Package leaflet: Information for the patient

Zerbaxa® 1 g / 0.5 g powder for concentrate for solution for infusion
ceftolozane / tazobactam

Read all of this leaflet carefully before you start taking 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 pharmacist.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Zerbaxa is and what it is used for

Zerbaxa is a medicine used to treat a range of bacterial infections. It contains two active substances:
- ceftolozane, an antibiotic that belongs to the group of "cephalosporins" and which can kill certain bacteria that can cause infection;
- tazobactam, which blocks the action of certain enzymes called beta-lactamases. These enzymes make bacteria resistant to ceftolozane by breaking down the antibiotic before it can act. By blocking their action, tazobactam makes ceftolozane more effective at killing bacteria.

Zerbaxa is used in all age groups to treat complicated infections within the abdomen, and kidney and urinary system.

Zerbaxa is also used in adults to treat an infection of the lungs called "pneumonia".

2. What you need to know before you take Zerbaxa

Do not take Zerbaxa
- if you are allergic to ceftolozane, tazobactam or any of the other ingredients of this medicine (listed in section 6).
- if you are allergic to medicines known as "cephalosporins".
- if you have had a severe allergic reaction (e.g., severe skin peeling; swelling of the face, hands, feet, lips, tongue or throat; or difficulty swallowing or breathing) to certain other antibiotics (e.g., penicillins or carbapenems).

Warnings and precautions
Talk to your doctor or pharmacist before taking Zerbaxa if you know you are, or have previously been allergic to cephalosporins, penicillins or other antibiotics.

Talk to your doctor or pharmacist if you develop diarrhoea while taking Zerbaxa.

Infections caused by bacteria that are not sensitive to Zerbaxa or caused by a fungus can occur during or following treatment with Zerbaxa. Tell your doctor if you think you may have another infection.

Treatment with Zerbaxa sometimes causes production of antibodies that react with your red blood cells. If you are told that you have an abnormal blood test (called Coombs test) tell your doctor that you are having or have recently had Zerbaxa.

Children and adolescents
This medicine should not be given to children under 18 years old to treat pneumonia because there is not enough information on use in this age group for the treatment of this infection.

Other medicines and Zerbaxa
Tell your doctor or pharmacist if you are taking, have recently taken, or might take any other medicines.

Some medicines may interact with ceftolozane and tazobactam. These include:
- Probenecid (a medicine for gout). This can increase the time it takes for tazobactam to leave your body.

Pregnancy and breast-feeding
If you are pregnant or breast-feeding, or think you may be pregnant, ask your doctor or pharmacist for advice before taking this medicine. Your doctor will advise if you should receive Zerbaxa during pregnancy.

If you are breast-feeding, your doctor will advise you on whether you should stop breast-feeding or stop or avoid Zerbaxa therapy, taking into account the benefit of breast-feeding for the child and the benefit of therapy for you.

Driving and using machines
Zerbaxa may cause dizziness, which can affect your ability to drive and use machines.

Zerbaxa contains sodium
This medicine contains 230 mg sodium (main component of cooking/table salt) in each vial. This is equivalent to 11.5% of the recommended maximum daily dietary intake of sodium for an adult. The reconstituted vial with 10 mL of 0.9% sodium chloride (normal saline) for injection contains 265 mg sodium in each vial. This is equivalent to 13.3% of the recommended maximum daily dietary intake of sodium for an adult.

3. How to take Zerbaxa

Your doctor or other healthcare professional will give you this medicine into one of your veins through an infusion (a drip) lasting one hour. The dose of medicine given to you depends on whether or not you have kidney problems.

The dose depends on the type of infection that you have, where the infection is in your body and how serious the infection is. Your doctor will decide on the dose that you need.

Use in adults
The recommended dose of Zerbaxa is 1 g of ceftolozane and 0.5 g of tazobactam or 2 g of ceftolozane and 1 g of tazobactam every 8 hours, which is given into one of your veins (directly into the bloodstream).

Treatment with Zerbaxa normally lasts between 4 and 14 days, depending on the severity and location of the infection and on how your body responds to the treatment.

Use in children and adolescents
The recommended dose of Zerbaxa is 20 mg/kg of ceftolozane and 10 mg/kg of tazobactam every 8 hours, which is given into one of your veins (directly into the bloodstream). The dose should not exceed 1 g of ceftolozane and 0.5 g of tazobactam.

Treatment with Zerbaxa normally lasts between 5 and 14 days, depending on the severity and location of the infection and on how your body responds to the treatment.

Patients with kidney problems
Your doctor may need to reduce the dose of Zerbaxa or decide how often Zerbaxa is given to you. Your doctor may also want to test your blood to make sure you receive an appropriate dose, especially if you have to take this medicine for a long time.

If you take more Zerbaxa than you should
As this product is given by a doctor or other healthcare professional, it is very unlikely that you will be given too much Zerbaxa. However, if you have any concerns you should let your doctor, nurse or pharmacist know immediately.

If you stop taking Zerbaxa
If you think you have not been given a dose of Zerbaxa, tell your doctor or other healthcare professional immediately.

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

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Tell your doctor straight away if you get these symptoms as you may need urgent medical treatment:

- Sudden swelling of your lips, face, throat or tongue; a severe rash; and, swallowing or breathing problems. These may be signs of a severe allergic reaction (anaphylaxis) and may be life-threatening
- Diarrhoea that becomes severe or does not go away or stool that contains blood or mucus during or after treatment with Zerbaxa. In this situation, you should not take medicines that stop or slow bowel movement

Adults treated for complicated infections within the abdomen, and kidney and urinary system

Common side effects (may affect up to 1 in 10 people):
Headache, stomach ache, constipation, diarrhoea, nausea, vomiting, increase in liver enzymes (from blood tests), rash, fever (high temperature), decrease in blood pressure, decrease in potassium (from blood tests), increase in the number of certain types of blood cells known as platelets, dizziness, anxiety, difficulty sleeping, infusion site reactions

Uncommon side effects (may affect up to 1 in 100 people):
Inflammation of the large intestine due to *C. difficile* bacteria, inflammation of the stomach, abdominal distension, indigestion, excessive gas in stomach or bowel, obstruction of the intestine, yeast infection in the mouth (thrush), yeast infection of female genitalia, fungal urinary tract infection, increase in sugar (glucose) levels (from blood tests), decrease in magnesium levels (from blood tests), decrease in phosphate levels (from blood tests), ischemic stroke (stroke caused by reduced blood flow in brain), irritation or inflammation of a vein at injection site, venous thrombosis (blood clot in a vein), low red blood cell counts, atrial fibrillation (rapid or irregular heartbeat), fast heartbeat, angina pectoris (chest pain or feeling of tightness, pressure or heaviness in chest), itchy rash or swellings on the skin, hives, Coombs test positive (a blood test that looks for antibodies that may fight against your red blood cells), kidney problems, kidney disease, shortness of breath

Additional side effects observed in children and adolescents treated for complicated infections within the abdomen, and kidney and urinary system
Common side effects (may affect up to 1 in 10 people):
Increased appetite, low white blood cell counts, altered taste

Adults treated for an infection of the lungs called “pneumonia”

Common side effects (may affect up to 1 in 10 people):
Inflammation of the large intestine due to *C. difficile* bacteria, diarrhoea, vomiting, increase in liver enzymes (from blood tests)

Uncommon side effects (may affect up to 1 in 100 people):
Infection due to *C. difficile* bacteria, *C. difficile* test positive (from stool test), Coombs test positive (a blood test that looks for antibodies that may fight against your red blood cells)

Reporting of side effects
If you get any side effects, talk to your doctor or pharmacist. 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 effects you can help provide more information on the safety of this medicine.

5. How to store Zerbaxa

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 carton and vial after "EXP." The expiry date refers to the last day of that month.

Unopened vials: Store in a refrigerator (2°C – 8°C).

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

Do not throw away any medicines via wastewater. Any unused medicinal product or waste material should be disposed of in accordance with local requirements. These measures will help protect the environment.

6. Contents of the pack and other information

What Zerbaxa contains
- The active substances are ceftolozane and tazobactam.
- Each vial contains ceftolozane sulfate equivalent to 1 g ceftolozane and tazobactam sodium equivalent to 0.5 g tazobactam. For doses above 1 g ceftolozane and 0.5 g tazobactam, two vials are used.
- The other excipients are sodium chloride, arginine, and citric acid, anhydrous.

What Zerbaxa looks like and contents of the pack
Zerbaxa is a white to slightly yellow powder for concentrate for solution for infusion (powder for concentrate) supplied in a vial.

Zerbaxa is available in packs containing 20 mL Type I clear glass vial with stopper (bromobutyl rubber) and flip-off seal.

Pack size of 10 vials.

Marketing Authorisation Holder and Manufacturer

Marketing Authorisation Holder: Merck Sharp & Dohme (UK) Limited, 120 Moorgate, London, EC2M 6UR, United Kingdom.

Manufacturer: FAREVA Mirabel, Route de Marsat, Riom, 63963, Clermont-Ferrand Cedex 9, France.

For any information about this medicine, please contact:
Merck Sharp & Dohme (UK) Limited
Tel: +44 (0) 208 154 8000

Email: medicalinformationuk@msd.com

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The following information is intended for healthcare professionals only:

Preparation of solutions

Each vial is for single use only.
Aseptic technique must be followed in preparing the infusion solution.

Preparation of doses

The powder for concentrate for solution for infusion for each vial is reconstituted with 10 mL of water for injections or sodium chloride 9 mg/mL (0.9%) solution for injection per vial; following reconstitution the vial should be shaken gently to dissolve the powder. The final volume is approximately 11.4 mL per vial. The resultant concentration is approximately 132 mg/mL (88 mg/mL of ceftolozane and 44 mg/mL of tazobactam) per vial.

CAUTION: THE RECONSTITUTED SOLUTION IS NOT FOR DIRECT INJECTION.

Zerbaxa solution for infusion is clear and colourless to slightly yellow.

Variations in colour within this range do not affect the potency of the product.

After reconstitution and dilution, chemical and physical in-use stability has been demonstrated for 24 hours at room temperature or 4 days at 2 to 8 ºC. The medicinal product is photosensitive and should be protected from light when not stored in the original carton.

See section 4.2 of the Summary of Product Characteristics for recommended dose regimens for Zerbaxa based on indication and renal function. The preparation for each dose is shown below.

Instructions for preparing adult doses in INFUSION BAG:

For preparation of the 2 g ceftolozane / 1 g tazobactam dose: Withdraw the entire contents from two reconstituted vials (approximately 11.4 mL per vial) using a syringe and add it to an infusion bag containing 100 mL of 0.9% sodium chloride for injection (normal saline) or 5% glucose injection.

For preparation of the 1.5 g ceftolozane / 0.75 g tazobactam dose: Withdraw the entire contents from one reconstituted vial (approximately 11.4 mL per vial) and 5.7 mL from a second reconstituted vial using a syringe and add it to an infusion bag containing 100 mL of 0.9% sodium chloride for injection (normal saline) or 5% glucose injection.

For preparation of the 1 g ceftolozane/ 0.5 g tazobactam dose: Withdraw the entire contents (approximately 11.4 mL) of the reconstituted vial using a syringe and add it to an infusion bag containing 100 mL of 0.9% sodium chloride for injection (normal saline) or 5% glucose injection.

For preparation of the 500 mg ceftolozane / 250 mg tazobactam dose: Withdraw 5.7 mL of the contents of the reconstituted vial and add it to an infusion bag containing 100 mL of 0.9% sodium chloride for injection (normal saline) or 5% glucose injection.

For preparation of the 300 mg ceftolozane / 150 mg tazobactam dose: Withdraw 3.5 mL of the contents of the reconstituted vial and add it to an infusion bag containing 100 mL of 0.9% sodium chloride for injection (normal saline) or 5% glucose injection.

For preparation of the 250 mg ceftolozane / 125 mg tazobactam dose: Withdraw 2.9 mL of the contents of the reconstituted vial and add it to an infusion bag containing 100 mL of 0.9% sodium chloride for injection (normal saline) or 5% glucose injection.

For preparation of the 100 mg ceftolozane / 50 mg tazobactam dose: Withdraw 1.2 mL of the contents of the reconstituted vial and add it to an infusion bag containing 100 mL of 0.9% sodium chloride for injection (normal saline) or 5% glucose injection.

Instructions for preparing paediatric doses in INFUSION BAG or in INFUSION SYRINGE:

NOTE: The following procedure describes the steps to prepare 100 mL of stock solution with a final concentration of 10 mg/mL ceftolozane / 5 mg/mL tazobactam. The volume of this stock solution to be administered to the paediatric patient will be based on calculating the appropriate dose based on the patient's weight (see section 4.2 of the Summary of Product Characteristics). Detailed steps and calculations are provided.

1. Preparing the stock solution (100 mL of 10 mg/mL ceftolozane / 5 mg/mL tazobactam): Withdraw the entire contents (approximately 11.4 mL) of the reconstituted vial using a syringe and add it to an infusion bag containing 89 mL of 0.9% sodium chloride for injection (normal saline) or 5% glucose injection.
2. Preparing the required volume of stock solution for infusion:
    a. Calculate the appropriate amount of Zerbaxa (in mg) to deliver the required dose to the paediatric patient. Based on this dose in mg, calculate the appropriate volume of the 10 mg/mL ceftolozane / 5 mg/mL tazobactam stock solution to be administered. Refer to Table 1 below to confirm the calculations. Note that the table is NOT inclusive of all possible calculated doses but may be utilised to estimate the approximate volume to verify the calculation.
    b. Transfer an appropriately calculated volume of stock solution to an adequately sized infusion bag or infusion syringe. Values shown in Table 1 are approximate, and it may be necessary to round to the nearest graduation mark of an appropriately sized syringe for smaller volumes.

Table 1: Preparation of Zerbaxa for paediatric patients (from birth* to below 18 years of age) from the 100 mL stock solution of 10 mg/mL ceftolozane / 5 mg/mL tazobactam

Zerbaxa dose (mg/kg)	Weight (kg)	Calculated amount of ceftolozane (mg)	Calculated amount of tazobactam (mg)	Volume of stock solution to administer to patient (mL)
20 mg/kg ceftolozane / 10 mg/kg tazobactam**	50 and greater	1 000	500	100
	40	800	400	80
	30	600	300	60
	20	400	200	40
	15	300	150	30
	10	200	100	20
	5	100	50	10
	3	60	30	6
	1.5	30	15	3

*Defined as > 32 weeks gestational age and ≥ 7 days postnatal.
**Children weighing > 50 kg and with eGFR > 50 mL/min/1.73 m^2 should not exceed the maximum dose of 1 g ceftolozane / 0.5 g tazobactam.

From a microbiological point of view, the medicinal product should be used immediately upon reconstitution. 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 to 8°C, unless reconstitution/dilution has taken place in controlled and validated aseptic conditions.

One of the active ingredients, ceftolozane, may have harmful effects if it reaches the aquatic environment. Do not throw away any unused medicinal product or waste material via wastewater. Any unused medicinal product or waste material should be disposed of in accordance with local requirements. These measures will help protect the environment.

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