# UNIVERSITÀ DEGLI STUDI DI TORINO

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

### SECONDA SESSIONE 2016

## PROVA SCRITTA

**Tema n. 1**
Le insuline umane.

**Tema n. 2**
Preparazioni liquide estemporanee: il ruolo del farmacista nel supportare il cliente nel loro corretto utilizzo.

**Tema n. 3**
Normativa sulla cannabis.

## 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.

**UNIVERSITÀ DEGLI STUDI DI TORINO**

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

**SECONDA SESSIONE 2016**

**PROVA PRATICA: Dosamento del Farmaco**

**Cognome e nome……**

Trenta compresse del peso di 4,500 grammi contenenti nimesulide (PM: 308,3) ed eccipienti inerti sono state polverizzate e sciolte in acetone in un matraccio da 50,00 mL; dopo aver portato a volume si è ottenuta la soluzione A.

25,00 mL della soluzione A sono stati prelevati e diluiti a 250 mL con acqua a dare la soluzione B.

25,00 mL della soluzione B sono stati titolati secondo Ph. Eur. 8. La titolazione ha richiesto 4,90 mL di sodio idrossido 0,1000 M.

Si calcoli:

a) la concentrazione molare della soluzione B;

b) la concentrazione molare della soluzione A;

c) ogni compressa dovrebbe contenere 100 mg di principio attivo con una variabilità del 5 %. Si identifichi l'intervallo di peso del principio attivo (espresso in mg) che può essere contenuto nella compressa perché questa sia considerata conforme alle specifiche.

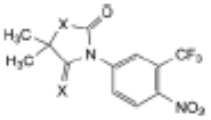
Risposte ai quesiti:

a) _____

b) _____

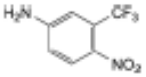
c) _____

N.B. Insieme alla prova al candidato viene fornita copia della monografia ufficiale di Ph. Eur. 8 della nimesulide.

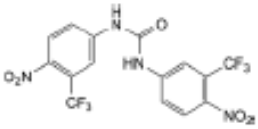


A. X = NH: 5-imino-4,4-dimethyl-1-[4-nitro-3-(trifluoromethyl)phenyl]imidazolidin-2-one,

C. X = O: 5,5-dimethyl-3-[4-nitro-3-(trifluoromethyl)phenyl]-oxazolidine-2,4-dione,



B. 4-nitro-3-(trifluoromethyl)aniline (nifeline),

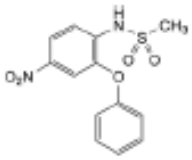


D. 1,3-bis[4-nitro-3-(trifluoromethyl)phenyl]urea.

**07/2013:1548**

# NIMESULIDE

## Nimesulidum



$C_{13}H_{12}N_2O_5S$ $M_r$ 308.3
[51803-78-2]

DEFINITION

*N*-(4-Nitro-2-phenoxyphenyl)methanesulfonamide.

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

CHARACTERS

*Appearance*: yellowish, crystalline powder.

*Solubility*: practically insoluble in water, freely soluble in acetone, slightly soluble in anhydrous ethanol.

mp: about 149 °C.

It shows polymorphism (*5.9*).

IDENTIFICATION

Infrared absorption spectrophotometry (*2.2.24*).

*Comparison*: *nimesulide CRS*.

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

TESTS

**Absorbance** (*2.2.25*): maximum 0.50 at 450 nm.

Dissolve 1.0 g in *acetone R* and dilute to 10.0 mL with the same solvent.

**Related substances**. Liquid chromatography (*2.2.29*).

*Test solution*. Dissolve 20 mg of the substance to be examined in 8 mL of *acetonitrile R* and dilute to 20.0 mL with *water R*.

*Reference solution (a)*. Dissolve 5 mg of *2-phenoxyaniline R* (impurity C) in 10 mL of *acetonitrile R* and dilute to 25.0 mL with *water R*. Dilute 1.0 mL of the solution to 50.0 mL with the mobile phase. Mix 1.0 mL of this solution with the contents of a vial of *nimesulide impurity D CRS* previously dissolved in 1.0 mL of *acetonitrile R*.

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

*Reference solution (c)*. Dissolve 4 mg of *nimesulide for peak identification CRS* (containing impurities A, B, E and F) in 4.0 mL of *acetonitrile R* and dilute to 10.0 mL with the mobile phase.

*Column*:

- *size*: *l* = 0.125 m, Ø = 4.0 mm;
- *stationary phase*: *octadecylsilyl silica gel for chromatography R* (5 µm).

*Mobile phase*. Mix 35 volumes of *acetonitrile R* and 65 volumes of a 1.15 g/L solution of *ammonium dihydrogen phosphate R* previously adjusted to pH 7.0 with *ammonia R*.

*Flow rate*: 1.3 mL/min.

*Detection*: spectrophotometer at 230 nm.

*Injection*: 20 µL.

*Run time*: 7 times the retention time of nimesulide.

*Identification of impurities*: use the chromatogram supplied with *nimesulide for peak identification CRS* and the chromatogram obtained with reference solution (c) to identify the peaks due to impurities A, B, E and F; use the chromatogram obtained with reference solution (a) to identify the peaks due to impurities C and D.

*Relative retention* with reference to nimesulide (retention time = about 5 min): impurity A = about 0.3; impurity B = about 2.4; impurity C = about 3.2; impurity D = about 3.7; impurity E = about 4.2; impurity F = about 6.1.

*System suitability*: reference solution (a):

- *resolution*: minimum 2.0 between the peaks due to impurities C and D.

*Limits*:

- *correction factors*: for the calculation of content, multiply the peak areas of the following impurities by the corresponding correction factor: impurity C = 0.7; impurity E = 1.4;
- *impurity E*: not more than twice the area of the principal peak in the chromatogram obtained with reference solution (b) (0.2 per cent);
- *impurities A, B, C, D, F*: for each impurity, not more than 1.5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.15 per cent);
- *unspecified impurities*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (0.10 per cent);
- *total*: not more than 5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.5 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).

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

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

**Loss on drying** (*2.2.32*): maximum 0.5 per cent, determined on 1.000 g by drying in an oven at 105 °C for 4 h.

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

ASSAY

Dissolve 0.240 g in 30 mL of previously neutralised *acetone R* and add 20 mL of *water R*. Titrate with *0.1 M sodium hydroxide*, determining the end-point potentiometrically (*2.2.20*).

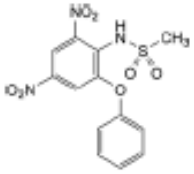
1 mL of *0.1 M sodium hydroxide* is equivalent to 30.83 mg of $C_{13}H_{12}N_2O_5S$.

Monographs

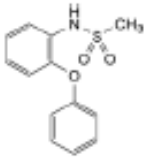
IMPURITIES

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

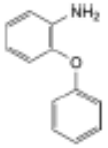
*Other detectable impurities* (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph *Substances for pharmaceutical use (2034)*. It is therefore not necessary to identify these impurities for demonstration of compliance. See also *5.10. Control of impurities in substances for pharmaceutical use*): *G.*



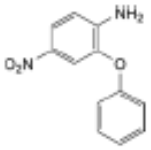
A. *N*-(2,4-dinitro-6-phenoxyphenyl)methanesulfonamide,



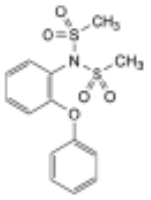
B. *N*-(2-phenoxyphenyl)methanesulfonamide,



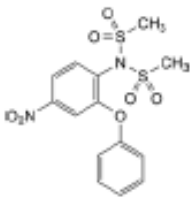
C. 2-phenoxyaniline,



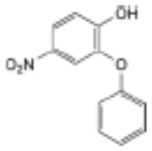
D. 4-nitro-2-phenoxyaniline,



E. *N*,*N*-bis(methylsulfonyl)-2-phenoxyaniline,



F. *N*,*N*-bis(methylsulfonyl)-4-nitro-2-phenoxyaniline,

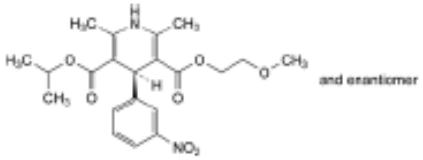


G. 4-nitro-2-phenoxyphenol.

**01/2008:1245**
**corrected 6.0**

# NIMODIPINE

## Nimodipinum



$C_{21}H_{26}N_2O_7$ $M_r$ 418.4
[66085-59-4]

DEFINITION

2-Methoxyethyl 1-methylethyl (4*RS*)-2,6-dimethyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate.

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

CHARACTERS

*Appearance*: light yellow or yellow, crystalline powder.

*Solubility*: practically insoluble in water, freely soluble in ethyl acetate, sparingly soluble in anhydrous ethanol.

It shows polymorphism (*5.9*).

Exposure to ultraviolet light leads to the formation of a nitrophenylpyridine derivative.

*Prepare solutions immediately before use either protected from light or under long-wavelength light (> 420 nm).*

IDENTIFICATION

Infrared absorption spectrophotometry (*2.2.24*).

*Comparison*: *nimodipine CRS.*

If the spectra obtained in the solid state show differences, record new spectra using 20 g/L solutions in *methylene chloride R* and a 0.2 mm cell.

TESTS

**Solution S**. Dissolve 1.0 g in *acetone R* and dilute to 20.0 mL with the same solvent.

**Appearance of solution**. Solution S is clear (*2.2.1*).

**Optical rotation** (*2.2.7*): − 0.10° to + 0.10°, determined on solution S.

**Related substances**. Liquid chromatography (*2.2.29*).

*Test solution.* Dissolve 40.0 mg of the substance to be examined in 2.5 mL of *tetrahydrofuran R* and dilute to 25.0 mL with the mobile phase.

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

*Reference solution (b). Nimodipine impurity A CRS.*

*Reference solution (c).* Dilute the test solution as described in the leaflet accompanying *nimodipine impurity A CRS.*

*Reference solution (d).* Mix reference solution (b) and reference solution (c) as described in the leaflet accompanying *nimodipine impurity A CRS.*

*Column*:

– *size*: *l* = 0.125 m, Ø = 4.6 mm;

Monographs N-O

**UNIVERSITÀ DEGLI STUDI DI TORINO**

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

## SECONDA SESSIONE 2016

## PROVA PRATICA: Prova di 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 corredati dalle rispettive monografie provenienti dalla Farmacopea Europea (Ph. Eur. 8.).

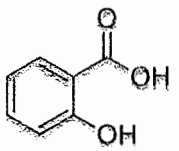
Al candidato viene richiesto di:

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

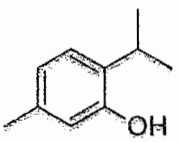
**Riconoscimento del farmaco: *primo riconoscimento***

Il farmaco in esame all'analisi elementare risulta contenere i seguenti elementi: C, H, O
Il farmaco in esame si presenta come un solido moderatamente solubile in acqua e molto solubile in EtOH. La solubilità migliora quando lo si scioglie in una soluzione acquosa di NaOH 2M.
Per quanto riguarda la sua reattività il farmaco in esame è in grado di decolorare una soluzione acquosa di $KMnO_4$ all'1%.

In base alle caratteristiche sopra riportate sono stati individuati tra i farmaci a disposizione 2 possibili candidati: **acido salicilico** e **timolo.**



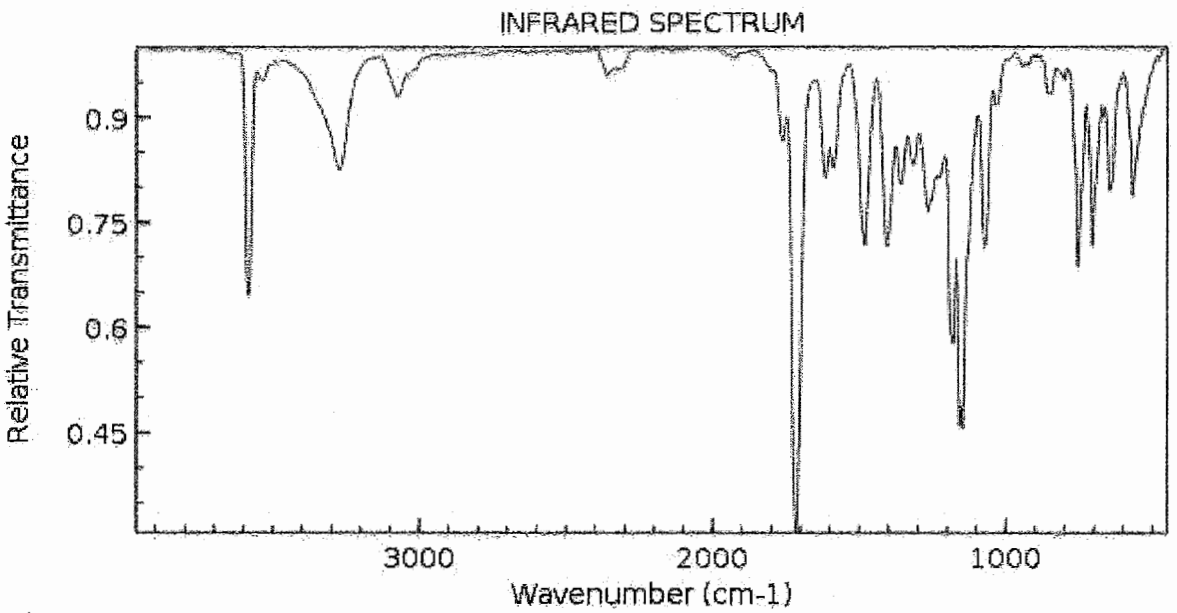

ACIDO SALICILICO




TIMOLO

Quando si aggiunge una soluzione di $FeCl_3$ ad una soluzione del farmaco in esame si ha lo sviluppo di una colorazione violetta.

Come prescritto dalla Farmacopea Europea (Ph. Eur. 8.) si è registrato lo spettro IR del farmaco incognito e sotto è riportato lo spettro ottenuto.



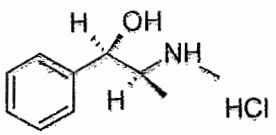

Indicare quale farmaco corrisponde al profilo sperimentale fornito motivando brevemente tale scelta e proporre un'ulteriore prova sperimentale per validare la scelta effettuata.

**Riconoscimento del farmaco: *secondo riconoscimento***

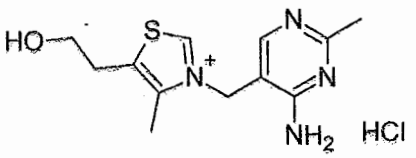
Il farmaco in esame si presenta come polvere cristallina bianca o gialla solubile in EtOH ed in acqua.

Quando ad una soluzione del farmaco in esame si aggiungono alcune gocce di una soluzione di acido nitrico diluito ed alcune gocce di una soluzione di $AgNO_3$ si ha la formazione di un precipitato bianco caseoso.

In base a queste caratteristiche sono stati individuati tra i farmaci a disposizione 2 possibili candidati: **efedrina cloridrato** e **tiamina cloridrato.**




EFEDRINA CLORIDRATO




TIAMINA CLORIDRATO

Dopo aver preparato una soluzione del farmaco da analizzare si aggiungono 1 mL di acqua ed alcune gocce di una soluzione acquosa di $CuSO_4$, quindi si aggiunge 1 mL di una soluzione di NaOH concentrata e si osserva la formazione di una colorazione violetta. Aggiungendo poi alcuni mL di $Et_2O$ ed agitando il colore viola passa in fase eterea e la fase acquosa assume una colorazione blu.

Indicare a quale dei due farmaci corrisponde il profilo sperimentale fornito motivando tale scelta e proporre almeno due ulteriori prove sperimentali per validare la scelta effettuata.

*Reference solution (c).* Dilute 6.0 mL of *ammonium standard solution (100 ppm $NH_4$) R* to 50.0 mL with solution A. Dilute 1.0 mL of this solution to 100.0 mL with solution A.

*Reference solution (d).* Dissolve 30 mg of *isoleucine R* (impurity D) and 30 mg of *leucine R* in solution A and dilute to 50.0 mL with solution A. Dilute 1.0 mL of the solution to 200.0 mL with solution A.

*Blank solution*: solution A.

Inject suitable, equal amounts of the test, blank and reference solutions into the amino acid analyser. Run a program suitable for the determination of physiological amino acids.

*System suitability*: reference solution (d):

- *resolution*: minimum 1.5 between the peaks due to impurity D and leucine.

*Calculation of percentage contents*:

- for any ninhydrin-positive substance detected at 570 nm, use the concentration of threonine in reference solution (a);
- for any ninhydrin-positive substance detected at 440 nm, use the concentration of proline in reference solution (b); if a peak is above the reporting threshold at both wavelengths, use the result obtained at 570 nm for quantification.

*Limits*:

- *any ninhydrin-positive substance*: for each impurity, maximum 0.2 per cent;
- *total*: maximum 0.5 per cent;
- *reporting threshold*: 0.05 per cent.

The thresholds indicated under Related substances (Table 2034.-1) in the general monograph *Substances for pharmaceutical use (2034)* do not apply.

**Chlorides** (*2.4.4*): maximum 200 ppm.

Dilute 10 mL of solution S to 15 mL with *water R*.

**Sulfates** (*2.4.13*): maximum 300 ppm.

Dissolve 0.5 g in *distilled water R* and dilute to 15 mL with the same solvent.

**Ammonium**. Amino acid analysis (*2.2.56*) as described in the test for ninhydrin-positive substances with the following modifications.

*Injection*: test solution, reference solution (c) and blank solution.

*Limit*:

- *ammonium at 570 nm*: not more than the area of the corresponding peak in the chromatogram obtained with reference solution (c) (0.02 per cent), taking into account the peak due to ammonium in the chromatogram obtained with the blank solution.

**Iron** (*2.4.9*): maximum 10 ppm.

In a separating funnel, dissolve 1.0 g in 10 mL of *dilute hydrochloric acid R*. Shake with 3 quantities, each of 10 mL, of *methyl isobutyl ketone R1*, shaking for 3 min each time. To the combined organic layers add 10 mL of *water R* and shake for 3 min. Use the aqueous layer.

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

0.5 g complies with test G. Prepare the reference solution using 0.5 mL of *lead standard solution (10 ppm Pb) R*.

**Loss on drying** (*2.2.32*): maximum 0.5 per cent, determined on 1.000 g by drying in an oven at 105 °C.

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

ASSAY

Dissolve 0.100 g in 5 mL of *anhydrous formic acid R*. Add 30 mL of *anhydrous acetic acid R*. Titrate with *0.1 M perchloric acid*, determining the end-point potentiometrically (*2.2.20*).

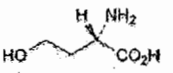
1 mL of *0.1 M perchloric acid* is equivalent to 11.91 mg of $C_4H_9NO_3$.

STORAGE

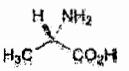
Protected from light.

IMPURITIES

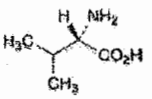
*Other detectable impurities* (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities. It is therefore not necessary to identify these impurities for demonstration of compliance. See also *5.10. Control of impurities in substances for pharmaceutical use*): *A, B, C, D, E*.



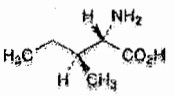
A. (2*S*)-2-amino-4-hydroxybutanoic acid (homoserine),



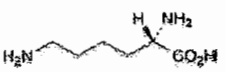
B. (2*S*)-2-aminopropanoic acid (alanine),



C. (2*S*)-2-amino-3-methylbutanoic acid (valine),



D. (2*S*,3*S*)-2-amino-3-methylpentanoic acid (isoleucine),

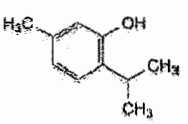


E. (2*S*)-2,6-diaminohexanoic acid (lysine).

**01/2008:0791**

# THYMOL

## Thymolum



$C_{10}H_{14}O$ $M_r$ 150.2

[89-83-8]

DEFINITION

5-Methyl-2-(methylethyl)phenol.

CHARACTERS

*Appearance*: colourless crystals.

*Solubility*: very slightly soluble in water, very soluble in ethanol (96 per cent), freely soluble in essential oils and in fatty oils, sparingly soluble in glycerol. It dissolves in dilute solutions of alkali hydroxides.

IDENTIFICATION

*First identification*: *B*.

*Second identification*: *A, C, D*.

A. Melting point (*2.2.14*): 48 °C to 52 °C.

B. Infrared absorption spectrophotometry (*2.2.24*).

*Comparison*: *thymol CRS*.

C. Dissolve 0.2 g with heating in 2 mL of *dilute sodium hydroxide solution R* and add 0.2 mL of *chloroform R*. Heat on a water-bath. A violet colour develops.

D. Dissolve about 2 mg in 1 mL of *anhydrous acetic acid R*. Add 0.15 mL of *sulfuric acid R* and 0.05 mL of *nitric acid R*. A bluish-green colour develops.

TESTS

**Appearance of solution**. The solution is not more opalescent than reference suspension IV (*2.2.1*) and not more intensely coloured than reference solution $R_6$ (*2.2.2, Method II*).

Dissolve 1.0 g in 10 mL of *dilute sodium hydroxide solution R*.

**Acidity**. To 1.0 g in a 100 mL glass-stoppered conical flask add 20 mL of *water R*. Boil until dissolution is complete, cool and stopper the flask. Shake vigorously for 1 min. Add a few crystals of the substance to be examined to initiate crystallisation. Shake vigorously for 1 min and filter. To 5 mL of the filtrate add 0.05 mL of *methyl red solution R* and 0.05 mL of *0.01 M sodium hydroxide*. The solution is yellow.

**Related substances**. Gas chromatography (*2.2.28*).

*Test solution*. Dissolve 0.100 g of the substance to be examined in *ethanol (96 per cent) R* and dilute to 10.0 mL with the same solvent.

*Reference solution (a)*. Dilute 1 mL of the test solution to 100 mL with *ethanol (96 per cent) R*.

*Reference solution (b)*. Dilute 1 mL of reference solution (a) to 10 mL with *ethanol (96 per cent) R*.

*Reference solution (c)*. Dilute 5 mL of reference solution (b) to 10 mL with *ethanol (96 per cent) R*.

*Column*:

- *material*: glass or steel;
- *size*: $l$ = 4 m, Ø = 2 mm;
- *stationary phase*: *diatomaceous earth for gas chromatography R*, impregnated with a mixture suitable for the separation of free fatty acids.

*Carrier gas*: *nitrogen for chromatography R*.

*Flow rate*: 30 mL/min.

*Temperature*:

| | Time (min) | Temperature (°C) |
|---|---|---|
| Column | 0 - 2 | 80 |
| | 2 - 22 | 80 → 240 |
| | 22 - 37 | 240 |
| Injection port | | 250 |
| Detector | | 300 |

*Detection*: flame ionisation.

*Injection*: 1 µL.

*System suitability*: reference solution (b):

- *signal-to-noise ratio*: minimum 5 for the principal peak.

*Limits*:

- *total*: not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (1.0 per cent);
- *disregard limit*: the area of the principal peak in the chromatogram obtained with reference solution (c) (0.05 per cent).

**Residue on evaporation**: maximum 0.05 per cent.

Evaporate 2.00 g on a water-bath and heat in an oven at 100-105 °C for 1 h. The residue weighs not more than 1.0 mg.

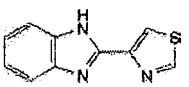
STORAGE

Protected from light.

01/2008:0866

# TIABENDAZOLE

## Tiabendazolum



$C_{10}H_7N_3S$ $M_r$ 201.2
[148-79-8]

DEFINITION

Tiabendazole contains not less than 98.0 per cent and not more than the equivalent of 101.0 per cent of 2-(thiazol-4-yl)-1*H*-benzimidazole, calculated with reference to the anhydrous substance.

CHARACTERS

A white or almost white, crystalline powder, practically insoluble in water, slightly soluble in alcohol and in methylene chloride. It dissolves in dilute mineral acids. It melts at about 300 °C.

IDENTIFICATION

*First identification*: B.

*Second identification*: A, C, D.

A. Dissolve 25 mg in *0.1 M hydrochloric acid* and dilute to 100.0 mL with the same acid. Dilute 2.0 mL of the solution to 100.0 mL with *0.1 M hydrochloric acid*. Examined between 230 nm and 350 nm (*2.2.25*), the solution shows two absorption maxima, at 243 nm and 302 nm. The ratio of the absorbance measured at the maximum at 302 nm to that measured at the maximum at 243 nm is 1.8 to 2.1.

B. Examine by infrared absorption spectrophotometry (*2.2.24*), comparing with the spectrum obtained with *tiabendazole CRS*. Examine the substances prepared as discs.

C. Examine the chromatograms obtained in the test for related substances in ultraviolet light at 254 nm. The principal spot in the chromatogram obtained with test solution (b) is similar in position and size to the principal spot in the chromatogram obtained with reference solution (a).

D. Dissolve about 5 mg in *0.1 M hydrochloric acid* and dilute to 5 mL with the same acid. Add 3 mg of *p-phenylenediamine dihydrochloride R* and shake until dissolved. Add 0.1 g of *zinc powder R*, mix, allow to stand for 2 min and add 5 mL of *ferric ammonium sulfate solution R2*. A bluish-violet colour develops.

TESTS

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

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

*Test solution (b)*. Dilute 2 mL of test solution (a) to 20 mL with *methanol R*.

*Reference solution (a)*. Dissolve 20 mg of *tiabendazole CRS* in *methanol R* and dilute to 20 mL with the same solvent.

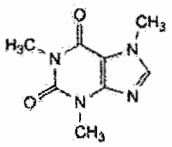
*Reference solution (b)*. Dilute 1 mL of test solution (b) to 10 mL with *methanol R*.

*Reference solution (c)*. Dilute 1 mL of test solution (b) to 25 mL with *methanol R*.

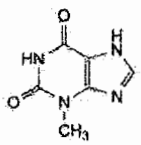
Apply separately to the plate 20 µL of each solution. Develop over a path of 15 cm using a mixture of 2.5 volumes of *water R*, 10 volumes of *acetone R*, 25 volumes of *glacial acetic acid R* and 62.5 volumes of *toluene R*. Allow the plate to dry in air and examine in ultraviolet light at 254 nm. Any spot in the chromatogram obtained with test solution (a), apart from

IMPURITIES

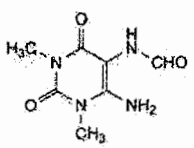
*Other detectable impurities* (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph *Substances for pharmaceutical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



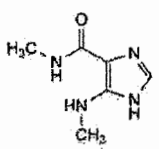
A. 1,3,7-trimethyl-3,7-dihydro-1*H*-purine-2,6-dione (caffeine),



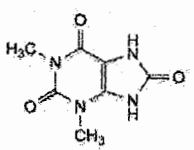
B. 3-methyl-3,7-dihydro-1*H*-purine-2,6-dione,



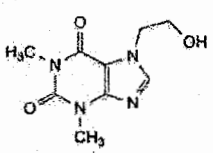
C. *N*-(6-amino-1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-5-yl)formamide,



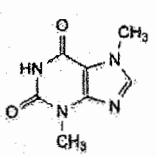
D. *N*-methyl-5-(methylamino)-1*H*-imidazole-4-carboxamide,



E. 1,3-dimethyl-7,9-dihydro-1*H*-purine-2,6,8(3*H*)-trione,



F. 7-(2-hydroxyethyl)-1,3-dimethyl-3,7-dihydro-1*H*-purine-2,6-dione (etofylline),

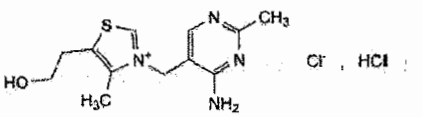


G. 3,7-dimethyl-3,7-dihydro-1*H*-purine-2,6-dione (theobromine).

01/2016:0303

# THIAMINE HYDROCHLORIDE

## Thiamini hydrochloridum



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

DEFINITION

3-[(4-Amino-2-methylpyrimidin-5-yl)methyl]-5-(2-hydroxyethyl)-4-methyl-1,3-thiazol-3-ium chloride hydrochloride.

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

CHARACTERS

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

*Solubility*: freely soluble in water, soluble in glycerol, slightly soluble in ethanol (96 per cent), practically insoluble in heptane.

IDENTIFICATION

*First identification*: A, C.

*Second identification*: B, C.

A. Infrared absorption spectrophotometry (*2.2.24*).

*Comparison*: *thiamine hydrochloride CRS*.

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

B. Dissolve about 20 mg in 10 mL of *water R*, add 1 mL of *dilute acetic acid R* and 1.6 mL of *1 M sodium hydroxide*, heat on a water-bath for 30 min and allow to cool. Add 5 mL of *dilute sodium hydroxide solution R*, 10 mL of *potassium ferricyanide solution R* and 10 mL of *butanol R* and shake vigorously for 2 min. The upper alcoholic layer shows an intense light-blue fluorescence, especially in ultraviolet light at 365 nm. Repeat the test using 0.9 mL of *1 M sodium hydroxide* and 0.1 g of *anhydrous sodium sulfite R* instead of 1.6 mL of *1 M sodium hydroxide*. Practically no fluorescence is seen.

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

TESTS

**Solution S**. Dissolve 2.5 g in *carbon dioxide-free water R* and dilute to 25 mL with the same solvent.

**Appearance of solution**. The solution is clear (*2.2.1*) and not more intensely coloured than reference solution $Y_7$ or $GY_7$ (*2.2.2. Method II*).

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

**pH** (*2.2.3*): 2.7 to 3.3.

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

**Related substances**. Liquid chromatography (*2.2.29*).

*Test solution*. Dissolve 0.35 g of the substance to be examined in 15.0 mL of a 5 per cent *V/V* solution of *glacial acetic acid R* and dilute to 100.0 mL with *water R*.

*Reference solution (a)*. Dissolve the contents of a vial of *thiamine for system suitability CRS* (containing impurities A, B and C) in 1.0 mL of a 0.75 per cent *V/V* solution of *glacial acetic acid R*.

*Reference solution (b)*. Dilute 1.0 mL of the test solution to 100.0 mL with *water R*. Dilute 1.0 mL of this solution to 10.0 mL with *water R*.

*Column*:

- *size*: *l* = 0.25 m, Ø = 4.0 mm;
- *stationary phase*: *end-capped octadecylsilyl silica gel for chromatography R* (5 µm);
- *temperature*: 45 °C.

*Mobile phase*:

- *mobile phase A*: 3.764 g/L solution of *sodium hexanesulfonate R* adjusted to pH 3.1 with *phosphoric acid R*;
- *mobile phase B*: *methanol R2*;

| Time (min) | Mobile phase A (per cent *V/V*) | Mobile phase B (per cent *V/V*) |
|---|---|---|
| 0 - 2 | 90 | 10 |
| 2 - 27 | 90 → 70 | 10 → 30 |
| 27 - 35 | 70 → 50 | 30 → 50 |
| 35 - 42 | 50 | 50 |

*Flow rate*: 1.0 mL/min.

*Detection*: spectrophotometer at 248 nm.

*Injection*: 25 µL.

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

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

*System suitability*: reference solution (a):

- *resolution*: minimum 3.0 between the peaks due to impurity B and thiamine; minimum 2.0 between the peaks due to thiamine and impurity C.

*Calculation of percentage contents*:

- for each impurity, use the concentration of thiamine in reference solution (b).

*Limits*:

- *impurity B*: maximum 0.3 per cent;
- *impurities A, C*: for each impurity, maximum 0.15 per cent;
- *unspecified impurities*: for each impurity, maximum 0.10 per cent;
- *total*: maximum 0.5 per cent;
- *reporting threshold*: 0.05 per cent.

**Sulfates** (*2.4.13*): maximum 300 ppm.

Dilute 5 mL of solution S to 15 mL with *distilled water R*.

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

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

**Water** (*2.5.12*): maximum 5.0 per cent, determined on 0.400 g.

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

ASSAY

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

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

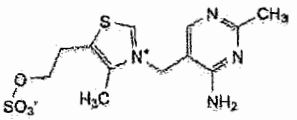
STORAGE

In a non-metallic container, protected from light.

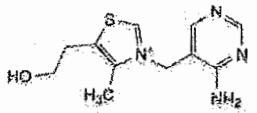
IMPURITIES

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

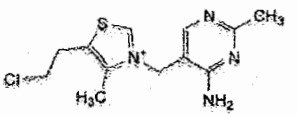
*Other detectable impurities* (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph *Substances for pharmaceutical use (2034)*. It is therefore not necessary to identify these impurities for demonstration of compliance. See also *5.10. Control of impurities in substances for pharmaceutical use*): *D, E, F, G, H.*



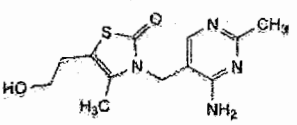
A. 2-[3-[(4-amino-2-methylpyrimidin-5-yl)methyl]-4-methyl-1,3-thiazol-3-ium-5-yl]ethyl sulfate (thiamine sulfate ester),



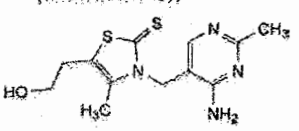
B. 3-[(4-aminopyrimidin-5-yl)methyl]-5-(2-hydroxyethyl)-4-methyl-1,3-thiazol-3-ium (desmethylthiamine),



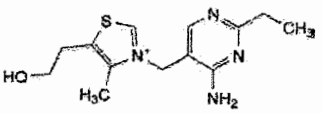
C. 3-[(4-amino-2-methylpyrimidin-5-yl)methyl]-5-(2-chloroethyl)-4-methyl-1,3-thiazol-3-ium (chlorothiamine),



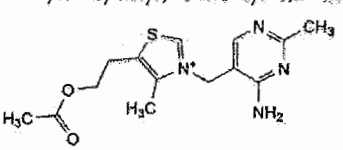
D. 3-[(4-amino-2-methylpyrimidin-5-yl)methyl]-5-(2-hydroxyethyl)-4-methyl-1,3-thiazol-2(3*H*)-one (oxothiamine),



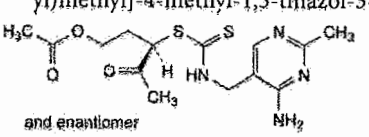
E. 3-[(4-amino-2-methylpyrimidin-5-yl)methyl]-5-(2-hydroxyethyl)-4-methyl-1,3-thiazol-2(3*H*)-thione (thioxothiamine),



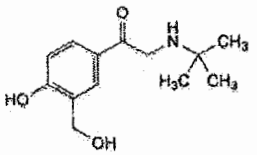
F. 3-[(4-amino-2-ethylpyrimidin-5-yl)methyl]-5-(2-hydroxyethyl)-4-methyl-1,3-thiazol-3-ium (ethylthiamine),



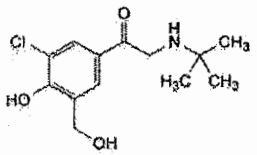
G. 5-[2-(acetyloxy)ethyl]-3-[(4-amino-2-methylpyrimidin-5-yl)methyl]-4-methyl-1,3-thiazol-3-ium (acetylthiamine),



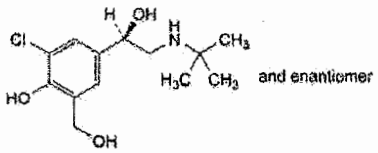

H. (3*RS*)-3-[[[(4-amino-2-methylpyrimidin-5-yl)methyl]thiocarbamoyl]sulfanyl]-4-oxopentyl acetate (ketodithiocarbamate).



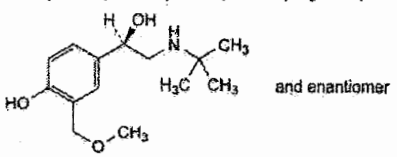
J. 2-[(1,1-dimethylethyl)amino]-1-[4-hydroxy-3-(hydroxymethyl)phenyl]ethanone (salbutamone),



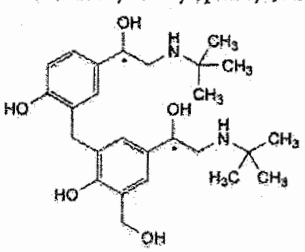
K. 2-[(1,1-dimethylethyl)amino]-1-[3-chloro-4-hydroxy-5-(hydroxymethyl)phenyl]ethanone,




L. (1*RS*)-2-[(1,1-dimethylethyl)amino]-1-[3-chloro-4-hydroxy-5-(hydroxymethyl)phenyl]ethanol,




M. (1*RS*)-2-[(1,1-dimethylethyl)amino]-1-[4-hydroxy-3-(methoxymethyl)phenyl]ethanol,



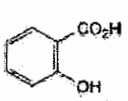
N. 2-[(1,1-dimethylethyl)amino]-1-[3-[[5-[2-[(1,1-dimethylethyl)amino]-1-hydroxyethyl]-2-hydroxyphenyl]methyl]-4-hydroxy-5-(hydroxymethyl)phenyl]ethanol,

O. unknown structure.

**01/2008:0366**
**corrected 6.0**

# SALICYLIC ACID

## Acidum salicylicum



$C_7H_6O_3$ $M_r$ 138.1
[69-72-7]

DEFINITION

2-Hydroxybenzenecarboxylic acid.

*Content*: 99.0 per cent to 100.5 per cent (dried substance).

CHARACTERS

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

*Solubility*: slightly soluble in water, freely soluble in ethanol (96 per cent), sparingly soluble in methylene chloride.

IDENTIFICATION

*First identification*: A, B.

*Second identification*: A, C.

A. Melting point (*2.2.14*): 158 °C to 161 °C.

B. Infrared absorption spectrophotometry (*2.2.24*).
*Comparison*: *salicylic acid CRS*.

C. Dissolve about 30 mg in 5 mL of *0.05 M sodium hydroxide*, neutralise if necessary and dilute to 20 mL with *water R*. 1 mL of the solution gives reaction (a) of salicylates (*2.3.1*).

TESTS

**Solution S**. Dissolve 2.5 g in 50 mL of boiling *distilled water R*, cool and filter.

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

Dissolve 1 g in 10 mL of *ethanol (96 per cent) R*.

**Related substances**. Liquid chromatography (*2.2.29*).

*Test solution*. Dissolve 0.50 g of the substance to be examined in the mobile phase and dilute to 100.0 mL with the mobile phase.

*Reference solution (a)*. Dissolve 10 mg of *phenol R* (impurity C) in the mobile phase and dilute to 100.0 mL with the mobile phase.

*Reference solution (b)*. Dissolve 5 mg of *salicylic acid impurity B CRS* in the mobile phase and dilute to 20.0 mL with the mobile phase.

*Reference solution (c)*. Dissolve 50 mg of *4-hydroxybenzoic acid R* (impurity A) in the mobile phase and dilute to 100.0 mL with the mobile phase.

*Reference solution (d)*. Dilute 1.0 mL of reference solution (a) to 10.0 mL with the mobile phase.

*Reference solution (e)*. Dilute a mixture of 1.0 mL of each of reference solutions (a), (b) and (c) to 10.0 mL with the mobile phase.

*Reference solution (f)*. Dilute a mixture of 0.1 mL of each of reference solutions (a), (b) and (c) to 10.0 mL with the mobile phase.

*Column*:

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

*Mobile phase*: *glacial acetic acid R, methanol R, water R* (1:40:60 *V/V/V*).

*Flow rate*: 0.5 mL/min.

*Detection*: spectrophotometer at 270 nm.

*Injection*: 10 µL of the test solution and reference solutions (d), (e) and (f).

*Relative retention* with reference to impurity C: impurity A = about 0.70; impurity B = about 0.90.

*System suitability*: reference solution (e):

- the 3rd peak in the chromatogram corresponds to the peak due to phenol in the chromatogram obtained with reference solution (d);
- *resolution*: minimum 1.0 between the peaks due to impurities B and C; if necessary, adjust the quantity of acetic acid in the mobile phase.

*Limits*:

- *impurity A*: not more than the area of the corresponding peak in the chromatogram obtained with reference solution (f) (0.1 per cent);
- *impurity B*: not more than the area of the corresponding peak in the chromatogram obtained with reference solution (f) (0.05 per cent);

- *impurity C*: not more than the area of the corresponding peak in the chromatogram obtained with reference solution (f) (0.02 per cent);
- *any other impurity*: for each impurity, not more than the area of the peak due to impurity B in the chromatogram obtained with reference solution (f) (0.05 per cent);
- *total*: not more than twice the area of the peak due to impurity A in the chromatogram obtained with reference solution (f) (0.2 per cent);
- *disregard limit*: 0.01 times the area of the principal peak in the chromatogram obtained with reference solution (f).

**Chlorides** (*2.4.4*): maximum 100 ppm.

Dilute 10 mL of solution S to 15 mL with *water R*.

**Sulfates**: maximum 200 ppm.

Dissolve 1.0 g in 5 mL of *dimethylformamide R* and add 4 mL of *water R*. Mix thoroughly. Add 0.2 mL of *dilute hydrochloric acid R* and 0.5 mL of a 25 per cent *m/m* solution of *barium chloride R*. After 15 min any opalescence in the solution is not more intense than that in a standard prepared as follows: to 2 mL of *sulfate standard solution (100 ppm $SO_4$) R* add 0.2 mL of *dilute hydrochloric acid R*, 0.5 mL of a 25 per cent *m/m* solution of *barium chloride R*, 3 mL of *water R* and 5 mL of *dimethylformamide R*.

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

Dissolve 2.0 g in 15 mL of *ethanol (96 per cent) R* and add 5 mL of *water R*. 12 mL of the solution complies with test B. Prepare the reference solution using lead standard solution (2 ppm Pb) prepared by diluting *lead standard solution (100 ppm Pb) R* with a mixture of 5 volumes of *water R* and 15 volumes of *ethanol (96 per cent) R*.

**Loss on drying** (*2.2.32*): maximum 0.5 per cent, determined on 1.000 g by drying in a desiccator.

**Sulfated ash** (*2.4.14*): maximum 0.1 per cent, determined on 2.0 g.

## ASSAY

Dissolve 0.120 g in 30 mL of *ethanol (96 per cent) R* and add 20 mL of *water R*. Titrate with *0.1 M sodium hydroxide*, using 0.1 mL of *phenol red solution R* as indicator.

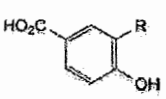
1 mL of *0.1 M sodium hydroxide* is equivalent to 13.81 mg of $C_7H_6O_3$.

## STORAGE

Protected from light.

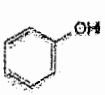
## IMPURITIES

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




A. R = H: 4-hydroxybenzoic acid,

B. R = $CO_2H$: 4-hydroxyisophthalic acid,

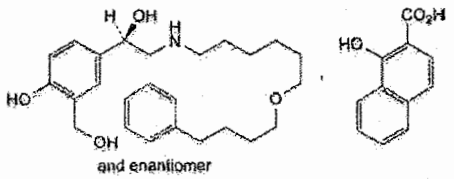



C. phenol.

**01/2008:1765**

# SALMETEROL XINAFOATE

## Salmeteroli xinafoas




$C_{36}H_{45}NO_7$ $M_r$ 604

[94749-08-3]

## DEFINITION

(1*RS*)-1-[4-Hydroxy-3-(hydroxymethyl)phenyl]-2-[[6-(4-phenylbutoxy)hexyl]amino]ethanol 1-hydroxynaphthalene-2-carboxylate.

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

## CHARACTERS

*Appearance*: white or almost white powder.

*Solubility*: practically insoluble in water, soluble in methanol, slightly soluble in anhydrous ethanol.

## IDENTIFICATION

Infrared absorption spectrophotometry (*2.2.24*).

*Comparison*: *salmeterol xinafoate CRS*.

## TESTS

**Related substances**. Liquid chromatography (*2.2.29*). *Protect the solutions from light.*

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

*Test solution*. Dissolve 50.0 mg of the substance to be examined in the solvent mixture and dilute to 10.0 mL with the solvent mixture.

*Reference solution (a)*. Dissolve 11 mg of *salmeterol xinafoate for system suitability CRS* (salmeterol containing impurities E and G) in the solvent mixture and dilute to 2 mL with the solvent mixture.

*Reference solution (b)*. 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.

*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 24 volumes of a 7.71 g/L solution of *ammonium acetate R* with 24 volumes of a 28.84 g/L solution of *sodium dodecyl sulfate R* and adjust to pH 2.7 with *glacial acetic acid R*; mix with 52 volumes of *acetonitrile R*;
- *mobile phase B*: *acetonitrile R*;

| Time (min) | Mobile phase A (per cent *V/V*) | Mobile phase B (per cent *V/V*) |
|---|---|---|
| 0 - 16 | 100 | 0 |
| 16 - 36 | 100 → 30 | 0 → 70 |
| 36 - 45 | 30 | 70 |
| 45 - 50 | 30 → 100 | 70 → 0 |

*Flow rate*: 2 mL/min.

*Detection*: spectrophotometer at 278 nm.

*Injection*: 20 µL; inject the solvent mixture as a blank solution.

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

ASSAY

Dissolve 0.200 g in 5 mL of *alcohol R* and add 20.0 mL of *0.1 M hydrochloric acid*. Using 0.05 mL of *methyl red solution R* as indicator, titrate with *0.1 M sodium hydroxide* until a yellow colour is obtained.

1 mL of *0.1 M hydrochloric acid* is equivalent to 16.52 mg of $C_{10}H_{15}NO$.

STORAGE

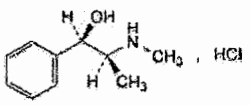
Store protected from light.

**01/2008:0487**
**corrected 6.0**

Monographs D-E

# EPHEDRINE HYDROCHLORIDE

## Ephedrini hydrochloridum




$C_{10}H_{16}ClNO$ $M_r$ 201.7
[50-98-6]

DEFINITION

(1*R*,2*S*)-2-(Methylamino)-1-phenylpropan-1-ol hydrochloride.

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

CHARACTERS

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

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

mp: about 219 °C.

IDENTIFICATION

*First identification*: *B, E.*

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

A. Specific optical rotation (see Tests).

B. Infrared absorption spectrophotometry (*2.2.24*).

*Comparison*: *ephedrine hydrochloride CRS.*

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

*Test solution.* Dissolve 20 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 *ephedrine hydrochloride CRS* in *methanol R* and dilute to 5 mL with the same solvent.

*Plate*: *TLC silica gel plate R.*

*Mobile phase*: *methylene chloride R, concentrated ammonia R, 2-propanol R* (5:15:80 *V/V/V*).

*Application*: 10 µL.

*Development*: over 2/3 of the plate.

*Drying*: in air.

*Detection*: spray with *ninhydrin solution R*; heat at 110 °C for 5 min.

*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.

D. To 0.1 mL of solution S (see Tests) add 1 mL of *water R*, 0.2 mL of *copper sulfate solution R* and 1 mL of *strong sodium hydroxide solution R*. A violet colour is produced. Add 2 mL of *methylene chloride R* and shake. The lower (organic) layer is dark grey and the upper (aqueous) layer is blue.

E. To 5 mL of solution S (see Tests) add 5 mL of *water R*. The solution gives reaction (a) of chlorides (*2.3.1*).

TESTS

**Solution S.** Dissolve 5.00 g in *distilled water R* and dilute to 50.0 mL with the same solvent.

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

**Acidity or alkalinity.** To 10 mL of solution S add 0.1 mL of *methyl red solution R* and 0.2 mL of *0.01 M sodium hydroxide*. The solution is yellow. Add 0.4 mL of *0.01 M hydrochloric acid*. The solution is red.

**Specific optical rotation** (*2.2.7*): − 33.5 to − 35.5 (dried substance).

Dilute 12.5 mL of solution S to 25.0 mL with *water R*.

**Related substances.** Liquid chromatography (*2.2.29*).

*Test solution.* Dissolve 75 mg of the substance to be examined in the mobile phase and dilute to 10 mL with the mobile phase.

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

*Reference solution (b).* Dissolve 5 mg of the substance to be examined and 5 mg of *pseudoephedrine hydrochloride CRS* in the mobile phase and dilute to 50 mL with the mobile phase.

*Column*:

- *size*: *l* = 0.15 m, Ø = 4.6 mm;
- *stationary phase*: spherical *phenylsilyl silica gel for chromatography R* (3 µm).

*Mobile phase*: mix 6 volumes of *methanol R* and 94 volumes of a 11.6 g/L solution of *ammonium acetate R* adjusted to pH 4.0 with *glacial acetic acid R*.

*Flow rate*: 1.0 mL/min.

*Detection*: spectrophotometer at 257 nm.

*Injection*: 20 µL.

*Run time*: 2.5 times the retention time of ephedrine.

*Relative retention* with reference to ephedrine (retention time = about 8 min): impurity B = about 1.1; impurity A = about 1.4.

*System suitability*: reference solution (b):

- *resolution*: minimum 2.0 between the peaks due to ephedrine and impurity B.

*Limits*:

- *correction factor*: for the calculation of content, multiply the peak area of impurity A by 0.4;
- *impurity A*: 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) (0.1 per cent);
- *sum of impurities other than A*: not more than 2.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.5 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).

**Sulfates** (*2.4.13*): maximum 100 ppm, determined on solution S.

**Loss on drying** (*2.2.32*): maximum 0.5 per cent, determined on 1.000 g by drying in an oven at 105 °C.

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

ASSAY

Dissolve 0.150 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 20.17 mg of $C_{10}H_{16}ClNO$.

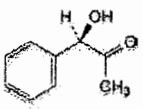
STORAGE

Protected from light.

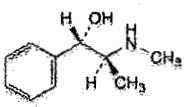
IMPURITIES

*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.



A. (−)-(1*R*)-1-hydroxy-1-phenylpropan-2-one,

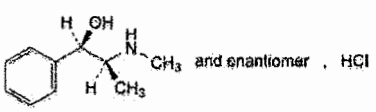


B. (1*S*,2*S*)-2-(methylamino)-1-phenylpropan-1-ol (pseudoephedrine).

**01/2008:0715 corrected 6.0**

# EPHEDRINE HYDROCHLORIDE, RACEMIC

## Ephedrini racemici hydrochloridum




$C_{10}H_{16}ClNO$ $M_r$ 201.7
[134-71-4]

DEFINITION

Racemic ephedrine hydrochloride contains not less than 99.0 per cent and not more than the equivalent of 101.0 per cent of (1*RS*,2*SR*)-2-(methylamino)-1-phenylpropan-1-ol hydrochloride, calculated with reference to the dried substance.

CHARACTERS

A white or almost white, crystalline powder or colourless crystals, freely soluble in water, soluble in ethanol (96 per cent).

It melts at about 188 °C.

IDENTIFICATION

*First identification*: B, E.

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

A. Optical rotation (see Tests).

B. Examine by infrared absorption spectrophotometry (*2.2.24*), comparing with the spectrum obtained with *racemic ephedrine hydrochloride CRS*. Examine the substances prepared as discs.

C. Examine the chromatograms obtained in the test for related substances. The principal spot in the chromatogram obtained with test solution (b) is similar in position, colour and size to the principal spot in the chromatogram obtained with reference solution (a).

D. To 0.1 mL of solution S (see Tests) add 1 mL of *water R*, 0.2 mL of *copper sulfate solution R* and 1 mL of *strong sodium hydroxide solution R*. A violet colour is produced. Add 2 mL of *ether R* and shake. The ether layer is purple and the aqueous layer is blue.

E. To 5 mL of solution S add 5 mL of *water R*. The solution gives reaction (a) of chlorides (*2.3.1*).

TESTS

**Solution S**. Dissolve 5.00 g in *distilled water R* and dilute to 50.0 mL with the same solvent.

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

**Acidity or alkalinity**. To 10 mL of solution S add 0.1 mL of *methyl red solution R* and 0.1 mL of *0.01 M sodium hydroxide*; the solution is yellow. Add 0.2 mL of *0.01 M hydrochloric acid*; the solution is red.

**Optical rotation** (*2.2.7*): + 0.2° to − 0.2°, determined on solution S.

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

*Test solution (a)*. Dissolve 0.20 g of the substance to be examined in *methanol R* and dilute to 10 mL with the same solvent.

*Test solution (b)*. Dilute 1 mL of test solution (a) to 10 mL with *methanol R*.

*Reference solution (a)*. Dissolve 20 mg of *racemic ephedrine hydrochloride CRS* in *methanol R* and dilute to 10 mL with the same solvent.

*Reference solution (b)*. Dilute 1 mL of test solution (a) to 200 mL with *methanol R*.

Apply separately to the plate 10 µL of each solution. Develop over a path of 15 cm using a mixture of 5 volumes of *chloroform R*, 15 volumes of *concentrated ammonia R* and 80 volumes of *2-propanol R*. Allow the plate to dry in air. Spray with *ninhydrin solution R* and heat at 110 °C for 5 min. Any spot in the chromatogram obtained with test solution (a), apart from the principal spot, is not more intense than the spot in the chromatogram obtained with reference solution (b) (0.5 per cent). Disregard any spot of lighter colour than the background.

**Sulfates** (*2.4.13*). 15 mL of solution S complies with the limit test for sulfates (100 ppm).

**Loss on drying** (*2.2.32*). Not more than 0.5 per cent, determined on 1.000 g by drying in an oven at 105 °C.

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

ASSAY

Dissolve 0.170 g in 30 mL of *ethanol (96 per cent) R*. 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 two points of inflexion.

1 mL of *0.1 M sodium hydroxide* corresponds to 20.17 mg of $C_{10}H_{16}ClNO$.

STORAGE

Store protected from light.

# 2.3. IDENTIFICATION

01/2008:20301

## 2.3.1. IDENTIFICATION REACTIONS OF IONS AND FUNCTIONAL GROUPS

ACETATES

a) Heat the substance to be examined with an equal quantity of *oxalic acid R*. Acid vapours with the characteristic odour of acetic acid are liberated, showing an acid reaction (*2.2.4*).

b) Dissolve about 30 mg of the substance to be examined in 3 mL of *water R* or use 3 mL of the prescribed solution. Add successively 0.25 mL of *lanthanum nitrate solution R*, 0.1 mL of *0.05 M iodine* and 0.05 mL of *dilute ammonia R2*. Heat carefully to boiling. Within a few minutes a blue precipitate is formed or a dark blue colour develops.

ACETYL

In a test-tube about 180 mm long and 18 mm in external diameter, place about 15 mg of the substance to be examined, or the prescribed quantity, and 0.15 mL of *phosphoric acid R*. Close the tube with a stopper through which passes a small test-tube about 100 mm long and 10 mm in external diameter containing *water R* to act as a condenser. On the outside of the smaller tube, hang a drop of *lanthanum nitrate solution R*. Except for substances hydrolysable only with difficulty, place the apparatus in a water-bath for 5 min, then take out the smaller tube. Remove the drop and mix it with 0.05 mL of *0.01 M iodine* on a tile. Add at the edge 0.05 mL of *dilute ammonia R2*. After 1 min to 2 min, a blue colour develops at the junction of the two drops; the colour intensifies and persists for a short time.

For *substances hydrolysable only with difficulty* heat the mixture slowly to boiling over an open flame and then proceed as prescribed above.

ALKALOIDS

Dissolve a few milligrams of the substance to be examined, or the prescribed quantity, in 5 mL of *water R*, add *dilute hydrochloric acid R* until an acid reaction occurs (*2.2.4*), then 1 mL of *potassium iodobismuthate solution R*. An orange or orange-red precipitate is formed immediately.

ALUMINIUM

Dissolve about 15 mg of the substance to be examined in 2 mL of *water R* or use 2 mL of the prescribed solution. Add about 0.5 mL of *dilute hydrochloric acid R* and about 0.5 mL of *thioacetamide reagent R*. No precipitate is formed. Add dropwise *dilute sodium hydroxide solution R*. A gelatinous white precipitate is formed which dissolves on further addition of *dilute sodium hydroxide solution R*. Gradually add *ammonium chloride solution R*. The gelatinous white precipitate is re-formed.

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 *β-naphthol solution R*. An intense orange or red colour and usually a precipitate of the same colour are produced.

AMMONIUM SALTS

To the prescribed solution add 0.2 g of *magnesium oxide R*. Pass a current of air through the mixture and direct the gas that escapes just beneath the surface of a mixture of 1 mL of *0.1 M hydrochloric acid* and 0.05 mL of *methyl red solution R*. The colour of the indicator changes to yellow. On addition of 1 mL of a freshly prepared 100 g/L solution of *sodium cobaltinitrite R* a yellow precipitate is formed.

AMMONIUM SALTS AND SALTS OF VOLATILE BASES

Dissolve about 20 mg of the substance to be examined in 2 mL of *water R* or use 2 mL of the prescribed solution. Add 2 mL of *dilute sodium hydroxide solution R*. On heating, the solution gives off vapour that can be identified by its odour and by its alkaline reaction (*2.2.4*).

ANTIMONY

Dissolve with gentle heating about 10 mg of the substance to be examined in a solution of 0.5 g of *sodium potassium tartrate R* in 10 mL of *water R* and allow to cool: to 2 mL of this solution, or to 2 mL of the prescribed solution, add *sodium sulfide solution R* dropwise; an orange-red precipitate is formed which dissolves on addition of *dilute sodium hydroxide solution R*.

ARSENIC

Heat 5 mL of the prescribed solution on a water-bath with an equal volume of *hypophosphorous reagent R*. A brown precipitate is formed.

BARBITURATES, NON-NITROGEN SUBSTITUTED

Dissolve about 5 mg of the substance to be examined in 3 mL of *methanol R*, add 0.1 mL of a solution containing 100 g/L of *cobalt nitrate R* and 100 g/L of *calcium chloride R*. Mix and add, with shaking, 0.1 mL of *dilute sodium hydroxide solution R*. A violet-blue colour and precipitate are formed.

BENZOATES

a) To 1 mL of the prescribed solution add 0.5 mL of *ferric chloride solution R1*. A dull-yellow precipitate, soluble in *ether R*, is formed.

b) Place 0.2 g of the substance to be examined, treated if necessary as prescribed, in a test-tube. Moisten with 0.2 mL to 0.3 mL of *sulfuric acid R*. Gently warm the bottom of the tube. A white sublimate is deposited on the inner wall of the tube.

c) Dissolve 0.5 g of the substance to be examined in 10 mL of *water R* or use 10 mL of the prescribed solution. Add 0.5 mL of *hydrochloric acid R*. The precipitate obtained, after crystallisation from warm *water R* and drying *in vacuo*, has a melting point (*2.2.14*) of 120 °C to 124 °C.

BISMUTH

a) To 0.5 g of the substance to be examined add 10 mL of *dilute hydrochloric acid R* or use 10 mL of the prescribed solution. Heat to boiling for 1 min. Cool and filter if necessary. To 1 mL of the solution obtained add 20 mL of *water R*. A white or slightly yellow precipitate is formed which on addition of 0.05 mL to 0.1 mL of *sodium sulfide solution R* turns brown.

b) To about 45 mg of the substance to be examined add 10 mL of *dilute nitric acid R* or use 10 mL of the prescribed solution. Boil for 1 min. Allow to cool and filter if necessary. To 5 mL of the solution obtained add 2 mL of a 100 g/L solution of *thiourea R*. A yellowish-orange colour or an orange precipitate is formed. Add 4 mL of a 25 g/L solution of *sodium fluoride R*. The solution is not decolorised within 30 min.

BROMIDES

a) Dissolve in 2 mL of *water R* a quantity of the substance to be examined equivalent to about 3 mg of bromide ($Br^-$) 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, pale yellow 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 obtained in 2 mL of *water R* and add 1.5 mL of *ammonia R*. The precipitate dissolves with difficulty.

b) Introduce into a small test-tube a quantity of the substance to be examined equivalent to about 5 mg of bromide ($Br^-$) or the prescribed quantity. Add 0.25 mL of *water R*, about 75 mg

of *lead dioxide R*, 0.25 mL of *acetic acid R* and shake gently. Dry the inside of the upper part of the test-tube with a piece of filter paper and allow to stand for 5 min. Prepare a strip of suitable filter paper of appropriate size. Impregnate it by capillarity, by dipping the tip in a drop of *decolorised fuchsin solution R* and introduce the impregnated part immediately into the tube. Starting from the tip, a violet colour appears within 10 s that is clearly distinguishable from the red colour of fuchsin, which may be visible on a small area at the top of the impregnated part of the paper strip.

CALCIUM

a) To 0.2 mL of a neutral solution containing a quantity of the substance to be examined equivalent to about 0.2 mg of calcium ($Ca^{2+}$) per millilitre or to 0.2 mL of the prescribed solution add 0.5 mL of a 2 g/L solution of *glyoxalhydroxyanil R* in *ethanol (96 per cent) R*, 0.2 mL of *dilute sodium hydroxide solution R* and 0.2 mL of *sodium carbonate solution R*. Shake with 1 mL to 2 mL of *chloroform R* and add 1 mL to 2 mL of *water R*. The chloroform layer is coloured red.

b) Dissolve about 20 mg of the substance to be examined or the prescribed quantity in 5 mL of *acetic acid R*. Add 0.5 mL of *potassium ferrocyanide solution R*. The solution remains clear. Add about 50 mg of *ammonium chloride R*. A white, crystalline precipitate is formed.

CARBONATES AND BICARBONATES

Introduce into a test-tube 0.1 g of the substance to be examined and suspend in 2 mL of *water R* or use 2 mL of the prescribed solution. Add 3 mL of *dilute acetic acid R*. Close the tube immediately using a stopper fitted with a glass tube bent twice at right angles. The solution or the suspension becomes effervescent and gives off a colourless and odourless gas. Heat gently and collect the gas in 5 mL of *barium hydroxide solution R*. A white precipitate is formed that dissolves on addition of an excess of *hydrochloric acid R1*.

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.

CITRATES

Dissolve in 5 mL of *water R* a quantity of the substance to be examined equivalent to about 50 mg of citric acid or use 5 mL of the prescribed solution. Add 0.5 mL of *sulfuric acid R* and 1 mL of *potassium permanganate solution R*. Warm until the colour of the permanganate is discharged. Add 0.5 mL of a 100 g/L solution of *sodium nitroprusside R* in *dilute sulfuric acid R* and 4 g of *sulfamic acid R*. Make alkaline with *concentrated ammonia R*, added dropwise until all the sulfamic acid has dissolved. Addition of an excess of *concentrated ammonia R* produces a violet colour, turning to violet-blue.

ESTERS

To about 30 mg of the substance to be examined or the prescribed quantity add 0.5 mL of a 70 g/L solution of *hydroxylamine hydrochloride R* in *methanol R* and 0.5 mL of a 100 g/L solution of *potassium hydroxide R* in *ethanol (96 per cent) R*. Heat to boiling, cool, acidify with *dilute hydrochloric acid R* and add 0.2 mL of *ferric chloride solution R1* diluted ten times. A bluish-red or red colour is produced.

IODIDES

a) Dissolve a quantity of the substance to be examined equivalent to about 4 mg of iodide ($I^-$) in 2 mL of *water R* 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, pale-yellow precipitate is formed. Centrifuge and wash 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 does not dissolve.

b) To 0.2 mL of a solution of the substance to be examined containing about 5 mg of iodide ($I^-$) per millilitre, or to 0.2 mL of the prescribed solution, add 0.5 mL of *dilute sulfuric acid R*, 0.1 mL of *potassium dichromate solution R*, 2 mL of *water R* and 2 mL of *chloroform R*. Shake for a few seconds and allow to stand. The chloroform layer is coloured violet or violet-red.

IRON

a) Dissolve a quantity of the substance to be examined equivalent to about 10 mg of iron ($Fe^{2+}$) in 1 mL of *water R* or use 1 mL of the prescribed solution. Add 1 mL of *potassium ferricyanide solution R*. A blue precipitate is formed that does not dissolve on addition of 5 mL of *dilute hydrochloric acid R*.

b) Dissolve a quantity of the substance to be examined equivalent to about 1 mg of iron ($Fe^{3+}$) in 30 mL of *water R*. To 3 mL of this solution or to 3 mL of the prescribed solution, add 1 mL of *dilute hydrochloric acid R* and 1 mL of *potassium thiocyanate solution R*. The solution is coloured red. Take two portions, each of 1 mL, of the mixture. To one portion add 5 mL of *isoamyl alcohol R* or 5 mL of *ether R*. Shake and allow to stand. The organic layer is coloured pink. To the other portion add 2 mL of *mercuric chloride solution R*. The red colour disappears.

c) Dissolve a quantity of the substance to be examined equivalent to not less than 1 mg of iron ($Fe^{3+}$) in 1 mL of *water R* or use 1 mL of the prescribed solution. Add 1 mL of *potassium ferrocyanide solution R*. A blue precipitate is formed that does not dissolve on addition of 5 mL of *dilute hydrochloric acid R*.

LACTATES

Dissolve a quantity of the substance to be examined equivalent to about 5 mg of lactic acid in 5 mL of *water R* or use 5 mL of the prescribed solution. Add 1 mL of *bromine water R* and 0.5 mL of *dilute sulfuric acid R*. Heat on a water-bath until the colour is discharged, stirring occasionally with a glass rod. Add 4 g of *ammonium sulfate R* and mix. Add dropwise and without mixing 0.2 mL of a 100 g/L solution of *sodium nitroprusside R* in *dilute sulfuric acid R*. Still without mixing add 1 mL of *concentrated ammonia R*. Allow to stand for 30 min. A dark green ring appears at the junction of the two liquids.

LEAD

a) Dissolve 0.1 g of the substance to be examined in 1 mL of *acetic acid R* or use 1 mL of the prescribed solution. Add 2 mL of *potassium chromate solution R*. A yellow precipitate is formed that dissolves on addition of 2 mL of *strong sodium hydroxide solution R*.

b) Dissolve 50 mg of the substance to be examined in 1 mL of *acetic acid R* or use 1 mL of the prescribed solution. Add 10 mL of *water R* and 0.2 mL of *potassium iodide solution R*. A yellow precipitate is formed. Heat to boiling for 1 min to 2 min. The precipitate dissolves. Allow to cool. The precipitate is re-formed as glistening, yellow plates.

MAGNESIUM

Dissolve about 15 mg of the substance to be examined in 2 mL of *water R* or use 2 mL of the prescribed solution. Add 1 mL of *dilute ammonia R1*. A white precipitate is formed that dissolves on addition of 1 mL of *ammonium chloride solution R*. Add 1 mL of *disodium hydrogen phosphate solution R*. A white crystalline precipitate is formed.

MERCURY

a) Place about 0.1 mL of a solution of the substance to be examined on well-scraped copper foil. A dark-grey stain that becomes shiny on rubbing is formed. Dry the foil and heat in a test-tube. The spot disappears.

b) To the prescribed solution add *dilute sodium hydroxide solution R* until strongly alkaline (*2.2.4*). A dense yellow precipitate is formed (mercuric salts).

NITRATES

To a mixture of 0.1 mL of *nitrobenzene R* and 0.2 mL of *sulfuric acid R*, add a quantity of the powdered substance equivalent to about 1 mg of nitrate ($NO_3^-$) or the prescribed quantity. Allow to stand for 5 min. Cool in iced water and add slowly and with mixing 5 mL of *water R*, then 5 mL of *strong sodium hydroxide solution R*. Add 5 mL of *acetone R*. Shake and allow to stand. The upper layer is coloured deep violet.

PHOSPHATES (ORTHOPHOSPHATES)

a) To 5 mL of the prescribed solution, neutralised if necessary, add 5 mL of *silver nitrate solution R1*. A yellow precipitate is formed whose colour is not changed by boiling and which dissolves on addition of *ammonia R*.

b) Mix 1 mL of the prescribed solution with 2 mL of *molybdovanadic reagent R*. A yellow colour develops.

POTASSIUM

a) Dissolve 0.1 g of the substance to be examined in 2 mL of *water R* or use 2 mL of the prescribed solution. Add 1 mL of *sodium carbonate solution R* and heat. No precipitate is formed. Add to the hot solution 0.05 mL of *sodium sulfide solution R*. No precipitate is formed. Cool in iced water and add 2 mL of a 150 g/L solution of *tartaric acid R*. Allow to stand. A white crystalline precipitate is formed.

b) Dissolve about 40 mg of the substance to be examined in 1 mL of *water R* or use 1 mL of the prescribed solution. Add 1 mL of *dilute acetic acid R* and 1 mL of a freshly prepared 100 g/L solution of *sodium cobaltinitrite R*. A yellow or orange-yellow precipitate is formed immediately.

SALICYLATES

a) To 1 mL of the prescribed solution add 0.5 mL of *ferric chloride solution R1*. A violet colour is produced that persists after the addition of 0.1 mL of *acetic acid R*.

b) Dissolve 0.5 g of the substance to be examined in 10 mL of *water R* or use 10 mL of the prescribed solution. Add 0.5 mL of *hydrochloric acid R*. The precipitate obtained, after recrystallisation from hot *water R* and drying *in vacuo*, has a melting point (*2.2.14*) of 156 °C to 161 °C.

SILICATES

Mix the prescribed quantity of the substance to be examined in a lead or platinum crucible by means of a copper wire with about 10 mg of *sodium fluoride R* and a few drops of *sulfuric acid R* to give a thin slurry. Cover the crucible with a thin, transparent plate of plastic under which a drop of *water R* is suspended and warm gently. Within a short time a white ring is rapidly formed around the drop of water.

SILVER

Dissolve about 10 mg of the substance to be examined in 10 mL of *water R* or use 10 mL of the prescribed solution. Add 0.3 mL of *hydrochloric acid R1*. A curdled, white precipitate is formed that dissolves on addition of 3 mL of *dilute ammonia R1*.

SODIUM

a) Dissolve 0.1 g of the substance to be examined in 2 mL of *water R* or use 2 mL of the prescribed solution. Add 2 mL of a 150 g/L solution of *potassium carbonate R* and heat to boiling. No precipitate is formed. Add 4 mL of *potassium pyroantimonate solution R* and heat to boiling. Allow to cool in iced water and if necessary rub the inside of the test-tube with a glass rod. A dense white precipitate is formed.

b) Dissolve a quantity of the substance to be examined equivalent to about 2 mg of sodium ($Na^+$) in 0.5 mL of *water R* or use 0.5 mL of the prescribed solution. Add 1.5 mL of *methoxyphenylacetic reagent R* and cool in ice-water for 30 min. A voluminous, white, crystalline precipitate is formed. Place in water at 20 °C and stir for 5 min. The precipitate does not disappear. Add 1 mL of *dilute ammonia R1*. The precipitate dissolves completely. Add 1 mL of *ammonium carbonate solution R*. No precipitate is formed.

SULFATES

a) Dissolve about 45 mg of the substance to be examined in 5 mL of *water R* or use 5 mL of the prescribed solution. Add 1 mL of *dilute hydrochloric acid R* and 1 mL of *barium chloride solution R1*. A white precipitate is formed.

b) To the suspension obtained during reaction (a), add 0.1 mL of *0.05 M iodine*. The suspension remains yellow (distinction from sulfites and dithionites), but is decolorised by adding dropwise *stannous chloride solution R* (distinction from iodates). Boil the mixture. No coloured precipitate is formed (distinction from selenates and tungstates).

TARTRATES

a) Dissolve about 15 mg of the substance to be examined in 5 mL of *water R* or use 5 mL of the prescribed solution. Add 0.05 mL of a 10 g/L solution of *ferrous sulfate R* and 0.05 mL of *dilute hydrogen peroxide solution R*. A transient yellow colour is produced. After the colour has disappeared add *dilute sodium hydroxide solution R* dropwise. A violet or purple colour is produced.

b) To 0.1 mL of a solution of the substance to be examined containing the equivalent of about 15 mg of tartaric acid per millilitre or to 0.1 mL of the prescribed solution add 0.1 mL of a 100 g/L solution of *potassium bromide R*, 0.1 mL of a 20 g/L solution of *resorcinol R* and 3 mL of *sulfuric acid R*. Heat on a water-bath for 5 min to 10 min. A dark-blue colour develops. Allow to cool and pour the solution into *water R*. The colour changes to red.

XANTHINES

To a few milligrams of the substance to be examined or the prescribed quantity add 0.1 mL of *strong hydrogen peroxide solution R* and 0.3 mL of *dilute hydrochloric acid R*. Heat to dryness on a water-bath until a yellowish-red residue is obtained. Add 0.1 mL of *dilute ammonia R2*. The colour of the residue changes to violet-red.

ZINC

Dissolve 0.1 g of the substance to be examined in 5 mL of *water R* or use 5 mL of the prescribed solution. Add 0.2 mL of *strong sodium hydroxide solution R*. A white precipitate is formed. Add a further 2 mL of *strong sodium hydroxide solution R*. The precipitate dissolves. Add 10 mL of *ammonium chloride solution R*. The solution remains clear. Add 0.1 mL of *sodium sulfide solution R*. A flocculent white precipitate is formed.

**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**

**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 □ registrazione registro EU
□ coloranti o corrosivi
□ sostanze vietate per doping

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

| | |
|---|---|
| | |
| **n°**……**li**……**Dott.**…… | |
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| **Avvertenze**…… | |
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| …… | |
| **Precauzioni**…… | |
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| …… | |
| **Posologia**…… | |
| …… | |
| …… | |
| **Data limite di utilizzo**…… | |
| **Sig.**…… | |

| | |
|---|---|
| KETOPROFENE | costo d’acquisto 0,47 €/g |

## Scadenza materie prime

| | |
|---|---|
| KETOPROFENE | 21 novembre 2017 |
| MAGNESIO STEARATO | 21 novembre 2019 |
| AMIDO DI RISO | 21 novembre 2017 |

*Segue:* **TABELLA N. 8**

| Sostanza | Vie di somministrazione | Dosi abituali | | Dosi massime | |
|---|---|---|---|---|---|
| | | Per ogni dose grammi | Nelle 24 ore grammi | Per ogni dose grammi | Nelle 24 ore grammi |
| Isoconazolo | top. | 1% | – | – | – |
| Isoconazolo nitrato | top. | 1% | – | – | – |
| Isoleucina | fleboclisi | In combinazione con altri amminoacidi nelle soluzioni perfusionali per la nutrizione parenterale. | | | |
| Isoniazide | per os | 0,05-0,15 | 0,50 | 0,30 | 1 |
| Isoprenalina cloridrato * | e.v. lenta<br>s.c./i.m.<br>per os<br>s.l. | –<br>–<br>–<br>– | –<br>–<br>–<br>– | 0,000060<br>0,000200<br>0,030<br>0,030 | –<br>–<br>0,84<br>0,180 |
| Isoprenalina solfato | s.l. | 0,005-0,01 | 0,02-0,03 | 0,015 | 0,04 |
| Isosorbide dinitrato | per os<br>s.l.<br>fleboclisi | 0,005-0,04<br>0,005-0,01<br>0,02-0,01/h | 0,015-0,08<br>–<br>– | –<br>0,01<br>– | 0.12<br>0.01/h<br>– |
| Isosorbide mononitrato diluito | per os | 0,02 | 0,04-0,06 | 0,02 | 0,12 |
| Isotretinoina | per os | 0,005-0,02 | 0,05 | – | – |
| Isoxsuprina cloridrato | per os<br>i.m.<br>e.v. | 0,02<br>0,01<br>Nell'arresto del parto prematuro, si somministra una soluzione contenente 0,0002/ml alla velocità di infusione di 0,0002-0,0003/min fino ad un massimo di 0,0005/min. Successivamente, si somministra per via i.m. 0,001 ogni 3 h per 24 h, ogni 4-6 h per 48 h e, infine, 0,04-0,08 per os in dosi frazionate. | 0,08<br>0,03 | 0,02<br>0,01 | 0,08<br>0,03 |
| Isradipina * | per os | – | – | 0,010 | 0,020 |
| Itraconazolo | per os | – | – | 0,4 | 0,6 |
| Ivermectina * | per os | – | – | 0,012 | 0,012 |
| Kanamicina solfato | per os<br>i.m. | 0,50<br>0,50 | 1-2<br>1 | 1<br>1 | 4<br>1,50 |
| Ketamina cloridrato | e.v. | 0,05-0,01 | – | – | – |
| Ketobemidone cloridrato * | per os | – | – | 0,010 | 0,020 |
| Ketoconazolo | per os o top. | 0,2 | – | 0,4 | – |
| Ketoprofene | per os o top. | 0,05-0,1 | 0,15 | 0,15 | 0,3 |
| Labetalolo cloridrato | per os o e.v. | 0,1-0,2 | 0,3 | 0,2 | 0,6 |
| Lanatoside C | per os | 0,00025 | 0,001 | 0,0005 | 0,002 |
| Lattitolo monoidrato * | per os | – | – | 0,23/kg | 0,7/kg |
| Lattulosio | per os | – | – | 20 | 120 |
| Lattulosio soluzione | per os | 3,0-5,0 | 10,0-20,0 | 20,0-40,0 | 100,0 |
| Lefetamina | per os<br>i.m.<br>rett. | 0,05-0,10<br>0,06<br>0,05 | 0,20<br>0,06–0,12<br>0,15 | 0,10<br>0,12<br>0,05 | 0,20<br>0,12<br>0,20 |
| Leucina | fleboclisi | In combinazione con altri amminoacidi nelle soluzioni perfusionali per la nutrizione parenterale. | | | |
| Leuprorelina * | s.c.<br>i.m. | – | – | 0,0036<br>0,0072 | 0,0036<br>0,0072 |
| Levamisolo cloridrato | per os | Ad.: 0,12 - 0,15 a dose singola; ped. 0,003/kg. In casi gravi una seconda dose può essere somministrata dopo 7 giorni dalla prima. | | | |

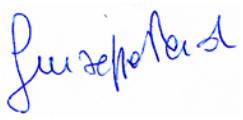
Dott. Giuseppe Verdi
Via Francesco Baracca, 22
Torino
Tel. 0112436904

Giuseppina Turchese

Ketoprofene 50 mg
Magnesio stearato 5 mg
Amido di riso q.b. a 900 mg

Di una tali 10 capsule

1 capsula ogni 8 ore



26/10/2016

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

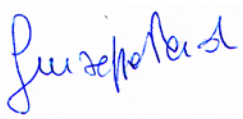
Dott. Giuseppe Verdi
Via Francesco Baracca, 22
Torino
Tel. 0112436904

Giuseppina Turchese

Ketoprofene 50 mg
Magnesio stearato 5 mg
Amido di riso q.b. a 900 mg

Di una tali 12 capsule

1 capsula ogni 8 ore



26/10/2016

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

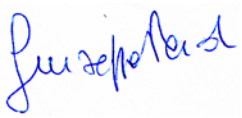
Dott. Giuseppe Verdi
Via Francesco Baracca, 22
Torino
Tel. 0112436904

Giuseppina Turchese

Ketoprofene 50 mg
Magnesio stearato 5 mg
Amido di riso q.b. a 900 mg

Di una tali 14 capsule

1 capsula ogni 8 ore



26/10/2016

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

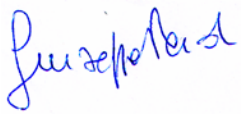
Dott. Giuseppe Verdi
Via Francesco Baracca, 22
Torino
Tel. 0112436904

Giuseppina Turchese

Ketoprofene 50 mg
Magnesio stearato 5 mg
Amido di riso q.b. a 900 mg

Di una tali 15 capsule

1 capsula ogni 8 ore



26/10/2016

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

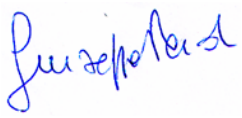
Dott. Giuseppe Verdi
Via Francesco Baracca, 22
Torino
Tel. 0112436904

Giuseppina Turchese

Ketoprofene 50 mg
Magnesio stearato 5 mg
Amido di riso q.b. a 900 mg

Di una tali 18 capsule

1 capsula ogni 8 ore



26/10/2016

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

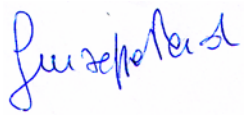
Dott. Giuseppe Verdi
Via Francesco Baracca, 22
Torino
Tel. 0112436904

Giuseppina Turchese

Ketoprofene 50 mg
Magnesio stearato 5 mg
Amido di riso q.b. a 900 mg

Di una tali 20 capsule

1 capsula ogni 8 ore



26/10/2016

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

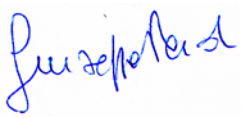
Dott. Giuseppe Verdi
Via Francesco Baracca, 22
Torino
Tel. 0112436904

Giuseppina Turchese

Ketoprofene 50 mg
Magnesio stearato 5 mg
Amido di riso q.b. a 900 mg

Di una tali 22 capsule

1 capsula ogni 8 ore



26/10/2016

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

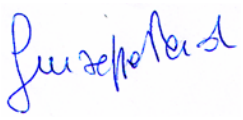
Dott. Giuseppe Verdi
Via Francesco Baracca, 22
Torino
Tel. 0112436904

Giuseppina Turchese

Ketoprofene150 mg
Magnesio stearato 5 mg
Amido di riso q.b. a 900 mg

Di una tali 22 capsule

1 capsula al dì



18/11/2016

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

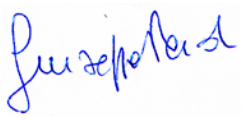
Dott. Giuseppe Verdi
Via Francesco Baracca, 22
Torino
Tel. 0112436904

Giuseppina Turchese

Ketoprofene 150 mg
Magnesio stearato 5 mg
Amido di riso q.b. a 900 mg

Di una tali 24 capsule

1 capsula al dì



18/11/2016

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

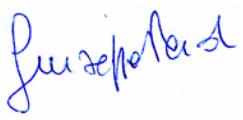
Dott. Giuseppe Verdi
Via Francesco Baracca, 22
Torino
Tel. 0112436904

Giuseppina Turchese

Ketoprofene 150 mg
Magnesio stearato 5 mg
Amido di riso q.b. a 900 mg

Di una tali 25 capsule

1 capsula al dì



18/11/2016

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

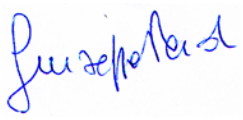
Dott. Giuseppe Verdi
Via Francesco Baracca, 22
Torino
Tel. 0112436904

Giuseppina Turchese

Ketoprofene 150 mg
Magnesio stearato 5 mg
Amido di riso q.b. a 900 mg

Di una tali 30 capsule

1 capsula al dì



18/11/2016

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

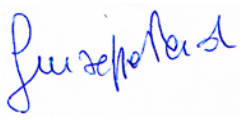
Dott. Giuseppe Verdi
Via Francesco Baracca, 22
Torino
Tel. 0112436904

Giuseppina Turchese

Ketoprofene 150 mg
Magnesio stearato 5 mg
Amido di riso q.b. a 900 mg

Di una tali 32 capsule

1 capsula al dì



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

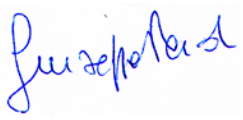
Dott. Giuseppe Verdi
Via Francesco Baracca, 22
Torino
Tel. 0112436904

Giuseppina Turchese

Ketoprofene 150 mg
Magnesio stearato 5 mg
Amido di riso q.b. a 900 mg

Di una tali 34 capsule

1 capsula al dì



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

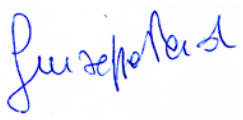
Dott. Giuseppe Verdi
Via Francesco Baracca, 22
Torino
Tel. 0112436904

Giuseppina Turchese

Ketoprofene 150 mg
Magnesio stearato 5 mg
Amido di riso q.b. a 900 mg

Di una tali 35 capsule

1 capsula al dì



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

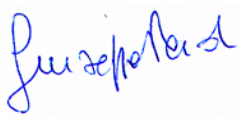
Dott. Giuseppe Verdi
Via Francesco Baracca, 22
Torino
Tel. 0112436904

Giuseppina Turchese

Ketoprofene 150 mg
Magnesio stearato 5 mg
Amido di riso q.b. a 900 mg

Di una tali 38 capsule

1 capsula al dì



21/11/2016

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

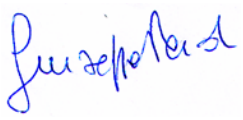
Dott. Giuseppe Verdi
Via Francesco Baracca, 22
Torino
Tel. 0112436904

Giuseppina Turchese

Ketoprofene 150 mg
Magnesio stearato 5 mg
Amido di riso q.b. a 900 mg

Di una tali 40 capsule

2 capsule al dì



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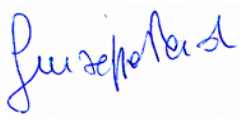
Dott. Giuseppe Verdi
Via Francesco Baracca, 22
Torino
Tel. 0112436904

Giuseppina Turchese

Ketoprofene 150 mg
Magnesio stearato 10 mg
Amido di riso q.b. a 900 mg

Di una tali 10 capsule

2 capsule al dì



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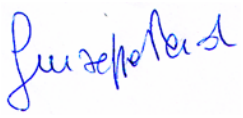
Dott. Giuseppe Verdi
Via Francesco Baracca, 22
Torino
Tel. 0112436904

Giuseppina Turchese

Ketoprofene 150 mg
Magnesio stearato 10 mg
Amido di riso q.b. a 900 mg

Di una tali 12 capsule

2 capsule al dì



21/11/2016

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

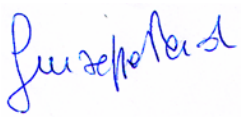
Dott. Giuseppe Verdi
Via Francesco Baracca, 22
Torino
Tel. 0112436904

Giuseppina Turchese

Ketoprofene 150 mg
Magnesio stearato 10 mg
Amido di riso q.b. a 900 mg

Di una tali 14 capsule

2 capsule al dì



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

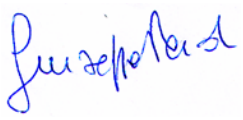
Dott. Giuseppe Verdi
Via Francesco Baracca, 22
Torino
Tel. 0112436904

Giuseppina Turchese

Ketoprofene 150 mg
Magnesio stearato 10 mg
Amido di riso q.b. a 900 mg

Di una tali 15 capsule

2 capsule al dì



21/11/2016

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

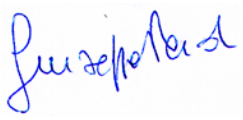
Dott. Giuseppe Verdi
Via Francesco Baracca, 22
Torino
Tel. 0112436904

Giuseppina Turchese

Ketoprofene 150 mg
Magnesio stearato 10 mg
Amido di riso q.b. a 900 mg

Di una tali 18 capsule

2 capsule al dì



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

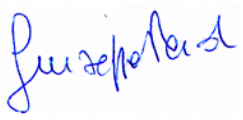
Dott. Giuseppe Verdi
Via Francesco Baracca, 22
Torino
Tel. 0112436904

Giuseppina Turchese

Ketoprofene 150 mg
Magnesio stearato 10 mg
Amido di riso q.b. a 900 mg

Di una tali 20 capsule

2 capsule al dì



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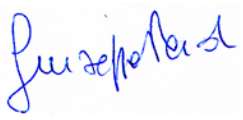
Dott. Giuseppe Verdi
Via Francesco Baracca, 22
Torino
Tel. 0112436904

Giuseppina Turchese

Ketoprofene 150 mg
Magnesio stearato 10 mg
Amido di riso q.b. a 900 mg

Di una tali 22 capsule

2 capsule al dì



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Dott. Giuseppe Verdi

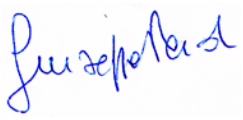
Via Francesco Baracca, 22
Torino
Tel. 0112436904

Giuseppina Turchese

Ketoprofene 150 mg
Magnesio stearato 10 mg
Amido di riso q.b. a 900 mg

Di una tali 24 capsule

2 capsule al dì



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