NEW DRUGS

New drugs

Ceftolozane sulfate with tazobactam sodium

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Approved indication: specified infections

Zerbaxa (Merck, Sharp and Dohme)
vials containing 1000 mg/500 mg powder for reconstitution
Australian Medicines Handbook section 5.1.3

Antibiotic resistance is a growing problem. This combination of ceftolozane (a cephalosporin) with tazobactam (a beta-lactamase inhibitor) is an attempt to address multidrug resistant Gram-negative bacteria. These organisms can cause severe intra-abdominal infections and complicated urinary tract infections.

Ceftolozane has a bactericidal action. Its spectrum of activity is extended by combining with tazobactam to inhibit the beta-lactamase enzymes produced by organisms such as *Escherichia coli* and *Klebsiella* species. The combination also has efficacy against bacteria such as *Pseudomonas aeruginosa*, *Enterobacter* and *Proteus mirabilis*. It is not effective for infections caused by *Staphylococcus aureus* or enterococci.

The combination has to be given by intravenous infusion. The reconstituted solution is diluted and infused over an hour every eight hours. Most of the dose is renally excreted, so lower doses are needed in patients with a creatinine clearance below 50 mL/minute. As there is a potential for hypersensitivity reactions, the infusion should be given where there are facilities for managing anaphylaxis.

A multicentre study enrolled patients with pyelonephritis or complicated lower urinary tract infections. One group of 543 was randomised to receive infusions of ceftolozane with tazobactam, while 540 received infusions of levofloxacin (a quinolone). Approximately 74% of the patients had a positive urine culture. Most of them were infected with *E. coli*. Treatment for seven days with the combination eradicated the organisms in 80.4% of patients compared with 72.1% with levofloxacin. There was a clinical cure in 92% of these patients treated with the combination and 88.6% of those given levofloxacin.[1]

Another trial studied patients with complicated intra-abdominal infections such as appendiceal abscess or perforation. A group of 487 patients was randomised to receive ceftolozane/tazobactam and metronidazole, while 506 were randomised to intravenous meropenem. *E. coli* was frequently found, but most of the infections were polymicrobial. Treatment was for 4–10 days, but could continue for 14 days. At the end of therapy there was a clinical cure in 89.2% of the patients treated with the combination and 92.3% of those given meropenem. When the patients were assessed a median of 27 days after the start of therapy, the clinical cure rates were 83% with the combination and 87.3% with meropenem.[2]

In the clinical trials the most frequent adverse events in patients taking the combination of ceftolozane with tazobactam were nausea, headache and diarrhoea. In some cases the diarrhoea was associated with *Clostridium difficile*. Although 12 patients treated with the combination died, none of these deaths were considered to be related to treatment.

There are no studies of the combination in pregnancy. It is also unknown if the drugs are excreted in breast milk.

While the clinical trials show that ceftolozane with tazobactam is effective, the combination should probably be reserved for severe cases where a multidrug resistant organism is suspected. In Australia cephalosporins are not usually first-line drugs. Therapeutic Guidelines[3] recommends that an empirical therapy for severe pyelonephritis is gentamicin with ampicillin or amoxycillin.

T manufacturer provided the product information

REFERENCES *†A

1. Wagenlehner FM, Umeh O, Steenbergen J, Yuan G, Darouiche RO. Ceftolozane-tazobactam compared with levofloxacin in the treatment of complicated urinary-tract infections, including pyelonephritis: a randomised, double-blind, phase 3 trial (ASPECT-cUTI). Lancet 2015;385:1949-56. http://dx.doi.org/10.1016/S0140-6736(14)62220-0
2. Solomkin J, Hershberger E, Miller B, Popejoy M, Friedland I, Steenbergen J, et al. Ceftolozane/tazobactam plus metronidazole for complicated intra-abdominal infections in an era of multidrug resistance: results from a randomized, double-blind, phase 3 trial (ASPECT-cIAI). Clin Infect Dis 2015;60:1462-71.
3. eTG complete [Internet]. Melbourne: Therapeutic Guidelines Limited; 2014. http://www.tg.org.au/index.php?sectionid=71 [cited 2016 Apr 11]

A Some of the views expressed in the following notes on newly approved products should be regarded as preliminary, as there may be limited published data at the time of publication, and little experience in Australia of their safety or efficacy. However, the Editorial Executive Committee believes that comments made in good faith at an early stage may still be of value. Before new drugs are prescribed, the Committee believes it is important that more detailed information is obtained from the manufacturer's approved product information, a drug information centre or some other appropriate source.

The Transparency score (T) is explained in 'New drugs: transparency', Aust Prescr 2014;37:27.

* At the time the comment was prepared, information about this drug was available on the website of the Food and Drug Administration in the USA (www.fda.gov).

† At the time the comment was prepared, a scientific discussion about this drug was available on the website of the European Medicines Agency (www.ema.europa.eu).

A At the time the comment was prepared, information about this drug was available on the website of the Therapeutic Goods Administration (www.tga.gov.au/industry/pm-auspar.htm).

Announcement

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Due to the transition to the new NPS MedicineWise website, continuing professional development (CPD) activities for *Australian Prescriber* articles are not currently available.

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Back issues of *Australian Prescriber* from the last two years, and copies of the Anaphylaxis wallchart and Switching-antidepressants poster, are available in hard copy on request.

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ANSWERS TO SELF-TEST QUESTIONS

1 False 2 True

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