פייזר פי אף אי פרמצבטיקה ישראל בע"מ
רח' שנקר 9, ת.ד. 12133
הרצליה פיתוח, ישראל 46725
טל: 972-9-9700500 פקס: 972-9-9700501

יולי 2023

רופא/ה, רוקח/ת נכבד/ה,

ברצוננו להודיעך על עדכונים בעלון לרופא של **Zavicefta ; זביספטה**:

הודעה זו כוללת את המידע הנוגע לשינוי בהתוויות ובמשטר המינון של התכשיר (מסומנים בקו תחתון בגוף ההודעה), וכן עדכונים המהווים החמרה במידע הבטיחותי (מסומנים עם רקע צהוב בגוף ההודעה) , למידע מלא יש לעיין בעלון המאושר.

המרכיבים הפעילים:

ceftazidime pentahydrate equivalent to 2 g ceftazidime
avibactam sodium equivalent to 0.5 g avibactam

להלן העדכונים העיקריים בעלון לרופא:

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Zavicefta® is indicated in adults and paediatric patients aged 3 months and older for the treatment of the following infections:

- *Complicated intra-abdominal infection (cIAI), used in combination with Metronidazole*
- *Complicated urinary tract infection (cUTI), including pyelonephritis*
- *Hospital-acquired pneumonia (HAP), including ventilator associated pneumonia (VAP)*

Treatment of adult patients with bacteraemia that occurs in association with, or is suspected to be associated with, any of the infections listed above.

Zavicefta® is also indicated for the treatment of infections due to aerobic Gram-negative organisms in adults and paediatric patients aged 3 months and older with limited treatment options.

Consideration should be given to official guidance on the appropriate use of antibacterial agents.

4.2 Posology and method of administration

It is recommended that Zavicefta® should be used to treat infections due to aerobic Gram-negative organisms in adults and paediatric patients aged 3 months and older, with limited treatment options only after consultation with a physician with appropriate experience in the management of infectious diseases

Posology

Dosage in adults with creatinine clearance (CrCL) > 50 mL/min

Table 1 shows the recommended intravenous dose for adults with estimated creatinine clearance (CrCL) > 50 mL/min.

Table 1 Recommended dose for adults with estimated CrCL > 50 mL/min[1]

Type of infection	Dose of ceftazidime/avibactam	Frequency	Infusion time	Duration of treatment
cIAI[2, 3]	2 g/0.5 g	Every 8 hours	2 hours	5-14 days
cUTI, including pyelonephritis[3]	2 g/0.5 g	Every 8 hours	2 hours	5-10 days[4]
HAP/ VAP[3]	2 g/0.5 g	Every 8 hours	2 hours	7-14 days

Bacteraemia associated with, or suspected to be associated with any of the above infections	2 g/0.5 g	Every 8 hours	2 hours	Duration of treatment should be in accordance with the site of infection.
Infections due to aerobic Gram-negative organisms in patients with limited treatment options[2,3]	2 g/0.5 g	Every 8 hours	2 hours	Guided by the severity of the infection, the pathogen(s) and the patient's clinical and bacteriological progress[5]

[1] CrCL estimated using the Cockcroft-Gault formula

[2] To be used in combination with metronidazole when anaerobic pathogens are known or suspected to be contributing to the infectious process

[3] To be used in combination with an antibacterial agent active against Gram-positive pathogens when these are known or suspected to be contributing to the infectious process

[4] The total duration shown may include intravenous Zavicefta® followed by appropriate oral therapy

[5] There is very limited experience with the use of Zavicefta® for more than 14 days

Dosage in paediatric patients with creatinine clearance (CrCL) >50 mL/min/1.73 m^2

Table 2 shows the recommended intravenous doses for paediatric patients with estimated creatinine clearance (CrCL) > 50 mL/min*/1.73 m^2*.

Table 2: Recommended dose for paediatric patients with estimated CrCL[1] > 50 mL/min/1.73 m^2

Type of infection	Age group	Dose of ceftazidime/avibactam[7]	Frequency	Infusion time	Duration of treatment
cIAI[2,3] OR cUTI including pyelonephritis[3] OR HAP/VAP[3] OR Infections due to aerobic Gram-negative organisms in patients with limited treatment options (LTO)[2,3]	6 months to <18 years	50 mg/kg/12.5 mg/kg **to a maximum of** 2 g/0.5 g	Every 8 hours	2 hours	cIAI: 5 – 14 days cUTI[4]: 5 – 14 days HAP/VAP: 7 – 14 days LTO: Guided by the severity of the infection, the pathogen(s) and the patient's clinical and bacteriological progress[5]
			Every 8 hours	2 hours	
	3 months to <6 months[6]	40 mg/kg/10 mg/kg	Every 8 hours	2 hours	

[1] CrCL estimated using the Schwartz bedside formula.

[2] To be used in combination with metronidazole when anaerobic pathogens are known or suspected to be contributing to the infectious process.

[3] To be used in combination with an antibacterial agent active against Gram-positive pathogens when these are known or suspected to be contributing to the infectious process.

[4] The total treatment duration shown may include intravenous Zavicefta followed by appropriate oral therapy.

[5] There is very limited experience with the use of Zavicefta for more than 14 days.

[6] There is limited experience with the use of Zavicefta in paediatric patients 3 months to < 6 months

[7] Ceftazidime/avibactam is a combination product in a fixed 4:1 ratio and dosage recommendations are based on the ceftazidime component only.

Special populations

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Table 3 shows the recommended dose adjustments for adults with estimated CrCL[1] ≤ 50 mL/min.

Dosage in adults with CrCL ≤ 50 mL/min

Table 3 Recommended dose for adults with estimated CrCL [1] ≤ 50 mL/min

Age Group	Estimated CrCL (mL/min)	Dose of ceftazidime/avibactam[2, 4]	Frequency	Infusion time
Adults	31-50	1 g/0.25 g	Every 8 hours	2 hours
	16-30	0.75 g/0.1875 g	Every 12 hours	
	6-15		Every 24 hours	
	End Stage Renal Disease including on haemodialysis[3]		Every 48 hours	

[1] CrCL estimated using the Cockcroft-Gault formula

[2] Dose recommendations are based on pharmacokinetic modelling.

[3] Ceftazidime and avibactam are removed by haemodialysis. Dosing of Zavicefta® on haemodialysis days should occur after completion of haemodialysis.

4 Ceftazidime/ avibactam is a combination product in a fixed 4:1 ratio and dosage recommendations are based on the ceftazidime component only.

Table 4 and Table 5 show the recommended dose adjustments for paediatric patients with estimated CrCL ≤ 50 mL/min/1.73 m^2 according to different age groups.

Dosage in paediatric patients ≥ 2 years of age with CrCl ≤ 50 mL/min/1.73 m^2

Table 4: Recommended dose for paediatric patients with estimated CrCL[1] ≤ 50 mL/min/1.73 m^2

Age Group	Estimated CrCL (mL/min/1.73 m^2)	Dose of ceftazidime/avibactam[2, 4]	Frequency	Infusion time
Paediatric patients aged 2 years to <18 years	31-50	25 mg/kg/6.25 mg/kg **to a maximum of** 1 g/0.25 g	Every 8 hours	2 hours
	16-30	18.75 mg/kg/4.7 mg/kg **to a maximum of** 0.75 g/0.1875 g	Every 12 hours	
	6-15		Every 24 hours	
	End Stage Renal Disease including on haemodialysis[3]		Every 48 hours	

[1] CrCL estimated using the Schwartz bedside formula.

[2] Dose recommendations are based on pharmacokinetic modelling.

[3] Ceftazidime and avibactam are removed by haemodialysis. Dosing of Zavicefta on haemodialysis days should occur after completion of haemodialysis.

[4] Ceftazidime/avibactam is a combination product in a fixed 4:1 ratio and dosage recommendations are based on the ceftazidime component only.

Dosage in paediatric patients <2 years of age with CrCl ≤ 50 mL/min/1.73 m^2

Table 5: Recommended dose for paediatric patients with estimated CrCL[1] ≤ 50 mL/min/1.73 m^2

Age Group	**Estimated CrCL (mL/min/1.73 m^2)**	**Dose of ceftazidime/avibactam [2,3]**	**Frequency**	**Infusion time**
3 to < 6 months	31 to 50	20 mg/kg/5 mg/kg	Every 8 hours	2 hours
6 months to < 2 years		25 mg/kg/6.25 mg/kg	Every 8 hours	
3 to < 6 months	16 to 30	15 mg/kg/3.75 mg/kg	Every 12 hours	
6 months to < 2 years		18.75 mg/kg/4.7 mg/kg	Every 12 hours	

Age Group	Estimated CrCL (mL/min/1.73 m^2)	Dose of ceftazidime/avibactam [2,3]	Frequency	Infusion time

[1] Calculated using the Schwartz bedside formula

[2] Dose recommendations are based on pharmacokinetic modelling.

[3] Ceftazidime/avibactam is a combination product in a fixed 4:1 ratio and dosage recommendations are based on the ceftazidime component only.

There is insufficient information to recommend a dosage regimen for paediatric patients < 2 years of age that have a CrCL < 16 mL/min/1.73 m^2.

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Paediatric population

The safety and efficacy of Zavicefta in paediatric patients < 3 months old have not been established. No data are available.

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4.4 Special warnings and precautions for use

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Paediatric population

There is a potential risk of overdosing, particularly for paediatric patients aged from 3 to less than 12 months of age. Care should be taken when calculating the volume of administration of the dose

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4.8 Undesirable effects

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Paediatric population

The safety assessment in paediatric patients is based on the safety data from two trials in which 61 patients (aged from 3 years to less than 18 years) with cIAI and 67 patients with cUTI (aged from 3 months to less than 18 years) received Zavicefta. Overall, the safety profile in these 128 paediatric patients was similar to that observed in the adult population with cIAI and cUTI.

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5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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Paediatric population

Zavicefta has been evaluated in paediatric patients aged 3 months to < 18 years in two Phase 2 single-blind, randomised, comparative clinical studies, one in patients with cIAI and one in patients with cUTI. The primary objective in each study was to assess safety and tolerability of ceftazidime-avibactam (+/- metronidazole). Secondary objectives included assessment of pharmacokinetics and efficacy; efficacy was a descriptive endpoint in both studies. Clinical cure rate at TOC (ITT) was 91.8% (56/61) for Zavicefta compared to 95.5% (21/22) for meropenem in paediatric patients with cIAI. Microbiological eradication rate at TOC (micro-ITT) was 79.6% (43/54) for Zavicefta compared to 60.9% (14/23) for cefepime in paediatric patients with cUTI.

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5.2 Pharmacokinetic properties

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Paediatric population

The pharmacokinetics of ceftazidime and avibactam were evaluated in paediatric patients from 3 months to < 18 years of age with suspected or confirmed infections following a single dose of ceftazidime 50 mg/kg and avibactam 12.5 mg/kg for patients weighing < 40 kg or Zavicefta 2 g/0.5 g (ceftazidime 2 grams and avibactam 0.5 grams) for patients weighing ≥ 40 kg. Plasma concentrations of ceftazidime and avibactam were similar across all four age cohorts in the study (3 months to < 2 years, 2 to < 6 years, 6 to < 12 years, and 12 to < 18 years). Ceftazidime and avibactam $AUC_{0\text{-}t}$ and C_{max} values in the two older cohorts (paediatric patients from 6 to < 18 years), which had more extensive pharmacokinetic sampling, were similar to those observed in healthy adult subjects with normal renal function that received Zavicefta 2 g/0.5 g. Data from this study and the two Phase 2 paediatric studies in patients with cIAI and cUTI were pooled with PK data

from adults (Phase 1 to Phase 3) to update the population PK model, which was used to conduct simulations to assess PK/PD target attainment. Results from these simulations demonstrated that the recommended dose regimens for paediatric patients with cIAI, cUTI and HAP/VAP, including dose adjustments for patients with renal impairment, result in systemic exposure and PK/PD target attainment values that are similar to those in adults at the approved Zavicefta dose of 2 g/0.5 g administered over 2 hours, every 8 hours.
There is limited experience with the use of ceftazidime plus avibactam in the paediatric groups of 3 months to < 6 months. The recommended dosing regimens are based on simulations conducted using the final population PK models. Simulations demonstrated that the recommended dose regimens result in comparable exposures to other age groups with PK/PD target attainment > 90%. Based on data from the completed paediatric clinical trials, at the recommended dose regimens, there was no evidence of over or under exposure in the subjects aged 3 months to < 6 months.
In addition, there is very limited data in paediatric patients aged 3 months to < 2 years with impaired renal function (CrCL ≤ 50 mL/min/1.73m^2), with no data in severe renal impairment from the completed paediatric clinical trials. Population PK models for ceftazidime and avibactam were used to conduct simulations for patients with impaired renal function.

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6.3 Shelf life

6.2 Incompatibilities

The compatibility of Zavicefta with other medicines has not been established. Zavicefta should not be mixed with or physically added to solutions containing other medicinal products.
This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

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After dilution

Infusion syringes

The chemical and physical in-use stability has been demonstrated (from initial vial puncture) for up to 6 hours at not more than 25°C.
From a microbiological point of view, the medicinal product should be used immediately unless reconstitution and dilution have taken place in controlled and validated aseptic conditions. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and must not exceed 6 hours at not more than 25°C.

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6.6 Special precautions for disposal and other handling

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Instructions for preparing adult and paediatric doses in INFUSION BAG or in INFUSION SYRINGE:
NOTE: The following procedure describes the steps to prepare an infusion solution with a final concentration of 8-40 mg/mL of ceftazidime. All calculations should be completed prior to initiating these steps. **For paediatric patients aged 3 to 12 months**, detailed steps to prepare a 20 mg/mL concentration (sufficient for most scenarios) are also provided.

1. Prepare the **reconstituted solution** (**167.3 mg/mL** of ceftazidime):
   a) Insert the syringe needle through the vial closure and inject 10 mL of sterile water for injections.
   b) Withdraw the needle and shake the vial to give a clear solution.
   c) Insert a gas relief needle through the vial closure **after** the product has dissolved to relieve the internal pressure (this is important to preserve product sterility).
2. Prepare the **final solution** for infusion (final concentration must be **8-40 mg/mL** of ceftazidime):
   a) Infusion bag: Further dilute the reconstituted solution by transferring an appropriately calculated volume of the reconstituted solution to an infusion bag containing any of the following: sodium chloride 9 mg/mL (0.9%) solution for injection, dextrose 50 mg/mL (5%) solution for injection, or Lactated Ringer's solution.
   b) Infusion syringe: Further dilute the reconstituted solution by transferring an appropriately calculated volume of the reconstituted solution combined with a sufficient volume of diluent (sodium chloride 9 mg/mL (0.9%) solution for injection or dextrose 50 mg/mL (5%) solution for injection) to an infusion syringe.

Refer to Table 7 below.
Table 7: Preparation of Zavicefta for adult and paediatric doses in INFUSION BAG or in INFUSION SYRINGE.

Zavicefta Dose (ceftazidime)[1]	**Volume to withdraw from reconstituted vial**	**Final volume after dilution in infusion bag[2]**	**Final volume in infusion syringe**
2 g	Entire contents (approximately 12 mL)	50 mL to 250 mL	50 mL
1g	6 mL	25 mL to 125 mL	25 mL to 50 mL
0.75 g	4.5 mL	19 mL to 93 mL	19 mL to 50 mL
All other doses	Volume (mL) calculated based on dose required: **Dose (mg ceftazidime) ÷ 167.3 mg/mL ceftazidime**	Volume (mL) will vary based on infusion bag size availability and preferred final concentration (must be 8-40 mg/mL of ceftazidime)	

[1] Based on ceftazidime component only.

[2] Dilute to final ceftazidime concentration of 8 mg/mL for in-use stability up to 12 hours at 2 - 8°C, followed by up to 4 hours at not more than 25°C (i.e. dilute 2 g dose of ceftazidime in 250 mL, 1 g dose of ceftazidime in 125 mL, 0.75 g dose of ceftazidime in 93 mL, etc.). All other ceftazidime concentrations (> 8 mg/mL to 40 mg/mL) have in-use stability up to 4 hours at not more than 25°C.

Preparation of Zavicefta for use in paediatric patients aged 3 to 12 months of age in INFUSION SYRINGE:
NOTE: The following procedure describes the steps to prepare an infusion solution with a final concentration of 20 mg/mL of ceftazidime (sufficient for most scenarios). Alternative concentrations may be prepared, but must have a final concentration range of 8-40 mg/mL of ceftazidime.

1. Prepare the **reconstituted solution** (**167.3 mg/mL** of ceftazidime):
   a) Insert the syringe needle through the vial closure and inject 10 mL of sterile water for injections.
   b) Withdraw the needle and shake the vial to give a clear solution.
   c) Insert a gas relief needle through the vial closure **after** the product has dissolved to relieve the internal pressure (this is important to preserve product sterility).
2. Prepare the **final solution** for infusion to a final concentration of **20 mg/mL** of ceftazidime:
   a) Further dilute the reconstituted solution by transferring an appropriately calculated volume of the reconstituted solution combined with a sufficient volume of diluent (sodium chloride 9 mg/mL (0.9%) solution for injection or dextrose 50 mg/mL (5%) solution for injection) to an infusion syringe.
   b) Refer to Table 8, 9, or 10 below to confirm the calculations. Values shown are approximate as it may be necessary to round to the nearest graduation mark of an appropriately sized syringe. Note that the tables are NOT inclusive of all possible calculated doses but may be utilized to estimate the approximate volume to verify the calculation.

Table 8: Preparation of Zavicefta (final concentration of 20 mg/mL of ceftazidime) in paediatric patients 3 to 12 months of age with creatinine clearance (CrCL) > 50 mL/min/1.73 m^2

Age and Zavicefta Dose (mg/kg)[1]	**Weight (kg)**	**Dose (mg ceftazidime)**	**Volume of reconstituted solution to be withdrawn from vial (mL)**	**Volume of diluent to add for mixing (mL)**
6 months to 12 months **50 mg/kg of ceftazidime**	5	250	1.5	11
	6	300	1.8	13
	7	350	2.1	15
	8	400	2.4	18
	9	450	2.7	20
	10	500	3	22
	11	550	3.3	24
	12	600	3.6	27
3 months to < 6 months **40 mg/kg of ceftazidime**	4	160	1	7.4
	5	200	1.2	8.8
	6	240	1.4	10
	7	280	1.7	13
	8	320	1.9	14
	9	360	2.2	16
	10	400	2.4	18

[1] Based on ceftazidime component only.

Table 9: Preparation of Zavicefta (final concentration of 20 mg/mL of ceftazidime) in paediatric patients 3 to 12 months of age with CrCL 31 to 50 mL/min/1.73 m^2

Age and Zavicefta Dose (mg/kg)[1]	**Weight (kg)**	**Dose (mg ceftazidime)**	**Volume of reconstituted solution to be withdrawn from vial (mL)**	**Volume of diluent to add for mixing (mL)**
6 months to 12 months **25 mg/kg of ceftazidime**	5	125	0.75	5.5
	6	150	0.9	6.6
	7	175	1	7.4
	8	200	1.2	8.8
	9	225	1.3	9.6
	10	250	1.5	11
	11	275	1.6	12
	12	300	1.8	13
3 months to < 6 months **20 mg/kg of ceftazidime**	4	80	0.48	3.5
	5	100	0.6	4.4
	6	120	0.72	5.3
	7	140	0.84	6.2
	8	160	1	7.4
	9	180	1.1	8.1
	10	200	1.2	8.8

[1] Based on ceftazidime component only.

Table 10: Preparation of Zavicefta (final concentration of 20 mg/mL of ceftazidime) in paediatric patients 3 to 12 months of age with CrCL 16 to 30 mL/min/1.73 m^2

Age and Zavicefta Dose (mg/kg) [1]	**Weight (kg)**	**Dose (mg ceftazidime)**	**Volume of reconstituted solution to be withdrawn from vial (mL)**	**Volume of diluent to add for mixing (mL)**
6 months to 12 months **18.75 mg/kg of ceftazidime**	5	93.75	0.56	4.1
	6	112.5	0.67	4.9
	7	131.25	0.78	5.7
	8	150	0.9	6.6
	9	168.75	1	7.4
	10	187.5	1.1	8.1
	11	206.25	1.2	8.8
	12	225	1.3	9.6
3 months to < 6 months **15 mg/kg of ceftazidime**	4	60	0.36	2.7
	5	75	0.45	3.3
	6	90	0.54	4
	7	105	0.63	4.6
	8	120	0.72	5.3
	9	135	0.81	6
	10	150	0.9	6.6

[1] Based on ceftazidime component only.

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בברכה,
עידית שלם אבידר
רוקחת ממונה

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