**Definiton**

Lisinopril dihydrate contains not less than 98.5 per cent and not more than the equivalent of 101.5 per cent of \((2S)-1\{(2S)-6\text{-amino-2\{[(1S)-1\text{-carboxy-3-phenylpropylamine\}hexanoyl]pyrrole-2-carboxylic acid, calculated with reference to the anhydrous substance.

**Characteristics**

A white or almost white, crystalline powder, soluble in water, sparingly soluble in methanol, practically insoluble in acetone and in ethanol.

**Identification**

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

**Tests**

**Specific optical rotation** (2.2.7). Dissolve 0.5 g in *zinc acetate solution R* and dilute to 50.0 ml with the same solvent. The specific optical rotation is 43 to 47, calculated with reference to the anhydrous substance.

**Related substances**. Examine by 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 the same mobile phase.

**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.

The chromatographic procedure may be carried out using:

- a stainless steel column 0.25 m long and 4.6 mm in internal diameter packed with octadecylsilyl silica gel for chromatography R (5 µm),
- as mobile phase at a flow rate of 1.8 ml/min:
  - a 10 µl loop injector.

Inject reference solution (c). Adjust the sensitivity of the system so that the height of the peaks are at least 50 per cent of the full scale of the recorder. Inject each reference solution and determine the peak areas.

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

**Storage**

Store protected from light.

**Labelling**

The label states whether the drug is peeled or unpeeled.
peaks due to impurity A and impurity E and the heights $B_1$ and $B_2$ above the baseline of the lowest points of the curve separating these peaks from the peak due to lisinopril. The test is not valid unless $A_1$ is greater than nine times $B_1$ and $A_2$ is greater than nine times $B_2$.

If necessary, adjust the pH of the mobile phase to 4.5 with phosphoric acid R and repeat the chromatography. 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 min to 45 min from the start of the chromatogram. Maintain this concentration for a further 10 min. Return the concentration of mobile phase A to 100 per cent over the next 10 min prior to the next injection.

Inject 20 µl of the test solution and 20 µl of reference solution (b). In the chromatogram obtained with the test solution: the area of any peak due to impurity E is not greater than 0.3 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.3 per cent); the area of any peak, apart from the principal peak and any peak due to impurity E, is not greater than 0.3 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.3 per cent) and the sum of the areas of all such peaks is not greater than half the area of the principal peak in the chromatogram obtained with reference solution (b). Disregard any peak due to the solvent, any peak occurring in the first 3 minutes and any peak with an area less than 0.05 times the area of the principal peak in the chromatogram obtained with reference solution (b).

Water (2.5.12): 8.0 to 9.5 per cent, determined on 0.200 g by the semi-micro determination of water.

Sulphated ash (2.4.14). Not more than 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

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

B. 4-methylbenzenesulphonic acid,