S_3 = sum of the areas of the peaks due to teicoplanin $A_{2\text{-}3}$ group in the chromatogram obtained with the test solution;

S_4 = area of the peak due to teicoplanin $A_{2\text{-}4}$ in the chromatogram obtained with the test solution;

S_5 = sum of the areas of the peaks due to teicoplanin $A_{2\text{-}5}$ group in the chromatogram obtained with the test solution.

Limits:

- *teicoplanin A_2 group*: minimum 80.0 per cent;
- *teicoplanin $A_{2\text{-}2}$*: 35.0 per cent to 55.0 per cent;
- *teicoplanin $A_{2\text{-}1}$ group*: maximum 20.0 per cent;
- *teicoplanin $A_{2\text{-}3}$ group*: maximum 20.0 per cent;
- *teicoplanin $A_{2\text{-}4}$*: maximum 20.0 per cent;
- *teicoplanin $A_{2\text{-}5}$ group*: maximum 20.0 per cent;
- *teicoplanin A_3 group*: maximum 15.0 per cent;
- *total of impurities other than mesityl oxide with a relative retention more than 1.25*: maximum 5.0 per cent;
- *disregard limit*: the area of the peak due to teicoplanin $A_{2\text{-}2}$ in the chromatogram obtained with reference solution (b) (0.25 per cent).

Chlorides: maximum 5.0 per cent, expressed as sodium chloride (anhydrous substance).

Dissolve 1.000 g in 300 mL of *water R*, stir and acidify with 2 mL of *nitric acid R*. Titrate with *0.1 M silver nitrate*, determining the end-point potentiometrically (*2.2.20*).

1 mL of *0.1 M silver nitrate* is equivalent to 5.844 mg of NaCl.

Heavy metals (*2.4.8*): maximum 20 ppm.

0.50 g complies with test G. Prepare the reference solution using 100 µL of *lead standard solution (100 ppm Pb) R*. Filter the solutions through a membrane filter (nominal pore size 0.45 µm).

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

Injection: 20 µL of the test solution and reference solution (c).

Relative retention with reference to teicoplanin $A_{2\text{-}2}$ (retention time = about 18 min): impurity A = about 0.6.

Limits:

- *impurity A*: maximum twice the area of the principal peak in the chromatogram obtained with reference solution (c) (0.2 per cent).

Water (*2.5.12*): maximum 15.0 per cent, determined on 0.300 g.

Bacterial endotoxins (*2.6.14*): less than 0.31 IU/mg.

ASSAY

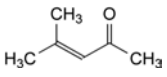
Carry out the microbiological assay of antibiotics (*2.7.2*), using the diffusion method. Use *teicoplanin CRS* as the reference substance.

STORAGE

Protected from light, at a temperature of 2 °C to 8 °C.

IMPURITIES

Specified impurities: A.

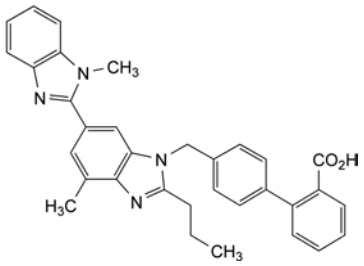


A. 4-methylpent-3-en-2-one (mesityl oxide).

07/2008:2154
corrected 6.3

TELMISARTAN

Telmisartanum



$C_{33}H_{30}N_4O_2$ M_r 514.6
[144701-48-4]

DEFINITION

4′-[[4-Methyl-6-(1-methyl-1*H*-benzimidazol-2-yl)-2-propyl-1*H*-benzimidazol-1-yl]methyl]biphenyl-2-carboxylic acid.

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

CHARACTERS

Appearance: white or slightly yellowish, crystalline powder.

Solubility: practically insoluble in water, slightly soluble in methanol, sparingly soluble in methylene chloride. It dissolves in 1 M sodium hydroxide.

It shows polymorphism (*5.9*).

IDENTIFICATION

Infrared absorption spectrophotometry (*2.2.24*).

Comparison: *telmisartan CRS*.

If the spectra obtained in the solid state show differences, dissolve the substance to be examined and the reference substance separately in hot *anhydrous ethanol R*, evaporate to dryness and record new spectra using the residues.

TESTS

Appearance of solution. The solution is not more intensely coloured than reference solution Y_4 (*2.2.2, Method II*).

Dissolve 0.5 g in *1 M sodium hydroxide* and dilute to 10 mL with the same solvent.

Related substances. Liquid chromatography (*2.2.29*).

Test solution. To 25 mg of the substance to be examined add about 5 mL of *methanol R* and 100 µL of a 40 g/L solution of *sodium hydroxide R*. Dissolve with the aid of ultrasound and dilute to 50 mL with *methanol R*.

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

Reference solution (b). Dissolve the contents of a vial of *telmisartan for system suitability CRS* (containing impurities A, B, C, E and F) in 2 mL of *methanol R*.

Reference solution (c). To 5 mg of *telmisartan for peak identification CRS* (containing impurity D) add about 5 mL of *methanol R* and 100 µL of a 40 g/L solution of *sodium hydroxide R*. Dissolve with the aid of ultrasound and dilute to 10 mL with *methanol R*.

Column:

- *size*: *l* = 0.125 m, Ø = 4.0 mm;
- *stationary phase*: *octadecylsilyl silica gel for chromatography R* (5 µm) with a pore size of 10 nm;
- *temperature*: 40 °C.

Mobile phase:

– *mobile phase A*: dissolve 2.0 g of *potassium dihydrogen phosphate R* and 3.8 g of *sodium pentanesulfonate monohydrate R1* in *water R*, adjust to pH 3.0 with *dilute phosphoric acid R* and dilute to 1000 mL with *water R*;

– *mobile phase B*: *methanol R2, acetonitrile R1* (20:80 *V/V*);

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 3	70	30
3 - 28	70 → 20	30 → 80

Flow rate: 1 mL/min.

Detection: spectrophotometer at 230 nm.

Injection: 10 µL.

Identification of impurities: use the chromatogram supplied with *telmisartan for system suitability CRS* and the chromatogram obtained with reference solution (b) to identify the peaks due to impurities A, B, C, E and F; use the chromatogram supplied with *telmisartan for peak identification CRS* and the chromatogram obtained with reference solution (c) to identify the peak due to impurity D.

Relative retention with reference to telmisartan (retention time = about 15 min): impurity A = about 0.2; impurity E = about 0.6; impurity F = about 0.7; impurity B = about 0.9; impurity C = about 1.5; impurity D = about 1.6.

System suitability: reference solution (b):

– the chromatogram obtained with reference solution (b) is similar to the chromatogram supplied with *telmisartan for system suitability CRS*;

– *resolution*: minimum 3.0 between the peaks due to impurity B and telmisartan.

Limits:

– *impurities C, D*: for each impurity, not more than twice the area of the principal peak in the chromatogram obtained with reference solution (a) (0.2 per cent);

– *impurities A, B*: for each impurity, not more than 1.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.15 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 10 times the area of the principal peak in the chromatogram obtained with reference solution (a) (1.0 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.

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

ASSAY

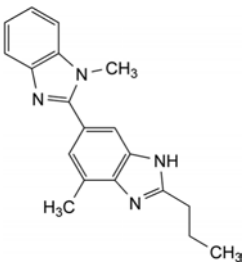
Dissolve 0.190 g in 5 mL of *anhydrous formic acid R*. Add 75 mL of *acetic anhydride R*. Titrate with *0.1 M perchloric acid*, determining the end-point potentiometrically (*2.2.20*).

1 mL of *0.1 M perchloric acid* is equivalent to 25.73 mg of $C_{33}H_{30}N_4O_2$.

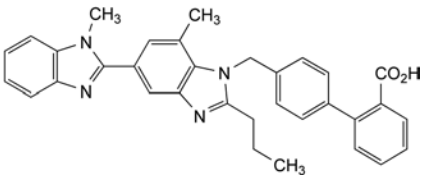
IMPURITIES

Specified impurities: A, B, C, D.

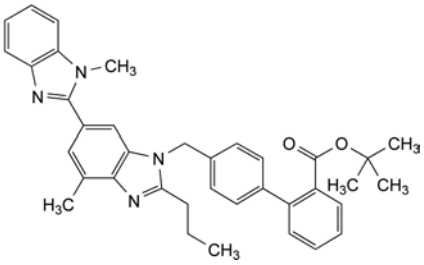
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph *Substances for pharmaceutical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



A. 4-methyl-6-(1-methyl-1*H*-benzimidazol-2-yl)-2-propyl-1*H*-benzimidazole,

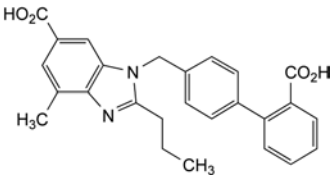


B. 4′-[[7-methyl-5-(1-methyl-1*H*-benzimidazol-2-yl)-2-propyl-1*H*-benzimidazol-1-yl]methyl]biphenyl-2-carboxylic acid,

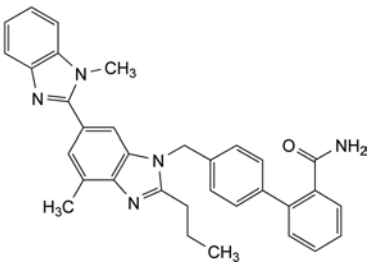


C. 1,1-dimethylethyl 4′-[[4-methyl-6-(1-methyl-1*H*-benzimidazol-2-yl)-2-propyl-1*H*-benzimidazol-1-yl]methyl]biphenyl-2-carboxylate,

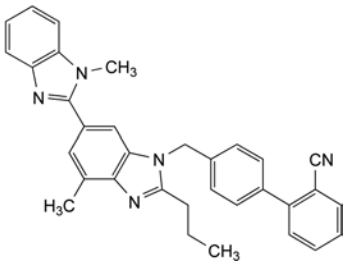
D. unidentified impurity,



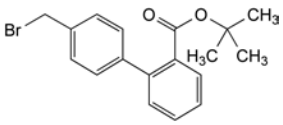
E. 1-[(2′-carboxybiphenyl-4-yl)methyl]-4-methyl-2-propyl-1*H*-benzimidazol-6-carboxylic acid,



F. 4′-[[4-methyl-6-(1-methyl-1*H*-benzimidazol-2-yl)-2-propyl-1*H*-benzimidazol-1-yl]methyl]biphenyl-2-carboxamide,



G. 4′-[[4-methyl-6-(1-methyl-1*H*-benzimidazol-2-yl)-2-propyl-1*H*-benzimidazol-1-yl]methyl]biphenyl-2-carbonitrile,

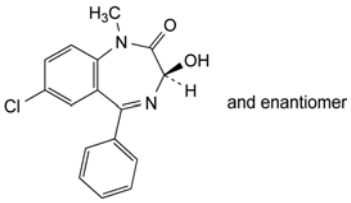


H. 1,1-dimethylethyl 4′-(bromomethyl)biphenyl-2-carboxylate.

01/2008:0954
corrected 6.0

TEMAZEPAM

Temazepamum



$C_{16}H_{13}ClN_2O_2$ M_r 300.7
[846-50-4]

DEFINITION

(3*RS*)-7-Chloro-3-hydroxy-1-methyl-5-phenyl-1,3-dihydro-2*H*-1,4-benzodiazepin-2-one.

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

CHARACTERS

Appearance: white or almost white, crystalline powder.

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

IDENTIFICATION

Infrared absorption spectrophotometry (*2.2.24*).

Comparison: *temazepam CRS*.

TESTS

Impurity A: maximum 0.05 per cent.

Dissolve 0.400 g in *methylene chloride R* and dilute to 20.0 mL with the same solvent. The absorbance (*2.2.25*) is not greater than 0.30 at 409 nm.

Related substances. Liquid chromatography (*2.2.29*).

Test solution. Dissolve 10.0 mg of the substance to be examined in a mixture of 1 volume of *water R* and 9 volumes of *methanol R* and dilute to 50.0 mL with the same mixture of solvents.

Reference solution (a). Dilute 1.0 mL of the test solution to 100.0 mL with a mixture of 1 volume of *water R* and 9 volumes of *methanol R*. Dilute 2.0 mL of this solution to 10.0 mL with a mixture of 1 volume of *water R* and 9 volumes of *methanol R*.

Reference solution (b). Dissolve 1 mg of *oxazepam R*, 1 mg of *temazepam impurity F CRS* and 1 mg of *temazepam impurity G CRS* in a mixture of 1 volume of *water R* and 9 volumes of *methanol R* and dilute to 25 mL with the same mixture of solvents.

Reference solution (c). Dissolve 1 mg of *temazepam impurity C CRS* and 1 mg of *temazepam impurity D CRS* with a mixture of 1 volume of *water R* and 9 volumes of *methanol R* and dilute to 25 mL with the same mixture of solvents.

Column:

– *size*: *l* = 0.15 m, Ø = 4.6 mm;
– *stationary phase*: *end-capped octadecylsilyl silica gel for chromatography R* (3.5 µm).

Mobile phase:

– *mobile phase A*: solution containing 4.9 g/L of *sodium dihydrogen phosphate R* and 0.63 g/L of *disodium hydrogen phosphate R* (pH 5.6);
– *mobile phase B*: *methanol R*;
– *mobile phase C*: *acetonitrile R*;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)	Mobile phase C (per cent *V/V*)
0 - 18	54	39	7
18 - 25	54 → 22	39 → 63	7 → 15
25 - 31	22	63	15
31 - 37	22 → 54	63 → 39	15 → 7

Flow rate: 1.5 mL/min.

Detection: spectrophotometer at 230 nm.

Injection: 20 µL.

Relative retention with reference to temazepam (retention time = about 16 min): impurity E = about 0.55; impurity F = about 0.67; impurity G = about 0.73; impurity B = about 0.8; impurity D = about 1.2; impurity C = about 1.3; impurity A = about 1.5.

System suitability: reference solution (b):

– *resolution*: minimum 1.5 between the peaks due to impurity F and impurity G;
– *peak-to-valley ratio*: minimum 1.7, where H_p = height above the baseline of the peak due to impurity G and H_v = height above the baseline of the lowest point of the curve separating this peak from the peak due to impurity B.

Limits:

– *correction factors*: for the calculation of contents, multiply the peak areas of the following impurities by the corresponding correction factor: impurity F = 3.2; impurity G = 3.1;
– *impurities B, C, D, E, F, G*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.2 per cent);
– *unspecified impurities*: for each impurity, not more than 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.10 per cent);
– *total*: not more than 2.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.5 per cent);
– *disregard limit*: 0.25 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 0.250 g in 50 mL of *nitroethane 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 30.07 mg of $C_{16}H_{13}ClN_2O_2$.