EAG/Panel/Working Party	Antibiotics
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Deadline for Comment	31st December 2018
Target Publication Date (subject to change)	BP 2020
Notes: Revised Monograph. Changes made to the Related Substances and assay methods, based on Ph. Eur. drug substance monograph. Comments on the performability of the method are specifically requested.	

Erythromycin Lactobionate for Infusion

Erythromycin Lactobionate Infusion

Erythromycin Lactobionate for Intravenous Infusion

DEFINITION

Erythromycin Lactobionate for Infusion is a sterile material consisting of Erythromycin Lactobionate with or without excipients. It is supplied in a sealed container.

The contents of the sealed container comply with the requirements for Powders for Injections or Infusions stated under Parenteral Preparations and with the following requirements.

Content of erythromycins, calculated as the sum of erythromycin A ($C_{37}H_{67}NO_{13}$), erythromycin B ($C_{37}H_{67}NO_{12}$) and erythromycin C ($C_{36}H_{65}NO_{13}$)
95.0 to 110.0% of the stated amount of erythromycin.

IDENTIFICATION

A. The *infrared absorption spectrum*, Appendix II A, is concordant with the *reference spectrum* of erythromycin lactobionate *(RS 126)*.

B. In the test for Assay, the retention time of the principal peak in the chromatogram obtained with solution (1) is similar to that of the peak due to erythromycin A in the chromatogram obtained with solution (2).

TESTS

Acidity or alkalinity
pH of a solution containing the equivalent of 1.34% w/v of erythromycin, 6.5 to 7.5, Appendix V L.

Related substances
Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in a solvent mixture of 40 volumes of a 1.15 % w/v solution of *dipotassium hydrogen phosphate* previously adjusted to pH 8.0 using *dilute phosphoric acid* and 60 volumes of *methanol.*

Carry out the following procedure protected from light and prepare solutions immediately before use.

(1) Dissolve a quantity of the contents of a sealed container to produce a solution containing 0.4% w/v erythromycin.

(2) Dilute 1 volume of solution (1) to 100 volumes.

(3) 0.4% w/v of *erythromycin A EPCRS*.

(4) 0.02% w/v of each of *erythromycin B EPCRS* and *erythromycin C EPCRS*.

(5) 0.4% w/v of *erythromycin for system suitability EPCRS* in the solvent mixture.

CHROMATOGRAPHIC CONDITIONS

(a) Use a column (25 cm × 4.6 mm) packed with *end-capped polar-embedded octadecylsilyl amorphous organosilica polymer* (3.5 µm) (XTerra RP18 is suitable).

(b) Use gradient elution and the mobile phase described below.

(c) Use a flow rate of 1.0 mL per minute.

(d) Maintain the temperature of the column and at least one third of the tubing preceding the column at 65°.

(e) Use a detection wavelength of 210 nm.

(f) Inject 100 µL of each solution.

MOBILE PHASE

Mobile phase A 5 volumes of *phosphate buffer solution pH 7.0 R7*, 35 volumes of *acetonitrile* and 60 volumes of *water.*

Mobile phase B 5 volumes of *phosphate buffer solution pH 7.0 R7*, 45 volumes of *water* and 50 volumes of *acetonitrile.*

Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
0 – *44*	100	0	isocratic
44 – 46	100→0	0→100	linear gradient
46 – 61	0	100	isocratic
61 – 63	0→100	100→0	linear gradient
63 – 78	100	0	re-equilibration

When the chromatograms are recorded using the prescribed conditions the retention time of erythromycin A is about 23 minutes. The retention times relative to erythromycin A are: impurity A, about 0.4; impurity B, about 0.5; erythromycin C, about 0.55; impurity L, about 0.63; impurity C, about 0.9; impurity D, about 1.61; erythromycin B, about 1.75; impurity F, about 1.81; impurity E, about 2.3.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (5):

the *resolution factor* between the peaks corresponding to impurity B and erythromycin C is at least 1.2;

the peak-to-valley ratio is at least 1.5 where Hp is the height above the baseline of the peak due to impurity F and Hv is the height above the baseline of the lowest point of the curve separating this peak from the peak due to erythromycin B;

the peak-to-valley ratio is at least 2.0 where Hp is the height above the baseline of the peak due to impurity C and Hv is the height above the baseline of the lowest point of the curve separating this peak from the peak due to erythromycin A.

If necessary, adjust the concentration of *acetonitrile* in the mobile phases and/or the gradient to obtain the required separation.

LIMITS

Identify any peaks in the chromatogram obtained with solution (1) corresponding to impurities D, E, F and L using solution (5) and multiply the areas of these peaks by the corresponding correction factors: impurity D, 2.00; impurity E, 0.08; impurity F, 0.08; impurity L, 0.11.

In the chromatogram obtained with solution (1):

The area of any peak corresponding to impurity C is not greater than 3 times the area of the principal peak in the chromatogram obtained with solution (2) (3%);

The area of any peak corresponding to impurity A or B is not greater than 2 times the area of the principal peak in the chromatogram obtained with solution (2) (2%);

The area of any peak corresponding to impurity D, E, or F, is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (1%);

The area of any peak corresponding to impurity L is not greater than 0.4 times the area of the principal peak in the chromatogram obtained with solution (2) (0.4%);

the area of any other secondary peak, other than those peaks corresponding to erythromycin A, erythromycin B and erythromycin C, is not greater than 0.4 times the area of the principal peak in the chromatogram obtained with solution (2) (0.4%);

the sum of the areas of any such peaks is not greater than 7 times the area of the principal peak in the chromatogram obtained with solution (2) (7%).

Disregard any peaks due to excipients and any peak with an area less than 0.05 times the area of the principal peak in the chromatogram obtained with solution (2) (0.05%).

The content of each of erythromycin B and erythromycin C, as determined under Assay, is not more than 5%.

ASSAY

Determine the weight of the contents of 10 containers as described in the test for *uniformity of weight*, Appendix XII C1, Powders for Parenteral Administration.

Carry out the method for liquid chromatography, Appendix III D, using the following solutions in a solvent mixture of 40 volumes of a 1.15 % w/v solution of *dipotassium hydrogen phosphate* previously adjusted to pH 8.0 using *dilute phosphoric acid* and 60 volumes of *methanol*.

Carry out the following procedure protected from light and prepare solutions immediately before use.

(1) Dissolve a quantity of the contents of a sealed container to produce a solution containing 0.4% w/v erythromycin.

(2) 0.4% w/v of *erythromycin A EPCRS*.

(3) 0.02% w/v of each of *erythromycin B EPCRS* and *erythromycin C EPCRS*.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions under Related substances may be used.

DETERMINATION OF CONTENT

Calculate the content of erythromycin A ($C_{37}H_{67}NO_{13}$), erythromycin B ($C_{37}H_{67}NO_{12}$) and erythromycin C ($C_{36}H_{65}NO_{13}$) in the infusion using the declared content of $C_{37}H_{67}NO_{13}$ in *erythromycin A EPCRS*, $C_{37}H_{67}NO_{12}$ in *erythromycin B EPCRS* and $C_{36}H_{65}NO_{13}$ in *erythromycin C EPCRS*.

LABELLING

The label of the sealed container states the quantity of active ingredient contained in it in terms of the equivalent amount of erythromycin.

IMPURITIES

The impurities limited by the requirements of this monograph include those listed under Erythromycin.