NEW DRUGS

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Ceftazidime/avibactam

Approved indication: specified infections

Zavicefta (Pfizer)
vials containing 2000 mg/500 mg as powder for reconstitution

Bacterial resistance to cephalosporins is increasing. The bacteria produce beta-lactamase enzymes which reduce the efficacy of beta-lactam antibiotics, such as penicillins and cephalosporins. Combining the antibiotic with an inhibitor of beta-lactamase can help to overcome bacterial resistance. One example is the combination of amoxicillin and clavulanic acid. Similarly, ceftazidime pentahydrate has been combined with the beta-lactamase inhibitor avibactam sodium. This combination aims to overcome resistance in serious infections caused by organisms such as the Enterobacteriaceae and *Pseudomonas aeruginosa*.

The formulation of ceftazidime and avibactam has to be reconstituted with water and then added to an infusion bag. This solution is then infused intravenously over two hours. The infusion is repeated every eight hours with the recommended duration of treatment being guided by the type of infection.

The activity of the combination is correlated with the concentration of free drug. The penetration of ceftazidime across the blood–brain barrier is poor, but this increases if the meninges are inflamed. Ceftazidime can cross the placenta and is excreted in breast milk. There is some evidence of reproductive toxicity with avibactam in animal studies.

The combination has a half-life of approximately two hours. Both components are excreted unchanged into the urine. Dose adjustment is required in patients with moderate or severe renal impairment.

An open-label trial assessed the efficacy of the combination of ceftazidime with avibactam in treating infections caused by Gram-negative bacteria resistant to ceftazidime. The 333 patients in the study mainly had complicated infections of the urinary tract, such as pyelonephritis, but some had complicated intra-abdominal infections. They received either the combination or the best available therapy, for example a carbapenem such as meropenem. When assessed 7–10 days after the final infusion there was a clinical cure in 91% of each treatment group.[1]

The double-blind RECLAIM trials compared ceftazidime/avibactam plus metronidazole to meropenem. RECLAIM 1 and 2 randomised 1066 patients with complicated intra-abdominal infections requiring surgical intervention or percutaneous drainage. It was possible to isolate the pathogens in 823 patients. In 111 patients there was a ceftazidime-resistant aerobic Gram-negative organism. When the 823 patients were assessed 28–35 days after randomisation there had been a cure in 81.6% of those treated with the combination and metronidazole compared with 85.1% of the meropenem group. The outcomes were similar in the patients with ceftazidime-resistant Gram-negative infections – 83% (39/47) versus 85.9% (55/64).[2]

A similar trial, RECLAIM 3, involved 441 patients in Asia. When they were evaluated 28–35 days after randomisation the proportion with a clinical cure was almost the same for the combination plus metronidazole as it was for meropenem (93.8% vs 94%). In 239 cases, the cause of the complicated intra-abdominal infection was identified as one of the Enterobacteriaceae. These patients were analysed in an intention-to-treat group. The clinical cure rate in this group was 83.2% with the combination plus metronidazole, and 88.8% with meropenem.[3]

The combination was also compared with meropenem in a study of nosocomial pneumonia. The double-blind REPROVE trial involved 817 patients including 246 with ventilator-associated pneumonia. Gram-negative bacteria, such as *Klebsiella pneumoniae* and *Pseudomonas aeruginosa*, were identified in 355 patients. In the patients who were clinically evaluable 21–25 days after randomisation there was a clinical cure in 77.4% (199/257) of the combination group and 78.1% (211/270) of the meropenem group. For an intention-to-treat population the corresponding results were 68.8% (245/356) and 73% (270/370). There were 38 deaths (9%) in the patients treated with ceftazidime/avibactam and 30 (7%) in the meropenem group.[4]

Ceftazidime/avibactam has been compared with doripenem, another carbapenem, in the treatment of complicated urinary tract infections, such as pyelonephritis. The two double-blind RECAPTURE trials randomised 1033 patients including 810 with identified bacteria. *Escherichia coli* was the most frequently isolated organism. The bacteria were resistant to ceftazidime in 19.6% of the patients. After five days of treatment, symptoms had resolved in 70.2% of the combination group and 66.2% of the doripenem group. At 21–25 days after randomisation infection had been eradicated in 77.4% of the patients treated with the combination and 71% of those infused with doripenem. The clinical cure rates were identical (89.3%) in the patients infected with ceftazidime-resistant bacteria.[5]

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As ceftazidime has been available for many years its adverse effects such as hypersensitivity are well known. It is not yet clear what additional adverse effects the combination with avibactam may have. Based on analysis of 2024 patients who received ceftazidime/avibactam in clinical trials, adverse events were reported in 49.2%. Not considering deaths due to disease progression, 2% died with most deaths occurring in patients with pneumonia.[4] Common adverse effects include nausea, vomiting and diarrhoea. Some cases of diarrhoea may be associated with *Clostridioides difficile*.

Adding avibactam extends the range of bacteria that can be treated with ceftazidime. As it is important to reserve antibiotics against resistant bacteria, the use of ceftazidime/avibactam should be limited to the conditions studied in the trials. The combination has therefore been approved for complicated urinary tract infections, hospital-acquired pneumonia, and complicated intra-abdominal infections in combination with metronidazole. Although the overall outcomes were statistically non-inferior to meropenem for intra-abdominal infections, there was a trend favouring meropenem in patients with moderate renal impairment.[2] Close monitoring of renal function will be needed. It is important to remember that the combination will have little activity against Gram-positive bacteria.

T manufacturer provided the product information

The Transparency Score is explained in New drugs: transparency, Vol 37 No 1, Aust Prescr 2014;37:27.

At the time the comment was prepared, information about this drug was available on the websites of the Food and Drug Administration in the USA, and the European Medicines Agency and the Therapeutic Goods Administration.

REFERENCES

1. Carmeli Y, Armstrong J, Laud PJ, Newell P, Stone G, Wardman A, et al. Ceftazidime-avibactam or best available therapy in patients with ceftazidime-resistant Enterobacteriaceae and *Pseudomonas aeruginosa* complicated urinary tract infections or complicated intra-abdominal infections (REPRISE): a randomised, pathogen-directed, phase 3 study. Lancet Infect Dis 2016;16:661-73. https://doi.org/10.1016/S1473-3099(16)30004-4
2. Mazuski JE, Gasink LB, Armstrong J, Broadhurst H, Stone GG, Rank D, et al. Efficacy and safety of ceftazidime-avibactam plus metronidazole versus meropenem in the treatment of complicated intra-abdominal infection: results from a randomized, controlled, double-blind, phase 3 program. Clin Infect Dis 2016;62:1380-9. https://doi.org/10.1093/cid/ciw133
3. Qin X, Tran BG, Kim MJ, Wang L, Nguyen DA, Chen Q, et al. A randomised, double-blind, phase 3 study comparing the efficacy and safety of ceftazidime/avibactam plus metronidazole versus meropenem for complicated intra-abdominal infections in hospitalised adults in Asia. Int J Antimicrob Agents 2017;49:579-88. https://doi.org/10.1016/j.ijantimicag.2017.01.010
4. Torres A, Zhong N, Pachl J, Timsit JF, Kollef M, Chen Z, et al. Ceftazidime-avibactam versus meropenem in nosocomial pneumonia, including ventilator-associated pneumonia (REPROVE): a randomised, double-blind, phase 3 non-inferiority trial. Lancet Infect Dis 2018;18:285-95. https://doi.org/10.1016/S1473-3099(17)30747-8
5. Wagenlehner FM, Sobel JD, Newell P, Armstrong J, Huang X, Stone GG, et al. Ceftazidime-avibactam versus doripenem for the treatment of complicated urinary tract infections, including acute pyelonephritis: RECAPTURE, a phase 3 randomized trial program. Clin Infect Dis 2016;63:754-62. https://doi.org/10.1093/cid/ciw378