

PART 441—PENEM ANTIBIOTIC DRUGS

Subpart A—Bulk Drugs

Sec.

441.20a Sterile imipenem monohydrate.

Subpart B [Reserved]

Subpart C—Injectable Dosage Forms

441.220 Imipenem monohydrate-cilastatin sodium injectable dosage forms.

441.220a Sterile imipenem monohydrate-cilastatin sodium.

441.220b Imipenem monohydrate-cilastatin sodium for injection.

AUTHORITY: 21 U.S.C. 357.

Subpart A—Bulk Drugs

§ 441.20a Sterile imipenem monohydrate.

(a) *Requirements for certification—(1) Standards of identity, strength, quality, and purity.* Imipenem monohydrate is the monohydrate form of [5*R*-[5 α , 6 α , (*R*^{*})]-6-(1-hydroxyethyl)-3-[[2-[(iminomethyl) amino]ethyl]thio]-7-oxo-1-azabicyclo[3.2.0]-hept-2-ene-2-carboxylic acid. It is a white to tan colored powder. It is so purified and dried that:

(i) Its potency is not less than 900 micrograms and not more than 1,050 micrograms of imipenem per milligram on an anhydrous basis.

(ii) It is sterile.

(iii) It is nonpyrogenic.

(iv) Its loss on drying is not less than 5.0 percent and not more than 8.0 percent.

(v) Its specific rotation in an aqueous solution containing 5 milligrams of imipenem per milliliter at 25 °C is +85° to +95° on an anhydrous basis.

(vi) It gives a positive identity test.

(vii) It is crystalline.

(2) *Labeling.* It shall be labeled in accordance with the requirements of § 432.5 of this chapter.

(3) *Requests for certification; samples.* In addition to complying with the requirements of § 431.1 of this chapter, each such request shall contain:

(i) Results of tests and assays on the batch for potency, sterility, pyrogens, loss on drying, specific rotation, identity, and crystallinity.

(ii) Samples, if required by the Director, Center for Drug Evaluation and Research:

(a) For all tests except sterility: 10 packages, each containing approximately 500 milligrams.

(b) For sterility testing: 20 packages, each containing equal portions of approximately 300 milligrams.

(b) *Tests and methods of assay—(1) Potency.* Proceed as directed in § 436.216 of this chapter, using a column heater which will maintain a 50 °C column temperature, and ultraviolet detection system operating at a wavelength of 254 nanometers, a column packed with microparticulate (3 to 10 micrometers in diameter) reversed phase packing material such as octyl or octadecyl hydrocarbon bonded silicas, a flow rate of 2.0 milliliters per minute, and a known injection volume of 10 microliters. Reagents, working standard and sample solutions, system suitability requirements, and calculations are as follows:

(i) *Reagents—(a) Phosphate buffer, 0.001M.* Dissolve 272 milligrams of monobasic potassium phosphate in 1,800 milliliters of deionized water. Adjust the pH to 6.8 with 0.5*N* sodium hydroxide or dilute phosphoric acid. Dilute to 2,000 milliliters with deionized water and filter prior to use.

(b) *Mobile phase.* Dissolve 2.0 grams of 1-hexanesulfonic acid, sodium salt in 800 milliliters of phosphate buffer, 0.001*M*. Adjust the pH to 6.8 with 0.5*N* sodium hydroxide or dilute phosphoric acid and dilute to 1,000 milliliters with phosphate buffer, 0.001*M*. Filter and degas the mobile phase just prior to its introduction into the chromatograph pumping system.

(c) *0.1 Percent bicarbonate solution.* Dissolve 50 milligrams of sodium bicarbonate in 40 milliliters of phosphate buffer, 0.001*M*, and dilute to 50 milliliters with phosphate buffer, 0.001*M*.

(d) *0.9 Percent saline solution.* Dissolve 9.0 grams of sodium chloride in 800 milliliters of deionized water and dilute to 1.0 liter with deionized water.

(ii) *Preparations of working standard and sample solutions—(a) Working standard solution.* Accurately weigh approximately 25 milligrams of the imipenem working standard into a 50-milliliter volumetric flask. Immediately prior to

analysis, add 10 milliliters of 0.9 percent saline solution and 1 milliliter of 0.1 percent bicarbonate solution. Add phosphate buffer, 0.001M, and shake until dissolved. Sonicate, if necessary, but for no longer than 1 minute. Dilute to volume with phosphate buffer, 0.001M, to obtain a solution containing approximately 500 micrograms of imipenem per milliliter. Mix well and inject immediately.

(b) *Sample solution.* Dissolve an accurately weighed portion (approximately 25 milligrams) of the sample with 10 milliliters of 0.9 percent saline solution and 1 milliliter of 0.1 percent bicarbonate solution in a 50-milliliter volumetric flask. Dilute the sample solution to volume with phosphate buffer, 0.001M, to obtain a solution containing 500 micrograms of imipenem per milliliter (estimated).

(iii) *System suitability requirements—*

(a) *Tailing factor.* The tailing factor (*T*) is satisfactory if it is not more than 1.5 at 10 percent of peak height in lieu of 5 percent of peak height.

(b) *Efficiency of the column.* The efficiency of the column (*n*) is satisfactory if it is greater than 600 theoretical plates for a 30-centimeter column.

(c) *Resolution.* The resolution (*R*) between the peaks for thienamycin and imipenem is satisfactory if it is not less than 2.0.

(d) *Coefficient of variation (relative standard deviation).* The coefficient of variation (*S_R* in percent) of 5 replicate injections is satisfactory if it is not more than 2.0 percent.

If the system suitability requirements have been met, then proceed as described in §436.216(b) of this chapter. Alternate chromatographic conditions are acceptable provided reproducibility and resolution are comparable to the system. However, the sample preparation described in paragraph (b)(1)(ii)(b) of this section should not be changed.

(iv) *Calculations.* Calculate the micrograms of imipenem per milligram of sample as follows:

$$\frac{\text{Micrograms of imipenem per milligram}}{\text{milligram}} = \frac{A_u \times P_s \times 100}{A_s \times C_u \times (100 - L)}$$

where:

A_u=Area of the imipenem peak in the chromatogram of the sample (at a retention

time equal to that observed for the standard);

A_s=Area of the imipenem peak in the chromatogram of the imipenem working standard;

P_s=Anhydrous imipenem activity in the imipenem working standard solution in micrograms per milliliter;

C_u=Milligrams of sample per milliliter of sample solution; and

L=Percent loss on drying of the sample.

(2) *Sterility.* Proceed as directed in §436.20 of this chapter, using the method described in paragraph (e)(1) of that section.

(3) *Pyrogens.* Proceed as directed in §436.32(a) of this chapter, using a solution containing 5.0 milligrams of imipenem per milliliter, except inject 10 milliliters per kilogram of rabbit weight.

(4) *Loss on drying.* Proceed as directed in §436.200(i) of this chapter.

(5) *Specific rotation.* Dilute an accurately weighed sample with sufficient pH 7.0 phosphate buffer to give a concentration of approximately 5.0 milligrams of imipenem per milliliter. Proceed as directed in §436.210 of this chapter, using a 1.0-decimeter polarimeter tube. To prepare the pH 7.0 phosphate buffer, transfer 5 grams of monobasic potassium phosphate and 11 grams of dibasic potassium phosphate to a 1.0-liter volumetric flask. Dissolve and dilute to volume with distilled water.

(6) *Identity.* Proceed as directed in §436.211 of this chapter, using the sample preparation described in paragraph (b)(2) of that section.

(7) *Crystallinity.* Proceed as directed in §436.203(a) of this chapter.

[51 FR 11573, Apr. 4, 1986; 51 FR 16517, May 5, 1986, as amended at 55 FR 11582, Mar. 29, 1990; 59 FR 8133, Feb. 18, 1994]

Subpart B—[Reserved]

Subpart C—Injectable Dosage Forms

§ 441.220 Imipenem monohydrate-cilastatin sodium injectable dosage forms.

§ 441.220a Sterile imipenem monohydrate-cilastatin sodium.

(a) *Requirements for certification—(1) Standards of identity, strength, quality, and purity.* Imipenem monohydrate-