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Utgivare: Chefsjurist Pär Ödman, Socialstyrelsen

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Utkom från trycket den 18 april 2017

Läkemedelsverkets föreskrifter om ikraftträdande av reviderad monografi för erythromycin ethylsuccinate i Europafarmakopén;

beslutade den 10 april 2017.

Läkemedelsverket föreskriver följande på förslag av Svenska farmakopékommittén och med stöd av 9 kap. 11 § läkemedelsförordningen (2015:458).

1 § Monografin för erythromycin ethylsuccinate i nionde utgåvan av Europafarmakopén (European Pharmacopoeia Ed. 9.0) ska ersättas med monografin enligt bilagan till dessa föreskrifter och ska gälla som föreskrifter i Sverige i frågor som rör läkemedelslagen (2015:315).

Dessa föreskrifter träder i kraft den 1 maj 2017.

Läkemedelsverket

CATARINA ANDERSSON FORSMAN

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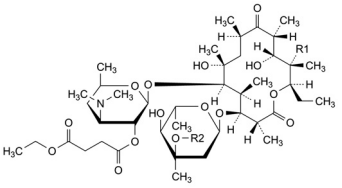
05/2017:0274

ERYTHROMYCIN ETHYLSUCCINATE

Erythromycini ethylsuccinas



Erythromycin (ethylsuccinate)	Mol. Formula	*M*,	R1	R2
A	$C_{43}H_{75}NO_{16}$	862	OH	CH_3
B	$C_{43}H_{75}NO_{15}$	846	H	CH_3
C	$C_{42}H_{73}NO_{16}$	848	OH	H

DEFINITION

Mixture of the ethylsuccinate esters of erythromycin.

Main component: (3*R*,4*S*,5*S*,6*R*,7*R*,9*R*,11*R*,12*R*,13*S*,14*R*)-4-[(2,6-dideoxy-3-*C*-methyl-3-*O*-methyl-α-L-*ribo*-hexopyranosyl)oxy]-14-ethyl-7,12,13-trihydroxy-3,5,7,9,11,13-hexamethyl-6-[[3,4,6-trideoxy-3-(dimethylamino)-2-*O*-(4-ethoxy-4-oxobutanoyl)-β-D-*xylo*-hexopyranosyl]oxy]oxacyclotetradecane-2,10-dione (erythromycin A 2″-(ethyl succinate)).

Semi-synthetic product derived from a fermentation product obtained using a strain of *Streptomyces erythreus*.

Content:

– *sum of erythromycins A, B and C expressed as ethylsuccinates*: 93.0 per cent to 102.0 per cent (anhydrous substance);

– *erythromycin B ethylsuccinate*: maximum 5.0 per cent (anhydrous substance);

– *erythromycin C ethylsuccinate*: maximum 5.0 per cent (anhydrous substance).

CHARACTERS

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

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

IDENTIFICATION

Infrared absorption spectrophotometry (*2.2.24*).

Comparison: *erythromycin ethylsuccinate CRS*.

TESTS

Related substances. Liquid chromatography (*2.2.29*).

Hydrolysis solution. A 20 g/L solution of *dipotassium hydrogen phosphate R* adjusted to pH 8.0 with *phosphoric acid R*.

Test solution. Dissolve 0.115 g of the substance to be examined in 25 mL of *methanol R*. Add 20 mL of the hydrolysis solution, mix and allow to stand at room temperature for at least 12 h. Dilute to 50.0 mL with the hydrolysis solution.

Reference solution (a). Dissolve 40.0 mg of *erythromycin A CRS* in 10 mL of *methanol R* and dilute to 20.0 mL with the hydrolysis solution.

Reference solution (b). Dissolve 10.0 mg of *erythromycin B CRS* and 10.0 mg of *erythromycin C CRS* in 50 mL of *methanol R*. Add 5.0 mL of reference solution (a) and dilute to 100.0 mL with the hydrolysis solution.

Reference solution (c). Dissolve 2 mg of *N-demethylerythromycin A CRS* in 20 mL of reference solution (b).

Reference solution (d). Dilute 3.0 mL of reference solution (a) to 100.0 mL with a mixture of equal volumes of *methanol R* and the hydrolysis solution.

Reference solution (e). Dissolve 40 mg of *erythromycin A CRS*, previously heated at 130 °C for 3 h, in 10 mL of *methanol R* and dilute to 20 mL with the hydrolysis solution.

Column:

- *size*: *l* = 0.25 m, Ø = 4.6 mm;
- *stationary phase*: *styrene-divinylbenzene copolymer R* (8 µm)(1) with a pore size of 100 nm;
- *temperature*: 70 °C using a water-bath for the column and at least one-third of the tubing preceding the column.

Mobile phase: to 50 mL of a 35 g/L solution of *dipotassium hydrogen phosphate R* adjusted to pH 8.0 with *dilute phosphoric acid R*, add 400 mL of *water for chromatography R*, 165 mL of *2-methyl-2-propanol R* and 30 mL of *acetonitrile R1*, and dilute to 1000 mL with *water for chromatography R*.

Flow rate: 2.0 mL/min.

Detection: spectrophotometer at 215 nm.

Injection: 200 µL of the test solution and reference solutions (a), (c), (d) and (e).

Run time: 5 times the retention time of erythromycin A; begin integration after the hydrolysis peak.

Relative retention with reference to erythromycin A (retention time = about 15 min): hydrolysis peak = less than 0.3; impurity B = about 0.45; erythromycin C = about 0.5; impurity C = about 0.9; impurity G = about 1.3; impurity D = about 1.4; impurity F = about 1.5; erythromycin B = about 1.8; impurity E = about 4.3.

System suitability: reference solution (c):

- *resolution*: minimum 0.8 between the peaks due to impurity B and erythromycin C and minimum 5.5 between the peaks due to impurity B and erythromycin A.

Limits:

(1) PLRP-S 1000 Å is suitable.

- *correction factors*: for the calculation of contents, multiply the peak areas of the following impurities by the corresponding correction factor: impurity E = 0.09; impurity F = 0.15; impurity G = 0.14; use the chromatogram obtained with reference solution (e) to identify the peaks due to impurities E and F;
- *any impurity*: not more than the area of the principal peak in the chromatogram obtained with reference solution (d) (3.0 per cent);
- *total*: not more than 1.67 times the area of the principal peak in the chromatogram obtained with reference solution (d) (5.0 per cent);
- *disregard limit*: 0.02 times the area of the principal peak in the chromatogram obtained with reference solution (d) (0.06 per cent).

Free erythromycin. Liquid chromatography (*2.2.29*).

Test solution. Dissolve 0.250 g of the substance to be examined in *acetonitrile R1* and dilute to 50.0 mL with the same solvent.

Reference solution. Dissolve 75.0 mg of *erythromycin A CRS* in *acetonitrile R1* and dilute to 50.0 mL with the same solvent. Dilute 5.0 mL of the solution to 25.0 mL with *acetonitrile R1*.

Column:

- *size*: *l* = 0.25 m, Ø = 4.6 mm;
- *stationary phase*: *octylsilyl silica gel for chromatography R*(2) (5 µm);
- *temperature*: 30 °C.

Mobile phase: mix 35 volumes of *acetonitrile R1* and 65 volumes of a solution containing 3.4 g/L of *potassium dihydrogen phosphate R* and 2.0 g/L of *triethylamine R*, previously adjusted to pH 3.0 with *dilute phosphoric acid R*.

Flow rate: 1 mL/min.

Detection: spectrophotometer at 195 nm.

Injection: 20 µL.

Run time: twice the retention time of erythromycin A (retention time = about 8 min) for the reference solution; twice the retention time of erythromycin ethylsuccinate (retention time = about 24 min) for the test solution.

Limit:

- *free erythromycin*: not more than the area of the principal peak in the chromatogram obtained with the reference solution (6.0 per cent).

Water (*2.5.12*): maximum 3.0 per cent, determined on 0.300 g.

Use a 100 g/L solution of *imidazole R* in *anhydrous methanol R* as the solvent.

Sulfated ash (*2.4.14*): maximum 0.3 per cent, determined on 1.0 g.

ASSAY

Liquid chromatography (*2.2.29*). *Prepare the solutions immediately before use (apart from the test solution).*

(2) Nucleosil C8 is suitable.

Solution A (hydrolysis solution). Dissolve 11.5 g of *dipotassium hydrogen phosphate R* in 900 mL of *water R*, adjust to pH 8.0 with *dilute phosphoric acid R* and dilute to 1000 mL with *water R*.

Solvent mixture: *methanol R*, solution A (40:60 *V/V*).

Test solution. Dissolve 11.5 mg of the substance to be examined in 2.5 mL of *methanol R*. Add 2 mL of solution A, mix and allow to stand at room temperature for at least 12 h. Dilute to 5.0 mL with solution A.

Reference solution (a). Dissolve 40.0 mg of *erythromycin A CRS* in 10.0 mL of *methanol R* and dilute to 20.0 mL with solution A.

Reference solution (b). Dissolve 10.0 mg of *erythromycin B CRS* and 10.0 mg of *erythromycin C CRS* in 50.0 mL of *methanol R* and dilute to 100.0 mL with solution A.

Column:

- *size*: l = 0.25 m, Ø = 4.6 mm;
- *stationary phase*: *end-capped polar-embedded octadecylsilyl amorphous organosilica polymer R* (3.5 µm)(3);
- *temperature*: 65 °C; preheating the mobile phase may be required, for instance by extending the inlet tubing in the oven to 30 cm.

Mobile phase:

- *mobile phase A*: *phosphate buffer solution pH 7.0 R7*, *acetonitrile R1*, *water for chromatography R* (5:35:60 *V/V/V*);
- *mobile phase B*: *phosphate buffer solution pH 7.0 R7*, *water for chromatography R*, *acetonitrile R1* (5:45:50 *V/V/V*);

Time(4) (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - t_R	100	0
t_R - (t_R + 2)	100 → 0	0 → 100
(t_R + 2) - (t_R + 15)	0	100

t_R = retention time of erythromycin B, determined by injecting 20 µL of reference solution (b) and eluting with mobile phase A

Flow rate: 1.0 mL/min.

Detection: spectrophotometer at 210 nm.

Autosampler: set at 4 °C.

Injection: 200 µL.

System suitability: reference solution (a):

- *symmetry factor*: maximum 2.0 for the peak due to erythromycin A;
- *repeatability*: maximum relative standard deviation of 1.0 per cent determined on 6 injections.

Calculate the percentage content of erythromycin A ($C_{37}H_{67}NO_{13}$) using the chromatogram obtained with reference solution (a). Calculate the percentage contents of erythromycin B ($C_{37}H_{67}NO_{12}$) and erythromycin C ($C_{36}H_{65}NO_{13}$) using the chromatogram obtained with reference solution (b).

(3) XTerra RP18 is suitable.
(4) D_0 (dwell volume used for development of the method) = 2.5 mL.

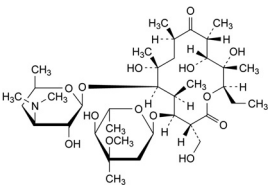
Express the results as erythromycin A ethylsuccinate, erythromycin B ethylsuccinate and erythromycin C ethylsuccinate by multiplying the percentage content of erythromycin A by 1.1744, the percentage content of erythromycin B by 1.1783 and the percentage content of erythromycin C by 1.1777.

For the calculation of content of erythromycin ethylsuccinate, use the sum of erythromycins A, B and C expressed as ethylsuccinates as described above.

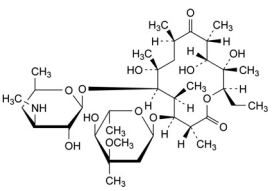
STORAGE

In an airtight container, protected from light.

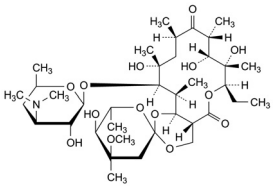
IMPURITIES



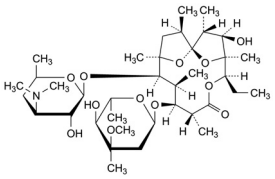
A. (3*R*,4*S*,5*S*,6*R*,7*R*,9*R*,11*R*,12*R*,13*S*,14*R*)-4-[(2,6-dideoxy-3-*C*-methyl-3-*O*-methyl-α-L-*ribo*-hexopyranosyl)oxy]-14-ethyl-7,12,13-trihydroxy-3-(hydroxymethyl)-5,7,9,11,13-pentamethyl-6-[[3,4,6-trideoxy-3-(dimethylamino)-β-D-*xylo*-hexopyranosyl]oxy]oxacyclotetradecane-2,10-dione (erythromycin F),



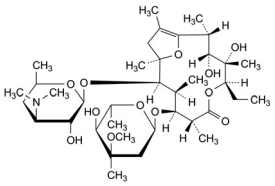
B. (3*R*,4*S*,5*S*,6*R*,7*R*,9*R*,11*R*,12*R*,13*S*,14*R*)-4-[(2,6-dideoxy-3-*C*-methyl-3-*O*-methyl-α-L-*ribo*-hexopyranosyl)oxy]-14-ethyl-7,12,13-trihydroxy-3,5,7,9,11,13-hexamethyl-6-[[3,4,6-trideoxy-3-(methylamino)-β-D-*xylo*-hexopyranosyl]oxy]oxacyclotetradecane-2,10-dione (3″-*N*-demethylerythromycin A),



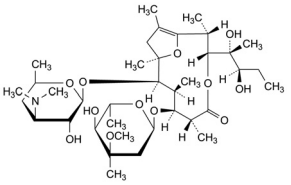
C. (2*S*,4a*R*,4′*R*,5′*S*,6′*S*,7*R*,8*S*,9*R*,10*R*,12*R*,14*R*,15*R*,16*S*,16a*S*)-7-ethyl-5′,8,9,14-tetrahydroxy-4′-methoxy-4′,6′,8,10,12,14,16-heptamethyl-15-[[3,4,6-trideoxy-3-(dimethylamino)-β-D-*xylo*-hexopyranosyl]oxy]hexadecahydrospiro[5*H*,11*H*-1,3-dioxino[5,4-*c*]oxacyclotetradecin-2,2′-pyrane]-5,11-dione (erythromycin E),



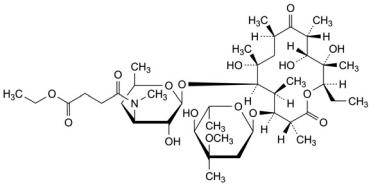
D. (1*S*,2*R*,3*R*,4*S*,5*R*,8*R*,9*S*,10*S*,11*R*,12*R*,14*R*)-9-[(2,6-dideoxy-3-*C*-methyl-3-*O*-methyl-α-L-*ribo*-hexopyranosyl)oxy]-5-ethyl-3-hydroxy-2,4,8,10,12,14-hexamethyl-11-[[3,4,6-trideoxy-3-(dimethylamino)-β-D-*xylo*-hexopyranosyl]oxy]-6,15,16-trioxatricyclo[10.2.1.1^{1,4}]hexadecan-7-one (anhydroerythromycin A),



E. (2*R*,3*R*,4*S*,5*R*,8*R*,9*S*,10*S*,11*R*,12*R*)-9-[(2,6-dideoxy-3-*C*-methyl-3-*O*-methyl-α-L-*ribo*-hexopyranosyl)oxy]-5-ethyl-3,4-dihydroxy-2,4,8,10,12,14-hexamethyl-11-[[3,4,6-trideoxy-3-(dimethylamino)-β-D-*xylo*-hexopyranosyl]oxy]-6,15-dioxabicyclo[10.2.1]pentadec-1(14)-en-7-one (erythromycin A enol ether),



F. (2*R*,3*R*,6*R*,7*S*,8*S*,9*R*,10*R*)-7-[(2,6-dideoxy-3-*C*-methyl-3-*O*-methyl-α-L-*ribo*-hexopyranosyl)oxy]-3-[(1*R*,2*R*)-1,2-dihydroxy-1-methylbutyl]-2,6,8,10,12-pentamethyl-9-[[3,4,6-trideoxy-3-(dimethylamino)-β-D-*xylo*-hexopyranosyl]oxy]-4,13-dioxabicyclo[8.2.1]tridec-1(12)-en-5-one (pseudoerythromycin A enol ether),



G. (3*R*,4*S*,5*S*,6*R*,7*R*,9*R*,11*R*,12*R*,13*S*,14*R*)-4-[(2,6-dideoxy-3-*C*-methyl-3-*O*-methyl-α-L-*ribo*-hexopyranosyl)oxy]-14-ethyl-7,12,13-trihydroxy-3,5,7,9,11,13-hexamethyl-6-[[3,4,6-trideoxy-3-[(4-ethoxy-4-oxobutanoyl)methylamino]-β-D-*xylo*-hexopyranosyl]oxy]oxacyclotetradecane-2,10-dione (3″-*N*-demethyl-3″-*N*-(ethoxysuccinyl)erythromycin A).

HSLF-FS kan laddas ner via Läkemedelsverket.
Webb: www.lakemedelsverket.se

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