

**§ 442.216 Ceftazidime injectable dosage forms.****§ 442.216a Ceftazidime pentahydrate for injection.**

(a) *Requirements of certification—(1) Standards of identity, strength, quality, and purity.* Ceftazidime pentahydrate for injection is a dry mixture of ceftazidime pentahydrate and sodium carbonate or *L*-arginine. Its ceftazidime potency is satisfactory if each milligram of ceftazidime pentahydrate for injection contains not less than 900 micrograms and not more than 1,050 micrograms of ceftazidime activity when corrected for both loss on drying and its sodium carbonate or *L*-arginine content, as appropriate for the formulation. Its ceftazidime content is satisfactory if it is not less than 90 percent and not more than 120 percent of the number of milligrams of ceftazidime that it is represented to contain. It is sterile. It is nonpyrogenic. Its loss on drying is not more than 12.5 percent if it contains *L*-arginine and not more than 13.5 percent if it contains sodium carbonate. The pH of its aqueous solution is not less than 5.0 and not more than 7.5. Its pyridine content, if it contains sodium carbonate, is not more than 0.4 percent, except that for the issuance of a certificate for each batch of the sodium carbonate formulation, the pyridine content is not more than 0.12 percent. Its pyridine content, if it contains *L*-arginine, is not more than 0.3 percent, except that for the issuance of a certificate, the pyridine content of the *L*-arginine formulation is not more than 0.10 percent. The ceftazidime pentahydrate conforms to the standard prescribed by § 442.16a(a)(1).

(2) *Labeling.* In addition to the requirements of § 432.5 of this chapter, each package of the *L*-arginine formulation shall bear on its outside wrapper or container and on the immediate container the statement “For Patients 12 years and Older”.

(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:

(a) The ceftazidime pentahydrate used in making the batch for potency,

loss on drying, pH, crystallinity, identity, and high molecular weight polymer content.

(b) The batch for ceftazidime potency, ceftazidime content, sterility, pyrogens, loss on drying, pH, and pyridine content.

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

(a) The ceftazidime pentahydrate used in making the batch: 10 packages, each containing approximately 500 milligrams.

(b) The batch:

(1) For all tests except sterility: A minimum of 10 immediate containers.

(2) For sterility testing: 20 immediate containers, collected at regular intervals throughout each filling operation.

(b) *Tests and methods of assay—(1) Ceftazidime potency and content.* Determine both micrograms of ceftazidime per milligram of sample and milligrams of ceftazidime per container. Proceed as directed in § 442.16a(b)(1), preparing the sample solutions and calculating the potency and content as follows:

(i) *Preparation of sample solutions.* Use separate containers for preparation of each sample solution as described in paragraphs (b)(1)(i) (a) and (b) of this section.

(a) *Ceftazidime potency (micrograms of ceftazidime per milligram).* Accurately weigh and dissolve approximately 350 milligrams of ceftazidime sample in distilled water and dilute to volume in a 250-milliliter volumetric flask to obtain a stock solution containing approximately 1,000 micrograms of ceftazidime per milliliter. Mix well. Immediately prior to chromatography, further dilute 5 milliliters of stock solution to 50 milliliters with water to obtain a solution containing 100 micrograms of ceftazidime activity per milliliter (estimated).

(b) *Ceftazidime content (milligrams of ceftazidime per vial).* Reconstitute the sample as directed in the labeling. Then, using a suitable hypodermic needle and syringe, remove all of the withdrawable contents if it is represented as a single-dose container; or, if the labeling specifies the amount of

potency in a given volume of the resultant preparation, remove an accurately measured representative portion from each container. Further dilute an aliquot of this solution with distilled water to obtain a concentration of 1.0 milligram per milliliter (estimated). Immediately prior to chromatography, dilute 5.0 milliliters of the sample solution to 50 milliliters with water.

(ii) *Calculations*—(a) *Ceftazidime potency (micrograms per milligram)*. Calculate the micrograms of ceftazidime per milligram as follows:

$$\text{Micrograms of ceftazidime per milligram} = \frac{A_u \times P_s \times 100}{A_s \times C_u \times (100 - m - S - A)}$$

where:

$A_u$  = Area of the ceftazidime peak in the chromatogram of the sample (at a retention time equal to that observed for the standard);

$A_s$  = Area of the ceftazidime peak in the chromatogram of the ceftazidime working standard;

$P_s$  = Ceftazidime activity in the ceftazidime working standard solution in micrograms per milliliter;

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

$m$  = Percent loss on drying (determined as directed in § 436.200(h) of this chapter if the formulation contains sodium carbonate and determined as directed in § 436.200(g) of this chapter if the formulation contains *L*-arginine);

$S$  = Percent sodium carbonate content of the sample (determined as directed in § 436.357 of this chapter); and

$A$  = Percent *L*-arginine content of the sample (determined as directed in § 455.204 of this chapter, except use ceftazidime instead of aztreonam in the working standard solution and use water instead of mobile phase). Prepare the sample solution by diluting an accurately weighed portion of the contents of a vial with water to 0.2 milligram per milliliter (estimated). The resolution between the ceftazidime peak and the arginine peak is not less than 6.0, the asymmetry factor for the arginine peak is not more than 4.0).

(b) *Ceftazidime content (milligrams of ceftazidime per vial)*. Calculate the ceftazidime content of the vial as follows:

$$\text{Milligrams of ceftazidime per vial} = \frac{A_u \times P_s \times d}{A_s \times 1,000}$$

where:

$A_u$  = Area of the ceftazidime peak in the chromatogram of the sample (at a retention time equal to that observed for the standard);

$A_s$  = Area of the ceftazidime peak in the chromatogram of the ceftazidime working standard;

$P_s$  = Ceftazidime activity in the ceftazidime working standard solution in micrograms per milliliter; and

$d$  = Dilution factor 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(b) of this chapter, using a solution containing 80 milligrams of ceftazidime per milliliter.

(4) *Loss on drying*. Proceed as directed in § 436.200(h) of this chapter if the formulation contains sodium carbonate and as directed in § 436.200(g) of this chapter if the formulation contains *L*-arginine.

(5) *pH*. Proceed as directed in § 436.202 of this chapter, preparing the sample solution as follows: reconstitute the sample in the sealed container to give an aqueous solution containing approximately 100 milligrams per milliliter, relieving the pressure inside the container if necessary during the reconstitution.

(6) *Pyridine content*. Proceed as directed in § 436.358 of this chapter, using a temperature of 40 °C, an ultraviolet detection system operating at a wavelength of 254 nanometers, a column packed with microparticulate (5 micrometers in diameter) reversed phase packing material such as octadecyl hydrocarbon bonded silicas, a flow rate of 1.6 milliliters per minute, and a known injection volume from 10 to 20 microliters. Reagents, working standard and sample solutions, system suitability requirements, and calculations are as follows:

(i) *Reagents*—(a) *Phosphate buffer, pH 7.0*. Dissolve 5.68 grams of sodium phosphate, dibasic, anhydrous and 3.63 grams of potassium phosphate, monobasic, in water and dilute to 1,000 milliliters.

(b) *Mobile phase*. Mix 300 milliliters of acetonitrile and 100 milliliters of 0.25M ammonium phosphate, monobasic, dilute to 1,000 milliliters with water and add sufficient 10M ammonia solution to

give a pH of 7.0±0.1. Filter the mobile phase through a suitable glass fiber filter or equivalent that is capable of removing particulate contamination to 1 micron in diameter. Degas the mobile phase just prior to its introduction into the chromatograph pumping system.

(c) *System suitability test solution.* Prepare a solution in phosphate buffer, pH 7.0, containing 25 micrograms of pyridine and 25 micrograms of an authentic sample of (6*R*, 7*R*)-7-[(*Z*)-2-(2-Aminothiazol-4-yl)-2-(2-*t*-butoxycarbonylprop-2-yloxyimino)acetamido]-3-(1-pyridiniummethyl)ceph-3-em-4-carboxylate (*t*-butyl ceftazidime) per milliliter. Note, if no *t*-butyl ceftazidime is present in the sample solution, the working standard solution may be substituted for the system suitability test solution and the system suitability requirement for resolution for *t*-butyl ceftazidime is omitted.

(ii) *Preparation of working standard and sample solutions—(a) Working standard solution.* Accurately weigh approximately 250 milligrams of pyridine into a 100-milliliter volumetric flask and dilute to volume with water to obtain a stock solution containing approximately 2,500 micrograms of pyridine per milliliter. Mix well. Immediately prior to chromatography, further dilute 2.0 milliliters of stock solution to 200 milliliters with phosphate buffer, pH 7.0, to obtain a solution containing 25 micrograms of pyridine per milliliter.

(b) *Sample solution.* Accurately weigh approximately 660 milligrams of the sample into a 100-milliliter volumetric flask and add 50 milliliters of phosphate buffer, pH 7.0. Shake until dissolved and dilute to volume with phosphate buffer, pH 7.0. Mix well. Store the solution at a temperature below 15 °C and inject into the chromatograph within 1 hour of preparation.

(iii) *System suitability requirements—(a) Tailing factor.* The tailing factor (*T*) is satisfactory if it is not more than 2.5 at 5 percent of peak height.

(b) *Resolution.* The resolution (*R*) between the peak for pyridine and the peak for *t*-butyl ceftazidime is satisfactory if it is not less than 3.

(c) *Coefficient of variation.* The coefficient of variation (*S<sub>R</sub>* in percent) of five replicate injections is satisfactory if it is not more than 3 percent.

If the system suitability requirements have been met, then proceed as described in §436.358(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)(6)(ii)(b) of this section should not be changed.

(iv) *Calculations.* Calculate the pyridine content in percent of the sample as follows:

$$\text{Pyridine content in percent} = \frac{H_u \times P_s \times 0.1}{H_s \times C_u}$$

where:

*H<sub>u</sub>*=Height of the pyridine peak in the chromatogram of the sample (at a retention time equal to that observed for the standard);

*H<sub>s</sub>*=Height of the pyridine peak in the chromatogram of the pyridine working standard;

*P<sub>s</sub>*=Pyridine content of the pyridine working standard solution in micrograms per milliliter; and

*C<sub>u</sub>*=Milligrams of sample per milliliter of sample solution.

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#### § 442.216b Ceftazidime sodium injection.

(a) *Requirements for certification—(1) Standards of identity, strength, quality, and purity.* Ceftazidime sodium injection is a frozen, aqueous, iso-osmotic solution of ceftazidime sodium which may contain one or more suitable and harmless buffer substances and a tonicity adjusting agent. Each milliliter contains ceftazidime sodium equivalent to 10, 20, or 40 milligrams of ceftazidime per milliliter. Its ceftazidime content is satisfactory if it is not less than 90 percent and not more than 120 percent of the number of milligrams of ceftazidime that it is represented to contain. It is sterile. It is nonpyrogenic. Its pH is not less than 5.0 and not more than 7.5 It passes the