NIHR | Innovation Observatory

Newcastle University

Health Technology Briefing
November 2022

Ceftobiprole medocaril for treating hospital-acquired pneumonia or community-acquired pneumonia requiring hospitalisation in children

Company/Developer	Advanz Pharma

☐ New Active Substance ☒ Significant Licence Extension (SLE)

NIHRIO ID: 28893	NICE ID: 11819	UKPS ID: Not available

Licensing and Market Availability Plans

Currently in phase III clinical trial.

Summary

Ceftobiprole medocaril is in clinical development for the treatment of paediatric community-acquired pneumonia (CAP) or hospital-acquired pneumonia (HAP) requiring hospitalisation. Pneumonia is a type of chest infection where tiny air sacs in your lungs, called alveoli, get inflamed and fill with fluid, making it harder to breathe. The most common type of pneumonia is CAP- where pneumonia affects somebody not in hospital. HAP is when pneumonia develops while you're in hospital being treated for another condition. Many kinds of bacteria and viruses can cause pneumonia. Symptoms of pneumonia include coughing, feeling unwell and tired, a high temperature, difficulty breathing, chest pain or discomfort and loss of appetite. In adult patients, morbidity and mortality has been reduced. However, paediatric mortality and hospital admissions remain high, with the disease claiming the lives of around 40 children in England and Wales each year.

Ceftobiprole medocaril is a cephalosporin which kills bacteria by binding to important penicillin-binding proteins in susceptible species of bacteria that can cause pneumonia. Ceftobiprole, the active component of ceftobiprole medocaril, is an advanced-generation intravenous (IV) cephalosporin with broad activity against different pathogens. If approved, ceftobiprole medocaril would provide an additional treatment option for paediatric HAP or CAP.

This briefing reflects the evidence available at the time of writing and a limited literature search. It is not intended to be a definitive statement on the safety, efficacy or effectiveness of the health technology covered and should not be used for commercial purposes or commissioning without additional information. A version of the briefing was sent to the company for a factual accuracy check. The company was unavailable to comment.

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Proposed Indication

Treatment of paediatric community-acquired pneumonia (CAP) or hospital-acquired pneumonia (HAP) requiring hospitalisation.[1]

Technology

Description

Ceftobiprole medocaril (Zevtera) is a cephalosporin which exerts bactericidal activity through binding to important penicillin-binding proteins (PBPs) in susceptible species. In Gram-positive bacteria, including methicillin-resistant Staphylococcus aureus (MRSA), ceftobiprole binds to PBP2a. Ceftobiprole has demonstrated in vitro activity against strains with divergent mecA homolog (mecC or mecALGA251). Ceftobiprole also binds to PBP2b in Streptococcus pneumoniae (penicillin-intermediate), PBP2x in Streptococcus pneumoniae (penicillin resistant), and to PBP5 in Enterococcus faecalis.[2]

Ceftobiprole medocaril is in clinical development for the treatment of CAP or HAP requiring hospitalisation in paediatric patients. In the phase III clinical trial (NCT03439124) ceftobiprole medocaril was administered at age-adjusted doses (10, 15 or 20mg/kg) and intravenous (IV) infusion durations (2 or 4 hours) every 8 hours. The maximum dose, regardless of body weight, was 500mg ceftobiprole every 8 hours (maximum total daily dose of 1500mg ceftobiprole).[1]

Key Innovation

Although morbidity and mortality due to pneumonia in adult patients have been reduced dramatically over the past decade, paediatric CAP is still associated with high mortality and accounts for up to 20% of paediatric hospital admissions in high income countries.[3] It can cause mild to life-threatening illness in people of all ages, however it is the single largest infectious cause of death in children worldwide.[4]

Ceftobiprole, the active moiety of the prodrug ceftobiprole medocaril, is an advanced-generation IV cephalosporin with broad *in vitro* activity against Gram-positive (including MRSA) and Gram-negative pathogens. In the phase III trial (NCT03439124), ceftobiprole demonstrated similar efficacy to standard of care (SoC) cephalosporins in paediatric patients with HAP or CAP requiring hospitalisation, which includes ceftazidime or ceftriaxone.[5] If licensed, ceftobiprole medocaril will offer an additional treatment option for paediatric patients with CAP or HAP.

Regulatory & Development Status

Ceftobiprole medocaril is currently licensed for the following indications in adults:[2]

- HAP excluding ventilator-associated pneumonia (VAP)
- CAP

Patient Group

Disease Area and Clinical Need

Pneumonia is a type of chest infection caused by many kinds of bacteria and viruses. It affects the tiny air sacs in lungs, called alveoli. When a patient has pneumonia, these air sacs get inflamed and fill with fluid making breathing more difficult. CAP is when pneumonia affects somebody who is not already in hospital.[6] The most common cause of CAP is a bacterium called Streptococcus pneumoniae but there are many other causes.[6,7] HAP is when pneumonia develops while you're in hospital being treated for another condition

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or having an operation. People in intensive care on breathing machines are at most risk.[6] More people get pneumonia in winter because respiratory viral infections that spread easily from person to person, such as flu, are more common in the winter, and these increase your risk of developing pneumonia.[6,8] Babies and young children are particularly at high risk.[6] In young children, it's most commonly caused by a viral infection (such as adenoviruses, rhinovirus, influenza virus, respiratory syncytial virus and parainfluenza virus).[9] Symptoms of pneumonia include mainly coughing, as well as feeling generally unwell, weak and tired.[6]

Pneumonia is becoming less common thanks to the introduction of the pneumococcal vaccine for babies in 2006, which offers protection against one of the most common causes of bacterial pneumonia. Despite vaccinations being available, there are still around 700 reported cases of pneumonia in the under-fives in the UK every year, with around 40 children in England and Wales dying.[9] In 2012, the British Lung Foundation reported the number of people per 100,000 who developed pneumonia by age group 0-15 years was a total of 651.[10] In England (2021-22), there were 414,802 finished consultant episodes (FCEs) and 189,979 admissions for a primary diagnosis of influenza & pneumonia (ICD-10 code J09-J18), which resulted in 2,113 day cases and 1,742,309 FCE bed days for all ages. There were 11,837 patients aged 0-17 years with a primary diagnosis of influenza & pneumonia.[11] The specific population likely to be eligible to receive ceftobiprole medocaril could not be estimated from available published sources.

Recommended Treatment Options

For CAP, NICE currently recommend the following treatment in children and young people under 18 years:[12]

- Amoxicillin, as a first-choice oral antibiotic for children 1 month and over if non-severe symptoms or signs
- Alternative oral antibiotics if non-severe symptoms or signs (based on clinical judgement), for penicillin allergy or if amoxicillin unsuitable (for example, atypical pathogens suspected), which includes clarithromycin, erythromycin or doxycycline
- First-choice antibiotic(s) if severe symptoms or signs, which includes co-amoxiclav, clarithromycin or erythromycin
- Alternative antibiotics if severe symptoms or signs (based on clinical judgement), for penicillin allergy (guided by microbiological results when available), by consulting local microbiologist

For HAP, NICE currently recommend the following treatment in children and young people under 18 years:[13]

- Co-amoxiclav, as a first-choice oral antibiotic for children aged 1 month and over if non-severe symptoms or signs and not at higher risk of resistance
- Alternative oral antibiotic for children aged 1 month and over if non-severe symptoms or signs and not at higher risk of resistance, for penicillin allergy or if co-amoxiclav unsuitable, which includes clarithromycin
- First-choice IV antibiotics if severe symptoms or signs (for example, symptoms or signs of sepsis), or at higher risk of resistance, which includes piperacillin with tazobactam, ceftazidime or ceftriaxone
- Antibiotics to be added if suspected or confirmed methicillin-resistant Staphylococcus aureus infection, which includes teicoplanin, vancomycin or linezolid

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Clinical Trial Information

Trial	NCT03439124; A Multicentre, Randomized, Investigator-blind, Active-controlled Study to Evaluate the Safety, Tolerability, Pharmacokinetics and Efficacy of Ceftobiprole Versus Intravenous Standard-of-care Cephalosporin Treatment With or Without Vancomycin in Pediatric Patients Aged From 3 Months to Less Than 18 Years With Hospital-acquired Pneumonia or Community-acquired Pneumonia Requiring Hospitalisation **Phase III –** Completed **Location(s) –** 4 countries in EU **Study completion date –** March 2020
Trial Design	Randomised, parallel assignment, single blinded
Population	N = 138 (actual); Diagnosis of either HAP or CAP requiring hospitalisation and administration of IV antibiotic therapy; 3 months to 17 years
Intervention(s)	Ceftobiprole medocaril was administered at age-adjusted doses (10, 15 or 20 mg/kg) and IV infusion durations (2 or 4 hours) every 8 hours. The maximum dose, regardless of body weight, was 500 mg ceftobiprole every 8 hours (maximum total daily dose of 1500 mg ceftobiprole).
Comparator(s)	Standard of care
Outcome(s)	Adverse events [Time frame: analysis of AEs assessed during the first 3 days of IV therapy and while on IV, a median of 7 days] See trial record for full list of other outcomes
Results (efficacy)	Early clinical response rates at day 4 in the intention-to-treat population were 95.7% and 93.2% (between-group difference, 2.6%; 95% confidence interval, −5.5% to 14.7%) in the ceftobiprole and comparator groups, and clinical cure rates at the test-of-cure visit were 90.4% and 97.7% (between-group difference, −7.3%; 95% confidence interval, −15.7% to 3.6%), respectively.[5]
Results (safety)	While on IV therapy, adverse events and treatment-related adverse events were reported by 20.2% and 8.5% of ceftobiprole-treated patients and 18.2% and 0% of SoC cephalosporin-treated patients.[5]

Estimated Cost

The NHS indicative price (hospital only) of ceftobiprole medocaril is £396.30 for 10 x 500mg powder for concentrate for solution for infusion vials.[14]

Relevant Guidance

NICE Guidance

- NICE guideline. Pneumonia (community-acquired): antimicrobial prescribing (NG138). September 2019.
- NICE guideline. Pneumonia (hospital-acquired): antimicrobial prescribing (NG139). September 2019.

NHS England (Policy/Commissioning) Guidance

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No relevant guidance identified.

Other Guidance

- Leicester Children's Hospital. Community Acquired Pneumonia in Children. September 2022.[15]
- The Royal Children's Hospital Melbourne. Community acquired pneumonia. February 2020.[16]
- NHSGGC Paediatrics for Health Professionals. Pneumonia, community acquired: guideline in children. November 2017.[17]

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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