Package leaflet: Information for the user

Zavicefta 2 g/0.5 g powder for concentrate for solution for infusion
ceftazidime/avibactam

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or nurse.
- If you get any side effects, talk to your doctor or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet:

1. What Zavicefta is and what it is used for

What Zavicefta is
Zavicefta is an antibiotic medicine that contains two active substances ceftazidime and avibactam.
- Ceftazidime belongs to the group of antibiotics called "cephalosporins". It can kill many types of bacteria.
- Avibactam is a "beta-lactamase inhibitor" that helps ceftazidime kill some bacteria that it cannot kill on its own.

What Zavicefta is used for
Zavicefta is used in adults and paediatric patients aged 3 months and over to treat:
- infections of the stomach and gut (abdomen)
- infections of the bladder or kidneys called "urinary tract infections"
- an infection of the lungs called "pneumonia"
- infections caused by bacteria that other antibiotics may not be able to kill

Zavicefta is used in adults to treat infection of the blood associated with infections of the abdomen, urinary tract, or pneumonia.

How Zavicefta works
Zavicefta works by killing certain types of bacteria, which can cause serious infections.

2. What you need to know before you use Zavicefta

Do not use Zavicefta if:
- you are allergic to ceftazidime, avibactam or any of the other ingredients of this medicine (listed in section 6)
- you are allergic to other cephalosporin antibiotics
- you have ever had a severe allergic reaction to other antibiotics belonging to the penicillin or carbapenem groups

Do not use Zavicefta if any of the above apply to you. If you are not sure, talk to your doctor or nurse before using Zavicefta.

Warnings and precautions
Talk to your doctor or nurse before using Zavicefta if:
- you have ever had any allergic reaction (even if only a skin rash) to other antibiotics belonging to the penicillin or carbapenem groups
- you have kidney problems - your doctor may give you a lower dose to make sure you don't get too much medicine. This could cause symptoms such as fits (see section **If you use more Zavicefta than you should**)

If any of the above apply to you (or you are not sure), talk to your doctor or nurse before using Zavicefta.

Talk to your doctor or nurse if you suffer from diarrhoea during your treatment.

Other infections
There is a small possibility that you may get a different infection caused by another bacteria during or after treatment with Zavicefta. These include thrush (fungal infections of the mouth or genital area).

Lab tests
Tell your doctor that you are taking Zavicefta if you are going to have any tests. This is because you may get an abnormal result with a test called "DAGT" or "Coombs". This test looks for antibodies that fight against your red blood cells.

Zavicefta can also affect the results of some urine tests for sugar. Tell the person taking the sample that you have been given Zavicefta.

Paediatric patients
Zavicefta should not be used in paediatric patients aged under 3 months. This is because it is not known if the medicine is safe to use in this age group.

Other medicines and Zavicefta
Tell your doctor or nurse if you are using, have recently used or might use any other medicines.

Talk to your doctor before using Zavicefta if you are taking any of the following medicines:
- an antibiotic called chloramphenicol
- a type of antibiotic called an aminoglycoside – such as gentamicin, tobramycin
- a water tablet called furosemide
- a medicine for gout called probenecid

Tell your doctor before using Zavicefta if any of the above apply to you.

Pregnancy and breast-feeding
If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor for advice before using this medicine.

Driving and using machines
Zavicefta may make you feel dizzy. This may affect you being able to drive, use tools or machines.

Zavicefta contains sodium
This medicine contains approximately 146 mg sodium (main component of cooking/table salt) in each vial. This is equivalent to 7.3% of the recommended maximum daily dietary intake for sodium for an adult.

Talk to your doctor or pharmacist if you need 3 or more vials daily for a prolonged period, especially if you have been advised to have a low salt (sodium) diet.

3. How to use Zavicefta

Zavicefta will be given to you by a doctor or a nurse.

How much to use
The recommended dose for adults is one vial (2 g of ceftazidime and 0.5 g of avibactam), every 8 hours. The dose for paediatric patients aged 3 months and over will be calculated by the doctor based on the weight and age of the child.

It is given as a drip into a vein – this will normally take about 2 hours.

A course of treatment usually lasts from 5 to up to 14 days, depending on the type of infection you have and how you respond to treatment.

People with kidney problems
If you have kidney problems your doctor may lower your dose. This is because Zavicefta is removed from your body by the kidneys.

If you use more Zavicefta than you should
Zavicefta will be given to you by a doctor or a nurse, so it is unlikely you will be given the wrong dose. However, if you have side effects or think you have been given too much Zavicefta, tell your doctor or nurse straight away. If you have too much Zavicefta it could have an effect on the brain and cause fits or coma.

If you miss a dose of Zavicefta
If you think you have missed a dose, tell your doctor or nurse straight away.

If you have any further questions on the use of this medicine, ask your doctor or nurse.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them. The following side effects may happen with this medicine:

Serious side effects
Tell your doctor straight away if you notice any of the following serious side effects - you may need urgent medical treatment:
- severe allergic reactions – signs include sudden swelling of your lips, face, throat or tongue, a severe rash or other severe skin reactions, difficulty swallowing or breathing, or sudden chest pain (which may be a sign of Kounis syndrome). These reactions may be life-threatening.
- diarrhoea that keeps getting worse or does not go away, or stools that contains blood or mucus – this may happen during or after treatment is stopped with Zavicefta. If this happens do not take medicines that stop or slow bowel movement.

Tell your doctor straight away if you notice any of the serious side effects above.

Other side effects
Tell your doctor or nurse if you notice any of the following side effects:

Very common: (may affect more than 1 in 10 people)
- abnormal result with a test called “DAGT” or “Coombs”. This test looks for antibodies that fight against your red blood cells. It is possible that this could cause anaemia (which may make you feel tired) and jaundice (yellowing of the skin and eyes)

Common: (may affect up to 1 in 10 people)
- fungal infections, including those of the mouth and vagina

- change in the number of some types of blood cells (called “eosinophils” and “thrombocytes”) – shown in blood tests
- headache
- feeling dizzy
- feeling sick (nausea) or being sick (vomiting)
- stomach pain
- diarrhoea
- increase in the amount of some enzymes produced by your liver - shown in blood tests
- raised itchy skin rash (“hives”)
- itchiness
- redness, pain or swelling where Zavicefta was given into a vein
- fever

Uncommon: (may affect up to 1 in 100 people)
- increase in the number of a type of blood cell (called “lymphocytes”) – shown in blood tests
- decrease in the number of some types of blood cells (called “leucocytes”) - shown in blood tests
- tingling or numbness
- bad taste in your mouth
- an increase in the level of some types of substances in your blood (called “creatinine” and “urea”). These show how well your kidneys are working.

Very rare: (may affect up to 1 in 10,000 people)
- swelling in a part of the kidney that causes a reduction in its normal working function

Not known: (frequency cannot be estimated from the available data)
- significant decrease in the type of white blood cells used to fight infection - shown in blood tests
- decrease in the number of red blood cells (haemolytic anaemia) – shown in blood tests
- severe allergic reaction (see **Serious side effects**, above)
- yellowing of the whites of the eyes or skin
- sudden onset of a severe rash or blistering or peeling skin, possibly accompanied by a high fever or joint pain (these may be signs of more serious medical conditions such as toxic epidermal necrolysis, Stevens-Johnson syndrome, erythema multiforme or a condition known as DRESS, Drug Reaction with Eosinophilia and Systemic Symptoms)
- swelling under the skin, particularly lips and around the eyes

Tell your doctor or nurse if you notice any of the side effects listed above.

Reporting of side effects
If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store. By reporting side affects you can help provide more information on the safety of this medicine.

5. How to store Zavicefta

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the container. The expiry date refers to the last day of that month.

Store in the original package in order to protect from light.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer require. These measures will help to protect the environment.

6. Contents of the pack and other information

What Zavicefta contains

- The active substances are ceftazidime and avibactam. Each vial contains ceftazidime pentahydrate equivalent to 2 g ceftazidime and avibactam sodium equivalent to 0.5 g avibactam.
- The other ingredient is sodium carbonate (anhydrous) (see section 2 “Zavicefta contains sodium”).

What Zavicefta looks like and contents of the pack
Zavicefta is a white to yellow powder for concentrate for solution for infusion in a vial. It is available in packs containing 10 vials.

Marketing Authorisation Holder
Pfizer Limited,
Ramsgate Road,
Sandwich,
Kent
CT13 9NJ,
UK.

Manufacturer
ACS Dobfar S.p.A.
Via Alessandro Fleming 2
Verona 37135
Italy

For any information about this medicine, please contact:
Medical Information, Pfizer Ltd, Walton Oaks, Dorking Road, Tadworth, Surrey, KT20 7NS.
Telephone 01304 616161.

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The following information is intended for healthcare professionals only:

Important: Please refer to the Summary of Product Characteristics before prescribing.

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.

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 a pale yellow solution and is free of particles.

Mix gently to reconstitute and check to see that the contents have dissolved completely. Parenteral medicinal products should be inspected visually for particulate matter prior to administration.

Infusion bags

If the intravenous solution is prepared with diluents listed in section 6.6 (ceftazidime concentration 8 mg/mL), the chemical and physical in-use stability has been demonstrated (from initial vial puncture) for up to 12 hours at 2 - 8°C, followed by up to 4 hours at not more than 25°C.

If the intravenous solution is prepared with diluents listed in section 6.6 (ceftazidime concentration > 8 mg/mL to 40 mg/mL), the chemical and physical in-use stability has been demonstrated (from initial vial puncture) for up to 4 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 those stated above.

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.

Zavicefta (ceftazidime/avibactam) is a combination product; each vial contains 2 g of ceftazidime and 0.5 g of avibactam in a fixed 4:1 ratio. Dosage recommendations are based on the ceftazidime component only.

Standard aseptic techniques should be used for solution preparation and administration. Doses may be prepared in an appropriately sized infusion bag or infusion syringe.
The resulting solution should be administered over 120 minutes.

Each vial is for single use only.

Any unused product or waste material should be disposed of in accordance with local requirements.

The total time interval between starting reconstitution and completing preparation of the intravenous infusion should not exceed 30 minutes.

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 the Table below.

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)	Volume (mL) will vary based on infusion syringe 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 the Tables 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.

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	5	250	1.5	11
	6	300	1.8	13
	7	350	2.1	15

50 mg/kg of ceftazidime	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.

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.

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	4	60	0.36	2.7
	5	75	0.45	3.3

15 mg/kg of ceftazidime	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.