ZAVICEFTA
(ceftazidime-avibactam)

Stability after reconstitution and dilution

Please refer to the full Prescribing Information on important treatment considerations for ZAVICEFTA via the following link: www.pfizer.com.tw.

Note: Select prescribing information is excerpted further in the document.

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This letter regarding ZAVICEFTA (ceftazidime-avibactam) includes information of an off-label nature. Pfizer does not suggest or recommend the use of ZAVICEFTA any manner other than as described in the Prescribing Information approved by Taiwan FDA.

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Special precautions for disposal and other handling[1]

The powder must be reconstituted with water for injections and the resulting concentrate must then be immediately diluted prior to use. The reconstituted solution is pale yellow solution and free of particles.

Standard aseptic techniques should be used for solution preparation and administration.

1. Introduce the syringe needle through the vial closure and inject 10 mL of sterile water for injections.
2. Withdraw the needle and shake the vial to give a clear solution.
3. Do not insert a gas relief needle until the product has completely dissolved. Insert a gas relief needle through the vial closure to relieve the internal pressure.
4. Transfer the entire contents (approximately 12.0 mL) of the resultant solution to an infusion bag immediately. Reduced doses may be achieved by transfer of an appropriate volume of the resultant solution to an infusion bag, based upon ceftazidime and avibactam content of 167.3 mg/mL and 41.8 mg/mL, respectively. A dose of 1000 mg/250 mg or 750 mg/187.5 mg is achieved with 6.0 mL or 4.5 mL aliquots, respectively.

Vials of ceftazidime-avibactam powder should be reconstituted with 10 ml of sterile water for injections, followed by shaking until the content dissolves. An infusion bag may contain any of the following: sodium chloride 9 mg/ml (0.9%) solution for injection, dextrose 50 mg/ml (5%) solution for injection, sodium chloride 4.5 mg/ml and dextrose 25 mg/ml solution for injection (0.45% sodium chloride and 2.5% dextrose) or Lactated Ringer's solution. A 100 ml infusion bag can be used to prepare the infusion, based on the patient's volume requirements. The total time interval between starting reconstitution and completing preparation of the intravenous infusion should not exceed 30 minutes.

Shelf life[1]

<u>After reconstitution:</u>

The reconstituted vial should be used immediately.

<u>After dilution:</u>

The chemical and physical in-use stability has been demonstrated for up to 24 hours at 2 - 8°C, followed by up to 12 hours at not more than 25°C.

From a microbiological point of view, the medicinal product after reconstitution and dilution should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2 - 8°C, unless reconstitution/dilution has taken place in controlled and validated aseptic conditions.

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INTERNAL DATA

Reconstituted solutions[2]

Diluent	ZAVICEFTA were reconstituted with 10 mL of commercially available infusion diluents; Sterile Water for Injection USP (sWFI), 0.9% sodium chloride, 5% dextrose, 2.5% dextrose/0.45% sodium chloride (combined diluent) and Hartmann's solution (equivalent to Lactated Ringer's solution)
Testing Concentration	Final concentrations equivalent to those in the product label (approximately ceftazidime 167 mg/mL and avibactam 42 mg/mL)
Condition	The constituted vials were **stored at room temperature for a period of 30 minutes** and were **exposed to normal room light conditions**.
Tests	Samples were taken for analysis at initial time point and after storage for 30 minutes.
Results	The stability of the reconstituted drug product has been demonstrated in sWFI, 0.9% sodium chloride, 5% dextrose, 2.5% dextrose/0.45% sodium chloride (combined diluent) and Hartmann's solution (equivalent to Lactated Ringer's solution) over a period of 30 minutes, when stored at room temperature.

Diluted solutions[2]

Diluent	Infusion solutions were prepared in common IV diluents; 0.9% sodium chloride, 5% dextrose, 2.5% dextrose/0.45% sodium chloride (combined diluent) and Hartmann's solution (equivalent to Lactated Ringer's solution). Unless otherwise stated, drug product vials were reconstituted with sterile Water for Injection (USP).
Testing Concentration	ceftazidime and avibactam concentrations of 8 and 2 mg/mL, 20 and 5 mg/mL and 40 and 10 mg/mL, respectively (equivalent to IV bag volumes of 250, 100 and 50 mL, respectively)
Condition	The studies were undertaken on prepared infusion solutions **stored at 2ºC to 8ºC for 24 hours, followed by a period of 12 hours stored at room temperature**. All solutions were **stored refrigerated in the dark and exposed to normal room light conditions at room temperature**.
Tests	The ceftazidime component of the drug product has been evaluated by comparison with the commercially available product Ceftazidime for Injection (USP). Ceftazidime results for assay and degradation products have therefore been presented as rates of degradation to enable comparison of data.
Results	An in-use shelf life of 24 hours at 2ºC to 8ºC, followed by 12 hours at controlled room temperature would therefore be appropriate to ensure the quality of the ceftazidime active component.

Data obtained from all in-use stability and compatibility studies support the use of the drug Product with IV bags and infusion lines containing polyvinyl chloride (PVC), polyolefin (PO), polyamide (PA), polypropylene (PP), polyethylene (PE), ethylene vinyl acetate (EVA) and in-line filters and the Baxter MINIBAG plus® container system.

REFERENCES

1. Zavicefta (ceftazidime-avibactam) Package Insert. Pfizer Limited Taiwan. Available at: http://www.pfizer.com/tw.
2. Zavicefta Data on file (TW1). Pfizer.