IQWiG Reports – Commission No. A20-26

Ceftolozane/tazobactam (nosocomial pneumonia) –

Benefit assessment according to §35a Social Code Book V[1]

Extract

[1] Translation of Sections 2.1 to 2.6 of the dossier assessment Ceftolozan/Tazobactam *(nosokomiale Pneumonie) – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 29 June 2020). Please note: This translation is provided as a service by IQWiG to English-language readers. However, solely the German original text is absolutely authoritative and legally binding.

Publishing details

Publisher

Institute for Quality and Efficiency in Health Care

Topic

Ceftolozane/tazobactam (nosocomial pneumonia) – Benefit assessment according to §35a Social Code Book V

Commissioning agency

Federal Joint Committee

Commission awarded on

17 March 2020

Internal Commission No.

A20-26

Address of publisher

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Keywords: Ceftolozane, Tazobactam, Pneumonia, Benefit Assessment

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[2] Table numbers start with “2” as numbering follows that of the full dossier assessment.

List of abbreviations

Abbreviations	Meaning
A. baumanii	*Acinetobacter baumanii*
ACT	appropriate comparator therapy
APACHE	Acute Physiology and Chronic Health Evaluation
EMA	European Medicines Agency
ESBL	Extended-Spectrum Beta-Lactamase
EUCAST	European Committee on Antimicrobial Susceptibility Testing
FDA	Food and Drug Administration
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
ITT	Intention to treat
KRINKO	Kommission für Krankenhaushygiene und Infektionsprävention (Commission for Hospital Hygiene and Infection Prevention)
MIC	minimum inhibitory concentration
mITT	Microbiological Intention to treat
MRGN	multi-resistant Gram-negative pathogens
MRP	multi-resistant pathogen
MRSA	methicillin-resistant Staphylococcus aureus
P. aeruginosa	*Pseudomonas aeruginosa*
RCT	randomized controlled trial
S. aureus	*Staphylococcus aureus*
SGB	Sozialgesetzbuch (Social Code Book)
SPC	Summary of Product Characteristics

2 Benefit assessment

2.1 Executive summary of the benefit assessment

Background

In accordance with §35a Social Code Book (SGB) V, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to assess the benefit of the drug combination ceftolozane/tazobactam. The assessment was based on a dossier compiled by the pharmaceutical company (hereinafter referred to as the "company"). The dossier was sent to IQWiG on 17 March 2020.

Due to the working conditions during the corona pandemic, the present assessment was carried out without using strictly confidential data in Module 5 of the company's dossier.

Research question

The aim of the present report is the assessment of the added benefit of the drug combination ceftolozane/tazobactam in comparison with individual antibiotic therapy as appropriate comparator therapy (ACT) in adult patients with hospital-acquired (nosocomial) pneumonia including ventilator-associated pneumonia.

Table 2 shows the research question of the benefit assessment and the ACT specified by the G-BA.

Table 2: Research question of the benefit assessment of ceftolozane/tazobactam

Research question	Therapeutic indication	ACT[a]
1	Adult patients with hospital-acquired (nosocomial) pneumonia including ventilator-associated pneumonia	Individual antibiotic therapy[b] under consideration of ▪ the local pathogen spectrum, ▪ the (local) resistance profile, ▪ the risk of infections with multi-resistant pathogens according to the generally accepted state of scientific knowledge, ▪ the pathogen sensitivity (if the antibiogram is available)

a. Presentation of the respective ACT specified by the G-BA.
b. According to the G-BA, the recommendations for the appropriate use of antibiotics must be observed. The respective approval status of the antibiotics and the recommended duration of use depending on the pathogen to be treated must be considered. In case of pathogen detection, targeted treatment must be implemented both in the comparator arm and the verum arm.

ACT: appropriate comparator therapy; G-BA: Federal Joint Committee

The company stated that it followed the specification of the G-BA and therefore also designated an individual antibiotic therapy as ACT. However, the company, in contrast, only used the drug meropenem for the benefit assessment. The present assessment was conducted in comparison with the GBA's ACT described in Table 2.

The assessment was conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier. Randomized controlled trials (RCTs) with a minimum duration of 28 days were used for the derivation of the added benefit.

Results

Assessment of the added benefit

The company used the PN008 study for the benefit assessment.

The PN008 study presented by the company is unsuitable for the assessment of the added benefit of ceftolozane/tazobactam since this study does not compare ceftolozane/tazobactam with an individual antibiotic therapy that corresponds to the G-BA's specification. The PN008 study is described below, and its lack of suitability for the benefit assessment is explained in more detail.

Study PN008

The PN008 study is a randomized, double-blind, multicentre phase 3 study on the comparison of ceftolozane/tazobactam with meropenem. The study included adult patients with ventilated nosocomial pneumonia, including ventilator-associated pneumonia.

The study included a total of 726 patients, randomly assigned either to treatment with ceftolozane/tazobactam (N = 362) or meropenem (N = 364). Randomization was stratified by the factors "age" (< 65 years vs. ≥ 65 years) and "diagnosis" (ventilated nocosomial pneumonia vs. ventilator-associated pneumonia).

In the study, ceftolozane/tazobactam and meropenem were administered without relevant deviations from the recommendations of the respective Summary of Product Characteristics (SPCs).

The planned primary outcome of the study differed between the European Medicines Agency (EMA) and the Food and Drug Administration (FDA): for the EMA, it was defined as the clinical response at the time of the test of cure, and for the FDA it was defined as all-cause mortality on day 28.

No implementation of an individual antibiotic therapy in the PN008 study

The G-BA specified individual antibiotic therapy under consideration of the local pathogen spectrum, the (local) resistance profile, the risk of infection with multi-resistant pathogens based on the generally accepted state of scientific knowledge and the pathogen sensitivity (if the antibiogram is available) as ACT.

The drug meropenem in combination with further drugs was applied as comparator in the PN008 study used by the company. Below, it will be described separately for both the calculated and the targeted therapy why the therapy used in the comparator arm did not meet the criteria of the ACT for the patients included in the study.

Calculated therapy: therapy used in the comparator arm is no adequate implementation of the ACT

Based on the available data, it is not assumed that the choice of treatment was regularly based on an individual consideration in the PN008 study. Rather, administration of meropenem and of an agent against Gram-positive pathogens (linezolid or an adequate alternative) was planned for all patients in the comparator arm of the study until an infection with *staphylococcus aureus* (*S. aureus*) was ruled out in the antibiogram. However, combined administration (for up to 72 hours after the first administration of the study medication) with an additional drug against Gram-negative pathogens (amikacin or an adequate alternative) was only allowed in centres with existing pathogen resistances to meropenem (meropenem-resistant *Pseudomonas aeruginosa* [*P. aeruginosa* ≥ 15%]). However, this treatment regimen may render the therapy used in the comparator arm unsuitable as an individual treatment for the majority of patients in the sense of the ACT or the recommendations of the S3 guideline.

According to the factors of the S3 and S2k guidelines on the classification of the risk of infections with multi-resistant pathogens (MRPs), the majority of the patients included in the PN008 study have a risk of infections with MRPs.

For patients with nosocomial pneumonia with MRP risk and invasive ventilation, as those included in the PN008 study, a combination therapy of the following drugs is indicated as calculated therapy according to the recommendations of the German S3 guideline for the treatment of nosocomial pneumonia:

- a pseudomonas-effective beta-lactam (e.g. meropenem or piperacillin/tazobactam or cefepime) and
- an additional drug against Gram-negative MRPs (selected drugs from the fluoroquinolones or amino glycosides) as well as
- in case of suspected infection with methicillin-resistant *Staphylococcus aureus* (MRSA): an additional drug against Gram-positive MRPs (linezolid or vancomycin effective against MRSA).

For most patients, the combination therapy recommended by the guidelines for the calculated therapy was not implemented in the PN008 study. All patients in the comparator arm of the PN008 study were treated with meropenem, which the S3 guideline specified as one of the options for the combination therapy under consideration of the MRP risk described above and the disease characteristics. However, deviating from the recommendation in the guideline, only 30.8% of the patients in the comparator arm received the indicated combination with an additional drug for the treatment of Gram-negative infections at study entry. In contrast, when included in the study, 95.9% of the patients in the comparator arm received a therapy for the treatment of Gram-positive infections. The available data do not explain the reasons for this extension of the efficacy spectrum and whether it was indicated for these patients.

Moreover, according to the guidelines, the local pathogen spectrum and the local resistance situation must be taken into account when selecting the respective drugs for the combination therapy. However, the study documents provide no information on whether the drug selection for the calculated therapy was regularly based on the resistance situation in the respective study centres in the PN008 study.

Overall, it cannot be assumed that the therapy applied in the comparator arm was a suitable calculated therapy for the patients included in PN008 according to the specification of the G-BA.

Targeted therapy: therapy used in the comparator arm is no appropriate implementation of the ACT

According to the guideline recommendations, a switch to a targeted therapy with the narrowest possible efficacy spectrum (de-escalation) should take place depending on the pathogen detection and the pathogen sensitivity when the antibiogram is available. Based on the data available for the benefit assessment it is not assumed that a treatment switch took place on a regular basis once the antibiogram was available in the PN008 study. Rather, the majority of patients in the comparator arm (74.5%) did entirely complete the planned treatment with meropenem.

Meropenem is an option for a targeted therapy in the presence of extended-spectrum beta-lactamase (ESBL)-forming enterobacteria, *P. aeruginosa* and *Acinetobacter baumannii* (*A. baumanii*). However, based on the antibiogram, less than 50% of the patients in the study had ESBL-forming enterobacteria, *P. aeruginosa* and *A. baumanii* at baseline. These data show that, according to the S3 guideline, a treatment switch should have been performed for a significant proportion of the patients.

Overall, it can be derived neither that a targeted individual antibiotic therapy in accordance with the specification of the G-BA and the criteria specified in the guidelines had been implemented in the PN008 study, nor that the treatment applied in the comparator arm of the study represented such therapy.

Summary

The company presented no suitable data for the assessment of the added benefit of ceftolozane/tazobactam versus an individual antibiotic therapy as ACT for adult patients with nosocomial pneumonia including ventilator-associated pneumonia. This resulted in no hint of an added benefit of ceftolozane/tazobactam in comparison with the ACT; an added benefit is therefore not proven.

In vitro data

The company used in vitro data for the assessment of the resistance situation. From its information retrieval, the company identified no study it considered relevant. Irrespective of its information retrieval, it presented a study called Kresken 2019, which investigated clinical

isolates with Gram-negative pathogens from hospitalized patients across localizations. However, the presented data are unsuitable for the assessment of the added benefit of ceftolozane/tazobactam.

For instance, the company did not consider all drugs named by the G-BA in the respective therapeutic indication comprised by the ACT. Moreover, measurements of the pathogens' sensitivity to combinations of drugs that are suitable treatment options for patients in the therapeutic indication were not performed in the study. Moreover, the analyses of the company's sensitivity measurements across localizations complicate the interpretation of the data since it remains unclear whether the resistance spectrum of the isolates collected in Kresken 2019 was substantially influenced by the isolation site.

An advantage based on in vitro data is principally conceivable in situations where the new drug shows high efficacy, whilst the drugs hitherto available in the therapeutic indication show (almost) no efficacy. The available analyses of the company, however, demonstrate that at least one other drug is effective for each investigated pathogen and presents a possible treatment option besides ceftolozane/tazobactam.

Probability and extent of added benefit, patient groups with therapeutically important added benefit[3]

Table 3 shows a summary of probability and extent of the added benefit of ceftolozane/ tazobactam.

[3] On the basis of the scientific data analysed, IQWiG draws conclusions on the (added) benefit or harm of an intervention for each patient-relevant outcome. Depending on the number of studies analysed, the certainty of their results, and the direction and statistical significance of treatment effects, conclusions on the probability of (added) benefit or harm are graded into 4 categories: (1) "proof", (2) "indication", (3) "hint", or (4) none of the first 3 categories applies (i.e., no data available or conclusions 1 to 3 cannot be drawn from the available data). The extent of added benefit or harm is graded into 3 categories: (1) major, (2) considerable, (3) minor (in addition, 3 further categories may apply: non-quantifiable extent of added benefit, added benefit not proven, or less benefit). For further details see [1,2].

Table 3: Ceftolozane/tazobactam – probability and extent of added benefit

Therapeutic indication	**ACT[a]**	**Probability and extent of added benefit**
Adult patients with hospital-acquired (nosocomial) pneumonia including ventilator-associated pneumonia	Individual antibiotic therapy[b] under consideration of ▪ the local pathogen spectrum, ▪ the (local) resistance profile, ▪ the risk of infections with multi-resistant pathogens according to the generally accepted state of scientific knowledge, ▪ the pathogen sensitivity (if the antibiogram is available)	Added benefit not proven

a. Presentation of the respective ACT specified by the G-BA.
b. According to the G-BA, the recommendations for the appropriate use of antibiotics must be observed. The respective approval status of the antibiotics and the recommended duration of use depending on the pathogen to be treated must be considered. In case of pathogen detection, targeted treatment must be implemented in both the comparator arm and the verum arm.

ACT: appropriate comparator therapy; G-BA: Federal Joint Committee

The G-BA decides on the added benefit.

2.2 Research question

Aim of the present report was the assessment of the added benefit of the drug combination ceftolozane/tazobactam in comparison with an individual antibiotic therapy as ACT in adult patients with hospital-acquired (nosocomial) pneumonia, including ventilator-associated pneumonia.

Table 4 shows the research question of the benefit assessment and the ACT specified by the G-BA.

Table 4: Research question of the benefit assessment of ceftolozane/tazobactam

Research question	Subindication	ACT[a]
1	Adult patients with hospital-acquired (nosocomial) pneumonia including ventilator-associated pneumonia	Individual antibiotic therapy[b] under consideration of ▪ the local pathogen spectrum, ▪ the (local) resistance profile, ▪ the risk of infections with multi-resistant pathogens according to the generally accepted state of scientific knowledge, ▪ the pathogen sensitivity (if the antibiogram is available)

a. Presentation of the respective ACT specified by the G-BA.
b. According to the G-BA, the recommendations for the appropriate use of antibiotics must be observed. The respective approval status of the antibiotics and the recommended duration of use depending on the pathogen to be treated must be considered. In case of pathogen detection, targeted treatment must be implemented in both the comparator arm and the verum arm.

ACT: appropriate comparator therapy; G-BA: Federal Joint Committee

The company stated that it followed the specification of the G-BA and therefore also designated an individual antibiotic therapy as ACT. However, the company, in contrast, only used the drug meropenem for the benefit assessment. This was not appropriate. The present assessment was conducted in comparison with the G-BA's ACT described in Table 4.

The assessment was conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier. RCTs with a minimum duration of 28 days were used for the derivation of the added benefit. This deviated from the company's approach, which specified no minimum study duration.

2.3 Assessment of the added benefit

2.3.1 Information retrieval and study pool

The study pool of the assessment was compiled on the basis of the following information:

Sources of the company in the dossier:

- study list on ceftolozane/tazobactam (status: 22 January 2020)
- bibliographical literature search on ceftolozane/tazobactam (last search on 23 December 2019)
- search in trial registries for studies on ceftolozane/tazobactam (last search on 19 December 2019)

To check the completeness of the study pool:

- search in trial registries for studies on ceftolozane/tazobactam (last search on 7 April 2020)

The check of the completeness of the study pool produced no relevant studies on the comparison of ceftolozane/tazobactam versus the ACT. The company identified the RCTs PN009 [3] and PN008 [4-6], but only used PN008 for the assessment of the added benefit.

The PN009 study was a randomized, open-label, phase 3 study on the comparison of ceftolozane/tazobactam with piperacillin/tazobactam. Adult patients with ventilator-associated pneumonia were included. Patient recruitment was terminated prematurely and the study was discontinued. In total, 4 patients were enrolled in the study. The company neither presented nor included the results for the benefit assessment. The PN009 study will not be further commented in the present assessment.

The PN008 study presented by the company is unsuitable for the assessment of the added benefit of ceftolozane/tazobactam since this study does not compare ceftolozane/tazobactam with an individual antibiotic therapy according to the G-BA's specification. The PN008 study is described below, and its lack of suitability for the benefit assessment is explained in more detail.

Study PN008

The PN008 study is a randomized, double-blind, multicentre phase 3 study on the comparison of ceftolozane/tazobactam with meropenem. The study included adult patients with nosocomial pneumonia requiring artificial ventilation, including ventilator-associated pneumonia.

To be included in the study, patients had to show clinical signs and/or symptoms of pneumonia as well as new or progressive infiltrates pointing to bacterial pneumonia in the thorax x-ray or the computed tomography. The study included patients whose clinical signs and/or symptoms of pneumonia occurred within 24 hours before intubation or 48 hours after intubation and who had either been hospitalized for ≥ 48 hours or discharged from hospital within the last 7 days. Patients who had undergone mechanical ventilation ≥ for 48 hours were also included.

The study included a total of 726 patients, randomized in a 1:1 ratio either to treatment with ceftolozane/tazobactam (N = 362) or meropenem (N = 364). Randomization was stratified by the factors "age" (< 65 years vs. ≥ 65 years) and "diagnosis" ventilated nosocomial pneumonia vs. ventilator-associated pneumonia). The proportion of patients with ventilator-associated pneumonia included in the study was 71.5%. 28.5% of the patients were diagnosed with ventilated nocosomial pneumonia.

Patients received either 3000 mg ceftolozane/tazobactam or 1000 mg meropenem every 8 (± 2) hours as intravenous infusion. Adjustment of the dosage in patients with kidney dysfunctions (creatinine clearance 15–50 mL/min) was possible in both study arms. To ensure blinding in case of dose adjustments, placebo infusions were added to the treatment regimen. Within the study, the patients were hospitalized for 8 to 14 days to undergo treatment. Moreover, all patients were to receive treatment (linezolid or an appropriate alternative) exclusively effective against Gram-positive pathogens until it was proven that the antibiogram showed no *S. aureus*.

Combined administration with an additional drug for the treatment of Gram-negative infections (amikacin or an appropriate alternative) was permitted for up to 72 hours following the first administration of the study medication in study centres in which at least 15% of the *P. aeruginosa* isolates were meropenem-resistant. Overall, ceftolozane/tazobactam and meropenem were administered without relevant deviations from the SPC [7,8] in the study.

The planned primary outcome of the study differed between the EMA and the FDA: for the EMA, it was the clinical response at the time the test of cure was performed, and for the FDA it was all-cause mortality on day 28.

The presented inclusion and exclusion criteria of the PN008 study correspond to the information provided in the guidelines on the diagnosis of nosocomial pneumonia, although according to the guidelines there is no generally accepted time frame after discharge from hospital to classify pneumonia as nosocomial [9,10]. The time frame of up to 7 days following discharge from hospital used in the study is in line with the EMA recommendations [11].

The selected inclusion and exclusion criteria of the PN008 study do not completely reflect the therapeutic indication of ceftolozane/tazobactam relevant for the present benefit assessment, as the study included no patients with nosocomial pneumonia who did not require mechanical ventilation.

No implementation of an individual antibiotic therapy in the PN008 study

The G-BA specified individual antibiotic therapy under consideration of the local pathogen spectrum, the (local) resistance profile, the risk of infection with multi-resistant pathogens based on the generally accepted state of scientific knowledge and the pathogen sensitivity (if the antibiogram is available) as ACT.

Approach of the company

The drug meropenem in combination with further drugs was applied as comparator in the PN008 study used by the company. The company did not differentiate between calculated and targeted therapy. It did not address the suitability of the combination therapy used and only justified the suitability of meropenem as individual antibiotic therapy with the recommendation of guidelines, the frequency of use and a good availability of meropenem.

An antibiotic therapy is usually initiated as calculated therapy with the aim of covering the assumed pathogen spectrum in the best possible way if a concrete pathogen has not been detected yet. The guidelines differentiate between certain patient populations, e.g. based on the severity of the disease, for which they recommend different treatment options for the calculated therapy, with one drug or possibly several drugs being chosen under consideration of the local pathogen spectrum or the local resistance profile [9,10,12]. When the antibiogram is available (after approx. 72 hours), the condition of the patient and the antibiotic therapy should be reassessed, and a switch to a targeted therapy with the narrowest possible efficacy spectrum

(de-escalation) should be performed depending on the pathogen detection and the pathogen sensitivity [9,10,12-14].

Below, it will be explained separately for both the calculated and the targeted therapy why the therapy used in the comparator arm did not meet the criteria of the ACT for the patients included in the PN008 study. The following data refer to all randomized patients (intention to treat [ITT] population). In isolated cases, information on the ITT population is lacking; in these cases, information on the microbiological ITT (mITT) population or the safety population is presented below and specified accordingly. The mITT population was a subset of the ITT population comprising all randomized patients who received at least one dose of the study drug and in whom at least one pathogen was isolated (except for: only non-streptococcal Gram-positive pathogens) that was sensitive to at least one study drug (mITT population: 70% of the ITT population). The safety population comprises all randomized patients who received the study medication at least once.

Calculated therapy: therapy used in the comparator arm is no adequate implementation of the ACT

According to the available data, it is not assumed that the choice of the calculated therapy was regularly based on an individual balancing, for example, according to the criteria mentioned in the S3 guideline in the PN008 study. Rather, the administration of meropenem and of an agent against Gram-positive pathogens (linezolid or an appropriate alternative) was planned for all patients in the comparator arm of the study, until an infection with *S. aureus* was ruled out in the antibiogram. In contrast, combined administration (for up to 72 hours after the first administration of the study medication) with an additional agent against Gram-negative pathogens (amikacin or an appropriate alternative) was only permitted in centres with existing pathogen resistance to meropenem (meropenem-resistant *P. aeruginosa* ≥ 15%). However, this treatment regimen may render the therapy used in the comparator arm unsuitable as an individual treatment in the sense of the ACT or the recommendations of the S3 guideline.

The majority of the patients included in PN008 had a risk of infections with MRPs. For the patients included, prior antibiotic therapy within the past 90 days (88.3%), pneumonia that developed 5 days after hospitalization at the earliest (“late-onset” pneumonia; 66.0%) and medical care in a high-prevalence country for MRPs (63.8%) counted among the most frequent risk factors for MRP infection according to the S3 guideline. According to the company, 98.9% of the patients included in the study had one or several risk factors according to the S3 guideline. At least 63.8% of the patients had ≥ 2 risk factors. According to the company, 77.4% of the patients are to be allocated to group III on the basis of the S2k guideline rating scheme, which corresponds to a high risk of MRP infection.

According to the recommendations of the German S3 guideline for the treatment of nosocomial pneumonia, a combination therapy of the following drugs is indicated as calculated therapy for patients with nosocomial pneumonia with MRP risk and invasive ventilation, like those included in the PN008 study [9]:

- a pseudomonas-effective beta-lactam (e.g. meropenem or piperacillin/tazobactam or cefepime) and
- an additional drug against Gram-negative MRPs (selected drugs from the fluoroquinolones or amino glycosides) as well as
- in case of suspected infection with MRSA: an additional drug against Gram-positive MRPs (linezolid or vancomycin, which are effective against MRSA).

The European guideline also recommends a corresponding combination therapy in case of a high risk of MRP and serious illness. In case of severe disease, the guideline considers a monotherapy unsuitable [15]. The Acute Physiology and Chronic Health Evaluation (APACHE)-II score of ≥ 15 at baseline in 74.5% of the patients demonstrates that the included patients must be assumed to have severe disease. Moreover, all patients were receiving invasive ventilation and were unconscious upon randomization. 92.0% of the patients were receiving medical care in an ICU upon randomization.

For most patients, the combination therapy recommended for the calculated therapy by the guidelines was not implemented in the PN008 study. All patients in the comparator arm of the PN008 study were treated with meropenem, which the S3 guideline specified as one of the options for the combination therapy under consideration of the MRP risk described above and the disease characteristics. However, deviating from the recommendation in the guideline, only 30.8% of the patients in the comparator arm received the indicated combination with an additional drug for the treatment of Gram-negative infections at study entry. In contrast, when included in the study, 95.9% of the patients in the comparator arm received a therapy for the treatment of Gram-positive infections. The available data do not explain the reasons for this extension of the efficacy spectrum and whether it was indicated for these patients.

Moreover, according to the guidelines, the local pathogen spectrum and the local resistance situation must be taken into account when selecting the respective drugs for the combination therapy. However, it cannot be inferred from the study documents whether the drug selection for the calculated therapy was regularly based on the resistance situation in the respective study centres in the PN008 study. For example, it remains questionable whether meropenem would be the treatment of choice for all patients regardless of the country and centre of treatment also under consideration of the local pathogen spectrum or resistance profile.

Overall, it cannot be assumed that the therapy applied in the comparator arm was a suitable calculated therapy for the patients included in PN008 according to the specification of the G-BA.

Targeted therapy: therapy used in the comparator arm is no appropriate implementation of the ACT

In the PN008 study, samples were taken from the lower respiratory tract within 36 hours before the first dose of the study medication to detect the pathogen and to measure pathogen sensitivity.

The results were to be available within 72 hours after the start of treatment with the study medication. Sensitivity measurements were only planned for the two study medications and partially for the concomitant medications.

As already described, the specifications of the guideline request a switch to a targeted therapy with the narrowest possible spectrum of action (de-escalation) depending on pathogen detection and pathogen sensitivity as soon as the antibiogram is available. Based on the data available for the benefit assessment it is not assumed that a treatment switch took place on a regular basis once the antibiogram was available in the PN008 study. Rather, the majority of patients in the comparator arm (74.5%) did entirely complete the planned treatment with meropenem.

Meropenem is a suitable option for targeted therapy in patients with ESBL-forming enterobacteria, *P. aeruginosa* and *A. baumanii* [9]. However, at baseline, the antibiogram only detected these pathogens in 50% of the patients (ESBL-forming enterobacteria: 21.9%; *P. aeruginosa*: 17.6%; *A. baumanii*: 7.4% [mITT population]). These data show that, according to the S3 guideline, a treatment switch should have been performed for a significant proportion of the patients.

In the PN008 study, administration of the combined drugs against Gram-negative and Gram-positive pathogens was only permitted until the antibiogram was available (after 72 hours). If *S. aureus* was detected in a patient, treatment with a drug against Gram-positive pathogens was to be continued for at least 8 days; otherwise, it was to be discontinued. In contrast to the procedure for other pathogens (see above), this procedure for Gram-positive pathogens reflects the treatment switch based on the result of the antibiogram.

Overall, it can be derived neither that a targeted individual antibiotic therapy in accordance with the specification of the G-BA and the criteria specified in the guidelines had been implemented in the PN008 study, nor that the treatment applied in the comparator arm of the study represented such therapy.

2.3.2 Results on added benefit

The company presented no suitable data for the assessment of the added benefit of ceftolozane/tazobactam versus an individual antibiotic therapy as ACT for adult patients with nosocomial pneumonia including ventilator-associated pneumonia. This resulted in no hint of an added benefit of ceftolozane/tazobactam in comparison with the ACT; an added benefit is therefore not proven.

2.4 In vitro data

2.4.1 Information retrieval

The company used in vitro data for the assessment of the resistance situation. In the section “Further studies” of Module 4 A, the company presented a separate information retrieval for the in vitro data:

Sources of the company in the dossier:

- study list on ceftolozane/tazobactam (status: 21 January 2020)
- bibliographical literature search on ceftolozane/tazobactam (last search on 2 January 2020)
- search in trial registries for studies on ceftolozane/tazobactam (last search on 2 January 2020)

From its information retrieval, the company identified no study it considered relevant. Independent of its information retrieval, it presented a study named Kresken 2019 for the assessment of the resistance situation in Section 4.3.2.3 of Module 4 A [16]. The company's statements on this study are based on result tables for in vitro data ("data on file").

The Kresken 2019 study presented by the company is unsuitable for an assessment of the added benefit of ceftolozane/tazobactam (for reasons, see Section 2.4.2 on the assessment of the data presented).

Description of the Kresken 2019 study presented by the company

Kresken 2019 is a study on clinical isolates for the determination of the pathogen sensitivity to different antibiotics in vitro. 2571 clinical isolates with Gram-negative pathogens from hospitalized patients with bloodstream infections, lower respiratory tract infections, intra-abdominal infections and urinary tract infections were investigated. At 20 centres in Germany, the isolates were collected from blood, respiratory tract samples, intra-abdominal samples and urine samples between January 2016 and April 2017.

Sensitivity was measured by determination of the minimum inhibitory concentration (MIC) according to ISO 20776-1. The classification of the measured MIC as sensitive, sensitive at increased exposure or resistant to an antibiotic was based on the threshold values of European Committee on Antimicrobial Susceptibility Testing (EUCAST), Version 10.0, applicable to the tested substance. The tested antibiotics comprised ceftolozane/tazobactam and a selection of further drugs.

The company stated that for the assessment of the in vitro efficacy of ceftolozane/tazobactam it had considered only those pathogens for which the clinical efficacy of ceftolozane/tazobactam had been proven or could have been suspected according to the SPC. For these pathogens, the company analysed the results on the sensitivity irrespective of the type of infection, i.e. across localizations. It provides a descriptive presentation of the results as proportions of isolates per pathogen species that are sensitive, sensitive at elevated exposure or resistant to individual agents. For MRPs, the company presented separate analyses for each drug. According to the company, multi-resistant Gram-negative pathogens with resistance to 3 or 4 of the 4 antibiotic groups according to the definition of the Commission for Hospital Hygiene and Infection Prevention (KRINKO) [17] (3MRGN or 4MRGN), carbapeneme-resistant *P. aeruginosa* and

ESBL-forming enterobacteriales present the major problem in Germany. According to the company, combating these pathogens is the highest priority in Germany. Therefore, it only considered the results on the sensitivity of these pathogens when deriving the added benefit of ceftolozane/tazobactam.

2.4.2 Assessment of the presented in vitro data from the Kresken 2019 study

The transfer of in vitro data to the in vivo or clinical situation is only possible to a limited extent [18,19]. Therefore, the benefit assessment of antibiotics must also always be based on clinical evidence with an adequate comparison. Consideration of the resistance situation in such clinical trials is possible and is also recommended by guidelines [9,10,12]. In special situations, however, in vitro data could substantiate an advantage of a new antibiotic over the existing treatment options. Such advantage is basically conceivable in a situation where the new drug shows a high efficacy, but the drugs previously available in the therapeutic indication show (almost) no efficacy. Since appropriate antibiotic therapy may involve a treatment switch after pathogen detection (targeted antibiotic therapy), it is particularly relevant that such an advantage would result from the in vitro data if the existing therapy options (including combination therapies) were exhausted. It must be assumed that such an advantage would be pathogen-specific and would not cover the entire spectrum of pathogens relevant for the therapeutic indication. Therefore, the derivation of an advantage of a new antibiotic solely on the basis of in vitro data requires a study for the determination of the pathogen sensitivity to all treatment options available in the respective therapeutic indication.

However, the in vitro data submitted by the company do not meet these requirements for deriving a benefit of ceftolozane/tazobactam:

- The company did not consider all the drugs included in the ACT that were designated by the G-BA in the respective therapeutic indication.
- Measurements of the pathogens' sensitivity to combinations of drugs presenting potential treatment options for patients in the therapeutic indication and for which a synergistic effect is possible were not carried out in the study. Such tests are generally possible and are carried out in particular for resistant pathogens [20,21].
- The company's analyses of the sensitivity measurements across localizations complicate the interpretation of the data. It is unclear whether a localization-specific analysis would yield different results (i.e. analysis only of those isolates collected in the respective therapeutic indication, in the present case "nosocomial pneumonia, including ventilator-associated pneumonia"). This is because the data presented by the company do not clearly state whether the resistance spectrum of the isolates obtained in Kresken 2019 is substantially influenced by the isolation site.

Independent of the fact that the data submitted by the company are not suitable to derive an advantage of ceftolozane/tazobactam for the reasons explained above, they would not provide evidence of an advantage of ceftolozane/tazobactam either. The available analyses of the

company show that at least one other drug is effective for each pathogen investigated and represents a possible treatment option besides ceftolozane/tazobactam. The differences in the pathogen sensitivity presented by the company did not show that all drugs hitherto available in the therapeutic indication are (almost) ineffective.

2.5 Probability and extent of added benefit

The result of the assessment of the added benefit of ceftolozane/tazobactam in comparison with the ACT is summarized in Table 5.

Table 5: Ceftolozane/tazobactam – probability and extent of added benefit

Therapeutic indication	**ACT[a]**	**Probability and extent of added benefit**
Adult patients with hospital-acquired (nosocomial) pneumonia including ventilator-associated pneumonia	Individual antibiotic therapy[b] under consideration of ▪ the local pathogen spectrum, ▪ the (local) resistance profile, ▪ the risk of infections with multi-resistant pathogens according to the generally accepted state of scientific knowledge, ▪ the pathogen sensitivity (if the antibiogram is available)	Added benefit not proven
a. Presentation of the respective ACT specified by the G-BA. b. According to the G-BA, the recommendations for the appropriate use of antibiotics must be observed. The respective approval status of the antibiotics and the recommended duration of use depending on the pathogen to be treated must be considered. In case of pathogen detection, targeted treatment must be implemented in both the comparator arm and the verum arm. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee		

The assessment described above deviates from that of the company, which used the presented RCT to prove the equivalence of the treatment options ceftolozane/tazobactam and meropenem and derived an indication of major added benefit only on the basis of the in vitro data (Kresken 2019) for ceftolozane/tazobactam.

The G-BA decides on the added benefit.

References for English extract

Please see full dossier assessment for full reference list.

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