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/P46/013

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 P903-23 D3720C00004 (A Multicenter, Randomized, Observer-Blinded, Active-Controlled Study to Evaluate the Safety, Tolerability, Efficacy, and Pharmacokinetics of Ceftaroline Versus Comparator in Paediatric Subjects With Acute Bacterial Skin and Skin Structure Infections).

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 active comparator in paediatric patients, ages 2 months to < 18 years, with ABSSI including patients with infection due to methicillin-resistant Staphylococcus aureus (MRSA) and is a completed study from the EU Pharmacovigilance Plan and the Paediatric Investigation Plan (PIP Study 3).

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 D3720C00004

Study design

This was a phase 2/3 multicenter, randomized, observer-blinded, active-controlled, parallel-group study to evaluate the efficacy, safety, and PK of intravenous (IV) ceftaroline versus IV comparator (vancomycin or cefazolin with or without aztreonam) in paediatric subjects from the ages of 2 months to < 18 years with ABSSSI. Aztreonam was available for administration, if required, during IV treatment with comparator, if an infection involving a Gram-negative pathogen was identified or suspected.

Subjects were stratified by age cohort and region and were randomly assigned to treatment in a 2:1 ratio, ceftaroline fosamil to comparator. 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 (cephalexin [preferred oral switch], 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.

Subjects with ABSSSI presenting to the hospital or acute care facility were to receive their first dose of antimicrobial therapy within a medically appropriate time frame. Study Day 1 was defined as the first day of IV study drug administration, and subsequent study days were defined by the number of consecutive calendar days thereafter. The End-of-Intravenous Study Drug (EOIV) visit assessments were performed within 24 hours after administration of the last dose of IV study drug, and before oral switch, if applicable. The End-of Therapy (EOT) visit assessments were performed within 48 hours after the last dose of oral study drug. The Test-of-Cure (TOC) visit assessments were performed 8 - 15 days after the final dose of study drug (IV or oral, whichever was given last), and the Late-Follow-up (LFU) visit assessments were performed 21 - 35 days after the last dose of study drug (IV or oral). At the time of premature discontinuation of study drug or early withdrawal from study during IV or oral therapy (eg, Study Days 4 to ≤ 14), EOIV (if on IV study drug) or EOT (if on oral study drug) assessments were to be performed on the day of premature discontinuation of study drug or withdrawal from study.

Study site and dates

The study was conducted by Cerexa, US between 21/08/2012 and 13/05/2014. The study had appropriate ethics approval and was performed according to GCP. Seventy one sites were enrolled but only 38 actually enrolled patients for the study.

Study Objectives

Primary

-To evaluate the safety and tolerability of ceftaroline versus vancomycin or cefazolin with or without aztreonam in paediatric patients, ages 2 months to <18 years, with cSSTI.

Secondary

-To evaluate the efficacy of ceftaroline versus vancomycin or cefazolin with or without aztreonam in paediatric patients, ages 2 months to <18 years, with cSSTI.

-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; ABSSSI with measurable margins of erythema (ie, cellulitis), edema, or induration, that included deeper (subdermal tissue, including subcutaneous fat) and/or extensive soft tissue involvement (eg, deep and extensive cellulitis, erysipelas, or major abscess), or required significant therapeutic surgical intervention (ie, a major invasive therapeutic procedure that did not include commonly performed minor procedures such as suture removal, superficial debridement of devitalized tissue, or routine wound care, eg, abscess or an infected wound [postoperative surgical or traumatic]) and at least 1 of the following local signs and symptoms of acute infection (present for < 10 days): purulent or seropurulent drainage or discharge, induration/edema, fluctuance, or heat or localized warmth.

Study medications

Investigational Product, Dose, and Mode of Administration:

IV ceftaroline fosamil infused over 60 (± 10) minutes every 8 hours (q8h [± 1 hour]) as follows:

Children ≥ 6 months: ceftaroline fosamil 12 mg/kg for subjects weighing ≤ 33 kg or 400 mg for subjects weighing > 33 kg

Children < 6 months: ceftaroline fosamil 8 mg/kg

Reference Therapy, Dosage, and Mode of Administration:

IV vancomycin 15 mg/kg every 6 hours (q6h) (± 1 hour) infused over at least 60 minutes (or at a maximum of 10 mg/min, whichever was longer) or

IV cefazolin 75 mg/kg/day divided q8h (± 1 hour) infused over 60 (± 10) minutes.

Subjects receiving comparator could receive optional IV aztreonam 30 mg/kg q8h (± 1 hour) infused over 60 (± 10) minutes, at any time during IV therapy if an infection involving a Gram-negative pathogen was identified or suspected.

Optional Oral Switch, Dose and Mode of Administration:

Subjects may have been switched from IV to open-label oral study drug (cephalexin at 25 mg/kg q6h [preferred switch], clindamycin 10 mg/kg q8h, or linezolid [600 mg every 12 hours (q12h) [Cohort 1] or 10 mg/kg q8h [Cohorts 2, 3, and 4]) on or after Study Day 4.

Duration of Treatment

Total duration of study drug therapy (IV and oral, or IV alone) was 5 to 14 days; a minimum of 3 days (7 infusions for subjects randomized to ceftaroline fosamil) of IV study drug therapy was required. The total duration of subject participation was expected to be 26 to 50 days.

Criteria for Evaluation

Efficacy:

Clinical response at Study Day 3 in the MITT Population according to the following definitions:

- Definition 1: ≥ 20% reduction from baseline in total infection area (length × width)
- Definition 2: cessation of spread relative to baseline as measured by total infection area (ie, the total infection area on Study Day 3 was less than or equal to that at baseline)
- Definition 3: cessation of spread relative to baseline as measured by length and width, separately (ie, both length and width on Study Day 3 was less than or equal to their respective measurements at baseline), AND temperature was < 37.6°C on Study Day 3, irrespective of temperature collection method and baseline temperature

Clinical outcome at End-of-Intravenous Study Drug (EOIV), End-of-Therapy (EOT), and Test-of-Cure (TOC) in the MITT and CE populations

Clinical and microbiological outcomes by subject and by baseline pathogen at TOC in the mMITT and ME populations

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
Safety Population: all randomized subjects who received any amount of IV study drug
MITT Population: all randomized subjects who receive any amount of IV study drug and who had a confirmed diagnosis of ABSSSI
CE Population: a subset of the MITT Population and included subjects who met minimal disease criteria for ABSSSI and all evaluability criteria
mMITT Population: a subset of the MITT Population and included subjects for whom at least 1 typical bacterial pathogen was identified from a blood culture or from an appropriate microbiological tissue specimen of the primary ABSSSI at baseline
ME Population: all subjects who met the criteria for both the CE and mMITT populations.
Pharmacokinetic (PK) Population: a subset of the Safety Population and included 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: The study was not powered for comparative inferential analysis, and no efficacy endpoint was identified as primary. Efficacy response was analyzed using the MITT, CE, mMITT, and ME populations. Proportions of subjects with favourable efficacy responses were displayed by treatment group, both overall and within each age cohort. The difference between treatment groups in efficacy response rates was calculated, along with 95% confidence intervals (CI) for both the within-group response rates and the between-group difference 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

163 subjects were randomized (2:1) to receive study drug (110 subjects to ceftaroline fosamil and 53 subjects to comparator) (ITT Population), and 159 subjects received IV study drug). The 2:1 randomization scheme was appropriately maintained for all age cohorts and all regions that enrolled subjects. The highest enrollment by age cohort (52 subjects) was in Cohort 2 (ie, children from 6 years to < 12 years); the remaining cohorts each enrolled between 35 - 39 subjects.

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

Subject Status *Study Population* *Reasons for Exclusion*[a]	*Ceftaroline (N = 110) n (%)*	*Comparator (N = 53) n (%)*	*Total (N = 163) n (%)*
ITT Population	**110 (100)**	**53 (100)**	**163 (100)**
Safety Population	**107 (97.3)**[b]	**52 (98.1)**[b]	**159 (97.5)**[b]
No study drug taken	3 (2.7)	1 (1.9)	4 (2.5)
MITT Population	**107 (97.3)**	**52 (98.1)**	**159 (97.5)**
No study drug taken	3 (2.7)	1 (1.9)	4 (2.5)
No confirmed ABSSSI[c]	0	0	0
mMITT Population	**52 (47.3)**	**22 (41.5)**	**74 (45.4)**
Not in MITT Population	3 (2.7)	1 (1.9)	4 (2.5)
No baseline pathogen	57 (51.8)	31 (58.5)	88 (54.0)
CE Population	**96 (87.3)**	**45 (84.9)**	**141 (86.5)**
Not in MITT Population	3 (2.7)	1 (1.9)	4 (2.5)
Test-of-cure visit out of window	10 (9.1)	7 (13.2)	17 (10.4)
Received incorrect study drug	2 (1.8)	0	2 (1.2)
Additional inclusion/exclusion criteria violation[d]	2 (1.8)	2 (3.8)	4 (2.5)
ME Population	**46 (41.8)**	**17 (32.1)**	**63 (38.7)**
Not in CE Population	14 (12.7)	8 (15.1)	22 (13.5)
Not in mMITT Population	58 (52.7)	31 (58.5)	89 (54.6)

Table 10.2-1. Subject Disposition and Reasons for Premature Discontinuations—ITT Population

Subject Status *Reason for Discontinuation/Withdrawal*	*Ceftaroline (N = 110) n (%)*	*Comparator (N = 53) n (%)*	*Total (N = 163) n (%)*
Completed study drug	**100 (90.9)**	**47 (88.7)**	**147 (90.2)**
Premature discontinuation of IV study drug	**7 (6.4)**	**4 (7.5)**	**11 (6.7)**
Subject randomized, but did not receive drug[a]	3 (2.7)	1 (1.9)	4 (2.5)
Adverse event	2 (1.8)	1 (1.9)	3 (1.8)
Withdrew consent	2 (1.8)	0	2 (1.2)
Other reasons	0	2 (3.8)	2 (1.2)
Premature discontinuation of oral study drug	**3 (2.7)**	**2 (3.8)**	**5 (3.1)**
Adverse event	0	1 (1.9)	1 (0.6)
Request of Sponsor or Investigator	2 (1.8)	0	2 (1.2)
Withdrew consent	1 (0.9)	0	1 (0.6)
Lost to follow-up	0	1 (1.9)	1 (0.6)
Premature discontinuation of any (IV or oral) study drug	**10 (9.1)**	**6 (11.3)**	**16 (9.8)**
Subject randomized, but did not receive drug[a]	3 (2.7)	1 (1.9)	4 (2.5)
Adverse event	2 (1.8)	2 (3.8)	4 (2.5)
Request of Sponsor or Investigator	2 (1.8)	0	2 (1.2)
Withdrew consent	3 (2.7)	0	3 (1.8)
Lost to follow-up	0	1 (1.9)	1 (0.6)
Other reasons	0	2 (3.8)	2 (1.2)
Completed study	**103 (93.6)**	**48 (90.6)**	**151 (92.6)**
Premature withdrawal from study	**7 (6.4)**	**5 (9.4)**	**12 (7.4)**
Subject did not meet inclusion/exclusion criteria	0	1 (1.9)	1 (0.6)
Withdrew consent	5 (4.5)	2 (3.8)	7 (4.3)
Lost to follow-up	0	2 (3.8)	2 (1.2)
Other reasons	2 (1.8)	0	2 (1.2)

Demographics and Baseline Characteristics

The majority of subjects in the MITT Population were male (55.3%), white (87.4%), with a mean age of 7 years (range 9 weeks - 17 years). Demographic characteristics were generally similar across the 2 treatment groups. With the exception of Cohort 2, the age cohorts were evenly distributed within each treatment group. Both treatment groups had the highest percentage of enrolment in Cohort 2. The majority of subjects had normal or mildly impaired renal function. Staphylococcus aureus was the most common pathogen identified (40.2% of subjects in the ceftaroline group and 42.3% of subjects in the comparator group), and the majority of S. aureus pathogens were methicillin-sensitive.

Efficacy

-The clinical response rates at Study Day 3 were, by all 3 definitions of response, high and similar between the 2 treatment groups for the MITT population: (Definition 1: 85.0% vs. 84.6%; Definition 2: 91.6% vs. 90.4%; and Definition 3: 80.4% vs. 75.0%).

Table 11.4.1.1–1. Clinical Response at Study Day 3 by Treatment Group Overall —MITT Population

Response	*Ceftaroline (N = 107) n (%)*	*Comparator (N = 52) n (%)*	*Difference*
Definition 1: ≥ 20% reduction from baseline infection area			
Responder	91 (85.0)	44 (84.6)	0.4%
95% CI	(76.9, 91.2)	(71.9, 93.1)	(–10.7, 13.9)
Non-responder	11 (10.3)	4 (7.7)	—
Incomplete data	5 (4.7)	4 (7.7)	—
Definition 2: Cessation of spread measured by total infection area			
Responder	98 (91.6)	47 (90.4)	1.2%
95% CI	(84.6, 96.1)	(79.0, 96.8)	(–7.7, 13.0)
Non-responder	4 (3.7)	1 (1.9)	—
Incomplete data	5 (4.7)	4 (7.7)	—
Definition 3: Cessation of spread measured by infection length and width separately, and temperature < 37.6°C			
Responder	86 (80.4)	39 (75.0)	5.4%
95% CI	(71.6, 87.4)	(61.1, 86.0)	(–7.8, 20.3)
Non-responder	16 (15.0)	9 (17.3)	—
Incomplete data	5 (4.7)	4 (7.7)	—

-Clinical cure rates at TOC were high and similar for both the ceftaroline and comparator groups for both the MITT (94.4% and 86.5%, respectively) and CE populations (100% and 97.8%, respectively). Similar results in clinical outcomes were also observed at the EOIV and EOT assessments. No subject in either treatment group had a relapse at the LFU assessment.

Table 11.4.1.2–1. Clinical Outcomes at TOC by Treatment Group Overall —MITT Population

Outcome	*Ceftaroline (N = 107) n (%)*	*Comparator (N = 52) n (%)*	*Difference*
Clinical cure	101 (94.4)	45 (86.5)	7.9%
95% CI	(88.2, 97.9)	(74.2, 94.4)	(–1.2, 20.2)
Clinical failure	0	1 (1.9)	—
Observed failure at EOIV	0	1 (1.9)	—
Observed failure at EOT	0	0	—
Observed failure at TOC	0	0	—
Indeterminate	6 (5.6)	6 (11.5)	—

-Microbiological outcomes by subject and by baseline pathogens at TOC assessments for the mMITT Population showed a favorable microbiological outcome (eradication or presumed eradication) for the majority (94.2% in the ceftaroline group and 81.8% in the comparator group) of subjects.

Table 11.4.1.4.1–1. Microbiological Outcomes at TOC by Treatment Group Overall-mMITT Population

Outcome	*Ceftaroline (N = 52) n (%)*	*Comparator (N = 22) n (%)*	*Difference*
Favorable microbiological outcome	49 (94.2)	18 (81.8)	12.4%
95% CI	(84.1, 98.8)	(59.7, 94.8)	(-2.1, 33.6)
Eradication	0	0	—
Presumed Eradication	49 (94.2)	18 (81.8)	—
Unfavorable microbiological outcome	0	0	—
Persistence	0	0	—
Presumed persistence	0	0	—
Indeterminate	3 (5.8)	4 (18.2)	—

Safety results

-Study drug exposure was similar between the ceftaroline and comparator treatment groups. The median duration of IV treatment was 5.0 days in both treatment groups. More than half of the subjects switched to oral study drug and the median duration of exposure to study drug (IV and oral combined) was 10 days in both treatment groups.

-Similar percentages of subjects in each treatment group reported at least one treatment-emergent AE (48% vs. 43%). Few SAEs were reported, with 6 SAEs reported for 5 subjects (4 [3.8%] subjects in the ceftaroline group, and one [1.9%] subject in comparator group). Two of the SAEs (Clostridium difficile colitis and hypersensitivity) in the ceftaroline group and no SAEs in the comparator group were considered related to IV study drug treatment. Two subjects (1.8%) in the ceftaroline group discontinued IV study drug due to an SAE (drug hypersensitivity and osteomyelitis, one subject each).

Table 12.2.1–1. Summary of Adverse Events by Treatment Group Overall—Safety Population

Adverse Event Category	*Ceftaroline (N = 106) n (%)*	*Comparator (N = 53) n (%)*	*Total (N = 159) n (%)*
Number of subjects with:			
Any TEAE	51 (48.1)	23 (43.4)	74 (46.5)
Any study drug-related TEAEs	23 (21.7)	12 (22.6)	35 (22.0)
Any SAEs	4 (3.8)	1 (1.9)	5 (3.1)
Any study drug-related SAEs	2 (1.9)	0	2 (1.3)
Discontinuations of any study drug (IV or oral) due to AE	4 (3.8)	2 (3.8)	6 (3.8)
Discontinuations of any IV study drug due to AE	2 (1.9)	1 (1.9)	3 (1.9)
Deaths	0	0	0

-No deaths were reported during this study.

-No trends were seen in shifts from baseline for clinical laboratory parameters. The rates of occurrence of potentially clinically significant (PCS) hematology, chemistry, and other laboratory parameter abnormalities were low. The Coombs test seroconversion rate was 17.2% and was as expected for subjects in the ceftaroline group, and no cases of hemolytic anemia occurred. No subject met Hy's law laboratory criteria that were applied to the paediatric population in the study.

-Mean changes over time in vital signs measurements, were similar between both treatments.

Applicant's Conclusion

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

2.3. Discussion

This phase 2/3 study was conducted to address the FDA paediatric PMR (PMR 1692-003) and the EMA PIP commitment (PIP Study 3) to perform a randomized comparison of ceftaroline fosamil and comparators in paediatric subjects with ABSSSI, including subjects with infection caused by MRSA.

The ceftaroline fosamil dose regimen of 12 mg/kg (up to 400 mg for children weighing > 33 kg) q8h as a 60-minute infusion for children 6 months and older and 8 mg/kg q8h as a 60-minute infusion for subjects younger than 6 months was predicted to result in ceftaroline free drug % T > MIC values that were similar to or greater than median model-derived values for adult patients dosed with the currently approved dose of 600 mg q12h. Based on the simulations for this dose regimen, > 90% of patients 2 months to < 18 years of age were predicted to achieve PK/pharmacodynamic (PD) targets in plasma associated with 1-log kill of S. aureus and S. pneumoniae in the murine thigh infection model (36% and 44% T > MIC, respectively) for organisms with MIC values up to 1 mg/L for S. aureus and 0.5 mg/L for S. pneumoniae. The high PK/PD target attainment was expected to result in efficacy for paediatric patients comparable to that demonstrated for ceftaroline in adult patients with ABSSSI and CABP. The median Cmax and AUC values in children with normal renal function 2 months to < 18 years of age dosed with 12 mg/kg (up to 400 mg) q8h were predicted to be up to approximately 12% and 38% greater, respectively, than the median Cmax and AUC values in adults dosed with 600 mg q12h.

The comparators and their dosing regimens were based on their approved indications, clinical guidelines, and local prescribing preferences.

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. These doses are slightly different to those utilised in study P024 in paediatric patients with CAP. The MAH should comment on this during review of the final paediatric submission.

Study enrolment met minimum target numbers of subjects in each cohort. Overall, demographics were generally balanced between the 2 treatment groups with baseline clinical signs and symptoms of ABSSSI as anticipated for this study population.

The overall clinical response to treatment with ceftaroline fosamil at Study Day 3 was generally similar to that of comparator in the MITT Population. Clinical cure rates at TOC in the MITT and CE populations were high and similar between both treatment groups. No subject in either treatment group had relapse at the LFU assessment.

The safety data indicate that ceftaroline fosamil was safe and well tolerated when administered for 3 up to 14 days. The occurrence of TEAEs was similar between the 2 treatment groups. Mean values and changes from baseline over time for vital signs measurements were similar between both treatment groups.

In addition to this study, further paediatric 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 active comparator in paediatric patients, aged 2 months to < 18 years, with ABSSI, 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 literature related to the paediatric population will be taken upon completion of all the clinical studies planned in this population under the PIP. The MAH should comment on the different dosing regimens for ABSSI and CAP used in paediatric patients during review of the final paediatric submission.