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Summary of the risk management plan (RMP) for Zerbaxa (ceftolozane / tazobactam)

This is a summary of the risk management plan (RMP) for Zerbaxa, which details the measures to be taken in order to ensure that Zerbaxa is used as safely as possible. For more information on RMP summaries, see here.

This RMP summary should be read in conjunction with the EPAR summary and the product information for Zerbaxa, which can be found on Zerbaxa's EPAR page.

Overview of disease epidemiology

Zerbaxa is a medicine used to treat complicated bacterial infections (those that are difficult to treat) affecting the organs inside the abdomen (belly) or the kidneys and structures that carry urine (the urinary tract).

Complicated intra-abdominal infections

Infections within the abdominal cavity (intra-abdominal infections) such as peritonitis (infection of the membrane lining the abdomen) and formation of abscesses may be serious or life-threatening. Peritonitis is a medical emergency and requires immediate treatment. Complications of peritonitis can include bacteria spreading into the blood stream. Intra-abdominal infections can be caused by a variety of different bacteria and are a common cause of illness and hospital admission worldwide. In 2012 a study of over 2,000 patients in Europe who developed peritonitis or abscesses found that acute appendicitis was the most common cause of severe infection (37%). Around 13% of patients were admitted in a critical condition and about 8% of affected patients died.

Complicated urinary-tract infections

Urinary tract infections are among the most common infections and are usually not severe or complicated. They occur more often in women than in men and are less common in children. More severe or complicated urinary tract infections, including kidney infection (pyelonephritis) tend to occur either when a patient has an abnormality or blockage of the urinary tract (e.g. caused by kidney stones or enlarged prostate gland) or when the patient has a urinary catheter (tube inserted into the bladder). Complications of a urinary tract infection can be serious and lead to kidney failure or spread of bacteria into the blood stream.

In Europe, about 40% of hospital-acquired infections in urology departments are urinary tract infections and there are around 11 cases for every 1,000 days spent by patients in hospital. Life-threatening spread of infection to the bloodstream and elsewhere (sepsis) can occur: about 5% of severe sepsis cases are related to urinary tract infections. Sepsis is more common in men than in women.

Summary of treatment benefits

Zerbaxa contains the active substance ceftolozane, an antibiotic of the group known as cephalosporins, together with tazobactam, a substance that blocks certain bacterial enzymes that break down this type of antibiotic and make bacteria resistant to its action. The medicine has been shown to be at least as effective as other antibiotics in curing infections in two main studies.

One study involved 1,083 patients who mostly had kidney infection or in some cases a complicated urinary-tract infection. Zerbaxa successfully treated the infection in about 85% of the cases where it was given (288 of 340), compared with 75% (266 of 353) of those given another antibiotic called levofloxacin.

The second study involved 993 patients with complicated intra-abdominal infections. Zerbaxa was compared with another antibiotic, meropenem. Both medicines produced a cure in about 94% of patients (353 out of 375 given Zerbaxa and 375 out of 399 given meropenem).

Unknowns relating to treatment benefits

Most of the patients in the main studies supporting licensing of Zerbaxa were white Eastern Europeans. There is no evidence to suggest that results would be any different in non-white patients. The effects of Zerbaxa have not been studied in patients with severe kidney disease or in patients with weakened immune systems. There is some evidence that the efficacy would be similar in patients with severe kidney disease or weakened immune systems.

Summary of safety concerns

Important identified risks

Risk	**What is known**	**Preventability**
Allergic reactions (hypersensitivity)	Allergic reactions, which can be severe, may occur in patients receiving antibiotics.	Patients should tell their doctor about any severe allergic reactions that they have had before receiving Zerbaxa. Patients who have had a severe allergic reaction to certain types of antibiotics (e.g. penicillin, cephalosporin, monobactam or carbapenem) should not receive treatment with Zerbaxa.
Clostridium difficile-associated diarrhoea	Some antibiotics can decrease normal protective bacteria in the gut, allowing *Clostridium difficile* bacteria to multiply and cause symptoms such as cramping pain, fever, and diarrhoea. Sometimes these symptoms have been reported to occur over 2 months after receiving antibiotic treatment. Cases have been reported uncommonly (in less than 1 patient in 100) in those treated with Zerbaxa.	Patients should tell their doctor or pharmacist if they are suffering from diarrhoea before they take Zerbaxa or if they have suffered from diarrhoea whilst taking antibiotics in the past. They should contact their doctor straightaway if they develop diarrhoea during or after Zerbaxa treatment and should check with the doctor before attempting to treat the condition. If *Clostridium difficile*-associated diarrhoea is confirmed, Zerbaxa may be stopped and other antibiotic treatment for *C. difficile*

Risk	What is known	Preventability
		given.
Reduced functioning of the kidney (renal impairment)	Reduced kidney function was seen in about 1 patient in 100 (11 of 1015 patients) given Zerbaxa in studies supporting licensing of the medicine. Only 2 of these 11 cases were severe and the majority of patients recovered. Affected patients generally had abnormal kidney function prior to receiving the medicine.	Patients should tell their doctor about any kidney problems they have had before treatment with Zerbaxa. Doctors should monitor kidney function in patients whose kidney function is already reduced, and adjust the dose of Zerbaxa depending on the severity of the reduction.
Mistakes in supplying and labelling the medicine (medication errors)	Medication errors by pharmacy staff occurred in the United States after Zerbaxa was approved for use in that country.	Changes were made to the vial and packaging label of Zerbaxa to reduce the chance of medication errors. Healthcare providers should be aware of the correct dosing, preparation, and administration of Zerbaxa, as detailed in the product information, before giving it to patients.

Important potential risks

Risk	What is known
Development of bacteria that cannot be treated by specific antibiotics (drug-resistant bacteria)	About 1 patient in 200 with complicated urinary-tract infection taking Zerbaxa in the main clinical trial developed bacteria that could not be killed by the medicine. Infections caused by these bacteria can be harder to treat.
Serious skin reactions that meet certain criteria, such as reactions requiring hospitalisation (severe skin reactions)	Serious skin reactions may occur in patients receiving antibiotics. However, severe skin reactions have not been reported for Zerbaxa. Patients who have had a serious skin reaction to certain types of antibiotics (e.g. penicillin, cephalosporin, monobactam or carbapenem) should not receive treatment with Zerbaxa.
Anaemia caused by breakage of red blood cells (haemolytic anaemia)	Haemolytic anaemia, which is sometimes indicated by a blood test called a Coombs test, has been reported in patients who have received other cephalosporin antibiotics. In clinical trials of Zerbaxa, around 2 patients in 1,000 were reported to have a positive Coombs test but haemolytic anaemia was not observed.

Missing information

Risk	What is known
Safety and effectiveness in patients less than 18 years old	The main clinical trials only included patients who were older than 18 years and so there are no data concerning patients under 18 years of age. Studies are planned to study the efficacy of Zerbaxa in young patients.
Experience in pregnant or breast-feeding women	There are no data from the use of Zerbaxa in pregnant women. Zerbaxa should not be used in pregnancy unless the benefit to the woman outweighs the potential risk. It is unknown whether Zerbaxa passes into human milk. A decision must be made as to whether to stop breastfeeding or to stop or avoid the medicine, taking into account the possible risks versus the benefit of breast-feeding for the child and the benefit of therapy.
Safety and effectiveness in patients with a weakened immune system (immunocompromised patients)	Patients with weakened immune systems were not studied in clinical trials, thus the effectiveness of Zerbaxa in such patients is not known.
Use for bacterial infections other than complicated urinary tract infections and complicated infections within the abdominal cavity (off-label use)	There is a risk that Zerbaxa may be used to treat infections for which its safety and effectiveness have not been studied. It is not known to what extent this may happen in practice, and whether it would have consequences for the safety profile of the medicine, but measures are in place to monitor this after marketing.

Summary of risk minimisation measures by safety concern

All medicines have a summary of product characteristics (SmPC) which provides physicians, pharmacists and other healthcare professionals with details on how to use the medicine, and also describes the risks and recommendations for minimising them. Information for patients is available in lay language in the package leaflet. The measures listed in these documents are known as 'routine risk minimisation measures'.

The SmPC and the package leaflet are part of the medicine's product information. The product information for Zerbaxa can be found on Zerbaxa's EPAR page.

This medicine has no additional risk minimisation measures.

Planned post-authorisation development plan

Not applicable.

Studies which are a condition of the marketing authorisation

No studies are required as a condition of the marketing authorisation.

Summary of changes to the risk management plan over time

Not applicable.

This summary was last updated in 08-2015.