Justification

Gemeinsamer Bundesausschuss

to the Resolution of the Federal Joint Committee (G-BA) on an Amendment of the Pharmaceuticals Directive (AM-RL): Annex XII – Benefit Assessment of Medicinal Products with New Active Ingredients According to Section 35a SGB V Brentuximab Vedotin (new therapeutic indication: Hodgkin lymphoma, first line)

of 5 September 2019

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.

For medicinal products for the treatment of a rare disease (orphan drugs) that are approved according to Regulation (EC) No. 141/2000 of the European Parliament and of the Council of 16 December 1999, according to Section 35a, paragraph 1, sentence 11, 1st half of the sentence SGB V, the additional medical benefit is deemed to be proven through the grant of the marketing authorisation. Evidence of the medical benefit and the additional medicinal benefit in relation to the appropriate comparator therapy need not be submitted (Section 35a, paragraph 1, sentence 11, 2nd half of the sentence SGB V). Section 35a, paragraph 1, sentence 11 1st half of the sentence SGB V thus guarantees an additional benefit for an approved orphan drug, although an assessment of the orphan drug in accordance with the principles laid down in Section 35a, paragraph 1, sentence 3, numbers 2 and 3 SGB V in conjunction with the Chapter 5, Sections 5 et seq. of the Rules of Procedure, G-BA (VerfO) has not been carried out. Only the extent of the additional benefit has to be demonstrated.

However, the restrictions on the benefit assessment of orphan drugs resulting from the statutory obligation to the marketing authorisation do not apply if the turnover of the medicinal product with the SHI at pharmacy retail prices including VAT exceeds €50 million in the last 12 calendar months. According to Section 35a, paragraph 1, sentence 12 SGB V, the pharmaceutical company must then, within three months of being requested to do so by the G-BA, submit evidence according to Chapter 5, Section 5, subsection 1–6 VerfO, in particular regarding the additional medical benefit in relation to the appropriate comparator therapy as defined by the G-BA according to Chapter 5, Section 6 VerfO and prove the additional benefit in comparison with the appropriate comparator therapy.

In accordance with Section 35a, paragraph 2 SGB V, the G-BA decides whether to carry out the benefit assessment itself or to commission the Institute for Quality and Efficiency in Health Care (IQWiG). Based on the legal requirement in Section 35a paragraph 1 sentence 11 SGB V that the additional benefit of an orphan drug is considered to be proven through the grant of the marketing authorisation, the G-BA modified the procedure for the benefit assessment of orphan drugs at its session on 15 March 2012 to the effect that, in the case of orphan drugs, the G-BA initially no longer independently determines an appropriate comparator therapy as the basis for the legally permissible assessment of the extent of an additional benefit to be assumed by law. Rather, the extent of the additional benefit provided by the G-BA is evaluated exclusively on the basis of the approval studies.

Accordingly, at its session on 15 March 2012, the G-BA amended the mandate issued to the IQWiG by the resolution of 1 August 2011 for the benefit assessment of medicinal products with new active ingredients in accordance with Section 35a, paragraph 2 SGB V to that effect that, in the case of orphan drugs, the IQWiG is only commissioned to carry out a benefit assessment in the case of a previously defined comparator therapy when the sales volume of the medicinal product concerned has exceeded the legal limit of €50 million and is therefore subject to an unrestricted benefit assessment (*cf* Section 35a, paragraph 1, sentence 12 SGB V). According to Section 35a, paragraph 2 SGB V, the assessment by the G-BA 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 forms part of the Pharmaceuticals Directive.

2. Key points of the resolution

The active ingredient brentuximab vedotin was listed for the first time on 1 December 2012 in the "LAUER-TAXE®", the extensive German registry of available drugs and their prices.

On 6 February 2019, brentuximab vedotin received marketing authorisation for a new therapeutic indication ("ADCETRIS® is indicated for adult patients with previously untreated CD30+ Stage IV Hodgkin lymphoma (HL) in combination with doxorubicin, vinblastine and dacarbazine (AVD)") to be classified as a major type 2 variation as defined according to Annex 2 number 2a to Regulation (EC) No. 1234/2008 of the commission of 24 November 2008 concerning the examination of variations to the terms of marketing authorisations for medicinal products for human use and veterinary medicinal products (OJ L 334, 12 December 2008, p. 7).

On 4 March 2019, the pharmaceutical company has submitted a dossier in accordance with Section 4, paragraph 3, number 2 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with Chapter 5, Section 8, paragraph 1, number 2 of the Rules of Procedure (VerfO) of the G-BA on the active ingredient brentuximab vedotin with the new therapeutic indication in due time (i.e. at the latest within four weeks after informing the pharmaceutical company about the approval for a new therapeutic indication).

Brentuximab vedotin for the treatment of Hodgkin lymphoma is approved as a medicinal product for the treatment of a rare disease under Regulation (EC) No 141/2000 of the European Parliament and the Council of 16 December 1999.

According to Section 35a, paragraph 1, sentence 11, 1st half of the sentence SGB V, the additional benefit is considered to be already proven by the marketing authorisation. The extent of the additional benefit is assessed on the basis of the approval studies by the G-BA.

The G-BA carried out the benefit assessment and commissioned the IQWiG to evaluate the information provided by the pharmaceutical company in Module 3 of the dossier on treatment costs and patient numbers. The benefit assessment was published on 17 June 2019 together with the IQWiG assessment on the website of the G-BA (www.g-ba.de), thus initiating the written statement procedure. In addition, an oral hearing was held.

The G-BA passed its resolution on the basis of the dossier of the pharmaceutical company, the dossier evaluation carried out by the G-BA, the assessment of treatment costs and patient numbers (IQWiG G19-09) prepared by IQWiG, and the comments submitted in the written and oral hearing procedure as well as the amendment to the dossier assessment prepared by the G-BA. In order to determine the extent of the additional benefit, the G-BA has evaluated the studies relevant for marketing authorisation with regard to their therapeutic relevance (qualitative) in accordance with the criteria laid down in Chapter 5, Section 5, paragraph 7, sentence 1 numbers 1 through 4 VerfO. The methodology proposed by the IQWiG in accordance with the General Methods [1] was not used in the benefit assessment of brentuximab vedotin.

In the light of the above and taking into account the comments received and the oral hearing, the G-BA has arrived at the following assessment:

[1] General Methods, Version 5.0 dated 10 July 2017. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen [Institute for Quality and Efficiency in Health Care], Cologne.

2.1 Additional benefit of the medicinal product

2.1.1 Approved therapeutic indication of brentuximab vedotin (Adcetris®) in accordance with the product information

ADCETRIS® is indicated for adult patients with previously untreated CD30+ Stage IV Hodgkin lymphoma (HL) in combination with doxorubicin, vinblastine and dacarbazine (AVD) (see sections 4.2 and 5.1).

2.1.2 Extent of the additional benefit

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

For brentuximab vedotin for the treatment of adult patients with previously untreated CD30+ Stage IV Hodgkin lymphoma (HL) in combination with doxorubicin, vinblastine and dacarbazine (AVD), there is a non-quantifiable additional benefit.

Justification:

To answer the question about the extent of the additional benefit of brentuximab vedotin in combination with doxorubicin, vinblastine, and dacarbazine (A+AVD) for the treatment of adult patients with CD30+ Stage IV Hodgkin lymphoma (HL), results of the multi-centre, open, randomised Phase III study ECHELON-1 are available.

Study ECHELON-1

The study was conducted in previously untreated adult patients with advanced classical HL in Stage III and IV. The marketing authorisation of A+AVD is limited to stage IV patients because a positive risk-benefit ratio for Stage III patients could not be established[2]. In the dossier, the pharmaceutical company submits analyses of the ECHELON-1 study for the evaluation-relevant subgroup in Stage IV. These are used for the present benefit assessment.

A total of 1,334 patients were randomised to the two study arms at a ratio of 1:1. They were stratified by region and International Prognostic Factor Project (IPFP) risk factors. Of these, 64% of patients in the A+AVD arm and 63% in the control arm had Stage IV HL. The median age of these patients was 36 or 38 years. More than half of the patients showed B symptoms and ≥ 2 IPFP risk factors. The majority of the patients had an ECOG Performance Status (PS) of 0–1 and an extra-nodal involvement at initial diagnosis.

Of the patients included, 425 and 421 patients respectively were in Stage IV. Of these, 424 or 413 were treated with the study medication. On day 1 and day 15 of a 28-day cycle, patients received either A+AVD or the control medication consisting of doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD). After two cycles, a PET- and CT-based disease assessment took place. Patients with a Deauville score ≤ 4 continued the assigned treatment according to randomisation for a maximum of four additional cycles. At the discretion of the medical study staff, patients with a Deauville score of 5 were able to receive an alternative therapy to continue first-line treatment. However, in the ECHELON 1 safety population, only 2% of Stage IV patients switched to first-line therapy. For patients with partial remission (PR) or PET-positive disease after completion of first-line therapy, consolidating radiotherapy was permitted. In accordance with the product information of brentuximab vedotin, prophylactic administration of G-CSF from the 1st cycle of A+AVD is recommended in order to prevent the occurrence of febrile neutropenia. In the ECHELON-1 study, this recommendation was only

[2] European Public Assessment Report- Variation- Adcetris® (13 March 2019)

communicated to the study centres after at least 86% of the patients had already been included. Thus, only a small proportion of the study population received prophylaxis with G-CSF (13% and 8%, respectively).

The ongoing study is being conducted at 218 study centres in 21 countries in Asia, Europe, and America. Patients were recruited from November 2012 to January 2016. The end of study was defined as the achievement of 112 events in the overall survival endpoint (approximately 5 years after inclusion of the last patient). For the present assessment, the results of the primary analysis data cut-off for the primary endpoint modified progression-free survival (mPFS) of 20 April 2017 are used. In the written statement procedure, the pharmaceutical company addresses a *post hoc* data cut-off of 18 April 2018, which was used to assess the regression of peripheral neuropathies. Because this is not a pre-specified data cut-off, which was not part of the marketing authorisation procedure, and also contains only selective information on the side effects endpoint category, this is not used for the present benefit assessment.

Uncertainties in the ECHELON-1 study

A major uncertainty of the ECHELON-1 study is that the ABVD regimen used in the control arm does not correspond to the generally accepted treatment standard in Germany for the patient population included in the study. German study centres were not involved in the ECHELON 1 study. According to the recommendations of the German S3 guideline[3], patients up to 60 years of age with advanced HL should be treated with $BEACOPP_{escalated}$[4]. Only for patients who cannot receive $BEACOPP_{escalated}$[4] because of their age, general condition, or relevant comorbidities, ABVD is used (according to guideline recommendations). However, in the ECHELON 1 study, only 14% of patients had an age of ≥ 60 years and only 5% had an ECOG PS of 2. In the written statement of medical associations, it was also pointed out that in Germany, the therapy standard for patients who tolerate intensive therapy is not ABVD but rather $BEACOPP_{escalated}$[4] .

In addition, the use of bleomycin over six chemotherapy cycles in the ECHELON-1 study no longer corresponds to the current state of medical knowledge. According to the German S3 guideline[3] , older patients with advanced HL should receive only two cycles of ABVD and then continue treatment with AVD (doxorubicin, vinblastine, and dacarbazine) for another 4 to 6 cycles.

From these points of view, it seems justified to attach only limited significance to the results of the ECHELON-1 study for the German healthcare context.

Mortality

In the ECHELON-1 study, overall survival was defined as the time from randomisation to the death of the patient regardless of the underlying cause. The present assessment is based on the stratified analysis of overall survival.

Treatment with A + AVD resulted in a statistically significant advantage in overall survival compared with ABVD (hazard ratio = 0.52 [0.27; 0.995], p value = 0.044). The median survival time was not achieved in both study arms. Because of the very few events that occurred in the study arms (3% and 6%), the results for the overall survival endpoint are not very meaningful.

[3] Oncology guideline program – S3 guideline Hodgkin lymphoma – Version 2.1 – April 2019
[4] Bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone (BEACOPP)

Morbidity

Modified progression-free survival (mPFS)/therapy failure

The primary endpoint of the ECHELON-1 study was modified progression-free survival. This was defined as the time from randomisation to first documentation of progressive disease, death of any cause, or in patients with incomplete response: the receipt of subsequent antineoplastic chemo- or radiotherapy for HL after scheduled completion of first-line treatment.

There is a statistically significant difference in favour of A+AVD. The median mPFS was not achieved in both study arms. The disease progression event occurred in > 60% of patients with an mPFS event. The mPFS outcome is thus significantly influenced by this event.

The mPFS endpoint is a combined endpoint composed of endpoints of the mortality and morbidity categories. In the present study, the endpoint component “mortality” was identified as an independent endpoint via the endpoint overall survival. The disease progression was assessed using the criteria of Cheson et al. 2007. The morbidity component was thus not assessed on the basis of symptoms but rather exclusively by means of morphological or imaging procedures.

Based on the present operationalisation of the mPFS endpoint, it is not possible to derive sufficiently robust conclusions on therapy effects with regard to therapy failure and thus failure of the healing attempt.

The aim of the therapy in this therapeutic indication is to achieve a CR that is the prerequisite for a possible curative outcome. However, not all events representing the non-achievement of CR (e.g. stable disease (SD), partial remission (PR)) were included in the individual component “disease progression” but rather only the event of a progressive disease (PD). In addition, an autologous stem cell transplantation was performed in a relevant proportion of patients who received at least one follow-up therapy (34% and 37%, respectively); this basically still has a curative potential in follow-up therapy.

In the context of the third individual component “receipt of a subsequent antineoplastic chemo- or radiotherapy for HL after scheduled completion of the first-line therapy”, it was not clear how the decision to initiate and the decision on the type of subsequent antineoplastic therapy were made. A consolidating radiotherapy, which in accordance with the operationalisation was evaluated as follow-up therapy within the framework of the mPFS, is a component of the first-line therapy according to guideline recommendations and therefore only conditionally to be evaluated as follow-up therapy.

For these reasons, the results for the mPFS endpoint are not used in this assessment.

Relapse-free survival

Based on the curative therapy approach presented here, relapses represent patient-relevant events.

In the written statement procedure, the pharmaceutical company presents evaluations of the *post hoc* defined endpoints of relapse-free survival (RFS) and time to relapse. RFS is defined as the time from CR to relapse or death of any cause in patients with CR. The time to relapse is defined as the time from CR to relapse in patients with CR after completion of first-line therapy.

According to the operationalisation of the RFS and time to relapse endpoints, only patients with CR or with CR after first-line therapy were considered. Because of the resulting randomisation break, the results of both endpoints are potentially highly distorted per se. For

the purposes of this assessment, the RFS endpoint, which includes a higher number of patients and also deaths, is used.

In the event time analysis, which takes into account the times of relapse events and deaths, a statistically significant difference in favour of A+AVD is found for the RFS endpoint. The median time to the occurrence of the respective events (relapse or death) is not reached in either treatment group. The event rates for the data cut-off of 20 April 2017 also show a statistically significant effect in favour of A+AVD.

One uncertainty of the RFS endpoint is that it also considers patients who have CR at the time of interim PET. Thus, relapses may also be detected before completion of first-line therapy. In addition, a potentially curative autologous stem cell transplantation was performed in a relevant proportion of patients who received at least one follow-up therapy (34% and 37%, respectively). This makes it difficult to interpret the results on RFS.

Because of the randomisation break and the other uncertainties described, the results of the RFS endpoint cannot be used to quantify the extent of the additional benefit.

Event-free survival

In the ECHELON-1 study, event-free survival was defined as the time from randomisation to therapy failure of any cause, defined as:

- Disease progression according to Cheson et al. 2007 (progressive disease (PD))
- premature discontinuation of treatment of any cause
- Death of any cause

Patients in the present therapeutic indication are treated with a curative therapy approach. The failure of a curative therapy approach is fundamentally patient-relevant.

With regard to the individual component “premature discontinuation of treatment of any cause”, the reasons for premature discontinuation of treatment were not reported.

Based on the present operationalisation of the PFS endpoint, it is not possible to derive sufficiently robust conclusions on therapy effects with regard to a failure of the curative therapy approach and thus of the healing attempt. An endpoint relevant to the benefit assessment should be operationalised in such a way as to detect the failure of the potential cure.

The aim of the therapy in this therapeutic indication is to achieve a CR that is the prerequisite for a possible curative outcome. However, not all events representing the non-achievement of CR (e.g. stable disease (SD), partial remission (PR)) were included in the individual component “disease progression” but rather only the event of a progressive disease (PD). In addition, an autologous stem cell transplantation was performed in a relevant proportion of patients who received at least one follow-up therapy (34% and 37%, respectively); this basically still has a curative potential in follow-up therapy.

Irrespective of the uncertainties of the present operationalisation of the EFS endpoint described above, there is no statistically significant difference between the treatment arms for this endpoint. The event “disease progression” occurred most frequently (in 14% and 17% of patients, respectively) followed by the event “premature termination of treatment of any cause” (in 8% and 6% of patients, respectively).

Health status (EQ-5D VAS)

In the ECHELON-1 study, health status was assessed using the visual analogue scale (VAS) of the EQ-5D questionnaire.

Based on the mean difference, there are no statistically significant differences between the study arms in the End of Treatment (EoT) visit and 9 months after EoT.

Symptomology (EORTC QLQ-C30)

In the ECHELON-1 study, the symptom scales of the EORTC QLQ-C30 questionnaire were used to record the symptomology. The evaluations of the EORTC QLQ-C30 submitted by the pharmaceutical company as part of the written statement procedure are used. The evaluation was performed according to pre-specification in the study protocol using the mean difference. Compared with mean value differences, responder analyses based on a MID have advantages for the clinical assessment of effects. For the EORTC QLQ-C30, there is a validated MID, which has already been used in earlier benefit assessments. From the point of view of the G-BA, an additional evaluation based on responder analyses would therefore have been desirable.

At the time of the EoT visit, there were statistically significant differences to the detriment of A+AVD in the scales fatigue, pain, nausea and vomiting as well in the item sleeplessness. However, it cannot be deduced with sufficient certainty that the effects are clinically relevant in each case (confidence interval of Hedges' g not completely outside the irrelevance range). At 9 months after EoT, a statistically significant difference in favour of A+AVD was observed in the diarrhoea item. However, a clinically relevant effect for this cannot be derived with sufficient certainty.

Quality of life

The functional scales of the EORTC QLQ-C30 questionnaire were used to measure health-related quality of life. The evaluations of the EORTC QLQ-C30 submitted by the pharmaceutical company as part of the written statement procedure are used. The evaluation was performed according to pre-specification in the study protocol using the mean difference. As described above, additional evaluations based on responder analyses would have been desirable from the point of view of the G-BA.

At the time of the EoT visit, there were statistically significant differences to the detriment of A+AVD in the scales physical function, role function, and social function. Because the confidence interval of Hedges' g is completely outside the irrelevance range for all three scales, the effects are evaluated as clinically relevant. For the scale of global health status/quality of life, there is a statistically significant difference to the disadvantage of A+AVD at the time of the EoT visit. However, because of the location of the confidence interval of Hedges' g, a clinically relevant effect cannot be derived with sufficient certainty.

At 9 months after EoT, there were no statistically significant differences between the study arms for the five scales of general health status/quality of life, physical function, role function, emotional function, and social function. For the cognitive function scale, there is a statistically significant difference in favour of A+AVD at 9 months after EoT. Based on the confidence interval of the Hedges' g, this effect cannot be interpreted as clinically relevant with sufficient certainty.

Taking into account the already intensive polychemotherapy ABVD in the control arm, which is stressful for the patients, as well as the curative therapy approach available, the G-BA considers the quality of life of the patients both during and after treatment to be relevant. In addition, at the oral hearing the medical societies, it was emphasised that because of the high cure rates already achieved with the use of $BEACOPP_{escalated}$ or ABVD, the focus is on reducing acute and long-term damage and improving the quality of life of patients both during and after treatment.

In the overall view, treatment with A+AVD has adverse effects on health-related quality of life compared with ABVD. There are no clinically relevant differences between the treatment arms with respect to the period after the end of treatment with A+AVD and ABVD.

Side effects

Adverse events occurred at least once in almost every patient in both study arms. The results for the “combined adverse events” endpoint are presented only on a supplementary basis.

Serious adverse events (SAE)

For serious adverse events, there is a statistically significant difference to the disadvantage of A+AVD.

AE (CTCAE grade ≥ 3)

For AE with CTCAE grade ≥3, there is a statistically significant difference to the disadvantage of A+AVD.

Discontinuation of ≥ 1 component of the study medication because of AE

For the discontinuation of at least one component of the study medication because of AE, there is a statistically significant difference in favour of A+AVD.

In the ECHELON-1 study, the discontinuation of bleomycin during ABVD therapy in the control arm was evaluated as an event. According to the current state of medical knowledge, bleomycin as part of the ABVD regimen should be regularly discontinued after two cycles of chemotherapy in patients of advanced age. It is therefore uncertain to what extent the observed effects for the endpoint “discontinuation of ≥ 1 component of the study medication because of AE” can be transferred to the current healthcare context for patients of advanced age.

AE with CTCAE grade ≥ 3 with incidence ≥ 1% in one study arm

With respect to AE with CTCTAE grade ≥ 3 with incidence ≥ 1%, in one study arm, there are statistically significant differences to the disadvantage of A+AVD for the following SOCs: Blood and lymphatic system disorders, investigations, investigations, gastrointestinal disorders, nervous system disorders, metabolism and nutrition disorders, musculoskeletal and connective tissue disorders, and psychiatric disorders

SAE with an incidence of ≥ 5% in one study arm

With respect to specific SAE with an incidence of ≥ 5%, in one study arm, there is a statistically significant difference between the System Organ Class (SOC) blood and lymphatic system disorders or the Preferred Term (PT) febrile neutropenia and the SOC gastrointestinal disorders to the disadvantage of A+AVD.

AE of special interest (CTCAE grade ≥ 3 and SAE)

With regard to AE of special interest, a statistically significant difference in favour of A+AVD for the Standardised MedDRA Query (SMQ) interstitial lung disease is observed. The pulmonary toxicity under ABVD is primarily attributed to the active ingredient bleomycin. In the ECHELON-1 study, bleomycin was administered over six cycles. As already mentioned above, in the current care context bleomycin as part of ABVD chemotherapy should be regularly discontinued after two cycles in patients of advanced age. It is therefore uncertain to what extent the effects observed can be transferred to the current healthcare context for patients of advanced age.

For the endpoints any peripheral neuropathy (SMQ), peripheral sensory neuropathy (SSQ), neutropenia, febrile neutropenia, and neutropenia of severity 3 or 4 with infection, there are statistically significant differences to the disadvantage of A+AVD. With regard to the endpoints neutropenia, febrile neutropenia and neutropenia of severity 3 or 4 with infection, the interpretation of the results is subject to uncertainties. According to the product information of brentuximab vedotin, prophylaxis with colony-stimulating factors (G-CSF) is recommended for the prevention of febrile neutropenia from the first treatment cycle with A+AVD. This recommendation was communicated to the study centres very late in the course of the ECHELON-1 study. Thus, only a few patients received G-CSF prophylaxis from the first treatment cycle (13% in the A+AVD arm).

Conclusion on side effects

In the overall view, the results for the side effects endpoint category mainly show disadvantages of A+AVD compared with ABVD. Advantages for A+AVD are only available for the endpoint discontinuation of ≥ 1 component of the study medication because of AE and the SMQ interstitial lung disease. Because of the no longer guideline-compliant use of ABVD in the control arm and the lack of prophylaxis with G-CSF in a large number of patients, there are uncertainties in the interpretation of the results for the endpoints discontinuation of ≥ 1 component of the study medication because of AE, interstitial lung diseases, and neutropenias (neutropenias, febrile neutropenias, neutropenias of severity 3 or 4 with infection).

Overall assessment

For the benefit assessment of brentuximab vedotin in combination with doxorubicin, vinblastine, and dacarbazine (A+AVD) for the treatment of adult patients with CD30+ Stage IV Hodgkin lymphoma (HL), results on mortality, morbidity, quality of life, and side effects compared with polychemotherapy ABVD (doxorubicin, bleomycin, vinblastine and dacarbazine) from the ECHELON-1 study are available. Because the ABVD regimen used in the control arm does not correspond to the German treatment standard $BEACOPP_{escalated}$, which is currently regarded as generally accepted, it seems justified to attribute only limited significance to the results of the ECHELON-1 study for the German healthcare context.

For the overall survival endpoint, there is a statistically significant advantage in favour of A+AVD. Because of the very few events that occurred, the results for the overall survival endpoint are not very meaningful.

The recurrence-free survival endpoint shows a statistically significant advantage in favour of A+AVD. Because of the present randomisation break and the other relevant uncertainties, the results of the RFS endpoint cannot be used to quantify the extent of the additional benefit.

For the other endpoints of the morbidity category (EQ-5D, EORTC QLQ-C30), there are no statistically significant or clinically relevant differences between the study arms.

The data on health-related quality of life show clinically relevant adverse effects on the scales of physical function, role function, and social function during treatment with A+AVD. With regard to the period after the end of treatment with A+AVD and ABVD, there are no effects for which clinical relevance can be derived with sufficient certainty.

The results for the side effects endpoint category mainly show disadvantages of A+AVD compared with ABVD. Because of the no longer guideline-compliant use of ABVD in the control arm and the failure to perform prophylaxis with G-CSF for the majority of patients, the interpretation of the results is subject to uncertainties.

As a result, the G-BA classifies the extent of the additional benefit of brentuximab vedotin as non-quantifiable based on the criteria in Section 5, paragraph 7 AM-NutzenV, taking into account the severity of the disease and the therapeutic objective in the treatment of the disease. According to Section 35a, paragraph 1, sentence 11, 1st half of sentence SGB V, there is an additional benefit; however, this is non-quantifiable.

2.1.3 Summary of the assessment

The present assessment concerns the benefit assessment of a new therapeutic indication for the active ingredient brentuximab vedotin. Adcetris® is authorised as an orphan drug and under special conditions. The therapeutic indication assessed here is as follows: “ADCETRIS® is indicated for adult patients with previously untreated CD30+ Stage IV Hodgkin lymphoma (HL) in combination with doxorubicin, vinblastine and dacarbazine (AVD)”.

For the benefit assessment, the pharmaceutical company presents the open, randomised, Phase III ECHELON-1 study. The study compared brentuximab vedotin + AVD with ABVD (doxorubicin, bleomycin, vinblastine, dacarbazine). The present assessment refers to patients with stage IV HL in accordance with the marketing authorisation. Because the ABVD regimen used in the control arm does not correspond to the German treatment standard $BEACOPP_{escalated}$, which is currently regarded as generally accepted, it seems justified to attribute only limited significance to the results of the ECHELON-1 study for the German healthcare context.

For the overall survival endpoint, there is an advantage for A+AVD. However, the results are less meaningful because of fewer events.

The result of the relapse-free survival endpoint, which shows an advantage of A+AVD, cannot be used to quantify the extent of the additional benefit because of the randomisation break and other relevant uncertainties.

For other endpoints of the morbidity category (EQ-5D, EORTC QLQ-C30), there are no statistically significant differences or differences that can be interpreted as clinically relevant with sufficient certainty between the study arms.

The treatment with A+AVD has adverse effects on the health-related quality of life. There are no clinically relevant differences between the treatment arms that can be interpreted with sufficient certainty with regard to the period after the end of treatment.

In the side effects endpoint category, there are predominantly disadvantages of A+AVD. Because of the no longer guideline-compliant use of ABVD in the control arm and the failure to perform prophylaxis with G-CSF for the majority of patients, the interpretation of the results is subject to uncertainties.

Overall, a non-quantifiable additional benefit is identified.

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 will be based on the information from the dossier of the pharmaceutical company. The range of 12–19% for adult patients with Hodgkin lymphoma Stage IV set by the pharmaceutical company is subject to uncertainties because the transferability of data from the UK, Denmark, and the US to Germany is uncertain.

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 Adcetris® (active ingredient: brentuximab vedotin) at the following publicly accessible link (last access: 12 June 2019):

https://www.ema.europa.eu/documents/product-information/adcetris-epar-product-information_de.pdf

Treatment with brentuximab vedotin should only be initiated and monitored by specialists in internal medicine, haematology, and oncology experienced in the treatment of patients with Hodgkin lymphoma.

This medicinal product was authorised under "special conditions". This means that further evidence of the benefit of the medicinal product is anticipated. The European Medicines Agency will evaluate new information on this medicinal product at a minimum once per year and update the product information where necessary.

2.4 Treatment costs

The treatment costs are based on the contents of the product information and the information listed in the LAUER-TAXE® (last revised: 15 August 2019).

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

Treatment period:

Designation of the therapy	Treatment mode	Number of treatments/patient/year	Treatment duration/treatment (days)	Treatment days/patient/year
Medicinal product to be assessed				
Brentuximab vedotin	Day 1 and 15: 28-days cycle	6 cycles	2	12
Doxorubicin	Day 1 and 15: 28-days cycle	6 cycles	2	12
Vinblastine	Day 1 and 15: 28-days cycle	6 cycles	2	12
Dacarbazine	Day 1 and 15: 28-days cycle	6 cycles	2	12

Usage and consumption[5]:

For dosages depending on body weight (BW) or body surface area (BSA), the average body measurements from the official representative statistics "Microcensus 2017 – body measurements of the population" were used as a basis (average height: 1.72 m, average body

[5] Dosing from the ECHELON-1 study.

weight: 77 kg). From this, a body surface of 1.90 m² is calculated (calculation according to Du Bois 1916)[6].

Designation of the therapy	Dosage	Dose/patient/treatment day	Consumption by potency/treatment day	Treatment days/ patient/ year	Annual average consumption by potency
Medicinal product to be assessed					
Brentuximab vedotin	1.2 mg/kg	92.4 mg	2 × 50 mg	12	24 vials 50 mg
Doxorubicin	25 mg/m²	47.5 mg	1 × 50 mg	12	12 vials 50 mg
Vinblastine	6 mg/m²	11.4 mg	2 × 10 mg	12	24 vials 10 mg
Dacarbazine	375 mg/m²	712.5 mg	1 × 1000 mg	12	12 vials 1000 mg

Costs:

In order to improve comparability, the costs of the medicinal products were approximated both on the basis of the pharmacy retail price level and also deducting the statutory rebates in accordance with Sections 130 and 130 a 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 pharmaceutical costs were then calculated on the basis of the costs per pack after deduction of the statutory rebates.

Costs of the medicinal product:

Designation of the therapy	Package size	Costs (pharmacy wholesale price)	Rebate Section 130 SGB V	Rebate Section 130a SGB V	Costs after deduction of statutory rebates
Medicinal product to be assessed					
Brentuximab vedotin	1 vial, 50 mg	€ 3,766.83	€ 1.77	€ 211.85	€ 3,553.21
Doxorubicin	5 vials, 50 mg 1 vial, 50 mg	€ 681.82[7] € 150.93[7]	€ 1.77 € 1.77	€ 53.06 € 11.07	€ 626.99 € 138.09
Vinblastine	1 vial, 10 mg	€ 185.88	€ 1.77	€ 57.60	€ 126.51
Dacarbazine	1 vial, 1000 mg	€ 213.27	€ 1.77	€ 78.16	€ 133.34

Pharmaceutical retail price (LAUER-TAXE®) as last revised: 15 August 2019

6 Statistisches Bundesamt [German Federal Office for statistics] Microcensus 2017: Fragen zur Gesundheit; Körpermaße der Bevölkerung 2017 [Questions about health; body measurements of the 2017 population] [online]. 2 August 2018 [Accessed: 11 September 2018]. URL: https://www.destatis.de/DE/Publikationen/Thematisch/Gesundheit/Gesundheitszustand/Koerpermasse5239003179004.pdf?__blob=publicationFile.

7 Fixed amount Level I

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 costs for the necessary medical treatment or the prescription of other services when using the drug to be evaluated 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 standard expenditure in the course of the treatment are not shown.

Type of service	Cost per package	Cost after deduction of statutory rebates[8,9]	Cost per service	Treatment days per year	Cost per patient/year
Medicinal product to be assessed					
Brentuximab vedotin + doxorubicin + vinblastine + dacarbazine					
Primary prophylaxis with G-CSF					
Pegfilgrastim 1 PS, 6 mg	€ 1,273.72	€ 1,202.04 [€ 1.77 €; € 69.91]	€ 1,202.04	6	€ 7,212.24
PS = prefilled syringes					

Pharmaceutical retail price (LAUER-TAXE®) as last revised: 15 August 2019

Other services covered by SHI funds:

The special agreement on contractual unit costs of retail pharmacist services (Hilfstaxe; contract on price formation for substances and preparations of substances) is not fully used to calculate costs. Alternatively, the pharmacy retail price publicly accessible in the directory services in accordance with Section 131, paragraph 4 SGB V is a suitable basis for a standardised calculation.

According to the special agreement on contractual unit costs of retail pharmacist services [Hilfstaxe"] (last revised: arbitral award to determine the mg prices for parenteral preparations from proprietary medicinal products in oncology in the Hilfstaxe according to Section 129, paragraph 5c, sentences 2–5 SGB V of 19 January 2018), surcharges for the production of parenteral preparations containing cytostatic drugs of a maximum of € 81 per ready-to-use preparation and for the production of parenteral solutions containing monoclonal antibodies of a maximum of € 71 per ready-to-use unit shall be payable. These additional costs are not added to the pharmacy retail price but rather follow the rules for calculating the Hilfstaxe. The cost representation is based on the pharmacy retail price and the maximum surcharge for production and is only an approximation of the treatment costs. This presentation does not take into account, for example, the discounts on the pharmacy purchase price of the active ingredients, the invoicing of discards, and the calculation of application containers and carrier solutions according to the regulations of Annex 3 of the Hilfstaxe.

[8] Rebate according to Section 130 SGB V
[9] Rebate according to Section 130a SGB V

3. Bureaucratic costs

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

On 4 March 2019, the pharmaceutical company submitted a dossier for the benefit assessment of brentuximab vedotin to the G-BA in due time in accordance with Chapter 5, Section 8, number 2 VerfO.

The benefit assessment of the G-BA was published on 17 June 2019 together with the IQWiG assessment of treatment costs and patient numbers on the G-BA website (www.g-ba.de), thus initiating the written statement procedure. The deadline for submitting written statements was 8 July 2019.

The oral hearing was held on 23 July 2019.

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 were discussed at the session of the subcommittee on 27 August 2019, and the proposed resolution was approved.

At its session on 5 September 2019, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee Medicinal product	12 June 2019	Knowledge of the benefit assessment of the G-BA
Working group Section 35a	16 July 2019	Information on written statements received; preparation of the oral hearing
Subcommittee Medicinal product	23 July 2019	Conduct of the oral hearing
Working group Section 35a	31 July 2019 14 August 2019 21 August 2019	Consultation on the dossier evaluation by the G-BA, the assessment of treatment costs and patient numbers by IQWiG, and the evaluation of the statement procedure
Subcommittee Medicinal product	27 August 2019	Concluding discussion of the proposed resolution
Plenum	5 September 2019	Adoption of the resolution on the amendment of Annex XII AM-RL

Berlin, 5 September 2019

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

Prof Hecken