40 °C under a reflux condenser for 5 min. Cool and filter. Evaporate the filtrate to dryness. Dissolve the residue in 5.0 ml of *ether R*.

Reference solution. Dissolve 5.0 mg of *glycyrrhetic acid R* and 5.0 mg of *thymol R* in 5.0 ml of *ether R*.

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

Mobile phase: *concentrated ammonia R, water R, ethanol (96 per cent) R, ethyl acetate R* (1:9:25:65 *V/V/V/V*).

Application: 10 µl.

Development: over a path of 15 cm.

Drying: in air for 5 min.

Detection A: examine in ultraviolet light at 254 nm.

Results A: the chromatograms obtained with the test solution and with the reference solution show in the lower half a quenching zone due to glycyrrhetic acid.

Detection B: spray with *anisaldehyde solution R*, and heat at 100-105 °C for 5-10 min; examine in daylight.

Results B: the chromatogram obtained with the reference solution shows in the lower half a violet zone due to glycyrrhetic acid and in the upper third a red zone due to thymol. The chromatogram obtained with the test solution shows in the lower half a violet zone corresponding to the zone of glycyrrhetic acid in the chromatogram obtained with the reference solution and a yellow zone (isoliquiridigenine) in the upper third under the zone of thymol in the chromatogram obtained with the reference solution. Further zones may be present.

TESTS

Loss on drying (*2.2.32*): maximum 10.0 per cent, determined on 1.000 g of powdered drug (355) (*2.9.12*) by drying in an oven at 105 °C for 2 h.

Total ash (*2.4.16*): maximum 10.0 per cent for the unpeeled drug and maximum 6.0 per cent for the peeled drug.

Ash insoluble in hydrochloric acid (*2.8.1*): maximum 2.0 per cent for the unpeeled drug and maximum 0.5 per cent for the peeled drug.

ASSAY

Liquid chromatography (*2.2.29*).

Test solution. Place 1.000 g of the powdered drug (180) (*2.9.12*) in a 150 ml ground glass conical flask. Add 100.0 ml of an 8 g/l solution of *ammonia R* and treat in a ultrasonic bath for 30 min. Centrifuge a part of the solution and dilute 1.0 ml of the supernatant layer to 5.0 ml with an 8 g/l solution of *ammonia R*. Filter the solution through a filter (0.45 µm) and use the filtrate as the test solution.

Solution A. Dissolve 0.130 g of *monoammonium glycyrrhizate CRS* in an 8 g/l solution of *ammonia R* and dilute to 100.0 ml with the same solvent.

Reference solution (a). Dilute 5.0 ml of solution A to 100.0 ml with an 8 g/l solution of *ammonia R*.

Reference solution (b). Dilute 10.0 ml of solution A to 100.0 ml with an 8 g/l solution of *ammonia R*.

Reference solution (c). Dilute 15.0 ml of solution A to 100.0 ml with an 8 g/l solution of *ammonia R*.

Column:

- *size*: *l* = 0.10 m, Ø = 4 mm;
- *stationary phase*: *octadecylsilyl silica gel for chromatography R* (5 µm).

Mobile phase: *glacial acetic acid R, acetonitrile R, water R* (6:30:64 *V/V/V*).

Flow rate: 1.5 ml/min.

Detection: spectrophotometer at 254 nm.

Injection: 10 µl.

Establish a calibration curve with the concentration of the reference solutions (g/100 ml) as the abscissa and the corresponding areas as the ordinate.

Using the retention time and the peak area determined from the chromatograms obtained with the reference solutions, locate and integrate the peak due to glycyrrhizic acid in the chromatogram obtained with the test solution.

Calculate the percentage content of glycyrrhizic acid from the following expression:

$$A \times \frac{5}{m} \times B \times \frac{822}{840}$$

A = concentration of monoammonium glycyrrhizate in the test solution determined from the calibration curve, in g/100 ml;

B = declared percentage content of *monoammonium glycyrrhizate CRS*;

m = mass of the drug, in grams;

822 = molecular weight of glycyrrhizic acid;

840 = molecular weight of the monoammonium glycyrrhizate (without any water of crystallisation).

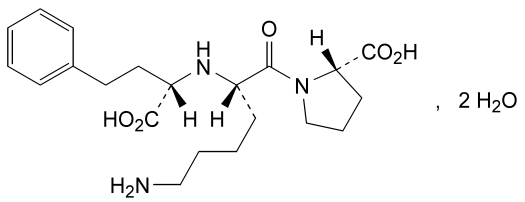
LABELLING

The label states whether the drug is peeled or unpeeled.

01/2008:1120
corrected 6.0

LISINOPRIL DIHYDRATE

Lisinoprilum dihydricum



$C_{21}H_{31}N_3O_5,2H_2O$ M_r 441.5
[83915-83-7]

DEFINITION

(2*S*)-1-[(2*S*)-6-Amino-2-[[(1*S*)-1-carboxy-3-phenylpropyl]-amino]hexanoyl]pyrrolidine-2-carboxylic acid dihydrate.

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

CHARACTERS

Appearance: white or almost white, crystalline powder.

Solubility: soluble in water, sparingly soluble in methanol, practically insoluble in acetone and in anhydrous ethanol.

IDENTIFICATION

Infrared absorption spectrophotometry (*2.2.24*).

Preparation: discs.

Comparison: *lisinopril dihydrate CRS*.

TESTS

Specific optical rotation (*2.2.7*): – 43 to – 47 (anhydrous substance).

Dissolve 0.5 g in *zinc acetate solution R* and dilute to 50.0 ml with the same solvent.

Related substances. Liquid chromatography (*2.2.29*).

Test solution. Dissolve 20.0 mg of the substance to be examined in mobile phase A and dilute to 10.0 ml with mobile phase A.

Reference solution (a). Dissolve the contents of 1 vial of *lisinopril dihydrate for performance test CRS* with 1.0 ml of mobile phase A.

Reference solution (b). Dilute 0.5 ml of the test solution to 50.0 ml with mobile phase A.

Column:

- *size*: *l* = 0.25 m, Ø = 4.6 mm;
- *stationary phase*: *octylsilyl silica gel for chromatography R*;
- *temperature*: 50 °C.

Mobile phase:

- *mobile phase A*: mix 30 volumes of *acetonitrile R* and 970 volumes of a 3.12 g/l *sodium dihydrogen phosphate R* solution adjusted to pH 5.0 with a 50 g/l solution of *sodium hydroxide R*;
- *mobile phase B*: mix 200 volumes of *acetonitrile R* and 800 volumes of a 3.12 g/l *sodium dihydrogen phosphate R* solution adjusted to pH 5.0 with a 50 g/l solution of *sodium hydroxide R*;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 35	100 → 70	0 → 30
35 - 45	70	30
45 - 50	70 → 100	30 → 0

Flow rate: 1.8 ml/min.

Detection: spectrophotometer at 210 nm.

Equilibration: with mobile phase A for at least 30 min.

Injection: 20 µl.

System suitability: reference solution (a):

- the chromatogram obtained is similar to the chromatogram supplied with *lisinopril dihydrate for performance test CRS* in that the peaks due to impurity A and impurity E fall on either side of the peak due to lisinopril;
- *peak-to-valley ratio*: minimum 9, where H_p = height above the baseline of the peak due to impurity A and H_v = height above the baseline of the lowest point of the curve separating this peak from the peak due to lisinopril, and minimum 9 where H_p = height above the baseline of the peak due to impurity E and H_v = height above the baseline of the lowest point of the curve separating this peak from the peak due to lisinopril; if necessary, adjust the pH of the mobile phase to 4.5 with *phosphoric acid R*; a further adjustment to pH 4.0 may be necessary with some columns before satisfactory separation of impurity A, lisinopril and impurity E is obtained; if, after adjustment, the retention time of the peak due to impurities C and D becomes extended to the point where integration becomes difficult, increase the content of mobile phase B from 30 per cent to 40 per cent over the interval from 35-45 min from the start of the chromatogram; maintain this concentration for a further 10 min and return the concentration of mobile phase A to 100 per cent over the next 10 min prior to the next injection.

Limits:

- *impurities A, B, C, D, E, F*: for each impurity, not more than 0.3 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.3 per cent);
- *sum of impurities other than E*: not more than 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.5 per cent);
- *disregard limit*: 0.05 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.05 per cent); disregard any peak occurring in the first 3 min.

Water (*2.5.12*): 8.0 per cent to 9.5 per cent, determined on 0.200 g.

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

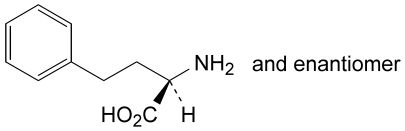
ASSAY

Dissolve 0.350 g in 50 ml of *distilled water R*. Titrate with *0.1 M sodium hydroxide*, determining the end-point potentiometrically (*2.2.20*).

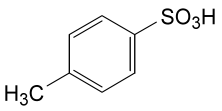
1 ml of *0.1 M sodium hydroxide* is equivalent to 40.55 mg of $C_{21}H_{31}N_3O_5$.

IMPURITIES

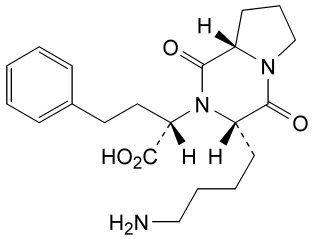
Specified impurities: A, B, C, D, E, F.



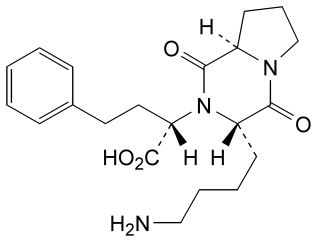
A. (2*RS*)-2-amino-4-phenylbutanoic acid,



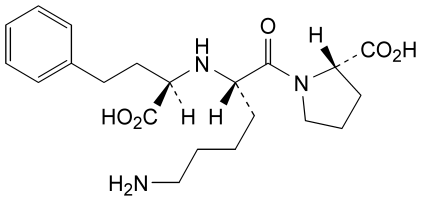
B. 4-methylbenzenesulphonic acid,



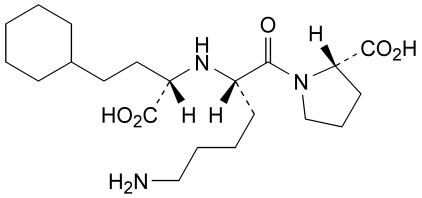
C. (2*S*)-2-[(3*S*,8a*S*)-3-(4-aminobutyl)-1,4-dioxohexahydropyrrolo[1,2-*a*]pyrazin-2(1*H*)-yl]-4-phenylbutanoic acid (*S*,*S*,*S*-diketopiperazine),



D. (2*S*)-2-[(3*S*,8a*R*)-3-(4-aminobutyl)-1,4-dioxohexahydropyrrolo[1,2-*a*]pyrazin-2(1*H*)-yl]-4-phenylbutanoic acid (*R*,*S*,*S*-diketopiperazine),



E. (2*S*)-1-[(2*S*)-6-amino-2-[[(1*R*)-1-carboxy-3-phenylpropyl]amino]hexanoyl]pyrrolidine-2-carboxylic acid (lisinopril *R,S,S*-isomer),



F. (2*S*)-1-[(2*S*)-6-amino-2-[[(1*S*)-1-carboxy-3-cyclohexylpropyl]amino]hexanoyl]pyrrolidine-2-carboxylic acid (cyclohexyl analogue).

01/2008:0228
corrected 6.0

LITHIUM CARBONATE

Lithii carbonas

Li_2CO_3 M_r 73.9
[554-13-2]

DEFINITION

Content: 98.5 per cent to 100.5 per cent.

CHARACTERS

Appearance: white or almost white powder.

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

IDENTIFICATION

A. When moistened with *hydrochloric acid R*, it gives a red colour to a non-luminous flame.

B. Dissolve 0.2 g in 1 ml of *hydrochloric acid R*. Evaporate to dryness on a water-bath. The residue dissolves in 3 ml of *ethanol (96 per cent) R*.

C. It gives the reaction of carbonates (*2.3.1*).

TESTS

Solution S. Suspend 10.0 g in 30 ml of *distilled water R* and dissolve by the addition of 22 ml of *nitric acid R*. Add *dilute sodium hydroxide solution R* until the solution is neutral and dilute to 100 ml with *distilled water R*.

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

Chlorides (*2.4.4*): maximum 200 ppm.

Dilute 2.5 ml of solution S to 15 ml with *water R*.

Sulphates (*2.4.13*): maximum 200 ppm.

Disperse 1.25 g in 5 ml of *distilled water R* and dissolve by adding 5 ml of *hydrochloric acid R1*. Boil for 2 min. Cool and add *dilute sodium hydroxide solution R* until neutral. Dilute to 25 ml with *distilled water R*.

Arsenic (*2.4.2, Method A*): maximum 2 ppm, determined on 0.5 g.

Calcium (*2.4.3*): maximum 200 ppm.

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

Iron (*2.4.9*): maximum 20 ppm.

Dilute 5 ml of solution S to 10 ml with *water R*.

Magnesium (*2.4.6*): maximum 150 ppm.

Dilute 1 ml of solution S to 10 ml with *water R*. Dilute 6.7 ml of this solution to 10 ml with *water R*.

Potassium: maximum 3.00×10^2 ppm.

Atomic emission spectrometry (*2.2.22, Method I*).

Test solution. Dissolve 1.0 g in 10 ml of *hydrochloric acid R1* and dilute to 50.0 ml with *water R*.

Reference solutions. Prepare the reference solutions using a solution of *potassium chloride R* containing 500 µg of K per millilitre, diluted as necessary with *water R*.

Wavelength: 766.5 nm.

Sodium: maximum 3.00×10^2 ppm.

Atomic emission spectrometry (*2.2.22, Method I*).

Test solution. Dissolve 1.0 g in 10 ml of *hydrochloric acid R1* and dilute to 50.0 ml with *water R*.

Reference solutions. Prepare the reference solutions using a solution of *sodium chloride R* containing 500 µg of Na per millilitre, diluted as necessary with *water R*.

Wavelength: 589 nm.

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*.

ASSAY

Dissolve 0.500 g in 25.0 ml of *1 M hydrochloric acid*. Titrate with *1 M sodium hydroxide*, using *methyl orange solution R* as indicator.

1 ml of *1 M hydrochloric acid* is equivalent to 36.95 mg of Li_2CO_3.

01/2008:0621

LITHIUM CITRATE

Lithii citras

$C_6H_5Li_3O_7,4H_2O$ M_r 282.0

DEFINITION

Trilithium 2-hydroxypropane-1,2,3-tricarboxylate tetrahydrate.

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

CHARACTERS

Appearance: white or almost white, fine crystalline powder.

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

IDENTIFICATION

A. When moistened with *hydrochloric acid R*, it gives a red colour to a non-luminous flame.

B. Dilute 3 ml of solution S (see Tests) to 10 ml with *water R*. Add 3 ml of *potassium ferriperiodate solution R*. A white or yellowish-white precipitate is formed.

C. To 1 ml of solution S add 4 ml of *water R*. The solution gives the reaction of citrates (*2.3.1*).