PATIENT PACKAGE INSERT IN ACCORDANCE WITH THE PHARMACISTS REGULATIONS (PREPARATIONS) 1986

This medicine is to be supplied upon physician's prescription only

ZERBAXA® 1 g/0.5 g

Powder for Concentrate for Solution for Infusion

Each vial contains:
Ceftolozane (as sulfate) 1 g
Tazobactam (as sodium) 0.5 g

For a list of inactive ingredients see section 6. "FURTHER INFORMATION". See also section 2.7 "Important information about some of the ingredients of **ZERBAXA**".

Read the entire leaflet carefully before you start using this medicine.

- This leaflet contains concise information about the medicine. If you have any further questions, refer to the doctor or the pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their medical condition seems similar to yours.

1. WHAT ZERBAXA IS INTENDED FOR?

ZERBAXA is used in adults to treat complicated infections within the abdomen, and kidney and urinary system infections.

ZERBAXA 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.

Therapeutic group: Antibacterials for systemic use, other cephalosporins and penems.

2. BEFORE USING ZERBAXA

2.1 Do not use ZERBAXA if:

- you are allergic to ceftolozane, tazobactam or any of the other ingredients of this medicine (listed in section 6).
- you are allergic to medicines known as "cephalosporins".
- 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).

2.2 Special warnings regarding use of ZERBAXA

Before starting treatment with ZERBAXA, tell your doctor 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**.

2.3 Taking other medicines
If you are taking, or have recently taken, other medicines including non-prescription medicines and nutritional supplements, you should tell the doctor or pharmacist.
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.

2.4 Children and Adolescent
No data is available for the safety and efficacy of this product in children and adolescents.

2.5 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, or plan to breast-feed, consult your doctor. Your doctor will discuss the possible risks and benefits of using **ZERBAXA** while you are breast-feeding.

2.6 Driving and operating machinery
ZERBAXA may cause dizziness, which can affect your ability to drive and use machines.

2.7 Important information about some of the ingredients of ZERBAXA
ZERBAXA contains 10.0 mmol (230 mg) of sodium per vial. The reconstituted vial with 10 mL of 0.9% sodium chloride (normal saline) for injection contains 11.5 mmol (265 mg) of sodium. This should be taken into consideration if you are on a controlled-sodium diet.

3. HOW SHOULD YOU USE 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 usually recommended dose is:

Adults
The recommended dose is one vial of **ZERBAXA** (containing 1 g of ceftolozane and 0.5 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.

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.

Do not exceed the recommended dose.

If you have accidentally taken a higher dose 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 the medicine
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. SIDE EFFECTS

As with any medicine, **ZERBAXA** may cause side effects in some patients.
Do not be alarmed by reading the list of side effects, you may not suffer from any of them.

Refer to the doctor immediately if you develop any of the following signs 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

Additional side effects
Common side effects - appear in 1-10 people in 100:
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 - appear in 1-10 people in 1,000:
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 heart beat, angina pectoris (chest pain or feeling of tightness, pressure or heaviness in chest), itchy rash or swellings on the skin, hives, Coombs test positive (from blood test), kidney problems, kidney disease, shortness of breath

If a side effect appears, if any of the side effects worsens or if you suffer from a side effect not mentioned in this leaflet, consult with the doctor.

Side effects can be reported to the Ministry of Health by using the link "Reporting side effects due to medicinal treatment" at the home page of the Ministry of Health's web site (www.health.gov.il) which refers to the online side effects reporting form, or by using the link:
https://forms.gov.il/globaldata/getsequence/getsequence.aspx?formType=AdversEffectMedic@moh.gov.il

5. HOW TO STORE ZERBAXA?

- Avoid Poisoning! This medicine and any other medicine must be stored in a safe place out of the reach and sight of children and/or infants, in order to avoid poisoning. Do not induce vomiting unless explicitly instructed to do so by a doctor.

- Do not use the medicine after the expiry date (exp. date) that appears on the packaging. The expiry date refers to the last day of the indicated month.
- **Storage conditions**:
  Unopened vials: Store in a refrigerator (2°C – 8°C).
  Store in the original package in order to protect from light.
- Medicines should not be disposed of via wastewater or household waste. Ask the pharmacist how to dispose of medicines you no longer use. These measures will help to protect the environment.

6. FURTHER INFORMATION

What ZERBAXA contains:
In addition to the active ingredients **ZERBAXA** also contains: L-arginine, sodium chloride, and citric acid, anhydrous.
ZERBAXA contains 10.0 mmol (230 mg) of sodium per vial. See also section 2.7 “Important information about some of the ingredients of **ZERBAXA**”.

What ZERBAXA looks like and the contents of the package:
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 authorization holder and address:
Merck Sharp & Dohme (Israel-1996) Company Ltd., P.O.Box 7121, Petah-Tikva 49170.

Manufacturer:
Merck Sharp & Dohme Corp., New-Jersey, USA.

This Leaflet was checked and approved by the Ministry of Health in April 2018.

Registration number of the medicine listed in the National Drug Registry of the Ministry of Health:
160-01-34967

Instructions for Healthcare Professionals

Preparation and Administration

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 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. The resultant concentration is approximately 132 mg/mL (88 mg/mL of ceftolozane and 44 mg/mL of tazobactam).

CAUTION: THE RECONSTITUTED SOLUTION IS NOT FOR DIRECT 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.

The preparations that follow relate to dose adjustments for renally impaired patients:

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 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.

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.

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

Shelf life

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

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, unless reconstitution/dilution has taken place in controlled and validated aseptic conditions and would normally not be longer than 24 hours at 2 to 8°C.