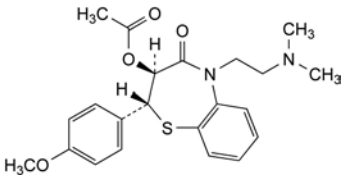
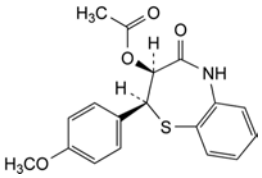
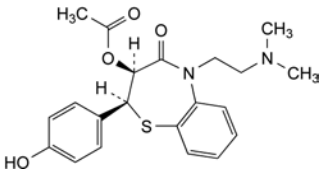
for demonstration of compliance. See also *5.10. Control of impurities in substances for pharmaceutical use*): *A, B, C, D, E, F.*



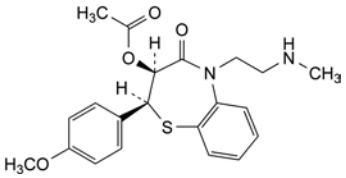
A. (2*R*,3*S*)-5-[2-(dimethylamino)ethyl]-2-(4-methoxyphenyl)-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl acetate,



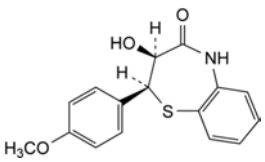
B. (2*S*,3*S*)-2-(4-methoxyphenyl)-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl acetate,



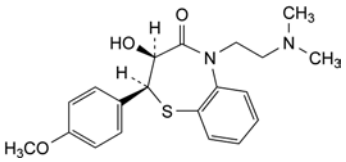
C. (2*S*,3*S*)-5-[2-(dimethylamino)ethyl]-2-(4-hydroxyphenyl)-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl acetate,



D. (2*S*,3*S*)-2-(4-methoxyphenyl)-5-[2-(methylamino)ethyl]-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl acetate,



E. (2*S*,3*S*)-3-hydroxy-2-(4-methoxyphenyl)-2,3-dihydro-1,5-benzothiazepin-4(5*H*)-one,

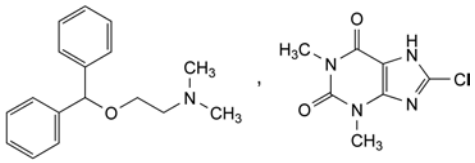


F. (2*S*,3*S*)-5-[2-(dimethylamino)ethyl]-3-hydroxy-2-(4-methoxyphenyl)-2,3-dihydro-1,5-benzothiazepin-4(5*H*)-one.

07/2009:0601

DIMENHYDRINATE

Dimenhydrinatum



$C_{24}H_{28}ClN_5O_3$ M_r 470.0
[523-87-5]

DEFINITION

Diphenhydramine [2-(diphenylmethoxy)-*N*,*N*-dimethylethanamine] 8-chlorotheophylline (8-chloro-1,3-dimethyl-3,7-dihydro-1*H*-purine-2,6-dione).

Content:

– *diphenhydramine* ($C_{17}H_{21}NO$; M_r 255.4): 53.0 per cent to 55.5 per cent (dried substance);
– *8-chlorotheophylline* ($C_7H_7ClN_4O_2$; M_r 214.6): 44.0 per cent to 46.5 per cent (dried substance).

CHARACTERS

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

Solubility: slightly soluble in water, freely soluble in ethanol (96 per cent).

IDENTIFICATION

First identification: C.

Second identification: A, B, D.

A. Melting point (*2.2.14*): 102 °C to 106 °C.

B. Dissolve 0.1 g in a mixture of 3 mL of *water R* and 3 mL of *ethanol (96 per cent) R*, add 6 mL of *water R* and 1 mL of *dilute hydrochloric acid R* and cool in iced water for 30 min, scratching the wall of the tube with a glass rod if necessary to initiate crystallisation. Dissolve about 10 mg of the precipitate obtained in 1 mL of *hydrochloric acid R*, add 0.1 g of *potassium chlorate R* and evaporate to dryness in a porcelain dish. A reddish residue is obtained that becomes violet-red when exposed to ammonia vapour.

C. Infrared absorption spectrophotometry (*2.2.24*).
Comparison: *dimenhydrinate CRS*.

D. Dissolve 0.2 g in 10 mL of *ethanol (96 per cent) R*. Add 10 mL of *picric acid solution R* and initiate crystallisation by scratching the wall of the tube with a glass rod. The precipitate, washed with *water R* and dried at 100-105 °C, melts (*2.2.14*) at 130 °C to 134 °C.

TESTS

Appearance of solution. The solution is clear (*2.2.1*) and colourless (*2.2.2, Method II*).

Dissolve 1.0 g in *ethanol (96 per cent) R* and dilute to 20 mL with the same solvent.

pH (*2.2.3*): 7.1 to 7.6 for the filtrate.

To 0.4 g add 20 mL of *carbon dioxide-free water R*, shake for 2 min and filter.

Related substances. Liquid chromatography (*2.2.29*).

Solvent mixture: *acetonitrile R, water R* (18:82 *V/V*).

Test solution. Dissolve 0.100 g of the substance to be examined in the solvent mixture and dilute to 100.0 mL with the solvent mixture.

Reference solution (a). Dissolve 57 mg of *diphenhydramine hydrochloride CRS* in the solvent mixture and dilute to 50.0 mL with the solvent mixture.

Reference solution (b). Dilute 1.0 mL of reference solution (a) to 100.0 mL with the solvent mixture. Dilute 2.0 mL of this solution to 10.0 mL with the solvent mixture.

Reference solution (c). Dissolve 5.0 mg of *diphenhydramine impurity A CRS* (impurity F) in 5.0 mL of reference solution (a) and dilute to 50.0 mL with the solvent mixture.

Reference solution (d). Dissolve the contents of a vial of *dimenhydrinate for peak identification CRS* (containing impurities A and E) in 1.0 mL of the solvent mixture.

Column:

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

Mobile phase:

– *mobile phase A*: dissolve 10.0 g of *triethylamine R2* in 950 mL of *water R*, adjust to pH 2.5 with *phosphoric acid R* and dilute to 1000 mL with *water R*;
– *mobile phase B*: *acetonitrile R1*;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)	Flow rate (mL/min)
0 - 2	82	18	1.2
2 - 15	82 → 50	18 → 50	1.2
15 - 20	50 → 20	50 → 80	1.2 → 2.0
20 - 30	20	80	2.0

Detection: spectrophotometer at 225 nm.

Injection: 10 µL.

Identification of impurities: use the chromatogram supplied with *dimenhydrinate for peak identification CRS* and the chromatogram obtained with reference solution (d) to identify the peaks due to impurities A and E; use the chromatogram obtained with reference solution (c) to identify impurity F.

Relative retention with reference to diphenhydramine (retention time = about 13 min): impurity A = about 0.3; impurity E = about 0.7; impurity F = about 0.95.

System suitability: reference solution (c):

– *resolution*: minimum 1.5 between the peaks due to impurity F and diphenhydramine.

Limits:

– *impurities A, F*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (0.2 per cent);
– *impurity E*: not more than 0.75 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.15 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 (b) (0.10 per cent);
– *total*: not more than 2.5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.5 per cent);
– *disregard limit*: 0.25 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 vacuo*.

Sulfated ash (*2.4.14*): maximum 0.2 per cent, determined on 1.0 g.

ASSAY

Diphenhydramine. Dissolve 0.200 g in 60 mL of *anhydrous acetic acid 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 25.54 mg of $C_{17}H_{21}NO$.

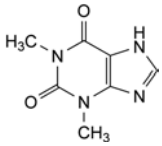
8-Chlorotheophylline. To 0.800 g add 50 mL of *water R*, 3 mL of *dilute ammonia R1* and 0.6 g of *ammonium nitrate R* and heat on a water-bath for 5 min. Add 25.0 mL of *0.1 M silver nitrate* and continue heating on a water-bath for 15 min with frequent swirling. Cool, add 25 mL of *dilute nitric acid R* and dilute to 250.0 mL with *water R*. Filter and discard the first 25 mL of the filtrate. Using 5 mL of *ferric ammonium sulfate solution R2* as indicator, titrate 100.0 mL of the filtrate with *0.1 M ammonium thiocyanate* until a yellowish-brown colour is obtained.

1 mL of *0.1 M silver nitrate* is equivalent to 21.46 mg of $C_7H_7ClN_4O_2$.

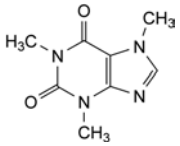
IMPURITIES

Specified impurities: A, E, F.

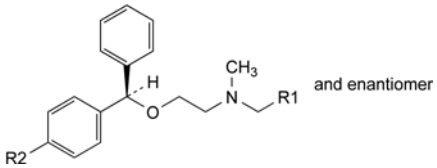
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph *Substances for pharmaceutical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



A. 1,3-dimethyl-3,7-dihydro-1*H*-purine-2,6-dione (theophylline),



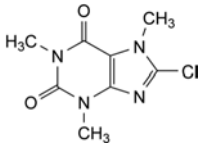
C. 1,3,7-trimethyl-3,7-dihydro-1*H*-purine-2,6-dione (caffeine),



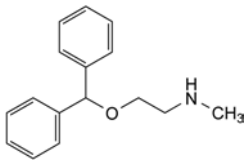
D. R1 = CH_2-N(CH_3)$_2$, R2 = H: *N*-[2-(diphenylmethoxy)ethyl]-*N*,*N*′,*N*′-trimethylethane-1,2-diamine,

G. R1 = H, R2 = CH_3: *N*,*N*-dimethyl-2-[(*RS*)-(4-methylphenyl)(phenyl)methoxy]ethanamine (4-methyldiphenhydramine),

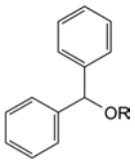
H. R1 = H, R2 = Br: 2-[(*RS*)-(4-bromophenyl)-(phenyl)methoxy]-*N*,*N*-dimethylethanamine (4-bromodiphenhydramine),



E. 8-chloro-1,3,7-trimethyl-3,7-dihydro-1*H*-purine-2,6-dione (8-chlorocaffeine),

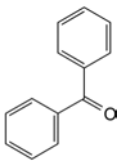


F. 2-(diphenylmethoxy)-*N*-methylethanamine (diphenhydramine impurity A),



I. R = H: diphenylmethanol (benzhydrol),

K. R = $CH(C_6H_5)_2$: [oxybis(methanetriyl)]tetrabenzene,

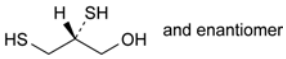


J. diphenylmethanone (benzophenone).

01/2008:0389

DIMERCAPROL

Dimercaprolum



$C_3H_8OS_2$ M_r 124.2
[59-52-9]

DEFINITION

(2*RS*)-2,3-Disulfanylpropan-1-ol.

Content: 98.5 per cent to 101.5 per cent.

CHARACTERS

Appearance: clear, colourless or slightly yellow liquid.

Solubility: soluble in water and in arachis oil, miscible with ethanol (96 per cent) and with benzyl benzoate.

IDENTIFICATION

A. Dissolve 0.05 mL in 2 mL of *water R*. Add 1 mL of *0.05 M iodine*. The colour of the iodine is discharged immediately.

B. Dissolve 0.1 mL in 5 mL of *water R* and add 2 mL of *copper sulfate solution R*. A bluish-black precipitate is formed which quickly becomes dark grey.

C. In a ground-glass-stoppered tube, suspend 0.6 g of *sodium bismuthate R*, previously heated to 200 °C for 2 h, in a mixture of 2.8 mL of *dilute phosphoric acid R* and 6 mL of *water R*. Add 0.2 mL of the substance to be examined, mix and allow to stand for 10 min with frequent shaking. To 1 mL of the supernatant liquid add 5 mL of a 4 g/L solution of *chromotropic acid, sodium salt R* in *sulfuric acid R* and mix. Heat in a water-bath for 15 min. A violet-red colour develops.

TESTS

Appearance. It is clear (*2.2.1*) and not more intensely coloured than reference solution B_6 or BY_6 (*2.2.2, Method II*).

Acidity or alkalinity. Dissolve 0.2 g in *carbon dioxide-free water R* and dilute to 10 mL with the same solvent. Add 0.25 mL of *bromocresol green solution R* and 0.3 mL of *0.01 M hydrochloric acid*. The solution is yellow. Not more than 0.5 mL of *0.01 M sodium hydroxide* is required to change the colour of the indicator to blue.

Refractive index (*2.2.6*): 1.568 to 1.574.

Halides. To 2.0 g add 25 mL of *alcoholic potassium hydroxide solution R* and boil under a reflux condenser for 2 h. Eliminate the ethanol by evaporation in a stream of hot air. Add 20 mL of *water R* and cool. Add 40 mL of *water R* and 10 mL of *strong hydrogen peroxide solution R*, boil gently for 10 min, cool and filter rapidly. Add 10 mL of *dilute nitric acid R* and 5.0 mL of *0.1 M silver nitrate*. Using 2 mL of *ferric ammonium sulfate solution R2* as indicator, titrate with *0.1 M ammonium thiocyanate* until a reddish-yellow colour is obtained. Carry out a blank titration. The difference between the titration volumes is not greater than 1.0 mL.

ASSAY

Dissolve 0.100 g in 40 mL of *methanol R*. Add 20 mL of *0.1 M hydrochloric acid* and 50.0 mL of *0.05 M iodine*. Allow to stand for 10 min and titrate with *0.1 M sodium thiosulfate*. Carry out a blank titration.

1 mL of *0.05 M iodine* is equivalent to 6.21 mg of $C_3H_8OS_2$.

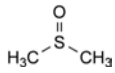
STORAGE

In a well-filled, airtight container, protected from light, at a temperature of 2 °C to 8 °C.

01/2008:0763

DIMETHYL SULFOXIDE

Dimethylis sulfoxidum



C_2H_6OS M_r 78.1
[67-68-5]

DEFINITION

Sulfinylbismethane.

CHARACTERS

Appearance: colourless liquid or colourless crystals, hygroscopic.

Solubility: miscible with water and with ethanol (96 per cent).

IDENTIFICATION

First identification: C.

Second identification: A, B, D.

A. Relative density (see Tests).

B. Refractive index (see Tests).

C. Infrared absorption spectrophotometry (*2.2.24*).
Comparison: *dimethyl sulfoxide CRS*.

D. Dissolve 50 mg of *nickel chloride R* in 5 mL of the substance to be examined. The solution is greenish-yellow. Heat in a water-bath at 50 °C. The colour changes to green or bluish-green. Cool. The colour changes to greenish-yellow.

TESTS

Acidity. Dissolve 50.0 g in 100 mL of *carbon dioxide-free water R*. Add 0.1 mL of *phenolphthalein solution R1*. Not more than 5.0 mL of *0.01 M sodium hydroxide* is required to produce a pink colour.

Relative density (*2.2.5*): 1.100 to 1.104.

Refractive index (*2.2.6*): 1.478 to 1.479.

Freezing point (*2.2.18*): minimum 18.3 °C.

Absorbance (*2.2.25*). Purge with *nitrogen R* for 15 min. The absorbance, measured using *water R* as the compensation liquid, is not more than 0.30 at 275 nm and not more than 0.20 at both 285 nm and 295 nm. Examined between 270 nm and 350 nm, the substance to be examined shows no absorption maximum.

Related substances. Gas chromatography (*2.2.28*).

Internal standard solution. Dissolve 0.125 g of *bibenzyl R* in *acetone R* and dilute to 50 mL with the same solvent.

Test solution (a). Dissolve 5.0 g of the substance to be examined in *acetone R* and dilute to 10.0 mL with the same solvent.

Test solution (b). Dissolve 5.0 g of the substance to be examined in *acetone R*, add 1.0 mL of the internal standard solution and dilute to 10.0 mL with *acetone R*.