

Report ZERBAXA® - ceftolozane / tazobactam

Product & Mechanism of action	Authorized indications Licensing status	Essential therapeutic features	NHS impact
<p>Substance: ceftolozane / tazobactam</p> <p>Brand Name: Zerbaxa</p> <p>Originator/licensee: Merck Sharp & Dohme B.V.</p> <p>Classification: NI</p> <p>ATC code: J01DI54</p> <p>Orphan Status: Eu: No (1) Us: No (2)</p> <p>Mechanism of action: Ceftolozane is a cephalosporin, which belongs to the beta-lactams. It works by interfering with the production of molecules that bacteria need to build their protective cell walls causing weakness in the bacterial cell walls which become prone to collapse, leading to the death of the bacteria. Tazobactam blocks the action of bacterial enzymes beta-lactamases. These enzymes enable bacteria to break down beta-lactam antibiotics like ceftolozane, making the bacteria resistant to the antibiotic's action. Blocking these enzymes, tazobactam allows ceftolozane to act against bacteria that would otherwise be resistant to ceftolozane (1).</p>	<p>Authorized Indication:</p> <p>EMA: is indicated for the treatment of the following infections in adult and paediatric pts:</p> <ul style="list-style-type: none">- Complicated intra-abdominal infections;- Acute pyelonephritis;- Complicated urinary tract infections (3). <p>Route of administration: IV</p> <p>Licensing status EU CHMP P.O. date: EU M.A. date: 23/06/2022 (3) FDA M.A. date: 21/04/2022 (2)</p> <p>EU Speed Approval Pathway: No (1) FDA Speed Approval Pathway: Yes (2)</p> <p>-----</p> <p>ABBREVIATIONS: AEs: Adverse Events IV: intravenous Pts: patients</p>	<p>Summary of clinical EFFICACY: Study NCT03217136: phase 2, randomized, active comparator-controlled, multicenter, double-blind trial to study safety and efficacy of ceftolozane/tazobactam+metronidazole (70 pts) vs meropenem+placebo in pediatric pts (21 pts) with complicated intra-abdominal infection. The primary outcomes were: a) the number of pts experiencing ≥1 AEs up to 75 days; b) the number of pts who discontinued study therapy due to AEs up to 18 days. a) 56/70 (80%) pts with ceftolozane/tazobactam +metronidazole vs 13/21 (61.9%) pts with meropenem+placebo experienced ≥1 AEs up to 75 days (difference in percentage 18.1; CI 95% -2.6 - 41.1). b) 2/70 (2.9%) pts with ceftolozane/tazobactam+metronidazole vs 0/21 (0%) pts with meropenem+placebo discontinued study therapy due to AEs up to 18 days (difference in percentage 2.9; CI 95% 12.9 - 9.9) (4).</p> <p>Study NCT03230838: phase 2, randomized, active comparator-controlled, multicenter, double-blind clinical trial to study the safety and efficacy of ceftolozane/tazobactam (100 pts) versus meropenem (33 pts) in pediatric pts with complicated urinary tract infection, including pyelonephritis. Primary outcome measures were: a) the number of pts with ≥1 AEs up to day 88; b) the number of pts discontinuing study therapy due to AEs up to day 15. a) 59/100 (59%) pts with ceftolozane/tazobactam vs 20/33 (60.6%) pts with meropenem experienced ≥1 AEs up to 88 days. b) 1/100 (1%) pts with ceftolozane/tazobactam vs 0/33 (0%) pts with meropenem discontinued study therapy due to AEs up to 15 days (5).</p> <p>Summary of clinical SAFETY: Study NCT03217136: 46/70 (65.71%) pts treated with ceftolozane/tazobactam+metronidazole were affected by non serious AEs vs 10/21 (47.62%) pts treated with meropenem+placebo. The most frequent non serious AEs in the treatment group were: diarrhea (18.57%); pyrexia (12.86%); incision site pain (10.00%); abdominal pain (10.00%); vomiting (10.00%). 11.43% of pts treated with ceftolozane/tazobactam + metronidazole were affected by serious AEs vs none treated with meropenem+placebo. No deaths were reported. Serious AEs in the treatment group were: constipation, faecaloma, intestinal obstruction, intra-abdomina fluid collection, abdominal sepsis, arthritis bacterial, lower respiratory tract infection, white blood cell count increased (1.43%), pneumonia (2.86%)(4).</p> <p>Study NCT03230838: 25/100 (25.00%) pts treated with ceftolozane/tazobactam were affected by non serious AEs vs 10/33 (30.30%) pts treated with meropenem. The most frequent non serious AEs in the treatment group were: thrombocytosis (7.00%), diarrhea (7.00%), pyrexia (6.00%). 3.00% of pts treated with ceftolozane/tazobactam were affected by serious AEs vs (6.06%) pts treated with meropenem. Serious AEs in the treatment group were: pyelonephritis, pyelonephritis acute, upper respiratory tract infection each (1.00%). No deaths were reported (5).</p> <p>Ongoing studies:</p> <ul style="list-style-type: none">• For the same indication: No (6 - 7)• For other indications: No (8) <p>Discontinued studies (for the same indication): No (6-7)</p> <p>References:</p> <ol style="list-style-type: none">1. https://www.ema.europa.eu/en/medicines/human/EPAR/zerbaxa2. https://www.ema.europa.eu/en/documents/maop/chmp-poit-authorisation-summary-positive-opinion-zerbaxa_en.pdf3. https://www.accessdata.fda.gov/scripts/cder/da/indes.cfm?event=BasicSearch.process4. https://www.clinicaltrials.gov/ct2/show/NCT03217136?term=NCT03217136&rank=15. https://www.clinicaltrials.gov/ct2/show/NCT03230838?term=NCT03230838&rank=16. https://www.clinicaltrials.gov/ct2/results?term=ceftolozano+tazobactam&cond=Complicated+intra-abdominal+infection&age_v=&age=0&endr=&type=&rslt=&Search=Apply7. https://www.clinicaltrials.gov/ct2/results?term=ceftolozano+tazobactam&cond=Complicated+Urinary+Tract+infection&age_v=&age=0&endr=&type=&rslt=&Search=Apply8. https://www.clinicaltrials.gov/ct2/results?term=ceftolozano+tazobactam&age_v=&age=0&endr=&type=&rslt=&Search=Apply9. https://edilex.farnamdata.it/10. https://springerhealthcare.it/GIHTAD/2019/09/25/valutazione-dell'impatto-delle-strategie-antibiotiche-nel-trattamento-delle-infezioni-intradominali-complicate-in-un-policlinico-universitario/#:~:text=Secondo%20un%20studio%20italiano%20le,ciaj%20%5B6%5D11. https://www.nature.com/articles/s41585-020-0362-4.pdf12. https://www.biomedcentral.com/track/pdf/10.1186/s13017-021-00387-8.pdf13. https://56b0chluwz.cloudfront.net/documents/pocket-guidelines/EAU-Pocket-on-Urological-Infections-2022.pdf14. https://springerhealthcare.it/GIHTAD/wp-content/uploads/2019/09/GIHTAD-Piccone_12_4_0708.pdf	<p>Cost of therapy: the Italian ex-factory cost of 1 vial of Zerbaxa 1 g + 0,5 g is € 136,5. This dose correspond to the maximum single dose to be administered every 8 or 12 hours for 5 or 14 days. The cost for a 14 days treatment (T.I.D.) which correspond to the maximum dosage is € 5.733,00 (9).</p> <p>Epidemiology: In Italy, according to the last prevalence point survey (ECDC, 2016) are estimated from 450.000 to 700.000 infections a year, with an incidence between 5 and 8%. Intra-abdominal infections are 5.6% of nosocomial infections, and almost all present in a complicated form, mainly caused by Gram-negative bacteria such as Enterobacteriaceae, Pseudomonas aeruginosa and Acinetobacter spp. The Global Prevalence Study on Infections in Urology estimates that 1,866 of 19,756 (9.4%) urological pts hospitalized between 2005 and 2017 developed complicated urinary tract infection during their hospital stay. Urinary tract infections represent the 21% of the healthcare-related infection in Italy (10-11).</p> <p>-----</p> <p>POSSIBLE PLACE IN THERAPY: antibiotics are used to treat pts with intra-abdominal infections based upon susceptibility (anaerobic, pseudomonas, non-resistant enterococci, enterobacteriaceae, extended-spectrum beta-lactamase coverage). Options for anaerobic coverage are: amoxicillin/clavulanate, eravacycline, ertapenem, mipenem-cilastatin, meropenem, metronidazole, piperacillin/tazobactam, tigecycline. Options for pseudomonas coverage are: amikacin, ceftazidime, ciprofloxacin, imipenem-cilastatin, meropenem, piperacillin/tazobactam. Options for non-resistant enterococci coverage are: amoxicillin/clavulanate, eravacycline, piperacillin/tazobactam, tigecycline. Options for enterobacteriaceae coverage are: amikacin, ceftolozane/tazobactam, cefotaxime, ceftazidime, ceftriaxone, ertapenem, imipenem-cilastatin, meropenem, piperacillin/tazobactam. Options for extended-spectrum beta-lactamase are: ceftazidime/avibactam, ceftolozane/tazobactam, eravacycline, ertapenem, imipenem-cilastatin, meropenem, tigecycline.</p> <p>The European Association of Urology recommendation for complicated urinary tract infections propose to use the combination of: amoxicillin plus an aminoglycoside; a second generation cephalosporin plus an aminoglycoside; a third generation cephalosporin intravenously as empirical treatment of complicated urinary tract infections with systemic symptoms (12-13).</p> <p>OTHER INDICATIONS IN DEVELOPMENT Yes [Neutropenia, Febrile Hematologic Cancer, Ventilator-associated Pneumonia]</p> <p>SAME INDICATION IN EARLIER LINE(S) OF TREATMENT: No (6-7)</p> <p>OTHER DRUGS IN DEVELOPMENT for the SAME INDICATION Yes [Cefiderocol, benzilpenicillin] [if it is..] *Service reorganization Y/N No *Possible off label use Y/N No</p>

