REPUBLIC OF BULGARIA
NATIONAL COUNCIL ON PRICES AND
REIMBURSEMENT OF MEDICINAL PRODUCTS

# HEALTH TECHNOLOGY ASSESSMENT

## ZERBAXA

**Powder for concentrate for solution for infusion 1g/0,5g x 10**

**Ceftolozane/Tazobactam**

**Merck Sharp & Dohme, B.V., The Netherlands**

| | |
|---|---|
| Therapeutic indications | Zerbaxa is indicated for the treatment of the following infections in adults<br>- complicated intra-abdominal infections;<br>- complicated urinary tract infections; |
| Start – end of the procedure | 22.04.2019 – 27.01.2020 |
| Final decision | Inclusion in Annex 2 for purchase by medical establishments with state and/ or municipal participation and under Art. 5 of the Medical Establishments Act of the Positive Drug List (PDL) |

# Summary of the report on the clinical and pharmacoeconomic evaluation of the health technology of the medicinal product ZERBAXA

## Health problem

Resistant Gram-negative pathogens (*E. coli, K. pneumoniae, P. aeruginosa*) in hospital-treated infections such as complicated intra-abdominal infections (cIAIs) and complicated urinary tract infections (cUTIs) are associated with a high degree of treatment failure due to an inappropriate empirical therapy, poor clinical outcomes, mortality and increased cost of care.

Acute or chronic infection is sometimes associated with suppurative complications such as paraurethral abscesses, renal or perirenal abscesses, and metastatic infection, including bone and joint infection or endocarditis. These complications are more difficult for treatment than localized cUTIs and can lead to poor patient outcomes and even death. Bacteremia, urosepsis and septic shock are observed in patients with cUTIs.

Intra-abdominal infections (IAIs) are a wide range of conditions that result from the passage of microorganisms from the gastrointestinal tract to normally sterile areas in the abdomen. This peritoneal contamination can be a result of spontaneous perforation (e.g. appendicitis, perforated ulcer or diverticulitis), surgery or trauma, etc.

## Epidemiological data

### Complicated urinary tract infections (cUTIs)

To assess the incidence of nosocomial UTIs, a one-day study was conducted in 141 hospitals in 25 countries. 3.55 episodes of UTIs acquired in hospital/1000 patient-days were identified, with an estimated prevalence of 10.65 episodes/1000 patient-days. 63% of infections were diagnosed as catheter-related infections. The National Health Safety Network (NHSN) reports that catheter-related UTIs are the second most commonly reported healthcare associated infections. A review of the US literature shows that catheter-related

UTIs are the third most common infection in hospitals for active treatment with 1.87 cases/1000 medical devices per day. *Clostridium difficile* infections and surgical site infections, with a incidence rate of 3.85 cases/1000 patient-days and 1.98 cases/100 procedures per patient, were the two most common cases of infections associated with health care. In the data for EU5 (France, Germany, Italy, Spain, United Kingdom), the prevalence for 2014 is 1,738,670 cases of cUTIs. In 2015, a total of 3.54 million cases of UTIs caused by Gram-negative pathogens were reported in Europe. It is expected growth of 1.2% per year to 3.89 million in 2023.

**Complicated intra-abdominal infections (cIAIs)**

A study of healthcare-associated infections in 2,039 hospitals reported that abdominal infections were the second most common type of infection (3,598/16,019, 22.5%) after infections related to orthopedic surgery. The total number of patients with cIAIs caused by Gram-negative pathogens in Europe in 2015 was 224,280. This number is expected to increase by 1.2% per year and reach 229,110 in 2023. The Complicated Intra-abdominal Infection Observational Worldwide (CIAOW) study evaluates Gram-negative aerobic pathogens isolated from patients with complicated nosocomial IAIs, community-acquired and nosocomial cIAIs, and describes common sources of infection in cIAIs patients. The most common source of cIAIs is acute appendicitis (34.6%), followed by acute cholecystitis (14.8%), gastroduodenal complications (14.2%), perforation of the small intestine (7.5%) and others. A wide range of pathogens, including resistant strains, are responsible for cIAIs, most of which are Gram-negative bacteria. Enterobacteriaceae (*E. coli*, *Enterobacter spp., K. pneumoniae*), *P. aeruginosa* and *Acinetobacter spp.* are among the most commonly isolated bacteria in patients with cIAIs.

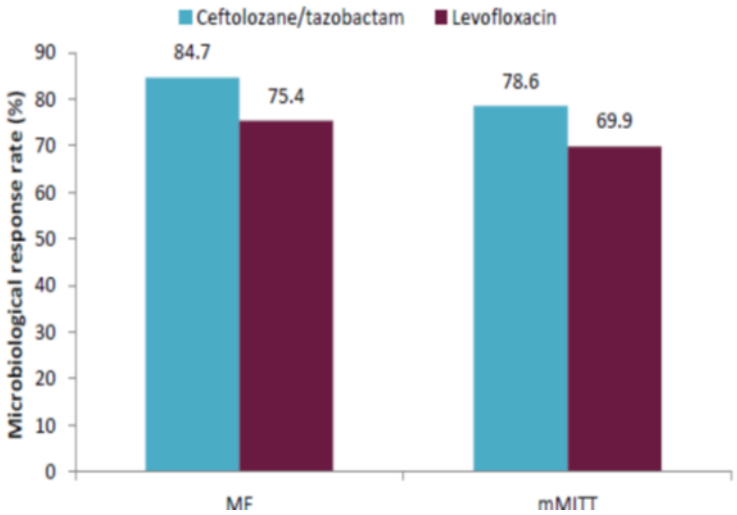
**Efficacy data**

Zerbaxa was evaluated in phase 3 clinical trials controlled with reference medicinal product, in cIAIs and cUTIs (including pyelonephritis) involving a total of 1,015 patients treated with Zerbaxa (1 g/0.5 g intravenously every 8 hours, adjusted according to renal function, where appropriate), for up to 14 days.

| Clinical trial | Brief description, method of conducting |
|---|---|
| ASPECT-cUTI | a multicenter, prospective, randomized, double-blind, double-dummy', phase 3 study to assess the efficacy of ceftolozane/tazobactam versus levofloxacin in adult patients with cUTI, including pyelonephritis. Number of patients participating in the trial - 1083. |
| ASPECT-cIAI | a multicenter, prospective, double-blind, randomized, phase 3 study to assess the efficacy of ceftolozan/tazobactam plus metronidazole versus meropenem in adult patients with cIAI. Number of patients participating in the trial -993. |

In ASPECT-cUTI, patients were randomized to receive ceftolozane/tazobactam or levofloxacin in a 1:1 ratio. The study covered three phases: a screening phase, a treatment phase (days 1 to 7) and a follow-up phase, including a visit at the end of treatment (EOT) (up to 24 hours after the last dose), a test-of-cure (TOC) visit (7 days ± 2 days after the last dose) and a late follow-up (LFU) visit (28 to 35 days after the last dose). Ceftolozane/tazobactam showed a higher degree of microbiological response compared to a high dose of levofloxacin in patients with cUTI, including pyelonephritis (Figure 1).

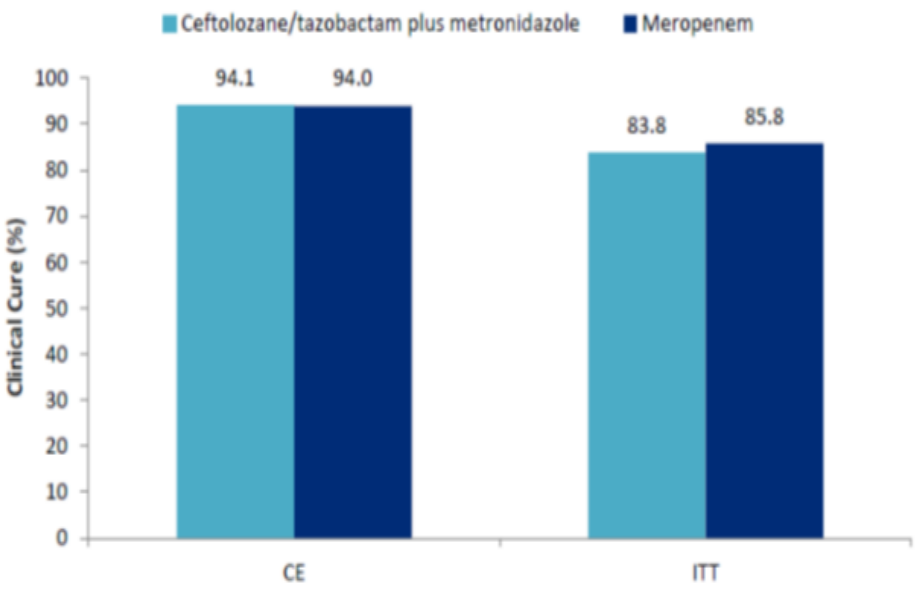
Fig.1




ME at TOC: microbiological evaluation at a test-of-cure; mMITT: microbiologically modified intent-to-treat population

In the ASPECT-cIAI clinical trial, 993 patients were studied in two groups. One group of patients received ceftolozane/tazobactam + metronidazole or meropenem in a 1: 1 ratio. The stratification is according to the place of the study and the primary site of infection: intestine (small or large intestine) relative to another site of IAI. The study covers three phases: screening phase; treatment phase (day 1 to day 10) and follow-up phase, including EOT visit (within 24 hours of the last treatment), TOC visit (26 to 30 days after the first dose of the investigated medicine) and LFU visit (38 to 45 days after the first dose of the investigated medicine). The total duration of treatment with the investigated medicine is from 4 to 10 days. Patients received the investigated medicine for up to 14 days if the criteria for discontinuation of treatment on day 10 of the study were not met (Fig. 2).

Fig. 2




Additional subgroup analyzes revealed that:

- Ceftolozane/tazobactam + metronidazole is effective in eradicating the most common Gram-negative pathogens causing cIAIs, including *E. coli*, *K. pneumoniae* and *P. aeruginosa*

- Ceftolozane/tazobactam + metronidazole demonstrates a high clinical cure rate in the most common resistant Gram-negative pathogens causing cIAI, including extended spectrum beta-lactamase (ESBL)-producing *E. coli* and ESBL-producing *K. Pneumoniae*

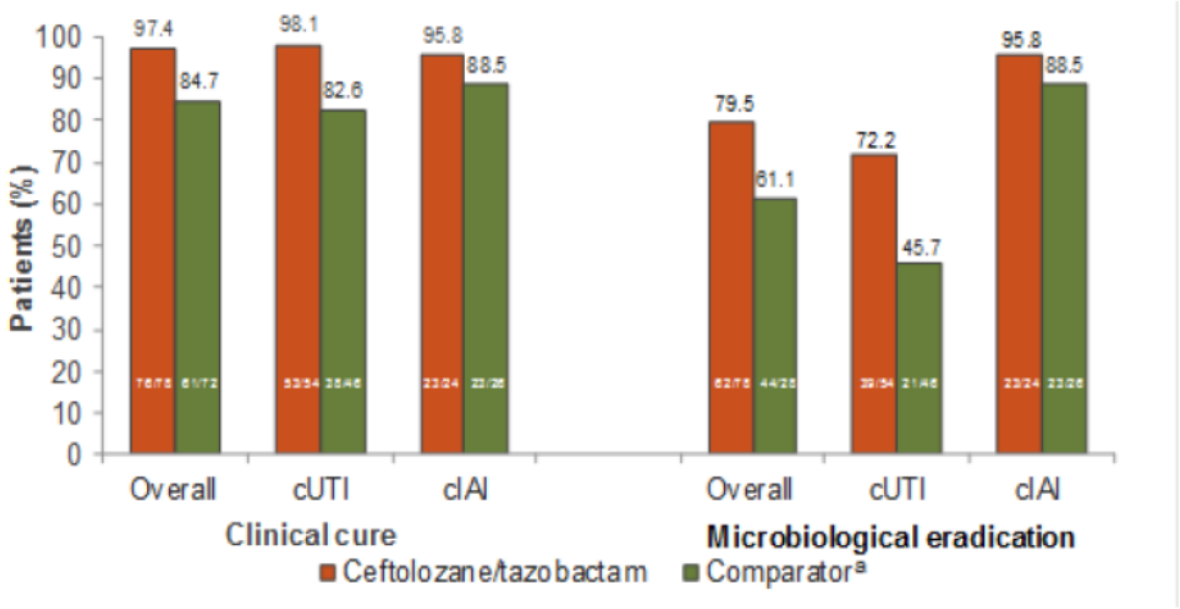
- Cases of antimicrobial resistance in patients treated with ceftolozane/tazobactam are rare.

- Ceftolozane/tazobactam demonstrates a high clinical cure rate in patients infected with resistant pathogens comparable to that of meropenem.

The integrated analysis pooled data from the ASPECT studies and aimed to assess clinical and microbiological outcomes for all patients in these studies infected with ESBL-producing Enterobacteriaceae. The clinical cure rate and microbiological eradication was higher in ceftolozane/tazobactam than in

patients with ESBL-producing pathogens, both in the analysis of the individual studies (ASPECT-cUTI and ASPECT-cIAI) and in the integrated subanalysis (Fig. 3).

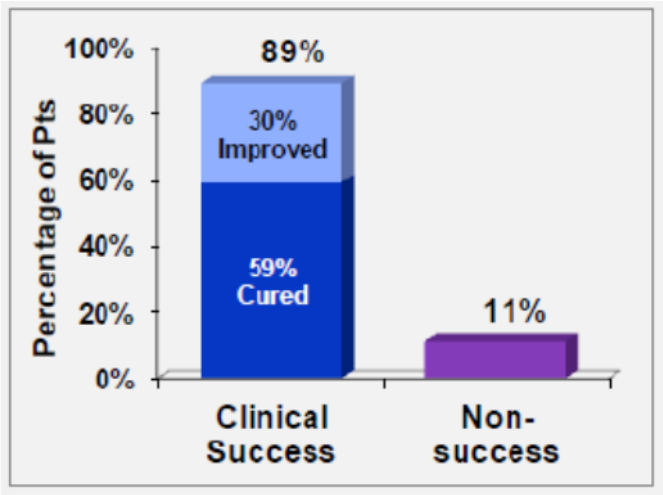
Fig. 3




Ceftolozane/tazobactam: outpatient treatment of Gram-negative infections at Physician Office Infusion Centers (POICs)

In 2016, the results of a multicenter retrospective review of data for 28 patients in 12 infusion centers receiving ceftolozane/tazobactam for the treatment of the following Gram-negative infections were published: complicated intra-abdominal infection (cIAI), complicated urinary tract infection (cUTI), respiratory tract infection (RI) and complicated skin and soft tissue infection (cSSTI). Ceftolozane/tazobactam was used in combination with other IV antimicrobials in 4 patients (14%), all with vancomycin (1 cIAI, 2 RI, 1 cSSTI). The reason for the use of ceftolozane/tazobactam is the lack of alternatives due to microorganisms with multidrug resistance (MDR) (54%) and failure of previous therapy (46%). The results of the study are as follows: 59% of patients were cured (n = 16) and 30% were with improvement (n = 8). Three of the patients with improvement continued to receive oral antimicrobials at discharge, and in 11% (n = 3) of the patients treatment failure was found due to inadequate response to therapy in two and one in connection with an adverse drug reaction (ADR) (Fig. 4).

Fig.4



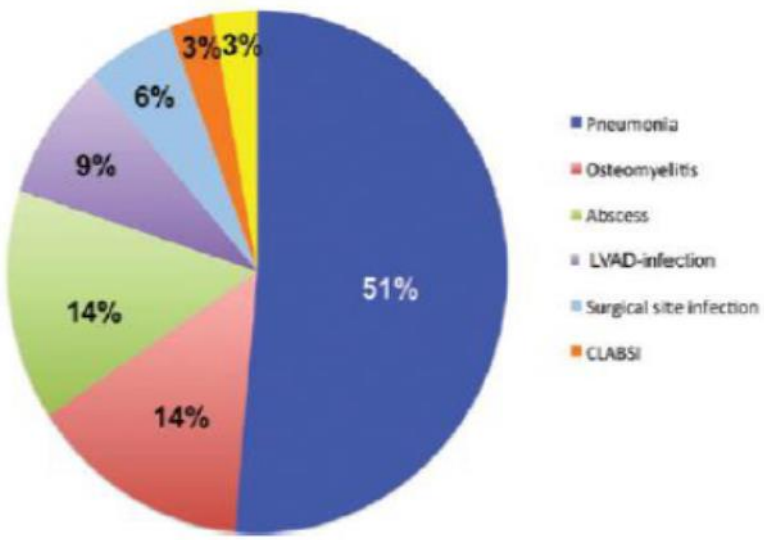

In terms of safety, a total of 16 ADRs (39%) occurred in 11 patients. In one patient, treatment was discontinued due to the development of maculopapular rash on day 7.

In 2016, the results of a study with ceftolozane/tazobactam were published, the main aim of which was to determine the degree of clinical and microbiological cure in patients receiving ceftolozane/tazobactam from the Cleveland Clinic Health System. 60 patients were evaluated between April 2015 and February 2016. Most of them were in the intensive care unit (ICU) (61.7%) and many of them received ceftolozane/tazobactam as combination therapy (48.3%). The average duration of ceftolozane/tazobactam use is 8 days. The most common infection was pneumonia (34 [56.7%]), followed by intra-abdominal infection (11 [18.3%]); 21.7% of patients have concomitant bacteremia. The primary isolated pathogen was *Pseudomonas aeruginosa* (*PsA*) in 52 (86.7%) cases; 40.4% of them are MDR and 25% are extensively drug resistant (XDR). The susceptibility of *PsA* to ceftolozane/tazobactam was 83% and 94.1%, 94.7% and 45.5% to non-MDR, MDR and XDR, respectively. The clinical and microbiological cure rates were 64.1% and 38.5%, respectively. Twenty-four patients died during the hospitalization.

Munita et al., in 2016 published the results of the use of Ceftolozane/tazobactam for severe infections caused by carbapenem-resistant *Pseudomonas aeruginosa* with the following localization: (Fig. 5).

Ceftolozane/tazobactam was used for a treatment of carbapenem-resistant infections in 35 patients (mean age 55 years, 23% women). Eighteen (51%) patients had nosocomial pneumonia, 3 of whom were complicated by empyema. A total of 6 patients had secondary bacteremia. Antipseudomonas antibiotics were taken before ceftolozane/tazobactam by 30 (86%) patients. Most isolates are resistant to ciprofloxacin and beta-lactams and are sensitive to colistin. It should be noted that despite the lack of previous exposure to ceftolozane/tazobactam 4 isolates are not sensitive to the antibiotic (Fig. 5).

Fig. 5




Clinical success was achieved in 26 (74%) patients; clinical failure was reported in 9 patients. The treatment in all patients infected with ceftolozane/tazobactam insensitive *P. aeruginosa* (n = 4) was unsuccessful. No serious ADRs have been reported.

In 2016 Merchant et al. published also the results of a large retrospective study with ceftolozane/tazobactam using an electronic health record database covering 26 integrated data delivery networks, 360 hospitals and over 50 million patients in the United States (Predictive Health Intelligence Environment EMR database). Ceftolozane/tazobactam was prescribed to 149 patients. All patients receiving ceftolozane/tazobactam as final therapy received prior this treatment

another antimicrobial therapy. *P. aeruginosa* was isolated in 48 of these 62 patients and 41 (85%) were sensitive to ceftolozane/tazobactam.

A meta-analysis of clinical trials with ceftolozane/tazobactam was also performed. The aim of the meta-analysis was to evaluate the efficacy and safety of ceftolozane/tazobactam compared to other antibiotics in the treatment of cUTI. In the ASPECT-cUTI study, ceftolozane/tazobactam demonstrated greater efficacy compared to levofloxacin in patients with complicated urinary tract infections, incl. pyelonephritis, based on a unified endpoint involving microbiological eradication and degree of clinical response. Ceftolozane/tazobactam is effective in eradicating the most common and problematic Gram-negative pathogens causing complicated urinary tract infections - *E. coli*, ESBL-producing Enterobacteriaceae and *P. aeruginosa*. Ceftolozane/tazobactam is more effective than levofloxacin in high-risk patients with baseline-resistant levofloxacin and/or ESBL-producing uropathogens and concomitant bacteremia. The other main study (ASPECT-cIAI) showed that, in combination with metronidazole, ceftolozane/tazobactam was comparable to meropenem in the treatment of complicated intra-abdominal infections. Therapeutic benefit is also pronounced in ESBL-producing Enterobacteriaceae, with a higher clinical cure rate than meropenem. The main results of the studies are confirmed by the secondary, additional and subgroup analyzes. In addition, cases of development of *Pseudomonas aeruginosa* and *Escherichia coli* resistance to ceftolozane/tazobactam are rare. In ASPECT-cUTI, after 7 days of therapy, only 2 (0.6%) of the pathogens developed resistance in 52 cases of microbiological failure in the arm with ceftolozane/tazobactam; in ASPECT-cIAI no development of resistance was reported in any of the arms.

The new health technology Zerbaxa has a pronounced effect against clinically significant strains resistant to carbapenems, cephalosporins, fluoroquinolones and Piperacillin/Tazobactam, including *Escherichia coli, Klebsiella pneumoniae* and other enterobacteria; it is one of the most potent agents tested against *P. aeruginosa* and is 2 to 8 times more potent than Ceftazidime or Cefepime. Zerbaxa is an alternative to therapies, some of which are associated with more common side effects, including severe ones such as in Tigecycline, while others are known for their greater nephrotoxicity such as Colistin and Amikacin.

**Safety data**

The most common adverse reactions (≥ 3% in pooled phase 3 trials) that occurred in patients treated with Zerbaxa were nausea, headache, constipation, diarrhea, and pyrexia, and were generally mild or moderate (Table 1).

Table 1

| System Organ Class | Common adverse effects (≥ 1/100 and < 1/10) | Uncommon adverse effects (≥ 1/1000 and < 1/100) |
|---|---|---|
| Infections and infestations | | Vulvovaginal candidiasis, colitis caused by *Clostridium difficile* |
| Blood and lymphatic system disorders | Thrombocytosis | Anemia |
| Metabolic and eating disorders | Hypokalemia | |
| Psychiatric disorders | Insomnia, anxiety | |
| Nervous system disorders | Headache, dizziness | |
| Heart disorders | | Atrial fibrillation |
| Vascular disorders | Hypotension | Phlebitis |
| Gastrointestinal disorders | Nausea, diarrhea, constipation, vomiting, abdominal pain | |
| Skin and subcutaneous tissue disorders | Rash | |
| General disorders and effects on application site | Pyrexia | |
| Laboratory tests | Elevated alanine aminotransferase, elevated aspartate aminotransferase | Positive Coombs test |

The incidence of serious adverse reactions during treatment is low and comparable between groups (8.1% with ceftolozane/tazobactam + metronidazole and 7.2% with meropenem). The frequency of treatment discontinuation is low and comparable in both arms.

**Comparators data**

Currently available therapies for cUTIs and cIAIs have limitations that emphasize the need for new treatment options. The most significant difficulties are related to resistance and toxicity, which reduce the usefulness of such therapies. Resistance among Enterobacteriaceae and non-fermentation gram-negative bacteria increasingly limits the use of fluoroquinolones, third-generation cephalosporins, and Piperacillin/Tazobactam as treatment regimens for cUTIs and cIAIs in many regions of the world. In addition, the increase in resistance to carbapenems should also be considered, as infections caused by CRE (Carbapenem-resistant Enterobacteriaceae) have few treatment options and are associated with high mortality.

Following the appearance of resistance to some commonly used antibiotics (fluoroquinolones, third-generation cephalosporins, Piperacillin/Tazobactam and carbapenems), antibiotic capabilities are limited in the treatment of cUTIs and cIAIs and are associated with several safety and toxicity issues. Aminoglycosides (e.g. Amikacin) and polymyxins (e.g. Colistin) have been reported to cause nephrotoxicity and/or ototoxicity. As a result, these therapies are considered a last step when other safe and effective antimicrobials are not appropriate. Aminoglycosides and tigecycline have been associated with a higher rate of treatment failure at the end of therapy than other therapies.

Zerbaxa's comparators, which could be partially or completely displaced with the introduction of the new technology, are the following:

1. Comparators for cIAIs are: meropenem; piperacillin/tazobactam; imipenem/cilastatin; cefepime + metronidazole; ceftazidime; metronidazole; tigecycline.

2. Comparators for cUTIs are: levofloxacin; piperacillin/tazobactam, imipenem/cilastatin; cefepime; ceftazidime; meropenem.

**Pharmacoeconomic indicators**

**Applied analysis**

It is applied an analysis for a evaluation of the cost-effectiveness of ceftolozane/tazobactam compared to the available alternatives in the treatment of complicated intra-abdominal infection and complicated urinary tract infection in hospital conditions from the point of view of the reimbursement system in Bulgaria. The introduction of the new health technology Zerbaxa in PDL has a

neutral impact on the budget of the National Health Insurance Fund (NHIF), as the treatment of complicated intra-abdominal infections and complicated urinary tract infections is paid from the budget of hospitals and medicines indicated for the treatment of these diseases are included in the value of the clinical pathways (CP).

The choice of all comparators is justified from the point of view of the Bulgarian therapeutic practice. The selected economic methods are cost-benefit analysis (CBA) and cost-minimization analysis (CMA), as a long-term result of the simulation, the pharmacoeconomic model takes into account the number of deaths and patients cured, as well as the acquired health benefits such as quality-adjusted life years (QALYs). The cost-minimum method is used when there is equivalent therapeutic efficacy between the alternatives. The selected time horizon in the model is for life.

**Costs for the assessed health technology**

The cost of therapy with the applicant medicinal product is calculated at the price of wholesaler with VAT for an average treatment period of seven days. The cost of therapy with all alternatives is lower than that of therapy with Ceftolozane/tazobactam.

The cost for the entire time horizon of the analysis was calculated after simulation of therapy in the model for evaluating the cost-effectiveness of therapeutic alternatives in the treatment of complicated intra-abdominal infections and complicated urinary tract infections. In addition to the costs for the therapy with the evaluated technologies, the model also includes costs for medical services in the treatment of complicated intra-abdominal infections and complicated urinary tract infections - clinical pathways CP196 and CP084.

A computer simulation model is applied, which conducts a simulation of therapy at the patient level (Monte Carlo simulation). The structure of the model follows the clinical course of treatment of both diagnoses after initiation of empirical treatment. As a long-term result of the simulation, the model takes into account the number of deaths and patients cured, as well as the acquired health benefits such as quality-adjusted life years (QALYs).

The model uses life expectancy data that are adapted for Bulgaria. Data on the therapeutic efficacy of Ceftolozane/tazobactam as well as data on efficacy of alternative therapies have been transferred from published literature data. The

therapeutic efficacy of Ceftolozane/tazobactam was associated with a higher rate of clinical cure compared to the alternatives. Shortened length of hospital stay with Ceftolozane/tazobactam therapy have a positive effect on patients' quality of life.

On the table 2 are presented the QALYs gained in Ceftolozane/tazobactam therapy versus alternatives.

| **Complicated intra-abdominal infections, Ceftolozane / tazobactam + metronidazole vs.** | ΔQALY |
|---|---|
| Piperacillin/tazobactam | +0,06 |
| Meropenem | Equivalent therapeutic efficacy |
| Cefepime | +0,06 |
| Imipenem/cilastatin | Equivalent therapeutic efficacy |
| Ceftazidime | +0,06 |
| Tigecycline | +0,58 |
| **Complicated urinary tract infections, Ceftolozane / tazobactam vs.** | |
| Piperacillin/tazobactam | +0,11 |
| Meropenem | Equivalent therapeutic efficacy |
| Cefepime | +0,14 |
| Imipenem/cilastatin | Equivalent therapeutic efficacy |
| Ceftazidime | +0,11 |
| Levofloxacin | +0,10 |

The results of the analysis show that Ceftolozane/tazobactam therapy is cost-effective compared to almost all alternatives, with an additional cost for QALY below 3 times gross domestic product (GDP) per capita. Ceftolozane/tazobactam therapy is dominated by Meropenem and Imipenem/cilastatin therapies.

A probabilistic and one-way (tornado diagram) analysis of the sensitivity of Ceftolozane/tazobactam to alternatives was performed.

In patients with complicated urinary tract infections, the probabilistic sensitivity analysis of Ceftolozane/tazobactam therapy to remain cost-effective compared

to alternatives is 100%. In the one-way sensitivity analysis, the results show that the incremental cost-benefit ratio is mostly influenced by mortality from inappropriately selected empirical antibiotic treatment, followed by mortality from appropriately selected empirical antibiotic treatment.

The incremental cost-benefit ratio is also significantly influenced by the health benefits for surviving patients and the resistance to alternative therapies.

Despite the significantly higher costs of therapy with the applicant drug, the conducted cost-benefit analysis shows that the therapy is cost-effective compared to some of the alternatives and could be included in PDL as a therapeutic option for patients with complicated intra-abdominal infections and complicated urinary tract infections. Modeling cost and results data in the period after the end of the clinical trials creates uncertainty about the therapeutic efficacy and cost-effectiveness, but in the sensitivity analyzes performed, the results of the cost-result analysis remain below the threshold.

**Budgetary impact**

The analysis of the budgetary impact was conducted from the point of view of the paying institution. The time horizon of the budgetary impact analysis is 5 years. The three main determinant factors influencing the budgetary impact are: the number of patients over a five-year period, the average cost of comparator drug therapy, and the cost of Zerbaxa therapy.

The prognostic model and tornado diagram for the budgetary impact of cIAIs are presented, and the dependence is mostly related to the cost of therapy with Zerbaxa (CEF/TAZ) and the cost of therapy with alternatives.

According to the presented model of the budgetary impact, the inclusion of the new reimbursement technology will lead to a change in the costs of the medical establishments for treatment of patients with cIAIs and cUTIs. The introduction of the new health technology leads to an increase in the treatment costs for patients with cIAIs and cUTIs.

The estimated number of patients for the new technology is 50 for the first year, and no significant increase is expected until the fifth year within up to 72 patients. The expected budgetary impact is positive with an increase in the cost of medical establishments, not taking into account patient access schemes, as well as agreed discounts.

## Conclusion

**Zerbaxa powder for concentrate for solution for infusion 1g/0.5g x 10 is a new therapeutic option for patients with severe complicated intra-abdominal and complicated urinary tract infections and in this regard is a strategic choice of antibiotic therapy as a last line therapy. In regard to the growing antimicrobial resistance worldwide and the challenges it puts on public health and healthcare systems, the availability of new therapeutic options is a key factor in improving health outcomes and health-related quality of life.**