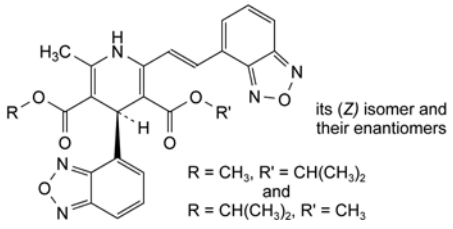
A. R = C_2H_5, R' = CH_3: ethyl methyl (4*RS*)-4-(2,1,3-benzoxadiazol-4-yl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate,

B. R = R' = $CH(CH_3)_2$: bis(1-methylethyl) (4*RS*)-4-(2,1,3-benzoxadiazol-4-yl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate,

C. R = R' = CH_3: dimethyl (4*RS*)-4-(2,1,3-benzoxadiazol-4-yl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate,



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

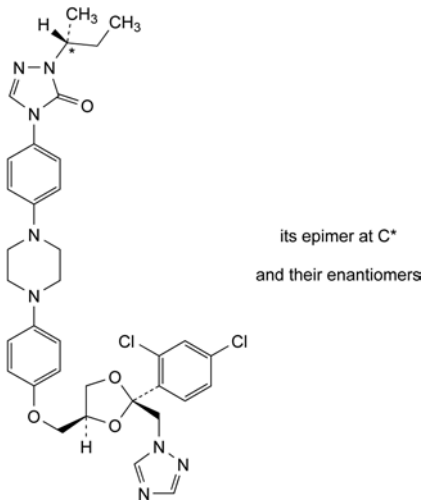


E. methyl 1-methylethyl (4*RS*)-4-(2,1,3-benzoxadiazol-4-yl)-2-[(*EZ*)-2-(2,1,3-benzoxadiazol-4-yl)ethenyl]-6-methyl-1,4-dihydropyridine-3,5-dicarboxylate.

01/2011:1335

ITRACONAZOLE

Itraconazolum



$C_{35}H_{38}Cl_2N_8O_4$ M_r 706
[84625-61-6]

DEFINITION

4-[4-[4-[4-[[*cis*-2-(2,4-Dichlorophenyl)-2-(1*H*-1,2,4-triazol-1-ylmethyl)-1,3-dioxolan-4-yl]methoxy]phenyl]piperazin-1-yl]phenyl]-2-[(1*RS*)-1-methylpropyl]-2,4-dihydro-3*H*-1,2,4-triazol-3-one.

Content: 99.0 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance: white or almost white powder.

Solubility: practically insoluble in water, freely soluble in methylene chloride, very slightly soluble in ethanol (96 per cent).

IDENTIFICATION

Infrared absorption spectrophotometry (*2.2.24*).

Comparison: *itraconazole CRS*.

TESTS

Solution S. Dissolve 2.0 g in *methylene chloride R* and dilute to 20.0 mL with the same solvent.

Appearance of solution. Solution S is clear (*2.2.1*) and not more intensely coloured than reference solution R_6 or B_6 (*2.2.2, Method II*).

Related substances. Liquid chromatography (*2.2.29*). *Prepare the solutions immediately before use.*

Test solution. Dissolve 0.100 g of the substance to be examined in *methanolic hydrochloric acid R* and dilute to 10.0 mL with the same solvent.

Reference solution (a). Dilute 1.0 mL of the test solution to 100.0 mL with *methanolic hydrochloric acid R*. Dilute 1.0 mL of this solution to 10.0 mL with *methanolic hydrochloric acid R*.

Reference solution (b). Dissolve 10 mg of *itraconazole for system suitability CRS* (containing impurities B, C, D, E, F and G) in 1.0 mL of *methanolic hydrochloric acid R*.

Column:

– *size*: *l* = 0.10 m, Ø = 4.6 mm;
– *stationary phase*: *base-deactivated end-capped octadecylsilyl silica gel for chromatography R* (3 µm or 3.5 µm);
– *temperature*: 30 °C.

Mobile phase:

– *mobile phase A*: 27.2 g/L solution of *tetrabutylammonium hydrogen sulfate R1*;

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

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 2	80	20
2 - 22	80 → 50	20 → 50
22 - 27	50	50

Flow rate: 1.5 mL/min.

Detection: spectrophotometer at 225 nm.

Injection: 10 µL.

Identification of impurities: use the chromatogram supplied with *itraconazole for system suitability CRS* and the chromatogram obtained with reference solution (b) to identify the peaks due to impurities B, C, D, E, F and G.

Relative retention with reference to itraconazole (retention time = about 14 min): impurity B = about 0.7; impurities C and D = about 0.8; impurity E = about 0.9; impurity F = about 1.05; impurity G = about 1.3.

System suitability: reference solution (b):

– *peak-to-valley ratio*: minimum 1.5, where H_p = height above the baseline of the peak due to impurity F and H_v = height above the baseline of the lowest point of the curve separating this peak from the peak due to itraconazole.

Limits:

– *impurities B, G*: for each impurity, not more than 3 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.3 per cent);

– *impurity E*: not more than twice the area of the principal peak in the chromatogram obtained with reference solution (a) (0.2 per cent);

– *sum of impurities C and D*: not more than 3 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.3 per cent);

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

– *total*: not more than 8 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.8 per cent);

– *disregard limit*: 0.5 times the area of the principal peak 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 for 4 h.

Sulfated ash (*2.4.14*): maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Dissolve 0.300 g in 70 mL of a mixture of 1 volume of *anhydrous acetic acid R* and 7 volumes of *methyl ethyl ketone R* by vigorous stirring for at least 10 min. Titrate with *0.1 M perchloric acid*, determining the end-point potentiometrically at the second point of inflexion (*2.2.20*).

1 mL of *0.1 M perchloric acid* is equivalent to 35.3 mg of $C_{35}H_{38}Cl_2N_8O_4$.

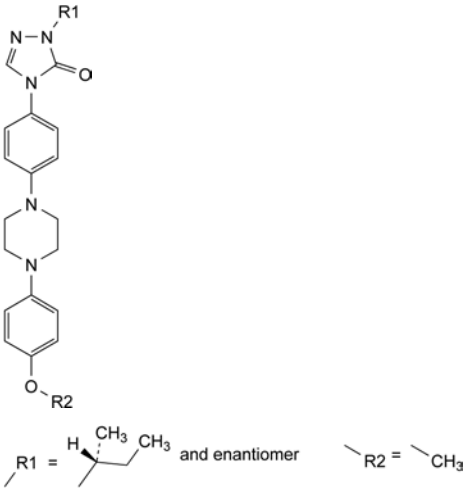
STORAGE

Protected from light.

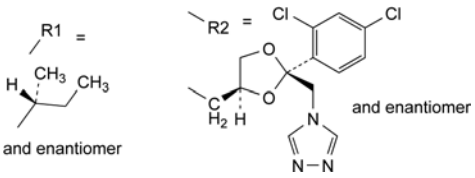
IMPURITIES

Specified impurities: B, C, D, E, G.

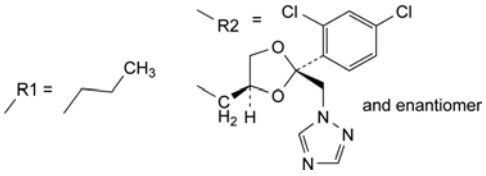
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph *Substances for pharmaceutical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



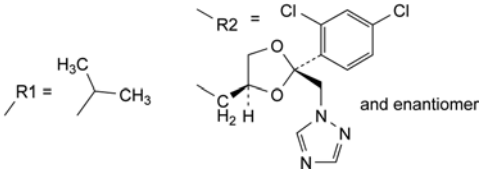
A. 4-[4-[4-(4-methoxyphenyl)piperazin-1-yl]phenyl]-2-[(1*RS*)-1-methylpropyl]-2,4-dihydro-3*H*-1,2,4-triazol-3-one,



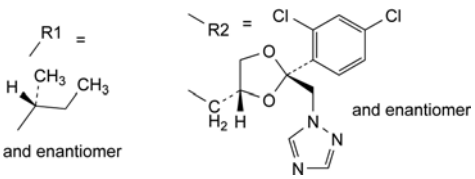
B. 4-[4-[4-[4-[[*cis*-2-(2,4-dichlorophenyl)-2-(4*H*-1,2,4-triazol-4-ylmethyl)-1,3-dioxolan-4-yl]methoxy]phenyl]piperazin-1-yl]phenyl]-2-[(1*RS*)-1-methylpropyl]-2,4-dihydro-3*H*-1,2,4-triazol-3-one,



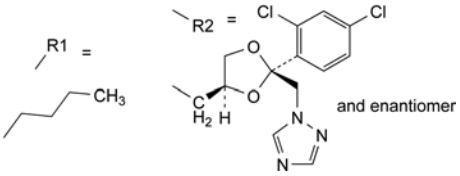
C. 4-[4-[4-[4-[[*cis*-2-(2,4-dichlorophenyl)-2-(1*H*-1,2,4-triazol-1-ylmethyl)-1,3-dioxolan-4-yl]methoxy]phenyl]piperazin-1-yl]phenyl]-2-propyl-2,4-dihydro-3*H*-1,2,4-triazol-3-one,



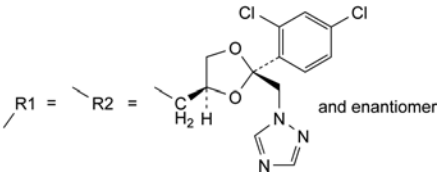
D. 4-[4-[4-[4-[[*cis*-2-(2,4-dichlorophenyl)-2-(1*H*-1,2,4-triazol-1-ylmethyl)-1,3-dioxolan-4-yl]methoxy]phenyl]piperazin-1-yl]phenyl]-2-(1-methylethyl)-2,4-dihydro-3*H*-1,2,4-triazol-3-one,



E. 4-[4-[4-[4-[[*trans*-2-(2,4-dichlorophenyl)-2-(1*H*-1,2,4-triazol-1-ylmethyl)-1,3-dioxolan-4-yl]methoxy]phenyl]piperazin-1-yl]phenyl]-2-[(1*RS*)-1-methylpropyl]-2,4-dihydro-3*H*-1,2,4-triazol- 3-one,



F. 2-butyl-4-[4-[4-[4-[[*cis*-2-(2,4-dichlorophenyl)-2-(1*H*-1,2,4-triazol-1-ylmethyl)-1,3-dioxolan-4-yl]methoxy]phenyl]piperazin-1-yl]phenyl]-2,4-dihydro-3*H*-1,2,4-triazol-3-one,

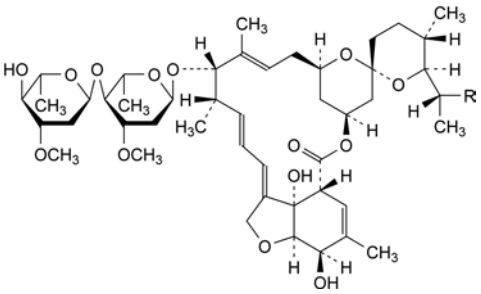


G. 4-[4-[4-[4-[[*cis*-2-(2,4-dichlorophenyl)-2-(1*H*-1,2,4-triazol-1-ylmethyl)-1,3-dioxolan-4-yl]methoxy]phenyl]piperazin-1-yl]phenyl]-2-[[*cis*-2-(2,4-dichlorophenyl)-2-(1*H*-1,2,4-triazol-1-ylmethyl)-1,3-dioxolan-4-yl]methyl]-2,4-dihydro-3*H*-1,2,4-triazol-3-one.

01/2008:1336
corrected 6.0

IVERMECTIN

Ivermectinum



Component	R	Molecular formula	M_r
H_2B_{1a}	CH_2-CH_3	$C_{48}H_{74}O_{14}$	875
H_2B_{1b}	CH_3	$C_{47}H_{72}O_{14}$	861

Ivermectin B1a: [70161-11-4]
Ivermectin B1b: [70288-86-7]

DEFINITION

Mixture of (2a*E*,4*E*,5′*S*,6*S*,6′*R*,7*S*,8*E*,11*R*,13*R*,15*S*,17a*R*,20*R*,20a*R*,20b*S*)-7-[[2,6-dideoxy-4-*O*-(2,6-dideoxy-3-*O*-methyl-α-L-*arabino*-hexopyranosyl)-3-*O*-methyl-α-L-*arabino*-hexopyranosyl]oxy]-20,20b-dihydroxy-5′,6,8,19-tetramethyl-6′-[(1*S*)-1-methylpropyl]-3′,4′,5′,6,6′,7,10,11,14,15,17a,20,20a,20b-tetradecahydrospiro[11,15-methano-2*H*,13*H*,17*H*-furo[4,3,2-*pq*][2,6]benzodioxacyclooctadecene-13,2′-[2*H*]pyran]-17-one (or 5-*O*-demethyl-22,23-dihydroavermectin A_{1a}) (component H_2B_{1a}) and (2a*E*,4*E*,5′*S*,6*S*,6′*R*,7*S*,8*E*,11*R*,13*R*,15*S*,17a*R*,20*R*,20a*R*,-20b*S*)-7-[[2,6-dideoxy-4-*O*-(2,6-dideoxy-3-*O*-methyl-α-L-*arabino*-hexopyranosyl)-3-*O*-methyl-α-L-*arabino*-hexopyranosyl]oxy]-20,20b-dihydroxy-5′,6,8,19-tetramethyl-6′-(1-methylethyl)-3′,4′,5′,6,6′,7,10,11,14,15,17a,20,20a,20b-tetradecahydrospiro[11,15-methano-2*H*,13*H*,17*H*-furo[4,3,2-*pq*][2,6]benzodioxacyclooctadecene-13,2′-[2*H*]pyran]-17-one (or 5-*O*-demethyl-25-de(1-methylpropyl)-25-(1-methylethyl)-22,23-dihydroavermectin A_{1a}) (component H_2B_{1b}).

Semi-synthetic product derived from a fermentation product.

Content:

– ivermectin (H_2B_{1a} + H_2B_{1b}): 95.0 per cent to 102.0 per cent (anhydrous substance),

– ratio $H_2B_{1a}/(H_2B_{1a} + H_2B_{1b})$ (areas by liquid chromatography): minimum 90.0 per cent.

CHARACTERS

Appearance: white or yellowish-white, crystalline powder, slightly hygroscopic.

Solubility: practically insoluble in water, freely soluble in methylene chloride, soluble in alcohol.

IDENTIFICATION

A. Infrared absorption spectrophotometry (*2.2.24*).
Comparison: *ivermectin CRS*.

B. Examine the chromatograms obtained in the assay.
Results: the retention times and sizes of the 2 principal peaks in the chromatogram obtained with the test solution are similar to those of the 2 principal peaks in the chromatogram obtained with reference solution (a).

TESTS

Appearance of solution. The solution is clear (*2.2.1*) and not more intensely coloured than reference solution BY_7 (*2.2.2, Method II*).

Dissolve 1.0 g in 50 mL of *toluene R*.

Specific optical rotation (*2.2.7*): – 17 to – 20 (anhydrous substance).

Dissolve 0.250 g in *methanol R* and dilute to 10.0 mL with the same solvent.

Related substances. Liquid chromatography (*2.2.29*).

Test solution. Dissolve 40.0 mg of the substance to be examined in *methanol R* and dilute to 50.0 mL with the same solvent.

Reference solution (a). Dissolve 40.0 mg of *ivermectin CRS* in *methanol R* and dilute to 50.0 mL with the same solvent.

Reference solution (b). Dilute 1.0 mL of reference solution (a) to 100.0 mL with *methanol R*.

Reference solution (c). Dilute 5.0 mL of reference solution (b) to 100.0 mL with *methanol R*.

Column:

– size: *l* = 0.25 m, Ø = 4.6 mm,
– *stationary phase*: *octadecylsilyl silica gel for chromatography R* (5 μm).

Mobile phase: *water R, methanol R, acetonitrile R* (15:34:51 *V/V/V*).

Flow rate: 1 mL/min.

Detection: spectrophotometer at 254 nm.

Injection: 20 μL.

System suitability:

– *resolution*: minimum of 3.0 between the first peak (component H_2B_{1b}) and the second peak (component H_2B_{1a}) in the chromatogram obtained with reference solution (a),
– *signal-to-noise ratio*: minimum of 10 for the principal peak in the chromatogram obtained with reference solution (c),
– *symmetry factor*: maximum of 2.5 for the principal peak in the chromatogram obtained with reference solution (a).

Limits:

– *impurity with a relative retention of 1.3 to 1.5* with reference to the principal peak: not more than 2.5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (2.5 per cent),
– *any other impurity* (apart from the 2 principal peaks): not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (1 per cent),
– *total*: not more than 5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (5 per cent),
– *disregard limit*: area of the principal peak in the chromatogram obtained with reference solution (c) (0.05 per cent).