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: Systemic Anaplastic Large Cell Lymphoma (sALCL))

of 3 December 2020

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 the Council of 16 December 1999, the additional medical benefit is considered to be proven through the grant of the marketing authorisation in accordance with Section 35a, paragraph 1, sentence 11, 1st half of the sentence SGB V. Evidence of the medical benefit and the additional medical 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, Nos. 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 selling prices and outside the scope of SHI-accredited medical care, including VAT, exceeds € 50 million during the last 12 calendar months. In accordance with 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 in accordance with Chapter 5, Section 5, paragraphs 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). On the basis of the statutory requirement in Section 35a, paragraph 1, sentence 11 SGB V that the additional benefit of an orphan drug is deemed to have been proven through the grant of 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 solely legally permissible assessment of the extent of an additional benefit to be assumed by law. Rather, the extent of the additional benefit provided is assessed exclusively on the basis of the pivotal 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 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 of 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 classified as a major variation of Type 2 according to Annex 2, number 2a to Regulation (EC) No. 1234/2008 of the Commission from 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 8 June 2020, the pharmaceutical company 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 combination with cyclophosphamide, doxorubicin and prednisone (CHP) is for adult patients with previously untreated systemic anaplastic large cell lymphoma (sALCL)).

Brentuximab vedotin for the treatment of previously untreated systemic anaplastic large cell lymphoma (sALCL) 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 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 by the G-BA on the basis of the pivotal studies.

The G-BA carried out the benefit assessment and commissioned the IQWiG to assess 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 15 September 2020 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 has adopted its resolution on the basis of the dossier of the pharmaceutical company, the dossier assessment carried out by the G-BA, the proposed amendment, the assessment of treatment costs and patient numbers (IQWiG G20-10) prepared by the IQWiG, and the statements submitted in the written statements and oral hearing procedure.

In order to determine the extent of the additional benefit, the G-BA has assessed 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 - 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 written statements 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 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 3 December 2020):

See therapeutic indication according to marketing authorisation

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 the additional benefit of brentuximab vedotin for the treatment of adult patients with previously untreated sALCL, the pharmaceutical company presents the results of the ECHELON-2 (SGN35-014) pivotal study.

ECHELON-2 is a multi-centre, double-blind, randomised-controlled Phase III study comparing brentuximab vedotin in combination with cyclophosphamide, doxorubicin, and prednisone (CHP) with cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP). Adult patients with various newly diagnosed CD30-positive peripheral T-cell lymphomas (PTCL) were included.

Patients were required to have an Eastern Cooperative Oncology Group-Performance Status (ECOG-PS) of ≤ 2 at inclusion and were aged between 18 and 85 years. For patients with sALCL ALK+, inclusion was limited to those with an IPI score ≥ 2. 452 patients were included in the ECHELON-2 study in a parallel group design (1:1); 226 patients were randomised to the intervention arm and 226 patients to the control arm. Stratification was by IPI score (0–1 vs 2–3 vs 4–5) and sALCL ALK+ status (yes vs no; no includes all other subtypes). Because of the authorisation status, only the sub-population of patients diagnosed with sALCL in a manner compliant with marketing authorisation is relevant for the present benefit assessment. These are patients with sALCL ALK- as well as patients with sALCL ALK+ with an IPI score ≥ 2 in accordance with local sALCL diagnosis. In terms of the population compliant with marketing authorisation, there are 162 sALCL patients in the intervention arm and 154 sALCL patients in the control arm. No subgroup analyses were submitted for the entities sALCL ALK+ and sALCL ALK- as part of the benefit assessment.

In both arms, the therapy was conducted over 6–8 21-day cycles. The sALCL patients were treated with brentuximab vedotin + CHOP for 6.1 cycles (median) or with CHOP for 5.7 cycles (median). The ECHELON-2 study was conducted in 132 centres in 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.

There are two data cut-offs. The first data cut-off of 15 August 2018 is the pre-specified analysis (occurrence of 238 PFS events or in August 2018) conducted after 219 PFS events.

Results for all endpoints surveyed are available for this data cut-off. The data of the 1st data cut-off are based on a tumour assessment by a blinded review committee. The second 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 overall survival, PFS, relapse-free survival (RFS), time to relapse, event-free survival (EFS), and sustained CR. The data of the 2nd data cut-off are based on a local investigator-assessed tumour assessment. With respect to the 2nd data cut-off, it should be taken into account that, in accordance with the study protocol, unblinding was planned after analysis of the primary endpoint. The pharmaceutical company states in the written statement procedure that only the sponsor was unblinded – but not the test personnel and the test subjects. However, this is not clear from the study documents.

For the benefit assessment, the data on the patient-relevant endpoints of the 2nd data cut-off are used if available. For complete remission (CR), patient-reported endpoints on morbidity and quality of life, and the endpoint category side effects, the 1st data cut-off is used. An addendum to the study report with the final OS data is expected in Q1 2021.

Uncertainties in the ECHELON-2 study

A major uncertainty of the ECHELON-2 study is that the CHOP regimen used in the control arm does not correspond to the standard of healthcare currently generally accepted in Germany for the larger part of the patient population included in the study. According to the statements of the clinical experts in the written statement procedure, in Germany patients ≤ 60 years are predominantly treated with cyclophosphamide, doxorubicin, vincristine, etoposide, and prednisone (CHOEP). In accordance with the clinical experts, CHOP is used only for patients who cannot receive CHOEP because of their age, general condition, or relevant comorbidities. Since the median age in the ECHELON-2 study was 55 years in the brentuximab vedotin + CHP arm and 54 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.

Mortality

Overall survival

Overall survival is defined as the time from randomisation to death regardless of cause.

For the endpoint overall survival, the survival rates showed a statistically significant advantage in favour of brentuximab vedotin + CHP. At the time of the 2nd data cut-off of 25 September 2019, median survival had not yet been reached in either study arm. Final analyses on the endpoint of overall survival are still pending.

For sALCL patients, treatment with brentuximab vedotin + CHP shows a statistically significant advantage for overall survival compared to treatment with CHOP; which is assessed as a relevant but no more than a minor improvement.

Morbidity

Progression-free survival (PFS)

Progression-free survival was the primary endpoint in the ECHELON-2 study. It is defined as the time from randomisation to the first documentation of progression, death by any cause, or receipt of follow-up antineoplastic therapy for the treatment of residual lymphoma (whichever occurs first). The endpoint component progression was recorded in accordance with the revised response criteria for malignant lymphomas according to Cheson et al. (2007).

The PFS in the intervention arm was significantly longer than in the control arm.

The PFS endpoint is a combined endpoint composed of endpoints of the mortality and morbidity categories. In the present study, the endpoint component “mortality” was surveyed as an independent endpoint using the endpoint overall survival.

The morbidity component was not assessed on the basis of symptoms but rather exclusively using imaging procedures (radiologically determined disease progression according to the Cheson criteria). Thus, the survey of the response in these areas is based on asymptomatic findings and is assessed as not directly relevant to the patient.

Taking the aforementioned factors into consideration, there are differing opinions within the G-BA regarding the relevance for patients of the PFS endpoint.

The overall statement on the extent of the additional benefit remains unaffected.

Relapse-free survival (RFS)

Based on the curative therapy approach presented here, relapses represent patient-relevant events. A relapse means that the attempt to cure the disease with the curative therapy approach was not successful.

In the dossier, the pharmaceutical company presents evaluations on the *post hoc defined* endpoint relapse-free survival (RFS). In the ECHELON-2 study, the endpoint RFS is defined as the time from end of treatment (EoT) to relapse or death by any cause in patients who had achieved CR at the end of treatment. On the data cut-off of 25 September 2019, relapse and complete remission (CR) were evaluated by local investigators in accordance with the criteria of Cheson 2007. According to the operationalisation of the endpoint RFS, only patients with a CR after completion of first-line treatment were considered. This results in a broken randomisation. Thus, the result of the endpoint is *per se* potentially highly biased. More patients from the intervention arm than from the comparison arm are included in the analysis. It is unclear how extensive, complete, and consistent the recording and assessment of relapses still was after the first data cut-off.

In the time-to-event analysis, which takes into account the time of relapse events or deaths, there is no statistically significant difference between the treatment arms for the endpoint RFS. The median time to the occurrence of the respective events (relapse or death) is not reached in either treatment arm.

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

Event-free survival (EFS)

Patients in the present therapeutic indication are treated with a curative therapy approach. The failure of a curative therapy approach is fundamentally patient-relevant. The significance of the endpoint in this regard depends on the extent to which the selected individual components are suitable for adequately depicting the failure of the potential cure by the present curative therapy approach.

In the dossier, the pharmaceutical company submits evaluations on the endpoint EFS defined *post hoc*; EFS is defined as time from randomisation to:

- disease progression
- the end of treatment without a complete CR
- a relapse after CR at the end of treatment
- death by any cause

Similar to the RFS, the assessment was carried out by local investigators in accordance with the 2007 Cheson criteria on the data cut-off of 25 September 2019. Unlike the RFS, however, there is no break in randomisation for the EFS endpoint.

An important aim of therapy in the present therapeutic indication is the achievement of a CR. However, not all events representing 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 "disease progression".

However, the component "End of treatment without achievement of a full CR" includes all other events that represent the non-achievement of a CR.

Uncertainties arise from the censoring. Furthermore, the uncertainty regarding the transferability of the study results to the German healthcare context for patients ≤ 60 years plays a special role for this endpoint because the advantage of CHOEP compared with CHOP was shown for this patient group – especially for the endpoint event-free survival[2]. In addition, the blinding and survey quality of relapses after the primary analysis is unclear. The *post hoc* definition of the endpoint and the uncertainties mentioned result in a high risk of bias overall.

For brentuximab vedotin in combination with CHP, there is a statistically significant advantage compared with CHOP for the endpoint EFS. The most common event was "progression/relapse" in 27% (brentuximab vedotin + CHP) and 37% (CHOP) of patients followed by the event "no CR at EoT" in 11% and 13% of patients, respectively.

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

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

The complete remission (CR) endpoint is an important prognostic factor and relevant for therapeutic decision. A CR associated with a noticeable decrease in disease symptoms for the patient is always relevant to patients for the benefit assessment. In the ECHELON-2 study, the CR endpoint was pre-specified using the Cheson criteria of 2007 by blood and bone marrow examinations. Thus, the endpoint was not assessed on the basis of symptoms but on the basis of laboratory tests. There is no validation of the CR as a surrogate parameter for patient-relevant endpoints (e.g. mortality).

For this reason, the CR is classified as an endpoint of unclear relevance in the present assessment and is only presented additionally. No statement can be derived on the extent of the additional benefit.

The CR in individuals with B symptomatology at the start of treatment is also presented in the dossier; which was evaluated *post hoc*. For the benefit assessment, the endpoint CR is assessed as patient-relevant in patients with B symptomatology at the start of study because this was associated with a reduction in symptoms. In the ECHELON-2 study, only 27% (n = 44) of sALCL patients in the intervention group and 35% (n = 54) in the control group had B symptomatology at the start of study; this reduces the reliability of data.

Regardless of the uncertainties of the present operationalisation of the endpoint CR in patients with B-symptomatology at the start of study described above, there is no statistically significant difference between the treatment arms for this endpoint.

Sustained CR

Sustained CR was defined as achieving a CR at the end of treatment without disease relapse or patient death by the end of observation. The endpoint is thus composed of the components CR and relapses.

[2] Schmitz N et al., Treatment and prognosis of mature T-cell and NK-cell lymphoma: an analysis of patients with T-cell lymphoma treated in studies of the German High-Grade Non-Hodgkin Lymphoma Study Group. Blood. 2010

In principle, the points of criticism already mentioned regarding the operationalisation of the CR and the RFS in the ECHELON-2 study also apply to the sustained CR. In contrast to the endpoint RFS, for the evaluation of the sustained CR shown, the ratio of individuals without disease relapse who had achieved a CR at the end of treatment was formed to the ITT population that was compliant with marketing authorisation; so there is no break in randomisation.

In the dossier, the pharmaceutical company presents evaluations on the endpoint sustained CR defined *post hoc*. No further information was provided on the extent to which this is an established endpoint in pivotal studies in the present therapeutic indication or an expert assessment of the significance of this endpoint.

Patients with a CR at the end of treatment who discontinued the study during the follow-up period were evaluated as sustained relapse-free. It is unclear how many of these drop-outs may still have had relapses.

This notwithstanding, a sufficiently long follow-up of the patients is crucial for the assessment of the sustainability of a CR. In the written statement procedure, the pharmaceutical company submits data for the observation period of patients who had not had a relapse at the time of the last observation. The median follow-up duration was 43.4 (brentuximab vedotin + CHP) and 45.2 months (CHOP), whereby at least one patient from each study arm was followed up for less than one month. In the absence of more detailed information on the distribution of follow-up duration, it is unclear how many patients in the treatment arms were observed equally briefly for the sustainability of their CR.

Based on the uncertainties mentioned, the endpoint sustained CR is not used to quantify the extent of the additional benefit.

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

Health status was assessed using the visual analogue scale (VAS) of the EQ-5D questionnaire. The EQ-5D visual analogue scale (VAS) ranges from 0 to 100 and is employed by adult study participants to assess their health status. A value of 0 corresponds to the worst conceivable health status and a value of 100 to the best conceivable health status. The EQ-5D-VAS was surveyed on Day 1 of each treatment cycle, at the end of treatment as well as every 3 months from Month 9 after the start of treatment. After 24 months or disease progression, the survey was conducted every 6 months until death or end of study.

The pharmaceutical company submitted time-to-event analysis operationalised as time to deterioration and time to improvement by ≥ 10 points covering the entire study period. Because of the low return rates in the two treatment arms after the end of treatment in combination with the different survey times in the case of disease progression, these evaluations are assessed as not usable.

Furthermore, the pharmaceutical company presented evaluations of the mean change (MMRM analyses). For the present assessment, the evaluations of the mean change at the end of treatment (EoT) compared with baseline are used; these are based on sufficiently high return rates (90.4% in the intervention arm and 90% in the control arm).

Based on the mean difference compared with EoT, there is no statistically significant difference between the treatment arms.

Symptomatology (EORTC QLQ-C30)

In the ECHELON-2 study, the symptomatology was measured using the symptom scales of the disease-specific questionnaire EORTC QLQ-C30. The EORTC QLQ-C30 was surveyed on Day 1 of each treatment cycle, at the end of treatment, and at Months 9, 12, 15, 18, 21, 24, and 30 after start of treatment or disease progression. The time to the first clinically relevant deterioration is defined here as an increase in score of at least 10 points from baseline.

For the EORTC QLQ-C30, the pharmaceutical company also submitted time-to-event analyses and mean change analyses (MMRM analyses) in the dossier for the benefit assessment.

The time-to-event analyses are not used for the benefit assessment for the same reasons given for the endpoint health status using the EQ-5D VAS.

The MMRM analyses are used for the present assessment. The return rates are sufficiently high (87.3% in the intervention arm and 77.1% in the control arm). Based on the mean difference to EoT, there is a statistically significant difference to the detriment of brentuximab vedotin for the pain, nausea and vomiting, and diarrhoea scales. 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 was not completely outside the irrelevance range of −0.2 to 0.2. Thus, it cannot be derived that the effects observed are clinically relevant.

Neurological symptomatology (FACT/GOG-Ntx)

Another patient-reported questionnaire used in the ECHELON-2 study was the FACT/GOG-Ntx sub-scale. It is used to map chemotherapy-induced neurological symptoms. The scale of the FACT/GOG-Ntx ranges from 0 to 44. Higher values correspond to a lower neurotoxicity.

For the FACT/GOG-Ntx, the pharmaceutical company submits MMRM analyses in the dossier for the benefit assessment; these are used for the benefit assessment. The return rates at EoT are sufficiently high (87.6 % in the intervention arm and 77.1% in the control arm).

Based on the mean difference compared with EoT, there is no statistically significant difference between the treatment arms.

In the overall consideration of the morbidity endpoints used for the present assessment, there is a statistically significant difference in favour of brentuximab vedotin in combination with CHP for the endpoint EFS. For the endpoint CR in patients with B symptomatology at the start of treatment, there is no statistically significant difference between treatment arms. Moreover, there are no statistically significant differences between the treatment arms in terms of health status, symptomatology endpoints, or neurological symptomatology. Overall, there is an advantage for brentuximab vedotin in combination with CHP compared with CHOP.

Health-related quality of life

Functional scales (EORTC QLQ-C30)

In the ECHELON-2 study, health-related quality of life was assessed using the functional scales of the disease-specific EORTC QLQ-C30 questionnaire. The time to the first clinically relevant improvement or deterioration is considered; which is defined as an increase or decrease in the score by at least 10 points compared with the baseline.

As already stated for the symptomatology endpoint, the pharmaceutical company submitted time-to-event analysis and MMRM analyses in the dossier for the benefit assessment. While the time-to-event analysis are not used for the benefit assessment for the reasons given, the MMRM analyses are taken into account.

Based on the mean difference compared with EoT, there is no statistically significant difference between the treatment arms.

In the overall consideration, neither advantages nor disadvantages for brentuximab vedotin in combination with CHP compared with CHOP can be derived for health-related quality of life.

Side effects

Total adverse events (AE)

Almost all study participants experienced AE. The results are presented additionally.

Severe AE (CTCAE grade ≥ 3), serious AE (SAE), therapy discontinuations because of AE, AE of special interest

For the endpoints severe AE (CTCAE grade ≥ 3), SAE, and therapy discontinuations because of AE, there are no significant differences between the treatment arms.

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

Overall assessment/conclusion

For the assessment of the additional benefit of brentuximab vedotin in combination with cyclophosphamide, doxorubicin, and prednisone (CHP) for the treatment of adult patients with previously untreated systemic anaplastic large cell lymphoma (sALCL), there are results on the endpoint categories mortality, morbidity, quality of life, and side effects.

The basis of the assessment is the ECHELON-2 study, which compares brentuximab vedotin + CHP with cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP). The results of the sub-population of patients with diagnosed sALCL, as defined in the marketing authorisation, are relevant for the assessment.

For overall survival, there is a statistically significant advantage for treatment with brentuximab vedotin + CHP compared to treatment with CHOP. This is considered a relevant but no more than a minor advantage.

In the morbidity endpoint category, there is a relevant advantage for brentuximab vedotin in combination with CHP compared to CHOP for the endpoint event-free survival (EFS). The significance of the EFS endpoint is thus subject to uncertainties. In view of the size of the effect, the result is nevertheless used for the present assessment. For the endpoint complete remission (CR) in patients with B symptomatology at the start of treatment, there is no statistically significant difference between treatment arms. Moreover, there are no statistically significant differences between the treatment arms in terms of health status, symptomatology endpoints, or neurological symptomatology.

Data on health-related quality of life are also available for the present assessment. There are no statistically significant differences between the treatment arms for the functional scales of the EORTC QLQ-C30 questionnaire. Thus, neither an advantage nor a disadvantage for brentuximab vedotin in combination with CHP compared with CHOP can be derived for health-related quality of life.

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

In the overall view of the results on the patient-relevant endpoints, there is a relevant, but no more than minor advantage in terms of overall survival as well as a relevant advantage in terms of morbidity, which is, however, subject to uncertainties.

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

Significance of the evidence

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

At the study level, the risk of bias is classified 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 included in the study does not correspond to the standard of healthcare currently generally accepted in Germany.

Furthermore, uncertainties arise because of the unclear blinding and survey quality of relapses after the primary analysis.

At the endpoint level, uncertainties arise, from the wide confidence interval to the effect estimator (upper limit of 0.99) in the overall survival result. The significance of the endpoint event-free survival (EFS) is also subject to uncertainty.

Overall, the data basis shows uncertainties, which lead to a downgrading of the reliability of data for the overall assessment. The reliability of data supporting the finding of an additional benefit is therefore classified as a “hint”.

2.1.3 Limitation of the period of validity of the resolution

The limitation of the period of validity of the resolution on the benefit assessment of brentuximab vedotin has its legal basis in Section 35a, paragraph 3, sentence 4 SGB V. Thereafter, the G-BA may limit the validity of the resolution on the benefit assessment of a medicinal product. In this case, the limitation is justified by objective reasons consistent with the purpose of the benefit assessment according to Section 35a, paragraph 1 SGB V:

The present results on overall survival are based on the data cut-off of 25 September 2019 of the ECHELON-2 study, which was requested by the European Medicines Agency (EMA) as part of the marketing authorisation process. At the time of this non-pre-specified data cut-off, the median observation duration of overall survival had not yet been reached. Because of the low number of events for overall survival, the significance is limited. Final overall survival data from the ECHELON-2 study are expected in Q1 2021. The final data on overall survival are to be submitted to the European Medicines Agency (EMA).

In view of the fact that clinical data on overall survival relevant for the benefit assessment of the medicinal product are expected in the future, the G-BA considers it appropriate to limit the period of validity of the resolution until further scientific evidence on the extent of the additional benefit of brentuximab vedotin is available. The limitation allows the expected final results from the ECHELON-2 study to be included in the benefit assessment of the medicinal product in accordance with Section 35 a SGB V in a timely manner.

Conditions of the limitation:

For the renewed benefit assessment after the deadline, the results of the final data cut-off after obtaining the final data on overall survival from the ECHELON-2 study are to be presented in the dossier.

A limitation of the resolution until 1 July 2021 is considered to be appropriate.

The G-BA is able, in principle, to revise the limitation if it has been presented with clear justification that it is insufficient or too long.

In accordance with Section 3, paragraph 7 AM-NutzenV in conjunction with Chapter 5, Section 1, paragraph 2, number 7 VerfO, the procedure for the benefit assessment of brentuximab vedotin recommences when the deadline has expired. For this purpose, the pharmaceutical company must submit a dossier to the G-BA at the latest on the date of expiry to prove the extent of the additional benefit of brentuximab vedotin (Section 4, paragraph 3, number 5 AM-NutzenV in conjunction with Chapter 5, Section 8, number 5 VerfO).

The possibility that a benefit assessment for brentuximab vedotin can be carried out at an earlier point in time for other reasons (*cf* Chapter 5, Section 1, paragraph 2, Nos. 2 to 6 VerfO) remains unaffected by this.

2.1.4 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. Adcetris was

approved as an orphan drug. Brentuximab vedotin in combination with cyclophosphamide, doxorubicin and prednisone (CHP) is indicated for adult patients with previously untreated systemic anaplastic large cell lymphoma (sALCL).

For the assessment, the pharmaceutical company presents the results of the double-blind, randomised-controlled ECHELON-2 Phase III study in which brentuximab vedotin in combination with CHP is compared with cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP). The results of the sub-population of patients with diagnosed sALCL, as defined in the marketing authorisation, are relevant for the assessment.

For overall survival, there is a statistically significant advantage for treatment with brentuximab vedotin + CHP compared to treatment with CHOP. This is considered a relevant but no more than a minor advantage.

In the morbidity endpoint category, there is a relevant advantage for brentuximab vedotin in combination with CHP compared to CHOP for the endpoint event-free survival (EFS). The significance of the EFS endpoint is thus subject to uncertainties. However, in view of the size of the effect, the result is nevertheless used for the present assessment. For the other patient-relevant morbidity endpoints, there is no difference between the treatment arms.

There are no differences between the treatment arms in terms of quality of life and side effects.

Uncertainties remain in the interpretation of the results because of the comparator therapy selected (which does not reflect the German healthcare reality for most of the patients included) as well as the unclear blinding and survey quality for individual endpoints.

In conclusion, the G-BA found a hint for a minor additional benefit of brentuximab vedotin in combination with CHP compared with CHOP in the treatment of adult patients with previously untreated systemic anaplastic large cell lymphoma (sALCL).

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 stated by the pharmaceutical company in the dossier.

The information in the dossier is plausible despite minor methodological shortcomings in the order 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: 8 September 2020):

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

Treatment with brentuximab vedotin should be initiated and monitored only by specialists in internal medicine, haematology, and oncology experienced in the treatment of patients with peripheral T-cell lymphoma, especially sALCL.

This medicinal product received a conditional marketing authorisation. The EMA will evaluate new information on this medicinal product at a minimum once per year and update the product information where necessary.

There is no data available for patients with sALCL ALK+ with IPI status < 2 because 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: 15 November 2020).

The use of brentuximab vedotin in combination with cyclophosphamide, doxorubicin and prednisone is limited to 6–8 21-day cycles.

The dosages recommended in the product information on brentuximab vedotin and the ECHELON-2 pivotal studies were used as the basis for calculation.

For dosages depending on body weight (BW) or body surface, the average body measurements were used as a basis (average height: 1.72 m, average body weight: 77 kg). From this, a body surface area of 1.90 m² is calculated (calculation according to Du Bois 1916)[3].

Treatment duration:

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 × per 21-day cycle	6–8	1	6–8
Cyclophosphamide	1 × per 21-day cycle	6–8	1	6–8
Doxorubicin	1 × per 21-day cycle	6–8	1	6–8
Prednisone	On Day 1–5 of a 21-day cycle	6–8	5	30–40

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

Usage and consumption:

Designation of the therapy	Dosage/application	Dose/patient/treatment day	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 × 50 mg	6 8	18 × 50 mg – 24 × 50 mg
Cyclophosphamide	750 mg/m² = 1,425 mg	1,425 mg	1 × 1 g + 1 × 500 mg	6 – 8	6 × 1 g + 6 × 500 mg – 8 × 1 g + 8 × 500 mg
Doxorubicin	50 mg/m² = 95 mg	95 mg	2 × 50 mg	6 – 8	12 × 50 mg – 16 × 50 mg
Prednisone	100 mg	100 mg	2 × 50 mg	30 – 40	60 × 50 mg 80 × 50 mg

Costs:

Costs of the medicinal product:

Designation of the therapy	Package 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 PIC	€ 3,342.60	€ 1.77	€ 192.56	€ 3,148.27
Cyclophosphamide 1 g	6 PIJ	€ 120.58	€ 1.77	€ 6.24	€ 112.57
Cyclophosphamide 500 mg	6 PIJ	€ 79.91	€ 1.77	€ 8.98	€ 69.16
Cyclophosphamide 1 g	1 PIJ	€ 29.07	€ 1.77	€ 1.04	€ 26.26

Designation of the therapy	Package size	Costs (pharmacy sales price)	Rebate Section 130 SGB V	Rebate Section 130a SGB V	Costs after deduction of statutory rebates
Cyclophosphamide 500 mg	1 PIJ	€ 22.28	€ 1.77	€ 1.50	€ 19.01
Doxorubicin 50 mg[4]	1 IS	€ 147.18	€ 1.77	€ 11.07	€ 134.34
Prednisone 50 mg[3]	50 TAB	€ 66.07	€ 1.77	€ 4.49	€ 59.81
Prednisone 50 mg[3]	10 TAB	€ 22.34	€ 1.77	€ 0.94	€ 19.63
Abbreviations: IS = solution for infusion; PIJ = powder for the preparation of an injection solution; PIC = powder for the preparation of an infusion solution concentrate; TAB = tablets					

Pharmaceutical selling price (LAUER-TAXE®) as last revised: 15 November 2020

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 assessed 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[5,6]	Cost per service	Treatment days per year	Cost per patient/year
Medicinal product to be assessed					
Brentuximab vedotin + cyclophosphamide + doxorubicin + prednisone					
Primary prophylaxis with G-CSF					
Pegfilgrastim 1 PS, 6 mg	€ 922.65	€ 869.09 (€ 1.77; € 51.79)	€ 869.09	6–8	€ 5,214.54 – € 6,952.72
PS = prefilled syringes					

[4] Fixed reimbursement rate
[5] Rebate according to Section 130 SGB V
[6] Rebate according to Section 130a SGB V

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; Sections 4 and 5 Pharmaceutical Price Ordinance) of 1 October 2009 is not fully used to calculate the 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 *Hilfstaxe* in its currently valid version, surcharges for the production of parenteral preparations containing cytostatic agents 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 are to be payable. These additional other costs are not added to the pharmacy sales price but rather follow the rules for calculating in the *Hilfstaxe*. The cost representation is based on the pharmacy sales 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 according to the regulations in Annex 3 of the *Hilfstaxe*.

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 8 June 2020, 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 1, sentence 2 VerfO.

The benefit assessment of the G-BA was published on 15 September 2020 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 6 October 2020.

The oral hearing was held on 27 October 2020.

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 24 November 2020, and the proposed resolution was approved.

At its session on 3 December 2020, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee on Medicinal Products	15 September 2020	Information of the benefit assessment of the G-BA
Working group Section 35a	13 October 2020	Information on written statements received; preparation of the oral hearing
Subcommittee on Medicinal Products	27 October 2020	Conduct of the oral hearing
Working group Section 35a	3 November 2020 17 November 2020	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 on Medicinal Products	24 November 2020	Concluding discussion of the draft resolution
Plenum	3 December 2020	Adoption of the resolution on the amendment of Annex XII of the AM-RL

Berlin, 3 December 2020

Federal Joint Committee
in accordance with Section 91 SGB V
The Chair

Prof. Hecken