Reference solution (b). Dissolve 5.0 mg of *thiamazole impurity A CRS*, 5.0 mg of *1-methylimidazole R1* and 5.0 mg of *thiamazole impurity C CRS* in *chloroform R* and dilute to 50.0 ml with the same solvent. Dilute 1.0 ml of this solution to 10.0 ml with *chloroform R*.

Column:

- *material*: fused silica,
- *size*: *l* = 30.0 m, Ø = 0.25 mm,
- *stationary phase*: *poly(dimethyl)(diphenyl)siloxane R* with special deactivation for basic compounds (film thickness 0.5 µm).

Carrier gas: *helium for chromatography R*.

Flow rate: 1.5 ml/min.

Split ratio: 3:20.

Temperature:

	Time (min)	Temperature (°C)
Column	0 - 2	100
	2 - 7	100 → 250
	7 - 22	250
Injection port		150
Detector		250

Detection: flame ionisation.

Injection: 1 µl.

Relative retention with reference to thiamazole (retention time = about 6.5 min): impurity A = about 0.3; impurity B = about 0.4; impurity C = about 0.7.

System suitability: reference solution (b):

- *resolution*: minimum 1.5 between the peaks due to impurity A and impurity B.

Limits:

- *impurities A, B, C*: for each impurity, not more than the area of the corresponding peak in the chromatogram obtained with reference solution (b) (0.1 per cent),
- *any other impurity*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.1 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*: 0.2 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.02 per cent).

Heavy metals (*2.4.8*): maximum 10 ppm.

12 ml of solution S complies with limit test A. Prepare the reference solution using *lead standard solution (1 ppm Pb) R*.

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 2 h.

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

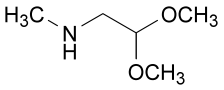
ASSAY

Dissolve 0.250 g in 75 ml of *water R*. Add 15.0 ml of *0.1 M sodium hydroxide*, mix and add with stirring, about 30 ml of *0.1 M silver nitrate*. Continue the titration with *0.1 M sodium hydroxide*, determining the end-point potentiometrically (*2.2.20*).

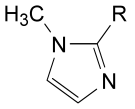
1 ml of *0.1 M sodium hydroxide* is equivalent to 11.42 mg of $C_4H_6N_2S$.

IMPURITIES

Specified impurities: A, B, C.



A. 2,2-dimethoxy-*N*-methylethanamine,



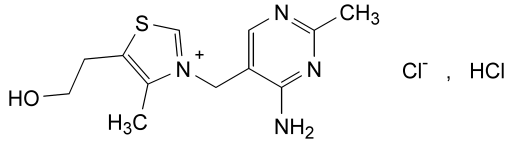
B. R = H: 1-methyl-1*H*-imidazole,

C. R = SCH_3: 1-methyl-2-(methylsulphanyl)-1*H*-imidazole.

01/2008:0303

THIAMINE HYDROCHLORIDE

Thiamini hydrochloridum



$C_{12}H_{18}Cl_2N_4OS$ M_r 337.3
[67-03-8]

DEFINITION

3-[(4-Amino-2-methylpyrimidin-5-yl)methyl]-5-(2-hydroxyethyl)-4-methylthiazolium chloride hydrochloride.

Content: 98.5 per cent to 101.0 per cent (anhydrous substance).

CHARACTERS

Appearance: white or almost white, crystalline powder or colourless crystals.

Solubility: freely soluble in water, soluble in glycerol, slightly soluble in alcohol.

IDENTIFICATION

First identification: A, C.

Second identification: B, C.

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

B. Dissolve about 20 mg in 10 ml of *water R*, add 1 ml of *dilute acetic acid R* and 1.6 ml of *1 M sodium hydroxide*, heat on a water-bath for 30 min and allow to cool. Add 5 ml of *dilute sodium hydroxide solution R*, 10 ml of *potassium ferricyanide solution R* and 10 ml of *butanol R* and shake vigorously for 2 min. The upper alcoholic layer shows an intense light-blue fluorescence, especially in ultraviolet light at 365 nm. Repeat the test using 0.9 ml of *1 M sodium hydroxide* and 0.2 g of *sodium sulphite R* instead of 1.6 ml of *1 M sodium hydroxide*. Practically no fluorescence is seen.

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

TESTS

Solution S. Dissolve 2.5 g in *distilled water R* and dilute to 25 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 or GY_7 (*2.2.2, Method II*).

Dilute 2.5 ml of solution S to 5 ml with *water R*.

pH (*2.2.3*): 2.7 to 3.3.

Dilute 2.5 ml of solution S to 10 ml with *water R*.

Related substances. Liquid chromatography (*2.2.29*).

Solution A. Add 5 volumes of *glacial acetic acid R* to 95 volumes of *water R* and mix.

Test solution. Dissolve 0.35 g of the substance to be examined in 15.0 ml of solution A and dilute to 100.0 ml with *water R*.

Reference solution (a). Dissolve 5 mg of the substance to be examined and 5 mg of *thiamine impurity E CRS* in 4 ml of solution A and dilute to 25.0 ml with *water R*. Dilute 5.0 ml of the solution to 25.0 ml with *water R*.

Reference solution (b). Dilute 1.0 ml of the test solution to 50.0 ml with *water R*. Dilute 5.0 ml of this solution to 25.0 ml with *water R*.

Column:

- *size*: *l* = 0.25 m, Ø = 4.0 mm,
- *stationary phase*: spherical *end-capped octadecylsilyl silica gel for chromatography R* (5 µm) with a specific surface area of 350 m^2/g and a pore size of 10 nm,
- *temperature*: 45 °C.

Mobile phase:

- *mobile phase A*: 3.764 g/l solution of *sodium hexanesulphonate R* adjusted to pH 3.1 with *phosphoric acid R*,
- *mobile phase B*: *methanol R2*,

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 25	90 → 70	10 → 30
25 - 33	70 → 50	30 → 50
33 - 40	50	50
40 - 45	50 → 90	50 → 10

Flow rate: 1.0 ml/min.

Detection: spectrophotometer at 248 nm.

Injection: 25 µl.

Relative retention with reference to thiamine (retention time = about 30 min): impurity A = about 0.3; impurity B = about 0.9; impurity C = about 1.2.

System suitability: reference solution (a):

- *resolution*: minimum 1.6 between the peaks due to impurity E and to thiamine.

Limits:

- *any impurity*: not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (0.4 per cent),
- *total*: not more than 2.5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (1.0 per cent),
- *disregard limit*: 0.125 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.05 per cent).

Sulphates (*2.4.13*): maximum 300 ppm.

5 ml of solution S diluted to 15 ml with *distilled water R* complies with the limit test for sulphates.

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

12 ml of solution S complies with limit test A. Prepare the standard using *lead standard solution (2 ppm Pb) R*.

Water (*2.5.12*): maximum 5.0 per cent, determined on 0.40 g.

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

ASSAY

Dissolve 0.110 g in 5 ml of *anhydrous formic acid R* and add 50 ml of *acetic anhydride R*. Titrate immediately with *0.1 M perchloric acid*, determining the end-point potentiometrically (*2.2.20*) and carrying out the titration within 2 min. Carry out a blank titration.

1 ml of *0.1 M perchloric acid* is equivalent to 16.86 mg of $C_{12}H_{18}Cl_2N_4OS$.

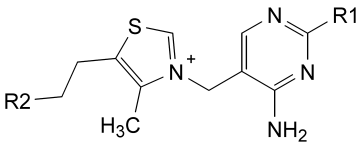
STORAGE

In a non-metallic container, protected from light.

IMPURITIES

Specified impurities: A, B, C.

Other detectable impurities: D, E, F, G, H.



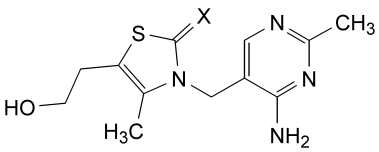
A. R1 = CH_3, R2 = O-SO_3^-: 3-[(4-amino-2-methylpyrimidin-5-yl)methyl]-4-methyl-5-[2-(sulphonatooxy)ethyl]thiazolium (thiamine sulphate ester),

B. R1 = H, R2 = OH: 3-[(4-aminopyrimidin-5-yl)methyl]-5-(2-hydroxyethyl)-4-methylthiazolium (desmethylthiamine),

C. R1 = CH_3, R2 = Cl: 3-[(4-amino-2-methylpyrimidin-5-yl)methyl]-5-(2-chloroethyl)-4-methylthiazolium (chlorothiamine),

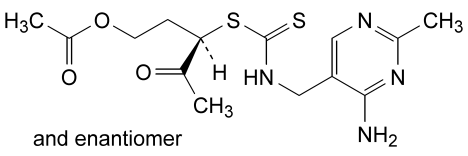
F. R1 = C_2H_5, R2 = OH: 3-[(4-amino-2-ethylpyrimidin-5-yl)methyl]-5-(2-hydroxyethyl)-4-methylthiazolium (ethylthiamine),

G. R1 = CH_3, R2 = O-CO-CH_3: 5-[2-(acetyloxy)ethyl]-3-[(4-amino-2-methylpyrimidin-5-yl)methyl]-4-methylthiazolium (acetylthiamine),



D. X = O: 3-[(4-amino-2-methylpyrimidin-5-yl)methyl]-5-(2-hydroxyethyl)-4-methylthiazol-2(3*H*)-one (oxothiamine),

E. X = S: 3-[(4-amino-2-methylpyrimidin-5-yl)methyl]-5-(2-hydroxyethyl)-4-methylthiazol-2(3*H*)-thione (thioxothiamine),



H. (3*RS*)-3-[[[(4-amino-2-methylpyrimidin-5-yl)methyl]thiocarbamoyl]sulphanyl]-4-oxopentyl acetate (ketodithiocarbamate).

ERRATA

In the following monographs, after the heading ‘Other detectable impurities’ in the Impurities section, read:

‘(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*)’

Articaine hydrochloride (1688)
Biperiden hydrochloride (1074)
Caffeine (0267)
Caffeine monohydrate (0268)
Ibuprofen (0721)
Ifosfamide (1529)
Metformin hydrochloride (0931)
Naphazoline hydrochloride (0730)
Norethisterone acetate (0850)
Oxaliplatin (2017)
Potassium clavulanate (1140)
Potassium clavulanate, diluted (1653)
Testosterone propionate (0297)
Thiamine hydrochloride (0303)
Thiamine nitrate (0531)
Tranexamic acid (0875)