IQWiG Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen

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

Extract

[1] Translation of Sections 2.1 to 2.5 of the dossier assessment *Pomalidomid – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 23 December 2015). 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
BSC	best supportive care
DGHO	German Society of Haematology and Oncology
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
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 pomalidomide. 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 30 September 2015.

Research question

The aim of this report was to assess the added benefit of pomalidomide in combination with dexamethasone compared with the appropriate comparator therapy (ACT) for the treatment of adult patients with relapsed and refractory multiple myeloma who have received at least 2 prior treatment regimens, including both lenalidomide and bortezomib, and have demonstrated disease progression on the last therapy.

The G-BA distinguished between 2 patient groups in its specification of the ACT. The resulting research questions are shown in Table 2.

Table 2: Appropriate comparator therapies specified by the G-BA

Research question	Subindication[a]	Appropriate comparator therapy
Treatment of adult patients with relapsed and refractory multiple myeloma who have received at least 2 prior treatment regimens, including both lenalidomide and bortezomib, and have demonstrated disease progression on the last therapy		
1	Patients who are eligible for targeted therapy	Individual targeted therapy specified by the physician[b]
2	Patients who are not eligible for targeted therapy	BSC[b, c]

a: It is assumed for the present therapeutic indication that high-dose chemotherapy with stem cell transplantation is not an option for the patients at the time point of their current treatment.
b: Depending on the prior therapies and the extent and duration of the respective response as well as under consideration of the approval of the respective drug.
c: BSC is understood as the therapy that ensures the best possible individually optimized supportive treatment to alleviate symptoms and improve the quality of life.
BSC: best supportive care; G-BA: Federal Joint Committee

Deviating from the G-BA, the company named high-dose dexamethasone as only comparator therapy for patients who are eligible for targeted therapy. For patients who are not eligible for targeted therapy, the company followed the G-BA's specification and chose best supportive care (BSC) as ACT.

Results

Research question 1: patients who are eligible for targeted therapy

The company presented one randomized active-controlled trial (MM-003) for research question 1 (patients who are eligible for targeted therapy). This study was unsuitable for the derivation of the added benefit of pomalidomide.

The MM-003 study was a randomized, active-controlled, open-label approval study sponsored by the company. In the study, pomalidomide in combination with low-dose dexamethasone was compared with high-dose dexamethasone. The study was unsuitable for the derivation of the added benefit of pomalidomide because the uniform regimen of high-dose dexamethasone administered to all patients in the comparator arm was no adequate implementation of the ACT. The ACT in the present therapeutic indication (patients who are eligible for targeted therapy) was individual targeted therapy specified by the physician. The company did not explain in its dossier that high-dose dexamethasone treatment was to be considered the individual targeted therapy for the patients of the study population.

In addition, dexamethasone was not administered in compliance with the approval in the comparator arm of the MM-003 study. In particular, the drug was administered at a dosage that was notably higher than recommended in the Summary of Product Characteristics (SPC).

Hence no suitable data were available for the assessment of the added benefit of pomalidomide in the treatment of adult patients with relapsed and refractory multiple myeloma who have received at least 2 prior treatment regimens, including both lenalidomide and bortezomib, and have demonstrated disease progression on the last therapy and who are eligible for targeted therapy specified by the physician. Hence there was no hint of an added benefit of pomalidomide in comparison with the ACT. An added benefit of pomalidomide is therefore not proven.

Research question 2: patients who are not eligible for targeted therapy

The company presented no relevant study for research questions 2. No data were available for the assessment of the added benefit of pomalidomide in adult patients with relapsed and refractory multiple myeloma who have received at least 2 prior treatment regimens, including both lenalidomide and bortezomib, and have demonstrated disease progression on the last therapy and who are not eligible for targeted therapy specified by the physician. Hence there was no hint of an added benefit of pomalidomide in comparison with the ACT. An added benefit of pomalidomide is therefore not proven.

Extent and probability of added benefit, patient groups with therapeutically important added benefit[4]

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

Table 3: Pomalidomide – extent and probability of added benefit

Research question	Subindication[a]	ACT[b]	Extent and probability of added benefit
Treatment of adult patients with relapsed and refractory multiple myeloma who have received at least 2 prior treatment regimens, including both lenalidomide and bortezomib, and have demonstrated disease progression on the last therapy			
1	Patients who are eligible for targeted therapy	Individual targeted therapy specified by the physician[c]	Added benefit not proven
2	Patients who are not eligible for targeted therapy	BSC[c, d]	Added benefit not proven

a: It is assumed for the present therapeutic indication that high-dose chemotherapy with stem cell transplantation is not an option for the patients at the time point of their current treatment.
b: 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.
c: Depending on the prior therapies and the extent and duration of the respective response as well as under consideration of the approval of the respective drug.
d: BSC is understood as the therapy that ensures the best possible individually optimized supportive treatment to alleviate symptoms and improve the quality of life.
ACT: appropriate comparator therapy; BSC: best supportive care; G-BA: Federal Joint Committee

The G-BA decides on the added benefit.

[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].

2.2 Research question

The aim of this report was to assess the added benefit of pomalidomide in combination with dexamethasone compared with the ACT for the treatment of adult patients with relapsed and refractory multiple myeloma who have received at least 2 prior treatment regimens, including both lenalidomide and bortezomib, and have demonstrated disease progression on the last therapy.

The G-BA distinguished between 2 patient groups in its specification of the ACT. The resulting research questions are shown in Table 4.

Table 4: Appropriate comparator therapies specified by the G-BA

Research question	Subindication[a]	Appropriate comparator therapy
Treatment of adult patients with relapsed and refractory multiple myeloma who have received at least 2 prior treatment regimens, including both lenalidomide and bortezomib, and have demonstrated disease progression on the last therapy		
1	Patients who are eligible for targeted therapy	Individual targeted therapy specified by the physician[b]
2	Patients who are not eligible for targeted therapy	BSC[b, c]
a: It is assumed for the present therapeutic indication that high-dose chemotherapy with stem cell transplantation is not an option for the patients at the time point of their current treatment. b: Depending on the prior therapies and the extent and duration of the respective response as well as under consideration of the approval of the respective drug. c: BSC is understood as the therapy that ensures the best possible individually optimized supportive treatment to alleviate symptoms and improve the quality of life. BSC: best supportive care; G-BA: Federal Joint Committee		

For easier presentation and better readability, the report uses the following terms for the 2 therapeutic indications:

- patients who are eligible for targeted therapy (research question 1)
- patients who are not eligible for targeted therapy (research question 2)

The G-BA defined individual targeted therapy specified by the physician depending on the prior therapies and the extent and duration of the respective response as well as under consideration of the approval of the respective drug as ACT for patients who are eligible for targeted therapy. Deviating from the G-BA, the company chose high-dose dexamethasone as only comparator therapy. This approach was not followed (see Section 2.6.1 of the full dossier assessment).

For patients who are not eligible for targeted therapy, the company followed the G-BA's specification and chose BSC as ACT. The present assessment was conducted in comparison with the G-BA's ACT.

The assessment was conducted based on patient-relevant outcomes and on the data provided by the company in the dossier.

2.3 Research question 1: patients who are eligible for targeted therapy

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 pomalidomide (status: 6 July 2015)
- bibliographical literature search on pomalidomide (last search on 6 July 2015)
- search in trial registries for studies on pomalidomide (last search on 6 July 2015)

To check the completeness of the study pool:

- search in trial registries for studies on pomalidomide (last search on 21 October 2015)

No relevant study was identified from the check.

Study pool of the company for the direct comparison

From the steps of information retrieval mentioned, the company identified one randomized, active-controlled study (CC-4047-MM-003, hereinafter referred to as "MM-003" [3]) for research question 1. This study was unsuitable to derive conclusions on the added benefit of pomalidomide in patients who are eligible for targeted therapy. This is justified below.

The MM-003 study was a randomized, active-controlled, open-label approval study sponsored by the company. In the study, pomalidomide in combination with low-dose dexamethasone was compared with high-dose dexamethasone.

Adult patients with relapsed and refractory multiple myeloma who had received at least 2 prior treatment regimens, including both lenalidomide and bortezomib, and had demonstrated disease progression on the last therapy, were included. The patient population investigated in the study therefore concurs with the approved target population of pomalidomide according to the SPC [4]. The medication administered in the intervention arm also complied with the specifications in the SPC of pomalidomide [4]. However, all patients in the comparator arm received a fixed regimen of high-dose dexamethasone. No antineoplastic agents in addition to the study medication were allowed to be administered at any time point during the course of the treatment. Patients of both treatment arms received drugs as needed to alleviate symptoms and for accompanying diseases. Treatment with the study medication was continued until disease progression, discontinuation due to unacceptable adverse events, death or withdrawal of consent.

Progression-free survival was the primary outcome of the study (the characteristics of the study are presented in Appendix A, Table 9 and Table 10, of the full dossier assessment).

Appropriate comparator therapy not implemented

The MM-003 study was not used for the present benefit assessment because the uniform regimen of high-dose dexamethasone administered to all patients in the comparator arm was no adequate implementation of the ACT. The ACT in the present therapeutic indication (patients who are eligible for targeted therapy) was individual targeted therapy specified by the physician. The company did not explain in its dossier that high-dose dexamethasone treatment was to be considered the individual targeted therapy for the patients of the study population. However, this has to be presented in a comprehensible way under consideration of individual factors such as prior therapies and response. The company did not justify why high-dose dexamethasone as individual substance is at least as suitable as or more suitable than other approved targeted therapies in the therapeutic indication for the patients of the study population.

Neither national guidelines such as the one of the German Society of Haematology and Oncology (DGHO) nor international guidelines contain an indication that monotherapy with high-dose dexamethasone is to be taken into consideration at all in relapsed and refractory multiple myeloma [5-9]. Instead, a number of possible other treatment regimens are cited [5-9]. Against this background, and irrespective of the concrete suitability for the population of the MM-003 study, it is overall questionable whether high-dose dexamethasone can be considered to be a regular targeted therapy in the present therapeutic indication at all.

Dexamethasone not administered in compliance with the SPC

In the comparator arm of the MM-003 study, dexamethasone was administered at a dosage that was notably higher than recommended in the SPC. According to the specifications of the SPC, dexamethasone in the palliative treatment of malignant tumours is to be administered at an initial dosage of 8 to 16 mg daily, and at a dosage of 4 to 12 mg daily for long-term treatment. The dosage should always be modified based on the individual patient response to the treatment [10]. Almost all patients in the comparator arm of the MM-003 study had already been pretreated with dexamethasone, and the maximum daily dose of dexamethasone to be administered was therefore limited to 12 mg. In a 28-day cycle, this corresponds to a total of 336 mg dexamethasone. The treatment regimen administered in the MM-003 study deviated considerably from these specifications. The administered dose of dexamethasone was 40 mg (in patients ≤ 75 years, about 92% of the patients in the MM-003 study) and 20 mg (in patients > 75 years) orally on day 1–4, 9–12 and 17–20 of a 28-day cycle (see also Table 10 of the full dossier assessment), and was therefore far above the maximum daily dose according to the SPC, even in initial treatment. Individual dose adjustments depending on the patient response to treatment were not envisaged. The total amount administered during a 28-day cycle (480 mg dexamethasone) was notably above the recommended maximum dose. The

literature provides indications that major toxicities are to be expected from treatment with such a high dosage of dexamethasone [11].

Furthermore, the SPC on dexamethasone notes that treatment should be switched to prednisone/prednisolone if long-term treatment is considered necessary after initial therapy because these drugs cause a lesser degree of adrenal cortex suppression [10]. Since almost all patients in the MM-003 study had already been pretreated with dexamethasone, the patients in the comparator arm of the study might have required treatment with prednisone/prednisolone already at the start of the study, or at least there should have been the option to switch the patients to treatment with prednisone/prednisolone during the course of the study. The G-BA explicitly pointed out the consideration of the approval status of the respective drugs in its specification of the ACT (see Table 4). Hence the MM-003 study could not be used for the benefit assessment also because of the use of dexamethasone, which was not in compliance with the approval.

Summary

In summary, the MM-003 study was unsuitable for the assessment of the added benefit of pomalidomide because of the inadequate implementation of the individual targeted therapy specified by the physician and because of the use of dexamethasone, which was not in compliance with the approval. Hence no relevant data for the assessment of the added benefit of pomalidomide in comparison with the ACT were available for research question 1.

2.3.2 Results on added benefit

No suitable data were available for the assessment of the added benefit of pomalidomide in adult patients with relapsed and refractory multiple myeloma who are eligible for targeted therapy specified by the physician. Hence there was no hint of an added benefit of pomalidomide in comparison with the ACT. An added benefit is therefore not proven.

2.3.3 Extent and probability of added benefit, patient groups with therapeutically important added benefit

Since the company presented no suitable data for adult patients with relapsed and refractory multiple myeloma who have received at least 2 prior treatment regimens, including both lenalidomide and bortezomib, and have demonstrated disease progression on the last therapy, and who are eligible for targeted therapy specified by the physician, an added benefit of pomalidomide is not proven for these patients.

2.3.4 List of included studies

Not applicable because the company presented no relevant data for the assessment of the added benefit of pomalidomide.

2.4 Research question 2: patients who are not eligible for targeted therapy

2.4.1 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 pomalidomide (status: 6 July 2015)
- bibliographical literature search on pomalidomide (last search on 6 July 2015)
- search in trial registries for studies on pomalidomide (last search on 6 July 2015)

To check the completeness of the study pool:

- search in trial registries for studies on pomalidomide (last search on 21 October 2015)

The company identified no relevant study. No relevant study was identified from the check either.

2.4.2 Results on added benefit

No data were available for the assessment of the added benefit of pomalidomide in adult patients with relapsed and refractory multiple myeloma who are not eligible for targeted therapy specified by the physician. Hence there was no hint of an added benefit of pomalidomide in comparison with the ACT. An added benefit is therefore not proven.

2.4.3 Extent and probability of added benefit

Since the company presented no data for adult patients with relapsed and refractory multiple myeloma who have received at least 2 prior treatment regimens, including both lenalidomide and bortezomib, and have demonstrated disease progression on the last therapy, and who are not eligible for targeted therapy specified by the physician, an added benefit of pomalidomide is not proven for these patients.

2.4.4 List of included studies

Not applicable because the company presented no data for the assessment of the added benefit of pomalidomide.

2.5 Extent and probability of added benefit – summary

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

Table 5: Pomalidomide – extent and probability of added benefit

Research question	**Subindication**[a]	**ACT**[b]	**Extent and probability of added benefit**
Treatment of adult patients with relapsed and refractory multiple myeloma who have received at least 2 prior treatment regimens, including both lenalidomide and bortezomib, and have demonstrated disease progression on the last therapy			
1	Patients who are eligible for targeted therapy	Individual targeted therapy specified by the physician[c]	Added benefit not proven
2	Patients who are not eligible for targeted therapy	BSC[c, d]	Added benefit not proven

a: It is assumed for the present therapeutic indication that high-dose chemotherapy with stem cell transplantation is not an option for the patients at the time point of their current treatment.
b: 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.
c: Depending on the prior therapies and the extent and duration of the respective response as well as under consideration of the approval of the respective drug.
d: BSC is understood as the therapy that ensures the best possible individually optimized supportive treatment to alleviate symptoms and improve the quality of life.
ACT: appropriate comparator therapy; BSC: best supportive care; G-BA: Federal Joint Committee

In summary, an added benefit of pomalidomide compared with the ACT in the treatment of adult patients with relapsed and refractory multiple myeloma who have received at least 2 prior treatment regimens, including both lenalidomide and bortezomib, and have demonstrated disease progression on the last therapy is not proven for patients who are eligible for targeted therapy specified by the physician (research question 1) or for patients who are not eligible for targeted therapy (research question 2).

The overall assessment deviates from that of the company, which claimed proof of a major added benefit of pomalidomide for patients who are eligible for targeted therapy specified by the physician. It claimed a hint of a major added benefit for patients who are not eligible for targeted therapy.

The G-BA decides on the added benefit.

References for English extract

Please see full dossier assessment for full reference list.

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