UNIVERSITÀ DEGLI STUDI DI TORINO

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

PRIMA SESSIONE 2014

PROVA SCRITTA

Tema n. 1
Medicinali in forma di sospensione presenti in farmacia: vie di somministrazione, razionale d'uso, ruolo del farmacista nel supportare il cliente nel loro corretto utilizzo.

Tema n. 2
Medicinali generici, modalità prescrittive e ruolo del farmacista nella spedizione della ricetta.

Tema n. 3
Farmaci dello scompenso cardiaco: i digitalici.

PROVA PRATICA

Prova n.1
Dosamento del farmaco.
Ad ogni candidato è stato fornito il risultato sperimentale di una prova di dosamento di un farmaco effettuata attraverso titolazione volumetrica. E' stato quindi posto un problema di calcolo stechiometrico costituito da tre quesiti.

Una compressa del peso di 1,500 g contenente ranitidina cloridrato (PM: 350,9) ed eccipienti inerti è stata sciolta in un matraccio da 50,00 mL e portata a volume ottenendo la soluzione A.

25,00 mL della soluzione A sono stati prelevati e titolati secondo Ph. Eur. 8. La titolazione ha richiesto 6,520 mL di NaOH 0,1000 M.

Si calcoli:

a) i g di ranitidina cloridrato contenuti nella compressa

b) il % p/p di principio attivo contenuto nella compressa

c) la concentrazione molare di ranitidina cloridrato nella soluzione A

- the chromatogram obtained with the blank solution does not show any peak with the same relative retention as the peak due to impurity A in the chromatogram obtained with reference solution (a).

Limits:

- *correction factor*: for the calculation of content, multiply the peak area of impurity J by 2;
- *impurity A*: not more than 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.5 per cent);
- *impurities B, C, D, E, F, G, H, I, J*: for each impurity, not more than 0.2 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.2 per cent);
- *unspecified impurities*: for each impurity, not more than 0.1 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.10 per cent);
- *sum of impurities other than A*: not more than 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.5 per cent);
- *disregard limit*: 0.05 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.05 per cent); disregard any peak due to the blank.

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

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

Loss on drying (*2.2.32*): maximum 0.75 per cent, determined on 1.000 g by drying under high vacuum at 60 °C.

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

ASSAY

Dissolve 0.280 g in 35 mL of *water R*. Titrate 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 35.09 mg of $C_{13}H_{23}ClN_4O_3S$.

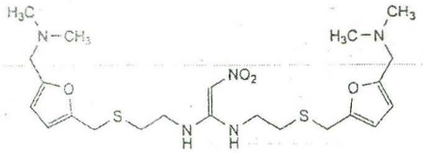
STORAGE

In airtight container, protected from light.

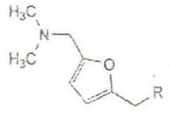
IMPURITIES

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

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*): *K*.



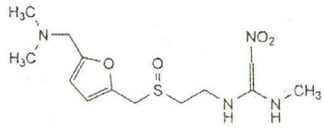
A. *N,N′*-bis[2-[[[5-[(dimethylamino)methyl]furan-2-yl]methyl]sulfanyl]ethyl]-2-nitroethene-1,1-diamine,



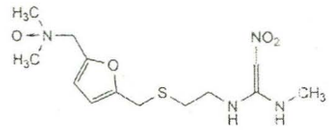
B. R = S-CH_2-CH_2-NH_2: 2-[[[5-[(dimethylamino)methyl]-furan-2-yl]methyl]sulfanyl]ethanamine,

D. R = S-CH_2-CH_2-NH-CO-CH_2-NO_2: *N*-[2-[[[5-[(dimethylamino)methyl]furan-2-yl]methyl]sulfanyl]ethyl]-2-nitroacetamide,

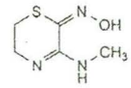
F. R = OH: [5-[(dimethylamino)methyl]furan-2-yl]methanol,



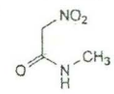
C. *N*-[2-[[[5-[(dimethylamino)methyl]furan-2-yl]methyl]sulfinyl]ethyl]-*N′*-methyl-2-nitroethene-1,1-diamine,



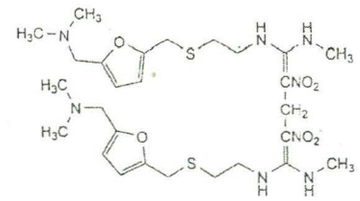
E. *N*-[2-[[[5-[(dimethyloxidoamino)methyl]furan-2-yl]methyl]sulfanyl]ethyl]-*N′*-methyl-2-nitroethene-1,1-diamine,



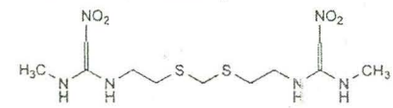
G. 3-(methylamino)-5,6-dihydro-2*H*-1,4-thiazin-2-one-oxime,



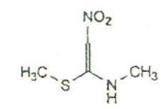
H. *N*-methyl-2-nitroacetamide,



I. 2,2′-methylenebis[*N*-[2-[[[5-[(dimethylamino)methyl]-furan-2-yl]methyl]sulfanyl]ethyl]-*N′*-methyl-2-nitro-ethene-1,1-diamine],



J. 1,1′-*N*-[methylenebis(sulfanediylethylene)]bis(*N′*-methyl-2-nitroethene-1,1-diamine),



K. *N*-methyl-1-methylthio-2-nitroethenamine.

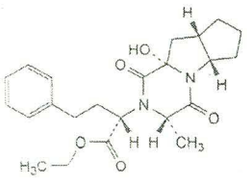
01/2010:1369

RAPESEED OIL, REFINED

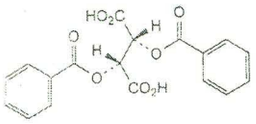
Rapae oleum raffinatum

DEFINITION

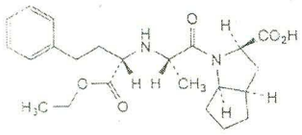
Fatty oil obtained from the seeds of *Brassica napus* L. and *Brassica campestris* L. by mechanical expression or by extraction. It is then refined. A suitable antioxidant may be added.



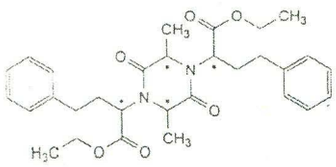
L. ethyl (2*S*)-2-[(3*S*,5a*S*,8a*S*,9a*S*)-9a-hydroxy-3-methyl-1,4-dioxodecahydro-2*H*-cyclopenta[4,5]pyrrolo[1,2-*a*]-pyrazin-2-yl]-4-phenylbutanoate (ramipril hydroxydiketopiperazine),



M. (2*R*,3*R*)-2,3-bis(benzoyloxy)butanedioic acid (dibenzoyltartric acid),



N. (2*R*,3a*R*,6a*R*)-1-[(2*S*)-2-[[(1*S*)-1-(ethoxycarbonyl)-3-phenylpropyl]amino]propanoyl]octahydrocyclopenta-[*b*]pyrrole-2-carboxylic acid ((*S*,*S*,*R*,*R*,*R*)-isomer of ramipril),

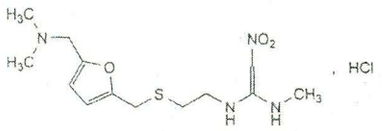


O. diethyl 2,2′-(2,5-dimethyl-3,6-dioxopiperazine-1,4-diyl)bis(4-phenylbutanoate).

01/2008:0946
corrected 7.0

RANITIDINE HYDROCHLORIDE

Ranitidini hydrochloridum



$C_{13}H_{23}ClN_4O_3S$ M_r 350.9
[66357-59-3]

DEFINITION

N-[2-[[[5-[(Dimethylamino)methyl]furan-2-yl]methyl]sulfanyl]ethyl]-*N*′-methyl-2-nitroethene-1,1-diamine hydrochloride.

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

CHARACTERS

Appearance: white or pale yellow, crystalline powder.

Solubility: freely soluble in water, sparingly soluble or slightly soluble in anhydrous ethanol, very slightly soluble in methylene chloride.

It shows polymorphism (5.9).

IDENTIFICATION

A. Infrared absorption spectrophotometry (2.2.24).

Comparison: *ranitidine hydrochloride CRS*.

If the spectra obtained in the solid state show differences, dissolve 10 mg of the substance to be examined and 10 mg of the reference substance separately in 0.5 mL of *methanol R* in an agate mortar. Evaporate to dryness under a stream of *nitrogen R*. Dry the residues under vacuum for 30 min. Add 3 drops of *liquid paraffin R* to the residues and triturate until the mull shows a milky appearance. Compress the mulls between 2 plates transparent to infrared radiation and record new spectra.

B. 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 100.0 mL with the same solvent.

Appearance of solution. Solution S is clear (2.2.1) and not more intensely coloured than reference solution BY$_7$ (2.2.2 *Method II*).

pH (2.2.3): 4.5 to 6.0 for solution S.

Related substances. Liquid chromatography (2.2.29).

Buffer solution. Dissolve 6.8 g of *potassium dihydrogen phosphate R* in 950 mL of *water R*. Adjust to pH 7.1 with *strong sodium hydroxide solution R* and dilute to 1000 mL with *water R*.

Test solution. Dissolve 13 mg of the substance to be examined in mobile phase A and dilute to 100.0 mL with mobile phase A.

Reference solution (a). Dissolve 6.5 mg of *ranitidine for system suitability CRS* (containing impurities A, D and H) in mobile phase A and dilute to 50.0 mL with mobile phase A.

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

Reference solution (c). Dissolve the contents of a vial of *ranitidine impurity J CRS* in 1.0 mL of test solution.

Column:

- *size*: *l* = 0.1 m, Ø = 4.6 mm;
- *stationary phase*: *octadecylsilyl amorphous organosilica polymer R* (3.5 µm);
- *temperature*: 35 °C.

Mobile phase:

- *mobile phase A*: *acetonitrile R*, buffer solution (2:98 *V/V*);
- *mobile phase B*: *acetonitrile R*, buffer solution (22:78 *V/V*);

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 10	100 → 0	0 → 100
10 - 15	0	100

Flow rate: 1.5 mL/min.

Detection: spectrophotometer at 230 nm.

Injection: 10 µL of the test solution, reference solutions (a), (b) and (c) and mobile phase A as a blank.

Relative retention with reference to ranitidine (retention time = about 6.8 min): impurity H = about 0.1; impurity G = about 0.2; impurity F = about 0.4; impurity B = about 0.5; impurity C = about 0.6; impurity E = about 0.7; impurity D = about 0.8; impurity J = about 0.9; impurity I = about 1.3; impurity A = about 1.7.

System suitability:

- *resolution*: minimum 1.5 between the peaks due to impurity J and ranitidine in the chromatogram obtained with reference solution (c);
- the chromatogram obtained with reference solution (a) is similar to the chromatogram supplied with *ranitidine for system suitability CRS*;

Prova n.2

Riconoscimento del farmaco.

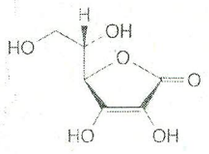
Ad ogni farmaco è stato fornito il profilo sperimentale e due possibili soluzioni (monografie di due farmaci iscritti nella Farmacopea Europea).

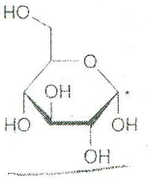
Al candidato è stato chiesto di:

- individuare il farmaco meglio rispondente al profilo fornito;
- motivare brevemente la propria scelta;
- proporre un'ulteriore prova sperimentale a conferma della propria scelta.

Il Farmaco in esame si presenta come una polvere bianca e mostra una buona solubilità acquosa (50 mg di composto si dissolvono completamente in 0.250 mL di acqua). La solubilità non sembra discostarsi sensibilmente da tale valore quando viene rilevata in 0,5 M HCl o 0,5 M NaOH. Al contrario, il Farmaco risulta meno solubile in alcool etilico (circa 3 mL/50 mg)) ed insolubile in etere dietilico. In termini di reattività, il Farmaco risulta in generale sensibile ad ossidanti forti (per es: $KMnO_4$, $K_2Cr_2O_7$) e quando trattato con soluzioni di Ag(I) o Rame (II) mostra positività del saggio con formazione di un precipitato scuro nel primo caso e di viraggio al rosso nel secondo.

Nel gruppo di Farmaci a vostra disposizione avete selezionato quali candidati il *Glucosio* e l'*acido Ascorbico* quali possibili candidati.



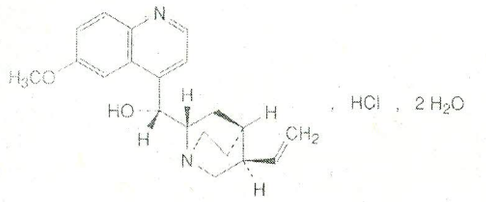


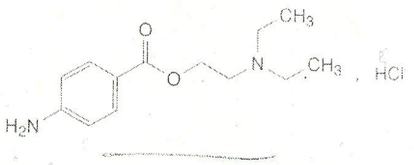
1) Indicare quale fra i due Farmaci risponde meglio al profilo sperimentale fornito, giustificando brevemente i criteri che hanno governato la selezione.
2) Quale passo successivo, proporre alcune ulteriori analisi/test che potrebbero meglio validare la scelta effettuata nel primo punto.

Il Farmaco in esame si presenta come una polvere bianca con una buona solubilità acquosa (150 mg di composto si dissolvono completamente in meno di 0,150 mL di acqua). Tale solubilità sembra ulteriormente migliorare quando viene rilevata in 0,5 M HCl mentre risulta notevolmente inferiore se rilevata in 0,5 M NaOH.

In termini di reattività, il Farmaco risulta in generale sensibile ad ossidanti forti (per es: $KMnO_4$, $K_2Cr_2O_7$) e quando trattato con soluzioni di Ag(I) mostra positività del saggio con formazione di un precipitato bianco caseoso. Se il Farmaco viene dissolto in Acido Cloridrico e la soluzione risultante trattata in sequenza *nitrito di sodio* e quindi *beta-naftolo* si osserva lo sviluppo di un caratteristico colore rosso.

Nel gruppo di Farmaci a vostra disposizione avete selezionato quali candidati la *Chinina cloridrato* e la *Procaina 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.

...aric-tartaric solution. *1023300*

...solution I. Dissolve 34.6 g of *copper sulphate R* in *water R* and dilute to 500 ml with the same solvent.

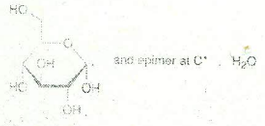
...solution II. Dissolve 173 g of *sodium potassium tartrate R* and 50 g of *sodium hydroxide R* in 400 ml of *water R*. Heat to boiling, allow to cool and dilute to 500 ml with *carbon dioxide-free water R*.

Mix equal volumes of the 2 solutions immediately before use.

01/2002:0178

GLUCOSE MONOHYDRATE

Glucosum monohydricum



$C_6H_{12}O_6,H_2O$ M_r 198.2

DEFINITION

Glucose monohydrate is the monohydrate of (+)-D-glucopyranose.

CHARACTERS

A white, crystalline powder, with a sweet taste, freely soluble in water, sparingly soluble in alcohol.

IDENTIFICATION

A. Specific optical rotation (see Tests): + 52.5 to + 53.3.

B. Examine by thin-layer chromatography (*2.2.27*), using *silica gel G R* as the coating substance.

Test solution. Dissolve 10 mg of the substance to be examined in a mixture of 2 volumes of *water R* and 3 volumes of *methanol R* and dilute to 20 ml with the same mixture of solvents.

Reference solution (a). Dissolve 10 mg of *glucose CRS* in a mixture of 2 volumes of *water R* and 3 volumes of *methanol R* and dilute to 20 ml with the same mixture of solvents.

Reference solution (b). Dissolve 10 mg each of *fructose CRS*, *glucose CRS*, *lactose CRS* and *sucrose CRS* in a mixture of 2 volumes of *water R* and 3 volumes of *methanol R* and dilute to 20 ml with the same mixture of solvents.

Apply separately to the plate 2 µl of each solution and thoroughly dry the starting points. Develop over a path of 15 cm using a mixture of 10 volumes of *water R*, 15 volumes of *methanol R*, 25 volumes of *anhydrous acetic acid R* and 50 volumes of *ethylene chloride R*. The solvents should be measured accurately since a slight excess of water produces cloudiness. Dry the plate in a current of warm air. Repeat the development immediately, after renewing the mobile phase. Dry the plate in a current of warm air and spray evenly with a solution of 0.5 g of *thymol R* in a mixture of 5 ml of *sulphuric acid R* and 95 ml of *alcohol R*. Heat at 130 °C for 10 min. 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 reference solution (a). The test is not valid unless the chromatogram obtained with reference solution (b) shows 4 clearly separated spots.

C. Dissolve 0.1 g in 10 ml of *water R*. Add 3 ml of *cupri-tartaric solution R* and heat. A red precipitate is formed.

TESTS

Solution S. Dissolve 10.0 g in *distilled water R* and dilute to 100 ml with the same solvent.

Appearance of solution. Dissolve 10.0 g in 15 ml of *water R*. The solution is clear (*2.2.1*), odourless, and not more intensely coloured than reference solution BY_7 (*2.2.2. Method II*).

Acidity or alkalinity. Dissolve 6.0 g in 25 ml of *carbon dioxide-free water R* and add 0.3 ml of *phenolphthalein solution R*. The solution is colourless. Not more than 0.15 ml of *0.1 M sodium hydroxide* is required to change the colour of the indicator to pink.

Specific optical rotation (*2.2.7*). Dissolve 10.0 g in 80 ml of *water R*, add 0.2 ml of *dilute ammonia R1*, allow to stand for 30 min and dilute to 100.0 ml with *water R*. The specific optical rotation is + 52.5 to + 53.3, calculated with reference to the anhydrous substance.

Foreign sugars, soluble starch, dextrins. Dissolve 1.0 g by boiling in 30 ml of *alcohol (90 per cent V/V) R*. Cool; the appearance of the solution shows no change.

Sulphites. Dissolve 5.0 g in 40 ml of *water R*, add 2.0 ml of *0.1 M sodium hydroxide* and dilute to 50.0 ml with *water R*. To 10.0 ml of the solution, add 1 ml of a 310 g/l solution of *hydrochloric acid R*, 2.0 ml of *decolorised fuchsin solution R1* and 2.0 ml of a 0.5 per cent V/V solution of *formaldehyde R*. Allow to stand for 30 min and measure the absorbance (*2.2.25*) at the maximum at 583 nm. Prepare a standard as follows. Dissolve 76 mg of *sodium metabisulphite R* in *water R* and dilute to 50.0 ml with the same solvent. Dilute 5.0 ml of this solution to 100.0 ml with *water R*. To 3.0 ml of this solution add 4.0 ml of *0.1 M sodium hydroxide* and dilute to 100.0 ml with *water R*. Immediately add to 10.0 ml of this solution 1 ml of a 310 g/l solution of *hydrochloric acid R*, 2.0 ml of *decolorised fuchsin solution R1* and 2.0 ml of a 0.5 per cent V/V solution of *formaldehyde R*. Allow to stand for 30 min and measure the absorbance at the maximum at 583 nm. Use as compensation liquid for both measurements a solution prepared in the same manner using 10.0 ml of *water R*. The absorbance of the test solution is not greater than that of the standard (15 ppm of SO_2).

Chlorides (*2.4.4*). 4 ml of solution S diluted to 15 ml with *water R* complies with the limit test for chlorides (125 ppm).

Sulphates (*2.4.13*). 7.5 ml of solution S diluted to 15 ml with *distilled water R* complies with the limit test for sulphates (200 ppm).

Arsenic (*2.4.2*). 1.0 g complies with limit test A for arsenic (1 ppm).

Barium. To 10 ml of solution S add 1 ml of *dilute sulphuric 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.

Calcium (*2.4.3*). 5 ml of solution S diluted to 15 ml with *distilled water R* complies with the limit test for calcium (200 ppm).

Lead in sugars (*2.4.10*). It complies with the limit test for lead in sugars (0.5 ppm).

Water (*2.5.12*). 7.0 per cent to 9.5 per cent, determined on 0.50 g by the semi-micro determination of water.

Sulphated ash (*2.4.14*). Not more than 0.1 per cent. Dissolve 5.0 g in 5 ml of *water R*, add 2 ml of *sulphuric acid R*, evaporate to dryness on a water-bath and ignite to constant mass. If necessary, repeat the heating with *sulphuric acid R*.

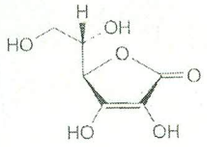
Pyrogens (*2.6.8*). If intended for use in large-volume preparations for parenteral use, the competent authority may require that it comply with the test for pyrogens carried out as follows. Inject per kilogram of the rabbit's mass 10 ml of a solution containing 55 mg per millilitre of the substance to be examined in *water for injections R*.

LABELLING

The label states where applicable, that the substance is apyrogenic.

ASCORBIC ACID

Acidum ascorbicum



$C_6H_8O_6$ M_r 176.1

DEFINITION

Ascorbic acid contains not less than 99.0 per cent and not more than the equivalent of 100.5 per cent of (5*R*)-5-[(1*S*)-1,2-dihydroxyethyl]-3,4-dihydroxyfuran-2(5*H*)-one.

CHARACTERS

A white or almost white, crystalline powder or colourless crystals, becoming discoloured on exposure to air and moisture, freely soluble in water, soluble in alcohol, practically insoluble in ether.

It melts at about 190 °C, with decomposition.

IDENTIFICATION

First identification: B, C.

Second identification: A, C, D.

A. Dissolve 0.10 g in *water R* and dilute immediately to 100.0 ml with the same solvent. To 10 ml of *0.1 M hydrochloric acid*, add 1.0 ml of the solution and dilute to 100.0 ml with *water R*. Measure the absorbance (*2.2.25*) at the maximum at 243 nm immediately after dissolution. The specific absorbance at the maximum is 545 to 585.

B. Examine by infrared absorption spectrophotometry (*2.2.24*), comparing with the spectrum obtained with *ascorbic acid CRS*. Examine the substance prepared as discs containing 1 mg.

C. The pH (*2.2.3*) of solution S (see Tests) is 2.1 to 2.6.

D. To 1 ml of solution S add 0.2 ml of *dilute nitric acid R* and 0.2 ml of *silver nitrate solution R2*. A grey precipitate is formed.

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 not more intensely coloured than reference solution BY_7 (*2.2.2, Method II*).

Specific optical rotation (*2.2.7*). Dissolve 2.50 g in *water R* and dilute to 25.0 ml with the same solvent. The specific optical rotation is + 20.5 to + 21.5.

Oxalic acid. Dissolve 0.25 g in 5 ml of *water R*. Neutralise to *red litmus paper R* using *dilute sodium hydroxide solution R* and add 1 ml of *dilute acetic acid R* and 0.5 ml of *calcium chloride solution R* (test solution). Prepare a reference solution as follows: dissolve 70 mg of *oxalic acid R* in *water R* and dilute to 500 ml with the same solvent; to 5 ml of this solution add 1 ml of *dilute acetic acid R* and 0.5 ml of *calcium chloride solution R* (reference solution). Allow the solutions to stand for 1 h. Any opalescence in the test solution is not more intense than that in the reference solution (0.2 per cent).

Copper. Not more than 5 ppm of Cu, determined by atomic absorption spectrometry (*2.2.23, Method I*).

Test solution. Dissolve 2.0 g of the substance to be examined in *0.1 M nitric acid* and dilute to 25.0 ml with the same acid.

Reference solutions. Prepare reference solutions containing 0.2 ppm, 0.4 ppm and 0.6 ppm of Cu by diluting *copper standard solution (10 ppm Cu) R* with *0.1 M nitric acid*.

Measure the absorbance at 324.8 nm using a copper hollow-cathode lamp as a source of radiation and an air-acetylene flame. Adjust the zero of the apparatus using *0.1 M nitric acid*.

Iron. Not more than 2 ppm of Fe, determined by atomic absorption spectrometry (*2.2.23, Method I*).

Test solution. Dissolve 5.0 g of the substance to be examined in *0.1 M nitric acid* and dilute to 25.0 ml with the same acid.

Reference solutions. Prepare reference solutions containing 0.2 ppm, 0.4 ppm and 0.6 ppm of Fe by diluting *iron standard solution (20 ppm Fe) R* with *0.1 M nitric acid*.

Measure the absorbance at 248.3 nm using an iron hollow-cathode lamp as a source of radiation and an air-acetylene flame. Adjust the zero of the apparatus using *0.1 M nitric acid*.

Heavy metals (*2.4.8*). Dissolve 2.0 g in *water R* and dilute to 20 ml with the same solvent. 12 ml of the solution complies with limit test A for heavy metals (10 ppm). Prepare the standard using *lead standard solution (1 ppm Pb) R*.

Sulphated ash (*2.4.14*). Not more than 0.1 per cent, determined on 1.0 g.

ASSAY

Dissolve 0.150 g in a mixture of 10 ml of *dilute sulphuric acid R* and 80 ml of *carbon dioxide-free water R*. Add 1 ml of *starch solution R*. Titrate with *0.05 M iodine* until a persistent violet-blue colour is obtained.

1 ml of *0.05 M iodine* is equivalent to 8.81 mg of $C_6H_8O_6$.

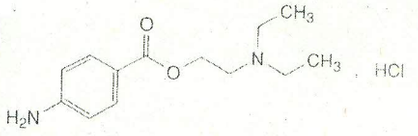
STORAGE

Store in a non-metallic container, protected from light.

01/2002:0050

PROCAINE HYDROCHLORIDE

Procaini hydrochloridum



$C_{13}H_{21}ClN_2O_2$ M_r 272.8

DEFINITION

Procaine hydrochloride contains not less than 99.0 per cent and not more than the equivalent of 101.0 per cent of 2-(diethylamino)ethyl 4-aminobenzoate hydrochloride, calculated with reference to the dried substance.

CHARACTERS

A white, crystalline powder or colourless crystals, very soluble in water, soluble in alcohol, practically insoluble in ether.

IDENTIFICATION

First identification: A, B, E.

Second identification: A, C, D, E, F.

A. Melting point (*2.2.14*): 154 °C to 158 °C.

B. Examine by infrared absorption spectrophotometry (*2.2.24*), comparing with the spectrum obtained with *procaine hydrochloride CRS*.

C. To about 5 mg add 0.5 ml of *fuming nitric acid R*. Evaporate to dryness on a water-bath, allow to cool and dissolve the residue in 5 ml of *acetone R*. Add 1 ml of *0.1 M alcoholic potassium hydroxide*. Only a brownish-red colour develops.

D. To 0.2 ml of solution S (see Tests) add 2 ml of *water R* and 0.5 ml of *dilute sulphuric acid R* and shake. Add 1 ml of a 1 g/l solution of *potassium permanganate R*. The colour is immediately discharged.

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

F. Dilute 1 ml of solution S to 100 ml with *water R*. 2 ml of this solution gives the reaction of primary aromatic amines (*2.3.1*).

TESTS

Solution S. Dissolve 2.5 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 colourless (*2.2.2, Method II*).

pH (*2.2.3*). Dilute 4 ml of solution S to 10 ml with *carbon dioxide-free water R*. The pH of the solution is 5.0 to 6.5.

Related substances. Examine by thin-layer chromatography (*2.2.27*), using *silica gel* GF_{254} *R* as the coating substance.

Test solution. Dissolve 1.0 g of the substance to be examined in *water R* and dilute to 10 ml with the same solvent.

Reference solution. Dissolve 50 mg of *4-aminobenzoic acid R* in *water R* and dilute to 100 ml with the same solvent. Dilute 1 ml of the solution to 10 ml with *water R*.

Apply separately to the plate 5 µl of each solution. Develop over a path of 10 cm using a mixture of 4 volumes of *glacial acetic acid R*, 16 volumes of *hexane R* and 80 volumes of *dibutyl ether R*. Dry the plate at 100 °C to 105 °C for 10 min and examine in ultraviolet light at 254 nm. Any spot in the chromatogram obtained with the test solution, apart from the principal spot, is not more intense than the spot in the chromatogram obtained with the reference solution (0.05 per cent). The principal spot in the chromatogram obtained with the test solution remains on the starting point.

Heavy metals (*2.4.8*). Dissolve 1.0 g in *water R* and dilute to 25.0 ml with the same solvent. Carry out the prefiltration. 10 ml of the prefiltrate complies with limit test E for heavy metals (5 ppm). Prepare the standard using 2 ml of *lead standard solution (1 ppm Pb) R*.

Loss on drying (*2.2.32*). Not more than 0.5 per cent, determined on 1.00 g by drying in an oven at 100 °C to 105 °C.

Sulphated ash (*2.4.14*). Not more than 0.1 per cent, determined on 1.0 g.

ASSAY

Dissolve 0.400 g in 50 ml of *dilute hydrochloric acid R*. Carry out the determination of primary aromatic amino nitrogen (*2.5.8*).

1 ml of *0.1 M sodium nitrite* is equivalent to 27.28 mg of $C_{13}H_{21}ClN_2O_2$.

STORAGE

Store protected from light.

CHLORIDES

a) Dissolve in 2 mL of *water R* a quantity of the substance to be examined equivalent to about 2 mg of chloride (Cl^-) or use 2 mL of the prescribed solution. Acidify with *dilute nitric acid R* and add 0.4 mL of *silver nitrate solution R1*. Shake and allow to stand. A curdled, white precipitate is formed. Centrifuge and wash the precipitate with three quantities, each of 1 mL, of *water R*. Carry out this operation rapidly in subdued light, disregarding the fact that the supernatant solution may not become perfectly clear. Suspend the precipitate in 2 mL of *water R* and add 1.5 mL of *ammonia R*. The precipitate dissolves easily with the possible exception of a few large particles which dissolve slowly.

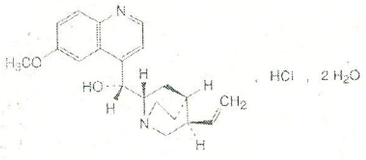
b) Introduce into a test-tube a quantity of the substance to be examined equivalent to about 15 mg of chloride (Cl^-) or the prescribed quantity. Add 0.2 g of *potassium dichromate R* and 1 mL of *sulfuric acid R*. Place a filter-paper strip impregnated with 0.1 mL of *diphenylcarbazide solution R* over the opening of the test-tube. The paper turns violet-red. The impregnated paper must not come into contact with the potassium dichromate.

AMINES, PRIMARY AROMATIC

Acidify the prescribed solution with *dilute hydrochloric acid R* and add 0.2 mL of *sodium nitrite solution R*. After 1 min to 2 min, add 1 mL of *βnaphthol solution R*. An intense orange or red colour and usually a precipitate of the same colour are produced.

QUININE HYDROCHLORIDE

Chinini hydrochloridum



$C_{20}H_{25}ClN_2O_2,2H_2O$ M_r 396.9

DEFINITION

Quinine hydrochloride contains not less than 99.0 per cent and not more than the equivalent of 101.0 per cent of alkaloid monohydrochlorides, calculated as (*R*)-[(2*S*,4*S*,5*R*)-5-ethenyl-1-azabicyclo[2.2.2]oct-2-yl](6-methoxyquinolin-4-yl)methanol hydrochloride, with reference to the dried substance.

CHARACTERS

Fine, silky needles, often in clusters, colourless, soluble in water, freely soluble in alcohol.

IDENTIFICATION

A. Examine by thin-layer chromatography (*2.2.27*), using a *TLC silica gel G plate R*.

Test solution. Dissolve 0.10 g of the substance to be examined in *methanol R* and dilute to 10 ml with the same solvent.

Reference solution. Dissolve 0.10 g of *quinine sulphate CRS* in *methanol R* and dilute to 10 ml with the same solvent.

Apply separately to the plate 5 µl of each solution. Develop over a path of 15 cm using a mixture of 10 volumes of *diethylamine R*, 24 volumes of *ether R* and 40 volumes of *toluene R*. Dry the plate in a current of air for 15 min and repeat the development. Dry the plate at 105 °C for 30 min, allow to cool and spray with *iodoplatinate reagent R*. 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.

B. Dissolve about 10 mg in *water R* and dilute to 10 ml with the same solvent. To 5 ml of the solution add 0.2 ml of *bromine water R* and 1 ml of *dilute ammonia R2*. A green colour develops.

C. Dissolve 0.1 g in 3 ml of *dilute sulphuric acid R* and dilute to 100 ml with *water R*. When examined in ultraviolet light at 366 nm, an intense blue fluorescence appears which disappears almost completely on the addition of 1 ml of *hydrochloric acid R*.

D. It gives the reactions of chlorides (*2.3.1*).

E. It complies with the test for pH (see Tests).

TESTS

Solution S. Dissolve 1.0 g in *carbon dioxide-free water R* prepared from *distilled 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*).

pH (*2.2.3*). Dilute 10 ml of solution S to 20 ml with *carbon dioxide-free water R*. The pH of the solution is 6.0 to 6.8.

Specific optical rotation (*2.2.7*). Dissolve 0.500 g in *0.1 M hydrochloric acid* and dilute to 25.0 ml with the same acid. The specific optical rotation is −245 to −258, calculated with reference to the dried substance.

Other cinchona alkaloids. Examine by liquid chromatography (*2.2.29*).

Test solution. Dissolve 20 mg of the substance to be examined, with gentle heating if necessary, in 5 ml of the mobile phase and dilute to 10 ml with the mobile phase.

Reference solution (a). Dissolve 20 mg of *quinine sulphate CRS*, with gentle heating if necessary, in 5 ml of the mobile phase and dilute to 10 ml with the mobile phase.

Reference solution (b). Dissolve 20 mg of *quinidine sulphate CRS*, with gentle heating if necessary, in 5 ml of the mobile phase and dilute to 10 ml with the mobile phase.

Reference solution (c). To 1 ml of reference solution (a) add 1 ml of reference solution (b).

Reference solution (d). Dilute 1.0 ml of reference solution (a) to 10.0 ml with the mobile phase. Dilute 1.0 ml of this solution to 50.0 ml with the mobile phase.

Reference solution (e). Dissolve 10 mg of *thiourea R* in the mobile phase and dilute to 10 ml with the mobile phase.

The chromatographic procedure may be carried out using:

- a stainless steel column 0.15 m to 0.25 m long and 4.6 mm in internal diameter packed with *octadecylsilyl silica gel for chromatography R* (5 µm or 10 µm),
- as mobile phase at a flow rate of 1.5 ml/min a mixture prepared as follows: dissolve 6.8 g of *potassium dihydrogen phosphate R* and 3.0 g of *hexylamine R* in 700 ml of *water R*, adjust to pH 2.8 with *dilute phosphoric acid R*, add 60 ml of *acetonitrile R* and dilute to 1000 ml with *water R*,
- as detector a spectrophotometer set at 250 nm for recording the chromatogram obtained with reference solution (e) and at 316 nm for the other solutions.

Inject 10 µl of reference solution (b) and 10 µl of reference solution (e). If necessary, adjust the concentration of acetonitrile in the mobile phase so that, in the chromatogram obtained with reference solution (b), the mass distribution factor of the peak corresponding to quinidine is 3.5 to 4.5, t_0 being calculated from the peak corresponding to thiourea in the chromatogram obtained with reference solution (e).

Inject 10 µl each of reference solutions (a), (b), (c) and (d). The chromatogram obtained with reference solution (a) shows a principal peak corresponding to quinine and a peak corresponding to dihydroquinine, with a retention time relative to quinine of about 1.4. The chromatogram obtained with reference solution (b) shows a principal peak corresponding to quinidine and a peak corresponding to dihydroquinidine with a retention time relative to quinidine of about 1.5. The chromatogram obtained with reference solution (c) shows 4 peaks corresponding to quinidine, quinine, dihydroquinidine and dihydroquinine, which are identified by comparison of their retention times with those of the corresponding peaks in the chromatograms obtained with reference solutions (a) and (b).

The chromatographic system is not satisfactory unless in the chromatogram obtained with reference solution (c), the resolution between the peaks corresponding to quinidine and quinidine is at least 3.0 and the resolution between the peaks corresponding to dihydroquinidine and quinine is at least 2.0 and the chromatogram obtained with reference solution (d) shows a principal peak with a signal-to-noise ratio of at least 4.

Inject 10 µl of the test solution. Record the chromatogram for 2.5 times the retention time of the principal peak. Calculate the percentage content of related substances from the areas of the peaks in the chromatogram obtained with the test solution by the normalisation procedure. Disregard any peaks with an area less than that of the principal peak in the chromatogram obtained with reference solution (d). The content of dihydroquinine is not greater than [illegible], the content of any related substance eluted before quinine is not greater than 5 per cent and the content of any other related substance is not greater than 2.5 per cent.

Sulphates (*2.4.13*). 15 ml of solution S complies with the limit test for sulphate (500 ppm).

Barium. To 15 ml of solution S add 1 ml of *dilute sulphuric acid R*. After at least 15 min, any opalescence in the solution is not more intense than that in a mixture of 15 ml of solution S and 1 ml of *distilled water R*.

Loss on drying (*2.2.32*). 6.0 per cent to 10.0 per cent, determined on 1.000 g by drying in an oven at [illegible] °C to 105 °C.

Sulphated ash (*2.4.14*). Not more than 0.1 per cent, determined on 1.0 g.

ASSAY

Dissolve 0.250 g in 50 ml of *alcohol R* and add 5.0 ml of *0.01 M hydrochloric acid*. Titrate with *0.1 M sodium hydroxide*, determining the end-point potentiometrically (*2.2.20*). Read the volume added between the 2 inflexion points.

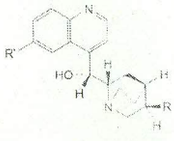
1 ml of *0.1 M sodium hydroxide* is equivalent to 30.07 mg of $C_{20}H_{25}ClN_2O_2$.

STORAGE

Store protected from light.

IMPURITIES

A. quinidine,



B. R = CH=CH$_2$, R' = H: (*R*)-[(2*S*,4*S*,5*R*)-5-ethenyl-1-azabicyclo[2.2.2]oct-2-yl](quinolin-4-yl)methanol (cinchonidine),

C. R = C_2H_5, R' = OCH_3: (*R*)-[(2*S*,4*S*,5*R*)-5-ethyl-1-azabicyclo[2.2.2]oct-2-yl](6-methoxyquinolin-4-yl)methanol (dihydroquinine).

CHLORIDES

a) Dissolve in 2 ml of *water R* a quantity of the substance to be examined equivalent to about 2 mg of chloride (Cl⁻) or use 2 ml of the prescribed solution. Acidify with *dilute nitric acid R* and add 0.4 ml of *silver nitrate solution R1*. Shake and allow to stand. A curdled, white precipitate is formed. Centrifuge and wash the precipitate with three quantities, each of 1 ml, of *water R*. Carry out this operation rapidly in subdued light, disregarding the fact that the supernatant solution may not become perfectly clear. Suspend the precipitate in 2 ml of *water R* and add 1.5 ml of *ammonia R*. The precipitate dissolves easily with the possible exception of a few large particles which dissolve slowly.

b) Introduce into a test-tube a quantity of the substance to be examined equivalent to about 13 mg of chloride (Cl⁻) or the prescribed quantity. Add 0.2 g of *potassium dichromate R* and 1 ml of *sulfuric acid R*. Place a filter-paper strip impregnated with 0.1 ml of *diphenylcarbazide solution R* over the opening of the test-tube. The paper turns violet-red. The impregnated paper must not come into contact with the potassium dichromate.

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

Prova n.3

Spedizione della ricetta.

Tariffazione, compilazione dell'etichetta e della scheda di preparazione di una formula magistrale di cui il candidato riceverà un fac-simile di ricetta. Compilazione di un breve questionario a risposta multipla inerente alla tipologia di ricetta, la sua spedibilità, le modalità di conservazione e gli eventuali obblighi di registrazione.

Dott.

Sig.ra

Codeina fosfato 5 mg
Paracetamolo 325 mg
Amido di riso q.b. a 700 mg

Di una tali 30 capsule

1 capsula al dì

UTILIZZARE IL FOGLIO PROTOCOLLO A QUADRETTI **UNICAMENTE** PER I CALCOLI

Cognome e Nome _____ **Prova n°**_____

SCHEDA DI PREPARAZIONE

Fonte di legittimazione: [O] Farmacopea_____

[M] Prescrizione medica del _____N°_____

Forma farmaceutica:_____

Riferimento alla procedura tecnologica_____

Avvertenze e precauzioni:_____

Componenti	*Cod.Interno*	*Lotto**	*Quantità unitarie*	**

** Compilare se preparazione allestita un'unica volta e che dunque non richiede foglio di allestimento.*
*** Barrare se impiegato per motivi tecnici*

Controlli previsti _____

Contenitore _____

Periodo di validità _____

Disciplina di vendita (senza ricetta, RR, RNR, RRM) _____

Metodo di preparazione

_____

OBBLIGO DI REGISTRAZIONE IN USCITA **SÌ** **NO**