Gemeinsamer Bundesausschuss

Justification

of the Resolution of the Federal Joint Committee (G-BA) on an Amendment of the Pharmaceuticals Directive: Annex XII – Benefit Assessment of Medicinal Products with New Active Ingredients according to Section 35a (SGB V) Daratumumab (reassessment after the deadline: multiple myeloma, first-line, unsuitable for stem cell transplantation, combination with bortezomib, melphalan and prednisone)

of 16 May 2024

Contents

1. Legal basis

According to Section 35a paragraph 1 German Social Code, Book Five (SGB V), the Federal Joint Committee (G-BA) assesses the benefit of reimbursable medicinal products with new active ingredients. This includes in particular the assessment of the additional benefit and its therapeutic significance. The benefit assessment is carried out on the basis of evidence provided by the pharmaceutical company, which must be submitted to the G-BA electronically, including all clinical trials the pharmaceutical company has conducted or commissioned, at the latest at the time of the first placing on the market as well as the marketing authorisation of new therapeutic indications of the medicinal product, and which must contain the following information in particular:

1. approved therapeutic indications,
2. medical benefit,
3. additional medical benefit in relation to the appropriate comparator therapy,
4. number of patients and patient groups for whom there is a therapeutically significant additional benefit,
5. treatment costs for the statutory health insurance funds,
6. requirements for a quality-assured application.

The G-BA may commission the Institute for Quality and Efficiency in Health Care (IQWiG) to carry out the benefit assessment. According to Section 35a, paragraph 2 SGB V, the assessment must be completed within three months of the relevant date for submission of the evidence and published on the internet.

According to Section 35a paragraph 3 SGB V, the G-BA decides on the benefit assessment within three months of its publication. The resolution is to be published on the internet and is part of the Pharmaceuticals Directive.

2. Key points of the resolution

The pharmaceutical company submitted a dossier for the early benefit assessment of the active ingredient daratumumab (Darzalex) on 28 September 2018. For the resolution of 22 March 2019 made by the G-BA in this procedure, a limitation up to 1 March 2022 was pronounced. At the request of the pharmaceutical company, this time limit was extended by a resolution of the G-BA from 2 December 2021 by a time limit until 15 May 2023 and extended again by a time limit until 1 December 2023 by resolution of 19 January 2023.

In accordance with Section 4, paragraph 3, No. 5 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with Chapter 5 Section 8, paragraph 1, number 5 VerfO, the procedure for the benefit assessment of the medicinal product Darzalex recommences when the deadline has expired.

The pharmaceutical company submitted the final dossier to the G-BA in accordance with Section 4, paragraph 3, number 5 of the Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with Chapter 5 Section 8, paragraph 1, number 5 VerfO on 30 November 2023.

The G-BA commissioned the IQWiG to carry out the dossier assessment. The benefit assessment was published on 1 March 2024 on the G-BA website (www.g-ba.de), thus initiating the written statement procedure. In addition, an oral hearing was held.

The G-BA came to a resolution on whether an additional benefit of daratumumab compared to the appropriate comparator therapy could be determined on the basis of the dossier of the pharmaceutical company, the dossier assessment prepared by the IQWiG, and the statements submitted in the written statement and oral hearing procedure. In order to determine the extent of the additional benefit, the G-BA has evaluated the data justifying the finding of an additional benefit on the basis of their therapeutic relevance (qualitative), in accordance with the criteria laid down in Chapter 5 Section 5, paragraph 7 VerfO. The methodology proposed by the IQWiG in accordance with the General Methods [1] was not used in the benefit assessment of daratumumab.

In the light of the above, and taking into account the statements received and the oral hearing, the G-BA has come to the following assessment:

2.1 Additional benefit of the medicinal product in relation to the appropriate comparator therapy

2.1.1 Approved therapeutic indication of Daratumumab (Darzalex) according to product information

Darzalex is indicated in combination with lenalidomide and dexamethasone or with bortezomib, melphalan and prednisone for the treatment of adult patients with newly diagnosed multiple myeloma who are ineligible for autologous stem cell transplant.

Therapeutic indication of the resolution (resolution of 16.05.2024):

Darzalex is indicated in combination with bortezomib, melphalan and prednisone for the treatment of adults with newly diagnosed multiple myeloma who are ineligible for autologous stem cell transplant.

[1] General Methods, version 7.0 from 19.09.2023. Institute for Quality and Efficiency in Health Care (IQWiG), Cologne.

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

Adults with newly diagnosed multiple myeloma who are ineligible for autologous stem cell transplant

Appropriate comparator therapy for daratumumab in combination with bortezomib, melphalan and prednisone:

– Daratumumab in combination with lenalidomide and dexamethasone

or

– Bortezomib in combination with melphalan and prednisone

or

– Bortezomib in combination with lenalidomide and dexamethasone

or

– Thalidomide in combination with melphalan and prednisone

or

– Bortezomib in combination with cyclophosphamide and dexamethasone [only for patients with peripheral polyneuropathy or an increased risk of developing peripheral polyneuropathy; see Annex VI to Section K of the Pharmaceuticals Directive]

Criteria according to Chapter 5 Section 6 of the Rules of Procedure of the G-BA and Section 6 para. 2 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV):

The appropriate comparator therapy must be an appropriate therapy in the therapeutic indication in accordance with the generally recognised state of medical knowledge (Section 12 SGB V), preferably a therapy for which endpoint studies are available and which has proven its worth in practical application unless contradicted by the guidelines under Section 92, paragraph 1 SGB V or the principle of economic efficiency.

In determining the appropriate comparator therapy, the following criteria, in particular, must be taken into account as specified in Chapter 5 Section 6, paragraph 3 VerfO:

1. To be considered as a comparator therapy, the medicinal product must, principally, have a marketing authorisation for the therapeutic indication.
2. If a non-medicinal treatment is considered as a comparator therapy, this must be available within the framework of the SHI system.

3. As comparator therapy, medicinal products or non-medicinal treatments for which the patient-relevant benefit has already been determined by the G-BA shall be preferred.

4. According to the generally recognised state of medical knowledge, the comparator therapy should be part of the appropriate therapy in the therapeutic indication.

According to Section 6, paragraph 2, sentence 2 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV), the determination of the appropriate comparator therapy must be based on the actual medical treatment situation as it would be without the medicinal product to be assessed. According to Section 6, paragraph 2, sentence 3 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV), the G-BA may exceptionally determine the off-label use of medicinal products as an appropriate comparator therapy or as part of the appropriate comparator therapy if it determines by resolution on the benefit assessment according to Section 7, paragraph 4 that, according to the generally recognised state of medical knowledge, this is considered a therapy standard in the therapeutic indication to be assessed or as part of the therapy standard in the medical treatment situation to be taken into account according to sentence 2, and

1. for the first time, a medicinal product approved in the therapeutic indication is available with the medicinal product to be assessed,

2. according to the generally recognised state of medical knowledge, the off-label use is generally preferable to the medicinal products previously approved in the therapeutic indication, or

3. according to the generally recognised state of medical knowledge, the off-label use for relevant patient groups or indication areas is generally preferable to the medicinal products previously approved in the therapeutic indication.

An appropriate comparator therapy may also be non-medicinal therapy, the best possible add-on therapy including symptomatic or palliative treatment, or monitoring wait-and-see approach.

<u>Justification based on the criteria set out in Chapter 5 Section 6, paragraph 3 VerfO and Section 6, paragraph 2 AM-NutzenV:</u>

on 1. In addition to daratumumab, the following active ingredients are approved in the present therapeutic indication:

bendamustine, carmustine, cyclophosphamide, doxorubicin, melphalan, vincristine, bortezomib, lenalidomide, thalidomide, dexamethasone, prednisolone and prednisone.

Some of the marketing authorisations are tied to (specific) concomitant active ingredients. In addition, the combination of bortezomib, cyclophosphamide and dexamethasone can be prescribed off-label.

on 2. According to the therapeutic indication, patients are ineligible for autologous stem cell transplant. A non-medicinal treatment option is not considered as an appropriate comparator therapy for the therapeutic indication in question.

on 3. Resolutions on the benefit assessment of medicinal products with new active ingredients according to Section 35a SGB V:

- Daratumumab – resolution of 18 March 2022 (combination with lenalidomide and dexamethasone)

The resolution on the benefit assessment of medicinal products with new active ingredients according to Section 35a SGB V for daratumumab from 22 March 2019 is available for the therapeutic indication of newly diagnosed multiple myeloma in case of unsuitability for autologous stem cell transplantation, and is replaced by the present resolution.

Annex VI to Section K of the Pharmaceuticals Directive - prescribability of approved medicinal products in non-approved therapeutic indications (off-label use):

- Bortezomib plus cyclophosphamide plus dexamethasone for the induction therapy of newly diagnosed multiple myeloma (resolution of 20 May 2021)

on 4. The generally recognised state of medical knowledge was illustrated by a systematic search for guidelines as well as systematic reviews of clinical studies in the present indication and is presented in the "Research and synopsis of the evidence to determine the appropriate comparator therapy according to Section 35a SGB V".

The scientific-medical societies and the Drugs Commission of the German Medical Association (AkdÄ) were also involved in writing on questions relating to the comparator therapy in the present therapeutic indication according to Section 35a, paragraph 7 SGB V. Written statements from the AkdÄ as well as the German Society for Haematology and Medical Oncology (DGHO) are available.

Among the approved active ingredients listed under 1.), only certain active ingredients named below will be included in the appropriate comparator therapy, taking into account the evidence on therapeutic benefit, the guideline recommendations and the reality of health care provision.

The available evidence on the treatment of patients with newly diagnosed multiple myeloma who are ineligible for autologous stem cell transplant recommends trio or tetra combination therapies based on an immunomodulator and/or proteasome inhibitor. In this regard, the combination therapies bortezomib + melphalan + prednisone, thalidomide + melphalan + prednisone, lenalidomide + melphalan + prednisone and the combination therapy bortezomib + lenalidomide + dexamethasone can be considered according to the authorisation status. The dual combination of

lenalidomide + dexamethasone is therefore not defined as an appropriate comparator therapy.

In addition, two combination therapies based on the CD38 antibody daratumumab are approved for patients with newly diagnosed multiple myeloma who are ineligible for autologous stem cell transplant. By resolution of 22 March 2019, the G-BA determined a considerable additional benefit of the combination therapy daratumumab + bortezomib + melphalan + prednisone, compared to a combination therapy according to doctor's instructions. The period of validity of this resolution is limited to 1 December 2023. By resolution of 18 March 2022, the G-BA identified a hint for a considerable additional benefit of the combination therapy daratumumab + lenalidomide + dexamethasone compared to lenalidomide + dexamethasone. Both combination therapies have found their way into current guidelines.

The subject of the present assessment is a reassessment of the combination therapy of daratumumab + bortezomib + melphalan + prednisone due to the expiry of the deadline. According to Section 6, paragraph 2, sentence 2 AM-NutzenV, the determination of the appropriate comparator therapy must be based on the actual medical treatment situation as it would be without the medicinal product to be assessed. Against this background, this combination cannot be considered as an appropriate comparator therapy.

Furthermore, the combination therapy of bortezomib, cyclophosphamide and dexamethasone can be prescribed off-label for patients with peripheral polyneuropathy or an increased risk of developing peripheral polyneuropathy in the therapeutic indication of newly diagnosed multiple myeloma, irrespective of the eligibility for stem cell transplantation. This combination is also recommended in the available evidence.

Overall, the combinations mentioned in the appropriate comparator therapy are equally appropriate comparator therapies.

The evidence for the combination therapy of lenalidomide + melphalan + prednisone is inferior overall compared to the other combination therapies. In contrast to bortezomib or thalidomide+ melphalan + prednisone, no advantage compared to melphalan + prednisone was shown with regard to survival. Lenalidomide + melphalan + prednisons is therefore not determined in the present therapeutic indication as an appropriate comparator therapy.

The findings in Annex XII do not restrict the scope of treatment required to fulfil the medical treatment mandate.

A change in the appropriate comparator therapy requires a resolution by the G-BA linked to the prior review of the criteria according to Chapter 5 Section 6, paragraph 3 Rules of Procedure.

2.1.3 Extent and probability of the additional benefit

In summary, the additional benefit of daratumumab is assessed as follows:

Adults with newly diagnosed multiple myeloma who are ineligible for autologous stem cell transplant

Indication of a considerable additional benefit

Justification:

The pharmaceutical company has submitted data from the open-label, randomised, controlled phase III ALCYONE and OCTANS studies for benefit assessment. The data from the OCTANS study were presented additionally, as they were unsuitable for deriving an additional benefit from the perspective of the pharmaceutical company.

These ongoing ALCYONE and OCTANS studies compare daratumumab in combination with bortezomib + melphalan + prednisone (D-VMP regimen) versus bortezomib + melphalan + prednisone (VMP regimen).

ALCYONE study:

In the ALCYONE study, a total of 706 patients were enrolled and randomised in a 1:1 ratio to the two study arms (N = 350 D-VMP; N = 356 VMP). The study has been conducted in 162 study sites in Australia, Europe, South America, USA and Asia since 2015. Stratification was by International Staging System (ISS) stage (I vs II vs III), region (Europe vs other), and age (< 75 years vs ≥ 75 years). The mean age of the patients was 71 years.

Overall, five data cut-offs are available. For the present benefit assessment, the fifth data cut-off from 31 May 2023 is used for the final analysis. This is the data cut-off after reaching approximately 382 events in the overall survival endpoint, whereby the number of events was increased by protocol amendment 8. Originally, the study was to be terminated after 330 deaths or 5 years after randomisation of the last patient. At the final data cut-off, results are available for the endpoint categories of mortality, morbidity, health-related quality of life and side effects.

OCTANS study:

A total of 220 patients in 39 study sites in the Asia-Pacific region were enrolled in the OCTANS study and randomised in a 2:1 ratio to the two study arms (N = 146 D-VMP; N = 74 VMP). Stratification was based on the same criteria as in the ALCYONE study. The mean age of the patients was 70 years. The start of study was December 2017.

Overall, three data cut-offs are available. For the present benefit assessment, the third data cut-off from 23.12.2022 is used for the pre-specified final analysis. Results of the endpoint categories of mortality, morbidity, health-related quality of life and side effects are available for this data cut-off.

The pharmaceutical company presented the OCTANS study only as a supplement and justifies this with the lack of transferability to the German healthcare context. The pharmaceutical company assumes that a relevant percentage of subjects in the Asia-Pacific region and particularly in China have not received an autologous stem cell transplant (ASCT), even though they would be suitable for one.

From a medical point of view, the higher percentage of potentially ASCT-eligible patients in the OCTANS study results in uncertainty with regard to transferability to the German healthcare context. From the oral and written statements of the scientific-medical societies, it can be deduced that there is at least some uncertainty regarding the transferability of the OCTANS study to the German healthcare context, particularly with regard to the transplantation of older patients with multiple myeloma and the availability of specific subsequent therapies. However, the scientific-medical societies also point out that the study results are comparable despite these possible differences. The subgroup analyses presented by the pharmaceutical company for the characteristic ASCT ineligibility also indicate very similar effects in decision-relevant endpoints (see below). Taking into account the aspects described, the results of the OCTANS study are assessed as adequately significant and used for the benefit assessment.

<u>On the eligibility criteria for autologous stem cell transplantation (ASCT) in the ALCYONE and OCTANS studies</u>

According to the inclusion criteria of the ALCYONE and OCTANS studies, patients had to be at least 65 years old or have significant comorbidities in order to be considered unsuitable for ASCT. Since the start of the studies, the generally recognised state of medical knowledge for the assessment of patients with regard to suitability for ASCT has developed further. Accordingly, biological age has become more important than chronological age, taking into account relevant comorbidities. As a result, patients may have been enrolled in the studies who would be suitable for ASCT according to the generally recognised state of medical knowledge. To address this issue, at the request of the European Medicines Agency (EMA), the pharmaceutical company presented ASCT ineligibility data for a sub-population, which was operationalised based on the criteria of age < 65 years with significant comorbidities or age 65 - 69 years with an ECOG-PS = 2 or age ≥ 70 years. These criteria were met by 77% (ALCYONE) and 55% (OCTANS) of the patients in the respective total populations (averaged over both studies: 72%).

For the total populations as well as for the post hoc defined sub-populations, the uncertainty arises that the percentage of patients who would actually not have been eligible for ASCT is unclear. The procedure chosen by the pharmaceutical company to operationalise the sub-populations (ASCT ineligibility) is understandable and is considered to be a sufficient approximation to the target population. Nevertheless, the resulting sub-populations, like the total populations, are subject to uncertainty, as the assessment of ASCT ineligibility would have to be patient-individual and independent of chronological age. The information required for this can no longer be determined post hoc. However, a comparison of the sub-populations

results with those of the total populations shows that the magnitude of the effect for the decision-relevant endpoints is very similar in each case. Therefore, the total populations in each case are used for the benefit assessment.

On the meta-analytic summary of the ALCYONE and OCTANS studies

The design and patient characteristics of the ALCYONE and OCTANS studies are comparable. In addition, there was no heterogeneity in the studies in the relevant endpoints for the benefit assessment. IQWIG therefore summarised the study results in a meta-analysis.

In the written statement procedure, the pharmaceutical company states that the OCTANS study enrolled a relevantly larger percentage of patients who could be suitable for ASCT according to the generally recognised state of medical knowledge.

Due to this additional uncertainty regarding the ASCT ineligibility, the pharmaceutical company presents the meta-analytic summary with the ALCYONE study only additionally.

From a medical point of view, the higher percentage of potentially ASCT-eligible patients in the OCTANS study results in additional uncertainty. However, as explained above, the study results of the OCTANS study are assessed as adequately significant and used for the benefit assessment.

Accordingly, the uncertainties described are not considered to be so serious that they prevent a meta-analytic summary, taking into account the comparable study designs and patient populations and the lack of heterogeneity between the studies. Therefore, the meta-analytic summary of the ALCYONE and OCTANS studies is used as the basis for the benefit assessment.

On the implementation of conditions for a time limit

According to the justification of the resolution of 22 March 2019, the limitation was that further clinical data from the ALCYONE study are expected, which may be relevant for the benefit assessment. For the renewed benefit assessment after the expiry of the deadline, the pharmaceutical company should submit the final results of the ALCYONE study on all patient-relevant endpoints.

By resolution of 19 January 2023 on the amendment of the limitation for the period of validity of the resolution of 22 March 2019, the presentation and discussion of a sensitivity analysis with censoring of all patients after the occurrence of 330 events in the overall survival endpoint was decided as a further time limit condition in order to enable the assessment of a risk of bias due to the subsequent increase in the necessary number of events in the overall survival endpoint for the final study analysis.

In the dossier, the pharmaceutical company presents the final results of the ALCYONE study and the results of the OCTANS study. In addition, the pharmaceutical company submits the commissioned sensitivity analysis after reaching 330 events in the overall survival endpoint for the ALCYONE study. The time limit requirements are therefore deemed to have been implemented.

Extent and probability of the additional benefit

Mortality

Overall survival was operationalised in the ALCYONE and OCTANS studies as the time between randomisation and the date of death from any cause. In the ALCYONE study, the required number of events in the overall survival endpoint for the time of the final analysis was increased from 330 events to 382 events with a protocol amendment in order to achieve the median overall survival in both study arms. For the benefit assessment, the results on overall survival after reaching the originally planned 330 events are primarily used, as the decision to postpone the final analysis was made with knowledge of the data and was therefore potentially event-driven.

In the meta-analytic summary of the ALCYONE and OCTANS studies, there was a statistically significant difference in favour of daratumumab + bortezomib + melphalan + prednisone compared to bortezomib + melphalan + prednisone.

The information on the subsequent therapies used following termination of the study medication in the ALCYONE and OCTANS studies shows that relatively few daratumumab-based combination therapies were used in the comparator arm.

In the written statement and oral hearing on the present benefit assessment procedure, the scientific-medical societies stated that the choice of subsequent therapies at the time of the treatment decision was in line with the guidelines.

From the G-BA's point of view, uncertainties arise in this respect against the background of a generally long course of disease with several successive lines of therapy, but these do not prevent a quantification of the extent of the effect in the overall survival endpoint, even taking into account the existing effect magnitude. Taking these considerations into account, the statistically significant advantage of the daratumumab combination in the overall survival endpoint is considered to be a significant prolongation of overall survival.

Morbidity

Progression-free survival (PFS)

Progression-free survival (PFS) is the primary endpoint of the ALCYONE study and a secondary endpoint of the OCTANS study. It is operationalised in each case as the time from randomisation to the onset of disease progression or death.

In the ALCYONE and OCTANS studies, there was a statistically significant difference in PFS in favour of daratumumab + bortezomib + melphalan + prednisone compared to bortezomib + melphalan + prednisone.

The PFS endpoint is a composite endpoint composed of endpoints of the categories "mortality" and "morbidity". The endpoint component "mortality" has already been assessed as an independent endpoint via the endpoint "overall survival". The morbidity component

"disease progression" is assessed according to IMWG criteria and thus, not in a symptom-related manner but by means of laboratory parametric, imaging, and haematological procedures. Taking into account the aspects mentioned above, there are different opinions within the G-BA regarding the patient-relevance of the endpoint PFS. The overall statement on the additional benefit remains unaffected.

EORTC QLQ-C30 - symptom scales

In the ALCYONE and OCTANS studies, disease symptomatology is assessed using the cancer-specific EORTC-QLQ-C30 questionnaire.

In the dossier, the pharmaceutical company presents responder analyses on both improvement and deterioration in disease symptomatology. Due to the expected progressive course of the disease in multiple myeloma, an analysis of the deterioration of symptomatology is primarily relevant for the present benefit assessment. The time to first deterioration of ≥ 10 points is therefore used for the present benefit assessment.

In the meta-analytic summary of ALCYONE and OCTANS, there is a statistically significant difference in favour of daratumumab + bortezomib + melphalan + prednisone compared to bortezomib + melphalan + prednisone for the fatigue symptom.

The meta-analytic summary of the ALCYONE and OCTANS studies showed no significant differences between the study arms for the other symptoms.

Overall, the daratumumab combination has therefore an advantage for the fatigue symptom.

Health status (EQ-5D VAS)

In the present studies, health status is assessed using the visual analogue scale (VAS) of the European Quality of Life Questionnaire 5 Dimensions (EQ-5D). For the present benefit assessment, the time to first deterioration in health status by ≥ 15 points is used.

In the meta-analytic summary of ALCYONE and OCTANS, no statistically significant difference was found between the study arms for health status.

Quality of life

EORTC QLQ-C30 - functional scales

Health-related quality of life will be assessed in the ALCYONE and OCTANS studies using the functional scales of the EORTC-QLQ-C30.

In the dossier, the pharmaceutical company presents responder analyses on both improvement and deterioration in health-related quality of life. Due to the expected progressive course of the disease in multiple myeloma, an analysis of the deterioration of quality of life is primarily relevant for the present benefit assessment. The time to first deterioration of ≥ 10 points is therefore used for the present benefit assessment.

In the meta-analytic summary of the ALCYONE and OCTANS studies, there is a statistically significant difference for global health status in favour of daratumumab + bortezomib + melphalan + prednisone compared to bortezomib + melphalan + prednisone.

In the meta-analytic summary of the ALCYONE and OCTANS studies, no statistically significant differences were found between the study arms for the other functional scales (physical functioning, role functioning, emotional functioning, cognitive functioning, social functioning).

Overall, the daratumumab combination therefore showed an advantage for the global health status in detail.

Side effects

Adverse events (AEs)

One adverse event occurred in almost all study participants in the ALCYONE study and in all study participants in the OCTANS study. The results were only presented additionally.

Serious AEs (SAEs), severe AEs and discontinuation due to AEs (at least 1 therapy component)

In the meta-analytic summary of the ALCYONE and OCTANS studies, no statistically significant differences were found between the study arms for the endpoints of SAEs, severe AEs and discontinuation due to AEs (at least 1 therapy component).

Specific AEs

The pharmaceutical company does not provide suitable data for the endpoint "infusion-related reaction", as this endpoint was only collected in the daratumumab arm in the ALCYONE and OCTANS studies. A comparison between the study arms is not possible on the basis of this endpoint.

The meta-analytic summary of ALCYONE and OCTANS studies shows no significant difference between the study arms in the endpoint "peripheral neuropathy (severe AEs)".

A meta-analytic summary is not possible for the specific AEs listed below, therefore the data from the ALCYONE study are used as an approximation for the benefit assessment.

For the endpoints "infections and infestations (severe AEs)", "vascular disorders (severe AEs)" and "respiratory, thoracic and mediastinal disorders (AEs)", there was a statistically significant difference to the disadvantage of the daratumumab combination in the ALCYONE study.

Conclusion on side effects

In the overall assessment, there were no statistically significant differences between the treatment arms in the endpoint category of side effects for SAEs, severe AEs, and discontinuations due to AEs. The ALCYONE study showed disadvantages of daratumumab combination therapy for some of the specific AEs. As these disadvantages are not reflected in the overall rates of AEs, SAEs and severe AEs in the meta-analytic summary of ALCYONE and

OCTANS studies, these differences do not lead to a change in the assessment of additional benefit.

Overall assessment

For the assessment of the additional benefit of daratumumab in combination with bortezomib, melphalan, and prednisone for the treatment of adult patients with newly diagnosed multiple myeloma who are not eligible for autologous stem cell transplantation, results from the ALCYONE and OCTANS studies are available regarding mortality, morbidity, quality of life, and side effects compared to the combination therapy of bortezomib + melphalan + prednisone. Both studies were subject to meta-analysis and summarised.

For overall survival, the meta-analysis shows a statistically significant difference to the advantage of the daratumumab combination, the overall extent of which is assessed as a clear prolongation of survival.

With regard to morbidity, the meta-analysis of the EORTC QLQ-C30 symptom scale of fatigue shows an advantage of daratumumab combination therapy. No significant differences between the study arms were found in the other symptom scales or in the EQ-5D VAS in the meta-analysis.

In terms of health-related quality of life, the meta-analysis shows a detailed advantage of daratumumab combination therapy for the global health status functional scale of the EORTC QLQ-C30. No significant differences between the study arms were found for the other functional scales in the meta-analysis.

With regard to the endpoint category of side effects, there are no statistically significant differences between the treatment arms for the overall rate of severe AEs, SAEs and discontinuation due to AEs. There are disadvantages of daratumumab combination therapy for some of the specific AEs. Since these disadvantages are not reflected in the overall rates of AEs, SAEs and severe AEs, these differences do not lead to a change in the assessment of additional benefit.

In summary, daratumumab in combination with bortezomib, melphalan and prednisone for the treatment of patients with newly diagnosed multiple myeloma who are ineligible for ASCT was found to have a considerable additional benefit compared with bortezomib, melphalan and prednisone.

Reliability of data (probability of additional benefit)

The present assessment is based on the results of the meta-analytic summary of the randomised, open-label, controlled phase III ALCYONE and OCTANS studies.

At the study level, the risk of bias is considered low. However, there are significant uncertainties as the studies also include patients who could be eligible for ASCT according to

current eligibility criteria. The information required to fully eliminate these uncertainties can no longer be determined post hoc.

The risk of bias at endpoint level is classified as low for overall survival and high for the other endpoints.

In the endpoint categories of morbidity and health-related quality of life, the lack of blinding leads to a high risk of bias. In the endpoint category of side effects, there is a high risk of bias in the endpoints of SAEs and discontinuation due to AEs (at least 1 therapy component), as the analysis included a few subjects who were followed up for longer than the maximum duration of observation. In addition, some endpoints of the side effects may be biased due to the lack of blinding.

Based on the increased reliability of data of the meta-analytic summary, an overall indication of an additional benefit of daratumumab can be derived, taking into account the relevant uncertainties mentioned above.

2.1.4 Summary of the assessment

The present assessment is the new benefit assessment of the active ingredient daratumumab due to the expiry of limitation of the resolution of 22 March 2019 on the benefit assessment of daratumumab in combination with bortezomib, melphalan and prednisone for the treatment of adults with newly diagnosed multiple myeloma who are ineligible for autologous stem cell transplantation. Bortezomib in combination with melphalan and prednisone was determined by the G-BA as an appropriate comparator therapy. For this benefit assessment, the pharmaceutical company presented the results from the randomised, controlled phase III ALCYONE and OCTANS studies. Both studies were subject to meta-analysis and summarised.

For overall survival, the meta-analysis shows a statistically significant difference to the advantage of the daratumumab combination, the overall extent of which is assessed as a clear prolongation of survival.

With regard to morbidity, the meta-analysis in the EORTC QLQ-C30 shows an advantage of the daratumumab combination for fatigue in detail. In the other symptom scales and in the EQ-5D VAS, neither advantages nor disadvantages were found in the meta-analysis.

With regard to health-related quality of life, the meta-analysis in the EORTC QLQ-C30 shows an advantage of the daratumumab combination in detail for global health status. For the other functional scales, neither advantages nor disadvantages can be identified in the meta-analysis.

With regard to the endpoint category of side effects, there are no statistically significant differences between the treatment arms for the overall rate of severe AEs, SAEs and discontinuation due to AEs. For some of the specific AEs, there are disadvantages of the daratumumab combination that do not lead to a change in the assessment of additional benefit.

In summary, daratumumab in combination with bortezomib, melphalan and prednisone for the treatment of patients with newly diagnosed multiple myeloma who are ineligible for ASCT was found to have a considerable additional benefit compared with bortezomib, melphalan and prednisone.

There are relevant uncertainties in the reliability of data, as the studies also include patients who could be eligible for ASCT according to current eligibility criteria. Overall, the reliability of data is rated as an indication.

2.2 Number of patients or demarcation of patient groups eligible for treatment

The information on the number of patients is based on the target population in statutory health insurance (SHI).

The resolution is based on the information from the dossier of the pharmaceutical company. Overall, the number of patients stated by the pharmaceutical company is plausible based on the data presented.

2.3 Requirements for a quality-assured application

The requirements in the product information are to be taken into account. The European Medicines Agency (EMA) provides the contents of the product information (summary of product characteristics, SmPC) for Darzalex (active ingredient: daratumumab) at the following publicly accessible link (last access: 4 April 2024):

https://www.ema.europa.eu/en/documents/product-information/darzalex-epar-product-information_en.pdf

Treatment with daratumumab should only be initiated and monitored by specialists in internal medicine, haematology and oncology experienced in the treatment of patients with multiple myeloma.

In accordance with the EMA requirements regarding additional risk minimisation measures, the pharmaceutical company must provide training material and a patient identification card. The training material for medical professionals and blood banks contains instructions on how to manage the risk of daratumumab interfering with blood typing (indirect antihuman globulin test or indirect Coombs test). Interference with blood typing induced by daratumumab may persist for up to 6 months after the last infusion of the medicinal product; therefore, medical professionals should advise patients to carry their patient identification card with them for up to 6 months after the end of the treatment.

2.4 Treatment costs

The treatment costs are based on the requirements in the product information and the information listed in the LAUER-TAXE® (last revised: 15 April 2024).

The annual treatment costs shown refer to the first year of treatment.

If no maximum treatment duration is specified in the product information, the treatment duration is assumed to be one year (365 days), even if the actual treatment duration varies from patient to patient and/or is shorter on average. The time unit "days" is used to calculate the "number of treatments/ patient/ year", time intervals between individual treatments and for the maximum treatment duration, if specified in the product information.

The (daily) doses recommended in the product information were used as the calculation basis.

For the cost representation, only the dosages of the general case are considered. Patient-individual dose adjustments (e.g. because of side effects or comorbidities) are not taken into account when calculating the annual treatment costs.

Treatment period:

Adults with newly diagnosed multiple myeloma who are ineligible for autologous stem cell transplant

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Medicinal product to be assessed				
Daratumumab in combination with bortezomib, melphalan and prednisone				
Daratumumab	42-day cycle: Week 1 - 6: 1 x every 7 days Week 7 - 54: every 21 days From week 55: every 28 days	8.7	2 - 6	21.4
Bortezomib	2 x within 7 days in weeks 1, 2, 4, 5 of the first 42-day cycle Subsequently, for each cycle	8.7	4 - 8	38.8

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
	(cycle 2 – 9): 1 x every 7 days in weeks 1, 2, 4, 5			
Melphalan	Day 1 - 4 of the 42-day cycles	8.7	4	34.8
Prednisone	Day 2 - 4 of the 42-day cycles	8.7	3	26.1
Appropriate comparator therapy				
Daratumumab in combination with lenalidomide and dexamethasone				
Daratumumab	Week 1 - 8: 1 x every 7 days Week 9 - 24: every 14 days From week 25: every 28 days	23	1	23
Lenalidomide	Day 1 - 21 28-day cycle	13.0	21	273
Dexamethasone	Day 1, 8, 15, 22 28-day cycle	13.0	0 (cycle 1 - 2) 2 (cycle 3 - 6) 3 (from cycle 7)	29[2]
Bortezomib in combination with melphalan and prednisone				
Bortezomib	42-day cycle: Cycles 1 - 4, 8 applications each; cycles 5 - 9, 4 applications each	8.7	4 – 8	50.8
Melphalan	Day 1 - 4 of the 42-day cycles	8.7	4	34.8
Prednisone	Day 1 - 4 of the 42-day cycles	8.7	4	34.8
Bortezomib in combination with lenalidomide and dexamethasone				
Induction				

[2] On the days of daratumumab administration, 20 mg of the dexamethasone dose is used as premedication and 20 mg on the day after daratumumab administration

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Bortezomib	On days 1, 4, 8 and 11 of a 21-day cycle	8	4	32
Lenalidomide	Day 1 – 14 of a 21-day cycle	8	14	112
Dexamethasone	On days 1, 2, 4, 5, 8, 9, 11 and 12 of a 21-day cycle	8	8	64
Follow-up treatment				
Lenalidomide	Day 1 – 21 of a 28-day cycle	7	21	147
Dexamethasone	On days 1, 8, 15 and 22 of a 28-day cycle	7	4	28
Thalidomide in combination with melphalan and prednisone				
Thalidomide	Day 1 – 42 of a 42-day cycle	8.7	42	365
Melphalan	Day 1 – 4 of a 42-day cycle	8.7	4	34.8
Prednisone	Day 1 – 4 of a 42-day cycle	8.7	4	34.8
Bortezomib in combination with cyclophosphamide and dexamethasone[3]				
Bortezomib	Day 1, 4, 8 and 11 of a 21-day cycle	17.4	4	69.6
Cyclophosphamide	Day 1 of a 21-day cycle	17.4	1	17.4
Dexamethasone	Day 1, 2, 4, 5, 8, 9, 11, 12 of a 21-day cycle	17.4	8	139.2

[3] cf. Annex VI to Section K of the Pharmaceuticals Directive - Prescribability of approved medicinal products in non-approved therapeutic indications (so-called off-label use):

Consumption:

For dosages depending on body weight (BW) or body surface area (BSA), the average body measurements from the official representative statistics "Microcensus 2021 – body measurements of the population" were applied (average body height: 1.72 m; average body weight: 77.7 kg). This results in a body surface area of 1.91 m² (calculated according to Du Bois 1916) [4].

As it is not always possible to achieve the exact calculated dose per day with the commercially available dose potencies, in these cases rounding up or down to the next higher or lower available dose that can be achieved with the commercially available dose potencies as well as the scalability of the respective dosage form.

Adults with newly diagnosed multiple myeloma who are ineligible for autologous stem cell transplant

Designation of the therapy	Dosage/ application	Dose/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
Medicinal product to be assessed					
Daratumumab	1,800 mg	1,800 mg	1 x 1,800 mg	21.4	21.4 x 1,800 mg
Bortezomib	1.3 mg/m² = 2.5 mg	2.5 mg	1 x 2.5 mg	38.8	38.8 x 2.5 mg
Melphalan	9 mg/m² = 17.2 mg	17.2 mg	9 x 2 mg	34.8	313.2 x 2 mg
Prednisone	60 mg/m² = 114.6 mg	114.6 mg	2 x 50 mg + 1 x 20 mg	26.1	52.2 x 50 mg + 26.1 x 20 mg
Appropriate comparator therapy					
Daratumumab in combination with lenalidomide and dexamethasone					
Daratumumab	1,800 mg	1,800 mg	1 x 1,800 mg	23	23 x 1,800 mg
Lenalidomide	25 mg	25 mg	1 x 25 mg	273	273 x 25 mg
Dexamethasone	40 mg	40 mg	40 mg	29	29 x 40 mg
Bortezomib in combination with melphalan and prednisone					

[4] Federal Health Reporting. Average body measurements of the population (2021, both sexes, 18 years and older), www.gbe-bund.de

Designation of the therapy	Dosage/ application	Dose/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
Bortezomib	1.3 mg/m^2 = 2.5 mg	2.5 mg	1 x 2.5 mg	50.8	50.8 x 2.5 mg
Melphalan	9 mg/m^2 = 17.2 mg	17.2 mg	9 x 2 mg	34.8	313.2 x 2 mg
Prednisone	60 mg/m^2 = 114.6 mg	114.6 mg	2 x 50 mg + 1 x 20 mg	34.8	69.6 x 50 mg + 34.8 x 20 mg
Bortezomib in combination with lenalidomide and dexamethasone					
Induction					
Bortezomib	1.3 mg/m^2 = 2.5 mg	2.5 mg	1 x 2.5 mg	32	32 x 2.5 mg
Lenalidomide	25 mg	25 mg	1 x 25 mg	112	112 x 25 mg
Dexamethasone	20 mg	20 mg	1 x 20 mg	64	64 x 20 mg
Follow-up treatment					
Lenalidomide	25 mg	25 mg	1 x 25 mg	147	147 x 25 mg
Dexamethasone	40 mg	40 mg	1 x 40 mg	28	28 x 40 mg
Thalidomide in combination with melphalan and prednisone					
Thalidomide	200 mg	200 mg	4 x 50 mg	365	1,460 x 50 mg
Melphalan	0.25 mg/kg = 19.4 mg	19.4 mg	10 x 2 mg	34.8	348 x 2 mg
Prednisone	2 mg/kg = 155.4 mg	155.4 mg	3 x 50 mg + 1 x 5 mg	34.8	104.4 x 50 mg + 34.8 x 5 mg
Bortezomib in combination with cyclophosphamide and dexamethasone					
Bortezomib	1.3 mg/m^2 = 2.5 mg	2.5 mg	1 x 2.5 mg	69.6	69.6 x 2.5 mg
Cyclophosphamide	900 mg/m^2 = 1,719 mg	1,719 mg	2 x 1,000 mg[5]	17.4	34.8 x 1,000 mg
Dexamethasone	40 mg	40 mg	1 x 40 mg	139.2	139.2 x 40 mg[2]

[5] The administration form must be intravenous according to Annex VI of the Pharmaceuticals Directive.

Costs:

In order to improve comparability, the costs of the medicinal products were approximated both on the basis of the pharmacy sales price level and also deducting the statutory rebates in accordance with Section 130 and Section 130a SGB V. To calculate the annual treatment costs, the required number of packs of a particular potency was first determined on the basis of consumption. Having determined the number of packs of a particular potency, the costs of the medicinal products were then calculated on the basis of the costs per pack after deduction of the statutory rebates. Any fixed reimbursement rates shown in the cost representation may not represent the cheapest available alternative.

Costs of the medicinal products:

Adults with newly diagnosed multiple myeloma who are ineligible for autologous stem cell transplant

Designation of the therapy	Packaging size	Costs (pharmacy sales price)	Rebate Section 130 SGB V	Rebate Section 130a SGB V	Costs after deduction of statutory rebates
Medicinal product to be assessed					
Daratumumab 1,800 mg	1 SFI	€ 5,937.34	€ 2.00	€ 0.00	€ 5,935.34
Bortezomib 2.5 mg	1 PSI	€ 185.37	€ 2.00	€ 8.26	€ 175.11
Melphalan 2 mg	50 FCT	€ 54.22	€ 2.00	€ 2.38	€ 49.84
Prednisone 20 mg[6]	50 TAB	€ 20.91	€ 2.00	€ 0.76	€ 18.15
Prednisone 50 mg6	50 TAB	€ 68.06	€ 2.00	€ 4.49	€ 61.57
Appropriate comparator therapy					
Bortezomib 2.5 mg	1 PSI	€ 185.37	€ 2.00	€ 8.26	€ 175.11
Cyclophosphamide 1,000 mg	6 PSI	€ 127.45	€ 2.00	€ 6.43	€ 119.02
Daratumumab 1,800 mg	1 SFI	€ 5,937.34	€ 2.00	€ 0.00	€ 5,935.34
Dexamethasone 40 mg[6]	50 TAB	€ 188.03	€ 2.00	€ 0.00	€ 186.03
Dexamethasone 20 mg[6]	50 TAB	€ 118.88	€ 2.00	€ 0.00	€ 116.88
Dexamethasone 20 mg[6]	20 TAB	€ 54.09	€ 2.00	€ 0.00	€ 52.09
Lenalidomide 25 mg[6]	63 HC	€ 117.32	€ 2.00	€ 8.38	€ 106.94
Melphalan 2 mg	50 FCT	€ 54.22	€ 2.00	€ 2.38	€ 49.84
Prednisone 5 mg[6]	50 TAB	€ 14.18	€ 2.00	€ 0.23	€ 11.95
Prednisone 20 mg[6]	50 TAB	€ 20.91	€ 2.00	€ 0.76	€ 18.15
Prednisone 50 mg[6]	50 TAB	€ 68.06	€ 2.00	€ 4.49	€ 61.57
Thalidomide 50 mg	28 HC	€ 568.02	€ 2.00	€ 31.84	€ 534.18
Abbreviations: FCT = film-coated tablets, HC = hard capsules; SFI = solution for injection; PSI = powder for solution for injection; TAB = tablets					

LAUER-TAXE® last revised: 15 April 2024

[6] Fixed reimbursement rate

Costs for additionally required SHI services:

Only costs directly related to the use of the medicinal product are taken into account. If there are regular differences in the necessary use of medical treatment or in the prescription of other services in the use of the medicinal product to be evaluated and the appropriate comparator therapy in accordance with the product information, the costs incurred for this must be taken into account as costs for additionally required SHI services.

Medical treatment costs, medical fee services, and costs incurred for routine examinations (e.g. regular laboratory services such as blood count tests) that do not exceed the standard expenditure in the course of the treatment are not shown.

Non-prescription medicinal products that are reimbursable at the expense of the statutory health insurance according to Annex I of the Pharmaceuticals Directive (so-called OTC exception list) are not subject to the current medicinal products price regulation. Instead, in accordance with Section 129 paragraph 5aSGB V, when a non-prescription medicinal product is dispensed and invoiced in accordance with Section 300, a medicinal product dispensing price in the amount of the dispensing price of the pharmaceutical company plus the surcharges in accordance with Sections 2 and 3 of the Pharmaceutical Price Ordinance in the version valid on 31 December 2003 applies to the insured.

Designation of the therapy	Packaging size	Costs (pharmacy sales price)	Rebate Section 130 SGB V	Rebate Section 130a SGB V	Costs after deduction of statutory rebates	Treatment days/ year	Costs/ patient/ year
Medicinal product to be assessed: Daratumumab (in combination with bortezomib, melphalan and prednisone)							
Dexamethasone 20 mg[6]	50 TAB	€ 118.88	€ 2.00	€ 0.00	€ 116.88	21.4	€ 50.02
Paracetamol 500 – 1,000 mg[6]	20 TAB (500 mg)	€ 3.47	€ 0.17	€ 0.15	€ 3.15	21.4	€ 3.37
	10 TAB (1,000 mg)	€ 3.32	€ 0.17	€ 0.14	€ 3.01		€ 6.44
Dimetindene IV 1 mg/10 kg	5 SFI (4 mg)	€ 23.72	€ 2.00	€ 5.29	€ 16.43	21.4	€ 140.64
Appropriate comparator therapy							
Daratumumab (in combination with lenalidomide and dexamethasone)							
Dexamethasone 40 mg[6]	50 TAB	€ 188.03	€ 2.00	€ 0.00	€ 186.03	23	€ 85.57
Paracetamol 500 – 1,000 mg[6]	20 TAB (500 mg)	€ 3.47	€ 0.17	€ 0.15	€ 3.15	23	€ 3.62
	10 TAB (1,000 mg)	€ 3.32	€ 0.17	€ 0.14	€ 3.01		€ 6.92

Designation of the therapy	Packaging size	Costs (pharmacy sales price)	Rebate Section 130 SGB V	Rebate Section 130a SGB V	Costs after deduction of statutory rebates	Treatment days/ year	Costs/ patient/ year
Dimetindene IV 1 mg/10 kg	5 SFI (4 mg)	€ 23.72	€ 2.00	€ 5.29	€ 16.43	23	€ 151.16
Abbreviations: SFI = solution for injection; TAB = tablets							

Patients receiving therapy with daratumumab and lenalidomide should be tested for the presence of a hepatitis B virus (HBV) infection before initiating the respective treatment. For the diagnosis of suspected chronic hepatitis B, sensibly coordinated steps are required[7]. A step-by-step serological diagnosis initially consists of the examination of HBs antigen and anti-HBc antibodies. If both are negative, a past HBV infection can be excluded. If HBs antigen is positive, an active HBV infection is detected.

In deviation from this, additional required SHI services are required for the diagnosis of suspected chronic hepatitis B, which usually differ between the medicinal product to be evaluated and the appropriate comparator therapy and are consequently considered as additionally required SHI services in the resolution.

Designation of the therapy	Designation of the service	Number	Unit cost	Costs/ patient/ year
Medicinal product to be assessed				
Daratumumab	HBs antigen (GOP 32781)	1	€ 5.50	€ 5.50
	Anti-HBs antibody (GOP 32617)	1	€ 5.50	€ 5.50
	Anti-HBc antibody (GOP 32614)	1	€ 5.90	€ 5.90
	HBV-DNA (GOP 32817)	1	€ 89.50	€ 89.50
Appropriate comparator therapy				
Daratumumab Lenalidomide Thalidomide	HBs antigen (GOP 32781)	1	€ 5.50	€ 5.50
	Anti-HBs antibody (GOP 32617)	1	€ 5.50	€ 5.50
	Anti-HBc antibody (GOP 32614)	1	€ 5.90	€ 5.90

7 Update of the S3 guideline on prevention, diagnosis and therapy of hepatitis B virus infection AWMF registry no.: 021/011" https://www.awmf.org/uploads/tx_szleitlinien/021-011l_S3_Hepatitis_B_Virusinfektionen_Prophylaxe_Diagnostik_Therapie_2011-abgelaufen.pdf
S3 guideline on prevention, diagnosis and therapy of hepatitis B virus infection AWMF registry no.: 021/011" https://register.awmf.org/assets/guidelines/021-011l_S3_Prophylaxe-Diagnostik-Therapie-der-Hepatitis-B-Virusinfektion_2021-07.pdf

Designation of the therapy	Designation of the service	Number	Unit cost	Costs/ patient/ year
Medicinal product to be assessed				
Daratumumab	HBs antigen (GOP 32781)	1	€ 5.50	€ 5.50
	Anti-HBs antibody (GOP 32617)	1	€ 5.50	€ 5.50
	Anti-HBc antibody (GOP 32614)	1	€ 5.90	€ 5.90
	HBV-DNA (GOP 32817)	1	€ 89.50	€ 89.50
	HBV-DNA (GOP 32817)	1	€ 89.50	€ 89.50

Other SHI benefits:

The special agreement on contractual unit costs of retail pharmacist services (Hilfstaxe) (Sections 4 and 5 of the Pharmaceutical Price Ordinance) from 01.10.2009 is not fully used to calculate costs. Alternatively, the pharmacy sales price publicly accessible in the directory services according to Section 131 paragraph 4 SGB V is a suitable basis for a standardised calculation.

According to the currently valid version of the special agreement on contractual unit costs of retail pharmacist services (Hilfstaxe), surcharges for the production of parenteral preparations containing cytostatic agents a maximum amount of € 100 per ready-to-use preparation, and for the production of parenteral solutions containing monoclonal antibodies a maximum of € 100 per ready-to-use unit are to be payable. These additional other costs do not add to the pharmacy sales price but follow the rules for calculation in the special agreement on contractual unit costs of retail pharmacist services (Hilfstaxe). The cost representation is based on the pharmacy retail price and the maximum surcharge for the preparation and is only an approximation of the treatment costs. This presentation does not take into account, for example, the rebates on the pharmacy purchase price of the active ingredient, the invoicing of discards, the calculation of application containers, and carrier solutions in accordance with the regulations in Annex 3 of the Hilfstaxe.

2.5 Designation of medicinal products with new active ingredients according to Section 35a, paragraph 3, sentence 4 SGB V that can be used in a combination therapy with the assessed medicinal product

According to Section 35a, paragraph 3, sentence 4, the G-BA designates all medicinal products with new active ingredients that can be used in a combination therapy with the assessed medicinal product for the therapeutic indication to be assessed on the basis of the marketing authorisation under Medicinal Products Act.

Basic principles of the assessed medicinal product

A designation in accordance with Section 35a, paragraph 3, sentence 4 SGB V requires that it is examined based on the product information for the assessed medicinal product whether it can be used in a combination therapy with other medicinal products in the assessed therapeutic indication. In the first step, the examination is carried out on the basis of all sections of the currently valid product information for the assessed medicinal product.

If the assessed medicinal product contains an active ingredient or a fixed combination of active ingredients in the therapeutic indication of the resolution (assessed therapeutic indication) and is approved exclusively for use in monotherapy, a combination therapy is not considered due to the marketing authorisation under Medicinal Products Act, which is why no designation is made.

A designation is also not considered if the G-BA has decided on an exemption as a reserve antibiotic for the assessed medicinal product in accordance with Section 35a, paragraph 1c, sentence 1 SGB V. The additional benefit is deemed to be proven if the G-BA has decided on an exemption for a reserve antibiotic in accordance with Section 35a, paragraph 1c, sentence 1 SGB V; the extent of the additional benefit and its therapeutic significance are not to be assessed by the G-BA. Due to the lack of an assessment mandate by the G-BA following the resolution on an exemption according to Section 35a, paragraph 1c, sentence 1 SGB V with regard to the extent of the additional benefit and the therapeutic significance of the reserve antibiotic to be assessed, there is a limitation due to the procedural privileging of the pharmaceutical companies to the effect that neither the proof of an existing nor an expected at least considerable additional benefit is possible for exempted reserve antibiotics in the procedures according to Section 35a paragraph 1 or 6 SGB V and Section 35a paragraph 1d SGB V. The procedural privileging of the reserve antibiotics exempted according to Section 35a, paragraph 1c, sentence 1 SGB V must therefore also be taken into account at the level of designation according to Section 35a, paragraph 3, sentence 4 SGB V in order to avoid valuation contradictions.

With regard to the further examination steps, a differentiation is made between a "determined" or "undetermined" combination, which may also be the basis for a designation.

A "determined combination" exists if one or more individual active ingredients which can be used in combination with the assessed medicinal product in the assessed therapeutic indication are specifically named.

An "undetermined combination" exists if there is information on a combination therapy, but no specific active ingredients are named. An undetermined combination may be present if the information on a combination therapy:

- names a product class or group from which some active ingredients not specified in detail can be used in combination therapy with the assessed medicinal product, or

- does not name any active ingredients, product classes or groups, but the assessed medicinal product is used in addition to a therapeutic indication described in more detail in the relevant product information, which, however, does not include information on active ingredients within the scope of this therapeutic indication.

Concomitant active ingredient

The concomitant active ingredient is a medicinal product with new active ingredients that can be used in combination therapy with the assessed medicinal product for the therapeutic indication to be assessed.

For a medicinal product to be considered as a concomitant active ingredient, it must be classified as a medicinal product with new active ingredients according to Section 2 paragraph 1 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with the corresponding regulations in Chapter 5 of the Rules of Procedure of the G-BA as of the date of the present resolution. In addition, the medicinal product must be approved in the assessed therapeutic indication, whereby a marketing authorisation is sufficient only for a sub-area of the assessed therapeutic indication.

Based on an "undetermined combination", the concomitant active ingredient must be attributable to the information on the product class or group or the therapeutic indication according to the product information of the assessed medicinal product in the assessed therapeutic indication, whereby the definition of a product class or group is based on the corresponding information in the product information of the assessed medicinal product.

In addition, there must be no reasons for exclusion of the concomitant active ingredient from a combination therapy with the assessed medicinal product, in particular no exclusive marketing authorisation as monotherapy.

In addition, all sections of the currently valid product information of the eligible concomitant active ingredient are checked to see whether there is any information that excludes its use in combination therapy with the assessed medicinal product in the assessed therapeutic indication under marketing authorisation regulations. Corresponding information can be, for example, dosage information or warnings. In the event that the medicinal product is used as part of a determined or undetermined combination which does not include the assessed medicinal product, a combination with the assessed medicinal product shall be excluded.

Furthermore, the product information of the assessed medicinal product must not contain any specific information that excludes its use in combination therapy with the eligible concomitant active ingredient in the assessed therapeutic indication under marketing authorisation regulations.

Medicinal products with new active ingredients for which the G-BA has decided on an exemption as a reserve antibiotic in accordance with Section 35a, paragraph 1c, sentence 1 SGB V are ineligible as concomitant active ingredients. The procedural privileging of the

reserve antibiotics exempted according to Section 35a, paragraph 1c, sentence 1 SGB V also applies accordingly to the medicinal product eligible as a concomitant active ingredient.

Designation

The medicinal products which have been determined as concomitant active ingredients in accordance with the above points of examination are named by indicating the relevant active ingredient and the invented name. The designation may include several active ingredients, provided that several medicinal products with new active ingredients may be used in the same combination therapy with the assessed medicinal product or different combinations with different medicinal products with new active ingredients form the basis of the designation.

If the present resolution on the assessed medicinal product in the assessed therapeutic indication contains several patient groups, the designation of concomitant active ingredients shall be made separately for each of the patient groups.

Exception to the designation

The designation excludes combination therapies for which - patient group-related - a considerable or major additional benefit has been determined by resolution according to Section 35a, paragraph 3, sentence 1 SGB V or it has been determined according to Section 35a, paragraph 1d, sentence 1 SGB V that at least considerable additional benefit of the combination can be expected. In this context, the combination therapy that is excluded from the designation must, as a rule, be identical to the combination therapy on which the preceding findings were based.

In the case of designations based on undetermined combinations, only those concomitant active ingredients - based on a resolution according to Section 35a, paragraph 3, sentence 1 SGB V on the assessed medicinal product in which a considerable or major additional benefit had been determined - which were approved at the time of this resolution are excluded from the designation.

Legal effects of the designation

The designation of combinations is carried out in accordance with the legal requirements according to Section 35a, paragraph 3, sentence 4 and is used exclusively to implement the combination discount according to Section 130e SGB V between health insurance funds and pharmaceutical companies. The designation is not associated with a statement as to the extent to which a therapy with the assessed medicinal products in combination with the designated medicinal products corresponds to the generally recognised state of medical knowledge. The examination was carried out exclusively on the basis of the possibility under Medicinal Products Act to use the medicinal products in combination therapy in the assessed therapeutic indication based on the product information; the generally recognised state of medical knowledge or the use of the medicinal products in the reality of care were not the

subject of the examination due to the lack of an assessment mandate of the G-BA within the framework of Section 35a, paragraph 3, sentence 4 SGB V.

The findings made neither restrict the scope of treatment required to fulfil the medical treatment mandate, nor do they make statements about expediency or economic feasibility.

Justification for the findings on designation in the present resolution:

Adults with newly diagnosed multiple myeloma who are ineligible for autologous stem cell transplant

No medicinal product with new active ingredients that can be used in a combination therapy and fulfils the requirements of Section 35a, paragraph 3, sentence 4 SGB V.

References:
Product information for daratumumab (Darzalex); Darzalex 1,800 mg solution for injection; last revised: February 2023

3. Bureaucratic costs calculation

The proposed resolution does not create any new or amended information obligations for care providers within the meaning of Annex II to Chapter 1 VerfO and, accordingly, no bureaucratic costs.

4. Process sequence

At its session on 22 May 2018, the Subcommittee on Medicinal Products determined the appropriate comparator therapy.

Several reviews of the appropriate comparator therapy took place. The Subcommittee on Medicinal Products last determined the appropriate comparator therapy at its session on 28 November 2023.

On 30 November 2023, the pharmaceutical company submitted a dossier for the benefit assessment of daratumumab to the G-BA in due time in accordance with Chapter 5, Section 8, paragraph 1, number 5 VerfO.

By letter dated 4 December 2023 in conjunction with the resolution of the G-BA of 1 August 2011 concerning the commissioning of the IQWiG to assess the benefits of medicinal products with new active ingredients in accordance with Section 35a SGB V, the G-BA commissioned the IQWiG to assess the dossier concerning the active ingredient daratumumab.

The dossier assessment by the IQWiG was submitted to the G-BA on 28 February 2024, and the written statement procedure was initiated with publication on the G-BA website on 1 March 2024. The deadline for submitting statements was 22 March 2024.

The oral hearing was held on 8 April 2024.

In order to prepare a recommendation for a resolution, the Subcommittee on Medicinal Products commissioned a working group (Section 35a) consisting of the members nominated by the leading organisations of the care providers, the members nominated by the SHI umbrella organisation, and representatives of the patient organisations. Representatives of the IQWiG also participate in the sessions.

The evaluation of the written statements received and the oral hearing was discussed at the session of the subcommittee on 7 May 2024, and the proposed resolution was approved.

At its session on 16 May 2024, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee Medicinal products	22 May 2018	Implementation of the appropriate comparator therapy
Subcommittee Medicinal products	28 November 2023	Last new implementation of the appropriate comparator therapy
Working group Section 35a	4 April 2024	Information on written statements received, preparation of the oral hearing
Subcommittee Medicinal products	8 April 2024	Conduct of the oral hearing
Working group Section 35a	17 April 2024 30 April 2024	Consultation on the dossier evaluation by the IQWiG and evaluation of the written statement procedure
Subcommittee Medicinal products	7 May 2024	Concluding discussion of the draft resolution
Plenum	16 May 2024	Adoption of the resolution on the amendment of the Pharmaceuticals Directive

Berlin, 16 May 2024

Federal Joint Committee (G-BA)
in accordance with Section 91 SGB V
The Chair

Prof. Hecken