IQWiG Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen

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Carfilzomib (multiple myeloma) –

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

Extract

[1] Translation of Sections 2.1 to 2.6 of the dossier assessment *Carfilzomib (multiples Myelom) – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 13 November 2017). 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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[3] Table numbers start with “2” as numbering follows that of the full dossier assessment.

List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
CTCAE	Common Terminology Criteria for Adverse Events
ECOG	Eastern Cooperative Oncology Group
EORTC	European Organisation for Research and Treatment of Cancer
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IMiD	immunomodulatory drug
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
ISS	International Staging System
MID	minimally important difference
PFS	progression-free survival
PT	Preferred Term
QLQ-C30	Quality of Life Questionnaire-Core 30
QLQ-MY20	Quality of Life Questionnaire-Multiple Myeloma Module 20
RCT	randomized controlled trial
SAE	serious adverse event
SGB	Sozialgesetzbuch (Social Code Book)
SOC	System Organ Class
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 carfilzomib. 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 15 August 2017.

Research question

The aim of the present report was to assess the added benefit of carfilzomib in combination with either lenalidomide and dexamethasone or dexamethasone alone in comparison with the appropriate comparator therapy (ACT) for the treatment of adult patients with multiple myeloma who have received at least 1 prior therapy.

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 carfilzomib

Research question	Therapeutic indication	ACT[a, b]
1	Adult patients with multiple myeloma who have received at least 1 prior therapy[c]	Bortezomib in combination with pegylated liposomal doxorubicin or **bortezomib in combination with dexamethasone** or **lenalidomide in combination with dexamethasone** or elotuzumab in combination with lenalidomide and dexamethasone
a: Presentation of the respective ACT specified by the G-BA. In cases where the company, because of the G-BA's specification of the ACT, could choose a comparator therapy from several options, the respective choice of the company is printed in **bold**. b: It is assumed for the present therapeutic indication that the use of carfilzomib is conducted in the framework of a remission-inducing induction treatment. High-dose chemotherapy with stem cell transplantation, which may be a subsequent treatment option, is therefore not an option as part of the ACT. c: According to the approval, carfilzomib is used in combination with either lenalidomide and dexamethasone or dexamethasone alone. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee		

The company chose lenalidomide in combination with dexamethasone and bortezomib in combination with dexamethasone as ACT. It thus generally followed the specification of the G-BA. Deviations had no consequence for the present benefit assessment.

The assessment was conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier.

Results

Study pool and study characteristics

The studies ASPIRE und ENDEAVOR presented by the company were principally relevant for the benefit assessment of carfilzomib in comparison with the ACT. Both studies were ongoing, open-label, randomized controlled trials (RCTs) including adult patients with multiple myeloma with a minimum of 1 and a maximum of 3 prior therapies.

Only the ASPIRE study was included in the present benefit assessment. The analyses presented by the company on the total population of the ENDEAVOR study were not used. This is justified below.

Study ENDEAVOR

The ENDEAVOR study compared carfilzomib + dexamethasone with bortezomib + dexamethasone. 464 patients were randomized to the carfilzomib arm, and 465 patients to the bortezomib arm. The dosages of the substances used in both study arms were in compliance with the approval of carfilzomib and bortezomib.

Suitability of the total population in the ENDEAVOR study for the benefit assessment unclear

Bortezomib is approved for patients with multiple myeloma who have received at least 1 prior therapy and who have already undergone or are unsuitable for haematopoietic stem cell transplantation. Before the start of the ENDEAVOR study, about 58% of the patients included had received stem cell transplantation and were therefore candidates for treatment with bortezomib. For the remaining approximately 42% of the patients included, it was not clear from the study documents whether and how many of these patients were actually unsuitable for stem cell transplantation.

Since it has not been clarified whether and how many patients without prior stem cell transplantation were actually unsuitable for this treatment, and since, in addition, the company did not address this problem at all in the dossier, the analyses presented by the company on the total population of the ENDEAVOR study were not used for the present benefit assessment.

Further limitation regarding the use of bortezomib

According to the Summary of Product Characteristics (SPC), pretreated patients achieving a response or a stable disease after 4 cycles of therapy with bortezomib + dexamethasone can continue to receive the same combination for a maximum of 4 additional cycles. In the ENDEAVOR study, however, it was possible to continue treatment with bortezomib + dexamethasone for longer than 8 cycles. No information was available regarding efficacy and safety of prolonged administration of bortezomib in the treatment regimen used.

Assessment of the ASPIRE study

The ASPIRE study compared a combination of carfilzomib + lenalidomide + dexamethasone with lenalidomide + dexamethasone. 396 pretreated patients with relapsed or progressive multiple myeloma were randomized to the carfilzomib arm and 396 patients to the comparator arm. The individual substances in the carfilzomib arm were used in compliance with the SPC on carfilzomib. In the comparator arm, the dosage of dexamethasone in combination with lenalidomide deviated considerably from the dosage recommended for pretreated patients in the SPC on lenalidomide. The specific handling of this issue is described below.

Treatment in both study arms was conducted in 28-day cycles until disease progression or occurrence of unacceptable toxicity. After discontinuation of the randomized study medication, subsequent therapies could be administered in both treatment arms.

The primary outcome of the study was progression-free survival (PFS). Further patient-relevant outcomes were overall survival, symptoms, health-related quality of life and adverse events (AEs).

Handling of the fact that dexamethasone was not used in compliance with the approval in the comparator arm of the ASPIRE study

A dexamethasone dosage deviating from the approval was used in the comparator arm of the ASPIRE study. The adequacy of this deviating dosing regimen is at least questionable. The same situation occurred in a study (ELOQUENT-2) in the benefit assessment of elotuzumab in the same therapeutic indication because the same dosing regimen of dexamethasone deviating from the approval was also used in the comparator arm of this study. The G-BA used this study because it considered there to be “a medical reason in the specific treatment and health care situation in the present therapeutic indication, providing the exceptional justification to use the data from the ELOQUENT-2 study to allow a benefit assessment of elotuzumab.” With reference to the G-BA’s decision and justification on elotuzumab, the ASPIRE study was included in the present benefit assessment in the present therapeutic indication despite the fact that the dosage of dexamethasone used in the comparator arm deviated from the approval.

Risk of bias at study level and outcome level

The risk of bias at study level for the ASPIRE study was rated as high. This was due to possible selective reporting. The main cause for this was that, with its dossier, the company only presented analyses on selected subscales of the questionnaires European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire-Core 30 (QLQ-C30) and Quality of Life Questionnaire-Multiple Myeloma Module 20 (QLQ-MY20), which were recorded completely in the study.

Correspondingly, the risk of bias at outcome level was also rated as high for all outcomes.

Non-usable data on morbidity, health-related quality of life and side effects (serious AEs [SAEs] and severe AEs)

Overall, no usable data were available for the outcomes "symptoms" and "health-related quality of life". With the dossier, the company only presented analyses on selected subscales of the questionnaires EORTC QLQ-C30 and QLQ-MY20, which were recorded completely in the study. These were not used for the benefit assessment because selective reporting was possible. No usable analyses were available for the outcomes "SAEs", "severe AEs (Common Terminology Criteria for Adverse Events [CTCAE] grade ≥ 3)" and "specific AEs", either, because the analyses presented by the company did not adequately consider the different median observation durations in the study arms of the ASPIRE study (carfilzomib arm: 88 weeks; comparator arm: 57 weeks).

Results

Mortality

A statistically significant difference in favour of carfilzomib + lenalidomide + dexamethasone in comparison with lenalidomide + dexamethasone was shown for the outcome "overall survival". In addition, there was a relevant effect modification by the characteristic "age" for this outcome. This resulted in a hint of an added benefit for the outcome "overall survival" for patients < 65 years of age. There was no hint of an added benefit of carfilzomib + lenalidomide + dexamethasone in comparison with lenalidomide + dexamethasone for older patients; an added benefit is not proven for these patients.

Morbidity, health-related quality of life, side effects – SAEs, severe AEs – CTCAE grade ≥ 3

As described above, no usable data were available for these outcomes.

This resulted in no hint of an added benefit of carfilzomib + lenalidomide + dexamethasone in comparison with lenalidomide + dexamethasone for these outcomes; an added benefit for these outcomes is therefore not proven.

Side effects – discontinuation due to AEs

No statistically significant difference between the treatment arms was shown for the outcome "discontinuation due to AEs", both for discontinuation of at least 1 study medication and for discontinuation of the total study medication. This resulted in no hint of greater or lesser harm from carfilzomib + lenalidomide + dexamethasone in comparison with lenalidomide + dexamethasone; greater or lesser harm is therefore not proven for this outcome.

Side effects – specific AEs

The company presented different AEs of particular interest (CTCAE grade ≥ 3). Since the analyses presented by the company on the basis of the incidence density ratio were inadequate in the present data situation, and, in addition, the company did not present a complete overview of all AEs at System Organ Class (SOC) and Preferred Term (PT) level, it was not possible to choose specific AEs.

Probability and extent of added benefit, patient groups with therapeutically important added benefit[4]

On the basis of the results presented, the probability and the extent of the added benefit of the drug carfilzomib compared with the ACT is assessed as follows:

The overall consideration of the usable data showed a positive effect of carfilzomib + lenalidomide + dexamethasone. For patients < 65 years of age, a hint of a considerable added benefit of carfilzomib + lenalidomide + dexamethasone versus lenalidomide + dexamethasone was shown in the outcome "overall survival". This positive effect was accompanied by pronounced uncertainties in the other outcome categories. The company only submitted selective data on the outcomes "symptoms" and "health-related quality of life" with the dossier. The company did not provide an adequate justification for this approach. Due the possible presence of selective reporting, the results on these outcomes in their totality were not interpretable. Hence, at most hints of an added benefit could be derived from the ASPIRE study. The company did not present adequate analyses for SAEs and severe AEs for the outcome category "side effects"; an assessment for this outcome category was therefore not possible. Greater harm from carfilzomib is possible, particularly considering the higher event rates for SAEs and severe AEs under carfilzomib + lenalidomide + dexamethasone.

For patients < 65 years of age, the present uncertainties overall did not result in completely questioning the considerable survival advantage of carfilzomib + lenalidomide + dexamethasone. Against the background of the uninterpretability of the side effect profile, the extent of added benefit was rated as non-quantifiable, however. Overall, this resulted in a hint of a non-quantifiable added benefit for these patients.

There was no survival advantage for patients ≥ 65 years of age. Overall, an added benefit for these patients is not proven. However, greater harm of carfilzomib + lenalidomide + dexamethasone, particularly regarding AEs, is possible.

No usable data were available for the combination of carfilzomib with dexamethasone.

Table 3 presents a summary of the probability and extent of the added benefit of carfilzomib.

[4] 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, no added benefit, or less benefit). For further details see [1,2].

Table 3: Carfilzomib – probability and extent of added benefit

Therapeutic indication	**ACT**[a, b]	**Extent and probability of added benefit**
Adult patients with multiple myeloma who have received at least 1 prior therapy[c]	Bortezomib in combination with pegylated liposomal doxorubicin or **bortezomib in combination with dexamethasone** or **lenalidomide in combination with dexamethasone** or elotuzumab in combination with lenalidomide and dexamethasone	In combination with lenalidomide and dexamethasone: ▪ patients < 65 years: hint of a non-quantifiable added benefit ▪ patients ≥ 65 years: added benefit not proven[d] In combination with dexamethasone: ▪ added benefit not proven

a: Presentation of the respective ACT specified by the G-BA. In cases where the company, because of the G-BA's specification of the ACT, could choose a comparator therapy from several options, the respective choice of the company is printed in **bold**.
b: It is assumed for the present therapeutic indication that the use of carfilzomib in combination with lenalidomide and dexamethasone or in combination with dexamethasone alone is conducted in the framework of a remission-inducing induction treatment. High-dose chemotherapy with stem cell transplantation, which may be a subsequent treatment option, is therefore not an option as part of the ACT.
c: According to the approval, carfilzomib is used in combination with either lenalidomide and dexamethasone or dexamethasone alone.
d: Greater harm, particularly regarding AEs, is possible.
ACT: appropriate comparator therapy; G-BA: Federal Joint Committee

The G-BA decides on the added benefit.

Supplementary note

The result of the assessment deviates from the results of the G-BA assessments both in the framework of the market entry in 2015 (carfilzomib + lenalidomide + dexamethasone) and of the new therapeutic indication from 2016 (carfilzomib + dexamethasone). In these assessments, the G-BA had derived a non-quantifiable added benefit for the combination of carfilzomib + lenalidomide + dexamethasone. This was based on the then pending final analyses on overall survival, which is why the decision was limited until 31 December 2017. The G-BA had derived a minor added benefit for the combination of carfilzomib + dexamethasone. In these assessments, the added benefit had been regarded as proven by the approval because of the special situation for orphan drugs, irrespective of the underlying data.

2.2 Research question

The aim of the present report was to assess the added benefit of carfilzomib in combination with either lenalidomide and dexamethasone or dexamethasone alone in comparison with the ACT for the treatment of adult patients with multiple myeloma who have received at least 1 prior therapy.

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 carfilzomib

Research question	**Therapeutic indication**	**ACT**[a, b]
1	Adult patients with multiple myeloma who have received at least 1 prior therapy[c]	Bortezomib in combination with pegylated liposomal doxorubicin or **bortezomib in combination with dexamethasone** or **lenalidomide in combination with dexamethasone** or elotuzumab in combination with lenalidomide and dexamethasone
a: Presentation of the respective ACT specified by the G-BA. In cases where the company, because of the G-BA's specification of the ACT, could choose a comparator therapy from several options, the respective choice of the company is printed in **bold**. b: It is assumed for the present therapeutic indication that the use of carfilzomib is conducted in the framework of a remission-inducing induction treatment. High-dose chemotherapy with stem cell transplantation, which may be a subsequent treatment option, is therefore not an option as part of the ACT. c: According to the approval, carfilzomib is used in combination with either lenalidomide and dexamethasone or dexamethasone alone. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee		

The company chose lenalidomide in combination with dexamethasone and bortezomib in combination with dexamethasone as ACT. It thus generally followed the specification of the G-BA. Deviations had no consequence for the present benefit assessment (see Section 2.7.1 of the full dossier assessment).

The assessment was conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier.

2.3 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 carfilzomib (status: 23 May 2017)
- bibliographical literature search on carfilzomib (last search on 23 May 2017)
- search in trial registries for studies on carfilzomib (last search on 23 May 2017)

To check the completeness of the study pool:

- search in trial registries for studies on carfilzomib (last search on 25 August 2017)

The check identified no additional relevant study.

2.3.1 Studies included

The studies listed in the following Table 5 were relevant for the benefit assessment.

Table 5: Study pool – RCT, direct comparison

Study	Study category		
	Study for approval of the drug to be assessed (yes/no)	Sponsored study[a] (yes/no)	Third-party study (yes/no)
Carfilzomib + lenalidomide + dexamethasone vs. lenalidomide + dexamethasone			
ASPIRE	Yes	Yes	No
Carfilzomib + dexamethasone vs. bortezomib + dexamethasone			
ENDEAVOR	Yes	Yes	No
a: Study for which the company was sponsor. RCT: randomized controlled trial; vs.: versus			

The ASPIRE study compared a combination of carfilzomib + lenalidomide + dexamethasone with lenalidomide + dexamethasone. The ENDEAVOR study compared the combination of carfilzomib + dexamethasone with bortezomib + dexamethasone. Both studies presented were generally relevant for the benefit assessment. Hence the study pool concurred with the one of the company.

However, the analyses presented by the company for the total population of the ENDEAVOR study could not be used for the present benefit assessment. This is justified below.

Description of the ENDEAVOR study

The ENDEAVOR study [3-9] is an ongoing, open-label RCT on the comparison of carfilzomib + dexamethasone with bortezomib + dexamethasone in adult patients with

relapsed or progressive multiple myeloma who have received at least 1 and at most 3 prior therapies. A total of 929 patients were randomized: 464 patients to the carfilzomib arm and 465 patients to the bortezomib arm. The dosages of the substances used in both study arms were in compliance with the approval of carfilzomib [10] and bortezomib [11].

Further information on the characteristics of the study and of the interventions of the ENDEAVOR study are presented in Appendix A of the full dossier assessment.

Suitability of the total population in the ENDEAVOR study for the benefit assessment unclear

Bortezomib is approved for patients with multiple myeloma who have received at least 1 prior therapy and who have already undergone or are unsuitable for haematopoietic stem cell transplantation [11]. Before the start of the ENDEAVOR study, about 58% of the patients included had received stem cell transplantation and were therefore candidates for treatment with bortezomib. For the remaining approximately 42% of the patients included, it was not clear from the study documents whether and how many of these patients were actually unsuitable for stem cell transplantation:

- Prior stem cell transplantation or non-eligibility for it was no criterion for inclusion in the ENDEAVOR study.
- The company did not provide reasons for the patients' non-eligibility for stem cell transplantation. Instead, the company did not address this problem at all in the dossier, although the limitation of the patient population regarding stem cell transplantation is clearly described in the SPC of bortezomib [11].
- The company did not present sufficient subgroup analyses for the characteristic of prior stem cell transplantation in the dossier. It was therefore not possible to assess the subpopulation with prior stem cell transplantation, which is comprised by the approval of bortezomib. Likewise, characteristics of the patients who had not yet received stem cell transplantation were therefore not available, either. This kind of information might have allowed an assessment concerning the non-eligibility for this therapy.

Since it has not been clarified whether and how many patients without prior stem cell transplantation were actually unsuitable for this treatment, and since, in addition, the company did not address this problem at all in the dossier, the analyses presented by the company on the total population of the ENDEAVOR study were not used for the present benefit assessment.

Further limitation regarding the use of bortezomib

According to the SPC [11], pretreated patients achieving a response or a stable disease after 4 cycles of therapy with bortezomib + dexamethasone can continue to receive the same combination for a maximum of 4 additional cycles. In the ENDEAVOR study, however, it was possible to continue treatment with bortezomib + dexamethasone for longer than

8 cycles. Treatment was stopped due to disease progression, unacceptable toxicity, physician's decision, death, or withdrawal of consent. The median number of cycles was 8 in the bortezomib arm, but at the time point of the second data cut-off in cycle 12, 154 of 456 (33.8%) patients of the safety population, and thus a relevant proportion, were still under bortezomib treatment.

The company described that both regimens were given until progression, occurrence of unacceptable side effects, withdrawal of consent, or death, in order to increase efficacy of the treatment regimens and ensure comparability of both study arms. The company cited various additional studies [12-16] to support this requirement for bortezomib + dexamethasone. The company's rationale was not followed. Furthermore, none of the publications cited by the company compared bortezomib + dexamethasone treatment for longer than the maximum number of treatment cycles versus approval-compliant administration. Hence no conclusions could be derived regarding efficacy and safety of prolonged bortezomib administration and it remained unclear whether this treatment with bortezomib caused bias to the study results in favour of carfilzomib.

Summary

The data presented by the company for adults with multiple myeloma who have received at least 1 prior therapy therefore allowed no conclusions on the added benefit of carfilzomib + dexamethasone in comparison with the ACT. The ASPIRE study was used for the assessment of the added benefit of carfilzomib + lenalidomide + dexamethasone in comparison with the ACT.

Section 2.6 contains a reference list for the ASPIRE study included.

2.3.2 Study characteristics of the ASPIRE study

Table 6 and Table 7 describe the ASPIRE study used for the benefit assessment.

Table 6: Characteristics of the study included – RCT, direct comparison: carfilzomib + lenalidomide + dexamethasone vs. lenalidomide + dexamethasone

Study	Study design	Population	Interventions (numbers of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
ASPIRE	RCT, open-label, parallel	Adult patients (≥ 18 years) with multiple myeloma with 1–3 prior therapies, documented relapse or disease progression on or after prior therapy[b], and ECOG PS 0–2	Carfilzomib + lenalidomide + dexamethasone (N = 396) Lenalidomide + dexamethasone (N = 396)	Screening: ≤ 21 days before randomization Treatment: until disease progression or occurrence of unacceptable toxicity (at most 18 cycles for carfilzomib) Observation: outcome-specific, at most until death, end of study, or withdrawal of consent	129 centres in Canada, Europe, Israel, Russia, USA 7/2010–ongoing First data cut-off: 16 June 2014 Second data cut-off: 28 April 2017	Primary: PFS Secondary: overall survival, health-related quality of life, symptoms, AEs

a: Primary outcomes include information without consideration of its relevance for this benefit assessment. Secondary outcomes exclusively include information on the relevant available outcomes for this benefit assessment.
b: Inclusion of patients with refractoriness to the last line of treatment allowed.
AE: adverse event; ECOG PS: Eastern Cooperative Oncology Group Performance Status; N: number of randomized (included) patients; PFS: progression-free survival; RCT: randomized controlled trial; vs.: versus

Table 7: Characteristics of the intervention – RCT, direct comparison: carfilzomib + lenalidomide + dexamethasone vs. lenalidomide + dexamethasone

Study	Intervention	Comparison
ASPIRE	Carfilzomib ▪ cycle 1: 20 mg/m² body surface area IV on days 1 and 2, and 27 mg/m² IV on days 8, 9, 15 and 16; ▪ cycles 2–12: 27 mg/m² IV on days 1, 2, 8, 9, 15 and 16; ▪ cycles 13–18: 27 mg/m² IV on days 1, 2, 15 and 16 + lenalidomide 25 mg/day, orally, on days 1–21 of each cycle[a] + dexamethasone 40 mg/day, orally or IV, on days 1, 8, 15 and 22 of each cycle[a] length of cycle: 28 days	Lenalidomide 25 mg/day, orally, on days 1–21 of each cycle + dexamethasone 40 mg/day, orally or IV, on days 1, 8, 15 and 22 of each cycle length of cycle: 28 days
	Dose adjustments:	
	Carfilzomib: according to the SPC possible, additional dose reduction to 11 mg/m² allowed Lenalidomide: according to the SPC allowed Dexamethasone: dose reduction or discontinuation allowed in case of toxicity	
	Pretreatment: ▪ Pretreatment with lenalidomide + dexamethasone was only allowed if the following criteria were met: no progression within the first 3 months after initiation of treatment; no progression during the most recent prior therapy. ▪ Pretreatment with bortezomib (alone or in the framework of a combination therapy) was only allowed if no progression occurred during the treatment. ▪ Not permitted: carfilzomib; chemotherapy within 6 weeks before randomization; radiotherapy to multiple sites; corticosteroids at a dosage equivalent to dexamethasone > 4 mg/day **Concomitant treatment** **Required:** ▪ ciprofloxacin[b] 500 mg/day, orally, in cycle 1 ▪ valaciclovir[b]: 500 mg/day, orally ▪ lansoprazole[b]: 15 mg/day, orally ▪ thrombosis prophylaxis, e.g. acetylsalicylic acid in the respective standard dosage ▪ Patients with a history of deep vein thrombosis: warfarin or low molecular weight heparin **Not allowed:** ▪ further cancer treatment ▪ corticosteroids for the use in non-malignant disease	

a: After cycle 18, further administration without carfilzomib: at the physician's decision, administration of comparable antibiotics such as fluoroquinolone or amoxicillin is also possible.
b: Or comparable substance.
IV: intravenous; RCT: randomized controlled trial; SPC: Summary of Product Characteristics; vs.: versus

Study design

The ASPIRE study is an ongoing, open-label RCT.

The study included adult patients with relapsed or progressive multiple myeloma who have received at least 1 and at most 3 prior therapies. In addition, the patients were required to have an Eastern Cooperative Oncology Group (ECOG) Performance Status of 0, 1 or 2 and were not allowed to have progressed under previous treatment with bortezomib and/or lenalidomide if this was the most recent line of treatment. Treatment-refractory patients could be included in the study if the refractoriness referred to the most recent line of treatment. Hence no data were available for patients with more than 3 prior therapies and patients with refractoriness to earlier lines of treatment.

The patients were stratified by prior lenalidomide and bortezomib therapy (in each case yes, no) and beta-2 microglobulin levels (< 2.5 mg/L, ≥ 2.5 mg/L). A total of 792 patients were randomized, 396 patients to the carfilzomib arm and 396 patients to the comparator arm.

The primary outcome of the study was PFS. Further patient-relevant outcomes were overall survival, symptoms, health-related quality of life and AEs.

The individual substances in the carfilzomib arm were used in compliance with the SPC on carfilzomib [10]. If treatment was conducted for longer than 18 cycles, carfilzomib was discontinued; hence only lenalidomide and dexamethasone were administered in the subsequent cycles. In the comparator arm, the dosage of dexamethasone in combination with lenalidomide deviated considerably from the dosage recommended for pretreated patients in the SPC on lenalidomide [17]. The specific handling of this issue is described below.

Treatment in both study arms was conducted in 28-day cycles until disease progression or occurrence of unacceptable toxicity. After discontinuation of the randomized study medication, subsequent therapies could be administered in both treatment arms. It was not clear from the study documents whether there were limitations regarding the subsequent therapy. At the time point of the second data cut-off (28 April 2017), the proportion of patients with subsequent therapy was 53.3% in the comparator arm and 46.0% in the intervention arm. At this time point, 8 patients (2.0%) from the comparator arm had initiated subsequent therapy with carfilzomib.

Handling of the fact that dexamethasone was not used in compliance with the approval in the comparator arm of the ASPIRE study

The dosing regimen of dexamethasone used in the comparator arm of the ASPIRE study deviated from the recommendations of the SPC of lenalidomide [17], which describes the approved dosing regimen of the combination partner dexamethasone in the present therapeutic indication. Table 8 compares the approval-compliant dosage of dexamethasone with the dosage given in the comparator arm of the ASPIRE study.

Table 8: Comparison of the approval-compliant dexamethasone dosage with the dexamethasone dosage given in the ASPIRE study

Dexamethasone dosage	**Cycle[a] 1–4**				**From cycle[a] 5**			
According to the approval [17][b]	**Cycle day**							
	1–4	**9–12**	**17-20**		**1–4**	**9–12**	**17–20**	
Daily dose (mg)	40	40	40		40	–	–	
Total dose per cycle[a] (mg)	480 (pulse administration)				160 (pulse administration)			
In the comparator arm of the ASPIRE study	**Cycle day**							
	1	**8**	**15**	**22**	**1**	**8**	**15**	**22**
Daily dose (mg)	40	40	40	40	40	40	40	40
Total dose per cycle[a] (mg)	160 (non-pulse administration)				160 (non-pulse administration)			

a: 28-day cycle.
b: In combination with lenalidomide in patients with multiple myeloma with at least 1 prior therapy.
–: no dexamethasone given

Hence the dosage regimen of dexamethasone used in the ASPIRE study deviated from the dosing regimen described in the SPC of lenalidomide [17] both in the dose per cycle and due to the missing pulse administration. The dosing regimen of dexamethasone in the comparator arm of the ASPIRE study therefore did not comply with the approval because the SPC of lenalidomide was decisive for this arm.

From the company's point of view, the dosage of dexamethasone used in the ASPIRE study in combination with lenalidomide adequately reflects the ACT and concurs with German everyday health care. The company referred to the G-BA decisions on elotuzumab [18,19] and on the combination of carfilzomib + lenalidomide + dexamethasone [20,21]. According to the company, this was also supported by a study investigating treatment of patients with multiple myeloma in Germany: The most common treatment in pretreated patients, which was consistently used across all cycles, was lenalidomide in combination with low-dose dexamethasone [22].

The adequacy of this deviating dosing regimen is at least questionable. It cannot be inferred from the decision on carfilzomib cited by the company or from the study presented that a lower dosage of dexamethasone is generally to be used in pretreated multiple myeloma.

The same situation as in the ASPIRE study occurred in the ELOQUENT-2 study submitted for the benefit assessment of elotuzumab. The dexamethasone dosing regimen deviating from the approval, which is described in Table 8, was also used in the comparator arm of this study. Nonetheless, the G-BA had used the study for the benefit assessment. In the justification [19] on the decision, the G-BA explained that the dexamethasone dosage prescribed in the SPC on lenalidomide was no longer used regularly in German everyday health care. Against this background, the G-BA considered there to be "a medical reason in the specific treatment and health care situation in the present therapeutic indication, providing the exceptional

justification to use the data from the ELOQUENT-2 study to allow a benefit assessment of elotuzumab" [19]. At the same time, the G-BA noted that, "insofar as the dexamethasone dosage used in this study as a comparison was not used in compliance with the SPC, […] no conclusions could be derived regarding the appropriateness in this therapeutic indication [19].

This had the consequence for the present benefit assessment that, with reference to the G-BA's decision and justification on elotuzumab, the ASPIRE study was considered in the present benefit assessment despite the fact that the dosage of dexamethasone used in the comparator arm deviated from the approval.

Data cut-offs

Analyses on 2 data cut-offs were available for the ASPIRE study:

- first data cut-off (16 June 2014): final analysis of the primary outcome "PFS" (planned after 526 progression events)
- second data cut-off (28 April 2017): final analysis of the outcome "overall survival" (planned after 510 deaths)

For the present benefit assessment, analyses on both data cut-offs were available for the outcome categories "mortality" and "side effects". The data of the most recent data cut-off were used for these outcomes for the benefit assessment. For the outcomes on morbidity and health-related quality of life, only results of the first data cut-off from 16 June 2014 were available. It can be inferred from the study documents that the questionnaires used for these outcomes (EORTC QLQ-C30 and QLQ-MY20) were no longer to be completed after the first data cut-off. For this reason, the results of the first data cut-off were used for the outcomes on morbidity and health-related quality of life.

Planned duration of follow-up

Table 9 shows the planned duration of follow-up of the patients for the individual outcomes.

Table 9: Planned duration of follow-up – RCT, direct comparison: carfilzomib + lenalidomide + dexamethasone vs. lenalidomide + dexamethasone

Study **Outcome category** **Outcome**	**Planned follow-up**
ASPIRE	
Mortality	
Overall survival	After treatment discontinuation (except due to progression): every 3 months until progression for up to 1 year, then every 6 months until progression or death; after progression: every 3 months for up to 1 year, then every 6 months until death, end of study, or withdrawal of consent
Morbidity	
Symptoms (EORTC QLQ-C30 and EORTC QLQ-MY20)	Up to 30 days after the last dose of the study medication or initiation of further myeloma treatment
Health-related quality of life (EORTC QLQ-C30 and EORTC QLQ-MY20)	Up to 30 days after the last dose of the study medication or initiation of further myeloma treatment
Side effects	Up to 30 days after the last dose of the study medication or initiation of further myeloma treatment
EORTC: European Organisation for Research and Treatment of Cancer; QLQ-C30: Quality of Life Questionnaire Core-30; QLQ-MY20: Quality of Life Questionnaire-Multiple Myeloma Module 20; RCT: randomized controlled trial; vs.: versus	

Only the outcome “overall survival” was recorded until the end of study participation.

The observation periods for the outcomes “morbidity”, “health-related quality of life” and “side effects” were systematically shortened because they were only recorded for the time period of treatment with the study medication (plus 30 days). To be able to draw a reliable conclusion on the total study period or the time until death of the patients, it would be necessary, however, to record these outcomes over the total period of time, as was the case for overall survival.

Characteristics of the study populations

Table 10 shows the characteristics of the patients in the study included.

Table 10: Characteristics of the study population – RCT, direct comparison: carfilzomib + lenalidomide + dexamethasone vs. lenalidomide + dexamethasone

Study Characteristics Category	**Carfilzomib + lenalidomide + dexamethasone**	**Lenalidomide + dexamethasone**
ASPIRE	N[a] = 396	N[a] = 396
Age [years], mean (SD)	63 (9)	65 (9)
Sex [F/M], %	46/54	41/59
Ethnic origin, n (%)		
White	377 (95.2)	377 (95.2)
Non-white	12 (3.0)	11 (2.8)
Other	7 (1.8)[b]	8 (2.1)[c]
ECOG PS, n (%)		
0	165 (41.7)	175 (44.2)
1	191 (48.2)	186 (47.0)
2	40 (10.1)	35 (8.8)
Type of myeloma, n (%)		
IgG	275 (69.4)	281 (71.0)
IgA	85 (21.5)	86 (21.7)
IgD	2 (0.5)	1 (0.3)
IgE	0 (0)	1 (0.3)
IgG IgA	1 (0.3)	0 (0)
Undetected	33 (8.3)	27 (6.8)
ISS stage at first diagnosis, n (%)		
I	64 (16.2)	74 (18.7)
II	99 (25.0)	94 (23.7)
III	185 (46.7)	161 (40.7)
Unknown	48 (12.1)	67 (16.9)
Disease duration: time between first diagnosis and randomization [years], median [min; max]	3.0 [0.4; 19.7]	3.2 [0.5; 27.3]
Prior therapies, n (%)[d]		
Systemic treatment	396 (100.0)	396 (100.0)
Stem cell therapy	217 (54.8)	229 (57.8)
Radiation	79 (19.9)	90 (22.7)
Bortezomib	261 (65.9)	260 (65.7)
IMiD	233 (58.8)	229 (57.8)
Bortezomib in the most recent regimen before randomization	194 (49.0)	174 (43.9)

(continued)

Table 10: Characteristics of the study population – RCT, direct comparison: carfilzomib + lenalidomide + dexamethasone vs. lenalidomide + dexamethasone (continued)

Study Characteristics Category	**Carfilzomib + lenalidomide + dexamethasone**	**Lenalidomide + dexamethasone**
ASPIRE	N[a] = 396	N[a] = 396
Number of prior therapies[e]		
1	184 (46.5)	157 (39.6)
2	120 (30.3)	139 (35.1)
3	91 (23.0)	99 (25.0)
4	1 (0.3)	1 (0.3)
Treatment discontinuation, n (%)	274 (69.2)	303 (76.5)
Study discontinuation, n (%)	ND	ND

a: Number of randomized patients.
b: Institute's calculation from "other" (6 patients) and Asian/native Hawaiian/other pacific islanders (1 patient).
c: Institute's calculation from "other" (4 patients), Asian/native Hawaiian/other pacific islanders (3 patients) and American Indian or Alaska native (1 patient).
d: Multiple answers possible.
ECOG PS: Eastern Cooperative Oncology Group Performance Status; F: female; IgX: immunoglobulin X; IMiD: immunomodulatory drug; ISS: International Staging System; M: male; max: maximum; min: minimum; n: number of patients in the category; N: number of randomized patients; ND: no data; RCT: randomized controlled trial; SD: standard deviation; vs.: versus

The patient characteristics were largely comparable between the treatment arms of the ASPIRE study. Most patients were white and had a mean age of 63 and 65 years respectively. About 43% of the patients already had stage III according to the International Staging System (ISS) at first diagnosis. According to the inclusion criteria, all patients had received systemic treatment for multiple myeloma before study inclusion; the proportion of bortezomib and an immunomodulatory drug (IMiD) as component of a prior therapy was comparable in both study arms.

Course of the study

Table 11 shows the median treatment duration of the patients and the median observation period for individual outcomes.

Table 11: Information on the course of the study – RCT, direct comparison: carfilzomib + lenalidomide + dexamethasone vs. lenalidomide + dexamethasone

Study **Duration of the study phase** **Outcome category**	**Carfilzomib + lenalidomide + dexamethasone**	**Lenalidomide + dexamethasone**
Study ASPIRE	N = 392	N = 389
Treatment duration [weeks]		
Data cut-off 16 June 2014		
Total[a], median [min; max]	88 [1; 185]	57 [1; 201]
Carfilzomib, median [min; max]	72 [1; 93]	-
Lenalidomide, median [min; max]	85 [0.1; 185]	57 [0.4; 201]
Dexamethasone, median [min; max]	80 [1; 178]	49 [1; 201]
Data cut-off 28 April 2017		
Total[a], median [min; max]	88 [1; 334]	57 [1; 324]
Observation period [weeks]		
Overall survival, median [95% CI][b]		
Data cut-off 16 June 2014	140.4 [137.8; 144.4][c]	137.0 [133.9; 141.3][c]
Data cut-off 28 April 2017	291.8 [ND]	291.8 [ND]
Morbidity[d], health-related quality of life[d], side effects	ND	ND

a: Definition of the treatment duration presented unclear because of discrepancy in comparison with individual substances.
b: ITT population: N = 396 in both study arms.
c: Institute's calculation.
d: Recorded with the questionnaires EORTC QLQ-C30 and QLQ-MY20.
CI: confidence interval; EORTC: European Organisation for Research and Treatment of Cancer; ITT: intention to treat; max: maximum; min: minimum; N: number of patients who have received at least 1 study medication (safety population); ND: no data; QLQ-C30: Quality of Life Questionnaire-Core 30; QLQ-MY20: Quality of Life Questionnaire-Multiple Myeloma Module 20; RCT: randomized controlled trial; vs.: versus

The median treatment duration cited by the company for the ASPIRE study was notably longer in the carfilzomib arm (88 weeks) than in the comparator arm (57 weeks). The difference in treatment durations was caused by differences in the rates of treatment discontinuation due to disease progression.

No information was available on the observation period of side effects. However, considering the information on the median treatment duration and assuming a 30-day follow-up observation period for AEs, there was a median observation period of about 92 weeks for the carfilzomib arm and of about 61 weeks for the comparator arm because side effects were recorded until 30 days after the study medication was ended (see Table 9).

Risk of bias at study level

Table 12 shows the risk of bias at study level.

Table 12: Risk of bias at study level – RCT, direct comparison: carfilzomib + lenalidomide + dexamethasone vs. lenalidomide + dexamethasone

Study	Adequate random sequence generation	Allocation concealment	Blinding		Reporting independent of the results	No additional aspects	Risk of bias at study level
			Patient	Treating staff			
ASPIRE	Yes	Yes	No	No	No	Yes	High
RCT: randomized controlled trial; vs.: versus							

The risk of bias at study level for the ASPIRE study was rated as high. This was due to possible selective reporting. The main reason for this was that, with the dossier, the company only presented analyses on selected subscales of the questionnaires EORTC QLQ-C30 and QLQ-MY20, which were recorded completely in the study (see Section 2.7.2.4.2 of the full dossier assessment).

Limitations resulting from the open-label study design are described in Section 2.4.2 with the outcome-specific risk of bias.

2.4 Results on added benefit

2.4.1 Outcomes included

The following patient-relevant outcomes were to be included in the assessment (for reasons, see Section 2.7.2.4.3 of the full dossier assessment):

- Mortality
  - overall survival
- Morbidity
  - symptoms measured with the symptom scales of the instruments EORTC QLQ-C30 and EORTC QLQ-MY20
- Health-related quality of life
  - measured with the functional scales of the EORTC QLQ-C30 and of the EORTC QLQ-MY20
- Side effects
  - SAEs
  - discontinuation due to AEs
  - severe AEs (CTCAE grade ≥ 3)
  - if applicable, further specific AEs

The choice of patient-relevant outcomes deviated from that of the company, which used further outcomes in the dossier (Module 4 A) (see Section 2.7.2.4.3 of the full dossier assessment).

Table 13 shows for which outcomes data were available in the study included.

Table 13: Matrix of outcomes – RCT, direct comparison: carfilzomib + lenalidomide + dexamethasone vs. lenalidomide + dexamethasone

Study	Outcomes					
	Overall survival	Symptoms (symptom scales EORTC QLQ-C30 and QLQ-MY20)	Health-related quality of life (EORTC QLQ-C30 and QLQ-MY20)	SAEs	Discontinuation due to AEs	Severe AEs (CTCAE grade ≥ 3)
ASPIRE	Yes	No[a]	No[a]	No[b]	Yes	No[b]

a: Data not completely presented by the company; see Section 2.4.2 and Section 2.7.2.4.2 of the full dossier assessment.
b: No usable analyses available; for reasons, see Section 2.4.2 and Section 2.7.2.4.2 of the full dossier assessment.
AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; EORTC: European Organisation for Research and Treatment of Cancer; QLQ-C30: Quality of Life Questionnaire-Core 30; QLQ-MY20: Quality of Life Questionnaire-Multiple Myeloma Module 20; RCT: randomized controlled trial; SAE: serious adverse event; vs.: versus

2.4.2 Risk of bias

Table 14 describes the risk of bias for the relevant outcomes.

Table 14: Risk of bias at study and outcome level – RCT, direct comparison: carfilzomib + lenalidomide + dexamethasone vs. lenalidomide + dexamethasone

Study		Outcomes					
	Study level	Overall survival	Symptoms (symptom scales of EORTC QLQ-C30 and QLQ-MY20)	Health-related quality of life (EORTC QLQ-C30 and QLQ-MY20)	SAEs	Discontinuation due to AEs	Severe AEs (CTCAE grade ≥ 3)
ASPIRE	H	H[a]	–[b]	–[b]	-[c]	H[a, d]	-[c]

a: High risk of bias at study level.
b: Data not completely presented by the company; see Section 2.7.2.4.2 of the full dossier assessment.
c: No usable analyses available; see Section 2.7.2.4.2 of the full dossier assessment.
d: Lack of blinding in subjective recording of outcomes.

AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; EORTC: European Organisation for Research and Treatment of Cancer; H: high; L: low; QLQ-C30: Quality of Life Questionnaire - Core 30; QLQ-MY20: Quality of Life Questionnaire-Multiple Myeloma Module 20; RCT: randomized controlled trial; SAE: serious adverse event; vs.: versus

Based on the high risk of bias at study level (see Section 2.3.2), the risk of bias for the outcome "overall survival" was rated as high. This deviates from the assessment of the company, which assumed a low risk of bias for this outcome.

Overall, no usable data were available for the outcomes "symptoms" and "health-related quality of life". With the dossier, the company only presented analyses on selected subscales of the questionnaires EORTC QLQ-C30 and QLQ-MY20, which were recorded completely in the ASPIRE study. These analyses on selected subscales were not used for the benefit assessment because selective reporting was possible (see Section 2.7.2.4.2 of the full dossier assessment). For this reason, the risk of bias for these outcomes was not assessed. This deviates from the assessment of the company, which used these outcomes for the assessment and assumed a high risk of bias for them.

No usable analyses were available for the outcomes "SAEs", "severe AEs (CTCAE grade ≥ 3)" and "specific AEs", either, because the analyses presented by the company did not adequately consider the different observation durations in the study arms of the ASPIRE study. This is explained in detail in Section 2.7.2.4.2 of the full dossier assessment. The risk of bias for the outcome "discontinuation due to AEs" was rated as high because of the high risk of bias at study level and the lack of blinding in subjective recording of outcomes. This

deviates from the assessment of the company, which derived a low risk of bias for all side effect outcomes.

2.4.3 Results

Table 15 summarizes the results for the comparison of carfilzomib + lenalidomide + dexamethasone with lenalidomide + dexamethasone in patients with multiple myeloma who have received at least 1 prior therapy. Where necessary, the data from the company's dossier were supplemented with the Institute's calculations.

If available, Kaplan-Meier curves on the outcomes included are presented in Appendix D of the full dossier assessment.

Table 15: Results (overall survival, morbidity, health-related quality of life and side effects) – RCT, direct comparison: carfilzomib + lenalidomide + dexamethasone vs. lenalidomide + dexamethasone

Study **Outcome category** **Outcome**	**Carfilzomib + lenalidomide + dexamethasone**		**Lenalidomide + dexamethasone**		**Carfilzomib + lenalidomide + dexamethasone vs. lenalidomide + dexamethasone**
	N	**Median survival time in months [95% CI]** **Patients with event n (%)**	**N**	**Median survival time in months [95% CI]** **Patients with event n (%)**	**HR [95% CI][a]; p-value**
ASPIRE					
Mortality (second data cut-off: 28 April 2017)					
Overall survival	396	48.3 [42.4; 52.8] 246 (62.1)	396	40.4 [33.6; 44.4] 267 (67.4)	0.794 [0.667; 0.945] 0.009[b]
Morbidity (first data cut-off: 16 June 2014)					
Symptoms (EORTC QLQ-C30) Symptoms (EORTC QLQ-MY20)	Data for symptoms presented incompletely[c]				
Health-related quality of life (first data cut-off: 16 June 2014)					
EORTC QLQ-C30 EORTC QLQ-MY20	Data for health-related quality of life presented incompletely[c]				
Side effects					
AEs (supplementary information)	392	ND 384 (98.0)	389	ND 381 (97.9)	-
SAEs	392	ND 257 (65.6)	389	ND 221 (56.8)	ND
Severe AEs (CTCAE grade ≥ 3)	392	ND 341 (87.0)	389	ND 323 (83.0)	ND
Discontinuation due to AEs					
Total study medication	392	ND 75 (19.1)	389	ND 80 (20.6)	RR: 0.93 [0.70; 1.23]; 0.683[d]
≥ 1 study medication	392	ND 131 (33.4)	389	ND 117 (30.1)	RR: 1.11 [0.90; 1.37]; 0.370[d]

(continued)

Table 15: Results (overall survival, morbidity, health-related quality of life and side effects) – RCT, direct comparison: carfilzomib + lenalidomide + dexamethasone vs. lenalidomide + dexamethasone (continued)

a: Unless stated otherwise.
b: 2-sided p-value, calculated using Cox regression, adjusted for pretreatment with bortezomib (yes, no), pretreatment with lenalidomide (yes, no) and beta-2 microglobulin (< 2.5 mg/L, ≥ 2.5 mg/L).
c: Despite complete recording of the instruments in the ASPIRE study, the company presented only analyses of selected subscales in the dossier.
d: Institute's calculation of RR, CI (asymptotic) and p-value (unconditional exact test, CSZ method according to [23]).

AE: adverse event; CI: confidence interval; CSZ: convexity, symmetry, z score; CTCAE: Common Terminology Criteria for Adverse Events; EORTC: European Organisation for Research and Treatment of Cancer; HR: hazard ratio; n: number of patients with (at least 1) event; N: number of analysed patients; ND: no data; QLQ-C30: Quality of Life Questionnaire-Core 30; QLQ-MY20: Quality of Life Questionnaire-Multiple Myeloma Module 20; RCT: randomized controlled trial; RR: relative risk; SAE: serious adverse event; vs.: versus

Based on the available data, at most hints, e.g. of an added benefit, can be derived for all outcomes for which usable data are available due to the high risk of bias.

Mortality

Overall survival

A statistically significant difference in favour of carfilzomib + lenalidomide + dexamethasone in comparison with lenalidomide + dexamethasone was shown for the outcome "overall survival". In addition, there was a relevant effect modification by the characteristic "age" for this outcome (see Section 2.4.4). The results were therefore interpreted separately for patients younger than 65 years and for older patients. This resulted in a hint of an added benefit for the outcome "overall survival" for patients < 65 years of age. There was no hint of an added benefit of carfilzomib + lenalidomide + dexamethasone in comparison with lenalidomide + dexamethasone for older patients; an added benefit is not proven for these patients.

This deviates from the assessment of the company, which did not consider any subgroup results for this outcome and derived proof of an added benefit of carfilzomib based on the analyses on the total population.

Morbidity

Symptoms

Symptom outcomes were recorded with the symptom scales of the disease-specific instrument EORTC QLQ-C30 and of the myeloma-specific supplementary tool EORTC QLQ-MY20. In Module 4 A, the company only presented results on the EORTC QLQ-C30 symptom scales "fatigue", "nausea and vomiting" and "pain", however; information on the symptom scales "dyspnoea", "insomnia", "appetite loss", "diarrhoea" and "constipation" was missing. Regarding the EORTC QLQ-MY20, the company presented the scales "disease symptoms" and "side effects" in Module 4 A.

The company presented responder analyses on the time to deterioration, defined by the minimally important difference (MID) of at least 10 points, for the selected symptom scales.

The analyses presented by the company on selected symptom scales of both questionnaires were not used for the present benefit assessment. Since the questionnaires EORTC QLQ-C20 and EORTC QLQ-MY20 were recorded completely in the ASPIRE study, complete presentation of all scales in the dossier was possible and meaningful. Selective reporting is possible (see also Section 2.7.2.4.2 of the full dossier assessment). This resulted in no hint of an added benefit of carfilzomib + lenalidomide + dexamethasone in comparison with lenalidomide + dexamethasone for this outcome; an added benefit is therefore not proven.

This deviates from the assessment of the company, which derived proof of an added benefit for this outcome.

The individual results on the symptom scales of the questionnaires used are presented as additional information in Appendix B of the full dossier assessment.

Health-related quality of life

Outcomes on health-related quality of life were recorded with the functional scales of the disease-specific instrument EORTC QLQ-C30 and of the myeloma-specific supplementary tool EORTC QLQ-MY20. As described for the outcome “symptoms”, the company presented analyses only on selected scales also for the outcome “health-related quality of life”: In Module 4 A, it presented the functional scales “physical functioning” and “role functioning” as well as the global health status of the EORTC QLQ-C30. The 3 functional scales of emotional, social and cognitive functioning were missing. The company also did not present the 2 functional scales “future perspective” and “body image” of the EORTC QLQ-MY20.

Analogous to the outcome “symptoms”, the analyses presented by the company on selected scales of both questionnaires were not used for the present benefit assessment. Analogous to the outcome “symptoms”, this is due to the selective presentation of individual scales despite complete recording of the questionnaires used. In addition, recording of all domains (physical, mental, social), and not only of a choice of these domains, is required for adequate recording of the multidimensional construct “health-related quality of life”. This resulted in no hint of an added benefit of carfilzomib + lenalidomide + dexamethasone in comparison with lenalidomide + dexamethasone for this outcome; an added benefit is therefore not proven.

This deviates from the assessment of the company, which derived proof of an added benefit for this outcome.

The individual results on the functional scales of the questionnaires used are presented as additional information in Appendix B of the full dossier assessment.

Side effects

Serious adverse events, severe adverse events (CTCAE grade ≥ 3)

The company did not present any usable analyses for the outcomes "SAEs" and "severe AEs (CTCAE grade ≥ 3)": The analyses presented by the company on the basis of the incidence density ratio were inadequate in the present data situation (see Section 2.7.2.4.2 of the full dossier assessment). This resulted in no hint of greater or lesser harm from carfilzomib + lenalidomide + dexamethasone in comparison with lenalidomide + dexamethasone; greater or lesser harm is therefore not proven for these outcomes.

This concurs with the company's assessment insofar as the company derived no additional harm from carfilzomib on the basis of the analyses presented based on the incidence density ratio.

Discontinuation due to adverse events

No statistically significant difference between the treatment arms was shown for the outcome "discontinuation due to AEs", both for discontinuation of at least 1 study medication and for discontinuation of the total study medication. This resulted in no hint of greater or lesser harm from carfilzomib + lenalidomide + dexamethasone in comparison with lenalidomide + dexamethasone; greater or lesser harm is therefore not proven for this outcome.

This concurs with the assessment of the company, which, deviating from the present benefit assessment, used analyses based on the incidence density ratio, however.

Specific adverse events

The company presented different AEs of particular interest (CTCAE grade ≥ 3). Since the analyses presented by the company on the basis of the incidence density ratio were inadequate in the present data situation (see Section 2.7.2.4.2 of the full dossier assessment), and, in addition, the company did not present a complete overview of all AEs at SOC and PT level, it was not possible to choose specific AEs.

2.4.4 Subgroups and other effect modifiers

The following subgroup characteristics were considered in the benefit assessment:

- age (< 65 years, ≥ 65 years)
- sex (men, women)
- ethnicity (white, black, other)
- ISS disease stage (I, II, III, unknown)
- number of prior therapies (1, 2, 3)
- bortezomib pretreatment (yes/no)
- lenalidomide pretreatment (yes/no)

Only the results with an effect modification with a statistically significant interaction between treatment and subgroup characteristic (p-value < 0.05) are presented. In addition, subgroup results are only presented if there is a statistically significant and relevant effect in at least 1 subgroup.

Table 16 summarizes the subgroup results on the comparison of carfilzomib + lenalidomide + dexamethasone with lenalidomide + dexamethasone in the ASPIRE study.

Table 16: Subgroups (overall survival, time to event) – RCT, direct comparison: carfilzomib + lenalidomide + dexamethasone vs. lenalidomide + dexamethasone

Study **Outcome** **Characteristic** **Subgroup**	**Carfilzomib + lenalidomide + dexamethasone**		**Lenalidomide + dexamethasone**		**Carfilzomib + lenalidomide + dexamethasone vs. lenalidomide + dexamethasone**	
	N	**Median survival time in months [95% CI]** **Patients with event n (%)**	**N**	**Median survival time in months [95% CI]** **Patients with event n (%)**	**HR [95% CI]**	**p-value**
Study ASPIRE						
Overall survival (second data cut-off 28 April 2017)						
Age						
< 65 years	211	55.6 [47.8; 69.0] 115 (54.5)	188	38.2 [31.8; 47.8] 122 (64.9)	0.68 [0.52; 0.87]	0.003[a]
≥ 65 years	185	36.6 [31.8; 47.2] 131 (70.8)	208	41.2 [30.9; 46.4] 145 (69.7)	0.96 [0.76; 1.22]	0.707
Total					Interaction:	0.048

a: Institute's calculation; 2-sided p-value based on the unstratified log-rank test.

CI: confidence interval; EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-C30; HR: hazard ratio; n: number of patients with event; N: number of analysed patients; RCT: randomized controlled trial; vs.: versus

Mortality

Overall survival

There was an effect modification by the characteristic "age" for the outcome "overall survival". A statistically significant difference in favour of carfilzomib + lenalidomide + dexamethasone in comparison with lenalidomide + dexamethasone was shown for patients < 65 years of age. This resulted in a hint of an added benefit of carfilzomib + lenalidomide + dexamethasone versus lenalidomide + dexamethasone for these patients. No statistically significant difference was observed for patients ≥ 65 years of age. Hence there was no hint of an added benefit of carfilzomib + lenalidomide + dexamethasone in comparison with

lenalidomide + dexamethasone for older patients; an added benefit is not proven for these patients.

This deviates from the approach of the company, which derived proof of an added benefit for the total population.

2.5 Probability and extent of added benefit

The derivation of probability and extent of the added benefit is presented below at outcome level, taking into account the different outcome categories and effect sizes. The methods used for this purpose are explained in the *General Methods* of IQWiG [1].

The approach for deriving an overall conclusion on added benefit based on the aggregation of conclusions derived at outcome level is a proposal by IQWiG. The G-BA decides on the added benefit.

2.5.1 Assessment of added benefit at outcome level

For patients < 65 years of age, the data presented in Section 2.4 resulted in a hint of an added benefit of carfilzomib + lenalidomide + dexamethasone versus lenalidomide + dexamethasone for the outcome “overall survival”. The extent of the respective added benefit at outcome level was estimated from these results (see Table 17).

Table 17: Extent of added benefit at outcome level: carfilzomib + lenalidomide + dexamethasone vs. lenalidomide + dexamethasone

Outcome category **Outcome** **Effect modifier** **Subgroup**	**Carfilzomib + lenalidomide + dexamethasone vs. lenalidomide + dexamethasone** **Quantile of time to event or proportion of events** **Effect estimate [95% CI]; p-value** **Probability**[a]	**Derivation of extent**[b]
Mortality		
Overall survival		
Age		
< 65 years	Median: 55.6 vs. 38.2 months HR: 0.68 [0.52; 0.87]; p = 0.003[c] probability: "hint"	Outcome category: mortality $0.85 \leq CI_u < 0.95$ added benefit, extent: "considerable"
≥ 65 years	Median: 36.6 vs. 41.2 months HR: 0.96 [0.76; 1.22]; p = 0.707	Lesser benefit/added benefit not proven
Morbidity		
Symptoms		
EORTC QLQ-C30 (symptom scales) – time to deterioration	Data for symptoms presented incompletely[d]	Lesser benefit/added benefit not proven
EORTC QLQ-MY20 – time to deterioration		
Health-related quality of life		
EORTC QLQ-C30 (functional scales) – time to deterioration	Data for health-related quality of life presented incompletely[d]	Lesser benefit/added benefit not proven
EORTC QLQ-MY20 – time to deterioration		
Side effects		
SAEs	No usable analyses	Greater/lesser harm not proven
Severe AEs (CTCAE grade ≥ 3)	No usable analyses	Greater/lesser harm not proven
Discontinuation due to AEs		
Total study medication	Proportion of events: 19.1% vs. 20.6% RR: 0.93 [0.70; 1.23]; p = 0.683[e]	Greater/lesser harm not proven
≥ 1 study medication	Proportion of events: 33.4% vs. 30.1% RR: 1.11 [0.90; 1.37]; p = 0.370[e]	

(continued)

Table 17: Extent of added benefit at outcome level: carfilzomib + lenalidomide + dexamethasone vs. lenalidomide + dexamethasone (continued)

a: Probability provided if a statistically significant and relevant effect is present. b: Estimations of effect size are made depending on the outcome category with different limits based on the CI_u. c: Institute's calculation; 2-sided p-value based on the unstratified log-rank test. d: Despite complete recording of the instruments, the company presented only analyses of selected subscales in the dossier. e: Institute's calculation of RR, CI (asymptotic) and p-value (unconditional exact test, CSZ method according to [23]). AE: adverse event; CI: confidence interval; CI_u: upper limit of confidence interval; CSZ: convexity, symmetry, z score; EORTC: European Organisation for Research and Treatment of Cancer; HR: hazard ratio; QLQ-C30: Quality of Life Questionnaire-Core 30; QLQ-MY20: Quality of Life Questionnaire-Multiple Myeloma Module 20; RR: relative risk; SAE: serious adverse event; vs.: versus

2.5.2 Overall conclusion on added benefit

Table 18 summarizes the results that were considered in the overall conclusion on the extent of added benefit.

Table 18: Positive and negative effects from the assessment of carfilzomib + lenalidomide + dexamethasone vs. lenalidomide + dexamethasone

Positive effects	**Negative effects**
Mortality ▪ Overall survival: ▫ age (< 65 years): hint of added benefit – extent: "considerable"	-
The company did not present the complete results on symptoms and health-related quality of life; the analyses submitted on individual side effect outcomes were inadequate.	
vs.: versus	

The overall consideration of the usable data showed a positive effect of carfilzomib + lenalidomide + dexamethasone. For patients < 65 years of age, a hint of a considerable added benefit of carfilzomib + lenalidomide + dexamethasone versus lenalidomide + dexamethasone was shown in the outcome "overall survival". This positive effect was accompanied by pronounced uncertainties in the other outcome categories. The company only submitted selective data on the outcomes "symptoms" and "health-related quality of life" with the dossier. The company did not provide an adequate justification for this approach (see Section 2.4.3). Due the possible presence of selective reporting, the results on these outcomes in their totality were not interpretable. Hence, at most hints of an added benefit could be derived from the ASPIRE study (see also Section 2.7.2.4.2 of the full dossier assessment).

The company did not present adequate analyses for SAEs and severe AEs for the outcome category "side effects"; an assessment for this outcome category was therefore not possible. Greater harm from carfilzomib is possible, particularly considering the higher event rates for SAEs and severe AEs under carfilzomib + lenalidomide + dexamethasone.

For patients < 65 years of age, the present uncertainties overall did not result in completely questioning the considerable survival advantage of carfilzomib + lenalidomide + dexamethasone. Against the background of the uninterpretability of the side effect profile, the extent of added benefit was rated as non-quantifiable, however. Overall, this resulted in a hint of a non-quantifiable added benefit for these patients.

There was no survival advantage for patients ≥ 65 years of age. Overall, an added benefit for these patients is not proven. However, greater harm of carfilzomib + lenalidomide + dexamethasone, particularly regarding AEs, is possible.

No usable data were available for the combination of carfilzomib with dexamethasone.

The result of the assessment of the added benefit of carfilzomib in comparison with the ACT is summarized in Table 19.

Table 19: Carfilzomib – probability and extent of added benefit

Therapeutic indication	**ACT**[a, b]	**Extent and probability of added benefit**
Adult patients with multiple myeloma who have received at least 1 prior therapy[c]	Bortezomib in combination with pegylated liposomal doxorubicin or **bortezomib in combination with dexamethasone** or **lenalidomide in combination with dexamethasone** or elotuzumab in combination with lenalidomide and dexamethasone	In combination with lenalidomide and dexamethasone: ▪ patients < 65 years: hint of a non-quantifiable added benefit ▪ patients ≥ 65 years: added benefit not proven[d] In combination with dexamethasone: ▪ added benefit not proven
a: Presentation of the respective ACT specified by the G-BA. In cases where the company, because of the G-BA's specification of the ACT, could choose a comparator therapy from several options, the respective choice of the company is printed in **bold**. b: It is assumed for the present therapeutic indication that the use of carfilzomib in combination with lenalidomide and dexamethasone or in combination with dexamethasone alone is conducted in the framework of a remission-inducing induction treatment. High-dose chemotherapy with stem cell transplantation, which may be a subsequent treatment option, is therefore not an option as part of the ACT. c: According to the approval, carfilzomib is used in combination with either lenalidomide and dexamethasone or dexamethasone alone. d: Greater harm, particularly regarding AEs, is possible. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee		

The assessment described above deviates from that of the company, which derived proof of considerable added benefit both for carfilzomib + lenalidomide + dexamethasone and for carfilzomib + dexamethasone in comparison with the ACT.

The G-BA decides on the added benefit.

Supplementary note

The result of the assessment deviates from the results of the G-BA assessments both in the framework of the market entry in 2015 (carfilzomib + lenalidomide + dexamethasone) and of the new therapeutic indication from 2016 (carfilzomib + dexamethasone). In these assessments, the G-BA had derived a non-quantifiable added benefit for the combination of carfilzomib + lenalidomide + dexamethasone. This was based on the then pending final analyses on overall survival, which is why the decision was limited until 31 December 2017 [20,21]. The G-BA had derived a minor added benefit for the combination of carfilzomib + dexamethasone. In these assessments, the added benefit had been regarded as proven by the approval because of the special situation for orphan drugs, irrespective of the underlying data.

2.6 List of included studies

ASPIRE

Amgen. A randomized, multicenter, phase 3 study comparing carfilzomib, lenalidomide, and dexamethasone vs. lenalidomide and dexamethasone in subjects with relapsed multiple myeloma: study PX-171-009; clinical study protocol amendment 4 [unpublished]. 2011.

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Onyx Therapeutics. A randomized, open-label, phase 3 study of carfilzomib plus dexamethasone vs bortezomib plus dexamethasone in patients with relapsed multiple myeloma [online]. In: EU Clinical Trials Register. [Accessed: 17.10.2017]. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2012-000128-16.

Stewart AK, Dimopoulos MA, Masszi T, Spicka I, Oriol A, Hajek R et al. Health-related quality of life results from the open-label, randomized, phase III ASPIRE trial evaluating carfilzomib, lenalidomide, and dexamethasone versus lenalidomide and dexamethasone in patients with relapsed multiple myeloma. J Clin Oncol 2016; 34(32): 3921-3930.

Stewart AK, Rajkumar SV, Dimopoulos MA, Masszi T, Spicka I, Oriol A et al. Carfilzomib, lenalidomide, and dexamethasone for relapsed multiple myeloma. N Engl J Med 2014; 372(2): 142-152.

ENDEAVOR

No information on the ENDEAVOR study is presented in this section because the company did not present any relevant data for the benefit assessment.

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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