New drugs

Ceftaroline fosamil

Approved indication: complicated skin and soft tissue infections, community-acquired pneumonia
Zinforo (AstraZeneca)
vials containing 600 mg powder for infusion
Australian Medicines Handbook section 5.1.3

Ceftaroline fosamil is a cephalosporin with broad-spectrum in vitro activity against Gram-positive bacteria, including *Staphylococcus aureus*, *Streptococcus pyogenes* and *S. pneumoniae,* and some Gram-negative bacteria, including *Escherichia coli*, *Haemophilus influenzae* and *Klebsiella pneumoniae*. It is also effective against methicillin-resistant *S. aureus* (MRSA) and penicillin non-susceptible *S. pneumoniae* because it binds to the altered penicillin-binding proteins produced by these bacteria.

Ceftaroline fosamil is a prodrug which is converted into active ceftaroline by phosphatases in the plasma. Following a single intravenous dose of 600 mg, almost 90% is excreted by the kidneys with a mean terminal half-life of 2.5 hours. Dose adjustment is required in patients with moderate renal impairment (creatinine clearance >30–50 mL/minute) and it is not recommended in severe renal impairment or end-stage renal disease. Pharmacokinetic drug interactions are not expected as ceftaroline does not inhibit or induce P450 cytochromes and is not metabolised by these enzymes.

The approval of ceftaroline for complicated skin and soft tissue infections is based on two similarly designed phase III randomised controlled trials – CANVAS 1 and 2. A total of 1378 patients requiring intravenous antibiotics received ceftaroline 600 mg or vancomycin 1 g plus aztreonam 1 g as a 60 minute infusion every 12 hours for 5–14 days. Most patients had cellulitis, a major abscess or an infected wound. Patients with diabetic foot ulcers, pressure sores, bites, necrotising fasciitis, gangrene and third degree burns or burns covering more than 5% of their body were excluded, as were those with monomicrobial *Pseudomonas aeruginosa* or anaerobic infections.[1]

In an integrated analysis of the trials, rates of clinical cure – defined as total resolution of infection or improvement that no longer required antibiotics – were similar with ceftaroline and vancomycin plus aztreonam (91.6% vs 92.7%). However, in a subset of patients with infections caused by Gram-negative organisms, ceftaroline was not as effective as the comparator, with clinical cure rates of 85.3% versus 100%.[1]

The most common treatment-emergent adverse events in the skin trials were nausea (5.9%), headache (5.2%), diarrhoea (4.9%), pruritus (3.5%), rash (3.2%) and vomiting (2.9%). Four patients receiving ceftaroline were withdrawn. One patient had *Clostridium difficile*-associated diarrhoea and the others had allergic reactions. There were three deaths in the ceftaroline group – causes included respiratory failure, neck cancer and cardiopulmonary insufficiency.

The approval of ceftaroline for community-acquired pneumonia is also based on two phase III randomised trials – FOCUS 1 and 2.[2] In total, 1228 hospitalised patients requiring intravenous antibiotics (but not in the intensive care unit) received ceftaroline 600 mg every 12 hours or ceftriaxone 1 g every 24 hours for 5–7 days. (The design of the trials was similar except that in FOCUS 1 all patients also received two doses of oral clarithromycin 500 mg on day 1). Patients with an infection caused solely by an atypical pathogen such as *Mycoplasma pneumoniae* or *Legionella* species were excluded. In an integrated analysis, clinical cure rates were 82.6% for ceftaroline and 76.6% for ceftriaxone.[2]

The most common pathogens isolated in patients with pneumonia were *S. pneumoniae* and methicillin-sensitive *S. aureus*. (Patients with MRSA infections were excluded from the trials because ceftriaxone does not have activity against MRSA. Thirteen patients were infected with *S. pneumoniae* strains which were resistant to two or more antibiotics including penicillin, macrolides, tetracycline, flouroquinolones, chloramphenicol, trimethoprim-sulfamethoxazole and cephalosporins. Of these, clinical cure was achieved in all four patients treated with ceftaroline and two of the nine patients treated with ceftriaxone.[2]

The most common treatment-emergent adverse events in the pneumonia trials were diarrhoea (4.2%), headache (3.4%) and insomnia (3.1%). One of the 15 deaths in the ceftaroline group was possibly related to the study drug and occurred in a 73-year-old woman after two days of treatment. She had a history of smoking and an abnormal ECG at baseline.[2]

Over 10% of patients in the phase III trials developed a positive Coombs test (a direct antiglobulin test). Although none of the patients had signs of haemolysis, haemolytic anaemia is a possibility with

Some of the views expressed in the following notes on newly approved products should be regarded as tentative, as there may be limited published data 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. As a result of fuller experience, initial comments may need to be modified. The Committee is prepared to do this. Before new drugs are prescribed, the Committee believes it is important that full information is obtained from the manufacturer's approved product information, a drug information centre or some other appropriate source.

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ceftaroline, as it is with other cephalosporins. Doctors should be aware that patients allergic to penicillins may also be allergic to ceftaroline.

There are no human data for ceftaroline in pregnancy or lactation so it should only be used if the benefits outweigh the potential harms. Interruption of breastfeeding is recommended. The safety and efficacy of ceftaroline in children is currently unknown.

Ceftaroline was non-inferior to comparative treatments in phase III trials and provides another option for hospitalised patients with complicated skin infections or community-acquired pneumonia. It has efficacy against infections caused by MRSA and drug-resistant *S. pneumoniae*, but is less effective against some Gram-negative pathogens. It should only be used for infections that are proven or are strongly suspected to be caused by susceptible bacteria. Antibiotic stewardship is important, particularly as ceftaroline has broad-spectrum activity.

T manufacturer provided the product information

REFERENCES *†

1. Corey GR, Wilcox M, Talbot GH, Friedland HD, Baculik T, Witherell GW, et al. Integrated analysis of CANVAS 1 and 2: phase 3, multicenter, randomized, double-blind studies to evaluate the safety and efficacy of ceftaroline versus vancomycin plus aztreonam in complicated skin and skin-structure infection. Clin Infect Dis 2010;51:641-50.
2. File TM Jr, Low DE, Eckburg PB, Talbot GH, Friedland D, Lee J, et al. Integrated analysis of FOCUS 1 and FOCUS 2: randomized, double-blinded, multicenter phase 3 trials of the efficacy and safety of ceftaroline fosamil versus ceftriaxone in patients with community-acquired pneumonia. Clin Infect Dis 2010;51:1395-405.

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The Transparency score (T) is explained in 'New drugs: T-score for transparency', Aust Prescr 2011;34:26–7.

* 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).