Justification

Gemeinsamer Bundesausschuss

to the Resolution of the Federal Joint Committee (G-BA) on an Amendment of the Pharmaceuticals Directive (AM-RL): Annex XII – Resolutions on the Benefit Assessment of Medicinal Products with New Active Ingredients According to Section 35a SGB V Blinatumomab (new therapeutic indication: acute lymphatic leukaemia, paediatric patients aged 1 year or older)

of 15 August 2019

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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 of the Council of 16 December 1999, according to Section 35a, paragraph 1, sentence 11, 1st half of the sentence SGB V, the additional medical benefit is considered to be proven through the grant of the marketing authorisation. Evidence of the medical benefit and the additional medicinal benefit in relation to the appropriate comparator therapy need not be submitted (Section 35a, paragraph 1, sentence 11, 2nd half of the sentence SGB V). Section 35a, paragraph 1, sentence 11 1st half of the sentence SGB V thus guarantees an additional benefit for an approved orphan drug, although an assessment of the orphan drug in accordance with the principles laid down in Section 35a, paragraph 1, sentence 3, numbers 2 and 3 SGB V in conjunction with the Chapter 5, Sections 5 et seq. of the Rules of Procedure, G-BA (VerfO) has not been carried out. Only the extent of the additional benefit has to be demonstrated.

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

In accordance with Section 35a, paragraph 2 SGB V, the G-BA decides whether to carry out the benefit assessment itself or to commission the Institute for Quality and Efficiency in Health Care (IQWiG). 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 legally permissible assessment of the extent of an additional benefit to be assumed by law. Rather, the extent of the additional benefit provided by the G-BA is evaluated exclusively on the basis of the approval studies.

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

According to Section 35a, paragraph 3 SGB V, the G-BA shall pass a resolution 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 blinatumomab was listed for the first time on 15 December 2015 in the "LAUER-TAXE®", the extensive German registry of available drugs and their prices.

On 23 August 2018, blinatumomab received marketing authorisation for a new therapeutic indication (for the treatment of paediatric patients aged 1 year or older with Philadelphia chromosome-negative, CD19-positive B-precursor ALL which is refractory or in relapse after receiving at least two prior therapies or in relapse after receiving prior allogeneic hematopoietic stem cell transplantation) to be classified as a major type 2 variation as defined according to Annex 2 number 2a to Regulation (EC) No. 1234/2008 of the commission of 24 November 2008 concerning the examination of variations to the terms of marketing authorisations for medicinal products for human use and veterinary medicinal products (OJ L 334, 12 December 2008, p. 7). Blinatumomab for the treatment of acute lymphocytic leukaemia in paediatric patients is approved as a medicinal product for the treatment of a rare disease under Regulation (EC) No 141/2000 of the European Parliament and the Council of 16 December 1999.

According to Section 35a, paragraph 1, sentence 10, 1st half of the sentence SGB V, the additional benefit is considered to be already proven by the marketing authorisation. The extent of the additional benefit is assessed on the basis of the approval studies by the G-BA.

On 23 February 2018, the pharmaceutical company filed an application to postpone the date for the start of the benefit assessment procedure for blinatumomab in the present therapeutic indication according to Section 35a, paragraph 5b SGB V. At its session on 17 May 2018, the G-BA approved the motion to postpone the relevant date in accordance with Section 35a, paragraph 5b SGB V. The benefit assessment of blinatumomab in the therapeutic indication ALL in paediatric patients begins at the same time as the benefit assessment of blinatumomab in the therapeutic indication ALL in MRD^+ patients, at the latest within 4 weeks after approval of the therapeutic indication ALL in MRD+ patients in accordance with Chapter 5, Section 8, number 2 of the VerfO, at the latest 6 months after the first relevant time point (4 weeks after marketing authorisation of the therapeutic indication ALL in paediatric patients).

On 13 February 2019, the pharmaceutical company has submitted a dossier in accordance with Section 4, paragraph 3, number 2 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with Chapter 5, Section 8, paragraph 1, number 2 of the Rules of Procedure (VerfO) of the G-BA on the active ingredient blinatumomab with the new therapeutic indication (treatment of acute lymphatic leukaemia in paediatric patients) in due time.

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 15 May 2019 together with the IQWiG assessment on the website of the G-BA (www.g-ba.de), thus initiating the written statement procedure. In addition, an oral hearing was held.

The G-BA adopted its resolution on the basis of the dossier of the pharmaceutical company, the dossier evaluation carried out by the G-BA, the assessment of treatment costs and patient numbers (G19-07) prepared by IQWiG, and the statements submitted in the written and oral hearing procedure. In order to determine the extent of the additional benefit, the G-BA has evaluated the studies relevant for marketing authorisation with regard to their therapeutic relevance (qualitative) in accordance with the criteria laid down in Chapter 5, Section 5, paragraph 7, sentence 1 numbers 1 through 4 VerfO. The methodology proposed

by the IQWiG in accordance with the General Methods[1] was not used in the benefit assessment of blinatumomab.

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

2.1 Additional benefit of the medicinal product

2.1.1 Approved therapeutic indication of blinatumomab (Blincyto®) in accordance with the product information

BLINCYTO is indicated as monotherapy for the treatment of paediatric patients aged 1 year or older with Philadelphia chromosome-negative, CD19-positive B-precursor ALL which is refractory or in relapse after receiving at least two prior therapies or in relapse after receiving prior allogeneic hematopoietic stem cell transplantation.

2.1.2 Extent of the additional benefit

Paediatric patients aged 1 year or older with Philadelphia chromosome-negative, CD19-positive B-precursor ALL that is refractory or in relapse after receiving at least two prior therapies or in relapse after receiving prior allogeneic hematopoietic stem cell transplantation.

For the benefit assessment of blinatumomab in paediatric patients, documents of several comparisons are used. The single-arm Phase II study MT103-205 was decisive for the marketing authorisation.

MT103-205 is an uncontrolled, multi-centre Phase I/II study to evaluate the efficacy and safety of blinatumomab in paediatric and adolescent patients with relapsed or refractory B precursor cell ALL. The study was divided into two parts starting with a dose-finding phase.

Patients under 18 years of age with a bone marrow blast rate of at least 25% at the time of study inclusion were included. Patients had to be in relapse after allogeneic stem cell transplantation or in second or later relapse after any other therapy or had to be refractory (without complete remission) to standard (re)induction therapy. The stem cell transplantation had to have taken place at least 3 months ago. Patients with active or immunosuppressed graft-versus-host disease and patients with relevant central nervous system disease were excluded from the study.

For the benefit assessment, only those patients whose blinatumomab dosage was compliant with marketing authorisation were considered. These 70 study patients were treated with blinatumomab in 6-week cycles (28-day treatment phase followed by a two-week treatment-free interval). The dosage was adjusted depending on the body surface area and was 5 µg/m^2/day in week 1 of the first cycle and 15 µg/m^2/day thereafter. Patients who achieved complete haematological remission after the first two cycles were able to receive up to three additional cycles of blinatumomab or an allogeneic stem cell transplant.

The primary endpoint of the study was the proportion of patients with complete remission within the first two treatment cycles. Secondary endpoints were overall survival, remission duration, and the proportion of patients who received allogeneic stem cell transplantation after treatment with blinatumomab. Exploratively, the proportion of patients with and without minimal residual disease was surveyed.

Study MT103-205 was completed on 24 May 2016.

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.

The results of the MT103-205 study are compared with the results of the studies described below using different approaches, whereby the benefit assessment dossier only takes into account a transfer of evidence from adults to paediatric patients for the quantification of the additional benefit by the pharmaceutical company. The other studies and comparisons mentioned are also not used by the pharmaceutical company but were the subject of discussion within the framework of the authorisation procedure.

In line with the assessment of the pharmaceutical company, the 20120215 and COG 1331 studies are not included in this assessment because no results were available at the time the dossier was submitted.

Study MT103-211 is not relevant for the present assessment because it investigated adult patients after a first relapse, thereby deviating from the therapeutic indication to be assessed.

Despite the agreement with the patient population studied with the present therapeutic indication, study 20130320 cannot be used because the observation period was very short (maximum of 7 months) and, in particular, because the dosage was not adjusted as a function of body weight but rather in stages depending on the blast proportion in the bone marrow. There is also an interim analysis of efficacy, which was not planned in the study protocol and which took place at a very early stage in the course of the study. Overall, the expanded access study should not be included in this assessment.

The Phase Ib/II trial 20130265 was conducted in paediatric patients in Japan. Because the limited sample size (preliminary results for only 9 patients are available), the study is not used to quantify the extent of the additional benefit.

In addition, results from four studies with historical control populations are discussed. All studies cannot be used for the comparative assessment of additional benefit for a number of reasons as explained below.

The study population of Study 20120310 includes only adult patients.

The population underlying study 120521 is derived from a meta-analysis of 62 studies in the indication ALL, 38 of which involve paediatric patients. However, for the studies included, the information provided in terms of sample size, study design, and endpoints considered is insufficient. Basic information on prognostic factors, therapies considered and other disease characteristics as well as demographic factors is completely lacking. Furthermore, in the absence of an adequate quality assessment of the studies considered, it cannot be ruled out that studies with different reliability of data were considered together. It is also unclear whether the operationalisation of the endpoints and the follow-up time are sufficiently similar in the various studies. Even if the meta-analysis itself is taken into account, a final assessment of the comparability with the population of the pivotal MT103-205 study is not possible because of the missing data mentioned above.

For a further historical comparison, results of the populations from the 20120299 and 20140228 studies are also available from public authorisation documents. The results considered together come from American and European study centres; with regard to their relapse and refractory status, the patients are fundamentally relevant for the present assessment. However, the basis on which the criteria the study centres were selected as well as the basis on which patients were included or excluded in the respective centres are not sufficiently explained. What is important, however, is the lack of information on the type and duration of previous therapies, the standardisation of data collection, and the extent and handling of missing values. Uncertainties also exist with regard to the information provided on the definition and operationalisation of the endpoints considered.

Considering the insufficiently presented information on baseline and disease characteristics, the pharmaceutical company also sees significant differences compared to the population of the pivotal study MT103-205. This mainly concerns the proportions of patients in first and second relapses and in the former, the time since the previous allogeneic stem cell transplantation. Because of differences in disease-specific characteristics to baseline, a

propensity score analysis was performed to adjust these factors as part of the authorisation process. The propensity score analysis can compensate for inequalities in patient characteristics that have been collected and taken into account. However, the points of criticism regarding the historical control population with regard to the selection of study centres or registries and the other points mentioned (e.g. the lack of information on the type and duration of previous therapies) remain.

Equally important for the rejection of the comparison is the fact that the selection of the adjustment factors considered for the analysis is not sufficiently justified. It cannot be excluded that relevant factors have not been taken into account or factors with knowledge of the ultimate results have been included or excluded.

In addition, only a part of the patient population of the control populations that had not been substantiated by the pharmaceutical company was included in the analysis.

In the overall view, these uncertainties are so serious that the propensity score analysis in the present case constellation is not suitable for generating results relevant for quantifying the additional benefit.

For a transfer of evidence from adult patients to the paediatric patients evaluated, the pharmaceutical company also uses Study 00103311 (TOWER). This is a randomised, controlled trial in adult ALL patients, which was also the basis for the benefit assessment of 7 December 2017.

From the TOWER study, results on overall survival, response, rate of allogeneic stem cell transplantation, and side effects compared with standard of care chemotherapy were available from 405 primary refractory patients.

The pharmaceutical company presents the results of the TOWER study in the benefit assessment dossier in conjunction with the results of the pivotal MT103-205 study in the paediatric patient population.

The evidence transfer is not used in the present case constellation because there are clear uncertainties as to whether the compared patient populations are sufficiently similar, especially with regard to response rates, therapy options, and prognosis.

Irrespective of the therapy line, study results cited by the pharmaceutical company generally suggest significantly higher response rates in paediatric patients than in adults. There are also differences with regard to the medicinal therapy options discussed in the guidelines for advanced treatment situations.

In addition, there are still uncertainties regarding the comparability of the two populations considered in the TOWER and MT103-205 studies because a higher proportion of patients in the MT103-205 study were in a more advanced therapy situation (in terms of number of previous therapies and proportion of patients with prior allogeneic stem cell transplantation) than in the TOWER study in adults.

Overall it was not proven with sufficient certainty that the populations compared are comparable in the present therapeutic indication. Thus, the basic prerequisites for a transfer of evidence are lacking. In its assessment, the EMA also does not focus primarily on the transfer of evidence also submitted in the context of the marketing authorisation. Only the MT103-205 study is described as the basis for approval.

Because of the limitations of the evidence presented, only the results of the non-comparative MT103-205 study should be used for the benefit assessment.

Mortality

At the end of study, 68.8% of the 70 patients treated with blinatumomab had died. The median survival time was 7.5 months.

Morbidity

Complete remission

In study MT103-205, complete remission was operationalised as the achievement of less than 5% blasts in the bone marrow combined with no evidence of circulating blasts or extramedullary disease as well as achievement of bone marrow status M1 with complete recovery of peripheral blood count.

In total, 38.6% of patients achieved complete remission within the first two blinatumomab cycles at the data cut-off of 12 January 2015.

The endpoint CR is an important prognostic factor and relevant for the therapy decision in the present indication. A CR associated with a noticeable decrease in disease symptoms for the patient is always relevant to the patient for the benefit assessment. In the present case, the endpoint was not determined on the basis of symptoms but rather on the basis of laboratory tests. There is no validation of CR as a surrogate parameter for further patient-relevant endpoints. In this assessment, the endpoint is classified as an endpoint of unclear relevance and is presented only as a supplement. No statement can be derived on the extent of the additional benefit.

MRD remission

A complete molecular remission within the first two treatment cycles (defined as reduction of leukaemia cells to less than 10^{-4}) was achieved by 15 patients in the MT103-205 study.

Achieving MRD negativity is considered an important prognostic factor in ALL therapy. Studies have also shown an association between MRD negativity and recurrence or mortality. There is no validation of MRD negativity as a surrogate parameter for overall survival. The endpoint is therefore presented as a supplement. No statement on the extent of the additional benefit is derived from the results.

Side effects

In the MT103-205 study, adverse events were assessed from start of treatment to 30 days after the last blinatumomab infusion, the end of study, or the start of a follow-up therapy. In the follow-up, only therapy-associated side effects were recorded.

All study patients showed an adverse event (AE) during the observation period. 87.1% of the patients had an AE with CTCAE grade ≥ 3; 55.7% of the patients had a serious AE (SAE). 4 of the 70 patients in the full analysis set population had to discontinue the study medication because of an adverse event.

With regard to the AE with CTCAE grade ≥ 3, anaemia, thrombocytopenia, febrile neutropenins, leukopenia, neutropenia, cytokine release syndromes, and hypokalemia occurred at the level of the Preferred Terms. Hypertonia, pyrexia, increases in alanine and aspartate aminotransferase, and low levels of neutrophils, thrombocytes and leukocytes also occurred with a frequency of more than 5%. For the SAE, this applies to the side effects of febrile neutropenia, cytokine release syndromes and pyrexia.

Overall assessment

For the benefit assessment of blinatumomab for the treatment of paediatric ALL patients, results on the endpoint categories mortality, morbidity, and side effects from the uncontrolled MT103-205 study are available.

The historical data provided are neither suitable for a naïve indirect comparison nor for an indirect comparison adjusted by propensity score matching. In particular, they are not considered suitable for demonstrating the additional benefit because of insufficient

information on the study populations and uncertainties regarding the adjustment procedure applied.

Because of the one-armed study design and the unsuitable historical control, a comparative assessment of the study results is not possible overall. Furthermore, a transfer of evidence is not appropriate.

Thus, a quantitative assessment of the extent of the effect and a quantification of the additional benefit on the basis of the data submitted are not possible.

As a result, the G-BA classifies the extent of the additional benefit of blinatumomab in the present indication as non-quantifiable because of the limited data basis based on the criteria in Section 5, paragraph 7 of the AM-NutzenV, taking into account the severity of the disease and the therapeutic objective in the treatment of the disease. According to Section 35a, paragraph 1, sentence 11, 1st half of sentence SGB V, there is an additional benefit; however, this is non-quantifiable because the scientific data basis does not allow this.

2.1.3 Summary of the assessment

The present assessment concerns the benefit assessment of the active ingredient blinatumomab in a new therapeutic indication:

“BLINCYTO is indicated as monotherapy for the treatment of paediatric patients aged 1 year or older with Philadelphia chromosome-negative, CD19-positive B-precursor ALL which is refractory or in relapse after receiving at least two prior therapies or in relapse after receiving prior allogeneic hematopoietic stem cell transplantation”.

Blinatumomab is a medicinal product used for the treatment of a rare disease.

For the assessment, the pharmaceutical company presents the results of the single-arm MT103-205 study, which is the basis for marketing authorisation. The results of this study are compared with the results of historical control populations. In particular because of a lack of information on the underlying patient populations and uncertainties regarding the adjustment procedure used, the comparative evaluations are not suitable for demonstrating an additional benefit. Furthermore, transfer of evidence from the results of the randomised controlled TOWER study in adult patients to the paediatric patient population is inappropriate.

Thus, a quantitative assessment of the extent of the effect and a quantification of the additional benefit on the basis of the data submitted are not possible. The extent of the additional benefit of blinatumomab in the present indication is therefore considered non-quantifiable.

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

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

The resolution will be based on the information from the dossier of the pharmaceutical company regarding the number of patients. The information provided there is generally comprehensible; however, there is uncertainty because the limited data basis.

Patients with recurrence after more than two therapy lines were not considered in the derivation. Furthermore, the literature used for the calculation partly included a heterogeneous total population for which the exact composition is not comprehensible with regard to all characteristics.

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 Blincyto® (active ingredient: blinatumomab) at the following publicly accessible link (last access: 10 May 2019):

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

Only specialists in internal medicine, haematology, and oncology experienced in the treatment of patients with acute lymphatic leukaemia or specialists in paediatrics and adolescent medicine with a focus on haematology and oncology may initiate and monitor treatment with blinatumomab.

In accordance with the specifications of the EMA regarding additional measures for risk minimisation, the pharmaceutical company must provide training material for doctors, pharmacists, medical specialists, and patients/nurses as well as a patient reminder card.

The training material contains, in particular, information on the administration of BLINCYTO® and on neurological events.

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 July 2019).

In order to improve comparability, the costs of the medicinal products were approximated both on the basis of the pharmacy retail price level and also deducting the statutory rebates in accordance with Sections 130 and 130a SGB V. To calculate the annual treatment costs, the required number of packs of a particular potency was first determined on the basis of consumption. Having determined the number of packs of a particular potency, the pharmaceutical costs were then calculated on the basis of the costs per pack after deduction of the statutory rebates.

Paediatric patients aged 1 year or older with Philadelphia chromosome-negative, CD19-positive B-precursor ALL that is refractory or in relapse after receiving at least two prior therapies or in relapse after receiving prior allogeneic hematopoietic stem cell transplantation.

Blinatumomab is used to treat Philadelphia chromosome-negative, relapsed, or refractory B precursor ALL over two induction cycles consisting of 28 treatment days. There is a 14-day treatment-free interval between the individual cycles. In the case of a complete remission after two cycles, a consolidation therapy for up to three further cycles can be performed afterwards.

Blinatumomab is administered as a continuous infusion. The dosage depends on the patient's body weight if the patient weighs less than 45 kg. Patients weighing 45 kg or more receive 9 µg/day on Day 1 to 7 of the first cycle and 28 µg/day on Day 8 to 28 of the first cycle as well as Day 1 to 28 of the subsequent cycles.

For patients with a body weight of less than 45 kg, the daily dose is 5 µg/m^2/day on Day 1 to 7 of the first cycle and 15 µg/m^2/day on Day 8 to 28 of the first cycle as well as Day 1 to 28 of the subsequent cycles.

For the cost calculation, a one-year-old child is used as the lower limit and a 17-year-old child as the upper limit.

For the dosage depending on body weight (BW) or body surface area (BSA), the average body measurements of one-year-old children were used as a basis (average body size: 0.83 m, average body weight: 11.6 kg). From this, a body surface area of 0.50 m² is calculated (calculation according to Du Bois 1916). According to official representative statistics "Microcensus 2017 – body measurements of the population", the body weight of 17-year-olds is 67.0 kg.[2] According to the product information, the dosage of these patients no longer depends on their body weight.

A single blinatumomab preparation can be infused for up to 96 h. According to the product information, this results in a consumption of 1 vial for a 96-hour infusion of 5 µg/ 0.5 m^2/day. The same applies to a 72-hour infusion. For the dosage of 15 µg/0.5 m^2/day, also in one-year-old patients, there is a consumption of 1 vial every 72 hours. The consumption for patients from a body weight of 45 kg consists of 1 vial per 72 h at a dosage of 9 µg/day and one vial per day at a dosage of 28 µg/day or 4 vials in a preparation for 96 h.

To calculate treatment costs, the infusion duration associated with the lowest consumption of blinatumomab was used.

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				
Blinatumomab	continuous on day 1–28 of a 42-day cycle	2 cycles of induction and up to 3 cycles of consolidation	28	56–140

Usage and consumption:

Designation of the therapy	Dosage	Dosage/patient/treatment days	Consumption by potency/treatment day	Treatment days/ patient/ year	Average annual consumption by potency
Medicinal product to be assessed					
Blinatumomab	Induction therapy				
	1-year-old child				
	1st cycle: Day 1–7: 5 µg/m^2/day	5 µg/m^2	5 µg/m^2	7 +	2 vials +
	Day 8–28: 15 µg/m^2/day	15 µg/m^2	15 µg/m^2	21	7 vials of 38.5 µg each
	2. cycle: Day 1–28: 15 µg/m^2/day	15 µg/m^2	15 µg/m^2/	28	10 vials of 38.5 µg each
	17-year-old adolescent				
	1. cycle:	9 µg	9 µg	7 +	3 vials +

[2] German Federal Office For Statistics, Wiesbaden 2018: http://www.gbe-bund.de/oowa921-install/servlet/oowa/aw92/dboowasys921.xwdevkit/xwd_init?gbe.isgbetol/xs_start_neu/&p_aid=3&p_aid=58307757&nummer=223&p_sprache=D&p_indsp=-&p_aid=58587598

Designation of the therapy	Dosage	Dosage/patient/treatment days	Consumption by potency/treatment day	Treatment days/ patient/ year	Average annual consumption by potency
	Day 1–7: 9 µg/day Day 8–28: 28 µg/day	28 µg	28 µg	21	21 vials of 38.5 µg each
	2. cycle: Day 1–28: 28 µg/day	28 µg	28 µg	28	28 vials of 38.5 µg each
	Consolidation therapy				
	1-year-old child				
	Cycle 3 to 5 15 µg/m^2/day	15 µg/m^2	15 µg/m^2	28 treatment days per cycle	10 vials of 38.5 µg each per cycle
	17-year-old adolescent				
	Cycle 3 to 5 28 µg/m^2/day	28 µg	28 µg	28 treatment days per cycle	28 vials of 38.5 µg each per cycle

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					
Blinatumomab	1 vial	€ 2,773.33	€ 1.77	€ 155.11	€ 2,616.45
Abbreviations: ***					

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

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 medical treatment or the prescription of other services when using 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 the usual expenditure in the course of the treatment are not shown.

No additionally required SHI services are taken into account for the cost representation.

Other SHI services:

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

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

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 13 February 2019, the pharmaceutical company submitted a dossier for the benefit assessment of blinatumomab 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 May 2019 together with the IQWiG assessment of treatment costs and patient numbers on the G-BA website (www.g-ba.de), thus initiating the written statement procedure. The deadline for submitting written statements was 5 June 2019.

The oral hearing was held on 24 June 2019.

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

The evaluation of the written statements received and the oral hearing were discussed at the session of the subcommittee on 6 August 2019, and the proposed resolution was approved.

At its session on 15 August 2019, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee Medicinal product	8 May 2019	Knowledge of the benefit assessment of the G-BA
Working group Section 35a	18 June 2019	Information on written statements received; preparation of the oral hearing
Subcommittee Medicinal product	24 June 2019	Conduct of the oral hearing
Working group Section 35a	3 July 2019 17 July 2019 31 July 2019	Consultation on the dossier evaluation by the G-BA, the assessment of treatment costs and patient numbers by the IQWiG, and the evaluation of the statement procedure
Subcommittee Medicinal product	6 August 2019	Concluding discussion of the proposed resolution
Plenum	15 August 2019	Adoption of the resolution on the amendment of Annex XII AM-RL

Berlin, 15 August 2019

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

Prof Hecken