EUnetHTA Joint Action 3 2016-2020

CEFIDEROCOL INDICATED FOR THE TREATMENT OF INFECTIONS DUE TO AEROBIC GRAM-NEGATIVE BACTERIA IN ADULT PATIENTS WITH LIMITED TREATMENT OPTIONS.

PROJECT ID: PTJA11

PROJECT DESCRIPTION AND PLANNING

AIFA, Italy

NOMA, Norway

Template Version 2, December 2018

VERSION LOG

Version number	Date	Modification	Reason for the modification
V0.1	08/09/2019	First draft of the Project Plan	Developed PICO for survey and incorporated feedback from Member States
V0.2	14/10/2019	Second draft of the Project Plan	Incorporated feedback from Dedicated Reviewers
V1.0	03/03/2020	Final version of the Project Plan	Final after positive CHMP opinion release
V2.0	17/04/2020	Final version of the Project Plan updated	Change in Authoring Team and update in timelines due to the COVID-19 outbreak

Disclaimer:
Due to the impact of the COVID-19 measures, a change in the Authoring Team and in the timelines was necessary. Please see the EUnetHTA response on the COVID-19 outbreak here.

CONTENTS

LIST OF TABLES

LIST OF ABBREVIATIONS

AE	Adverse event
BAT	Best available therapy
cIAI	complicated intraabdominal infections
CR	carbapenem-resistant
cUTI	complicated urinary tract infection
EA	early assessment
EOT	End of Treatment
BSI	bloodstream infections
EPAR	European Public Assessment Report
EUnetHTA	European Network for Health Technology Assessment
FUP	follow-up
HAP	Hospital-acquired Pneumonia
HCAP	Healthcare-Associated Pneumonia
HRQoL	Health-related quality of life
IV	Intravenous
pMAH	Prospective Marketing Authorisation Holder
SAE	Serious Adverse Event
TOC	Test-of-cure
VAP	Ventilator-associated Pneumonia

1 INTRODUCTION

On 13-06-2019, EUnetHTA and the prospective Marketing Authorisation Holder (pMAH) of cefiderocol (*Shionogi)* agreed that EUnetHTA will perform a joint relative effectiveness assessment of cefiderocol indicated for the treatment of infections due to aerobic Gram-negative bacteria in adult patients with limited treatment options.

Infections due to aerobic Gram-negative bacteria with significant resistance that limits treatment options, represent an urgent threat to global health. In particular, the increase in infections caused by carbapenem-resistant *Enterobacteriaceae* (CRE) is challenging due to its high prevalence and the lack of consolidated first line treatment options.

Infections with carbapenem-resistant Gram-negative bacteria may occur at various organ sites, and may result in bacteraemia and septic shock.

There are many guidelines, even at regional level, available regarding recommendations for the treatment of infections listed in the proposed indications. Carbapenem at high dose main retain activity against multiresistant gram.negative infections, while, with the efficacy of carbapenem compromised, the remaining treatment option for CRE are severely limited. Antibiotics which retain some broad in vitro activity include polymyxins and aminoglycosides, and new antibiotics such as ceftazidime/avabactam, meropemen/vaborbactam, and ceftolozane/tazobactam.

The selection of antibacterial agent(s) for the individual patient should be also guided by the results of pathogen identification and susceptibility testing, by knowledge of the local epidemiology (local resistance profile and local pathogen distribution), as well as by some patient specific factors, such as severity of illness and previous antibiotic exposure.

Specificities related to this product and its development are well acknowledged. Building on the experience gained with cefiderocol, authors will provide a short summary of the methodological issues encountered in the assessment. This will potentially benefit future evaluation of antimicrobial products by EUnetHTA teams. Such information will be provided in an attachment.

Once finalised this assessment is made publicly available and can be used by European HTA bodies for their national processes supporting reimbursement and pricing decisions.

2 RESEARCH QUESTION AND SCOPE

The aim of this project is to compare the clinical effectiveness and safety of cefiderocol in the target patient populations with relevant comparators. The target patient populations and relevant comparators (based on the requirements of the EUnetHTA partners) are defined in the project scope below.

The following table provides the scope identified for the assessment of cefiderocol.

Table 2-1: Assessment scope: relevant PICO(s) identified for the planned assessment

Description	Assessment scope
PICO	Research question: Do patients with aerobic Gram-negative infections and limited treatment option benefit from cefiderocol as an additional treatment option?
Population	Infections due to aerobic Gram-negative pathogens in adult patients with limited treatment option, which comprises: 1) Adult patients with documented infection by a carbapenem-resistant Gram-negative pathogen or other Gram-negative pathogen difficult to treat with limited treatment option; 2) Critically ill* adult patients with suspected infection by a carbapenem-resistant Gram-negative pathogen or other Gram-negative pathogen difficult to treat with limited treatment options **With life-threatening infection*
Intervention	Cefiderocol 2g IV as a 3 hr infusion every 8 hrs for 7-14 days
Comparison	Best available therapy (BAT)* BAT includes (but is not limited to) any of the following as monotherapy or in combination: • carbapenems (only for sensitive pathogens or in high dose/prolonged infusion time for carbapenem-resistant pathogens with an MIC close to the susceptibility/resistance breakpoint) • polymyxins • tigecycline • fosfomycin • aminoglycosides • ceftazidime-avibactam • meropenem–vaborbactam • ceftolozane-tazobactam **There are many guidelines, even at regional level, available regarding recommendations for the treatment of infections listed in the proposed indications. The selection of antibacterial agent(s) for the individual patient should be also guided by the results of pathogen identification and susceptibility testing, by knowledge of the local epidemiology (local resistance profile and local pathogen distribution), as well as by some patient specific factors, such as severity of illness and previous antibiotic exposure.*

Outcomes	Overall and stratified by site of infection (HAP/VAP/HCAP, cUTI; BSI/sepsis) as well as by pathogen (fermenters vs non-fermenters):
	• Efficacy:
	  • Clinical outcome at EA; EOT, TOC, FUP, and at the maximal pre-specified follow-up time
	  • Composite of microbiological eradication and clinical cure (where applicable) (time frame: TOC visit)
	  • Microbiological eradication at EOT,TOC, FUP, and at the maximal pre-specified follow-up time

Description	Assessment scope

Outcomes	• Microbiological and clinical outcome per pathogen and per patient at EA, EOT, TOC, FUP, and at the maximal pre-specified follow-up time
	• changes in susceptibility of pathogens between baseline and the time of failure and/or appearance of pathogens not present at baseline that are resistant to the assigned treatment. All-cause mortality at day 14 and 28, and at the maximal pre-specified follow-up time
	• Safety: Proportion and the relative group difference in the following
	  • AE, SAE
	  • grade ≥3 AE
	  • AE of special interest (e.g. *Clostridium difficile* infections)
	  • AE leading to drug discontinuation
	  • AE leading to death
	• Hospital utilization:
	  • Length of stay (LOS)
	  • Requirement of ICU admission
	  • Length of stay in ICU
	• Patient reported outcome (PRO):
	• Symptoms of disease
	• Quality of life

3 METHODS

The EUnetHTA Guidelines, available at http://www.eunethta.eu/eunethta-guidelines, will be consulted throughout the assessment process.

3.1 Inclusion criteria

During the assessment the inclusion criteria applied by the pMAH will be checked to evaluate if they capture the PICO defined for the assessment. In addition, the following criteria are considered relevant for study inclusion:

3.1.1 Inclusion criteria for clinical studies:

- Studies with mixed populations if they consider at least a subset of patients included in the PICO.
- Studies in adult population defined as patients more than 18 years old.
- English language studies will be included in this assessment as this is the language in common for the countries involved in this assessment and most often the language used in the relevant publications and reports to be assessed.

3.1.2 Exclusion criteria for clinical studies:

- Comments, editorials, narrative review articles, case reports
- Studies with patients taking the treatment of interest for conditions other than reported in the PICO
- Studies in patients less than 18 years old including mixed patients populations of adults and children as well as studies with mixed populations including populations other than specified in the PICO, if outcomes are not separated by population subgroup.
- Studies not evaluating the treatment of interest in at least one arm of the controlled trial.

Moreover, relevant systematic reviews will be searched to perform reference cross-checking.

3.2 Information retrieval

The assessment will be based on a submission dossier submitted by the pMAH. To allow for a meaningful assessment, the submission dossier has to be complete with regard to the available evidence relevant for the research question(s). This requires the systematic identification of all published and unpublished studies relevant to the assessment according to the research question and scope defined in Section 2 [7]. The assessment will investigate whether these requirements are met and thus whether the evidence base for the assessment is complete.

The cut-off date for the pMAH's list of sponsored studies and the searches should be a maximum of three months before submission (of the submission dossier). This cut-off date will also be relevant for the assessment. There will be no updates of searches beyond this cut-off by the authors of the assessment.

During the assessment, the evidence base with regard to the drug under assessment and comparators provided by the pMAH will be reviewed. Search strategies will be checked for appropriateness and the results of information retrieval included in the pMAH's submission dossier will be checked for completeness against a search in study registries (optional bibliographic databases if appropriate) and against the studies included in the regulatory assessment report. If there are major flaws in the search conducted by the manufacturer and the evidence provided in the submission dossier is incomplete it will not be supplemented by own searches or analyses by the authors. The incompleteness and its consequences for the conclusions of the report will be described in the assessment report.. The search date, complete search strategies and the results of these searches will be reported in the assessment.

3.3 Data analysis and synthesis

The assessment will be based on the data and analyses included in the submission dossier prepared by the pMAH. During the assessment, the completeness of data and analyses in the submission dossier will be verified. Furthermore, the methods for data analysis and synthesis applied by the pMAH will be checked against the requirements of the submission dossier and applicable EUnetHTA Guidelines and assessed with regard to scientific validity. The results of this assessment and the results of the included studies, as appropriate, will be presented in the assessment report according to the research questions defined in Section 2.

3.3.1 Data extraction

Information used for the assessment of benefits and harms will be extracted from the submission dossier and verified against the Clinical Study Reports (CSR) or other original documentation provided in the submission dossier.

3.3.2 Assessment of risk of bias

The assessment of risk of bias should follow the criteria described in the two EUnetHTA guidelines on the internal validity of randomised controlled trials [8] and non-randomised studies on interventions [9]. The risk of bias of the results of each included study should be described separately for each patient-relevant outcome. For this purpose, risk of bias should be assessed at the study level as well as at the outcome level.

If the outcome-specific risk of bias is classified as high for an outcome, this should not lead to exclusion of the corresponding data. Rather, the risk-of-bias classification should inform the discussion on heterogeneous study results and the determination of certainty of results.

During the assessment, the methods and outcome of the risk-of-bias assessment presented in the submission dossier will be evaluated. Risk-of-bias will be assessed by the authors only for outcomes (and studies) that are included based on the research question(s) (PICO). The result of the risk-of-bias assessment conducted by authors will be presented in the assessment report.

3.3.3 Description of design and results of individual studies

During the assessment, the information in the submission dossier on the study design, study methods, populations, endpoints (patient relevance, validity, and operationalization) and study results will be evaluated. Results should be also stratified by site of infection (HAP/VAP/HCAP, cUTI; BSI/sepsis) as well as by pathogen (fermenters vs non-fermenters). The results of this evaluation will be presented, used for identification of relevant analyses and considered for the conclusions of the assessment report.

3.3.4 Synthesis of study results

Meta-analyses

If several studies are available for the same PICO, they should be quantitatively pooled in a meta-analysis if they are sufficiently comparable from a clinical (e.g. patient groups) and methodological (e.g. study design) point of view [10]. Results should be presented as overall and also as stratified by site of infection (HAP/VAP/HCAP, cUTI; BSI/sepsis) and by pathogen (fermenters vs non-fermenters).

During the assessment, the methods applied for the meta-analyses presented in the submission dossier, and, if applicable, the justification for deviations from the procedures described above will be evaluated. The meta-analyses relevant for the research questions (see Section 2) will be presented in the assessment report.

Sensitivity analyses

To evaluate the robustness of results, sensitivity analyses with regard to methodological factors presented in the submission dossier and the corresponding methods applied will be evaluated. These methodological factors arise from decisions made within the framework of the retrieval and assessment of information, for example, the specification of cut-offs for the time point of data collection or the choice of effect measure. The sensitivity analysis should in particular consider the classification

of the risk of bias of study results. The result of the sensitivity analysis can affect the assessment of the certainty of results.

Subgroup analyses and other effect modifiers

During the assessment, the subgroup analyses examining potential effect modifiers presented in the submission dossier and the corresponding methods applied will be evaluated. The evaluation also includes the justification for the choice of cut-offs if quantitative characteristics were categorized. If potential effect modifiers are identified, the conclusions inferred from the effects observed in the complete patient group can possibly be formulated more precisely.

Indirect comparisons

If indirect comparisons are included in the submission dossier, the methods applied, and if applicable, the justification in the event of deviations from the required approaches will be evaluated [10]. The indirect comparisons relevant for the research questions (see Section 2) will be presented and examined in the assessment report.

3.4 Patient involvement

At the start of this Joint Assessment an open call for patient input was published on the EUnetHTA website. This open call specifically asked patient organisations to answer the questions, as they have the position to collect and present patient's and care-givers' views and experiences by engaging with a wide range of patients and their careers.

The open call used by EUnetHTA asks general questions to elicit patients' views on living with the disease, important outcomes to be considered in this assessment and expectations about the drug under assessment. The questions are based on the HTAi questionnaire template. For more information on the development of the HTAi questionnaire template please see their website.

Relevant European and national patient and consumer organisations were asked to provide an organisational perspective on the questions in English. In all parts of the open call, the term 'patient' refers to anyone living with, or who has lived with, the condition for which the new medicine is indicated.

The open call for patient input was online from 05 September – 27 December 2019. After this deadline, no patient or consumer organisations completed the survey.

4 PROJECT ORGANISATION

4.1 Participants

Table 4-1: Project participants

	Agency	Role in the project	Country	Distribution of work
Assessment team				
1.	Norwegian Medicines Agency [NOMA]	Co-Author of Project Plan Author of Assessment Report	Norway	• Develop first draft and final version of EUnetHTA project plan with Author of Project Plan • Relative effectiveness and safety assessment (EFF and SAF domains). • Adapt documents according to reviewers comments together with co-authors • Answer comments of expert and manufacturer together with co-authors • Prepare the final assessment including a final summary of the assessment
2.	Zorginstituut Nederland [ZIN]	Co-Author of Assessment Report	The Netherlands	• Responsible for supporting the authors in all project phases • Carry out the assessment prepare CUR and TEC Domains; support authors in EFF and SAF Domains. Support authors in Summary, Method and Discussion sections. • Check all steps
3.	Italian Medicines Agency [AIFA]	Author of Project Plan	Italy	• Develop first draft and final version of EUnetHTA project plan with co-author of Project Plan Due to the COVID-19 outbreak and its involvement in the management of this emergency, the AIFA team had to withdraw its authoring role from the joint assessment of cefiderocol. EUnetHTA would like to acknowledge the contribution of the Italian team in the entire scoping phase, including the elaboration of the PICO, and finalisation of the project plan.
4.	Zorginstituut Nederland [ZIN]	Information Specialist	The Netherlands	Review of information retrieval, conduct of searches required for checking completeness of information retrieval in submission dossier; reporting information

				retrieval check in the assessment report
5.	Norwegian Medicines Agency [NOMA]	Statistical specialist	Norway	Expert review of statistical analyses presented in submission dossier, statistical support for authors
6.	French National Authority for Health [HAS]	Dedicated Reviewer	France	
7.	Institute for Quality and Efficiency in Health Care [IQWiG]	Dedicated Reviewer	Germany	
8.	Spanish Agency of Medicine and Sanitary Products [AEMPS]	Dedicated Reviewer	Spain	
Contributors				
9.	Simone Lanini MD, MSc Specialist in Infectious Disease Epidemiology and Preclinical Research Department INMI Lazzaro Spallanzani IRCCS Rome Italy	External expert	Italy	Answer specific question during the assessment.
10.	Dr. Annie Navarro Rolon Hospital Universitario Mútua de Terrassa	External expert	Spain	Answer specific questions during the assessment.
11.	Nextgenediting	Medical Editor	United Kingdom	Responsible for the medical editing of the report
12.	Zorginstituut Nederland [ZIN]	Project Manager	Netherlands	Coordination between involved parties throughout the assessment period

4.2 Project stakeholders

Table 4-2: Project stakeholders

Organisation	**Role in the project**
Shionogi	Manufacturer [MAH]; Completing the submission dossier; Fact check of the 2nd draft assessment report

4.3 Milestones and deliverables

Table 4-3: Milestones and deliverables

Milestones/Deliverables	Start date	End date
Project duration	**19-06-2019**	**16-06-2020**
Letter of Intent received	19-06-2019	
Scoping phase	**30-08-2019**	**27-02-2020**
Scoping PICO and development of first draft Project Plan	30-08-2019	14-10-2019
PICO survey – request relevant PICO from Member States	09-09-2019	20-09-2019
Adapt draft Project Plan based on PICO survey	01-10-2019	14-10-2019
Open call for patient input	05-09-2019	27-12-2019
Review of first draft Project Plan	15-10-2019	24-10-2019
Development of second draft Project Plan & answers to DR comments	25-10-2019	31-10-2019
Receive scoping F2F meeting documents from pMAH	15-10-2019	
Pre-scoping e-meeting with the assessment team	31-10-2019	
Share discussion topics for Scoping F2F Meeting	07-11-2019	
Scoping F2F meeting with manufacturer	14-11-2019	
Share action points from F2F meeting with manufacturer	21-11-2019	
(pre-)Assessment phase	**30-01-2020**	**27-02-2020**
Receive Submission Dossier from pMAH	30-01-2020	
Check formal completeness of Submission Dossier	31-01-2020	10-02-2020
Receive missing items and comments on the requests from the formal completeness check from pMAH	15-02-2020	
Start writing Assessment (background, methods)	15-02-2020	27-02-2020
CHMP opinion	28-02-2020	
Final Project Plan	03-03-2020	
Grace period to revise Submission Dossier by pMAH (based on CHMP opinion)	02-03-2020	
Assessment phase	**24-03-2020**	**16-06-2020**
Writing first draft Joint Assessment	24-03-2020	01-05-2020
Review by DRs (and if applicable include experts)	04-05-2020	15-05-2020
Writing second draft Joint Assessment	16-05-2020	31-05-2020
Medical Editing	01-06-2020	05-06-2020
Fact Check by pMAH (parallel with medical editing)	01-06-2020	05-06-2020
Final Assessment + response Fact Check	15-06-2020	
Expected EPAR	22-05-2020	
Publication final version of rapid assessment	15-06-2020	16-06-2020

4.4 Conflict of interest management

Conflicts of interest will be handled according to the EUnetHTA Conflict of Interest Policy. All authors, co-authors, dedicated reviewers, observers, external experts (health care professionals, patients or patient representatives) involved in the production of this assessment have declared they have no conflicts of interest in relation to the technology and comparator(s) assessed according to the EUnetHTA declaration of interest (DOI) form, which was evaluated following the EUnetHTA Procedure Guidance for handling DOI form (https://eunethta.eu/doi).

Authors, co-authors and dedicated reviewers who declare a conflict of interest will be excluded from parts of or the whole work on this specific topic. However, they may still be included in other assessments.

For external experts and patients, conflict of interest declarations are collected with regard to the topic. External experts or patients who declare conflict of interest will be excluded from parts of or the whole work on this specific topic. However, they may still be included in other assessments.

5 REFERENCES

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