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Cilastatin and Imipenem for Infusion

Cilastatin and Imipenem for Injection

Details for the public consultation of this monograph are as follows:

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Deadline for Comment	31st March 2022
Target Publication (subject to change)	BP 2023
Notes:	**REVISED** **Acidity or Alkalinity** Updated to reflect product concentrations **Colour and Clarity of solution** Updated to reflect product concentrations **Related Substances** Various updates to reflect analytical procedure donor method **Assay** Update to diluent to reflect donor method If limits are too restrictive, please provide batch/stability data to demonstrate that an increase is required.

Action and use

Dehydropeptidase-I inhibitor; inhibition of the renal metabolism of imipenem + Carbapenem antibacterial

DEFINITION

Cilastatin and Imipenem for Infusion is a sterile mixture of Cilastatin Sodium and Imipenem Monohydrate 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 cilastatin, $C_{16}H_{25}N_2NaO_2S$

95.0 to 105.0% of the stated amount.

Content of imipenem, $C_{12}H_{17}N_3O_4S$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. To a quantity of the contents of a sealed container containing 500 mg of imipenem, add 4 mL of methanol and shake for 5 minutes. Add a further 3 mL of *methanol* and shake for a further 10 minutes. Filter the resulting suspension and reserve the filtrate for test B. The *infrared absorption spectrum* of the dried residue, Appendix II A, is concordant with that obtained with *imipenem monohydrate EPCRS*, prepared in the same manner.

B. Dry the filtrate reserved in test A at a temperature not exceeding 40°. The *infrared absorption spectrum* of the dried filtrate, Appendix II A, is concordant with that obtained with *cilastatin sodium EPCRS*, prepared in the same manner.

TESTS

Acidity or Alkalinity

pH of a solution containing the equivalent of 0.5% w/v cilastatin in 0.9% w/v sodium chloride, 6.5 to 8.5, Appendix V L.

Clarity and colour of solution

A solution containing the equivalent of 0.5% w/v of cilastatin in 0.9% w/v sodium chloride is not more intensely coloured than *reference solution, Y_5*, Appendix IV B.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in 0.9% w/v *sodium chloride*. *Prepare the solutions immediately before use.*

(1) Dissolve a quantity of the contents of a sealed container containing the equivalent of 160 mg of cilastatin in 0.9% w/v *sodium chloride*, and dilute to 100 mL.

(2) Dilute 1 volume of solution (1) to 200 volumes.

(3) 0.1% w/v of *cilastatin for system suitability 1 EPCRS* (containing cilastatin impurities A, B, E, F, G (epimer-2) and H).

(4) 0.15% w/v of *cilastatin for system suitability 2 EPCRS* (containing cilastatin impurities C and G (epimer-1)).

(5) Dissolve 5 mg of *imipenem EPCRS* in 8 mL of 0.005M *sulphuric acid* and shake at room temperature for 5 minutes. Add 10 mg of *sodium carbonate* and dilute to 10 mL with *water* (generation of imipenem impurity B).

(6) Dilute 1 volume of a solution containing 0.08% w/v each of *cilastatin EPCRS* and *imipenem EPCRS* to 100 volumes.

(7) 0.00064% w/v mesityl oxide (cilastatin impurity D).

(8) Dilute 1 volume of solution (2) to 5 volumes.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel colum (25 cm × 4.6 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (5 µm) (YMC Pack ODS-AQ is suitable).

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

(c) Use a flow rate of 1.5 mL per minute.

(d) Use a column temperature of 30°.

(e) Use an autosampler temperature of 5°.

(f) Use a detection wavelength of 210 nm.

(g) Inject 20 µL of each solution.

MOBILE PHASE

Mobile phase A A 13.6% w/v solution of *potassium dihydrogen orthophosphate* adjusted to pH to 5.6 with a 10% w/v solution of *potassium hydroxide*.

Mobile phase B 1 volume of a 13.6 % w/v solution of *potassium dihydrogen orthophosphate* previously adjusted to pH 3.0 with a 5% v/v solution of *orthophosphoric acid* and 1 volume of *acetonitrile R1*.

Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
0-3	100	0	isocratic
3-30	100→90	0→10	linear gradient
30-68	90→60	10→40	linear gradient
68-78	60→30	40→70	linear gradient
78-88	30	70	isocratic
88-89	30→100	70→0	linear gradient
89-95	100	0	re-equillibration

When the chromatograms are recorded under the prescribed conditions, the relative retentions with reference to cilastatin (retention time about 48 minutes) are: imipenem impurity B (epimer 1), about 0.08 ; imipenem impurity B (epimer 2), about 0.09; imipenem impurity A, about 0.18; imipenem, about 0.22; cilastatin impurity E, about 0.25; cilastatin impurity A (epimer 1), about 0.64; cilastatin impurity A (epimer 2), about 0.66; cilastatin impurity F, about 0.98; cilastatin impurity G (epimer 1), about 1.04; cilastatin impurity G (epimer 2), about 1.07; cilastatin impurity D, about 1.15; cilastatin impurity H, about 1.20; cilastatin impurity B, about 1.30; cilastatin impurity C, about 1.40.

SYSTEM SUITABILITY

The test is not valid unless:

in the chromatogram obtained with solution (4), the *peak-to-valley ratio* is at least 1.8 where *Hp* is the height above the baseline of the peak due to impurity G (epimer 1) and *Hv* is the height above the baseline of the lowest point of the curve separating this peak from the peak due to cilastatin;

in the chromatogram obtained with solution (5), the *peak-to-valley ratio* is at least 1.8 where *Hp* is the height above the baseline of the peak due to imipenem impurity B (epimer 1) and *Hv* is the height above the baseline of the lowest point of the curve separating this peak from the peak due to imipenem impurity B (epimer 2);

in the chromatogram obtained with solution (6), the symmetry factor of the peaks due to imipenem and cilastatin are not greater than 1.3.

Inject solution (6) not less than six times. The test is not valid unless the relative standard deviation of the peak areas of the imipenem and cilistatin peak is not more than 5.0%.

LIMITS

For imipenem

Identify any peaks corresponding to imipenem impurity A and impurity B in the chromatogram obtained with solution (1) using the relative retention times. Multiply the area of any peak corresponding to imipenem impurity A by a correction factor of 2.4.

In the chromatogram obtained with solution (1):

the area of any peak corresponding to imipenem impurity A is not greater than twice the area of the peak due to imipenem in the chromatogram obtained with solution (2) (1.0%);

the areas of any peaks corresponding to imipenem impurity B are not greater than 0.6 times the area of the peak due to imipenem in the chromatogram obtained with solution (2) (0.3% each);

the area of any other *secondary peak* is not greater than twice the area of the peak due to imipenem in the chromatogram obtained with solution (8) (0.2%);

the sum of the areas of any *secondary peaks* due to imipenem is not greater than 4 times the area of the peak due to imipenem in the chromatogram obtained with solution (2) (2.0%).

Disregard any peak with an area less than the area of the peak due to imipenem in the chromatogram obtained with solution (8) (0.1%) and any peak eluting after 20 minutes.

For cilastatin

Identify any peaks in the chromatogram obtained with solution (1) corresponding to cilistatin impurities A, B, E, F, G (epimer-2) and H with solution (3), to cilistatin impurities C and G (epimer-1) with solution (4) and to cilistatin impurity D with solution (7). Multiply the areas of the following peaks by the corresponding correction factors: impurity C, 1.3; impurity E, 3.3; impurity G, 1.6.

the sum of the areas of any peaks corresponding to cilastatin impurity A is not greater than the area of the peak due to cilastatin in the chromatogram obtained with solution (2) (0.5%);

the area of any peak corresponding to cilastatin impurity C is not greater than 0.8 times the area of the peak due to cilastatin in the chromatogram obtained with solution (2) (0.4%);

the area of any peak corresponding to cilastatin impurity E is not greater than 0.6 times the area of the peak due to cilastatin in the chromatogram obtained with solution (2) (0.3%);

the area of any peaks corresponding to cilastatin impurity B, F, G or H are not greater than 1.5 times the area of the peak due to cilastatin in the chromatogram obtained with solution (8) (0.15% each);

the area of any other *secondary peak* is not greater than the area of the peak due to cilastatin in the chromatogram obtained with solution (8) (0.1%);

the sum of the areas of any *secondary peaks* due to cilastatin is not greater than 3 times the area of the peak due to cilastatin in the chromatogram obtained with solution (2) (1.5%);

Disregard any peak due to impurity D (7), any peak with an area less than the area of the peak due to cilastatin in the chromatogram obtained with solution (8) (0.1%), and any peak eluting before 20 minutes.

Loss on drying

When dried *in vacuo* at 60°, at a pressure not exceeding 0.67 kPa for 3 hours, does not lose more than 3.5% of its weight. Use 0.3 g.

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 solution containing 0.0135% w/v potassium dihydrogen orthophosphate adjusted to pH 6.8 with 0.5N sodium hydroxide or 0.5M orthophosphoric acid (Solution A).

(1) Dissolve a quantity of mixed contents of the 10 containers, containing the equivalent of 0.5 g of cilastatin in 20 mL of 0.9% w/v sodium chloride and 100 mL solution A. Dilute 1 volume of the resulting solution to 10 volumes.
(2) 0.05% w/v of *imipenem EPCRS* in a solution containing 2 volumes of 0.1% w/v sodium bicarbonate, 20 volumes of 0.9% w/v sodium chloride and 78 volumes of solution A.
(3) 0.05% w/v of *cilastatin EPCRS* in a solution containing 2 volumes of 0.1% w/v sodium bicarbonate, 20 volumes of 0.9% w/v sodium chloride and 78 volumes of solution A..

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm x 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Hypersil-ODS is suitable).
(b) Use isocratic elution and the mobile phase described below.
(c) Use a flow rate of 2 mL per minute.
(d) Use a column temperature of 50°.
(e) Use a detection wavelength of 254 nm.
(f) Inject 10 µL of each solution.

MOBILE PHASE

Dissolve 2.0 g of sodium hexanesulphonate in 800 mL of solution A and adjust to pH 6.8 with 0.5N sodium hydroxide or 0.5M orthophosphoric acid. Dilute to 1000 mL with solution A.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (2), the *symmetry factor* of the peak due to imipenem is between 0.8 and 2.0.

The test is not valid unless, in the chromatogram obtained with solution (3), the *symmetry factor* of the peak due to cilastatin is between 0.8 and 2.0

DETERMINATION OF CONTENT

Calculate the content of imipenem, $C_{12}H_{17}N_3O_4S,H_2O$, in a container of average content weight from the chromatograms obtained and using the declared content of $C_{12}H_{17}N_3O_4S,H_2O$, in *imipenem EPCRS*.

Calculate the content of cilastatin, $C_{16}H_{25}N_2NaO_5S$, in a container of average content weight from the chromatograms obtained and using the declared content of $C_{16}H_{25}N_2NaO_5S$, in *cilastatin EPCRS*

LABELLING

The quantity of active ingredient is stated in terms of the equivalent amount of cilastatin and imipenem.

IMPURITIES

The impurities limited by the requirements of this monograph include those listed under Imipenem Monohydrate and Cilastatin Sodium