EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Committee for Medicinal Products for Human Use (CHMP)

# Zinforo

(Ceftaroline fosamil)

Procedure no.: EMA/H/C/002252/P46/014

Marketing Authorisation Holder: AZ

# CHMP assessment report for paediatric use studies submitted according to Article 46 of the Regulation (EC) No 1901/2006

**Assessment report as adopted by the CHMP with all commercially confidential information deleted**

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# Administrative information

| | |
|---|---|
| Invented name of the medicinal product: | Zinforo |
| INN (or common name) of the active substance(s): | Ceftaroline fosamil |
| MAH: | AZ |
| Currently approved Indication(s) | cSSTI and CAP |
| Pharmaceutical form(s) and strength(s): | 600 mg powder for concentrate for solution for infusion |

# 1. Introduction

The present paediatric data is submitted by the MAH in accordance with article 46 of Regulation EC No 1901/2006.

This submission for Ceftaroline, in the treatment of cSSTI and CAP, relates to the submission of the results from the clinical study P903-24 D3720C00013 (A Multicenter, Randomized, Observer-Blinded, Active- Controlled Study Evaluating the Safety, Tolerability, Pharmacokinetics, and Efficacy of Ceftaroline Versus Ceftriaxone Plus Vancomycin in Paediatric Subjects with Complicated Community-acquired Bacterial Pneumonia).

The full benefit and risk profile in the paediatric population will be evaluated when the additional studies in the PIP have been completed. Paediatric patient exposure will continue to be specified as missing information in the EU Risk Management Plan until the completion of the paediatric studies. In view of this no changes to the SPC and proposed at this stage.

The overall benefit to risk balance for Zinforo is not affected by this new information and therefore does not require taking further regulatory action on the marketing authorization for Zinforo at this stage.

*About the product*

Ceftaroline fosamil is the prodrug of ceftaroline and is rapidly converted to microbiologically active drug after intravenous (iv) administration. Ceftaroline, inhibits bacterial cell growth by interfering with cell wall biosynthesis. Ceftaroline has high affinity for PBP2a and is highly potent against resistant staphylococci. Ceftaroline has also been shown to bind with high affinity to PBPs in S. pneumoniae including modified forms of PBP2x which are common in penicillin-resistant S. pneumoniae (PRSP).

Ceftaroline is approved for treatment of adult patients with cSSTI and CAP in the EU since August 2012. The recommended dosing regimen is 600 mg (reduced to 400 mg for patients with creatinine clearance <30 to ≤50 mL/min) administered as a 60-minute infusion every 12 hours (q12h) for 5 to 14 days for cSSTI and 5 to 7 days for CAP.

# 2. Scientific discussion

## *2.1 Information on the development program*

The MAH stated that this study is a randomised, observer-blinded study to evaluate the safety and tolerability of ceftaroline versus ceftriaxone plus vancomycin in paediatric patients, ages 2 months to < 18 years, with complicated CAP at high risk of infection due to methicillin-resistant Staphylococcus aureus (MRSA) and is an additional study requested by the FDA to complement Study P903-31 (PIP Study 5) by utilizing an enrichment strategy for enrolment of patients with MRSA.

## *2.2 Clinical*

As part of the EU-RMP and PIP, the MAH conducted the clinical study. The study is described briefly below (for further details please refer to the full CSR).

**Study D3720C00013**

*Study design*

This study is a randomised, observer-blinded study to evaluate the safety and tolerability of ceftaroline versus ceftriaxone plus vancomycin in paediatric patients, ages 2 months to < 18 years, with complicated CAP at high risk of infection due to methicillin-resistant Staphylococcus aureus (MRSA).

Subjects were stratified by age cohort and region and were randomly assigned to treatment in a 3:1 ratio, ceftaroline fosamil to ceftriaxone. The following age cohorts were defined:

Cohort 1: children from 12 years to < 18 years
Cohort 2: children from 6 years to < 12 years
Cohort 3: children from 24 months to < 6 years
Cohort 4: young infants/toddlers from 2 months to < 24 months

A minimum of 7 intravenous (IV) doses was required for subjects randomized to ceftaroline fosamil. A switch to open label oral study drug (amoxicillin clavulanate, clindamycin, or linezolid) was allowed on or after Study Day 4 if a subject met the protocol-specified criteria. The total duration of study drug therapy(IV and oral, or IV alone) was 5 to 21 days.

The EOIV assessments were performed within 24 hours after administration of the last dose of IV study drug, and before oral switch, if applicable. The EOT assessments were performed within 48 hours after the last dose of oral study drug. The TOC assessments were performed 8–15 days after the final dose of study drug (IV or oral, whichever was given last), and the LFU visit assessments were performed 21–35 days after the last dose of study drug (IV or oral).

*Study site and dates*

The study was conducted by Cerexa, US between 23/01/2013 and 19/05/2014. The study had appropriate ethics approval and was performed according to GCP. Twenty four sites were enrolled but only 11 actually enrolled patients for the study.

*Study Objectives*

Primary
-To evaluate the safety and tolerability of ceftaroline versus ceftriaxone plus vancomycin in paediatric patients, ages 2 months to < 18 years, with complicated CAP.

Secondary
-To evaluate the efficacy of ceftaroline versus ceftriaxone plus vancomycin in paediatric patients, ages 2 months to < 18 years, with complicated CAP.
-To evaluate the pharmacokinetics (PK) of ceftaroline in these subjects (**This analysis is reported separately**).

*Study population*

Male and female subjects 2 months to < 18 years of age; complicated CABP (meeting the protocol-specified criteria) warranting 3 days of initial hospitalization and a minimum of 3 days of IV antibacterial therapy and a minimum of 5 days but no more than 21 days total of study therapy (IV and oral combined); confirmed presence of at least 1 indicator of complicated CABP or staphylococcal pneumonia; acute onset or worsening within the previous 5 days before randomization of at least 2 of the clinical signs or symptoms of CABP (cough, tachypnea, dyspnea, grunting, sputum production, chest pain, cyanosis, evidence of pneumonia with parenchymal consolidation, increased work of breathing); presence of at least 1of the following: organism consistent with a typical respiratory pathogen identified or isolated from a respiratory or blood culture, leukocytosis, >15% immature white blood cells (WBCs), leukopenia, or hypoxemia.

*Study medications*

Investigational Product, Dose, and Mode of Administration:

IV ceftaroline fosamil infused over 120 (± 10) minutes every 8 hours (q8h [± 1 hour]) as follows:

Children ≥ 6 months: ceftaroline fosamil 15 mg/kg for subjects weighing ≤ 40 kg or 600 mg for subjects weighing > 40 kg

Children < 6 months: ceftaroline fosamil 10 mg/kg

Reference Therapy, Dosage, and Mode of Administration:

IV ceftriaxone at a total daily dose of 75 mg/kg/day up to a maximum of 4 g/day, given in equally divided doses, each infused over 30 (± 10) minutes every 12 hours (q12h [± 2 hours]).

Optional Oral Switch, Dose and Mode of Administration:

Amoxicillin clavulanate was the drug preferred to be administered for the optional oral therapy. A recommended total daily dose of 45 to 90 mg/kg/day amoxicillin clavulanate was to be divided equally q12h. Clindamycin (13 mg/kg/dose q8h) was an alternative oral study drug for patients with proven or suspected MSSA or MRSA infections. Linezolid (600 mg q12h [Cohort 1] or 10 mg/kg q8h [Cohorts 2, 3, and 4]) was an alternative oral study drug for patients with clindamycin-resistant MRSA pathogens. Doses were based on institutional and local prescribing guidelines and information provided in the package inserts.

*Duration of Treatment*

Total duration of study drug therapy was 5 to 21 days; a minimum of 3 days of initial hospitalization and 3 days (72 hours) of IV study drug therapy (ceftaroline fosamil or comparators) were required. The total duration of subject participation was expected to be 26 to 57 days; the Late Follow-up (LFU) assessments were to occur 21 to 35 days after last dose of any study drug (IV or oral).

*Criteria for Evaluation*

Efficacy:

-Clinical response (defined as improvement in at least two and worsening of none of the following symptoms compared to baseline: Cough, Dyspnea, Sputum production, Chest pain, Chills or

rigors, Feeling of warmth/feverish, Exercise intolerance or lethargy) at Study Day 4 in the MITT and the mMITT populations

-Clinical stability (defined by having met all of the following criteria: Afebrile (temperature ≤ 38.0°C by any measurement method), Age-appropriate normal pulse and respiratory rates, Oxygen saturation ≥ 92% on room air, Worsening of none of the following symptoms relative to baseline: cough, dyspnea,chest pain, sputum production, chills or rigors, feeling of warmth / feverish, and exercise intolerance or lethargy) at Study Day 4 in the MITT and mMITT populations

-Clinical outcome at Test-of-Cure (TOC) in the MITT, Clinically Evaluable (CE), and mMITT Populations

-Clinical outcome at End of IV Study Drug (EOIV) and End of Therapy (EOT) in the MITT and CE populations

-Microbiological outcomes by subject and by baseline pathogen at TOC in the mMITT

-Clinical relapse at Late Follow-up (LFU) in the MITT Population

-Emergent infections in the mMITT Population

Safety:

Adverse events (AEs), serious adverse events (SAEs), deaths, and discontinuations due to AEs; clinical laboratory parameters; vital signs measurements

*Statistical methods*

The following study populations were defined:

-ITT Population: all randomized subjects with study drug assignment designated according to initial randomization, regardless of whether subjects receive study drug according to the randomization schedule, or receive a different drug from that to which they were randomized

-Safety Population: all randomized subjects who received any amount of study drug

-MITT Population: all randomized subjects who received any amount of IV study drug and who had a confirmed diagnosis of complicated CABP with risk factors for MRSA. Subjects with an atypical pathogen as the sole causative pathogen of infection based on immunoglobulin M (IgM) or IgG titers of baseline (or in some cases with IgG, paired baseline and post-baseline) serology samples were excluded.

-CE Population: a subset of the MITT Population and will include subjects who meet minimal disease criteria for CABP and all evaluability criteria as specified in the Statistical Analysis Plan.

-mMITT Population: a subset of the MITT Population, including subjects for whom at least 1 typical bacterial pathogen had been identified from an adequate microbiological specimen at baseline

-ME Population: all subjects who met the criteria for both the CE and mMITT populations.

-PK Population: all randomized subjects who received a known amount of ceftaroline fosamil and who had had at least 1 PK sample collected (excluding those who received blood or blood component transfusions within 24 hours before any PK sample was drawn)

Efficacy: Efficacy response was analyzed using the MITT, CE, and mMITT populations. Proportions of subjects with favorable efficacy responses were summarized by treatment group. Differences between treatment groups in efficacy response rates were calculated along with a two-sided 95% confidence interval (CI) for the difference between treatment groups in percentage of subjects for each efficacy response.

Safety: Safety parameters (AEs, SAEs, deaths, clinical laboratory parameters, and vital signs measurements) were summarized for the Safety Population.

*Study monitoring*

An external Data and Safety Monitoring Board (DSMB) was established to review safety data from this study, and other ongoing paediatric studies of ceftaroline fosamil, at prespecified intervals to ensure safety of all subjects enrolled.

## Results

*Study Disposition*

Subjects were stratified by region and age cohort. A total of 40 subjects were randomized 3:1 to receive study drug (30 subjects to ceftaroline fosamil and 10 subjects to ceftriaxone) (ITT Population).

**Table 10.1–1. Subject Populations and Reasons for Exclusions-ITT Population**

| *Subject Populations Reasons for Exclusion*[a] | *Ceftaroline (N = 30) n (%)* | *Comparator (N = 10) n (%)* | *Total (N = 40) n (%)* |
|---|---|---|---|
| ITT Population | 30 (100) | 10 (100) | 40 (100) |
| Safety Population | 30 (100) | 10 (100) | 40 (100) |
| MITT Population | 29 (96.7) | 9 (90.0) | 38 (95) |
| No study drug taken | 0 | 0 | 0 |
| No confirmed CABP[b] | 0 | 0 | 0 |
| Sole atypical pathogen | 1 (3.3) | 1 (10.0) | 2 (5.0) |
| mMITT Population | 15 (50.0) | 3 (30.0) | 18 (45.0) |
| Not in MITT Population | 1 (3.3) | 1 (10.0) | 2 (5.0) |
| No typical pathogen identified at baseline | 15 (50.0) | 7 (70.0) | 22 (55.0) |
| CE Population | 26 (86.7) | 9 (90.0) | 35 (87.5) |
| Not in MITT Population | 1 (3.3) | 1 (10.0) | 2 (5.0) |
| Received < 80% of study drug | 1 (3.3) | 0 | 1 (2.5) |
| Less than minimum number of days of IV or oral study drug | 0 | 0 | 0 |
| Test-of-Cure visit out of window | 1 (3.3) | 0 | 1 (2.5) |
| Concomitant antimicrobial violation | 1 (3.3) | 0 | 1 (2.5) |
| Received incorrect study drug | 0 | 0 | 0 |
| Unblinded prior to database lock | 0 | 0 | 0 |
| Additional inclusion/exclusion criteria violation[c] | 0 | 0 | 0 |
| ME Population | 13 (43.3) | 3 (30.0) | 16 (40.0) |
| Not in mMITT Population | 15 (50.0) | 7 (70.0) | 22 (55.0) |
| Not in CE Population | 4 (13.3) | 1 (10.0) | 5 (12.5) |

*Demographics and Baseline Characteristics*

The majority of subjects were white, with a mean age of 4 years (range 16 weeks through 17 years). Demographics and baseline characteristics were generally balanced between the 2 treatment groups. The majority of subjects had normal renal function, and no subjects had moderate or severe renal impairment.

*Efficacy*

-The clinical response and stability at Study Day 4 were greater than 50% in both groups, but slightly higher in the comparator group.

**Table 11.4.1.1–1. Clinical Response and Stability at Study Day 4-MITT Population**

| *Response/Stability* | *Ceftaroline (N = 29) n (%)* | *Comparator (N = 9) n (%)* | *Difference (%)* |
|---|---|---|---|
| **Clinical response** | | | |
| Responder | 15 (51.7) | 6 (66.7) | -14.9 |
| 95% CI | — | — | (-44.6, 22.0) |
| Non-Responder | 11 (37.9) | 3 (33.3) | — |
| Incomplete Data | 3 (10.3) | 0 | — |
| **Clinical stability** | | | |
| Stability | 6 (20.7) | 2 (22.2) | -1.5 |
| 95% CI | — | — | (-37.2, 23.8) |
| No stability | 22 (75.9) | 7 (77.8) | — |
| Incomplete Data | 1 (3.4) | 0 | — |

-Clinical cure rates at the TOC visit were high for both the ceftaroline and ceftriaxone treatment groups in both the MITT and CE populations but again slightly higher in the comparator. No subjects had relapse in either treatment group at the LFU assessment.

**Table 11.4.1.2–1. Clinical Outcome at the TOC Visit—MITT Population**

| *Outcome* | *Ceftaroline (N = 107) n (%)* | *Ceftriaxone (N = 36) n (%)* | *Difference (%)* |
|---|---|---|---|
| Clinical cure | 94 (87.9) | 32 (88.9) | -1.0 |
| 95% CI | (80.1, 93.4) | (73.9, 96.9) | (-11.5, 14.1) |
| Clinical failure | 8 (7.5) | 4 (11.1) | |
| At EOIV | 7 (7.5) | 3 (8.3) | |
| At EOT | 0 | 1 (2.8) | |
| At TOC | 1 (0.9) | 0 | |
| Indeterminate | 5 (4.7) | 0 | |

**Table 11.4.1.2–2. Clinical Outcomes at the TOC Visit-CE Population**

| *Outcome* | *Ceftaroline (N = 26) n (%)* | *Comparator (N = 9) n (%)* | *Difference (%)* |
|---|---|---|---|
| Clinical cure | 23 (88.5) | 9 (100.0) | -11.5 |
| 95% CI | — | — | (-29.3, 20.1) |
| Clinical failure | 3 (11.5) | 0 | — |
| Observed failure at EOIV | 3 (11.5) | 0 | — |
| Observed failure at EOT | 0 | 0 | — |
| Observed failure at TOC | 0 | 0 | — |

**Table 11.4.1.2–3. Clinical Outcomes at the TOC Visit-mMITT Population**

| *Outcome* | *Ceftaroline (N = 15) n (%)* | *Comparator (N = 3) n (%)* | *Difference (%)* |
|---|---|---|---|
| Clinical cure | 13 (86.7) | 3 (100.0) | -13.3 |
| 95% CI | — | — | (-38.7, 46.5) |
| Clinical failure | 2 (13.3) | 0 | — |
| Observed failure at EOIV | 2 (13.3) | 0 | — |
| Observed failure at EOT | 0 | 0 | — |
| Observed failure at TOC | 0 | 0 | — |
| Indeterminate | 0 | 0 | — |

The clinical cure rate was high, with only 3 subjects in the test group being labelled clinical failures, 2 due to AEs and 1 due to no therapeutic effect.

-Microbiological outcomes by subject and by baseline pathogen at TOC in the mMITT Population showed a favourable microbiological response (presumed eradication or eradication) in all subjects but two in the test groups.

*Safety results*

Study drug exposure was similar between the ceftaroline and ceftriaxone groups. The median duration of IV treatment was 9.0 and 7.5 days, respectively. Most subjects switched to oral study drug; the median duration of oral study drug treatment was 7.5 days in both the ceftaroline and ceftriaxone groups.

Fewer subjects in test group reported at least 1 TEAE. (40% and 80% in the ceftaroline and ceftriaxone groups, respectively). The incidence of SAEs was low. No SAEs were related to study drug. Two subjects in the ceftaroline group discontinued IV study drug due to an AE. No deaths were reported during the study.

**Table 12.2.1–1. Summary of Adverse Events-Safety Population**

| *Adverse Event Category* | *Ceftaroline (N = 30) n (%)* | *Comparator (N = 10) n (%)* | *Total (N = 40) n (%)* |
|---|---|---|---|
| **Number of subjects with:** | | | |
| Any TEAE | 12 (40.0) | 8 (80.0) | 20 (50.0) |
| Any (IV or oral) study drug-related TEAEs | 7 (23.3) | 3 (30.0) | 10 (25.0) |
| Any SAEs | 0 | 1 (10.0) | 1 (2.5) |
| Any (IV or oral) study drug-related SAEs | 0 | 0 | 0 |
| Discontinuations of any (IV or oral) study drug due to AE | 3 (10.0) | 0 | 3 (7.5) |
| Discontinuations of IV study drug due to AE | 2 (6.7) | 0 | 2 (5.0) |
| Deaths | 0 | 0 | 0 |

Table 12.2.2–1. Treatment Emergent Adverse Events Reported by at Least 3 Subjects in the Ceftaroline group or 2 Subjects in the Comparator Group-Safety Population

| *System Organ Class Preferred Term*[a] | *Ceftaroline (N = 30) n (%)* | *Comparator (N = 10) n (%)* |
|---|---|---|
| **Subjects with ≥ 1 TEAE** | 12 (40.0) | 8 (80.0) |
| **Blood and lymphatic system disorders** | | |
| Anemia | 3 (10.0) | 0 |
| **Gastrointestinal disorders** | | |
| Vomiting | 2 (6.7) | 2 (20.0) |
| **Infections and infestations** | | |
| Viral upper respiratory tract infection | 0 | 2 (20.0) |
| **Skin and subcutaneous tissue disorders** | | |
| Pruritus | 3 (10.0) | 0 |

No trends were seen in changes from baseline for clinical laboratory parameters. The incidence of potentially clinically significant laboratory abnormalities was low and no subject met potential Hy's law criteria. Mean changes over time in vital signs measurements were similar between both treatment groups and consistent with improvement in the underlying infection over the course of the study.

***Applicant's Conclusion***

Safety data indicate that treatment of paediatric subjects with CABP with ceftaroline fosamil was well tolerated. The clinical outcomes in the ceftaroline treatment group were comparable to those in the ceftriaxone treatment group.

## *2.3 Discussion*

This Phase 4 study was conducted to address the FDA paediatric PMR (PMR 1692-002) to perform a randomized comparison of ceftaroline fosamil and comparator in paediatric subjects with CABP. The safety and tolerability of IV ceftaroline fosamil versus IV ceftriaxone plus IV vancomycin (comparators) were evaluated in the treatment of paediatric subjects aged 2 months to < 18 years with complicated CABP. The study was designed to enrich for subjects at risk for infection due to MRSA. However only 1 subject enrolled (ceftaroline group) had MRSA identified.

The study was designed to primarily look at safety and tolerability of ceftaroline in the mentioned doses in patients with CABP requiring hospitalisation. Ceftriaxone was selected as an active comparator agent for its microbiological spectrum of activity, effectiveness as treatment for CABP, its widespread global use, and acceptance as a therapy for CABP based on expert opinion and national adult CAP guidelines. The switch to oral therapy at the investigator's discretion is based on normal clinical practice.

The selected ceftaroline dose regimens (15 mg/kg [600 mg if > 40 kg] for subjects ≥ 6 months and 10 mg/kg for subjects < 6 months of age, as a 2-hour infusion q8h) were predicted to achieve pharmacokinetic/pharmacodynamic (PK/PD) targets in plasma associated with 1-log kill of S. aureus in the murine pneumonia model for organisms with minimum inhibitory concentration (MIC) values up to 1 mg/L in > 90% of subjects ages2 months to < 18 years. The high PK/PD target attainment was expected to result inefficacy for paediatric subjects comparable to efficacy in adult subjects with CABP dosedwith ceftaroline 600 mg q8h. The median Cmax value in children 2 months to < 18 years with normal renal function dosed with 15 mg/kg q8h (up to 600 mg) as a 2-hour infusion, or 10 mg/kg q8h as a 2-hour infusion for children < 6 months, was predicted to be less than the median Cmax value in

adults dosed with 600 mg q8h as a 1-hour infusion. The median AUC0-24h (AUC from time zero to 24 hours) in children 2 months to < 18 years dosed with the above regimen was predicted to be up to 15% greater than in adults dosed with 600 mg q8h. The median %T > MIC for an MIC of 1 mg/L was predicted to be 84- 93% for the recommended paediatric dose regimens compared to 100% in adults dosed with 600 mg q8h.

In general, demographics were balanced between treatment groups. In the study there were no unexpected safety issues, the tolerability was acceptable and efficacy was similar to the comparator. Although PK results will be reported separately, it appears the choice of doses for the various cohorts was appropriate based on the efficacy seen.

In addition to this study, further studies are planned as part of PIP. Therefore no further action is proposed at this stage.

### *2.4 Changes to the product information*

The MAH proposed no changes to the Product Information, which is acceptable at this stage as further paediatric studies are planned.

## 3. Overall conclusion and impact on the benefit/risk balance

Based on the results of the newly completed study which evaluates the safety and tolerability of ceftaroline versus ceftriaxone plus vancomycin in paediatric patients, aged 2 months to < 18 years, with CAP, it is considered that the safety and efficacy of ceftaroline in this population is acceptable and no unexpected concerns have been identified.

Therefore this does not change the benefit/risk balance.

## 4. CHMP's overall conclusion and recommendation

### Overall conclusion

The benefit/risk balance remains positive in the approved indications at present. A final decision regarding any change to the product information related to the paediatric population will be taken upon completion of all the clinical studies planned in this population under the PIP.