Gemeinsamer Bundesausschuss

Justification

of 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 (reassessment after the deadline: systemic anaplastic large cell lymphoma; first-line; combination with Cyclophosphamide, Doxorubicin, and Prednisone)

of 16 December 2021

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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 the Council of 16 December 1999, the additional medical benefit is considered to be proven through the grant of the marketing authorisation according to Section 35a paragraph 1, sentence 11, 1st half of the sentence German Social Code, Book Five (SGB V), the additional medical benefit is considered to be proven through the grant of the marketing authorisation. Evidence of the medical benefit and the additional medical benefit in relation to the appropriate comparator therapy do not have to 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, No. 2 and 3 SGB V in conjunction with Chapter 5 Sections 5 et seq. of the Rules of Procedure (VerfO) of the G-BA has not been carried out. In accordance with Section 5, paragraph 8 AM-NutzenV, only the extent of the additional benefit is to be quantified, indicating the significance of the evidence.

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 sales prices and outside the scope of SHI-accredited medical care, 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, for orphan drugs, the G-BA initially no longer independently determines an appropriate comparator therapy as the basis for the solely legally permissible assessment of the extent of an additional benefit to be assumed by law. Rather, the extent of the additional benefit is assessed exclusively on the basis of the marketing authorisation studies by the G-BA, indicating the significance of the evidence.

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 (Adcetris) 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 12 May 2020, brentuximab vedotin received marketing authorisation for a new therapeutic indication to be classified as a major type 2 variation as defined according to Annex 2 number 2 letter a 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, 12.12.2008, p. 7).

The pharmaceutical company submitted a dossier for the early benefit assessment of the active ingredient brentuximab vedotin (Adcetris) on 8 June 2020. For the resolution of 3 December 2020 made by the G-BA in this procedure, a time limit of 1 July 2021 was pronounced.

In accordance with Section 4, paragraph 3, No. 5 of the 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 Adcetris 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 1 of the Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with Chapter 5, Section 8, paragraph 1, number 5 VerfO on 1 July 2021.

Brentuximab vedotin for the treatment of systemic anaplastic large-cell 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.

In accordance with Section 35a, paragraph 1, sentence 11, 1st half of the sentence SGB V, the additional benefit is considered to be proven through the grant of the marketing authorisation. The extent of the additional benefit and the significance of the evidence are assessed on the basis of the marketing authorisation 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 1 October 2021 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 made its resolution on the basis of the pharmaceutical company's dossier, the dossier assessment carried out by the G-BA, the IQWiG assessment of treatment costs and patient numbers (IQWiG G21-21) and the statements made in the written statement and oral hearing procedure, as well of the amendment drawn up by the G-BA on the benefit assessment.

In order to determine the extent of the additional benefit, the G-BA has assessed the studies relevant for the marketing authorisation considering their therapeutic relevance (qualitative) in accordance with the criteria laid down in Chapter 5, Section 5, paragraph 7, sentence 1, numbers 1 – 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.

2.1 Additional benefit of the medicinal product

2.1.1 Approved therapeutic indication of Brentuximab Vedotin (Adcetris) according to the product information

ADCETRIS in combination with cyclophosphamide, doxorubicin and prednisone (CHP) is indicated for adult patients with previously untreated systemic anaplastic large cell lymphoma (sALCL).

Therapeutic indication of the resolution (resolution of 16 December 2021):

See new therapeutic indication according to marketing authorisation

[1] General Methods, version 6.0 from 05.11.2020. Institute for Quality and Efficiency in Health Care (IQWiG), Cologne.

2.1.2 Extent of the additional benefit and significance of the evidence

Adult patients with previously untreated systemic anaplastic large cell lymphoma (sALCL)

In summary, the additional benefit of brentuximab vedotin in combination with cyclophosphamide, doxorubicin and prednisone (CHP) is assessed as follows:

Hint for a minor additional benefit

Justification:

To demonstrate the extent of additional benefit of brentuximab vedotin for the treatment of adults with previously untreated sALCL, the pharmaceutical company presents the results of the completed pivotal, randomised, double-blind phase III ECHELON-2 (SGN35-014) study.

The study compared brentuximab vedotin in combination with cyclophosphamide, doxorubicin and prednisone (A+CHP) versus cyclophosphamide, doxorubicin, vincristine and prednisone (CHOP). Adults aged 18 to 85 years with various newly diagnosed, CD30-positive peripheral T-cell lymphomas (PTCL) and an ECOG performance status (ECOG-PS) of ≤ 2 were enrolled in the study. Adults with ALK-positive sALCL were required to have an IPI score of ≥ 2.

The 452 patients enrolled in the study were randomised in a 1:1 ratio to the two study arms (N = 226 A + CHP; N = 226 CHOP). Randomisation was stratified by IPI score (0-1 vs 2-3 vs 4-5) and sALCL ALK-positive status (yes vs no; no includes all other subtypes).

Due to the marketing authorisation status, only the sub-population of patients with newly diagnosed sALCL that conforms to the marketing authorisation is relevant for the present benefit assessment. These were adult patients with ALK-negative sALCL and adult patients with ALK-positive sALCL with an IPI score ≥ 2 according to local sALCL diagnosis (N = 162 A + CHP; N = 154 CHOP). For the patient population relevant to the assessment, the pharmaceutical company does not present subgroup analyses according to ALK-positive and negative sALCL.

Therapy with A + CHP and CHOP was given in a 21-day cycle for six to a maximum of eight cycles. The median treatment duration in both arms was approximately six cycles. Due to the increased risk of febrile neutropenia, prevention with G-CSF is recommended in the product information from the first treatment cycle onwards when brentuximab vedotin is administered. The recommendation for G-CSF prevention was not implemented in the ECHELON-2 study until a large percentage of adults were already enrolled, therefore only 34% of the A+CHP arm and 27% of the CHOP arm received G-CSF primary prophylaxis.

Follow-up antineoplastic therapies were collected in the ECHELON-2 study until end of study or in the event of death. More subjects in the CHOP arm received follow-up subsequent antineoplastic therapy, including brentuximab vedotin, than in the A+CHP arm (36% versus 23%). In contrast, adult patients in the A+CHP arm were more likely to receive subsequent

consolidative -therapy (30% versus 15%), with autologous stem cell transplant being the most common (23% versus 13%).

The ECHELON-2 study was conducted in 132 study sites across Asia/Pacific, North America, the Middle East, and Europe (including Germany). Progression-free survival (PFS) was defined as the primary endpoint. Patient recruitment started in January 2013. A pre-specified interim analysis was performed on 15 August 2018 after 219 events in the PFS endpoint were reached. Results for all endpoints collected are available for this data cut-off. Another data cut-off of 25 September 2019 was requested by the European Medicines Agency (EMA) as part of the marketing authorisation process. For this non-pre-specified data cut-off, results are available for the endpoints of overall survival, progression-free survival (PFS), recurrence-free survival (RFS), time to recurrence, event-free survival (EFS), and sustained CR. The final data cut-off of the study was conducted on 5 November 2020. Results are available for this data cut-off for the same endpoints as the data cut-off of 25 September 2019, in addition to duration of response. Data from the first data cut-off are based on tumour assessment by a blinded review committee. The data of the second and final data cut-off are based on tumour assessment performed by the local principal investigator.

For the new benefit assessment of brentuximab vedotin, any available data on the patient-relevant endpoints of the final data cut-off are used in accordance with the time limit requirements. For complete remission (CR), patient-reported endpoints of morbidity and quality of life as well as endpoint category of side effects, the first data cut-off of 15 August 2018 is used.

Uncertainties of the ECHELON-2 study:

A major uncertainty of the ECHELON-2 study is that the CHOP regimen used in the control arm for the larger part of the patient population enrolled in the study does not correspond to the standard of care currently considered generally accepted in Germany. According to the statements of the clinical experts in the written statement procedure, patients aged ≤ 60 years in Germany are predominantly treated with cyclophosphamide, doxorubicin, vincristine, etoposide and prednisone (CHOEP). According to clinical experts, CHOP is used only for adult patients who cannot receive CHOEP due to age, general condition or relevant comorbidities. Since the median age of the assessment-relevant subgroup of the ECHELON-2 study was 53 years in the A + CHP arm and 52 years in the CHOP arm, it can be assumed that at least half of the patients in the study were not treated according to the German standard of care.

On the implementation of conditions for a time limit

According to the justification of the initial resolution of 3 December 2020, the reason for the limitation of the period of validity was that further clinical data from the ECHELON-2 study were expected, in particular on overall survival, which may be relevant for the benefit assessment of brentuximab vedotin in the present therapeutic indication. The initial resolution was based on the assessment of the data cut-offs of 15 August 2018 and 25 September 2019. At the time of the non-pre-specified data cut-off of 25 September 2019, few

events had occurred in the endpoint of overall survival, so the significance of data was limited. For the new benefit assessment after expiry of the deadline, the results of the final data cut-off as part of the final analysis on overall survival from the ECHELON-2 study should be presented in the dossier.

The pharmaceutical company submits the final data cut-off of the ECHELON-2 study for the reassessment after the deadline. Thus, the pharmaceutical company complies with the conditions of the limitation.

Mortality

The overall survival is defined in the ECHELON-2 study as the time from randomisation to death from any cause.

For the endpoint of overall survival, there was no statistically significant difference between the treatment arms when using the pre-specified stratified analysis.

In the dossier, the pharmaceutical company additionally presents the analysis of overall survival with a significance test, defined post hoc and based on a Cox regression model, adjusted with treatment as explanatory variable for the two factors ALK status and IPI score. This significance test of the adjusted analysis was not submitted in the initial procedure and, moreover, is reported exclusively for the endpoint of overall survival. In addition, the pharmaceutical company does not provide sufficient evidence from appropriate sources that the adjusted analysis defined post hoc is more appropriate in contrast to the pre-specified stratified analysis of overall survival. Therefore, the adjusted analysis is not used for the benefit assessment.

In the written statement procedure, the pharmaceutical company also submits the evaluation of overall survival using the elevation rule published by IQWiG[2]. According to the elevation rule, the treatment effect in the relevant sub-population can be tested at the elevated significance level of 15%, provided that specific statistical and substantive requirements are met. The goal of the test procedure on the elevated significance level is to increase power, which may be reduced by looking at a sub-population of the total study population. The statistical requirements for testing the treatment effect in the relevant sub-population at a significance level of 15%, as described in the working paper GA18-01, were tested and considered to be met for the endpoint of overall survival.

However, it is not clear to what extent the substantive conditions for the application of the elevation rule are met in the present case. On the one hand, a relatively large percentage of about 70% of the patients in the total study population belong to the sub-population relevant for the assessment. On the other, there was a statistically significant effect in the endpoint of overall survival for the data cut-offs of 15.08.2018 and 25.09.2019. Looking at the three data cut-offs of the ECHELON-2 study, there is a moderate, steady decrease in effect over time for

[2] IQWiG reports – No. 638: Investigating the statistical properties of procedures for transferability of study results to sub-populations; GA18-01, version 1.0, 20.06.2018

the treatment effect between the study arms in the endpoint of overall survival. Taking these aspects into account, it therefore appears questionable whether there is a relevant reduction of power in the present case which would justify the application of the elevation rule.

Furthermore, even taking into account the heterogeneity of peripheral T-cell lymphomas, it cannot be assessed on the basis of the documents submitted by the pharmaceutical company in the written statement procedure to what extent the results of the non-assessment-relevant sub-population from the total population of the ECHELON-2 study are sufficiently transferable to the sub-population relevant to the assessment from a clinical content perspective.

Overall, the pharmaceutical company's approach is therefore not followed, irrespective of whether the statistical conditions for the application of the elevation rule are met. The elevation rule is not used for the endpoint of overall survival.

Morbidity

Progression-free survival (PFS)

Progression-free survival is defined as the time from randomisation to the first documentation of disease progression, death from any cause, or administration of subsequent antineoplastic therapy for the treatment of residual lymphoma. The endpoint component of disease progression was recorded according to the revised response criteria for malignant lymphomas according to Cheson et al. (2007).

There was a statistically significant advantage in the PFS endpoint to the advantage of A + CHP.

The PFS endpoint is a combined endpoint composed of endpoints of the mortality and morbidity categories. The endpoint component “mortality” is already surveyed in the present study via the endpoint “overall survival” as an independent endpoint.

The present operationalisation of the PFS endpoint is inappropriate to represent the failure of a potential cure. It is unclear whether recurrences were also recorded in the single component of disease progression. In addition, the present operationalisation did not record all events that represent the failure of a possible curative therapeutic outcome.

The assessment of the morbidity component of disease progression was not done in a symptom-related manner but exclusively by means of imaging (disease progression assessed by radiology according to the Cheson criteria). Thus, the assessment of response is based on asymptomatic findings and is assessed not to be directly relevant to the patient.

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 extent of the additional benefit remains unaffected.

Recurrence-free survival (RFS)

Based on the curative therapeutic approach presented here, recurrences represent patient-relevant events. Recurrence means that the attempt at a cure by the curative therapeutic approach was unsuccessful.

The endpoint of recurrence-free survival (RFS) defined post hoc is the time from end of treatment to recurrence or death from any cause in adults who had achieved CR at the end of treatment. Assessment of recurrence and complete remission (CR) was performed by local investigators at the data cut-off of 5 November 2020 according to Cheson et al (2007) criteria.

In the time-to-event analysis, there was no statistically significant difference between the treatment arms for the RFS endpoint. The median time to occurrence of the respective events (recurrence or death) is not reached in both treatment arms.

In accordance with the operationalisation of the RFS endpoint, only adult patients with a CR after completion of first-line treatment were included. This results in interruption of randomisation, so the endpoint result has a potentially high risk of bias per se. Thus, more adult patients from the intervention arm than from the comparator arm are included in the analysis. Based on the assessment of recurrences by local investigators, it is also unclear how extensive, complete, and consistent the recording and assessment of recurrences still were after the first data cut-off.

For the reasons mentioned above, there are relevant uncertainties in the interpretation of the results for the RFS endpoint, which is why they are not used in the present assessment to quantify the extent of additional benefit.

Event-free survival (EFS)

Patients in the present therapeutic application are treated with a curative therapeutic approach. The failure of a curative therapeutic approach is fundamentally patient-relevant. The significance of the endpoint of event-free survival (EFS) depends on the extent to which the selected individual components are suitable for adequately reflecting the failure of potential cure by the present curative therapy approach.

In the dossier, the pharmaceutical company shall submit evaluations on the EFS endpoint, which is defined post hoc and is the time from randomisation to:

- disease progression
- the end of treatment without achieving a CR
- recurrence after CR at the end of treatment
- death from any cause

Similar to the RFS, the assessment of the data cut-off of 5 November 2020 was conducted by local investigators according to the criteria of Cheson et al (2007). However, unlike the RFS, there is no interruption in randomisation for the EFS endpoint.

An important goal of therapy in the present therapeutic application is the achievement of a CR. However, not all events, representing the **non-achievement** of a CR at the end of treatment (e.g. stable disease (SD) or partial remission (PR)) were recorded within the individual component of "disease progression".

However, the component "End of treatment without achieving a CR" is able to record all other events representing the non-achievement of a CR.

For brentuximab vedotin in combination with CHP, there is a statistically significant advantage over CHOP for the EFS endpoint. The most common event was "Disease progression/recurrence" in 22% (brentuximab vedotin + CHP) and 31% (CHOP) of patients, followed by the event "No CR at the end of treatment" in 19% and 21% of subjects, respectively. Compared to the initial assessment, the difference in treatment effect for the EFS endpoint between the study arms decreases.

Uncertainties arise in the interpretation of the effect. On the one hand, because of the assessment of recurrences by local investigators, it is unclear how extensive, complete, and consistent the recording and assessment of recurrences still were after the first data cut-off. On the other, the uncertainty regarding the transferability of the study results to the German health care context also plays a role in this efficacy endpoint due to the significance of CHOEP compared to CHOP for patients ≤ 60 years.

Despite the uncertainties described above regarding the significance of the EFS endpoint, the positive effect of brentuximab vedotin is also considered a relevant outcome for the present assessment in light of the magnitude of the effect.

Complete remission (CR) including CR in patients with B-symptomatology at the start of treatment

The endpoint of complete remission (CR) is an important prognostic factor and relevant for the treatment decision. A CR associated with a noticeable reduction in disease symptoms for the patient is generally relevant for the benefit assessment. In the ECHELON-2 study, the CR endpoint was pre-specified using the 2007 Cheson criteria by blood and bone marrow examinations. Thus, the endpoint was not assessed based on symptoms but on laboratory tests. A validation of CR as a surrogate parameter for patient-relevant endpoints, e.g. mortality, is not available. Therefore, the CR is classified as endpoint of unclear relevance in the present assessment and is only presented additionally. No statement on the extent of the additional benefit can be derived.

The dossier also presents the CR in subjects with B-symptomatology at the start of treatment, which was evaluated post hoc. For the benefit assessment, the CR endpoint in patients with B-symptomatology at the start of study is assessed as patient-relevant, as it was associated with a reduction in symptoms. In the ECHELON-2 study, only 27% of the intervention group and 35% of the control group of adults with sALCL had B-symptomatology at the start of study, which reduces the reliability of data.

For the analysis presented in the dossier, there is no statistically significant effect between the treatment arms.

In its written statement, the pharmaceutical company submits an evaluation for the CR endpoint in patients with B-symptomatology at the start of treatment using IQWiG's elevation rule[2]. Reference is made to the statements on the endpoint of overall survival. As it is not clear to what extent the substantive conditions for the application of the elevation rule are met, it is not applied to the present endpoint either.

Sustainable CR

The endpoint of sustained CR defined post hoc was operationalised as the achievement of a CR at the end of treatment without disease recurrence or patient death by the end of observation. The endpoint is thus composed of the components CR and recurrences.

The above points of criticism regarding operationalisation of the CR and the RFS also apply to the sustainable CR endpoint. In contrast to the RFS endpoint, the ratio of subjects without disease recurrence who had achieved a CR at the end of treatment to the ITT population compliant with the marketing authorisation was used to evaluate sustained CR, so that there was no interruption in randomisation.

Patients with a CR at the end of treatment who discontinued the study during the follow-up period were considered sustained recurrence-free. It is unclear how many adult patients who discontinued the study may still have had recurrences.

The definition of events that did not result in a sustained CR (progression, death, no CR at the end of treatment and cases where a subject with a CR discontinued the study are consistent with the definition of events and censoring of the EFS endpoint. In addition to the event rates, the operationalisation of events in the EFS endpoint also takes into account the individual observation period as part of the time-to-event analysis. Accordingly, the endpoint of sustained CR does not yield any information relevant to the benefit assessment that has not already been recorded in the EFS endpoint. Furthermore, there is no peer review on this endpoint and it remains unclear whether the endpoint of sustained CR is an established endpoint in pivotal studies in the present therapeutic application.

In summary, the endpoint of sustained CR is not used for the benefit assessment.

Health status (EQ-5D, visual analogue scale)

The health status was assessed using the visual analogue scale (VAS) of the EQ-5D questionnaire. The VAS of the EQ-5D is a visual analogue scale from 0 to 100 on which adult study participants rate their health status. A value of 0 corresponds to the worst possible health status and a value of 100 to the best possible health status. The EQ-5D-VAS was collected on day 1 of each treatment cycle, at the end of treatment, and every 3 months from month 9 after the start of treatment. After 24 months or disease progression, the assessment was conducted every 6 months until death or the end of study.

Although the endpoint in follow-up of overall survival was also collected every 6 months, no evaluations are available for the data cut-off of 5 November 2020. Therefore, the data from the first data cut-off of 15 August 2018 is considered. Mean change evaluations (MMRM analyses) from the start to the end of treatment submitted by the pharmaceutical company are used. An evaluation of the mean change from the start of treatment to follow-up in month 9, where the return rate is still >70%, was not available.

There was no statistically significant difference between the treatment arms based on the mean difference at the end of treatment.

Symptomatology (EORTC QLQ-C30)

Symptomatology was assessed in the ECHELON-2 study using the symptom scales of the disease-specific EORTC QLQ-C30 questionnaire. The EORTC QLQ-C30 was collected on day 1 of each treatment cycle, at the end of treatment, and in month 9, 12, 15, 18, 21, 24, and 30 after the start of treatment or disease progression. For the benefit assessment, the MMRM analyses from the start to the end of treatment submitted by the pharmaceutical company are used. Higher scores on the symptom scales mean more severe symptomatology.

Based on the mean difference at the end of treatment, there is a statistically significant difference to the disadvantage of brentuximab vedotin for the scales of pain, nausea and vomiting as well as diarrhoea. The standardised mean difference in the form of Hedges' g is used to assess the clinical relevance of the results. The 95% confidence interval of the standardised mean difference is not completely outside the irrelevance range between −0.2 and 0.2. Thus, it cannot be inferred that the observed effects are clinically relevant.

Neurological symptomatology (FACT/GOG-Ntx)

The other patient-reported questionnaire used in the ECHELON-2 study was the FACT/GOG-Ntx subscale, which is used to map chemotherapy-induced neurological symptoms. The FACT/GOG-Ntx scale includes values from 0 to 44. Higher values correspond to lower neurotoxicity.

For the benefit assessment, the MMRM analyses from the start to the end of treatment submitted by the pharmaceutical company are used. There is no statistically significant difference between the treatment arms based on the mean difference at the end of treatment.

Conclusion on morbidity

In the overall assessment of the morbidity endpoints used for the present assessment, a statistically significant difference to the advantage of brentuximab vedotin in combination with CHP is shown for the endpoint of EFS. For the endpoint of CR in patients with B symptomatology at the start of treatment, there is no statistically significant difference between the treatment arms. In addition, there were no statistically significant differences between the treatment arms neither for health status nor for the endpoints of

symptomatology and neurological symptomatology. Overall, an advantage of brentuximab vedotin in combination with CHP over CHOP can thus be identified.

Quality of life

Functional scales (EORTC QLQ-C30)

Health-related quality of life is assessed in the ECHELON-2 study using the functional scales of the disease-specific EORTC QLQ-C30 questionnaire. Higher values on the functional scales mean better function or quality of life.

For the benefit assessment, the MMRM analyses from the start to the end of treatment submitted by the pharmaceutical company are used. There is no statistically significant difference between the treatment arms based on the mean difference at the end of treatment.

Side effects

Adverse events (AEs) in total

AEs occurred in almost all study participants. The results were only presented additionally.

Severe AEs (CTCAE grade≥ 3), serious AEs (SAEs), therapy discontinuations due to AEs, AEs of special interest

For the endpoints of severe AEs (CTCAE grade≥ 3), SAEs, therapy discontinuations due to AEs, and AEs of special interest, there are no statistically significant differences between the treatment arms.

Conclusion on side effects

In the overall assessment of the side effects, there are no advantages or disadvantages of brentuximab vedotin in combination with CHP over CHOP.

Overall assessment

For the reassessment of the additional benefit of brentuximab vedotin in combination with cyclophosphamide, doxorubicin and prednisone (CHP) for the treatment of adults with previously untreated systemic anaplastic large-cell lymphoma (sALCL), the results of the ECHELON-2 study are available for the endpoint categories of mortality, morbidity, quality of life and side effects. The study compares brentuximab vedotin + CHP with cyclophosphamide, doxorubicin, vincristine and prednisone (CHOP). The results of the sub-population of adult patients with diagnosed sALCL compliant with the marketing authorisation are relevant to the assessment.

However, there were no statistically significant differences between the treatment arms for the overall survival.

In the endpoint category of morbidity, there is a relevant advantage for brentuximab vedotin in combination with CHP over CHOP for the endpoint of event-free survival (EFS). Uncertainties arise in the interpretation of the effect. In view of the magnitude of the effect,

the result is nevertheless used for the present assessment. For the endpoint of complete remission (CR) in patients with B symptomatology at the start of treatment, there is no statistically significant difference between the treatment arms. In addition, there were no statistically significant differences between the treatment arms neither for health status nor for the endpoints of symptomatology and neurological symptomatology.

Furthermore, data on health-related quality of life are available for the present assessment. There were no statistically significant differences between the treatment arms for the functional scales of the EORTC QLQ-C30 questionnaire. Thus, for health-related quality of life, no advantage or disadvantage can be found for brentuximab vedotin in combination with CHP over CHOP.

With regard to side effects, there are also no advantages or disadvantages of brentuximab vedotin in combination with CHP over CHOP.

In the overall assessment of the available results on the patient-relevant endpoints, there is a relevant advantage in morbidity, which is nevertheless subject to uncertainties.

The G-BA identified a minor additional benefit of brentuximab vedotin in combination with CHP compared to CHOP in the treatment of adult patients with previously untreated systemic anaplastic large-cell lymphoma (sALCL).

Significance of the evidence

The present assessment is based on the results of the double-blind, randomised, controlled phase III ECHELON-2 study, comparing brentuximab vedotin in combination with cyclophosphamide, doxorubicin and prednisone (CHP) to cyclophosphamide, doxorubicin, vincristine and prednisone (CHOP).

At the study level, the risk of bias is rated as low. A major uncertainty of the ECHELON-2 study is that the CHOP regimen used in the control arm for the larger part of the patient population enrolled in the study does not correspond to the standard of care currently considered generally accepted in Germany. This also leads to uncertainty in the interpretation of the effect in the EFS endpoint.

Furthermore, uncertainties arise regarding the assessment quality of recurrences after the primary analysis due to the assessment of recurrences by local investigators.

Overall, the present data basis has uncertainties, which lead to a downgrading of the reliability of data for the overall assessment. Therefore, the reliability of data for the additional benefit determined is classified in the category “hint”.

2.1.3 Summary of the assessment

The present assessment is the benefit assessment of a new therapeutic indication for the medicinal product Adcetris with the active ingredient brentuximab vedotin: "Brentuximab vedotin is indicated in combination with cyclophosphamide, doxorubicin, and prednisone

(CHP) in adult patients with previously untreated systemic anaplastic large-cell lymphoma (sALCL)." Adcetris was approved as an orphan drug.

For the assessment, the pharmaceutical company presents the results of the double-blind, randomised phase III ECHELON-2 study, in which brentuximab vedotin in combination with CHP is compared with CHOP. The results of the sub-population of adult patients with sALCL compliant with the marketing authorisation are relevant to the assessment.

For overall survival, there is no statistically significant difference.

In the endpoint category of morbidity, there is a relevant advantage for brentuximab vedotin in combination with CHP over CHOP for the endpoint of event-free survival. For the other patient-relevant morbidity endpoints, there were no statistically significant differences between the treatment arms.

For the quality of life and side effects, there were no statistically significant differences between the treatment arms.

Uncertainties remain in the interpretation of the results due to the selected study comparator, which does not reflect the reality of care in the German context for the majority of the enrolled patients, as well as due to the unclear survey quality of individual endpoints.

As a result, the G-BA found a hint of minor additional benefit.

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 G-BA bases its resolution on the patient numbers from the dossier submitted by the pharmaceutical company.

Despite minor methodological deficiencies, the data in the dossier are plausible in terms of magnitude.

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: 20 September 2021):

https://www.ema.europa.eu/documents/product-information/adcetris-epar-product-information_en.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 periphery T-cell lymphoma, in particular sALCL.

This medicine received a conditional marketing authorisation. 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.

No data are available for adult patients with sALCL ALK+ with IPI status < 2, as these patients were not included in the ECHELON-2 study.

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: 1 December 2021).

The use of brentuximab vedotin in combination with cyclophosphamide, doxorubicin, and prednisone is limited to six to eight 21-day cycles.

The brentuximab vedotin doses recommended in the product information and the marketing authorisation ECHELON-2 study were used as the basis for calculation.

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	1 x per 21-day cycle	6 - 8	1	6 - 8
Cyclophosphamide	1 x per 21-day cycle	6 - 8	1	6 - 8
Doxorubicin	1 x per 21-day cycle	6 - 8	1	6 - 8
Prednisone	on day 1 - 5 of a 21-day cycle	6 - 8	5	30 - 40

Consumption:

For dosages depending on body weight or body surface area, the average body measurements were applied (average body height: 1.72 m; average body weight: 77 kg). This results in a body surface area of 1.90 m² (calculated according to Du Bois 1916)[3].

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:					
Brentuximab Vedotin	1.8 mg/kg bw = 138.6 mg	138.6 mg	3 x 50 mg	6 – 8	18 x 50 mg - 24 x 50 mg
Cyclophosphamide	750 mg/m² = 1,425 mg	1,425 mg	1 x 1,000 mg + 1 x 500 mg	6 – 8	6 x 1,000 mg + 6 x 500 mg - 8 x 1000 mg + 8 x 500 mg
Doxorubicin	50 mg/m²	95 mg	2 x 50 mg	6 – 8	12 x 50 mg - 16 x 50 mg
Prednisone	100 mg	100 mg	2 x 50 mg	30 – 40	60 x 50 mg - 80 x 50 mg

Costs:

Costs of the medicinal products:

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:					
Brentuximab vedotin 50 mg	1 x PIC	€ 3,429.04	€ 1.77	€ 192.56	€ 3,234.71
Cyclophosphamide 500 mg	1 x PSI	€ 22.86	€ 1.77	€ 1.50	€ 19.59
Cyclophosphamide 500 mg	6 x PSI	€ 81.98	€ 1.77	€ 8.98	€ 71.23
Cyclophosphamide 1000 mg	1 x PSI	€ 29.82	€ 1.77	€ 1.04	€ 27.01
Cyclophosphamide 1000 mg	6 x PSI	€ 123.70	€ 1.77	€ 6.24	€ 115.69
Doxorubicin 50 mg[4]	1 x INF	€ 150.99	€ 1.77	€ 11.07	€ 138.15
Prednisone 50 mg[4]	50 x TAB	€ 67.78	€ 1.77	€ 4.49	€ 61.52
Prednisone 50 mg[4]	10 x TAB	€ 22.92	€ 1.77	€ 0.94	€ 20.21

[3] Federal Statistical Office, Wiesbaden 2018: https://www.destatis.de/DE/Themen/Gesellschaft-Umwelt/Gesundheit/Gesundheitszustand-Relevantes-Verhalten/Publikationen/Downloads-Gesundheitszustand/koerpermasse-5239003179004.pdf?__blob=publicationFile

[4] Fixed reimbursement rate

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
INF = infusion solution; PIC = powder for the preparation of an infusion solution concentrate; PSI = powder for the preparation of a solution for injection; TAB = tablets					

LAUER-TAXE® last revised: 1 December 2021

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.

Type of service	Cost per pack	Costs after deduction of statutory rebates[5,6]	Costs per service	Treatment days/ year	Costs/ patient/ year
Medicinal product to be assessed:					
Brentuximab Vedotin + Cyclophosphamide + Doxorubicin + Prednisone					
Primary prophylaxis with G-CSF					
Pegfilgrastim 1x SFI, 6 mg	€ 870.16	€ 820.82 (€ 1.77; € 47.57)	€ 820.82	6 - 8	€ 4,924.92 - € 6,566.56
SFI = solution for injection					

Other SHI services:

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

5 Rebate according to Section 130 SGB V
6 Rebate according to Section 130a SGB V

containing cytostatic drugs a maximum amount of € 81 per ready-to-use preparation, and for the production of parenteral solutions containing monoclonal antibodies a maximum of € 71 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.

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

On 1 July 2021, 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 5 VerfO.

The benefit assessment of the G-BA was published on 1 October 2021 together with the IQWiG assessment of treatment costs and patient numbers on the website of the G-BA (www.g-ba.de), thus initiating the written statement procedure. The deadline for submitting written statements was 22 October 2021.

The oral hearing was held on 8 November 2021.

An amendment to the benefit assessment with a supplementary assessment of data submitted in the written statement procedure was submitted on 26 November 2021.

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 subcommittee session on 7 December 2021, and the draft resolution was approved.

At its session on 16 December 2021, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee Medicinal product	28 September 2021	Information of the benefit assessment of the G-BA
Working group Section 35a	3 November 2021	Information on written statements received; preparation of the oral hearing
Subcommittee Medicinal product	8 November 2021	Conduct of the oral hearing
Working group Section 35a	17 November 2021 1 December 2021	Consultation on the dossier assessment by the G-BA, the assessment of treatment costs and patient numbers by the IQWiG, and the evaluation of the written statement procedure
Subcommittee Medicinal product	7 December 2021	Concluding discussion of the draft resolution
Plenum	16 December 2021	Adoption of the resolution on the amendment of Annex XII AM-RL

Berlin, 16 December 2021

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

Prof. Hecken