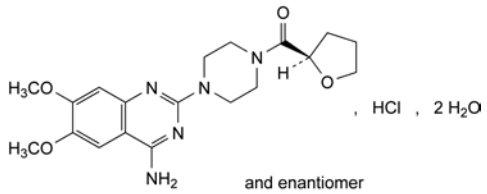
01/2008:2021

TERAZOSIN HYDROCHLORIDE DIHYDRATE

Terazosini hydrochloridum dihydricum



$C_{19}H_{26}ClN_5O_4,2H_2O$ M_r 459.9
[70024-40-7]

DEFINITION

1-(4-Amino-6,7-dimethoxyquinazolin-2-yl)-4-[[(2*RS*)-tetrahydrofuran-2-yl]carbonyl]piperazine hydrochloride dihydrate.

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

CHARACTERS

Appearance: white or slightly yellow, crystalline powder.

Solubility: sparingly soluble in water, slightly soluble in methanol, very slightly soluble in ethanol (96 per cent), practically insoluble in acetone.

IDENTIFICATION

A. Infrared absorption spectrophotometry (*2.2.24*).
Comparison: *terazosin hydrochloride dihydrate CRS*.

B. It gives reaction (a) of chlorides (*2.3.1*).

TESTS

Solution S. Dissolve 1.00 g in *carbon dioxide-free water R* and dilute to 50.0 mL with the same solvent.

Appearance of solution. The solution is clear (*2.2.1*) and not more intensely coloured than reference solution Y_7 (*2.2.2, Method II*).

Dilute 10 mL of solution S to 20 mL with *water R*.

pH (*2.2.3*): 3.0 to 5.0 for solution S.

Impurities N and O. Liquid chromatography (*2.2.29*).

Solvent mixture: *acetonitrile R1, water R* (20:80 *V/V*).

Test solution. Dissolve 50.0 mg of the substance to be examined in the solvent mixture and dilute to 50.0 mL with the solvent mixture.

Reference solution (a). Dissolve 5 mg of *terazosin impurity A CRS* and 5.0 mg of *terazosin impurity N CRS* in *acetonitrile R1* using sonication, add 5.0 mL of the test solution and dilute to 50.0 mL with *acetonitrile R1*. Dilute 10.0 mL of this solution to 100.0 mL with the solvent mixture.

Reference solution (b). Dilute 10.0 mL of reference solution (a) to 100.0 mL with the solvent mixture.

Column:
- *size*: *l* = 0.25 m, Ø = 4.0 mm;
- *stationary phase*: *octadecylsilyl silica gel for chromatography R* (5 µm);
- *temperature*: 25 °C.

Mobile phase: dissolve 2.80 g of *sodium laurilsulfate R* in 1000.0 mL of *water R* and add 11.0 mL of a solution containing 202.4 g/L of *triethylamine R* and 230.0 g/L of *phosphoric acid R*; adjust to pH 2.5 with *phosphoric acid R*; mix 600 volumes of this solution with 400 volumes of *acetonitrile R1*.

Flow rate: 1.0 mL/min.

Detection: spectrophotometer at 210 nm.

Injection: 20 µL.

Run time: 4 times the retention time of terazosin.

Relative retention with reference to terazosin (retention time = about 10 min): impurity O = about 0.2; impurity N = about 0.3; impurity A = about 0.4.

System suitability: reference solution (a):
- *resolution*: minimum 1.5 between the peaks due to impurities A and N.

Limits:
- *impurity N*: not more than the area of the corresponding peak in the chromatogram obtained with reference solution (b) (0.1 per cent);
- *impurity O*: not more than the area of the peak due to terazosin in the chromatogram obtained with reference solution (b) (0.1 per cent).

Related substances. Liquid chromatography (*2.2.29*).

Test solution. Dissolve 50.0 mg of the substance to be examined in the mobile phase and dilute to 100.0 mL with the mobile phase.

Reference solution (a). Dilute 2.0 mL of the test solution to 100.0 mL with the mobile phase. Dilute 5.0 mL of this solution to 100.0 mL with the mobile phase.

Reference solution (b). Dissolve the contents of a vial of *terazosin for system suitability CRS* (containing impurities A, B, C, J, K and M) in the mobile phase and dilute to 10 mL with the mobile phase.

Reference solution (c). Dissolve 5.0 mg of *terazosin impurity L CRS* in the mobile phase and dilute to 100.0 mL with the mobile phase. Dilute 1.0 mL of this solution to 100.0 mL with the mobile phase.

Reference solution (d). To 5 mg of *terazosin impurity E CRS*, add 70 mL of *methanol R* and 30 mL of *water R*. Allow to stand for at least 1 h to dissolve the substance. Use sonication if necessary.

Column:
- *size*: *l* = 0.25 m, Ø = 4.6 mm;
- *stationary phase*: *octylsilyl silica gel for chromatography R* (5 µm);
- *temperature*: 30 °C.

Mobile phase: mix 2 volumes of *triethylamine R*, 350 volumes of *acetonitrile R*, and 1650 volumes of a solution containing 6 g/L of *sodium citrate R* and 14.25 g/L of *anhydrous citric acid R*.

Flow rate: 1.0 mL/min.

Detection: spectrophotometer at 245 nm.

Injection: 20 µL.

Run time: 4 times the retention time of terazosin.

Identification of impurities: use the chromatogram supplied with *terazosin for system suitability CRS* and the chromatogram obtained with reference solution (b) to identify the peaks due to impurities A, B, C, J, K and M; use the chromatograms obtained with reference solutions (c) and (d) to identify the peaks due to impurities L and E respectively.

Retention time: terazosin = about 11 min.

System suitability: reference solution (b):
- *resolution*: minimum 1.5 between the peaks due to impurities B and J; if necessary, adjust the proportion of the aqueous component in the mobile phase (an increase in the proportion of the aqueous component increases the retention times);
- the chromatogram obtained is similar to the chromatogram supplied with *terazosin for system suitability CRS*; in case of insufficient separation of the impurities, reduce the amount of triethylamine in the mobile phase.

Limits:

- *correction factors*: for the calculation of content, multiply the peak areas of the following impurities by the corresponding correction factor: impurity C = 0.7; impurity M = 1.6;
- *impurities A, C, E, K*: for each impurity, not more than 5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.5 per cent);
- *impurity L*: not more than the area of the corresponding peak in the chromatogram obtained with reference solution (c) (0.1 per cent);
- *impurities B, J, M*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.1 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 5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.5 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).

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

1.0 g complies with test C. Prepare the reference solution using 2 mL of *lead standard solution (10 ppm) Pb R*.

Water (*2.5.12*): 7.0 per cent to 8.6 per cent, determined on 0.200 g.

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

ASSAY

Dissolve 0.300 g in a mixture of 5.0 mL of *0.01 M hydrochloric acid* and 50 mL of *methanol R*. Titrate with *0.1 M sodium hydroxide*, determining the end-point potentiometrically (*2.2.20*). Read the volume added between the 2 points of inflexion.

1 mL of *0.1 M sodium hydroxide* is equivalent to 42.39 mg of $C_{19}H_{26}ClN_5O_4$.

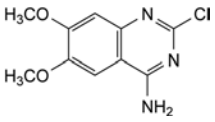
STORAGE

Protected from light.

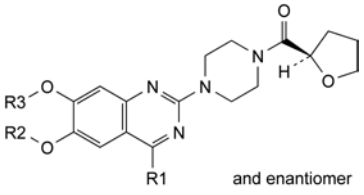
IMPURITIES

Specified impurities: A, B, C, E, J, K, L, M, N, O.

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*): *D, F, G, H, I.*



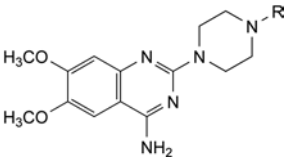
A. 2-chloro-6,7-dimethoxyquinazolin-4-amine,



B. R1 = OH, R2 = R3 = CH_3: 1-(4-hydroxy-6,7-dimethoxyquinazolin-2-yl)-4-[[(2*RS*)-tetrahydrofuran-2-yl]carbonyl]piperazine,

G. R1 = NH_2, R2 = H, R3 = CH_3: 1-(4-amino-6-hydroxy-7-methoxyquinazolin-2-yl)-4-[[(2*RS*)-tetrahydrofuran-2-yl]carbonyl]piperazine,

H. R1 = NH_2, R2 = CH_3, R3 = H: 1-(4-amino-7-hydroxy-6-methoxyquinazolin-2-yl)-4-[[(2*RS*)-tetrahydrofuran-2-yl]carbonyl]piperazine,

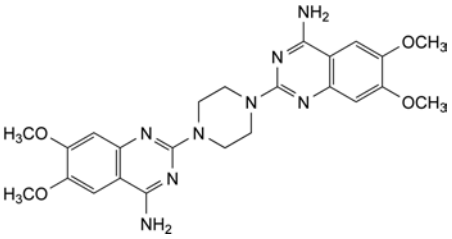


C. R = H: 6,7-dimethoxy-2-(piperazin-1-yl)quinazolin-4-amine,

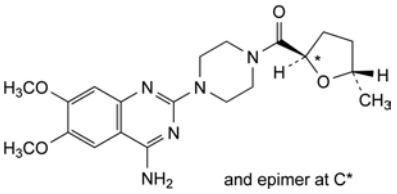
D. R = CHO: 1-(4-amino-6,7-dimethoxyquinazolin-2-yl)-4-formylpiperazine,

F. R = CO-$[CH_2]_4$-OH: 1-(4-amino-6,7-dimethoxyquinazolin-2-yl)-4-(5-hydroxypentanoyl)piperazine,

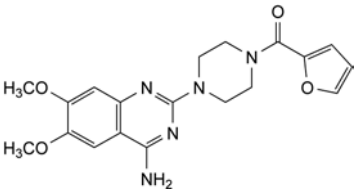
J. R = CO-CH(OH)-CH_2-CH_2-CH_3: 1-(4-amino-6,7-dimethoxyquinazolin-2-yl)-4-[(2*RS*)-2-hydroxypentanoyl]piperazine,



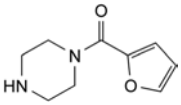
E. 2,2′-(piperazine-1,4-diyl)bis(6,7-dimethoxyquinazolin-4-amine),



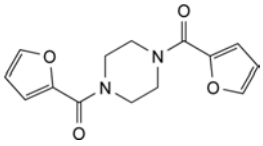
I. 1-(4-amino-6,7-dimethoxyquinazolin-2-yl)-4-[[(2*RS*,5*S*)-5-methyltetrahydrofuran-2-yl]carbonyl]piperazine,



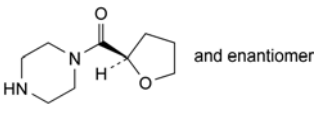
K. 1-(4-amino-6,7-dimethoxyquinazolin-2-yl)-4-(furan-2-ylcarbonyl)piperazine (prazosin),



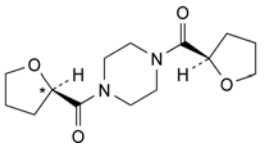
L. 1-(furan-2-ylcarbonyl)piperazine,



M. 1,4-bis(furan-2-ylcarbonyl)piperazine,



N. 1-[[(2*RS*)-tetrahydrofuran-2-yl]carbonyl]piperazine,

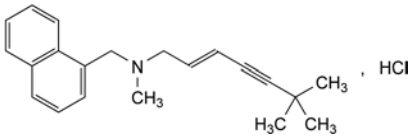


O. 1,4-bis[(tetrahydrofuran-2-yl)carbonyl]piperazine.

01/2010:1734

TERBINAFINE HYDROCHLORIDE

Terbinafini hydrochloridum



$C_{21}H_{26}ClN$ M_r 327.9
[78628-80-5]

DEFINITION

(2*E*)-*N*,6,6-Trimethyl-*N*-(naphthalen-1-ylmethyl)hept-2-en-4-yn-1-amine hydrochloride.

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

CHARACTERS

Appearance: white or almost white powder.

Solubility: very slightly or slightly soluble in water, freely soluble in anhydrous ethanol and in methanol, slightly soluble in acetone.

IDENTIFICATION

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

B. It gives reaction (a) of chlorides (*2.3.1*) using *anhydrous ethanol R* as solvent.

TESTS

Related substances. Liquid chromatography (*2.2.29*). *Carry out the test protected from light.*

Solvent mixture A: *acetonitrile R, water R* (50:50 *V/V*).

Solvent mixture B: *acetonitrile R, methanol R* (40:60 *V/V*).

Buffer solution. Dilute 2.0 mL of *triethylamine R1* to 950 mL with *water R*. Adjust to pH 7.5 with a mixture of 5 volumes of *glacial acetic acid R* and 95 volumes of *water R* and dilute to 1000.0 mL with *water R*.

Test solution. Dissolve 25 mg of the substance to be examined in solvent mixture A and dilute to 50.0 mL with solvent mixture A.

Reference solution (a). Dissolve 5 mg of *terbinafine for system suitability CRS* (containing impurities B and E) in 10.0 mL of solvent mixture A.

Reference solution (b). Dilute 1.0 mL of the test solution to 100.0 mL with solvent mixture A. Dilute 1.0 mL of this solution to 10.0 mL with solvent mixture A.

Column:

– *size*: *l* = 0.15 m, Ø = 3.0 mm;
– *stationary phase*: spherical *end-capped octadecylsilyl silica gel for chromatography R* (5 µm);
– *temperature*: 40 °C.

Mobile phase:

– *mobile phase A*: buffer solution, solvent mixture B (30:70 *V/V*);
– *mobile phase B*: buffer solution, solvent mixture B (5:95 *V/V*);

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 4	100	0
4 - 25	100 → 0	0 → 100
25 - 30	0	100

Flow rate: 0.8 mL/min.

Detection: spectrophotometer at 280 nm.

Injection: 20 µL.

Identification of impurities: use the chromatogram supplied with *terbinafine for system suitability CRS* and the chromatogram obtained with reference solution (a) to identify the peaks due to impurities B and E.

Relative retention with reference to terbinafine (retention time = about 15 min): impurity B = about 0.9; impurity E = about 1.7.

System suitability: reference solution (a):

– *resolution*: minimum 2.0 between the peaks due to impurity B and terbinafine.

Limits:

– *correction factor*: for the calculation of content, multiply the peak area of impurity E by 0.5;
– *impurity B*: not more than 1.5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.15 per cent);
– *impurity E*: not more than 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.05 per cent);
– *unspecified impurities*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (0.10 per cent);
– *total*: not more than 3 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.3 per cent);
– *disregard limit*: 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (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 0.250 g in 50 mL of *ethanol (96 per cent) R*, add 5 mL of *0.01 M hydrochloric acid*. Titrate with *0.1 M sodium hydroxide* determining the end-point potentiometrically (*2.2.20*). Read the volume added between the 2 points of inflexion.

1 mL of *0.1 M sodium hydroxide* is equivalent to 32.79 mg of $C_{21}H_{26}ClN$.

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, F.*