EMA/619847/2015

European Medicines Agency decision

P/0251/2015

of 30 October 2015

on the acceptance of a modification of an agreed paediatric investigation plan for ceftazidime / avibactam (EMEA-001313-PIP01-12-M04) in accordance with Regulation (EC) No 1901/2006 of the European Parliament and of the Council

Disclaimer

This Decision does not constitute entitlement to the rewards and incentives referred to in Title V of Regulation (EC) No 1901/2006.

Only the English text is authentic.

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The European Medicines Agency,

Having regard to the Treaty on the Functioning of the European Union,

Having regard to Regulation (EC) No 1901/2006 of the European Parliament and of the Council of 12 December 2006 on medicinal products for paediatric use and amending Regulation (EEC) No. 1768/92, Directive 2001/20/EC, Directive 2001/83/EC and Regulation (EC) No 726/2004[1],

Having regard to Regulation (EC) No 726/2004 of the European Parliament and of the Council of 31 March 2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency[2],

Having regard to the European Medicines Agency's decision P/0083/2013 issued on 26 April 2013, the decision P/0133/2014 issued on 10 June 2014, and the decision P/0052/2015 issued on 6 March 2015,

Having regard to the application submitted by AstraZeneca AB on 17 June 2015 under Article 22 of Regulation (EC) No 1901/2006 proposing changes to the agreed paediatric investigation plan with a deferral,

Having regard to the opinion of the Paediatric Committee of the European Medicines Agency, issued on 11 September 2015, in accordance with Article 22 of Regulation (EC) No 1901/2006,

Having regard to Article 25 of Regulation (EC) No 1901/2006,

Whereas:

(1) The Paediatric Committee of the European Medicines Agency has given an opinion on the acceptance of changes to the agreed paediatric investigation plan

(2) It is therefore appropriate to adopt a decision on the acceptance of changes to the agreed paediatric investigation plan.

[1] OJ L 378, 27.12.2006, p.1.
[2] OJ L 136, 30.4.2004, p. 1.

Has adopted this decision:

Article 1

Changes to the agreed paediatric investigation plan for ceftazidime / avibactam, powder for concentrate for solution for infusion, intravenous use, are hereby accepted in the scope set out in the opinion of the Paediatric Committee of the European Medicines Agency annexed hereto, together with its appendices.

Article 2

This decision is addressed to AstraZeneca AB, European Regulatory Affairs, Building 411A, Floor 4, S-151 85 – Södertälje, Sweden.

Done at London, 30 October 2015

For the European Medicines Agency
Zaïde Frias
Head of Division
Human Medicines Research and Development Support
(Signature on file)

EMA/PDCO/427522/2015
London, 11 September 2015

Opinion of the Paediatric Committee on the acceptance of a modification of an agreed Paediatric Investigation Plan

EMEA-001313-PIP01-12-M04

Scope of the application

Active substance(s):

Ceftazidime / avibactam

Condition(s):

Treatment of intra-abdominal infections

Treatment of urinary tract infections

Treatment of pneumonia

Treatment of Gram-negative bacterial infections

Pharmaceutical form(s):

Powder for concentrate for solution for infusion

Route(s) of administration:

Intravenous use

Name/corporate name of the PIP applicant:

AstraZeneca AB

Basis for opinion

Pursuant to Article 22 of Regulation (EC) No 1901/2006 as amended, AstraZeneca AB submitted to the European Medicines Agency on 17 June 2015 an application for modification of the agreed paediatric investigation plan with a deferral as set out in the European Medicines Agency's decision P/0083/2013 issued on 26 April 2013, the decision P/0133/2014 issued on 10 June 2014, and the decision P/0052/2015 issued on 6 March 2015.

The application for modification proposed changes to the agreed paediatric investigation plan.

The procedure started on 14 July 2015.

Scope of the modification

Some measures of the Paediatric Investigation Plan have been modified.

Opinion

1. The Paediatric Committee, having assessed the application in accordance with Article 22 of Regulation (EC) No 1901/2006 as amended, recommends as set out in the appended summary report:

   - to agree to changes to the paediatric investigation plan in the scope set out in the Annex I of this opinion.

   The Norwegian Paediatric Committee member agrees with the above-mentioned recommendation of the Paediatric Committee.

2. The measures and timelines of the paediatric investigation plan are set out in the Annex I.

This opinion is forwarded to the applicant and the Executive Director of the European Medicines Agency, together with its annex and appendix.

Annex I

The subset(s) of the paediatric population and condition(s) covered by the waiver and the measures and timelines of the agreed paediatric investigation plan (PIP)

1. Waiver

Not applicable.

2. Paediatric investigation plan

2.1. Condition:

Treatment of intra-abdominal infections

2.1.1. Indication(s) targeted by the PIP

Treatment of complicated intra-abdominal infections (cIAIs)

2.1.2. Subset(s) of the paediatric population concerned by the paediatric development

From birth to less than 18 years of age

2.1.3. Pharmaceutical form(s)

Powder for concentrate for solution for infusion

2.1.4. Measures

Area	Number of measures	Description
Quality-related studies	1	**Study 1** Development of an age-appropriate powder for concentrate for solution for infusion of ceftazidime and avibactam in a single vial.
Non-clinical studies	1	**Study 2** 14-day repeat dose toxicity study in juvenile rats.
Clinical studies	3	**Study 3 (D4280C00014)** Open-label, single dose trial to evaluate pharmacokinetics, safety and tolerability of ceftazidime and avibactam in children from 3 months to less than 18 years of age with suspected or confirmed bacterial infection and receiving other systemic antibiotic therapy. **Study 4 (D4280C00015)** Single-blind, randomised, active controlled, trial to evaluate safety, tolerability and efficacy of ceftazidime and avibactam in children from 3 months to less than 18 years of age with complicated intra-abdominal infections (cIAIs). **Study 6 (D4280C00017)** Open-label, single and multiple dose trial to evaluate pharmacokinetics, safety and tolerability of ceftazidime and

		avibactam in children from birth to less than 3 months of age with late onset sepsis.
Extrapolation, modelling and simulation studies	0	Not applicable.
Other studies	0	Not applicable.
Other measures	0	Not applicable.

2.2. Condition:

Treatment of urinary tract infections

2.2.1. Indication(s) targeted by the PIP

Treatment of complicated urinary tract infections (cUTIs)

2.2.2. Subset(s) of the paediatric population concerned by the paediatric development

From birth to less than 18 years of age

2.2.3. Pharmaceutical form(s)

Powder for concentrate for solution for infusion

2.2.4. Measures

Area	Number of measures	Description
Quality-related studies	1	**Study 1** Development of an age-appropriate powder for concentrate for solution for infusion of ceftazidime and avibactam in a single vial. *Same study as for condition 'treatment of intra-abdominal infections'*
Non-clinical studies	1	**Study 2** 14-day repeat dose toxicity study in juvenile rats. *Same study as for condition 'treatment of intra-abdominal infections'*
Clinical studies	3	**Study 3 (D4280C00014)** Open-label, single dose trial to evaluate pharmacokinetics, safety and tolerability of ceftazidime and avibactam in children from 3 months to less than 18 years of age with suspected or confirmed bacterial infection and receiving other systemic antibiotic therapy. *Same study as for condition 'treatment of intra-abdominal*

		infections' **Study 5 (D4280C00016)** Single-blind, randomised, active controlled, trial to evaluate safety, tolerability and efficacy of ceftazidime and avibactam in children from 3 months to less than 18 years of age with complicated urinary tract infections (cUTI). **Study 6 (D4280C00017)** Open-label, single and multiple dose trial to evaluate pharmacokinetics, safety and tolerability of ceftazidime and avibactam in children from birth to less than 3 months of age with late onset sepsis. *Same study as for condition 'treatment of intra-abdominal infections'*
Extrapolation, modelling and simulation studies	0	Not applicable.
Other studies	0	Not applicable.
Other measures	0	Not applicable.

2.3. Condition:

Treatment of pneumonia

2.3.1. Indication(s) targeted by the PIP

Treatment of nosocomial pneumonia

2.3.2. Subset(s) of the paediatric population concerned by the paediatric development

From birth to less than 18 years of age

2.3.3. Pharmaceutical form(s)

Powder for concentrate for solution for infusion

2.3.4. Measures

Area	Number of measures	Description
Quality-related studies	1	**Study 1** Development of an age-appropriate powder for concentrate for solution for infusion of ceftazidime and avibactam in a single vial. *Same study as for condition 'treatment of intra-abdominal infections'*

Non-clinical studies	1	**Study 2** 14-day repeat dose toxicity study in juvenile rats. *Same study as for condition 'treatment of intra-abdominal infections'*
Clinical studies	3	**Study 3 (D4280C00014)** Open-label, single dose trial to evaluate pharmacokinetics, safety and tolerability of ceftazidime and avibactam in children from 3 months to less than 18 years of age with suspected or confirmed bacterial infection and receiving other systemic antibiotic therapy. *Same study as for condition 'treatment of intra-abdominal infections'* **Study 6 (D4280C00017)** Open-label, single and multiple dose trial to evaluate pharmacokinetics, safety and tolerability of ceftazidime and avibactam in children from birth to less than 3 months of age with late onset sepsis. *Same study as for condition 'treatment of intra-abdominal infections'* **Study 8 (D4280C00028)** Open-label, single dose trial to evaluate pharmacokinetics, safety and tolerability of ceftazidime (CAZ) and avibactam (AVI) in children from 3 months to less than 18 years of age with suspected or confirmed bacterial nosocomial pneumonia (including ventilator associated pneumonia) and receiving other systemic antibiotic therapy.
Extrapolation, modelling and simulation studies	2	**Study 7 (CAZ-MS-PED-02)** Population pharmacokinetic (PK) modelling and PK/pharmacodynamic (PD) probability of target attainment (PTA) analysis for dose selection across paediatric age groups for patients with nosocomial pneumonia or with infections caused by Gram-negative bacteria. **Study 9 (CAZ-MS-PED-04)** Extrapolation study of the clinical efficacy and safety data for ceftazidime-avibactam (CAZ-AVI) from the adult Phase III and paediatric programmes to paediatrics patients with nosocomial pneumonia or with infections caused by Gram-negative bacteria.
Other studies	0	Not applicable.
Other measures	0	Not applicable.

2.4. Condition:

Treatment of Gram-negative bacterial infections

2.4.1. Indication(s) targeted by the PIP

Treatment of Gram-negative infections in patients with limited treatment options

2.4.2. Subset(s) of the paediatric population concerned by the paediatric development

From birth to less than 18 years of age

2.4.3. Pharmaceutical form(s)

Powder for concentrate for solution for infusion

2.4.4. Measures

Area	Number of measures	Description
Quality-related studies	1	**Study 1** Development of an age-appropriate powder for concentrate for solution for infusion of ceftazidime and avibactam in a single vial. *Same study as for condition 'treatment of intra-abdominal infections'*
Non-clinical studies	1	**Study 2** 14-day repeat dose toxicity study in juvenile rats. *Same study as for condition 'treatment of intra-abdominal infections'*
Clinical studies	2	**Study 3 (D4280C00014)** Open-label, single dose trial to evaluate pharmacokinetics, safety and tolerability of ceftazidime and avibactam in children from 3 months to less than 18 years of age with suspected or confirmed bacterial infection and receiving other systemic antibiotic therapy. *Same study as for condition 'treatment of intra-abdominal infections'* **Study 6 (D4280C00017)** Open-label, single and multiple dose trial to evaluate pharmacokinetics, safety and tolerability of ceftazidime and avibactam in children from birth to less than 3 months of age with late onset sepsis. *Same study as for condition 'treatment of intra-abdominal infections'*

Extrapolation, modelling and simulation studies	2	**Study 7 (CAZ-MS-PED-02)** Population pharmacokinetic (PK) modelling and PK/pharmacodynamic (PD) probability of target attainment (PTA) analysis for dose selection across paediatric age groups for patients with nosocomial pneumonia or with infections caused by Gram-negative bacteria. Same study as for condition 'treatment of pneumonia' **Study 9 (CAZ-MS-PED-04)** Extrapolation study of the clinical efficacy and safety data for ceftazidime-avibactam (CAZ-AVI) from the adult Phase III and paediatric programmes to paediatrics patients with nosocomial pneumonia or with infections caused by Gram-negative bacteria. Same study as for condition 'treatment of pneumonia'
Other studies	0	Not applicable.
Other measures	0	Not applicable.

3. Follow-up, completion and deferral of PIP

Concerns on potential long term safety/efficacy issues in relation to paediatric use:	No
Date of completion of the paediatric investigation plan:	By December 2021
Deferral for one or more measures contained in the paediatric investigation plan:	Yes