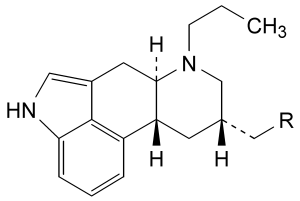


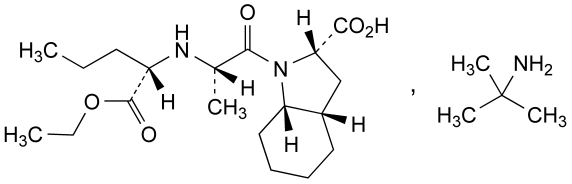
A. R = SO-$CH_3$: (6a*R*,9*R*,10a*R*)-9-[(methylsulphinyl)methyl]-7-propyl-4,6,6a,7,8,9,10,10a-octahydroindolo[4,3-*fg*]quinoline (pergolide sulphoxide),

B. R = $SO_2$-$CH_3$: (6a*R*,9*R*,10a*R*)-9-[(methylsulphonyl)methyl]-7-propyl-4,6,6a,7,8,9,10,10a-octahydroindolo[4,3-*fg*]quinoline (pergolide sulphone).

**01/2008:2019**

# PERINDOPRIL *tert*-BUTYLAMINE

## *tert*-Butylamini perindoprilum



$C_{23}H_{43}N_3O_5$ $M_r$ 441.6
[107133-36-8]

DEFINITION

2-Methylpropan-2-amine (2*S*,3a*S*,7a*S*)-1-[(2*S*)-2-[[(1*S*)-1-(ethoxycarbonyl)butyl]amino]propanoyl]octahydro-1*H*-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).

Dissolve 0.250 g in *ethanol (96 per cent) R* and dilute to 25.0 ml with the same solvent.

B. Infrared absorption spectrophotometry (*2.2.24*).

*Comparison*: *perindopril tert-butylamine 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 $R_F$ 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*).

*Test solution*. Dissolve 0.20 g of the substance to be examined in *methanol R* and dilute to 10.0 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 5.0 ml of reference solution (a) to 20.0 ml with *methanol R*.

*Reference solution (c)*. To 5 ml of reference solution (a) add 5 ml of a 20 g/l 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 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.

*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 *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 100.0 ml with *ethanol (96 per cent) R*. Dilute 1.0 ml of this solution to 10.0 ml with the same solvent.

*Reference solution (b)*. Dissolve 10 mg of *perindopril for stereochemical purity CRS* (containing impurity I) in *ethanol (96 per cent) R* and dilute to 5.0 ml with the same solvent.

*Column*:

– *size*: *l* = 0.25 m, Ø = 4.6 mm;

– *stationary phase*: spherical *octadecylsilyl silica gel for chromatography R* (5 µm);

– *temperature*: 50 °C for the column and the tubing preceding the column (the method has been developed with a temperature of 50 °C for at least 30 cm of the tubing preceding the column).

*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.

*Equilibration*: minimum 4 h.

*Injection*: 10 µl.

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

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

Monographs P

*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 stereochemical purity 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 $H_p$ = 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).

*Limits*:

- *impurity I*: not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.1 per cent);
- *unspecified impurities*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.10 per cent);
- *disregard limit*: disregard any peak with a relative retention with reference to perindopril of less than 0.6 or more than 1.4.

**Related substances**. Liquid chromatography (*2.2.29*). *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 octylsilyl silica 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*;

| Time (min) | Mobile phase A (per cent *V/V*) | Mobile phase B (per cent *V/V*) |
|---|---|---|
| 0 - (5 – *t*) | 95 | 5 |
| (5 – *t*) - (60 – *t*) | 95 → 40 | 5 → 60 |
| (60 – *t*) - (65 – *t*) | 40 → 95 | 60 → 5 |

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:

$$\frac{D - 2}{\text{flow rate}}$$

*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 $H_p$ = height above the baseline of the peak due to impurity B and $H_v$ = 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);
- *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);
- *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);
- *unspecified impurities*: for each impurity, not more than 0.2 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.10 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 (c) (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 $C_{23}H_{43}N_3O_5$.

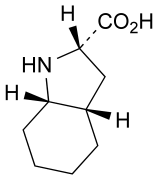
STORAGE

In an airtight container.

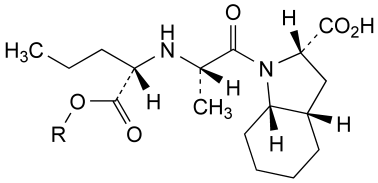
IMPURITIES

*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.*

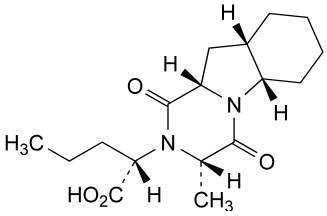


A. (2*S*,3a*S*,7a*S*)-octahydro-1*H*-indole-2-carboxylic acid,

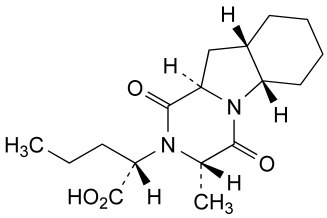


B. R = H: (2*S*,3a*S*,7a*S*)-1-[(2*S*)-2-[[(1*S*)-1-carboxybutyl]amino]propanoyl]octahydro-1*H*-indole-2-carboxylic acid (perindoprilat),

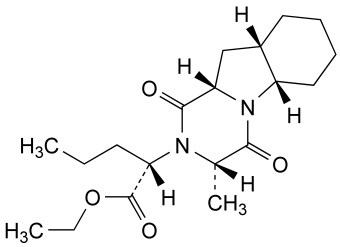
E. R = $CH(CH_3)_2$: (2*S*,3a*S*,7a*S*)-1-[(2*S*)-2-[[(1*S*)-1-[(1-methylethoxy)carbonyl]butyl]amino]propanoyl]octahydro-1*H*-indole-2-carboxylic acid,



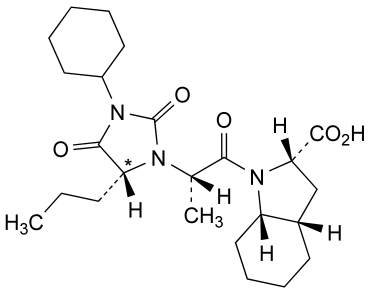
C. (2*S*)-2-[(3*S*,5a*S*,9a*S*,10a*S*)-3-methyl-1,4-dioxodecahydropyrazino[1,2-*a*]indol-2(1*H*)-yl]pentanoic acid,



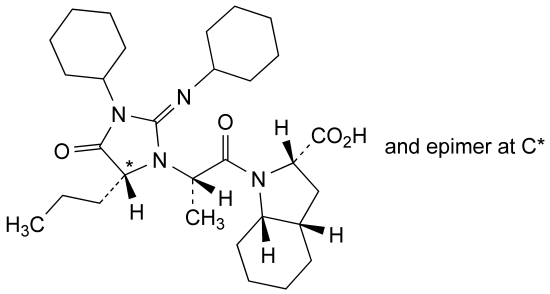
D. (2*S*)-2-[(3*S*,5a*S*,9a*S*,10a*R*)-3-methyl-1,4-dioxodecahydropyrazino[1,2-*a*]indol-2(1*H*)-yl]pentanoic acid,



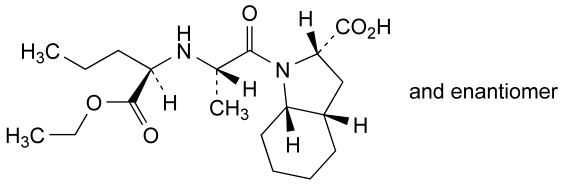
F. ethyl (2*S*)-2-[(3*S*,5a*S*,9a*S*,10a*S*)-3-methyl-1,4-dioxodecahydropyrazino[1,2-*a*]indol-2(1*H*)-yl]pentanoate,



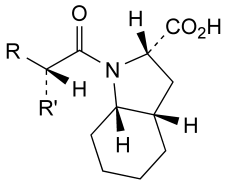

G. (2*S*,3a*S*,7a*S*)-1-[(2*S*)-2-[(5*RS*)-3-cyclohexyl-2,4-dioxo-5-propylimidazolidin-1-yl]propanoyl]octahydro-1*H*-indole-2-carboxylic acid,




H. (2*S*,3a*S*,7a*S*)-1-[(2*S*)-2-[(5*RS*)-3-cyclohexyl-2-(cyclohexylimino)-4-oxo-5-propylimidazolidin-1-yl]propanoyl]octahydro-1*H*-indole-2-carboxylic acid,

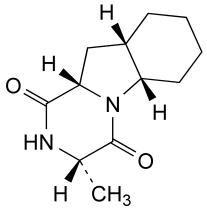



I. (2*RS*,3a*RS*,7a*RS*)-1-[(2*RS*)-2-[[(1*SR*)-1-(ethoxycarbonyl)butyl]amino]propanoyl]octahydro-1*H*-indole-2-carboxylic acid ((±)-1″-*epi*-perindopril),

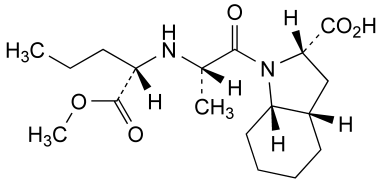


J. R = $NH_2$, R′ = $CH_3$: (2*S*,3a*S*,7a*S*)-1-[(2*S*)-2-aminopropanoyl]octahydro-1*H*-indole-2-carboxylic acid,

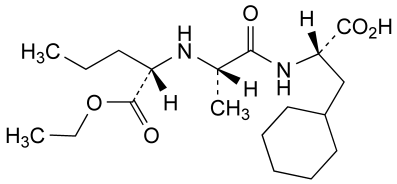
L. R = R′ = H: (2*S*,3a*S*,7a*S*)-1-acetyloctahydro-1*H*-indole-2-carboxylic acid,



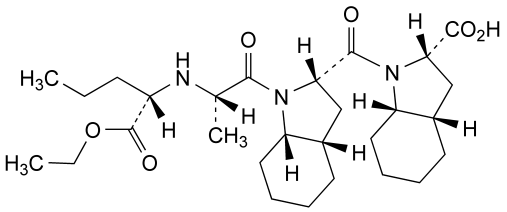
K. (3*S*,5a*S*,9a*S*,10a*S*)-3-methyldecahydropyrazino[1,2-*a*]indole-1,4-dione,



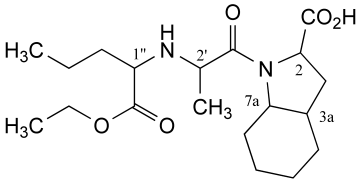
M. (2*S*,3a*S*,7a*S*)-1-[(2*S*)-2-[[(1*S*)-1-(methoxycarbonyl)butyl]amino]propanoyl]octahydro-1*H*-indole-2-carboxylic acid,



N. (2*S*)-3-cyclohexyl-2-[[(2*S*)-2-[[(1*S*)-1-(ethoxycarbonyl)-butyl]amino]propanoyl]amino]propanoic acid,



O. (2*S*,3a*S*,7a*S*)-1-[[(2*S*,3a*S*,7a*S*)-1-[(2*S*)-2-[[(1*S*)-1-(ethoxycarbonyl)butyl]amino]propanoyl]octahydro-1*H*-indol-2-yl]carbonyl]octahydro-1*H*-indole-2-carboxylic acid,



1-[2-[[1-(ethoxycarbonyl)butyl]amino]propanoyl]octahydro-1*H*-indole-2-carboxylic acid,

P. (2*RS*,3a*RS*,7a*RS*)-, (2′*SR*)-, (1″*RS*)-: (±)-2′-*epi*-perindopril,

Q. (2*RS*,3a*RS*,7a*SR*)-, (2′*RS*)-, (1″*RS*)-: (±)-7a-*epi*-perindopril,

R. (2*RS*,3a*SR*,7a*RS*)-, (2′*RS*)-, (1″*RS*)-: (±)-3a-*epi*-perindopril,

S. (2*SR*,3a*RS*,7a*RS*)-, (2′*RS*)-, (1″*RS*)-: (±)-2-*epi*-perindopril,

T. (2*RS*,3a*RS*,7a*RS*)-, (2′*SR*)-, (1″*SR*)-: (±)-1″,2′-di-*epi*-perindopril,

U. (2*RS*,3a*RS*,7a*SR*)-, (2′*RS*)-, (1″*SR*)-: (±)-1″,7a-di-*epi*-perindopril,

V. (2*SR*,3a*SR*,7a*RS*)-, (2′*RS*)-, (1″*RS*)-: (±)-2,3a-di-*epi*-perindopril,

W. (2*SR*,3a*RS*,7a*RS*)-, (2′*RS*)-, (1″*SR*)-: (±)-1″,2-di-*epi*-perindopril,

X. (2*SR*,3a*RS*,7a*SR*)-, (2′*RS*)-, (1″*RS*)-: (±)-2,7a-di-*epi*-perindopril,

Y. (2*SR*,3a*RS*,7a*RS*)-, (2′*SR*)-, (1″*RS*)-: (±)-2,2′-di-*epi*-perindopril,

Z. (2*RS*,3a*SR*,7a*RS*)-, (2′*RS*)-, (1″*SR*)-: (±)-1″,3a-di-*epi*-perindopril,

AA. (2*RS*,3a*SR*,7a*SR*)-, (2′*RS*)-, (1″*RS*)-: (±)-3a,7a-di-*epi*-perindopril,

BB. (2*RS*,3a*SR*,7a*RS*)-, (2′*SR*)-, (1″*RS*)-: (±)-2′,3a-di-*epi*-perindopril,

CC. (2*RS*,3a*RS*,7a*SR*)-, (2′*SR*)-, (1″*RS*)-: (±)-2′,7a-di-*epi*-perindopril.

**01/2008:0862**

# PERITONEAL DIALYSIS, SOLUTIONS FOR

## Solutiones ad peritonealem dialysim

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 0862.-1

| | Expression in mmol | Expression in mEq |
|---|---|---|
| Sodium | 125 - 150 | 125 - 150 |
| Potassium | 0 - 4.5 | 0 - 4.5 |
| Calcium | 0 - 2.5 | 0 - 5.0 |
| Magnesium | 0.25 - 1.5 | 0.50 - 3.0 |
| Acetate and/or lactate and/or hydrogen carbonate | 30 - 60 | 30 - 60 |
| Chloride | 90 - 120 | 90 - 120 |
| Glucose | 25 - 250 | |

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 such as metabisulphite salts are not added to the solutions.

IDENTIFICATION

According to the stated composition, the solution to be examined gives the following identification reactions (*2.3.1*):

- 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.

TESTS

**Appearance of solution**. The solution is clear (*2.2.1*) and not more intensely coloured than reference solution $Y_4$ (*2.2.2, Method I*).

**pH** (*2.2.3*). The pH of the solution is 5.0 to 6.5. If the solution contains hydrogen carbonate, the pH is 6.5 to 8.0.

**Hydroxymethylfurfural**. To a volume of the solution containing the equivalent of 25 mg of glucose, add 5.0 ml of a 100 g/l solution of *p-toluidine R* in *2-propanol R* containing