UNIVERSITÀ DEGLI STUDI DI TORINO

ESAME DI STATO PER L’ABILITAZIONE ALL’ESERCIZIO DELLA PROFESSIONE DI FARMACISTA

SECONDA SESSIONE 2017

PROVA SCRITTA

Tema n. 1
La tecnologia dei cerotti transdermici.

Tema n. 2

Il ruolo del farmacista nella DPC e le novità in tale modalità distributiva.

Tema n. 3
Le Incretine e la loro novità rispetto agli altri antidiabetici.

PROVA PRATICA

Prova n.1
Dosamento del farmaco.
Vedi allegato di seguito.

Prova n.2
Riconoscimento del farmaco.
Vedi allegato di seguito.

Prova n.3
Spedizione della ricetta.
Vedi allegato di seguito.

UNIVERSITA' DEGLI STUDI DI TORINO
ESAME DI STATO PER L'ABILITAZIONE ALL'ESERCIZIO DELLA PROFESSIONE DI FARMACISTA

SECONDA SESSIONE 2017

PROVA PRATICA-DOSAMENTO DEL FARMACO

Cognome e nome..

Cinque compresse dal peso complessivo di 5,118 g contenenti cimetidina (PM=252.3) ed eccipienti inerti sono state polverizzate. 3,078 g di polvere è stata sciolta in un matraccio da 100,00 mL con acido acetico anidro e portata a volume per ottenere la soluzione A.

25,00 mL della soluzione A sono stati esattamente prelevati e titolati secondo Ph. Eur. 9.0. La titolazione ha richiesto 11.89 mL di acido perclorico ($HClO_4$) 0.1000 M.

Si calcolino:

a) i grammi di cimetidina contenuti in una compressa
b) la % di principio attivo contenuta in una compressa
c) la concentrazione molare della cimetidina nella soluzione A

Risposte ai quesiti:

a) ______________________________

b) ______________________________

c) ______________________________

N.B. Insieme alla prova al candidato viene fornita copia della monografia ufficiale di Ph. Eur. 9.0 della cimetidina

Related substances. Liquid chromatography (*2.2.29*).

Test solution. Dissolve 25.0 mg of the substance to be examined in the mobile phase and dilute to 50.0 mL with the mobile phase.

Reference solution (a). Dilute 1.0 mL of the test solution to 50.0 mL with the mobile phase. Dilute 5.0 mL of this solution to 20.0 mL with the mobile phase.

Reference solution (b). Dissolve 5.0 mg of *cilazapril impurity D CRS* in the test solution and dilute to 10.0 mL with the test solution.

Column:

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

Mobile phase: mix 10 volumes of *triethylamine R* and 750 volumes of *water R*, adjust to pH 2.30 with *phosphoric acid R*, and add 200 volumes of *tetrahydrofuran R*.

Flow rate: 1.0 mL/min.

Detection: spectrophotometer at 214 nm.

Injection: 20 µL.

Run time: twice the retention time of cilazapril; when impurity A is present, it may be necessary to continue the chromatography until it is eluted.

Relative retention with reference to cilazapril: impurity B = about 0.6; impurity D = about 0.9; impurity C = about 1.6; impurity A = 4 to 5.

System suitability: reference solution (b):

- *resolution*: minimum 2.5 between the peaks due to impurity D and cilazapril;
- *symmetry factor*: maximum 3.0 for the peak due to cilazapril.

Limits:

- *impurity B*: not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.5 per cent);
- *impurity D*: not more than 0.4 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.2 per cent);
- *impurity C*: not more than 0.2 times 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 0.2 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.10 per cent);
- *total*: not more than twice the area of the principal peak in the chromatogram obtained with reference solution (a) (1 per cent);
- *disregard limit*: 0.1 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.05 per cent); disregard any peak due to impurity A.

Water (*2.5.12*): 3.5 per cent to 5.0 per cent, determined on 0.300 g.

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

ASSAY

Dissolve 0.300 g in 10 mL of *anhydrous ethanol R* and add 50 mL of *water R*. Titrate with *0.1 M sodium hydroxide*, determining the end-point potentiometrically (*2.2.20*). Carry out a blank titration.

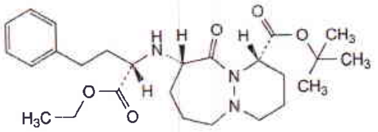
1 mL of *0.1 M sodium hydroxide* is equivalent to 41.75 mg of $C_{22}H_{31}N_3O_5$.

STORAGE

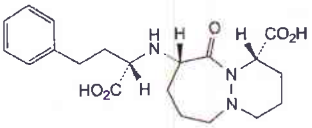
Protected from light.

IMPURITIES

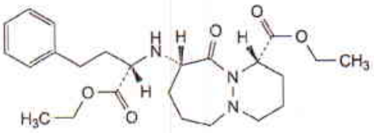
Specified impurities: *A, B, C, D*.



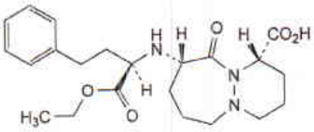
A. 1,1-dimethylethyl (1*S*,9*S*)-9-[[(*S*)-1-(ethoxycarbonyl)-3-phenylpropyl]amino]-10-oxooctahydro-6*H*-pyridazino[1,2-*a*][1,2]diazepine-1-carboxylate,



B. (1*S*,9*S*)-9-[[(*S*)-1-carboxy-3-phenylpropyl]amino]-10-oxooctahydro-6*H*-pyridazino[1,2-*a*][1,2]diazepine-1-carboxylic acid,



C. ethyl (1*S*,9*S*)-9-[[(*S*)-1-(ethoxycarbonyl)-3-phenylpropyl]amino]-10-oxooctahydro-6*H*-pyridazino[1,2-*a*][1,2]diazepine-1-carboxylate,



D. (1*S*,9*S*)-9-[[(*R*)-1-(ethoxycarbonyl)-3-phenylpropyl]-amino]-10-oxooctahydro-6*H*-pyridazino[1,2-*a*][1,2]-diazepine-1-carboxylic acid.

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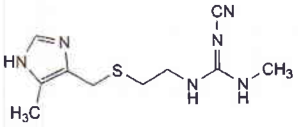
CIMETIDINE

Cimetidinum



$C_{10}H_{16}N_6S$ M_r 252.3

[51481-61-9]

DEFINITION

2-Cyano-1-methyl-3-[2-[[(5-methyl-1*H*-imidazol-4-yl)-methyl]sulfanyl]ethyl]guanidine.

Content: 98.5 per cent to 101.5 per cent (dried substance).

CHARACTERS

Appearance: white or almost white powder.

Solubility: slightly soluble in water, soluble in ethanol (96 per cent), practically insoluble in methylene chloride. It dissolves in dilute mineral acids.

It shows polymorphism (*5.9*).

IDENTIFICATION

First identification: *B*.

Second identification: *A, C*.

A. Melting point (*2.2.14*): 139 °C to 144 °C.

If necessary, dissolve the substance to be examined in *2-propanol R*, evaporate to dryness and determine the melting point again.

B. Infrared absorption spectrophotometry (*2.2.24*).

Comparison: *cimetidine CRS*.

If the spectra obtained in the solid state show differences, dissolve the substance to be examined and the reference substance separately in *2-propanol R*, evaporate to dryness and record new spectra using the residues.

C. Thin-layer chromatography (*2.2.27*).

Test solution. Dissolve 10 mg of the substance to be examined in *methanol R* and dilute to 10 mL with the same solvent.

Reference solution. Dissolve 10 mg of *cimetidine CRS* in *methanol R* and dilute to 10 mL with the same solvent.

Plate: *TLC silica gel GF_{254} plate R*.

Mobile phase: *concentrated ammonia R, methanol R, ethyl acetate R* (15:20:65 *V/V/V*).

Application: 5 µL.

Development: over 3/4 of the plate.

Drying: in a current of cold air.

Detection: expose to iodine vapour until maximum contrast has been obtained and examine in ultraviolet light at 254 nm.

Results: the principal spot in the chromatogram obtained with the test solution is similar in position and size to the principal spot in the chromatogram obtained with the reference solution.

TESTS

Appearance of solution. The solution is clear (*2.2.1*) and not more intensely coloured than reference solution Y_5 (*2.2.2, Method II*).

Dissolve 3.0 g in 12 mL of *1 M hydrochloric acid* and dilute to 20 mL with *water R*.

Related substances. Liquid chromatography (*2.2.29*).

Test solution. Dissolve 20 mg of the substance to be examined in mobile phase A and dilute to 50.0 mL with mobile phase A.

Reference solution (a). Dilute 1.0 mL of the test solution to 100.0 mL with mobile phase A. Dilute 2.0 mL of this solution to 10.0 mL with mobile phase A.

Reference solution (b). Dissolve the contents of a vial of *cimetidine for system suitability CRS* (containing impurities B, C, D, E, G and H) in 1.0 mL of mobile phase A.

Reference solution (c). Dissolve 4 mg of *cimetidine for peak identification CRS* (containing impurity F) in mobile phase A and dilute to 10.0 mL with mobile phase A.

Column:

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

Mobile phase A: mix 0.4 volumes of *diethylamine R* and 780 volumes of a 1.1 g/L solution of *sodium hexanesulfonate R*; adjust to pH 2.8 with *phosphoric acid R*; add 250 volumes of *methanol R2*;

Mobile phase B: *methanol R2*;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 60	100	0
60 - 65	100 → 90	0 → 10
65 - 120	90	10

Flow rate: 1.1 mL/min.

Detection: spectrophotometer at 220 nm.

Injection: 50 µl.

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

Relative retention with reference to cimetidine (retention time = about 18 min): impurity G = about 0.2; impurity E = about 0.4; impurity D = about 1.5; impurity C = about 1.6; impurity B = about 2.0; impurity H = about 2.3; impurity F = about 4.6.

System suitability: reference solution (b):

- *resolution*: minimum 1.5 between the peaks due to impurities D and C.

Limits:

- *correction factors*: for the calculation of content, multiply the peak areas of the following impurities by the corresponding correction factor: impurity C = 2.5; impurity D = 3.3; impurity E = 0.7; impurity G = 0.6.
- *impurities B, C, D, E, F, G, H*: 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 5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (1.0 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.

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

ASSAY

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 25.23 mg of $C_{10}H_{16}N_6S$

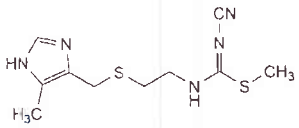
STORAGE

Protected from light.

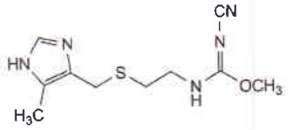
IMPURITIES

Specified impurities: *B, C, D, E, F, G, H*.

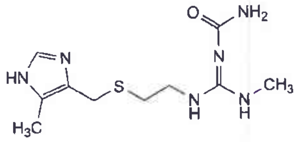
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph *Substances for pharmaceutical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



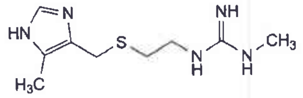
A. methyl 3-cyano-1-[2-[[(5-methyl-1*H*-imidazol-4-yl)-methyl]sulfanyl]ethyl]carbamimidothioate,



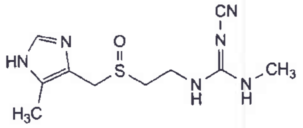
B. methyl 3-cyano-1-[2-[[(5-methyl-1*H*-imidazol-4-yl)-methyl]sulfanyl]ethyl]carbamimidate,



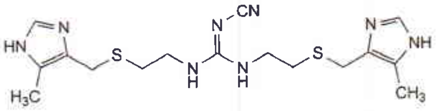
C. 1-[(methylamino)[[2-[[(5-methyl-1*H*-imidazol-4-yl)-methyl]sulfanyl]ethyl]amino]methylidene]urea,



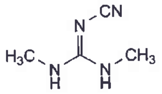
D. 1-methyl-3-[2-[[(5-methyl-1*H*-imidazol-4-yl)-methyl]sulfanyl]ethyl]guanidine,



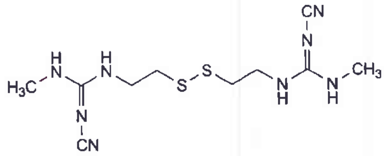
E. 2-cyano-1-methyl-3[2-[[(5-methyl-1*H*-imidazol-4-yl)-methyl]sulfinyl]ethyl]guanidine,



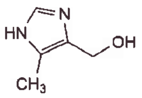
F. 2-cyano-1,3-bis[2-[[(5-methyl-1*H*-imidazol-4-yl)-methyl]sulfanyl]ethyl]guanidine,



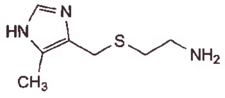
G. 2-cyano-1,3-dimethylguanidine,



H. 1,1′-(disulfanediyldiethylene)bis(2-cyano-3-methylguanidine),



I. (5-methyl-1*H*-imidazol-4-yl)methanol,



J. 2-[[(5-methyl-1*H*-imidazol-4-yl)methyl]sulfanyl]-ethanamine.

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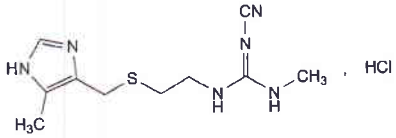
CIMETIDINE HYDROCHLORIDE

Cimetidini hydrochloridum



$C_{10}H_{17}ClN_6S$ M_r 288.8
[70059-30-2]

DEFINITION

2-Cyano-1-methyl-3-[2-[[(5-methyl-1*H*-imidazol-4-yl)-methyl]sulfanyl]ethyl]guanidine hydrochloride.

Content: 98.5 per cent to 101.5 per cent (dried substance).

CHARACTERS

Appearance: white or almost white, crystalline powder.

Solubility: freely soluble in water, sparingly soluble in anhydrous ethanol.

IDENTIFICATION

First identification: B, D.

Second identification: A, C, D.

A. Ultraviolet and visible absorption spectrophotometry (*2.2.25*).

Test solution. Dissolve 70 mg in *0.2 M sulfuric acid* and dilute to 100.0 mL with the same acid. Dilute 2.0 mL of this solution to 100.0 mL with *0.2 M sulfuric acid.*

Specific absorbance at the absorption maximum at 218 nm: 650 to 705.

B. Infrared absorption spectrophotometry (*2.2.24*).

Comparison: *cimetidine hydrochloride CRS.*

C. Thin-layer chromatography (*2.2.27*).

Test solution. Dissolve 10 mg of the substance to be examined in *methanol R* and dilute to 10 mL with the same solvent.

Reference solution. Dissolve 10 mg of *cimetidine hydrochloride CRS* in *methanol R* and dilute to 10 mL with the same solvent.

Plate: *TLC silica gel GF_{254} plate R.*

Mobile phase: *concentrated ammonia R, methanol R, ethyl acetate R* (15:20:65 *V/V/V*).

Application: 5 µL.

Development: over 3/4 of the plate.

Drying: in a current of cold air

Detection: expose to iodine vapour until maximum contrast has been obtained and examine in ultraviolet light at 254 nm.

Results: the principal spot in the chromatogram obtained with the test solution is similar in position and size to the principal spot in the chromatogram obtained with the reference solution.

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

TESTS

Appearance of solution. The solution is clear (*2.2.1*) and not more intensely coloured than reference solution Y_5 (*2.2.2, Method II*).

Dissolve 3.0 g in 12 mL of *1 M hydrochloric acid* and dilute to 20 mL with *water R.*

Esame di Stato per l' abilitazione alla Professione
di Farmacista
Università di Torino

2a Sessione 2017

PROVA PRATICA-RICONOSCIMENTO DEL FARMACO

Cognome e nome..

La prova consiste nel riconoscimento di due farmaci

Per ogni farmaco viene fornito il profilo sperimentale (sequenza delle analisi effettuate) ed una indicazione di possibili farmaci candidati qorredati dalle rispettive monografie provenienti dalla Farmacopea Europea (Ph. Eur. 9.0).

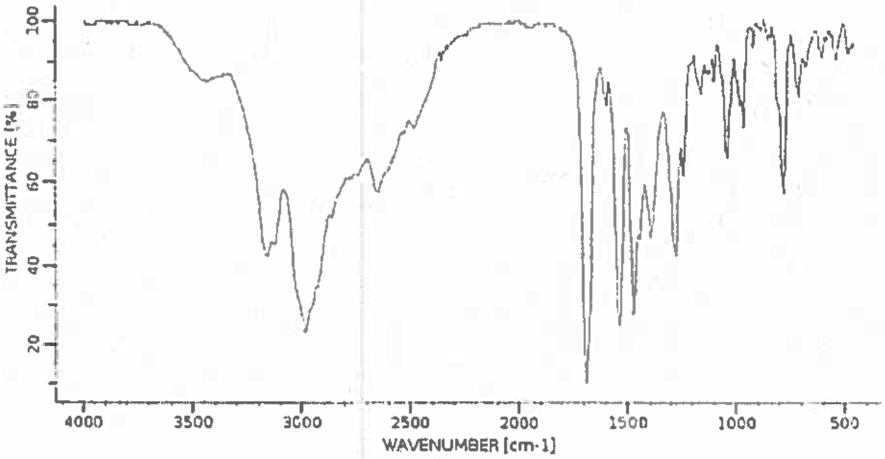
Al candidato viene richiesto di:

1. individuare il farmaco che meglio corrisponde al profilo fornito;
2. motivare brevemente la propria scelta;
3. proporre ulteriori prove sperimentali a conferma della scelta effettuata.

Esame di Stato per l' abilitazione alla Professione di Farmacista
Università di Torino

Primo riconoscimento

Il Farmaco in esame si mostra come una polvere bianca cristallina. In termini di solubilità il composto si scioglie bene in acqua (intervallo: <50 µl) e in Etanolo (intervallo: 50 µl - 500 µl). Come prescritto dalla farmacopea si è registrato lo spettro IR del farmaco incognito e sotto è riportato lo spettro ottenuto.



Se si trattano 5 mg di polvere con 0.5 ml di acido nitrico fumante R e si porta a secchezza la soluzione ottenuta scaldando su bagnomaria, il residuo raffreddato e ripreso con 5 ml di acetone R sviluppa una colorazione verde se trattato con 0.2 ml di soluzione alcolica di idrossido di potassio R.

Nel gruppo di Farmaci a vostra disposizione avete selezionato quali candidati la *Benzocaina* e la *Lidocaina Cloridrato* quali possibili candidati.

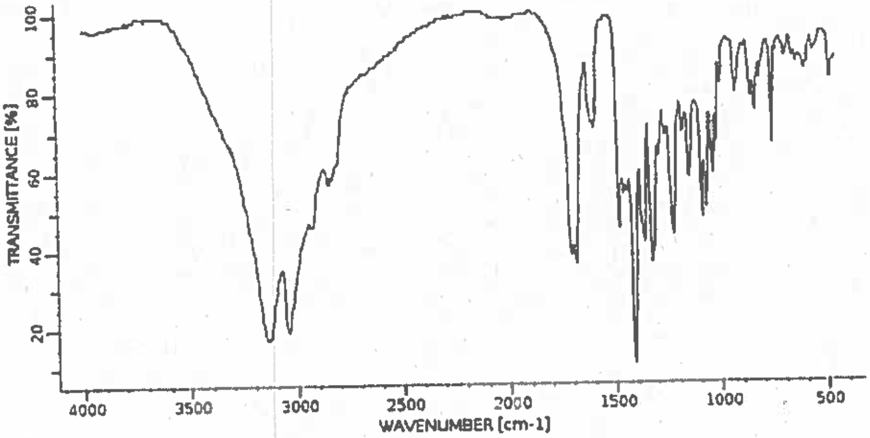
1) Indicare quale fra i due Farmaci risponde meglio al profilo sperimentale fornito, giustificando brevemente i criteri che hanno governato la selezione.
2) Quale passo successivo, proporre alcune ulteriori analisi/test che potrebbero meglio validare la scelta effettuata nel primo punto.

Esame di Stato per l' abilitazione alla Professione
di Farmacista
Università di Torino

Secondo riconoscimento

Il Farmaco in esame si mostra come una polvere bianca cristallina. In termini di solubilità il composto non si scioglie in acqua (intervallo: > 500 mL) ma è moderatamente solubile in Etanolo (intervallo: da 1.5 ml a 5 ml). La solubilità migliora quando lo si scioglie in una soluzione di NaOH 2M.

Come prescritto dalla farmacopea si è registrato lo spettro IR del farmaco incognito e sotto è riportato lo spettro ottenuto.



Si sciolgono 100 mg di polvere in 10 ml di etanolo (96%9) R (scaldando se necessario) e si aggiungono a 0.1 ml di questa soluzione, 2 ml di una soluzione appena preparata miscelando 1 volume di una soluzione di idrossilamina cloridrato R 250 g/L e 3 volumi di soluzione diluita di idrossido di sodio R. Alla soluzione così ottenuta, si aggiungono di 2 ml di acido cloridrico diluito R e 1 ml di soluzione di cloruro ferrico diluito R2. Agitando la miscela così ottenuta si sviluppa una colorazione violetta.

Nel gruppo di Farmaci a vostra disposizione avete selezionato quali candidati l'**Ibuprofene** e l' ***Indometacina*** quali possibili candidati.

1) Indicare quale fra i due Farmaci risponde meglio al profilo sperimentale fornito, giustificando brevemente i criteri che hanno governato la selezione.
2) Quale passo successivo, proporre alcune ulteriori analisi/test che potrebbero meglio validare la scelta effettuata nel primo punto.

Descriptive term	Approximate volume of solvent (in millilitres for 50 mg of solute)			
Very soluble	less than	50 µl	///	///
Freely soluble	from	50 µl	to	500 µl
Soluble	from	500 µl	to	1.5 ml
Sparingly soluble	from	1.5 ml	to	5 ml
Slightly soluble	from	5 ml	to	50 ml
Very slightly soluble	from	50 ml	to	500 ml
Practically insoluble	more than			500 ml

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 2	100	0
2 - 15	100 → 38.5	0 → 61.5

Flow rate: 1.5 mL/min.

Detection: spectrophotometer at 215 nm.

Injection: 10 μL.

Identification of impurities: use the chromatogram obtained with reference solution (b) to identify the peak due to impurity E.

Relative retention with reference to benzocaine (retention time = about 10 min): impurity E = about 0.9.

System suitability: reference solution (b):

- *resolution*: minimum 5.0 between the peaks due to impurity E and benzocaine.

Calculation of percentage contents:

- for each impurity, use the concentration of benzocaine in reference solution (a).

Limits:

- *unspecified impurities*: for each impurity, maximum 0.10 per cent;
- *total*: maximum 0.2 per cent;
- *reporting threshold*: 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 0.1 per cent, determined on 1.0 g.

ASSAY

Carry out the determination of primary aromatic amino-nitrogen (*2.5.8*), using 0.400 g dissolved in a mixture of 25 mL of *hydrochloric acid R* and 50 mL of *water R*.

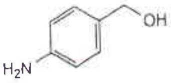
1 mL of *0.1 M sodium nitrite* is equivalent to 16.52 mg of $C_9H_{11}NO_2$.

STORAGE

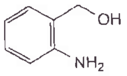
Protected from light.

IMPURITIES

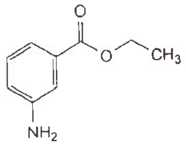
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph *Substances for pharmaceutical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



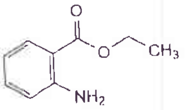
A. (4-aminophenyl)methanol,



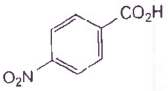
B. (2-aminophenyl)methanol,



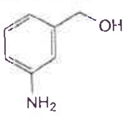
C. ethyl 3-aminobenzoate,



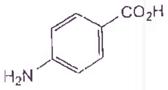
D. ethyl 2-aminobenzoate,



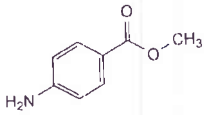
E. 4-nitrobenzoic acid,



F. (3-aminophenyl)methanol,



G. 4-aminobenzoic acid,

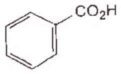


H. methyl 4-aminobenzoate.

01/2017:0066

BENZOIC ACID

Acidum benzoicum



$C_7H_6O_2$ M_r 122.1

[65-85-0]

DEFINITION

Benzenecarboxylic acid.

Content: 99.0 per cent to 100.5 per cent.

CHARACTERS

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

Solubility: slightly soluble in water, soluble in boiling water, freely soluble in ethanol (96 per cent) and in fatty oils.

IDENTIFICATION

A. Melting point (*2.2.14*): 121 °C to 124 °C.

B. Solution S (see Tests) gives reaction (a) of benzoates (*2.3.1*).

TESTS

Solution S. Dissolve 5.0 g in *ethanol (96 per cent) R* and dilute to 100 mL with the same solvent.

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

Carbonisable substances. Dissolve 0.5 g with shaking in 5 mL of *sulfuric acid R*. After 5 min, the solution is not more intensely coloured than reference solution Y_5 (*2.2.2, Method I*).

Oxidisable substances. Dissolve 0.2 g in 10 mL of boiling *water R*. Cool, shake and filter. To the filtrate add 1 mL of *dilute sulfuric acid R* and 0.2 mL of *0.02 M potassium permanganate*. After 5 min, the solution is still coloured pink.

IDENTIFICATION

A. Melting point (*2.2.14*): 158 °C to 164 °C, after drying at 105 °C for 4 h.

B. Thin-layer chromatography (*2.2.27*).

Test solution. Dissolve 25 mg of the substance to be examined in *water R* and dilute to 5 mL with the same solvent.

Reference solution. Dissolve 25 mg of *benzethonium chloride CRS* in *water R* and dilute to 5 mL with the same solvent.

Plate: *TLC silica gel F_{254} plate R.*

Mobile phase: *glacial acetic acid R, water R, methanol R* (5:5:100 *V/V/V*).

Application: 20 µL.

Development: over a path of 12 cm.

Drying: in a current of warm air.

Detection: examine in ultraviolet light at 254 nm.

Results: the principal spot in the chromatogram obtained with the test solution is similar in position and size to the principal spot in the chromatogram obtained with the reference solution.

C. To 5 mL of *dilute sodium hydroxide solution R* add 0.1 mL of *bromophenol blue solution R1* and 5 mL of *methylene chloride R* and shake. The lower layer is colourless. Add 0.1 mL of solution S (see Tests) and shake. A blue colour develops in the lower layer.

D. To 2 mL of solution S add 1 mL of *dilute nitric acid R*. A white precipitate is formed which dissolves upon addition of 5 mL of *ethanol (96 per cent) R*. The solution gives reaction (a) of chlorides (*2.3.1*).

TESTS

Solution S. Dissolve 5.0 g in *carbon dioxide-free water R* and dilute to 50 mL with the same solvent.

Appearance of solution. Solution S is clear (*2.2.1*) and not more intensely coloured than reference solution Y_6 (*2.2.2, Method II*).

Acidity or alkalinity. To 25 mL of solution S add 0.1 mL of *phenolphthalein solution R*. The solution is colourless. Add 0.3 mL of *0.01 M sodium hydroxide*. The solution is pink. Add 0.1 mL of *methyl red solution R* and 0.5 mL of *0.01 M hydrochloric acid*. The solution is orange-red.

Volatile bases and salts of volatile bases (*2.4.1, Method B*): maximum 50 ppm, determined on 0.20 g.

Prepare the standard using 0.1 mL of *ammonium standard solution (100 ppm NH_4) R*. Replace heavy magnesium oxide by 2.0 mL of *strong sodium hydroxide solution R*.

Loss on drying (*2.2.32*): maximum 5.0 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 2.000 g in *water R* and dilute to 100.0 mL with the same solvent. Transfer 25.0 mL of the solution to a separating funnel, add 10 mL of a 4 g/L solution of *sodium hydroxide R*, 10.0 mL of a freshly prepared 50 g/L solution of *potassium iodide R* and 25 mL of *methylene chloride R*. Shake vigorously, allow to separate and discard the lower layer. Shake the upper layer with 3 quantities, each of 10 mL, of *methylene chloride R* and discard the lower layers. To the upper layer add 40 mL of *hydrochloric acid R*, allow to cool and titrate with *0.05 M potassium iodate* until the deep brown colour is almost discharged. Add 4 mL of *methylene chloride R* and continue the titration, shaking vigorously, until the lower layer is no longer brown. Carry out a blank titration using a mixture of 10.0 mL of a freshly prepared 50 g/L solution of *potassium iodide R*, 20 mL of *water R* and 40 mL of *hydrochloric acid R*.

1 mL of *0.05 M potassium iodate* is equivalent to 44.81 mg of $C_{27}H_{42}ClNO_2$.

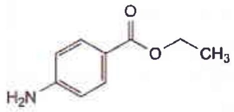
STORAGE

Protected from light.

07/2015:0011

BENZOCAINE

Benzocainum



$C_9H_{11}NO_2$ M_r 165.2
[94-09-7]

DEFINITION

Ethyl 4-aminobenzoate.

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

CHARACTERS

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

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

It shows polymorphism (*5.9*).

IDENTIFICATION

Infrared absorption spectrophotometry (*2.2.24*).

Comparison: *benzocaine CRS.*

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

TESTS

Related substances. Liquid chromatography (*2.2.29*).

Solvent mixture: *acetonitrile R1, water for chromatography R* (50:50 *V/V*).

Test solution. Dissolve 25.0 mg of the substance to be examined in 5 mL of *acetonitrile R1* and dilute to 50.0 mL with the solvent mixture.

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

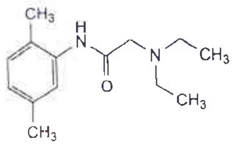
Reference solution (b). Dissolve 5 mg of the substance to be examined and 5 mg of *4-nitrobenzoic acid R* (impurity E) in 10.0 mL of the solvent mixture. Dilute 1.0 mL of the solution to 50.0 mL with the solvent mixture.

Column:

- *size*: l = 0.10 m, Ø = 4.6 mm;
- *stationary phase*: *end-capped octadecylsilyl silica gel for chromatography R* (3 µm);
- *temperature*: 35 °C.

Mobile phase:

- *mobile phase A*: dilute 1 mL of *perchloric acid R* to 100 mL with *water for chromatography R*; dilute 1 mL of the solution to 100 mL with *water for chromatography R*; mix 9 volumes of this solution and 1 volume of *acetonitrile R1*;
- *mobile phase B*: *acetonitrile R1*;

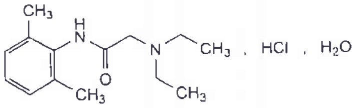


J. 2-(diethylamino)-*N*-(2,5-dimethylphenyl)acetamide.

01/2017:0227

LIDOCAINE HYDROCHLORIDE

Lidocaini hydrochloridum



$C_{14}H_{23}ClN_2O,H_2O$ M_r 288.8
[6108-05-0]

DEFINITION

2-(Diethylamino)-*N*-(2,6-dimethylphenyl)acetamide hydrochloride monohydrate.

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

CHARACTERS

Appearance: white or almost white, crystalline powder.

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

IDENTIFICATION

First identification: B, D.

Second identification: A, C, D.

A. Melting point (*2.2.14*): 74 °C to 79 °C, determined without previous drying.

B. Infrared absorption spectrophotometry (*2.2.24*).

Comparison: lidocaine hydrochloride CRS.

C. To about 5 mg add 0.5 mL of *fuming nitric acid R*. Evaporate to dryness on a water-bath, cool and dissolve the residue in 5 mL of *acetone R*. Add 0.2 mL of *alcoholic potassium hydroxide solution R*. A green colour is produced.

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

TESTS

Solution S. Dissolve 1.0 g in *carbon dioxide-free water R* and dilute to 20 mL with the same solvent.

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

pH (*2.2.3*): 4.0 to 5.5.

Dilute 1 mL of solution S to 10 mL with *carbon dioxide-free water R*.

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 10.0 mL with the mobile phase.

Reference solution (a). Dissolve 50.0 mg of *2,6-dimethylaniline R* (impurity A) in the mobile phase and dilute to 100.0 mL with the mobile phase. Dilute 10.0 mL of this solution to 100.0 mL with the mobile phase.

Reference solution (b). Dissolve 5 mg of *2-chloro-N-(2,6-dimethylphenyl)acetamide R* (impurity H) in the mobile phase and dilute to 10 mL with the mobile phase.

Reference solution (c). Dilute 1.0 mL of the test solution to 10.0 mL with the mobile phase.

Reference solution (d). Mix 1.0 mL of reference solution (a), 1.0 mL of reference solution (b) and 1.0 mL of reference solution (c) and dilute to 100.0 mL with the mobile phase.

Column:

- *size*: *l* = 0.15 m, Ø = 3.9 mm;
- *stationary phase*: *end-capped polar-embedded octadecylsilyl amorphous organosilica polymer R* (5 µm);
- *temperature*: 30 °C.

Mobile phase: mix 30 volumes of *acetonitrile for chromatography R* and 70 volumes of a 4.85 g/L solution of *potassium dihydrogen phosphate R* adjusted to pH 8.0 with *strong sodium hydroxide solution R*.

Flow rate: 1.0 mL/min.

Detection: spectrophotometer at 230 nm.

Injection: 20 µL.

Run time: 3.5 times the retention time of lidocaine.

Relative retention with reference to lidocaine (retention time = about 17 min): impurity H = about 0.37; impurity A = about 0.40.

System suitability: reference solution (d):

- *resolution*: minimum 1.5 between the peaks due to impurities H and A.

Limits:

- *impurity A*: not more than the area of the corresponding peak in the chromatogram obtained with reference solution (d) (0.01 per cent);
- *unspecified impurities*: for each impurity, not more than the area of the peak due to lidocaine in the chromatogram obtained with reference solution (d) (0.10 per cent);
- *total*: not more than 5 times the area of the peak due to lidocaine in the chromatogram obtained with reference solution (d) (0.5 per cent);
- *disregard limit*: 0.5 times the area of the peak due to lidocaine in the chromatogram obtained with reference solution (d) (0.05 per cent).

Water (*2.5.12*): 5.5 per cent to 7.0 per cent, determined on 0.25 g.

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

ASSAY

Dissolve 0.220 g in 50 mL of *ethanol (96 per cent) R* and add 5.0 mL of *0.01 M hydrochloric acid*. Carry out a potentiometric titration (*2.2.20*), using *0.1 M sodium hydroxide*. Read the volume added between the 2 points of inflexion.

1 mL of *0.1 M sodium hydroxide* is equivalent to 27.08 mg of $C_{14}H_{23}ClN_2O$.

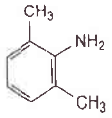
STORAGE

Protected from light.

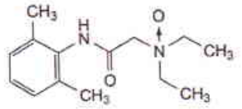
IMPURITIES

Specified impurities: A.

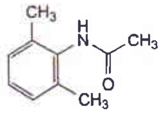
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph *Substances for pharmaceutical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



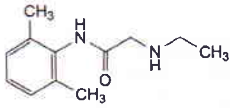
A. 2,6-dimethylaniline,



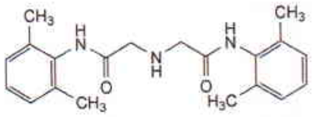
B. 2-(diethylazinoyl)-*N*-(2,6-dimethylphenyl)acetamide (lidocaine N^2-oxide),



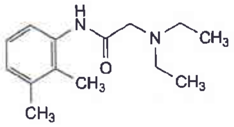
C. *N*-(2,6-dimethylphenyl)acetamide,



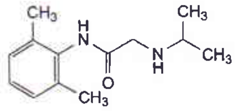
D. *N*-(2,6-dimethylphenyl)-2-(ethylamino)acetamide,



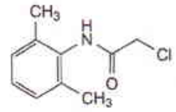
E. 2-2′-(azanediyl)bis[*N*-(2,6-dimethylphenyl)acetamide],



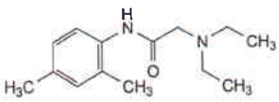
F. 2-(diethylamino)-*N*-(2,3-dimethylphenyl)acetamide,



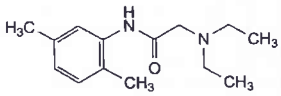
G. *N*-(2,6-dimethylphenyl)-2-[(1-methylethyl)amino]-acetamide,



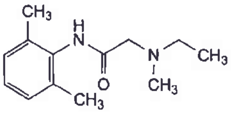
H. 2-chloro-*N*-(2,6-dimethylphenyl)acetamide,



I. 2-(diethylamino)-*N*-(2,4-dimethylphenyl)acetamide,



J. 2-(diethylamino)-*N*-(2,5-dimethylphenyl)acetamide,

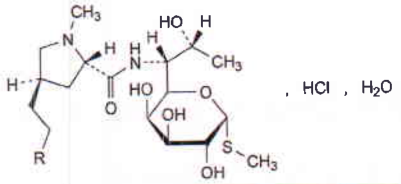


K. *N*-(2,6-dimethylphenyl)-2-(ethylmethylamino)acetamide.

01/2017:0583

LINCOMYCIN HYDROCHLORIDE

Lincomycini hydrochloridum



Compound	R	Molecular formula	M_r
Lincomycin	CH_3	$C_{18}H_{35}ClN_2O_6S,H_2O$	461.0
Lincomycin B	H	$C_{17}H_{33}ClN_2O_6S,H_2O$	447.0

Lincomycin hydrochloride monohydrate: [7179-49-9]

DEFINITION

Mixture of antibiotics produced by *Streptomyces lincolnensis* var. *lincolnensis* or obtained by any other means, the main component being methyl 6,8-dideoxy-6-[[[(2*S*,4*R*)-1-methyl-4-propylpyrrolidin-2-yl]carbonyl]amino]-1-thio-D-*erythro*-α-D-*galacto*-octopyranoside (lincomycin) hydrochloride monohydrate.

Content:

- *sum of the contents of lincomycin hydrochloride and lincomycin B hydrochloride*: 96.0 per cent to 102.0 per cent (anhydrous substance);
- *lincomycin B hydrochloride*: maximum 5.0 per cent (anhydrous substance).

CHARACTERS

Appearance: white or almost white, crystalline powder.

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

IDENTIFICATION

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

B. Dissolve 0.1 g in *water R* and dilute to 10 mL with the same solvent. The solution gives reaction (a) of chlorides (*2.3.1*).

TESTS

Solution S. Dissolve 2.0 g in *carbon dioxide-free water R* and dilute to 20 mL with the same solvent.

Appearance of solution. Solution S is clear (*2.2.1*) and not more intensely coloured than reference solution Y_6 (*2.2.2, Method II*).

pH (*2.2.3*): 3.5 to 5.5 for solution S.

Specific optical rotation (*2.2.7*): + 135 to + 150 (anhydrous substance).

Dissolve 1.000 g in *water R* and dilute to 25.0 mL with the same solvent.

Related substances. Liquid chromatography (*2.2.29*).

Test solution. Dissolve 25.0 mg of the substance to be examined in the mobile phase and dilute to 10.0 mL with the mobile phase.

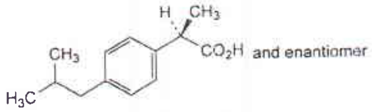
Reference solution (a). Dissolve 25.0 mg of *lincomycin hydrochloride CRS* in the mobile phase and dilute to 10.0 mL with the mobile phase.

Reference solution (b). Dissolve 5 mg of *lincomycin hydrochloride for system suitability CRS* (containing impurities A, B and C) in 2 mL of the mobile phase.

01/2017:0721

IBUPROFEN

Ibuprofenum



$C_{13}H_{18}O_2$ M_r 206.3

[15687-27-1]

DEFINITION

(2*RS*)-2-[4-(2-Methylpropyl)phenyl]propanoic acid.

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

CHARACTERS

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

Solubility: practically insoluble in water, freely soluble in acetone, in methanol and in methylene chloride. It dissolves in dilute solutions of alkali hydroxides and carbonates.

IDENTIFICATION

First identification: A, C.

Second identification: A, B, D.

A. Melting point (*2.2.14*): 75 °C to 78 °C.

B. Ultraviolet and visible absorption spectrophotometry (*2.2.25*).

Test solution. Dissolve 50.0 mg in a 4 g/L solution of *sodium hydroxide R* and dilute to 100.0 mL with the same alkaline solution.

Spectral range: 240-300 nm, using a spectrophotometer with a band width of 1.0 nm and a scan speed of not more than 50 nm/min.

Absorption maxima: at 264 nm and 272 nm.

Shoulder: at 258 nm.

Absorbance ratio:

- A_{264} / A_{258} = 1.20 to 1.30;
- A_{272} / A_{258} = 1.00 to 1.10.

C. Infrared absorption spectrophotometry (*2.2.24*).

Comparison: *ibuprofen CRS*.

D. Thin-layer chromatography (*2.2.27*).

Test solution. Dissolve 50 mg of the substance to be examined in *methylene chloride R* and dilute to 10 mL with the same solvent.

Reference solution. Dissolve 50 mg of *ibuprofen CRS* in *methylene chloride R* and dilute to 10 mL with the same solvent.

Plate: *TLC silica gel plate R*.

Mobile phase: *anhydrous acetic acid R, ethyl acetate R, hexane R* (5:24:71 *V/V/V*).

Application: 5 µL.

Development: over a path of 10 cm.

Drying: at 120 °C for 30 min.

Detection: lightly spray with a 10 g/L solution of *potassium permanganate R* in *dilute sulfuric acid R* and heat at 120 °C for 20 min; examine in ultraviolet light at 365 nm.

Results: the principal spot in the chromatogram obtained with the test solution is similar in position, colour and size to the principal spot in the chromatogram obtained with the reference solution.

TESTS

Solution S. Dissolve 2.0 g in *methanol R* and dilute to 20 mL with the same solvent.

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

Optical rotation (*2.2.7*): – 0.05° to + 0.05°.

Dissolve 0.50 g in *methanol R* and dilute to 20.0 mL with the same solvent.

Related substances. Liquid chromatography (*2.2.29*).

Test solution. Dissolve 20 mg of the substance to be examined in 2 mL of *acetonitrile R1* and dilute to 10.0 mL with mobile phase A.

Reference solution (a). Dilute 1.0 mL of the test solution to 100.0 mL with mobile phase A. Dilute 1.0 mL of this solution to 10.0 mL with mobile phase A.

Reference solution (b). Dilute 1.0 mL of *ibuprofen impurity B CRS* to 10.0 mL with *acetonitrile R1* (solution A). Dissolve 20 mg of *ibuprofen CRS* in 2 mL of *acetonitrile R1*, add 1.0 mL of solution A and dilute to 10.0 mL with mobile phase A.

Reference solution (c). Dissolve the contents of a vial of *ibuprofen for peak identification CRS* (mixture of impurities A, J and N) in 1 mL of *acetonitrile R1* and dilute to 5 mL with mobile phase A.

Column:

- *size*: *l* = 0.15 m, Ø = 4.6 mm;
- *stationary phase*: *octadecylsilyl silica gel for chromatography R* (5 µm).

Mobile phase:

- *mobile phase A*: mix 0.5 volumes of *phosphoric acid R*, 340 volumes of *acetonitrile R1* and 600 volumes of *water R*; allow to equilibrate and dilute to 1000 volumes with *water R*;
- *mobile phase B*: *acetonitrile R1*;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 25	100	0
25 - 55	100 → 15	0 → 85
55 - 70	15	85

Flow rate: 2 mL/min.

Detection: spectrophotometer at 214 nm.

Injection: 20 µL.

Identification of impurities: use the chromatogram supplied with *ibuprofen for peak identification CRS* and the chromatogram obtained with reference solution (c) to identify the peaks due to impurities A, J and N.

Relative retention with reference to ibuprofen (retention time = about 21 min): impurity J = about 0.2; impurity N = about 0.3; impurity A = about 0.9; impurity B = about 1.1.

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 B, and H_v = height above the baseline of the lowest point of the curve separating this peak from the peak due to ibuprofen. If necessary, adjust the concentration of acetonitrile in mobile phase A.

Limits:

- *impurities A, J, N*: 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 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.05 per cent);

- *total*: not more than twice the area of the principal peak in the chromatogram obtained with reference solution (a) (0.2 per cent);
- *disregard limit*: 0.3 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.03 per cent).

Impurity F. Gas chromatography (*2.2.28*): use the normalisation procedure.

Methylating solution. Dilute 1 mL of *N,N-dimethylformamide dimethylacetal R* and 1 mL of *pyridine R* to 10 mL with *ethyl acetate R*.

Test solution. Weigh about 50.0 mg of the substance to be examined into a sealable vial, dissolve in 1.0 mL of *ethyl acetate R*, add 1 mL of the methylating solution, seal and heat at 100 °C in a block heater for 20 min. Allow to cool. Remove the reagents under a stream of nitrogen at room temperature. Dissolve the residue in 5 mL of *ethyl acetate R*.

Reference solution (a). Dissolve 0.5 mg of *ibuprofen impurity F CRS* in *ethyl acetate R* and dilute to 10.0 mL with the same solvent.

Reference solution (b). Weigh about 50.0 mg of *ibuprofen CRS* into a sealable vial, dissolve in 1.0 mL of reference solution (a), add 1 mL of the methylating solution, seal and heat at 100 °C in a block heater for 20 min. Allow to cool. Remove the reagents under a stream of nitrogen at room temperature. Dissolve the residue in 5 mL of *ethyl acetate R*.

Column:
- *material*: fused silica;
- *size*: *l* = 25 m, Ø = 0.53 mm;
- *stationary phase*: *macrogol 20 000 R* (film thickness 2 μm).

Carrier gas: *helium for chromatography R*.

Flow rate: 5.0 mL/min.

Temperature:
- *column*: 150 °C;
- *injection port*: 200 °C;
- *detector*: 250 °C.

Detection: flame ionisation.

Injection: 1 μL of the test solution and reference solution (b).

Run time: twice the retention time of ibuprofen.

System suitability:
- *relative retention* with reference to ibuprofen (retention time = about 17 min): impurity F = about 1.5.

Limit:
- *impurity F*: maximum 0.1 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 0.1 per cent, determined on 1.0 g.

ASSAY

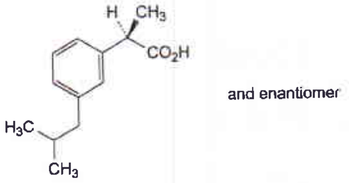
Dissolve 0.450 g in 50 mL of *methanol R*. Add 0.4 mL of *phenolphthalein solution R1*. Titrate with *0.1 M sodium hydroxide* until a red colour is obtained. Carry out a blank titration.

1 mL of *0.1 M sodium hydroxide* is equivalent to 20.63 mg of $C_{13}H_{18}O_2$.

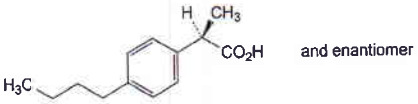
IMPURITIES

Specified impurities: *A, F, J, N.*

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*): *B, C, D, E, G, H, I, K, L, M, O, P, Q, R.*

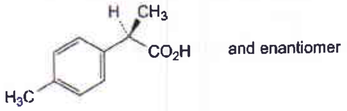


A. (2*RS*)-2-[3-(2-methylpropyl)phenyl]propanoic acid,

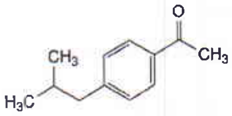


B. (2*RS*)-2-(4-butylphenyl)propanoic acid,

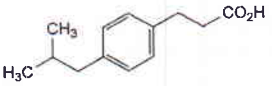
C. (2*RS*)-2-[4-(2-methylpropyl)phenyl]propanamide,



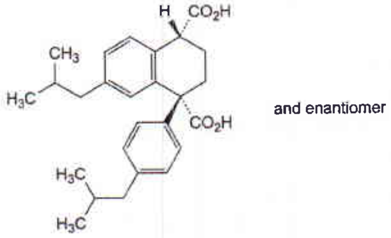
D. (2*RS*)-2-(4-methylphenyl)propanoic acid,



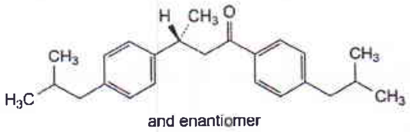
E. 1-[4-(2-methylpropyl)phenyl]ethanone,



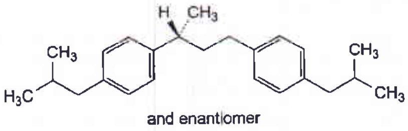
F. 3-[4-(2-methylpropyl)phenyl]propanoic acid,



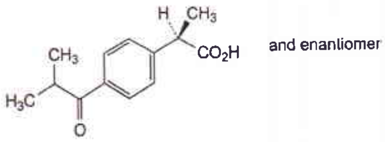
G. (1*RS*,4*RS*)-7-(2-methylpropyl)-1-[4-(2-methylpropyl)-phenyl]-1,2,3,4-tetrahydronaphthalene-1,4-dicarboxylic acid,



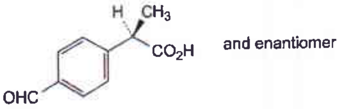
H. (3*RS*)-1,3-bis[4-(2-methylpropyl)phenyl]butan-1-one,



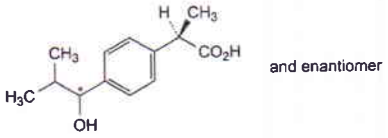
I. 1-(2-methylpropyl)-4-[(3*RS*)-3-[4-(2-methylpropyl)-phenyl]butyl]benzene,



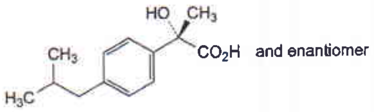
J. (2*RS*)-2-[4-(2-methylpropanoyl)phenyl]propanoic acid,



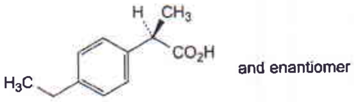
K. (2*RS*)-2-(4-formylphenyl)propanoic acid,



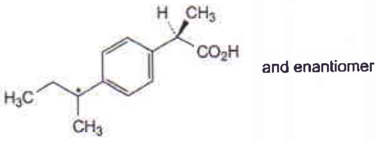
L. (2*RS*)-2-[4-(1-hydroxy-2-methylpropyl)phenyl]propanoic acid,



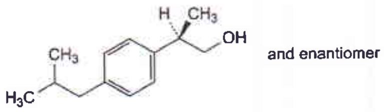
M. (2*RS*)-2-hydroxy-2-[4-(2-methylpropyl)phenyl]propanoic acid,



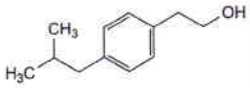
N. (2*RS*)-2-(4-ethylphenyl)propanoic acid,



O. (2*RS*)-2-[4-(1-methylpropyl)phenyl]propanoic acid,



P. (2*RS*)-2-[4-(2-methylpropyl)phenyl]propan-1-ol,



Q. 2-[4-(2-methylpropyl)phenyl]ethanol,

R. 1,1′-(ethane-1,1-diyl)-4,4′-(2-methylpropyl)dibenzene.

01/2008:0917
corrected 6.3

ICHTHAMMOL

Ichthammolum

DEFINITION

Ichthammol is obtained by distillation from certain bituminous schists, sulfonation of the distillate and neutralisation of the product with ammonia.

Content:

- *dry matter*: 50.0 per cent *m/m* to 56.0 per cent *m/m*;
- *total ammonia* (NH_3; M_r 17.03): 4.5 per cent *m/m* to 7.0 per cent *m/m* (dried substance);
- *organically combined sulfur*: minimum 10.5 per cent *m/m* (dried substance);
- *sulfur in the form of sulfate*: maximum 20.0 per cent *m/m* of the total sulfur.

CHARACTERS

Appearance: dense, blackish-brown liquid.

Solubility: miscible with water and with glycerol, slightly soluble in ethanol (96 per cent), in fatty oils and in liquid paraffin. It forms homogeneous mixtures with wool fat and soft paraffin.

IDENTIFICATION

A. Dissolve 1.5 g in 15 mL of *water R* (solution A). To 2 mL of solution A add 2 mL of *hydrochloric acid R*. A resinous precipitate is formed. Decant the supernatant. The precipitate is partly soluble in *ether R*.

B. 2 mL of solution A, obtained in identification test A, gives the reaction of ammonium salts and salts of volatile bases (*2.3.1*).

C. Evaporate and ignite the mixture of solution A and *dilute sodium hydroxide solution R* obtained in identification test B. Take up the residue with 5 mL of *dilute hydrochloric acid R*. Gas is evolved which turns *lead acetate paper R* brown or black. Filter the solution. The filtrate gives reaction (a) of sulfates (*2.3.1*).

TESTS

Acidity or alkalinity. To 10.0 mL of the clear filtrate obtained in the assay of total ammonia add 0.05 mL of *methyl red solution R*. Not more than 0.2 mL of *0.02 M hydrochloric acid* or *0.02 M sodium hydroxide* is required to change the colour of the indicator.

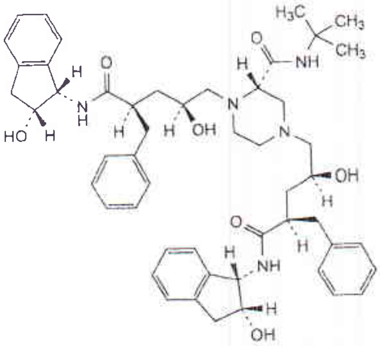
Relative density (*2.2.5*): 1.040 to 1.085, determined on a mixture of equal volumes of the substance to be examined and *water R*.

Sulfated ash (*2.4.14*): maximum 0.3 per cent, determined on 1.00 g.

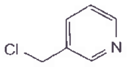
ASSAY

Dry matter. Weigh 1.000 g in a tared flask containing 2 g of *sand R*, previously dried to constant mass, and a small glass rod. Heat on a water-bath for 2 h with frequent stirring and dry in an oven at 100-105 °C until 2 consecutive weighings do not differ by more than 2.0 mg; the 2nd weighing is carried out after drying again for 1 h.

Total ammonia. Dissolve 2.50 g in 25 mL of warm *water R*. Rinse the solution into a 250 mL volumetric flask, add 200 mL of *sodium chloride solution R* and dilute to 250.0 mL with *water R*. Filter the solution, discarding the first 20 mL of filtrate. To 100.0 mL of the clear filtrate add 25 mL of



E. (2*S*)-1,4-bis[(2*S*,4*R*)-4-benzyl-2-hydroxy-5-[[(1*S*,2*R*)-2-hydroxy-2,3-dihydro-1*H*-inden-1-yl]amino]-5-oxopentyl]-*N*-(1,1-dimethylethyl)piperazine-2-carboxamide,

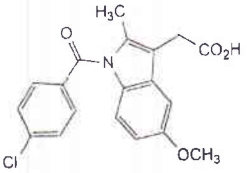


F. 3-(chloromethyl)pyridine (nicotinyl chloride).

01/2017:0092

INDOMETACIN

Indometacinum



$C_{19}H_{16}ClNO_4$ M_r 357.8

[53-86-1]

DEFINITION

2-[1-(4-Chlorobenzoyl)-5-methoxy-2-methyl-1*H*-indol-3-yl]acetic acid.

Content: 98.0 per cent to 102.0 per cent (dried substance).

CHARACTERS

Appearance: white or yellow, crystalline powder.

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

It shows polymorphism (*5.9*).

IDENTIFICATION

First identification: *A, C*.

Second identification: *A, B, D, E*.

A. Melting point (*2.2.14*): 158 °C to 162 °C.

B. Ultraviolet and visible absorption spectrophotometry (*2.2.25*).

Test solution. Dissolve 25 mg in a mixture of 1 volume of *1 M hydrochloric acid* and 9 volumes of *methanol R* and dilute to 100.0 mL with the same mixture of solvents. Dilute 10.0 mL of the solution to 100.0 mL with a mixture of 1 volume of *1 M hydrochloric acid* and 9 volumes of *methanol R*.

Spectral range: 300-350 nm.

Absorption maximum: at 318 nm.

Specific absorbance at the absorption maximum: 170 to 190.

C. Infrared absorption spectrophotometry (*2.2.24*), without recrystallisation.

Comparison: *indometacin CRS*.

D. Dissolve 0.1 g in 10 mL of *ethanol (96 per cent) R*, heating slightly if necessary. To 0.1 mL of the solution add 2 mL of a freshly prepared mixture of 1 volume of a 250 g/L solution of *hydroxylamine hydrochloride R* and 3 volumes of *dilute sodium hydroxide solution R*. Add 2 mL of *dilute hydrochloric acid R* and 1 mL of *ferric chloride solution R2* and mix. A violet-pink colour develops.

E. To 0.5 mL of the solution in ethanol (96 per cent) prepared in identification test D, add 0.5 mL of *dimethylaminobenzaldehyde solution R2*. A precipitate is formed that dissolves on shaking. Heat on a water-bath. A bluish-green colour is produced. Continue to heat for 5 min and cool in iced water for 2 min. A precipitate is formed and the colour changes to light greyish-green. Add 3 mL of *ethanol (96 per cent) R*. The solution is clear and violet-pink in colour.

TESTS

Related substances. Liquid chromatography (*2.2.29*).

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

Test solution. Dissolve 25.0 mg of the substance to be examined in the solvent mixture and dilute to 25.0 mL with the solvent mixture.

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

Reference solution (b). Dissolve the contents of a vial of *indometacin impurity mixture CRS* (impurities I and J) in 1.0 mL of the solvent mixture.

Column:

- *size*: *l* = 0.15 m, Ø = 4.6 mm;
- *stationary phase*: *end-capped phenylhexylsilyl silica gel for chromatography R* (3 μm);
- *temperature*: 40 °C.

Mobile phase:

- *mobile phase A*: 10 g/L solution of *acetic acid R*;
- *mobile phase B*: *acetonitrile R*;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 2	70	30
2 - 11	70 → 50	30 → 50
11 - 12	50	50
12	50 → 70	50 → 30
12 - 21	70 → 30	30 → 70
21 - 27	30	70

Flow rate: 1.0 mL/min.

Detection: spectrophotometer at 254 nm.

Injection: 20 μL.

Identification of impurities: use the chromatogram supplied with *indometacin impurity mixture CRS* and the chromatogram obtained with reference solution (b) to identify the peaks due to impurities I and J.

Relative retention with reference to indometacin (retention time = about 18 min): impurity I = about 1.3; impurity J = about 1.4.

System suitability: reference solution (b):

- *resolution*: minimum 1.5 between the peaks due to impurities I and J.

Calculation of percentage contents:

- for each impurity, use the concentration of indometacin in reference solution (a).

Limits:

- *unspecified impurities*: for each impurity, maximum 0.10 per cent;

- *total*: maximum 0.3 per cent;
- *reporting threshold*: 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

Liquid chromatography (*2.2.29*).

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

Test solution. Dissolve 25.0 mg of the substance to be examined in the solvent mixture and dilute to 25.0 mL with the solvent mixture. Dilute 1.0 mL of the solution to 10.0 mL with the solvent mixture.

Reference solution. Dissolve 25.0 mg of *indometacin CRS* in the solvent mixture and dilute to 25.0 mL with the solvent mixture. Dilute 1.0 mL of the solution to 10.0 mL with the solvent mixture.

Column:
- *size*: *l* = 0.10 m, Ø = 4.6 mm;
- *stationary phase*: *end-capped solid core octadecylsilyl silica gel for chromatography R* (2.6 µm);
- *temperature*: 50 °C.

Mobile phase:
- *mobile phase A*: 10 g/L solution of *acetic acid R*;
- *mobile phase B*: 10 g/L solution of *acetic acid R* in *acetonitrile R*;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 5	50	50
5 - 5.5	50 → 0	50 → 100
5.5 - 8	0	100

Flow rate: 0.8 mL/min.

Detection: spectrophotometer at 254 nm.

Injection: 10 µL.

Retention time: indometacin = about 4 min.

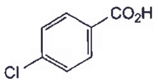
Calculate the percentage content of $C_{19}H_{16}ClNO_4$ taking into account the assigned content of *indometacin CRS*.

STORAGE

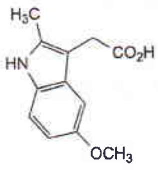
Protected from light.

IMPURITIES

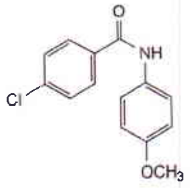
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph *Substances for pharmaceutical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



A. 4-chlorobenzoic acid,



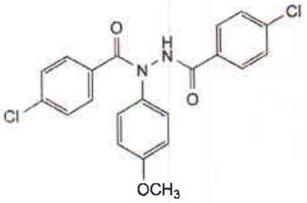
B. 2-(5-methoxy-2-methyl-1*H*-indol-3-yl)acetic acid,



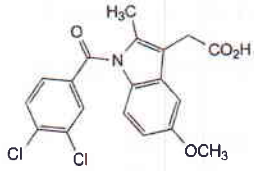
C. 4-chloro-*N*-(4-methoxyphenyl)benzamide,

D. 2-[1-(2-chlorobenzoyl)-5-methoxy-2-methyl-1*H*-indol-3-yl]acetic acid,

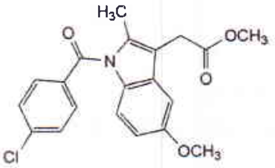
E. 2-[1-(3-chlorobenzoyl)-5-methoxy-2-methyl-1*H*-indol-3-yl]acetic acid,



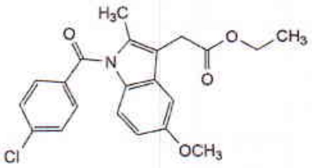
F. 4-chloro-*N'*-(4-chlorobenzoyl)-*N*-(4-methoxyphenyl)-benzohydrazide,



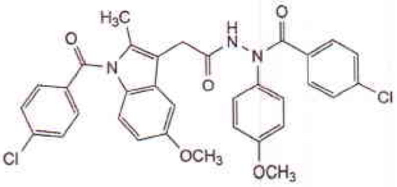
G. 2-[1-(3,4-dichlorobenzoyl)-5-methoxy-2-methyl-1*H*-indol-3-yl]acetic acid,



H. methyl 2-[1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1*H*-indol-3-yl]acetate,



I. ethyl 2-[1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1*H*-indol-3-yl]acetate,



J. 4-chloro-*N′*-[2-[1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1*H*-indol-3-yl]acetyl]-*N*-(4-methoxyphenyl)-benzohydrazide.

01/2008:1805
corrected 7.0

myo-INOSITOL

myo-Inositolum

$C_6H_{12}O_6$ M_r 180.2
[87-89-8]

DEFINITION

Cyclohexane-1,2,3,5/4,6-hexol.

Content: 97.0 per cent to 102.0 per cent (anhydrous substance).

CHARACTERS

Appearance: white or almost white, crystalline powder.

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

IDENTIFICATION

A. Infrared absorption spectrophotometry (*2.2.24*).

Comparison: *myo-inositol CRS*.

B. Examine the chromatograms obtained in the assay.

Results: the principal peak in the chromatogram obtained with the test solution is similar in retention time and size to the principal peak in the chromatogram obtained with reference solution (a).

TESTS

Solution S. Dissolve 10.0 g in *distilled water R* and dilute to 100.0 mL with the same solvent.

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

Conductivity (*2.2.38*): maximum 30 µS·cm^{-1}.

Dissolve 10.0 g in *carbon dioxide-free water R* prepared from *distilled water R*, with gentle warming if necessary, and dilute to 50.0 mL with the same solvent. Measure the conductivity of the solution while gently stirring with a magnetic stirrer.

Related substances. Liquid chromatography (*2.2.29*).

Test solution. Dissolve 0.500 g of the substance to be examined in *water R* and dilute to 10.0 mL with the same solvent.

Reference solution (a). Dissolve 0.500 g of *myo-inositol CRS* in *water R* and dilute to 10.0 mL with the same solvent.

Reference solution (b). Dilute 2.0 mL of the test solution to 100.0 mL with *water R*. Dilute 5.0 mL of this solution to 100.0 mL with *water R*.

Reference solution (c). Dissolve 0.5 g of *myo-inositol R* and 0.5 g of *mannitol R* in *water R* and dilute to 10 mL with the same solvent.

Column:

- *size*: *l* = 0.3 m, Ø = 7.8 mm;
- *stationary phase*: *strong cation-exchange resin (calcium form) R* (9 µm);
- *temperature*: 85 °C.

Mobile phase: *water R*.

Flow rate: 0.5 mL/min.

Detection: refractometer maintained at a constant temperature (at about 30-35 °C for example).

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

Run time: twice the retention time of *myo*-inositol.

Relative retention with reference to *myo*-inositol (retention time = about 17.5 min): impurity A = about 1.3; impurity B = about 1.4.

System suitability: reference solution (c):

- *resolution*: minimum 4 between the peaks due to *myo*-inositol and impurity A.

Limits:

- *impurities A, B*: for each impurity, not more than 3 times the area of the principal peak in the chromatogram obtained with reference solution (b) (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 (b) (0.10 per cent);
- *total*: not more than 10 times the area of the principal peak in the chromatogram obtained with reference solution (b) (1.0 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).

Barium. To 10 mL of solution S add 1 mL of *dilute sulfuric acid R*. When examined immediately, and after 1 h, any opalescence in the solution is not more intense than that in a mixture of 1 mL of *distilled water R* and 10 mL of solution S.

Lead (*2.4.10*): maximum 0.5 ppm.

Prepare the test solution by dissolving 20.0 g of the substance to be examined in 100 mL of *water R*, heating if necessary, and diluting to 200.0 mL with *dilute acetic acid R*.

Water (*2.5.12*): maximum 0.5 per cent, determined on 1.00 g.

ASSAY

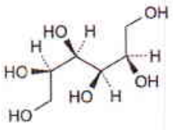
Liquid chromatography (*2.2.29*) as described in the test for related substances with the following modification.

Injection: test solution and reference solution (a).

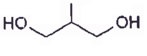
Calculate the percentage content of $C_6H_{12}O_6$ from the declared content of *myo-inositol CRS*.

IMPURITIES

Specified impurities: A, B.



A. D-mannitol,



B. propane-1,2,3-triol (glycerol).

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ESAME DI STATO PER L'ABILITAZIONE ALL'ESERCIZIO DELLA PROFESSIONE DI FARMACISTA

II SESSIONE 2017

Prova pratica n. 2

Spedizione della ricetta

Il candidato riceve in allegato un fac-simile di ricetta.
Il candidato dovrà provvedere alla tariffazione, alla compilazione della etichetta e a rispondere ad un breve questionario inerente alla tipologia della ricetta.

II SESSIONE 2017

Cognome e nome.. N° Ricetta...

Dott. XXX XXX
Medico Chirurgo
Via XXX, XXX

Sig. XXXX

R/ Resorcina		1 g
Amido di riso		
Zinco ossido	ana	5 g
Vaselina	qb	30 g

Torino, XXXX

XXXXX

ESAME DI STATO PER L'ABILITAZIONE ALL'ESERCIZIO DELLA PROFESSIONE DI FARMACISTA

II SESSIONE 2017

n°..............li..........................Dott...................................

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Avvertenze...

....

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Precauzioni...

....

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Posologia...

....

....

Data limite di utilizzo...

Sig...

Cognome e Nome ______________________________ **Prova n°** __________

Scheda ricetta

Tipologia

☐RR ☐RNR ☐RNR (tab 3) ☐RRM ☐SSN

La ricetta risulta spedibile?

☐sì

☐no perché?

Validità temporale ed eventuale ripetibilità della ricetta in oggetto:

Formalismi obbligatori per il **medico** per la ricetta in oggetto:

Formalismi obbligatori per il **farmacista** per la ricetta in oggetto:

Presenza di:

- ☐ veleni, sostanze tossiche
- ☐ sost. stupefacenti e psicotrope
- ☐ coloranti o corrosivi
- ☐ sostanze vietate per doping

☐ registrazione registro EU

Modalità e tempo di conservazione della ricetta

Data limite di utilizzo della preparazione

Uso
☐ UI ☐ UE

Forma farmaceutica

Controllo di qualità obbligatori per le NBP:

Attività terapeutica della preparazione

SCADENZA MATERIE PRIME

RESORCINA	30 giugno 2019
AMIDO DI RISO	31 marzo 2019
ZINCO OSSIDO	31 dicembre 2019
VASELINA	30 luglio 2019