Impurities in substances for pharmaceutical use for demonstration of compliance. See also (2034) by the general monograph acceptance criterion for other/unspecified impurities and/or the tests in the monograph. They are limited by the general if present at a sufficient level, be detected by one or other of

Other detectable impurities

Specified impurities: A.

PERINDOPRIL tert-BUTYLAMINE
tert-Butylamini perindoprilum

\[ \text{C}_{20}\text{H}_{30}\text{N}_{2}\text{O}_{3}\text{S}_{2} \]

DEFINITION
2-Methylpropan-2-amine (2S,3aS,7aS)-1-(2S)-2-[[1S]-1-(ethoxycarbonyl)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, slightly hygroscopic, crystalline powder.

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

It shows polymorphism (5.9).

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

B. Infrared absorption spectrophotometry (2.2.24).

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 \( R_{f} \) as the spot with the higher \( R_{f} \) in the chromatogram obtained with reference solution (c) ( tert-butylamine).

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

Reference solution (a). Dissolve 50 mg of perindopril impurity A CRS in methanol R and dilute to 10.0 mL with the same solvent.

Reference solution (b). Dilute 5.0 mL of reference solution (a) to 20.0 mL with methanol R.

Reference solution (c). To 5.0 mL of reference solution (a) add 5 mL of a 20 g/L solution of 1,1-dimethylpentylamine R in methanol R.

APPLICATION: 10 µL of the test solution and reference solutions (b) and (c).

Development: 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: reference solution (c):

– the chromatogram shows 2 clearly separated spots.

ASSAY
Liquid chromatography (2.2.29).

Solution A. Dissolve 5.0 mg of \( \psi \)-methionine R in 500 mL of 0.01 M hydrochloric acid. Add 500 mL of methanol R and mix.

Test solution. Dissolve 65.0 mg of the substance to be examined in solution A and dilute to 100.0 mL with solution A. Dilute 10.0 mL of this solution to 100.0 mL with solution A.

Reference solution. Dissolve 65.0 mg of pergolide mesilate CRS in solution A and dilute to 100.0 mL with solution A. Dilute 10.0 mL of this solution to 100.0 mL with solution A.

Column:
– size: \( l = 0.25 \) m, \( \phi = 4.6 \) mm;
– stationary phase: base-deactivated octylsilyl silica gel for chromatography R (5 µm);
– temperature: 40 °C.

Mobile phase: mix 1 volume of acetonitrile R, 1 volume of methanol R and 2 volumes of a mixture prepared as follows: dissolve 2.0 g of sodium octanesulfonate R in water R, add 1.0 mL of anhydrous acetic acid R and dilute to 1000 mL with water R.

Flow rate: 1 mL/min.

Detection: spectrophotometer at 280 nm.

Retention time: pergolide \( \approx 9 \) min.

System suitability: reference solution:
– symmetry factor: maximum 1.5 for the peak due to pergolide.

Calculate the percentage content of \( \text{C}_{20}\text{H}_{30}\text{N}_{2}\text{O}_{3}\text{S}_{2} \) from the declared content of pergolide mesilate CRS.

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. \( R = \text{SO}_{2}\text{CH}_{3}; \) (6aR,9R,10aR)-9-(methylsulfonyl)ethyl]-7-propyl-4,6,6a,7,8,9,10,10a-octahydroindolo[4,3-f]quinoline (pergolide sulfoxide).

B. \( R = \text{SO}_{2}\text{CH}_{3}; \) (6aR,9R,10aR)-9-(methylsulfonyl)ethyl]-7-propyl-4,6,6a,7,8,9,10,10a-octahydroindolo[4,3-f]quinoline (pergolide sulfone).

PERINDOPRIL tert-BUTYLAMINE

\[ \text{C}_{20}\text{H}_{30}\text{N}_{2}\text{O}_{3}\text{S}_{2} \]

M, 441.6

01/2008:2019

See the information section on general monographs (cover pages)
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).

**Stereoregularity.** Liquid chromatography (2.2.29).

**Test solutions.** Prepare the solutions immediately before use or maintain them at a temperature below 10 °C.

**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 3 mg of perindopril for peak identification CRS (containing impurities B, E, F, H and K) in 1 mL of mobile phase A.

**Reference solution (b).** Dilute 1.0 mL of the test solution to 200.0 mL with mobile phase A.

**Reference solution (c).** Dilute 1.0 mL of reference solution (b) to 10.0 mL with mobile phase A.

**Column:**
- size: l = 0.15 m, Ø = 4 mm;
- stationary phase: spherical end-capped octylsilica gel for chromatography R (5 µm) with a pore size of 15 nm;
- temperature: 60 °C for the column and the tubing preceding the column.

**Mobile phase:**
- mobile phase A: water R adjusted to pH 2.5 with a mixture of equal volumes of perchloric acid R and water R;
- mobile phase B: 0.03 per cent V/V solution of perchloric acid R in acetonitrile R1;

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>Mobile phase A</th>
<th>Mobile phase B</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 – (5 – t)</td>
<td>95</td>
<td>5</td>
</tr>
<tr>
<td>(5 – t) – (60 – t)</td>
<td>95 → 40</td>
<td>5 → 60</td>
</tr>
<tr>
<td>(60 – t) – (65 – t)</td>
<td>40 → 95</td>
<td>60 → 5</td>
</tr>
</tbody>
</table>

The isocratic step is described for a chromatographic system with a dwell volume (D) of 2 mL. If D is different from 2 mL, correct the gradient times with the value t, calculated using the following expression:

\[ D - 2 \frac{\text{Flow rate}}{t} \]

**Flow rate:** 1.0 mL/min.

**Detection:** spectrophotometer at 215 nm.

**Injection:** 20 µL.

**Identification of impurities:** use the chromatogram supplied with perindopril for stereoregularity CRS and the chromatogram obtained with reference solution (b) to identify the peaks due to impurity I.

**Run time:** 1.5 times the retention time of perindopril.

**Relative retention** with reference to perindopril (retention time = about 100 min): impurity I = about 0.9.

**System suitability:**
- the chromatogram obtained with reference solution (b) is similar to the chromatogram supplied with perindopril for stereoregularity CRS;
- signal-to-noise ratio: minimum 3 for the principal peak in the chromatogram obtained with reference solution (a);
- peak-to-valley ratio: minimum 3, where H = height above the baseline of the peak due to impurity I and H = height above the baseline of the lowest point of the peak separating this peak from the peak due to perindopril in the chromatogram obtained with reference solution (b).

**Limits:**
- impurity I: not more than 0.8 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.4 per cent);
- unspecified impurities: for each impurity, not more than 5 per cent of the area of the principal peak in the chromatogram obtained with reference solution (a) (0.20 per cent);
- disregard limit: disregard any peak with a relative retention with reference to perindopril greater than 1.4.

**Related substances:**

**Test solution.** Dissolve 20 mg 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 1.0 mL of the test solution to 10.0 mL with mobile phase A.

**Reference solution (b).** Dilute 1.0 mL of the test solution to 200.0 mL with mobile phase A.

**Reference solution (c).** Dilute 1.0 mL of reference solution (b) to 10.0 mL with mobile phase A.

**Column:**
- size: l = 0.15 m, Ø = 4 mm;
- stationary phase: spherical end-capped octylsilica gel for chromatography R (5 µm) with a pore size of 15 nm;
- temperature: 60 °C for the column and the tubing preceding the column.

**Mobile phase:**
- mobile phase A: water R adjusted to pH 2.5 with a mixture of equal volumes of perchloric acid R and water R;
- mobile phase B: 0.03 per cent V/V solution of perchloric acid R in acetonitrile R1;

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<th>Mobile phase B</th>
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<td>5</td>
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<td>95 → 40</td>
<td>5 → 60</td>
</tr>
<tr>
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<td>60 → 5</td>
</tr>
</tbody>
</table>

The isocratic step is described for a chromatographic system with a dwell volume (D) of 2 mL. If D is different from 2 mL, correct the gradient times with the value t, calculated using the following expression:

\[ D - 2 \frac{\text{Flow rate}}{t} \]

**Flow rate:** 1.0 mL/min.

**Detection:** spectrophotometer at 215 nm.

**Injection:** 20 µL.

**Identification of impurities:** use the chromatogram supplied with perindopril for peak identification CRS and the chromatogram obtained with reference solution (a) to identify the peaks due to impurities B, E, F, H and K.

**Relative retention** with reference to perindopril (retention time = about 25 min): impurity B = about 0.68; impurity K = about 0.72; impurity E = about 1.2; impurity F = about 1.6; impurity H = about 1.8 (impurity H may be eluted as 1 or 2 peaks).

**System suitability:** reference solution (a):
- peak-to-valley ratio: minimum 3, where H = height above the baseline of the peak due to impurity I and H = height above the baseline of the lowest point of the curve separating this peak from the peak due to impurity K.

**Limits:**
- 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);
- unspecified impurities: for each impurity, not more than 0.4 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.20 per cent);
- unspecified impurities: for each impurity, not more than 5 per cent of the area of the principal peak in the chromatogram obtained with reference solution (b) (0.20 per cent);
- total: not more than twice the area of the principal peak in the chromatogram obtained with reference solution (b) (1.0 per cent);
- disregard limit: 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.

**Sulfated 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 C$_2$H$_4$N$_3$O$_5$.

**STORAGE**
In an airtight container.

**IMPURITIES**
Specified impurities: A, B, E, F, H, I.
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): C, D, G, J, K, L, M, N, O, P, Q, R, S, T, U, V, W, X, Y, Z, AA, BB, CC.

A. (2S,3aS,7aS)-octahydro-1H-indole-2-carboxylic acid,

B. R = H: (2S,3aS,7aS)-1-{[(2S)-2-{[(1S)-1-carboxybutyl]amino}propanoyl]octahydro-1H-indole-2-carboxylic acid (perindoprilat),

C. (2S)-2-{(3S,5aS,9aS,10aS)-3-methyl-1,4-dioxodecahydropyrazino[1,2-α]indol-2(1H)-yl}pentanoic acid,

D. (2S)-2-{(3S,5aS,9aS,10aR)-3-methyl-1,4-dioxodecahydropyrazino[1,2-α]indol-2(1H)-yl}pentanoic acid,

E. R = CH(CH$_3$)$_2$: (2S,3aS,7aS)-1-{[(2S)-2-{[(1S)-1-methylethoxy]carbonyl}butyl]amino}propanoyl]octahydro-1H-indole-2-carboxylic acid,

F. ethyl (2S)-2-{[(3S,5aS,9aS,10aS)]-3-methyl-1,4-dioxodecahydropyrazino[1,2-α]indol-2(1H)-yl}pentanoate,

G. (2S,3aS,7aS)-1-{[(2S)-2-{[(1S)-1-carboxybutyl]amino}propanoyl]octahydro-1H-indole-2-carboxylic acid,

H. (2S,3aS,7aS)-1-{[(2S)-2-{[(5S)-3-cyclohexyl-2,4-dioxodecahydropyrazino[1,2-α]indol-2(1H)-yl]propanoyl]octahydro-1H-indole-2-carboxylic acid,

I. (2RS,3aRS,7aRS)-1-{[(2S)-2-{[(1SR)-1-ethoxycarbonyl]butyl]amino}propanoyl]octahydro-1H-indole-2-carboxylic acid ((±)-1″-epi-perindopril),

J. R = NH$_3$, R′ = CH$_3$: (2S,3aS,7aS)-1-{[(2S)-2-aminopropanoyl]octahydro-1H-indole-2-carboxylic acid,

K. (3S,5aS,9aS,10aS)-3-methyldecahydropyrazino[1,2-α]indole-1,4-dione,
PERITONEAL DIALYSIS, SOLUTIONS FOR

Solutiones ad peritonealem dialysim

DEFINITION
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 administration (3.2).

Several formulations are used. The concentrations of the components per litre of solution are usually in the following range (see Table 862.1):

<table>
<thead>
<tr>
<th>Component</th>
<th>Concentration in mmol/L</th>
<th>Concentration in mEq/L</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</td>
<td>30 - 60</td>
<td>30 - 60</td>
</tr>
<tr>
<td>Hydrogen carbonate</td>
<td>90 - 120</td>
<td>90 - 120</td>
</tr>
<tr>
<td>Glucose</td>
<td>25 - 250</td>
<td></td>
</tr>
</tbody>
</table>

When hydrogen carbonate is present, the solution of sodium hydrogen carbonate is supplied in a container or a separate compartment and is added to the electrolyte solution immediately before use.

Unless otherwise justified and authorised, antioxidants are not added to the solutions.

IDENTIFICATION
According to the stated composition, the solution to be examined gives the following identification reactions (2.3.I):
- potassium: reaction (b);
- calcium: reaction (a);
- sodium: reaction (b);
- chlorides: reaction (a);
- acetates: to 5 mL of the solution to be examined add 1 mL of hydrochloric acid R in a test-tube fitted with a stopper and a bent tube, heat and collect a few millilitres of distillate; carry out reaction (b) of acetates on the distillate;
- lactates, hydrogen carbonates: the identification is carried out together with the assay;
- magnesium: to 0.1 mL of titan yellow solution R add 10 mL of water R, 2 mL of the solution to be examined and 1 mL of 1 M sodium hydroxide; a pink colour is produced;
- glucose: to 5 mL of the solution to be examined, add 2 mL of dilute sodium hydroxide solution R and 0.05 mL of copper sulphate solution R; the solution is blue and clear; heat to boiling; an abundant red precipitate is formed.