Perindopril tert-butyramine

**DEFINITION**
2-Methylpropan-2-amine (2S,3aS,7aS)-1-[(2S)-2-[(1S)-1-(ethoxy carbonyl)butyl]amino]propanoyloctahydro-1H-indole-2-carboxylate.

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

**CHARACTERS**

**Appearance:** white or almost white, crystalline powder, slightly hygroscopic.

**Solubility:** freely soluble in water and in alcohol, sparingly soluble in methylene chloride.

**IDENTIFICATION**

**A.** Specific optical rotation (2.2.7): -66 to -69 (anhydrous substance).

Dissolve 0.250 g in alcohol R and dilute to 25.0 ml with the same solvent.

**B.** Infrared absorption spectrophotometry (2.2.24).

**Preparation:** discs.

Comparison: perindopril tert-butyramine CRS.

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

**C.** Examine the chromatograms obtained in the test for impurity A.

**Results:** in the chromatogram obtained with the test solution a spot is observed with the same Rf as the spot with the higher Rf in the chromatogram with reference solution (c) (tert-butyramine).

**TESTS**

**Impurity A.** Thin-layer chromatography (2.2.27).

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

**Reference solution (a).** Dissolve 5 mg of perindopril impurity A CRS in methanol R and dilute to 25.0 ml with the same solvent.

**Reference solution (b).** Dilute 5 ml of reference solution (a) to 20 ml with methanol R.

**Reference solution (c).** To 5 ml of reference solution (a) add 5 ml of a 20 g/1 solution of 1,1-dimethylethylamine R in methanol R.

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

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

**Application:** 10 µl; apply the test solution and reference solutions (b) and (c).

Development: in a saturated tank, over 2/3 of the plate.

Drying: in a current of warm air.

Detection: expose to iodine vapour for at least 20 h.

System suitability: the chromatogram obtained with reference solution (c) shows 2 clearly separated spots.

**Limit:**

- impurity A: any spot due to impurity A is not more intense than the spot in the chromatogram obtained with reference solution (b) (0.25 per cent).

**Stereochemical purity.** Liquid chromatography (2.2.29).

**Test solution.** Dissolve 20 mg of the substance to be examined in alcohol R and dilute to 10.0 ml with the same solvent.

**Reference solution (a).** Dilute 1.0 ml of the test solution to 200.0 ml with alcohol R.

**Reference solution (b).** Dissolve 10 mg of perindopril for stereochemical purity CRS in alcohol R and dilute to 5.0 ml with the same solvent.

**Reference solution (c).** Dilute 10.0 ml of reference solution (a) to 50.0 ml with alcohol R.

**Column:**

- size: l = 0.25 m, Ø = 4.6 mm.
Mobile phase: mix, in the following order, 21.7 volumes of acetonitrile R, 0.3 volumes of pentanol R and 78 volumes of a 1.50 g/l solution of sodium heptanesulphonate R, previously adjusted to pH 2.0 with a mixture of equal volumes of perchloric acid R and water R.

Flow rate: 0.8 ml/min.
Detection: spectrophotometer at 215 nm.
Injection: 10 µl.
Run time: 1.5 times the retention time of perindopril.
Retention time: perindopril = about 100 min.

System suitability:
- signal-to-noise ratio: minimum 3 for the principal peak in the chromatogram obtained with reference solution (c),
- peak-to-valley ratio: minimum 3, where \( H_s \) = height above the baseline of the peak due to impurity \( I \) and \( H_v \) = height above the baseline of the lowest point of the curve separating this peak from the peak due to perindopril in the chromatogram obtained with reference solution (b),
- the chromatogram obtained with reference solution (b) is similar to the chromatogram provided with perindopril for stereochemical purity CRS.

Limits:
- any impurity: not more than 0.2 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.1 per cent); disregard any peak with a retention time less than 0.6 times the retention time of perindopril and any peak with a retention time greater than 1.4 times the retention time of perindopril.

Related substances. Liquid chromatography (2.2.29).
Test solution. Dissolve 60 mg of the substance to be examined in mobile phase A and dilute to 20.0 ml with mobile phase A.
Reference solution (a). Dissolve 15 mg of perindopril for system suitability CRS in mobile phase A and dilute to 5.0 ml with mobile phase A.
Reference solution (b). Dilute 1.0 ml of the test solution to 200.0 ml with mobile phase A.

Column:
- size: \( l = 0.25 \) m, \( \Phi = 4 \) mm,
- stationary phase: spherical octadecylsilyle silica gel for chromatography R (4 µm) with a pore size of 6 nm,
- temperature: 70 °C.

Mobile phase:
- mobile phase A: dissolve 0.92 g of sodium heptanesulphonate R in 1000 ml of water R, add 1 ml of triethylamine R and adjust to pH 2.0 with a mixture of equal volumes of perchloric acid R and water R,
- mobile phase B: acetonitrile R1.

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>Mobile phase A (per cent V/V)</th>
<th>Mobile phase B (per cent V/V)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 - 1</td>
<td>70</td>
<td>30</td>
</tr>
<tr>
<td>1 - 20</td>
<td>40</td>
<td>60</td>
</tr>
<tr>
<td>20 - 25</td>
<td>40</td>
<td>60</td>
</tr>
<tr>
<td>25 - 35</td>
<td>40</td>
<td>60</td>
</tr>
<tr>
<td>35 - 40</td>
<td>20</td>
<td>60</td>
</tr>
<tr>
<td>40 - 45</td>
<td>0</td>
<td>100</td>
</tr>
</tbody>
</table>

Flow rate: 1.5 ml/min.
Detection: spectrophotometer at 215 nm.
Injection: 20 µl.
Relative retention with reference to perindopril (retention time = about 8 min); impurity B = about 0.4; impurity C = about 0.8; impurity D = about 0.9; impurity E = about 1.4; impurity F = about 1.7; impurity G = about 2.2 and 2.3; impurity H = about 3.6 and 3.7.

System suitability: reference solution (a):
- peak-to-valley ratio: minimum 10, where \( H_s \) = height above the baseline of the peak due to impurity D and \( H_v \) = height above the baseline of the lowest point of the curve separating this peak from the peak due to perindopril.

Limits:
- impurity B: not more than 0.6 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.3 per cent),
- impurity E: not more than 0.8 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.4 per cent),
- impurities F, H: for each impurity, not more than 0.4 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.2 per cent),
- any other impurity: not more than 0.2 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.1 per cent),
- total: not more than twice the area of the principal peak in the chromatogram obtained with reference solution (b) (1 per cent),
- disregard limit: 0.1 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.05 per cent).

Water (2.5.12): maximum 1.0 per cent, determined on 0.50 g.

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

ASSAY
Dissolve 0.160 g in 50 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 22.08 mg of \( \text{C}_{26}\text{H}_{36}\text{N}_{2}\text{O}_{8} \).

STORAGE
In an airtight container.

IMPURITIES
Specified impurities: A, B, E, F, H, I.
Other detectable impurities: C, D, G.
Peritoneal dialysis, solutions for

DEFINITION

Solutions for peritoneal dialysis are preparations for intraperitoneal use containing electrolytes with a concentration close to the electrolytic composition of plasma. They contain glucose in varying concentrations or other suitable osmotic agents.

Solutions for peritoneal dialysis are supplied in:
- rigid or semi-rigid plastic containers,
- flexible plastic containers fitted with a special connecting device; these are generally filled to a volume below their nominal capacity and presented in closed protective envelopes,
- glass containers.

The containers and closures comply with the requirements for containers for preparations for parenteral use (3.2.1 and 3.2.2).

Several formulations are used. The concentrations of the components per litre of solution are usually in the following range:

<table>
<thead>
<tr>
<th>Component</th>
<th>Expression in mmol</th>
<th>Expression in mEq</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sodium</td>
<td>125 - 150</td>
<td>125 - 150</td>
</tr>
<tr>
<td>Potassium</td>
<td>0 - 4.5</td>
<td>0 - 4.5</td>
</tr>
<tr>
<td>Calcium</td>
<td>0 - 2.5</td>
<td>0 - 5.0</td>
</tr>
<tr>
<td>Magnesium</td>
<td>0.25 - 1.5</td>
<td>0.50 - 3.0</td>
</tr>
<tr>
<td>Acetate and/or lactate</td>
<td>30 - 60</td>
<td>30 - 60</td>
</tr>
<tr>
<td>Chloride</td>
<td>90 - 120</td>
<td>90 - 120</td>
</tr>
<tr>
<td>Glucose</td>
<td>25 - 250</td>
<td></td>
</tr>
</tbody>
</table>

See the information section on general monographs (cover pages)