IQWiG Reports – Commission No. A20-28

Ceftolozane/tazobactam (complicated urinary tract 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 Harnwegsinfektionen) – 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 (complicated urinary tract infections) – Benefit assessment according to §35a Social Code Book V

Commissioning agency
Federal Joint Committee

Commission awarded on
17 March 2020

Internal Commission No.
A20-28

Address of publisher
Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
Im Mediapark 8
50670 Köln
Germany

Phone: +49 221 35685-0
Fax: +49 221 35685-1
E-mail: berichte@iqwig.de
Internet: www.iqwig.de

Medical and scientific advice

- Due to the Corona pandemic, no external experts were involved.

IQWiG employees involved in the dossier assessment

- Anne Hüning
- Lars Beckmann
- Charlotte Hecker
- Lisa Junge
- Thomas Kaiser
- Petra Kohlepp
- Sonja Schiller
- Dorothea Sow

Keywords: Ceftolozane, Tazobactam, Urinary Tract Infections, Benefit Assessment

Schlagwörter: Ceftolozan, Tazobactam, Harnwegsinfektionen, Nutzenbewertung

Table of contents

List of tables[2]

Page

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

List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
BLI	beta-lactamase inhibitor
E. coli	*Escherichia coli*
EAU	European Association of Urology
ESBL	extended-spectrum β-lactamase
EUCAST	European Committee on Antimicrobial Susceptibility Testing
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
IV	intravenous
KRINKO	Kommission für Krankenhaushygiene und Infektionsprävention (Commission for Hospital Hygiene and Infection Prevention)
MIC	minimum inhibitory concentration
mMITT	microbiological modified ITT
MRGN	multi-resistant Gram-negative
MRP	multi-resistant pathogen
RCT	randomized controlled trial
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 coronavirus pandemic, the present assessment was conducted without the use of strictly confidential data presented 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 patients with complicated urinary tract infections.

The GB-A's specification of the ACT resulted in the research question presented in Table 2 for the present benefit assessment.

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

Therapeutic indication	**ACT**[a]
Adult patients with complicated urinary tract infections	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 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 claimed that it followed the G-BA's specification and therefore also designated an individual antibiotic therapy as ACT. However, in contrast to this, the company only considered the drug levofloxacin 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 day were used for the derivation of the added benefit.

Results

Assessment of the added benefit

From its information retrieval, the company identified the RCT PN006 and used this study for the benefit assessment.

The study PN006 presented by the company is unsuitable for the assessment of the added benefit of ceftolozane/tazobactam, because this study does not compare ceftolozane/tazobactam with an individual antibiotic therapy corresponding to the G-BA's specification.

Study PN006

PN006 is a randomized, active-controlled, double-blind and multicentre phase 3 study on the comparison of ceftolozane/tazobactam with levofloxacin. The study included adult patients with complicated urinary tract infections or acute pyelonephritis who were hospitalized during the treatment phase. Overall, 1083 patients were randomly assigned to treatment with ceftolozane/tazobactam (N = 543) or levofloxacin (N = 540) in a 1:1 ratio. Randomization was stratified by study centre. The subpopulation of patients with complicated urinary tract infection comprised 116 (ceftolozane/tazobactam arm) or 114 (levofloxacin arm) patients (intention to treat [ITT] subpopulation). 70 or 74 patients of them received the study medication at least once and had at least one detected bacterial pathogen (microbiological modified ITT [mMITT] subpopulation).

Ceftolozane/tazobactam and levofloxacin were administered intravenously at doses of 1500 mg three times daily or at doses of 750 mg once daily.

Primary outcome of the study was the microbiological response at the time of the test for cure.

No implementation of an individual antibiotic therapy in study PN006

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 is available) as ACT.

In the study PN006 used by the company, the drug levofloxacin was used as sole comparator. Below, it is described separately for both the calculated and the targeted therapy why the comparator levofloxacin chosen in the study did not meet the criteria of the ACT for patients with complicated urinary tract infections.

Calculated therapy: levofloxacin is no adequate implementation of the ACT in the study presented

According to the S2k guideline on calculated parenteral initial treatment of bacterial diseases in adults, levofloxacin is only one of several treatment options for the calculated therapy of complicated urinary tract infections. According the G-BA's specification, both the pathogen sensitivity and the regional resistance situation of the expected pathogen spectrum must be taken into account when the drug to be used is chosen. Moreover, for therapy recommendations in the therapeutic indication to be assessed, a distinction must be made between urinary tract infections acquired on an outpatient basis and nosocomial or catheter-associated urinary tract infections.

The data provided by the company do not indicate the proportion of patients with urinary tract infections acquired on an outpatient basis or of those with nosocomial or catheter-associated urinary tract infections, nor whether the study included patients for whom, due to the source of the infection, an antibiotic particularly effective against multi-resistant pathogens was initially indicated.

Moreover, it cannot be inferred from the company's statements that in the PN006 study, levofloxacin was chosen as calculated therapy on the basis of the resistance situations in the respective study centres.

Overall, it cannot be assumed that according to the G-BA's specification levofloxacin is a suitable calculated therapy for the patients included in PN006.

Targeted therapy: levofloxacin is no adequate implementation of the ACT in the study presented

According to the guideline recommendations, treatment should be switched to a targeted therapy with the narrowest possible efficacy spectrum according to pathogen detection and pathogen sensitivity, if the antibiogram is available. However, it is not assumed that such switch took place in the PN006 study after the pathogen detection and the pathogen sensitivity had been available. This is justified below.

- In the comparator arm of the ITT total population, 74% of the patients received their study medication over the entire treatment period, 25% discontinued treatment with the study medication. In 17% of the patients, treatment was discontinued due to the lack of a qualified pathogen detection. Only for 6 patients (1%), the reason for the discontinuation was a lack of efficacy of the medication.
- In the comparator arm of the mMITT total population, a Gram-negative pathogen resistant to levofloxacin was detected in 28% of the patients. For these patients, a change of medication in the comparator arm according to an individual antibiotic therapy would have been reasonable after the pathogen sensitivity had been determined.

- Levofloxacin is no suitable treatment for patients in the comparator arm of the ITT subpopulation with detected infection with extended-spectrum β-lactamase (ESBL)-forming enterobacterales (approx. 19%).
- There is no information on the sensitivity of the isolated pathogens to other drugs that are an option for the targeted therapy of the patients included.

Overall, it can neither be derived that targeted individual antibiotic therapy according to the G-BA's specification and in line with the criteria listed in the guidelines was implemented in PN006, nor that levofloxacin represents such targeted therapy.

Summary

The company presented no suitable data for the assessment of the added benefit of ceftolozane/tazobactam versus the ACT for adult patients with complicated urinary tract infections. 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.

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

Therapeutic indication	ACT[a]	Probability and extent of added benefit
Adult patients with complicated urinary tract infections	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 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 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 patients with complicated urinary tract infections.

The GB-A's specification of the ACT resulted in the research question presented in Table 4 for the present benefit assessment.

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

Therapeutic infection	**ACT**[a]
Adult patients with complicated urinary tract infections	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 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. 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 deviates from the company's approach, which defined no minimum study duration for RCTs in the therapeutic indication.

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 study on the comparison of ceftolozane/tazobactam versus the ACT. Therefore, the company used the RCT PN006 for the benefit assessment [3-5].

The study PN006 presented by the company is unsuitable for the assessment of the added benefit of ceftolozane/tazobactam, because this study does not compare ceftolozane/tazobactam with an individual antibiotic therapy corresponding to the G-BA's specification. The study PN006 is described below and its lack of suitability for the benefit assessment is explained in more detail.

Study PN006

PN006 is a randomized, active-controlled, double-blind and multicentre phase 3 study on the comparison of ceftolozane/tazobactam with levofloxacin. The study included adult patients with complicated urinary tract infections or acute pyelonephritis who were hospitalized during the treatment. Overall, 1083 patients were randomly assigned to treatment with ceftolozane/tazobactam (N = 543) or levofloxacin (N = 540) in a 1:1 ratio. The subpopulation of patients with complicated urinary tract infections comprised 116 (ceftolozane/tazobactam arm) or 114 (levofloxacin arm) patients ITT subpopulation) and thus about 21% of the total study population. 70 or 74 patients of them received the study medication at least once and had at least one detected bacterial pathogen (mMITT subpopulation).

Randomization was stratified by study centre. The majority of the patients (about 75%) were enrolled in Eastern European study centres.

Ceftolozane/tazobactam was administered intravenously in doses of 1500 mg 3 times daily over an infusion period of 60 minutes each, according to the Summary of Product Characteristics (SPC) [6]. Levofloxacin was administered once daily intravenously over 90 minutes at a dosage of 750 mg. Blinding was maintained by placebo infusions.

Primary outcome of the study was the microbiological response at the time of the test for cure.

No implementation of an individual antibiotic therapy in study PN006

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 study PN006 used by the company, the drug levofloxacin was used as sole comparator. The company did not differentiate between calculated and targeted therapy. It justified the suitability of levofloxacin as individual antibiotic therapy with the significance and frequency of the application of fluoroquinolones (and thus also levofloxacin) in the investigated therapeutic indication. Moreover, the company cited the therapy recommendations for the parenteral initial therapy of complicated urinary tract infections acquired on an outpatient basis of the S2k guideline on calculated parenteral initial therapy of bacterial diseases in adults, which also comprise fluoroquinolones.

An antibiotic therapy is usually started as calculated therapy with the aim of covering the assumed pathogen spectrum in the best possible way if a concrete pathogen detection is not yet available. The guidelines distinguish between certain patient populations, e.g. on the basis of the severity of disease, for which they recommend different treatment options for the calculated therapy, whereby the choice of one drug or possibly several drugs should depend on the local pathogen spectrum or the local resistance profile [7-9]. When the antibiogram is available (after approx. 72 hours), the patient's condition and the antibiotic therapy should be re-assessed and, depending on the pathogen detection and the pathogen sensitivity, treatment should be switched to a targeted therapy with the narrowest possible efficacy spectrum (de-escalation) [7-11].

Below, it is described separately for both the calculated and the targeted therapy why the comparator levofloxacin chosen in the study did not meet the criteria of the ACT for patients with complicated urinary tract infections.

Calculated therapy: levofloxacin is no adequate implementation of the ACT in the study presented

According to the S2k guideline [7] levofloxacin is only one of several treatment options for the calculated therapy of complicated urinary tract infections. According the G-BA's specification, both the pathogen sensitivity and the regional resistance situation of the expected pathogen spectrum must be taken into account when the drug to be used is chosen.

Moreover, the S2k guideline differentiates between urinary tract infections acquired on an outpatient basis, those acquired nosocomially and those that are catheter-associated based on the way the infection was acquired. Since patients with nosocomially acquired or catheter-associated urinary tract infections are increasingly affected by multi-resistant pathogens an antibiotic that is also effective against rare and multi-resistant Gram-negative pathogens is recommended [7]. For this purpose, group 3b cephalosporins, including the cephalosporin/beta-lactamase inhibitor (BLI) combinations ceftolozane/tazobactam and ceftazidime/avibactam, or group 4 (cefepime), group 2 or 3 fluoroquinolones (e.g. ciprofloxacin or levofloxacin; local *Escherichia coli* [*E. coli*] resistance is to be considered) and carbapenems of group 1 (imipenem, meropenem) were named according to the S2k guideline. The data provided by the company do not indicate the proportion of patients with urinary tract infections acquired on an outpatient basis or of those with nosocomial or catheter-associated urinary tract infections, nor whether the study included patients for whom, due to the source of the infection, an antibiotic particularly effective against multi-resistant pathogens was initially indicated.

In addition to a differentiated therapy recommendation that takes the acquisition of the infections into account, treatment is also based on the expected pathogen spectrum. According to the S2k guideline, complicated urinary tract infections are mainly caused by *E. coli*. Specifically for this pathogen, the S2k guideline states that high resistance rates, especially in nosocomial infections, limit the use of fluoroquinolones in monotherapy as calculated initial therapy [7]. Regardless of how the infection was acquired (on an outpatient basis or

nosocomially), it can be learned from the SPC of levofloxacin that acquired resistances to levofloxacin may present a problem in *E. coli* infections [12].

Due to the currently high resistance rates e.g. to fluoroquinolones, the guideline of the European Association of Urology (EAU) even generally advises against their administration as calculated therapy for complicated urinary tract infections [9]. Moreover, it cannot be inferred from the company's statements that in the PN006 study, levofloxacin was chosen as calculated therapy on the basis of the resistance situations in the respective study centres. The company did not address the resistance situation in Module 4 C.

Overall, it cannot be assumed that according to the G-BA's specification levofloxacin is a suitable calculated therapy for the patients included in PN006.

Targeted therapy: levofloxacin is no adequate implementation of the ACT in the study 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) [7-11].

According to the inclusion criteria of PN006, a urine culture should be prepared within 24 or 36 hours before the first administration of the study medication (the information varies depending on the source [3,5,13,14]). To continue antibiotic therapy after day 3, a qualifying pathogen detection had to be available. If, as a result of the urine culture, there were resistances to the study medication, the investigators could adjust treatment with the study medication depending on the individual clinical response, according to the publication on the study [3]. The adjustment included treatment discontinuation or addition of, or replacement with, another antibiotic. However, it cannot be assumed that such switch took place in the PN006 study after the pathogen detection and the pathogen sensitivity had been available. This is justified as follows:

- In the comparator arm of the total ITT population, 399 of 540 patients (74%) received their study medication over the entire treatment period; 135 of the 540 patients (25%) discontinued treatment with the study medication, and 6 individuals received no study medication. In 93 patients (17%), treatment was discontinued due to the lack of a qualifying pathogen detection. Only in 6 patients (1%), the reason for the discontinuation was a lack of efficacy of the medication.
- Information on resistances to levofloxacin in the comparator arm are only available for the mMITT total population. In the comparator arm of the mMITT total population, a Gram-negative pathogen resistant to levofloxacin was detected in 104 of 367 patients (28%). For these patients, a change of medication according to an individual antibiotic therapy would have been reasonable after the pathogen sensitivity had been determined. Apparently, this was not often the case, as the rate of patients who discontinued the study medication (except in the absence of pathogen detection) is even lower than the rate of

patients with proof of resistance to levofloxacin. 64 of 144 patients (approx. 44%) of the mMITT subpopulation with complicated urinary tract infections had a pathogen resistant to levofloxacin (no differentiation by study arm and Gram-negative or Gram-positive).

- Moreover, ESBL-forming enterobacterales were detected in 22 of 114 patients (approx. 19%) in the comparator arm of the ITT subpopulation. In case of a suspected complicated urinary tract infection caused by this pathogen, the S2k guideline recommends a cephalosporin/BLI for the parenteral initial therapy, a group 2 carbapenem or, in case of simultaneously suspected pseudomonads, a cephalosporin/BLI or a group 1 carbapenem [7]. There is no indication that corresponding recommendations do not also apply to targeted therapy after detection of these pathogens. Thus, administration of levofloxacin would not present a suitable therapy for patients with ESBL-forming enterobacterales.
- There is no information on the sensitivity of the isolated pathogens to other drugs that are an option for the targeted therapy of the patients included. The company does not discuss in how far a drug other than Levofloxacin would be more suitable depending on the antibiogram. The statements in Module 4 C do not indicate that a treatment switch according to the G-BA and as recommended by guidelines based on an antibiogram was carried out in the study.

Overall, it can neither be derived that targeted individual antibiotic therapy took place in PN006 according to the G-BA's specifications and in line with the criteria listed in the guidelines, nor that levofloxacin represents such therapy.

Limitations in the study conduction

In addition to the lack of implementation of the ACT, the following further limitations result from the study conduction:

Dosage of levofloxacin deviates from the approval

According to the approval, a lower daily dose (500 mg) than in the study is indicated for levofloxacin [12]. In case of treatment with levofloxacin, the S2k guideline recommends the daily dose of 750 mg administered in the PN006 study [7].

Unclear indication for intravenous administration of the study medication for patients

In PN006, patients received ceftolozane/tazobactam and levofloxacin exclusively via intravenous (IV) administration. Whilst ceftolozane/tazobactam is only available for IV administration, levofloxacin can be administered both IV and orally. Initial parenteral antibiotic therapy is usually only indicated in severe clinical courses with general symptoms such as nausea and vomiting, or if sepsis is suspected [7]. The EAU guideline states the necessity of hospitalizing patients due to systemic symptoms as a further criterion for intravenous administration,[9].

Of the patients in the mMITT subpopulation, 19 patients (27%) in the intervention arm and 9 patients (12%) in the comparator arm had nausea or vomiting at baseline. Relevant data on the

proportion of patients of the ITT subpopulation are not available. 1 patient in the ITT subpopulation had bacteraemia at the start of the study. Accordingly, there was an indication for IV administration of the study medication for these patients.

Due to lack of information, it is not possible to assess the severity of the disease in the entire patient population with complicated urinary tract infections at baseline. The included patients were hospitalized during the treatment. However, it is unclear whether the hospitalization was due to the IV administration of the study medication or whether it was necessary due to the existing symptoms. The inclusion criteria of PN006 only describe that IV antibiotic therapy had to be required for the treatment of the suspected complicated urinary tract infection. Further criteria for the indication of an intravenous therapy were not specified, so that it remains unclear whether this necessity would also have existed in the German care context.

2.3.2 Results on added benefit

The company presented no suitable data for the assessment of the added benefit of ceftolozane/tazobactam versus the ACT for patients with complicated urinary tract infections. 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 C, 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 C [13]. 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) [15] (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 [16,17]. 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 [7-9].

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 [18,19].
- 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 urinary tract 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 urinary tract infection	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 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 assessment described above deviates from that of the company, which used the presented RCT to prove an equivalence of the treatment options ceftolozane/tazobactam and levofloxacin and derived an indication of major added benefit for ceftolozane/tazobactam exclusively on the basis of the in vitro data (Kresken 2019).

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.

1. Institute for Quality and Efficiency in Health Care. General methods: version 5.0 [online]. 10.07.2017 [Accessed: 01.07.2019]. URL: https://www.iqwig.de/download/General-Methods_Version-5-0.pdf.

2. Skipka G, Wieseler B, Kaiser T, Thomas S, Bender R, Windeler J et al. Methodological approach to determine minor, considerable, and major treatment effects in the early benefit assessment of new drugs. Biom J 2016; 58(1): 43-58.

3. Wagenlehner FM, Umeh O, Steenbergen JN, Yuan G, Darouiche RO. Ceftolozane-tazobactam compared with levofloxacin in the treatment of complicated urinary-tract infections, including pyelonephritis: a randomised, double-blind, phase 3 trial (ASPECT-cUTI). Lancet 2015; 385(9981): 1949-1956.

4. European Medicines Agency. Zerbaxa: European public assessment report [online]. 23.07.2015 [Accessed: 25.03.2020]. URL: https://www.ema.europa.eu/documents/assessment-report/zerbaxa-epar-public-assessment-report_en.pdf.

5. Food and Drug Administration. Ceftolozane/Tazobactam: application number 206829Orig1s000; medical review(s) [online]. 16.09.2014 [Accessed: 02.04.2020]. URL: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2014/206829Orig1s000MedR.pdf.

6. MSD. Zerbaxa: Fachinformation [online]. 08.2019 [Accessed: 25.03.2020]. URL: https://www.fachinfo.de.

7. Bodmann K-F, Grabein B, Kresken M, Derendorf H, Stahlmann R, Ott SR et al. S2k-Leitlinie Kalkulierte parenterale Initialtherapie bakterieller Erkrankungen bei erwachsenen Patienten: Update 2018 [online]. 25.07.2019. URL: https://www.awmf.org/uploads/tx_szleitlinien/082-006l_S2k_Parenterale_Antibiotika_2019-08.pdf.

8. Dalhoff K, Abele-Horn M, Andreas S, Deja M, Ewig S, Gastmeier P et al. Epidemiologie, Diagnostik und Therapie erwachsener Patienten mit nosokomialer Pneumonie; Update 2017 [online]. URL: https://www.awmf.org/uploads/tx_szleitlinien/020-013l_S3_Nosokomiale_Pneumonie_Erwachsener_2017-11.pdf.

9. Bonkat G, Pickard RS, Bartoletti R, Cai T, Bruyère F, Geerlings SE et al. EAU guidelines on urological infections [online]. URL: https://uroweb.org/wp-content/uploads/EAU-Guidelines-on-Urological-Infections-2018-large-text.pdf.

10. With KD, Wilke K, Kern WV, Strauß R, Kramme E, Friedrichs A et al. S3-Leitlinie: Strategien zur Sicherung rationaler Antibiotika-Anwendung im Krankenhaus; Update 2018 [online]. 31.01.2019. URL: https://www.awmf.org/uploads/tx_szleitlinien/092-001l_S3_Strategien-zur-Sicherung-rationaler-Antibiotika-Anwendung-im-Krankenhaus_2019-04.pdf.

11. Sartelli M, Catena F, Abu-Zidan FM, Ansaloni L, Biffl WL, Boermeester MA et al. Management of intra-abdominal infections. World J Emerg Surg 2017; 12(29).

12. Sanofi-Aventis Deutschland. Fachinformation Tavanic 5 mg/ml Infusionslösung: Stand November 2019 [online]. URL: https://www.lauer-fischer.de.

13. MSD Sharp & Dohme. Ceftolozan/Tazobactam (Zerbaxa): Dossier zur Nutzenbewertung gemäß § 35a SGB V; Modul 4 C; Behandlung von Erwachsenen mit komplizierten Harnwegsinfektionen; medizinischer Nutzen und medizinischer Zusatznutzen; Patientengruppen mit therapeutisch bedeutsamem Zusatznutzen. [Soon available under: https://www.g-ba.de/bewertungsverfahren/nutzenbewertung/538/].

14. Cubist Pharmaceuticals. Study comparing the safety and efficacy of intravenous CXA-201 and intravenous levofloxacin in complicated urinary tract infection, including pyelonephritis [online]. 25.10.2018. URL: https://ClinicalTrials.gov/show/NCT01345929.

15. Kommission für Krankenhaushygiene und Infektionsprävention beim Robert Koch-Institut. Hygienemaßnahmen bei Infektionen oder Besiedlung mit multiresistenten gramnegativen Stäbchen. Bundesgesundheitsbl Gesundheitsforsch Gesundheitsschutz 2012; 55: 1311-1354.

16. Rothery C, Woods B, Schmitt L, Claxton K, Palmer S, Sculpher M. Framework for value assessment of new antimicrobials: implications of alternative funding arrangements for NICE appraisal [online]. 09.2018 [Accessed: 27.05.2020]. URL: http://www.eepru.org.uk/wp-content/uploads/2017/11/eepru-report-amr-oct-2018-059.pdf.

17. Doern GV, Brecher SM. The clinical predictive value (or lack thereof) of the results of in vitro antimicrobial susceptibility tests. J Clin Microbiol 2011; 49(9 Suppl): 11-14.

18. Sun W, Weingarten RA, Xu M, Southall N, Dai S, Shinn P et al. Rapid antimicrobial susceptibility test for identification of new therapeutics and drug combinations against multidrug-resistant bacteria. Emerg Microbes Infect 2016; 5(11): e116.

19. Huang L, Wang M, Sun L. Synergy testing by E-test and microdilution checkerboard for fosfomycin combined with tigecycline against KPC-Producing Klebsiella pneumoniae. Clin Lab 2019; 65(12): 2369-2375.

The full report (German version) is published under https://www.iqwig.de/en/projects/a20-28.html.