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Imipenem and Cilastatin for Injection

» Imipenem and Cilastatin for Injection is a sterile mixture of Imipenem, Cilastatin Sodium, and Sodium Bicarbonate. It contains not less than 90.0 percent and not more than 115.0 percent of the labeled amounts of imipenem ($C_{12}H_{17}N_3O_4S$) and cilastatin ($C_{16}H_{26}N_2O_5S$).

Packaging and storage—Preserve as described in *Packaging and Storage Requirements ⟨659⟩, Injection Packaging, Packaging for constitution*, and store at controlled room temperature.

Labeling—Label it to indicate that after constitution it is to be solubilized in a suitable parenteral fluid prior to intravenous infusion.

USP Reference standards ⟨11⟩—

USP Cilastatin Ammonium Salt RS
USP Imipenem Monohydrate RS

Constituted solution—At the time of use, it meets the requirements for *Injections and Implanted Drug Products ⟨1⟩, Specific Tests, Completeness and clarity of solutions*.

Identification—The retention times of the peaks for imipenem and cilastatin in the chromatogram of the *Assay preparation* correspond to those in the chromatograms of the *Imipenem standard preparation* and the *Cilastatin standard preparation*, as obtained in the *Assay*.

Bacterial Endotoxins Test ⟨85⟩ —It contains not more than 0.17 USP Endotoxin Unit per mg of imipenem and not more than 0.17 USP Endotoxin Unit per mg of cilastatin.

Sterility Tests ⟨71⟩ —It meets the requirements when tested as directed for *Membrane Filtration* under *Test for Sterility of the Product to be Examined*, the specimen being dissolved in *Fluid A*.

pH ⟨791⟩: between 6.5 and 8.5, when constituted as directed in the labeling.

Uniformity of dosage units ⟨905⟩:meets the requirements.

Loss on drying ⟨731⟩—Dry about 100 mg in vacuum at a pressure not exceeding 5 mm of mercury at 60° for 3 hours: it loses not more than 3.5% of its weight.

Particulate Matter in Injections ⟨788⟩: meets the requirements for small-volume injections.

Assay—

pH 6.8 Buffer—Dissolve 0.54 g of monobasic potassium phosphate in 3600 mL of water, adjust with 0.5 N sodium hydroxide or 0.5 M phosphoric acid to a pH of 6.8 ± 0.1, dilute with water to make 4000 mL of solution, and mix. Pass this solution through a filter of 0.5-µm or finer porosity.

Mobile phase—Dissolve 2.0 g of sodium 1-hexanesul fonate in 800 mL of *pH 6.8 Buffer*, adjust with 0.5 N sodium hydroxide or 0.5 M phosphoric acid to a pH of 6.8 ± 0.1, and dilute with *pH 6.8 Buffer* to make 1000 mL of solution. Pass this solution through a filter of 0.5-µm or finer porosity, and degas. Make adjustments if necessary (see *System Suitability* under *Chromatography ⟨621⟩*).

Imipenem standard preparation—Transfer about 13 mg of USP Imipenem Monohydrate RS, accurately weighed, to a 25-mL volumetric flask. Add 5 mL of saline TS, 0.5 mL of a 0.1% solution of sodium bicarbonate, and about 15 mL of *pH 6.8 Buffer*, and dissolve by shaking and sonicating. [Note—The duration of sonication should not exceed 1 minute.] Dilute with *pH 6.8 Buffer* to volume, and mix. This solution contains the equivalent of about 500 µg of anhydrous imipenem per mL. Use this solution immediately.

Cilastatin standard preparation—Transfer about 12.5 mg of USP Cilastatin Ammonium Salt RS, accurately weighed, to a 25-mL volumetric flask. Add 5 mL of saline TS, 0.5 mL of a 0.1% solution of sodium bicarbonate, and about 15 mL of *pH 6.8 Buffer*, and dissolve by shaking and sonicating. [Note—The duration of sonication should not exceed 1 minute.] Dilute with *pH 6.8 Buffer* to volume, and mix. This solution contains the equivalent of about 500 µg of cilastatin per mL. Use this solution immediately.

Assay preparation—Constitute Imipenem and Cilastatin for Injection in a volume of saline TS, accurately measured, corresponding to the volume of solvent specified in the labeling. Quantitatively transfer this suspension to a 100-mL volumetric flask with the aid of *pH 6.8 Buffer*, dilute with *pH 6.8 Buffer* to volume, and mix. Dilute an accurately measured volume of this solution quantitatively with *pH 6.8 Buffer* to obtain an *Assay preparation* having a concentration of about 500 µg of imipenem per mL.

Chromatographic system (see *Chromatography ⟨621⟩*)—The liquid chromatograph is equipped with a 254-nm detector and a 4.6-mm × 30-cm column that contains packing L1, and is maintained at a temperature of 50 ± 1.0°. The flow rate is about 2 mL per minute. Chromatograph the *Imipenem standard preparation*, and record the peak responses as directed for *Procedure:* the column efficiency determined from the

imipenem peak is not less than 600 theoretical plates when calculated by the formula:

$$5.545(t/W_{h/2})^2$$

the tailing factor for the imipenem peak is not more than 1.5 when calculated by the formula:

$$W_{0.1}/2f$$

where $W_{0.1}$ is the width of the peak at 10% height, and the relative standard deviation for replicate injections is not more than 2.0%.

Chromatograph the *Cilastatin standard preparation*, and record the peak responses as directed for *Procedure:* the column efficiency determined from the cilastatin peak is not less than 600 theoretical plates when calculated by the formula:

$$5.545(t/W_{h/2})^2$$

the tailing factor for the cilastatin peak is not more than 1.5 when calculated by the formula:

$$W_{0.1}/2f$$

and the relative standard deviation for replicate injections is not more than 2.0%.

Procedure—Separately inject equal volumes (about 10 µL) of the *Imipenem standard preparation*, the *Cilastatin standard preparation*, and the *Assay preparation* into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the quantities, in mg, of anhydrous imipenem ($C_{12}H_{17}N_3O_4S$) and cilastatin ($C_{16}H_{26}N_2O_5S$) in the container, taken by the same formula:

$$(CPL/D)(r_U/r_S)$$

in which C is the concentration, in mg per mL, of USP Imipenem Monohydrate RS or USP Cilastatin Ammonium Salt RS in the appropriate *Standard preparation; P* is the content, in µg per mg, of anhydrous imipenem ($C_{12}H_{17}N_3O_4S$) or cilastatin ($C_{16}H_{26}N_2O_5S$) in the relevant Reference Standard; L is the labeled quantity, in mg, of imipenem or cilastatin in the container; D is the concentration, in µg per mL, of imipenem or cilastatin in the *Assay preparation* based on the labeled quantity in the container and the extent of dilution; and r_U and r_S are the peak responses of the corresponding analyte obtained from the *Assay preparation* and the appropriate *Standard preparation,* respectively.

Auxiliary Information - Please check for your question in the FAQs before contacting USP.

Topic/Question	Contact	Expert Committee
IMIPENEM AND CILASTATIN FOR INJECTION	Documentary Standards Support	SM12020 Small Molecules 1

Chromatographic Database Information: Chromatographic Database

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