Health Technology Briefing
April 2024

Cefepime-enmetazobactam for treating hospital-acquired pneumonia including ventilator-associated pneumonia

Company/Developer	Advanz Pharma

☒ New Active Substance ☐ Significant Licence Extension (SLE)

NIHRIO ID: 30344	NICE ID: Not available	UKPS ID: Not available

Licensing and Market Availability Plans

Currently in phase I/II clinical trial.

Summary

Cefepime-enmetazobactam is in clinical development for the treatment of adults with hospital-acquired pneumonia (HAP), including ventilator associated pneumonia (VAP). Pneumonia is a type of chest infection where tiny air sacs in lungs (alveoli) fill with fluid, making it harder to breathe. Symptoms include coughing, feeling tired, a high temperature, difficulty breathing, chest pain and loss of appetite. HAP is a type of pneumonia that occurs 48 hours or more after hospital admission and is not incubating at hospital admission. VAP is occurring in a patient within 48 hours or more after being on breathing machines in intensive care unit. HAP and VAP remain a significant cause of morbidity and mortality so there is a need to develop additional treatment options.

Cefepime-enmetazobactam is a new antibacterial combination for systemic (whole body) use. Cefepime is a type of antibiotic called a cephalosporin, which belongs to the wider group of antibiotics called "beta-lactams". It works by preventing certain bacteria from making their own cell walls, thereby killing the bacteria. Enmetazobactam blocks the action of some of the bacterial enzymes called beta-lactamases. These enzymes enable bacteria to break down beta-lactam antibiotics like cefepime, making the bacteria resistant to the antibiotic's action. By blocking the action of these enzymes, enmetazobactam allows cefepime to act against bacteria that would otherwise be resistant to this antibiotic. If licensed, cefepime-enmetazobactam will offer an additional treatment for adult patients with HAP including VAP.

Proposed Indication

Treating adults with hospital-acquired pneumonia (HAP), including ventilator associated pneumonia (VAP).[1]

Technology

Description

Cefepime-enmetazobactam (exblifep) is a combination of cefepime and enmetazobactam. Enmetazobactam (AAI101) is a new β-lactamase (a bacterial enzyme) inhibitor with increased bacterial cell penetration and potency. Enmetazobactam inhibits CTX-M, TEM, SHV, and other class A β-lactamases (except for Klebsiella pneumoniae carbapenemase (KPC)) but does not inhibit class B and D β-lactamases and carbapenemases. Enmetazobactam alone does not exhibit inhibitory activity against Gram-negative bacteria.[1,2]

Cefepime (renapime) is a broad-spectrum, bactericidal antibiotic, with activity against a wide range of Gram-positive and Gram-negative bacteria, including many strains resistant to aminoglycosides or third generation cephalosporins.[3] Cefepime is a fourth generation cephalosporin which exerts bactericidal activity by inhibiting peptidoglycan cell wall synthesis.[4] Cephalosporins are antibacterials that attach to penicillin binding proteins to interrupt cell wall biosynthesis, leading to bacterial cell lysis and death.[5]

Cefepime-enmetazobactam is in clinical development for the treatment of adults with HAP, including VAP.[1,6] In the Phase I clinical trial (NCT03680378), participants received cefepime 2 grams in combination with Enmetazobactam 1 gram via intravenous infusion.[7]

Key Innovation

Antibiotic-resistant pathogens, such as Pseudomonas aeruginosa and methicillin-resistant Staphylococcus aureus, are identified more frequently in patients with HAP and VAP than in those with community-acquired pneumonia.[8]Antimicrobial resistance is commonly due to the production of enzymes causing drug degradation or modification. Amongst enzymes which cause drug degradation or modification causing antimicrobial resistance, the extended-spectrum β-lactamases and carbapenemases carried by Enterobacteriaceae present an imminent threat.[9] One of the strategies to overcome β-lactamase-mediated resistance is the development of β-lactamase inhibitors (BLIs). These small molecule inhibitors were discovered and have been applied in combination with β-lactams for efficient therapy.[10] Enmetazobactam is a novel penicillanic acid sulfone BLI which is active against a wide range of class A β-lactamases. Enmetazobactam is being developed in combination with cefepime to protect the latter against hydrolysis by ambler class A enzymes.[11] Beta-lactamases enzymes enable bacteria to break down beta-lactam antibiotics like cefepime, making the bacteria resistant to the antibiotic's action. By blocking the action of these enzymes, enmetazobactam allows cefepime to act against bacteria that would otherwise be resistant to this antibiotic.[12] The potential efficacy of cefepime-enmetazobactam against class C and class D OXA-48 enzymes is conferred by the intrinsic stability of cefepime, while the combination is required for those organisms that coproduce class A and C enzymes.[11] If licensed, cefepime-enmetazobactam will offer an additional treatment option for adult patients with HAP, including VAP.

Regulatory & Development Status

Cefepime-enmetazobactam currently has Marketing Authorisation in the EU for the treatment of[12]

- complicated (difficult to treat) infections of the urinary tract (parts of the body that collect and pass out urine), including pyelonephritis (kidney infection);
- bacteraemia (bacteria in the blood) when it is associated or suspected to be associated with complicated urinary tract infection or hospital-acquired pneumonia.

Cefepime-enmetazobactam is currently in phase III/II clinical development for treatment of paediatric participants with complicated urinary tract infection.[13]

Patient Group

Disease Area and Clinical Need

Pneumonia is a type of chest infection. It affects the small air sacs in lungs called alveoli. When a patient has pneumonia, these air sacs become inflamed and fill with fluid making breathing more difficult.[14] Symptoms of pneumonia can start suddenly or gradually over a few days which include cough, shortness of breath, fever, chest pain, an aching body, feeling very tired, loss of appetite, making wheezing noises when breathing and feeling confused.[15] HAP is defined as pneumonia that occurs 48 hours or more after hospital admission and is not incubating at hospital admission.[16] VAP is pneumonia occurring in a patient within 48 hours or more after intubation with an endotracheal tube or tracheostomy tube and which was not present before. HAP and its subtype, VAP, remain two significant causes of morbidity and mortality worldwide.[17] It is also the most common and fatal infection of intensive care units.[18] HAP is estimated to increase hospital stays by 7–9 days and has a mortality of between 30% and 70%. These figures include VAP.[19]

In England (2022-23), there were around 20,181 finished consultant episodes (FCEs) and more than 7,978 admissions for specified and unspecified bacterial pneumonia (ICD10 codes J13x to J170) which resulted in around 117,718 FCE bed days and 576 day cases.[20]

The National Institute for Health and Care Excellence (NICE) currently recommend the following pharmacological treatments for adults with HAP (the guideline does not cover ventilator-associated pneumonia):[21]

First- choice oral antibiotic if non-severe symptoms or signs, and not at higher risk of resistance:

- Co-amoxiclav

Alternative oral antibiotics if non-severe symptoms or signs, and not at higher risk of resistance, for penicillin allergy or if co-amoxiclav unsuitable:

- Doxycycline
- Cefalexin
- Co-trimoxazole (off-label use)
- Levofloxacin

First-choice intravenous antibiotics if severe symptoms or signs (for example, symptoms or signs of sepsis) or at higher risk of resistance:

- Piperacillin with tazobactam
- Ceftazidime
- Ceftriaxone
- Cefuroxime

- Meropenem
- Ceftazidime with avibactam
- Levofloxacin

Antibiotics to be added if suspected or confirmed meticillin-resistant *Staphylococcus aureus* infection (dual therapy with a first-choice intravenous antibiotic):

- Vancomycin
- Teicoplanin
- Linezolid

Currently, there is no specific treatment option recommended by NICE for VAP.

Clinical Trial Information	
Trial	NCT03680378; A Phase I Open-Label, Single-Centre Study to Assess the Concentration of AAI101 and Cefepime in Epithelial Lining Fluid and Plasma in Healthy Volunteers **Phase I** -Completed **Location(s):** United Kingdom **Study completion date:** April 2019
Trial Design	Single group assignment
Population	N=19 (actual); Healthy adults aged 18 and over
Intervention(s)	Combination of cefepime 2 grams with enmetazobactam 1 gram
Comparator(s)	No comparator
Outcome(s)	Primary outcome measures: Maximum concentration of cefepime and enmetazobactam in bronchoalveolar lavage samples [Time frame: Change from baseline to 2 hours, 4 hours, 6 hours and 8 hours post dose] See trial record for full list of other outcomes.
Results (efficacy)	-
Results (safety)	-

Trial	NCT03687255; A Phase 3, Randomized, Double-Blind, Study to Evaluate the Efficacy and Safety of Cefepime-AAI101 Compared to Piperacillin/Tazobactam in the Treatment of Complicated Urinary Tract Infections, Including Acute Pyelonephritis **Phase III**- Completed **Location(s):** 11 European countries, US, and other countries **Study completion date:** February 2020
Trial Design	Randomized, parallel assignment, quadruple masked
Population	N=1043 (actual); adults aged 18 and over with complicated urinary tract infection (cUTI) or acute pyelonephritis

Intervention(s)	Combination of cefepime 2 grams with enmetazobactam 500 milligrams
Comparator(s)	Piperacillin 4 grams in combination with tazobactan 500 milligrams
Outcome(s)	Primary outcome measures: Proportion of patients in the microbiological modified intent to treat, population who achieve overall treatment success at test of cure (toc) [time frame: 7 days after EOT [±2 days] for patients receiving 7 days of treatment and 19 days after randomization [±2 days] for patients receiving more than 7 days of treatment.] See trial record for full list of other outcomes.
Results (efficacy)	The primary outcome occurred in 79.1% (273/345) of patients receiving cefepime/enmetazobactam compared with 58.9% (196/333) receiving piperacillin/tazobactam (between-group difference, 21.2% [95% CI, 14.3% to 27.9%]).[22]
Results (safety)	Treatment-emergent adverse events occurred in 50.0% (258/516) of patients treated with cefepime/enmetazobactam and 44.0% (228/518) with piperacillin/tazobactam; most were mild to moderate in severity (89.9% vs 88.6%, respectively). A total of 1.7% (9/516) of participants who received cefepime/enmetazobactam and 0.8% (4/518) of those who received piperacillin/tazobactam did not complete the assigned therapy due to adverse events.[22]

Estimated Cost

The cost of cefepime-enmetazobactam is not yet known.

Relevant Guidance

NICE Guidance

- NICE guideline in development. Pneumonia: diagnosis and management (update) (GID-NG10357). Expected publication date: To be confirmed.
- NICE guideline. Pneumonia (hospital-acquired): antimicrobial prescribing (NG139). September 2019.
- NICE clinical guideline. Pneumonia in adults: diagnosis and management (CG191). December 2014
- NICE quality standard. Pneumonia in adults (QS110). January 2016.

NHS England (Policy/Commissioning) Guidance

No relevant guidance identified.

Other Guidance

- Antoni Torres MSN, Jean Chastre, Santiago Ewig, Patricia Fernandez-Vandellos, Hakan Hanberger, Marin Kollef, Gianluigi Li Bassi, Carlos M. Luna, Ignacio Martin-Loeches, J. Artur Paiva, Robert C. Read, David Rigau, Jean François Timsit, Tobias Welte, Richard Wunderink. International ERS/ESICM/ESCMID/ALAT guidelines for the management of hospital-acquired pneumonia and ventilator-associated pneumonia. 2017.[23]

- Infectious Diseases Society of America (IDSA). ATS/IDSA clinical practice guidelines for the management of adults with hospital-acquired and ventilator-associated pneumonia. July 2016.[24]

Additional Information

Advanz Pharma did not enter information about this technology onto the UK PharmaScan database; the primary source of information for UK horizon scanning organisations on new medicines in development. As a result, the NIHR Innovation Observatory has had to obtain data from other sources. UK PharmaScan is an essential tool to support effective NHS forward planning; allowing more effective decision making and faster uptake of innovative new medicines for patients who could benefit. We urge pharmaceutical companies to use UK PharmaScan so that we can be assured of up-to-date, accurate and comprehensive information on new medicines.

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