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# Ceftolozane/tazobactam (complicated intra-abdominal infections) –

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

## Extract

[1] Translation of Sections 2.1 to 2.5 of the dossier assessment *Ceftolozan/Tazobactam (komplizierte intraabdominelle Infektionen) – 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.

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

**List of abbreviations**

| Abbreviation | Meaning |
|---|---|
| ACT | appropriate comparator therapy |
| APACHE | Acute Physiology and Chronic Health Evaluation |
| *E. coli* | *Escherichia coli* |
| EMA | European Medicines Agency |
| ESBL | extended-spectrum β-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 |
| *K. pneumoniae* | *Klebsiella pneumoniae* |
| KRINKO | Kommission für Krankenhaushygiene und Infektionsprävention (Commission for Hospital Hygiene and Infection Prevention) |
| MIC | minimum inhibitory concentration |
| MITT | microbiologial intention to treat |
| mMITT | modified microbiological intention to treat |
| MRGN | multi-resistant Gram-negative |
| MRP | multi-resistant pathogen |
| *P. aeruginosa* | *Pseudomonas aeruginosa* |
| RCT | randomized controlled trial |
| SGB | Sozialgesetzbuch (Social Code Book) |
| SPC | Summary of Product Characteristics |
| *spp.* | *species pluralis* |

# 2 Benefit assessment

## 2.1 Executive summary of the benefit assessment

### Background

In accordance with §35a Social Code 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 made 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 an individual antibiotic therapy as appropriate comparator therapy (ACT) in adult patients with complicated intra-abdominal infections.

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

| **Therapeutic indication** | **ACT[a]** |
|---|---|
| Adult patients with complicated intra-abdominal infections | Individual antibiotic therapy[b] under consideration of<br>▪ the local pathogen spectrum,<br>▪ the (local) resistance profile,<br>▪ the risk of infection with MRPs in accordance with the generally accepted state of scientific knowledge,<br>▪ the pathogen sensitivity (if the antibiogram is available). |
| a. Presentation of the ACT specified by the G-BA.<br>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.<br>ACT: appropriate comparator therapy; G-BA: Federal Joint Committee, MRP: multi-resistant pathogen | |

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*

From its information retrieval, the company identified the RCTs PN003 and PN012 and used these studies for the benefit assessment.

The studies PN003 and PN012 presented by the company are unsuitable for the assessment of the added benefit of ceftolozane/tazobactam, because these studies do not compare ceftolozane/tazobactam with an individual antibiotic therapy corresponding to the G-BA's specification. The studies PN003 and PN012 are described below and their lack of suitability for the benefit assessment is explained in more detail.

*Studies PN003 and PN012*

PN003 and PN012 are 2-arm, randomized, active-controlled, double-blind, multicentre phase 3 or phase 2 studies comparing ceftolozane/tazobactam in combination with metronidazole (hereinafter referred to as ceftolozane/tazobactam + metronidazole) with meropenem. The concomitant use of metronidazole in the intervention arm corresponds to the recommendations provided in the Summary of Product Characteristics (SPC) of ceftolozane/tazobactam. Each of the studies included adult patients with complicated intra-abdominal infections requiring surgery within 24 hours or after the first dose of the study medication for the treatment of the infection.

PN003 included a total of 993 patients, randomized either to treatment with ceftolozane/tazobactam + metronidazole (N = 487) or meropenem (N = 506) in a 1:1 ratio. Randomization was stratified by the factors "primary infection site" (small bowel or large bowel vs. other intra-abdominal infection sites) and "study centre".

PN012 included 122 patients, randomized either to treatment with ceftolozane/tazobactam + metronidazole (N = 83) or meropenem (N = 39) in a 2:1 ratio. Randomization was stratified by the primary infection site (localized complicated appendicitis vs. other intra-abdominal infection sites).

In both studies, ceftolozane/tazobactam, metronidazole and meropenem were administered without relevant deviations from the recommendations of the respective SPC.

Primary outcome of the studies PN003 and PN012 was "clinical response at the time of the test for cure".

*No implementation of an individual antibiotic therapy in the studies PN003 and PN012*

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

In the studies PN003 and PN012 used by the company, the drug meropenem was used as sole comparator. For the assessment, the company used a subpopulation from each of the studies in order to select patients for whom it considered meropenem to be the suitable individual antibiotic therapy in accordance with the ACT specified by the G-BA.

The company formed the subpopulations on the basis of the following 3 criteria:

1) patients with extended-spectrum β-lactamase (ESBL)-forming enterobacterales and/or
2) patients with diffuse peritonitis acquired on an outpatient basis and/or
3) patients in whom a previous antibiotic therapy has failed

The subpopulation used by the company comprised 423 of 993 randomized patients (42.6%) in PN003 and 45 of 122 randomized patients (36.9%) in PN012.

Below, it is described separately for both the calculated and the targeted therapy why the comparator meropenem chosen in the studies did not meet the criteria of the ACT for the respective subpopulation used by the company.

*Calculated therapy: meropenem is no adequate implementation of the ACT in the studies presented*

The presence of ESBL-forming enterobacterales (first criterion of the company for the formation of the subpopulations) can only be identified from the antibiogram and is therefore not a criterion to be considered in the choice of the calculated therapy. However, it must be considered in the decision on the targeted therapy, which is addressed in more detail in the corresponding section below.

Diffuse peritonitis acquired on an outpatient basis (second criterion of the company for the formation of subpopulations) is not suitable to justify meropenem as an option for the calculated therapy, because according to the German S2k guideline for the calculated parenteral therapy of bacterial diseases in adults, meropenem is not a treatment option for diffuse peritonitis acquired on an outpatient basis.

According to the German S2k guideline, failure of the previous antibiotic therapy (third criterion of the company for the formation of the subpopulations) is basically suitable to justify meropenem as an option for the calculated therapy. Failure of a previous antibiotic therapy occurred in only few patients, i.e. in 14.3% in the PN003 study and in 40.0% in the PN012 study.

There is no further information stating that in the studies the choice of meropenem as a calculated therapy was based on the local pathogen spectrum or the local resistance situation in the respective study centres.

The S2k guideline designates meropenem as an option for the calculated therapy for patients with

- nosocomial (postsurgical/tertiary) diffuse peritonitis with high MRP risk or
- particularly severe disease.

The available data (partially only available for the total populations of the studies) show that these criteria presumably also apply to only few patients of the subpopulation in the studies PN003 and PN012. It is assumed that more than 70% of the patients had an infection acquired on an outpatient basis. Nosocomial infection only appears probable for less than 10% of the patients. The proportion of patients with severe disease (Acute Physiology and Chronic Health Evaluation [APACHE] II score≥ 10) was only 22.6% in the subpopulation of PN003 and 31.1% in the subpopulation of PN012.

Overall, in both studies, meropenem is not a treatment option for the calculated therapy according to the S2k guideline for the majority of patients in the subpopulation considered by the company due to the disease characteristics of those patients. Based on the G-BA's specification, meropenem is thus no suitable calculated therapy for the patients of the subpopulations in the PN003 and PN012 studies.

*Targeted therapy: meropenem is no adequate implementation of the ACT in the studies presented*

Meropenem is a treatment option for a targeted therapy in the presence of ESBL-forming enterobacterales (according to the first criterion of the company for the formation of the subpopulation under consideration) or of *Pseudomonas species pluralis (spp.)*. The studies PN003 and PN012 provide no information on whether treatment switch or de-escalation of the therapy were possible when an antibiogram was available. Based on the available data, it must rather be assumed that treatment with meropenem was continued even without the detection of *ESBL-forming enterobacterales* or *Pseudomonas spp.*, and treatment switch or de-escalation was impossible even when an antibiogram was available, because, for instance, 93.5% of the patients in the total population of PN003 received meropenem over the entire planned treatment period.

Only few patients in the total population of the studies had *ESBL-forming enterobacterales* or *Pseudomonas aeruginosa (P. aeruginosa)* at baseline: less than 10% in each study. Moreover, according to the S2k guideline, treatment would have had to be de-escalated if resistant pathogens were not detected in the microbiological examination.

Overall, it can neither be derived that targeted individual antibiotic therapy was implemented according to the G-BA's specifications and in line with the criteria listed in the guidelines in PN003 and PN012, nor that meropenem represents such therapy.

*Summary*

In its dossier, the company thus 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 complicated intra-abdominal infections. This results 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.

The company did not consider all drugs specified by the G-BA in the respective therapeutic indication which are covered by the ACT. In addition, no sensitivity measurements of the pathogens to combinations of drugs included in the therapy options for patients in the therapeutic indication were carried out in the study. The company's analyses of the sensitivity measurements across localizations also complicate the interpretation of the data, as it remains unclear whether the resistance spectrum of the isolates obtained in Kresken 2019 is substantially influenced by the isolation site.

Based on in vitro data, an advantage is principally conceivable in a situation where the new drug shows high efficacy, whereas, however, the drugs hitherto available in the therapeutic indication show (almost) no efficacy. Based on the available analyses of the company, however, it becomes clear that for each investigated pathogen at least one other agent is effective and represents 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 complicated intra-abdominal infections | Individual antibiotic therapy[b] under consideration of<br>▪ the local pathogen spectrum,<br>▪ the (local) resistance profile,<br>▪ the risk of infection with MRPs in accordance with the generally accepted state of scientific knowledge,<br>▪ the pathogen sensitivity (if the antibiogram is available). | Added benefit not proven |

a. Presentation of the ACT specified by the G-BA.
b. According to the G-BA, the recommendations for the adequate use of antibiotics have to be considered. The respective approval status of the antibiotics as well as the recommended duration of use depending on the pathogen to be treated have to be considered. If the pathogen is detected, targeted treatment is to be performed in both the comparator and the verum arm.

ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; MRP: multi-resistant pathogen

The G-BA decides on the added benefit.

## 2.2 Research question

The aim of the present report is 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 complicated intra-abdominal infections.

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

| **Therapeutic indication** | **ACT**[a] |
|---|---|
| Adult patients with complicated intra-abdominal infections | Individual antibiotic therapy[b] under consideration of<br>▪ the local pathogen spectrum,<br>▪ the (local) resistance profile,<br>▪ the risk of infection with MRPs in accordance with the generally accepted state of scientific knowledge,<br>▪ the pathogen sensitivity (if the antibiogram is available). |
| a. Presentation of the ACT specified by the G-BA.<br>b. According to the G-BA, the recommendations for the adequate use of antibiotics have to be considered. The respective approval status of the antibiotics as well as the recommended duration of use depending on the pathogen to be treated have to be considered. If the pathogen was detected, targeted therapy is to be performed in both the comparator and the verum arm.<br>ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; MRP: multi-resistant pathogen | |

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 ceftolozane/tazobactam (last search on 19 December 2019)

To check the completeness of the study pool:

- search in trial registries for 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. In contrast to this, the company used the RCTs PN003 [3-5] and PN012 [4-6] for the benefit assessment.

The studies PN003 and PN012 presented by the company are unsuitable for the assessment of the added benefit of ceftolozane/tazobactam, because these studies do not compare ceftolozane/tazobactam with an individual antibiotic therapy corresponding to the G-BA's specification. The studies PN003 and PN012 are described below and their lack of suitability for the benefit assessment is explained in more detail.

**Studies PN003 and PN012**

The studies PN003 and PN012 are 2-arm, randomized, active-controlled, double-blind, multicentre phase 3 or phase 2 studies on the comparison of ceftolozane/tazobactam in combination with metronidazole (hereinafter referred to as ceftolozane/tazobactam + metronidazole) with meropenem. Thereby, the concomitant use of metronidazole in the intervention arm corresponds to the recommendations of the SPC of ceftolozane/tazobactam [7]. Each of the studies included adult patients with complicated intra-abdominal infections requiring surgery within 24 hours or after the first dose of the study medication for the treatment of the infection.

PN003 included a total of 993 patients, randomized either to treatment with ceftolozane/tazobactam + metronidazole (N = 487) or meropenem (N = 506) in a 1:1 ratio. 23 patients (11 in the ceftolozane/tazobactam + metronidazole arm, 12 in the meropenem arm) were excluded from the intention to treat (ITT) population due to concerns regarding the data integrity. Randomization was stratified by the factors "primary infection site" (small bowel or large bowel vs. other intra-abdominal infection sites) and "study centre". However, Module 4 B provides contradictory information on whether the stratification factor was study centre or region (North America vs. South America vs. Western Europe vs. Eastern Europe vs. rest of the world).

PN012 included a total of 122 patients, randomized either to treatment with ceftolozane/tazobactam + metronidazole (N = 83) or meropenem (N = 39) in a 2:1 ratio. Randomization was stratified by the primary infection site (localized complicated appendicitis vs. other intra-abdominal infection sites).

In both studies, patients received either ceftolozane/tazobactam (1500 mg intravenous [IV] every 8 ± 2 hours) plus metronidazole (500 mg IV every 8 ± 2 hours) or meropenem (1000 mg IV every 8 ± 2 hours) plus a placebo infusion for metronidazole. In PN003, patients were treated for 4 to 10 days, in PN012 for 4 to 7 days. In both studies, treatment could be extended to a

maximum of 14 days if the original source of infection could not be controlled. The use of ceftolozane/tazobactam + metronidazole and meropenem thus largely corresponded to the respective SPCs [7-9]. In the studies, the infusion time of 60 minutes for metronidazole and meropenem was slightly longer than the usual duration of 20 minutes for metronidazole and 15 to 30 minutes for meropenem described in the respective SPCs [8,9].

Primary outcome of the PN003 and PN012 studies was "clinical response at the time of the test for cure".

**No implementation of an individual antibiotic therapy in the studies PN003 and PN012**

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

***Approach of the company***

In the studies PN003 and PN012 used by the company, the drug meropenem was used as sole comparator. The company used a subpopulation from each of the studies for the assessment in order to select patients for whom it considered meropenem to be the suitable individual antibiotic therapy in accordance with the ACT defined by the G-BA.

The company formed the subpopulations on the basis of the following 3 criteria:

1) patients with ESBL-forming enterobacterales and/or
2) patients with diffuse peritonitis acquired on an outpatient basis and/or
3) patients in whom a previous antibiotic therapy has failed

In the PN003 study, the subpopulation used by the company comprised 423 of 993 randomized patients (42.6%); 11 patients were excluded from the ITT population due to concerns regarding the data integrity. In the PN012 study, the subpopulation used by the company comprised 45 of 122 randomized patients (36.9%).

The company did not differentiate between calculated and targeted therapy. It justified the suitability of meropenem as individual antibiotic therapy for the subpopulation with recommendations of guidelines, 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 [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 [10-14].

Below, it is described separately for both the calculated and the targeted therapy why the comparator meropenem chosen in the studies did not meet the criteria of the ACT for the respective subpopulation used by the company. Relevant information (e.g. on the pathogen spectrum at baseline) for the benefit assessment is missing for the subpopulations formed by the company. Therefore, conclusions are partially drawn on the basis of available data on the total population in the respective studies. The following data for the total population refer to the subset of patients of the ITT population (hereinafter referred to as microbiological ITT [MITT] in the PN003 study, or as modified microbiological ITT [mMITT]) in PN012), in whom at least one pathogen of the complicated intra-abdominal infection was detected at baseline and who had received at least one dose of the study medication (PN003: MITT: approx. 80% of the ITT population, PN012: mMITT: approx. 70% of the ITT population). The data for the subpopulation of the company, in contrast, refer to the ITT populations regardless of the detection of at least one pathogen.

***Calculated therapy: meropenem is no adequate implementation of the ACT in the studies presented***

The presence of ESBL-producing enterobacterales (first criterion of the company for the formation of the subpopulations) can only be verified from the results of the antibiogram and is therefore not a criterion to be considered in the choice of the calculated therapy. However, it must be considered in the decision on the targeted therapy, which is addressed in more detail in the corresponding section below.

Diffuse peritonitis acquired on an outpatient basis (second criterion of the company for the formation of subpopulations) is not suitable for justifying meropenem as an option for the calculated therapy, since according to the German S2k guideline meropenem is not a treatment option for the calculated parenteral therapy of bacterial diseases in adults with diffuse peritonitis acquired on an outpatient basis [10].

According to the German S2k guideline, failure of the previous antibiotic therapy (third criterion of the company for the formation of the subpopulations) is basically suitable to justify meropenem as an option for the calculated therapy. The S2k guideline indicates that a selected pathogen spectrum and a high risk of MRPs can be assumed when previous antibiotic therapy has failed. Overall, failure of previous antibiotic therapy occurred in only few patients: 14.3% of the patients in the PN003 study and 40.0% of the patients in the PN012 study.

There is no further information stating that in the studies the choice of meropenem as a calculated therapy was based on the local pathogen spectrum or the local resistance situation in the respective study centres.

The S2k guideline designates meropenem as an option for the calculated therapy for patients with

- nosocomial (postsurgical/tertiary) diffuse peritonitis with high MRP risk or
- particularly severe disease.

However, the available data show that these criteria presumably also apply to only few patients of the subpopulation in the studies PN003 and PN012.

- Proportion of patients with nosocomial peritonitis

  Data on the proportion of patients with nosocomial peritonitis are missing in both of the studies presented. Diagnoses that might have pointed to a nosocomial peritonitis ("peritonitis due to a perforated hollow organ or after prior surgical intervention" and "traumatic intestinal perforation") only affected 17% of the patients in the PN003 study and 11% of the patients in PN012. For the majority of patients in the studies, the aetiology of the complicated intra-abdominal infection is a spontaneous rupture: For both the total population of PN003 and the subpopulation of PN012, the proportion was more than 70% of the patients. Therefore, these patients more likely had infections acquired on an outpatient basis than nosocomial infections. Only approx. 8% of the patients in the total population of PN003 and 4% of the patients in the subpopulation of PN012 had post-surgical infection or trauma. A nosocomial infection seems likely here.

- Proportion of patients with particularly severe disease

  Patients with an immediately life-threatening disease (including lung failure or septic shock), a shorter life expectancy than the duration of the study and, for example, immunosuppression were excluded from the studies PN003 and PN012.

  In the studies, the APACHE II score [15] was recorded, which can be used for the assessment of the disease severity. The European Medicines Agency (EMA) and the Food and Drug Administration (FDA) describe an APACHE II score of > 15 as a criterion for severe disease [4,5].

  According to the assessment of EMA and FDA, only few severely ill patients were included in the total population of the PN003 study. The assessment of the disease severity was based on the low proportion of patients with an APACHE II score > 10 (approx. 20%) and the low proportion of patients whose infection originated in the small or large bowel (approx. 20%). As a rule, such infections are mixed infections characterised by a high number of pathogens [16]. In the subpopulations presented by the company in Module 4 B, these proportions did not substantially deviate from the data for the total population. The proportion of patients with an APACHE II score ≥ 10 was 22.6% in the subpopulation of study PN003 and 31.1% in study PN012. The proportion of patients with intra-abdominal infection originating in the small or large bowel was 24.8% in the PN003 study and 28.9% in PN012. Bacteraemia, which is also named by the EMA

as an indication of severe disease, occurred in only 1.9% of the patients in the subpopulation of the PN003 study and in none of the patients in PN012.

Overall, the assessments of the regulatory authorities EMA and FDA are in line with that of the S2k guideline, according to which the studies in the therapeutic indication principally include patients with rather mild intra-abdominal infections (APACHE II score approx. 6) [10]. The assessments of EMA and FDA are shared.

Moreover, it is known that 10.4% of the patients in the PN003 study and 35.6% of the patients in the PN012 study had local peritonitis, for which meropenem is clearly not a treatment option according to S2k guidelines.

In both studies, meropenem is overall no treatment option for the calculated therapy according to the S2k guideline for the majority of patients in the subpopulations used by the company due to the disease characteristics of those patients. Based on the G-BA's specification, meropenem is thus no suitable calculated therapy for the patients of the subpopulations in the PN003 and PN012 studies.

***Targeted therapy: meropenem is no adequate implementation of the ACT in the studies presented***

As already described, the guideline recommends the patient to switch to a targeted therapy with the narrowest possible efficacy spectrum (de-escalation) according to pathogen detection and pathogen sensitivity when the antibiogram is available (after approx. 72 hours) [10-14].

Meropenem is a treatment option for a targeted therapy in the presence of *ESBL-forming enterobacterales* (according to the first criterion of the company for the formation of the subpopulation under consideration) or *Pseudomonas spp*. [10]. The studies PN003 and PN012 provide no information on whether treatment switch or de-escalation of the ongoing therapy were possible when an antibiogram was available. Based on the available data, it must rather be assumed that treatment with meropenem was continued even without the detection of ESBL-forming Enterobacterales or *Pseudomonas spp.*, and treatment switch or de-escalation was impossible even when an antibiogram was available, because, for instance, 93.5% of the patients in the total population of PN003 received meropenem over the entire planned treatment period. There is no corresponding information for the PN012 study.

Only few patients in the total population of the studies had ESBL-forming enterobacterales or *Pseudomonas spp.* at baseline. In the PN003 study, ESBL-forming enterobacterales were detected in 7.2% and Pseudomonas aeruginosa (P. aeruginosa) in 8.9% of the patients. In the PN012 study, the percentages were 5.2% (based on 77 patients in the mMITT population with detection of at least 1 pathogen sensitive to at least 1 study drug) and 8.1% each. Moreover, according to the S2k guideline, treatment would have had to be de-escalated if resistant pathogens were not detected in the microbiological examination.

The FDA also commented on the risk of MRPs in the included patients. According to the FDA, the pathogen spectrum at baseline in the total population corresponds to the germ spectrum of

a normal intestinal flora (PN003: 65.1% *Escherichia coli [E. coli]*, 28.1% *Streptococcus spp.*, 9.4% *Klebsiella pneumoniae [K. pneumoniae]*, 8.9% *P. aeruginosa*, 13.8% *Bacteroides fragilis; PN012:* 69.8% *E. coli*, 15.1% *Streptococcus spp*., 10.5% *K. pneumoniae*, 10.5% *Enterococcus faecium*, 8.1% P. aeruginosa) [4]. The FDA's assessment is shared; on the basis of the described pathogen spectrum, it cannot be assumed that the patients had predominantly resistant pathogens.

Overall, it can be derived neither that targeted individual antibiotic therapy was implemented according to the G-BA's specifications and in line with the criteria listed in the guidelines in PN003 and PN012, nor that meropenem represents 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 in adult patients with complicated intra-abdominal infections. This results 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. For the in vitro data, the company presented a separate information retrieval in the Section "Further studies" of Module 4 B:

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 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 called Kresken 2019 in Section 4.3.2.3 of Module 4 B [17]. The statements of the company on this study are based on result tables on in vitro data ("data on file").

The Kresken 2019 study presented by the company is unsuitable for the 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) [18] (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 [19,20]. 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 [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 [21,22].
- 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 "complicated intra-abdominal infections"). 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 complicated intra-abdominal infections | Individual antibiotic therapy[b] under consideration of<br>▪ the local pathogen spectrum,<br>▪ the (local) resistance profile,<br>▪ the risk of infections with MRPs in accordance with the generally accepted state of scientific knowledge,<br>▪ the pathogen sensitivity (if the antibiogram is available). | Added benefit not proven |

a. Presentation of the ACT specified by the G-BA.
b. According to the G-BA, the recommendations for the adequate use of antibiotics have to be considered. The respective approval status of the antibiotics as well as the recommended duration of use depending on the pathogen to be treated have to be considered. If the pathogen is detected, targeted treatment is to be performed in both the comparator and the verum arm.

ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; MRP: multi-resistant pathogen

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.

The reference list contains citations provided by the company in which bibliographical information may be missing.

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