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

Blinatumomab (New Therapeutic Indication: B-precursor acute lymphoblastic leukaemia, relapsed or refractory, Ph+ CD19+)

of 15 July 2021

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 according to Section 35a paragraph 1, sentence 11, 1st half of the sentence 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 evaluation 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 approval 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 blinatumomab (Blincyto) 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 22 December 2020, blinatumomab 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 December 2008, p. 7).

Blinatumomab for the treatment of adults with CD19 positive relapsed or refractory B-precursor acute lymphoblastic leukaemia (ALL) 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 German Social Code, Book Five (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 authorisation studies by the G-BA.

On 18 January 2021, i.e. at the latest within four weeks after the disclosure, the pharmaceutical company on the approval of a new area of application, 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 (B-precursor acute lymphoblastic leukaemia, relapsed or refractory, CD19 positive).

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 03 May 2021 on 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 G21-04) and the statements made in the written statements and oral hearing process, 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 evaluated the studies relevant for the 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 blinatumomab.

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 adults with CD19 positive relapsed or refractory B-precursor acute lymphoblastic leukaemia (ALL). Patients with Philadelphia chromosome positive B-precursor ALL should have failed treatment with at least 2 tyrosine kinase inhibitors (TKIs) and have no alternative treatment options.

Therapeutic indication of the resolution (resolution of 15.07.2021):

Blincyto is indicated as monotherapy for the treatment of adults with Philadelphia chromosome positive CD19 positive relapsed or refractory B-precursor acute lymphoblastic leukaemia (ALL). Patients with Philadelphia chromosome positive B-precursor ALL should have failed treatment with at least 2 tyrosine kinase inhibitors (TKIs) and have no alternative treatment options.

2.1.2 Extend of the additional benefit and significance of the evidence

Adults with Philadelphia chromosome positive CD19 positive relapsed or refractory B-precursor acute lymphoblastic leukaemia (ALL), in whom treatment with at least 2 tyrosine kinase inhibitors (TKIs) has failed and who have no alternative treatment options

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

Hint for a non-quantifiable additional benefit since the scientific data does not allow a quantification.

Justification:

For the benefit assessment, the pharmaceutical company submitted data from the pivotal study ALCANTARA (20120216). In addition, the pharmaceutical company presented an indirect comparison in the form of propensity score-based analyses between the ALCANTARA study and a retrospective cohort study (study 20160462) on the endpoints of overall survival and complete remission. In addition, the pharmaceutical company draws on data from the TOWER study, which were included in the analysis model of the indirect comparison on the one hand and presented in the context of an evidence transfer for the assessment of

1 General Methods, version 6.0 from 5.11.2020. Institute for Quality and Efficiency in Health Care (IQWiG), Cologne.

symptomatology and quality of life using the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Core 30 (EORTC QLQ-C30) on the other.

ALCANTARA study

The ALCANTARA study is a one-arm, open-label, phase II study. The study was conducted in 19 centres in Europe and the United States from January 2014 to January 2017.

A total of 45 patients were included in the study. Of these, 84% had already received at least two tyrosine kinase inhibitors in accordance with the therapeutic indication. 44 % of the patients had previously been treated with an allogeneic stem cell transplantation. 70% of patients received at least one salvage therapy prior to the start of the study. The median time from diagnosis to the start of the study was 20 months. The last recurrence was diagnosed a median of 1 month before the start of the study. In addition to the presence of a Philadelphia chromosome, other cytogenetic abnormalities were documented for half of the patients. The median age of the patients was 55 years. Men and women were included in approximately equal numbers (53% vs 47%). 80% of patients had an ECOG status of 0 or 1.

The ALCANTARA study began with a three-week screening period during which dexamethasone was allowed to reduce disease burden and risk of tumour lysis syndrome. In the subsequent induction treatment, patients received 2 induction cycles of blinatumomab. If patients had achieved CR, CRh, or CRi within these two induction cycles, they could subsequently receive three additional cycles of blinatumomab as part of the consolidation treatment. The last dose of blinatumomab was followed by a safety follow-up of 30 days. In the subsequent 18-month long-term follow-up, response duration and overall survival continued to be assessed every 3 months.

The administration of blinatumomab was in accordance with the product information. The six-week cycles began with a four-week blinatumomab infusion followed by a two-week treatment-free period. In the first cycle, blinatumomab was initially administered at a dose of 9 µg, which was subsequently augmented to 28 µg. This dose was maintained during subsequent cycles. According to the study protocol, treatment was discontinued if remission was not achieved within the first two cycles or if disease progression occurred, if haematologic or extramedullary recurrence occurred after remission was achieved, or if there were safety concerns. If certain adverse events (AEs) occur, treatment should be interrupted according to protocol and resumed only after symptoms have resolved. All included patients received at least one dose of blinatumomab. 84% of patients had completed at least one treatment cycle, and 49% of patients had completed at least two treatment cycles.

To prevent the occurrence of cytokine release syndrome, patients were premedicated with dexamethasone. Furthermore, patients received intrathecal CNS prophylaxis according to institutional or national guidelines before treatment initiation and after each treatment cycle.

Provided that the patients were suitable, they could be submitted for allogeneic stem cell transplantation at any time after completion of the first induction cycle. This occurred in 20% of patients. Subsequent therapies were documented for 73% of the included patients. It is unclear how many patients were in remission or had relapsed at the time of subsequent therapy. Information on subsequent therapies in patients who did not respond to blinatumomab is not available.

The primary endpoint of the ALCANTARA study was the rate of patients who achieved CR or CRh within two treatment cycles.

The benefit assessment is based on data from the final data cut-off of 06.01.2017.

Indirect comparison with the 20160462 study

The 20160462 study is a retrospective, non-interventional cohort study based on databases from three study centres in Italy and Spain. In case of missing data, patient files were consulted. Between August and December 2017, patients were retrospectively identified from the databases who had a relapsed or refractory B-precursor ALL and had received qualifying salvage therapy. The observation period covered January 2000 to December 2017. A total of 55 patients were included. Patient data were collected starting at diagnosis until death or last follow-up. Qualifying salvage therapy was defined as salvage therapy used after the occurrence of refractarity to ≥ 1 second-generation TKI (dasatinib, nilotinib, bosutinib, ponatinib) or had a recurrence after this treatment or after the occurrence of intolerance to a second-generation TKI and intolerance or refractarity to imatinib mesylate. Exposure for comparison to blinatumomab was defined in each case as the last qualifying salvage therapy administered during the observation period.

In particular, this definition results in relevant uncertainties compared to the ALCANTARA study. For the patients who died during the observation period of the retrospective study (76%), the last salvage therapy of interest corresponds to the last salvage therapy before death. Thus, the exposure and the duration of observation depend on the occurrence of the endpoint of interest itself. This results in an artificially shortened observation time for overall survival compared to the ALCANTARA study. Furthermore, the definition of exposure results in differences with respect to prior and subsequent therapies. In the retrospective study, a higher proportion of patients had already received prior salvage therapy (87% vs 69%), whereas subsequent therapies were only administered in the ALCANTARA study. Furthermore, no information on the last salvage therapy is available from the retrospective study except for the type of therapy (chemotherapy and/or TKI). Overall, there is thus a substantial bias in observation time between the two studies for the endpoint overall survival.

In addition, there are further uncertainties and limitations. There is a lack of information on the centres, their selection process and also information on patient selection, so that a selection bias cannot be ruled out. Information on data quality is also missing.

Missing is also relevant information on (prognosis-determining) patient characteristics. These include tumour burden at the start of the last qualifying salvage therapy, health status, cytogenetics and possible mutations, comorbidities and prior extramedullary disease. Although the main inclusion and exclusion criteria of the two studies concur, there are uncertainties with regard to the inclusion criterion blast percentage, as no data are available for this criterion. Overall, it can be assumed that the inclusion and exclusion criteria in the ALCANTARA study resulted in an overall fitter patient population being included.

Since the observation period of the retrospective control study refers to a significantly earlier time period than that in the ALCANTARA study, differences exist concerning the availability of new therapy options (TKI), whereby changes in the prognosis cannot be ruled out.

Since, due to data availability, it cannot be assumed that all relevant and known confounders were taken into account in the propensity score-based analysis, structural equality cannot be assumed even after adjustment. To increase the propensity score-based comparison power, the pharmaceutical company used data from the TOWER study as a prior within a Bayes augmentation. A prerequisite for this procedure is the exchangeability of the study

population. However, this cannot be assumed in the present case. This is discussed concerning evidence transfer.

Overall, the indirect comparison between the ALCANTARA study and the 20160462 study is not included in this benefit assessment.

Evidence transfer of the TOWER study (00103311)

The TOWER controlled study evaluated blinatumomab versus salvage chemotherapy in the population of patients with relapsed or refractory Philadelphia chromosome negative B-precursor ALL. The pharmaceutical company assumes transferability of the data on symptomatology and quality of life to the Philadelphia chromosome positive patients, but does not present evidence for transferability.

However, the presence of a Philadelphia chromosome is associated with a worse prognosis. In addition, there are relevant differences between the ALCANTARA and TOWER studies with regard to prior therapies (number of prior salvage therapies and proportion of patients with prior stem cell transplantation).

Overall, there is insufficient evidence of transferability. Another limitation is the low return rate of the questionnaires (< 70 %) within the TOWER study.

Overall, the evidence transfer of the TOWER study is thus not considered.

Mortality

The endpoint overall survival was operationalised in the ALCANTARA study as time from the first infusion of blinatumomab in the first cycle of treatment to death from any cause.

At the final data cut-off, the median observation time was 25.1 months. Of the 45 patients included in the study, 37 (82.2%) were deceased at this time.

Since no comparative data are available, no overall conclusions on the extent of additional benefit in the mortality category can be derived from the results of the ALCANTARA study.

Morbidity

Complete remission

The endpoint complete remission was the primary endpoint in the ALCANTARA study. The endpoint was operationalised as the proportion of patients who achieved complete remission (CR) or complete remission with partial hematologic recovery (CRh) within 2 cycles of treatment. The response was measured based on a central bone marrow examination and a local peripheral blood count examination at the end of treatment of each cycle. In case of extramedullary lesions, these were evaluated according to the criteria of Cheson et al. 2007 and were considered as haematological relapse (disease progression).

In the ALCANTARA study, 14 (31.1%) of patients had achieved CR, 16 (35.6%) of patients had achieved CR or CRh, and 18 (40.0%) of patients had achieved CR, CRh, and CRi, respectively, after the first two cycles of treatment.

The endpoint 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 patient-relevant for the benefit assessment. In the present study, CR/CRh was assessed according to the criteria of Cheson et al. 2007, i.e. mainly by blood and bone marrow examinations. Thus, endpoints were not assessed based on symptoms but based on laboratory tests. A validation of CR as a surrogate parameter for patient-relevant endpoints,

e.g. mortality, is not available. Furthermore, it is unclear whether the achievement of CRh has a comparable clinical relevance as the achievement of CR. Therefore, the endpoints CR/CRh are classified as endpoints of unclear relevance in the present assessment and are only presented as supplementary information.

MRD remission

In the ALCANTARA study, MRD remission was operationalised as a reduction in leukaemia cells below 10^{-4} within two cycles of treatment. Complete MRD remission was achieved when no leukaemic cells were detected in the bone marrow sample. Real-time PCR or flow cytometry were used for the determination, although it is unclear in which cases the respective method was used.

After 2 cycles of treatment, MRD remission was present in 18 (40%) of patients. Complete remission was also present in 18 (40%) of patients.

Achieving MRD negativity is considered an important prognostic factor in the treatment of ALL. Studies in this regard specifically for the patient population with relapsed or refractory B-precursor ALL are not available. Regarding survival, validation of MRD negativity as a surrogate parameter was not available. Therefore, the endpoint MRD negativity is classified as endpoint of unclear relevance in the assessment and presented as a supplement.

Quality of life

No data on quality of life are available.

Side effects

Adverse events (AE) in total

The results were only presented additionally. One adverse event occurred in all patients included in the study.

Serious adverse events (SAEs)

A serious adverse event occurred in 28 (62.2%) patients. The most frequent SAEs are "Blood and lymphatic system disorders", "General disorders and administration site conditions", "Infections and infestations", "Musculoskeletal and connective tissue disorders", "Nervous system disorders" and "Respiratory, thoracic and mediastinal disorders".

Severe adverse events CTCAE grade ≥ 3

An adverse event CTCAE grade ≥ 3 occurred in 38 patients (84.8%) in the ALCANTARA study. The most frequent AEs of CTCAE grade ≥ 3 included "Blood and lymphatic system disorders", "Cardiac disorders", "Gastrointestinal disorders", "General disorders and administration site conditions, "Infections and infestations", "Investigations", "Metabolism and nutrition disorders", "Musculoskeletal and connective tissue disorders", "Nervous system disorders", "Respiratory, thoracic and mediastinal disorders" and "Vascular disorders".

Discontinuation because of AEs

AE occurred in 3 (6.7%) of the patients, leading to study discontinuation.

AE of special interest

AEs of special interest in the ALCANTARA study were "Acute pancreatitis", "Hematopoietic cytopenia", "Capillary leak syndrome", "Neurological events", "Cytokine release syndrome", "Decreased immunoglobulin levels", "Increased liver enzymes", "Immunogenicity",

"Infections", "Infusion reaction considering infusion duration", "Infusion reaction not considering infusion duration", "Lymphopenia", "Medication error", "Neutropenia", "Progressive multifocal leukoencephalopathy" and "Tumour lysis syndrome". Considering any CTCAE grade, the focus was on "hematopoietic cytopenia" as well as "neurological events", "infections", "infusion reaction considering infusion duration", "infusion reaction not considering infusion duration" and "neutropenia". With regard to AE of special interest with CTCAE grade ≥ 3, "hematopoietic cytopenia", "infections", and "neutropenia" should be mentioned in particular. The most common SAE of particular interest was "infections".

Since no comparative data are available, it is not possible to derive any overall conclusions on the extent of additional benefit in the category of side effects from the results of the ALCANTARA study.

Overall assessment/conclusion

The benefit assessment of blinatumomab for the treatment of adults with Philadelphia chromosome positive CD19 positive relapsed or refractory B-precursor acute lymphoblastic leukaemia (ALL), in whom . treatment with at least 2 tyrosine kinase inhibitors (TKIs) has failed and whohave no alternative treatment options is based on the results of the ALCANTARA study.

Results from the categories mortality, morbidity and adverse events are available.

Due to the single-arm design of the ALCANTARA study, a comparative assessment is not possible.

The propensity score-based comparison to the retrospective control study 20160462 presented by the pharmaceutical company is not used. Limitations are in particular, the definition of exposure in the control study, which results in relevant differences in the observation time for overall survival between the two studies. Other uncertainties include lack of information on patient characteristics and study sites and relevant differences in patient characteristics (e.g. prior therapies). It cannot be assumed that all relevant confounders were sufficiently taken into account within the indirect comparison. Furthermore, evidence transfer of the data from the TOWER study on quality of life and symptomatology was rejected, as the pharmaceutical company did not sufficiently substantiate the transferability.

Therefore, a quantitative assessment of the extent of the effect and a quantification of the additional benefit on the basis of the data presented is not possible.

As a result, the G-BA classifies the extent of the additional benefit of blinatumomab in the present indication due to the limited data on the basis of the criteria in Section 5, paragraph 7, of the Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) as non-quantifiable taking into account the severity of the disease and the therapeutic objective in the treatment of the disease. There is an additional benefit in accordance with Section 35a, paragraph 1, sentence 11, 1st half of the sentence SBG V, but it is non-quantifiable since the scientific data does not allow a quantification.

Significance of the evidence

The ALCANTARA study is a single-arm study so that a high risk of bias can be assumed. No adequate comparison is available.

Data reliability is assessed with a hint because only a single-arm study is available, and a comparative assessment is not possible.

In the overall review, the result is a hint for a non-quantifiable additional benefit concerning significance of the evidence.

2.1.3 Summary of the assessment

The present assessment is the benefit assessment of a new therapeutic indication for the active ingredient blinatumomab.

Blinatumomab was approved as an orphan drug.

The therapeutic indication assessed here is as follows: Treatment of adults with Philadelphia chromosome positive CD19 positive relapsed or refractory B-precursor acute lymphoblastic leukaemia (ALL), in whom treatment with at least 2 tyrosine kinase inhibitors (TKIs) has failed and who have no alternative treatment options.

The pharmaceutical company presents the final data cut-off results of the ALCANTARA study for the categories mortality, morbidity, and side effects.

Due to the single-arm design of this study, a comparative assessment is not possible.

The propensity score-based indirect comparison to the retrospective study 20160462 submitted by the pharmaceutical company is not used due to limitations. In particular, the diverging observation times for overall survival should be mentioned here. Other uncertainties include lack of information and disparities between patient populations. It cannot be assumed that all confounders have been sufficiently taken into account.

The evidence transfer from the TOWER study presented by the pharmaceutical company is also not considered due to the unproven comparability.

Overall, only data from a single-arm study are available, which do not allow a comparison. The data are therefore not suitable for quantifying the extent of the additional benefit.

Data reliability is assessed with a hint because only a single-arm study is available, and a comparative assessment is not possible.

In the overall assessment, a hint for a non-quantifiable additional benefit is determined for blinatumomab because the scientific data basis does not allow quantification.

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 information from the dossier of the pharmaceutical company. The procedure for calculating patient numbers is comprehensible from a mathematical point of view but is subject to uncertainties due to the limited data basis available and methodological deficiencies. In particular, this concerns the determination of patients who receive a new treatment with a TKI after treatment with a TKI (step 5), patients who are eligible for blinatumomab after the second recurrence after two TKI treatments (step 6) as well as the unconsidered treatment alternatives.

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: 28 May 2021):
https://www.ema.europa.eu/documents/product-information/blincyto-epar-product-information_de.pdf

Initiation and monitoring of treatment with blinatumomab should be performed only by specialists in internal medicine and haematology and oncology experienced in the therapy of patients with acute lymphoblastic leukaemia.

In accordance with the requirements of the EMA regarding additional risk minimisation measures, the pharmaceutical company must provide training material for physicians, pharmacists, healthcare professionals and patients/healthcare professionals, as well as a patient reminder card.

In particular, the training material contains instructions 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 June 2021).

Blinatumomab is used for the treatment of adults with recurrence or refractory B-precursor ALL over two induction cycles consisting of 28 days of treatment. There is a 14-day treatment-free interval between individual cycles. Consolidation therapy can be given for up to three more cycles if there is a complete remission after these two cycles.

Blinatumomab is administered as a continuous infusion. Patients weighing 45 kg or more receive 9 µg/day on days 1 through 7 of the first cycle and 28 µg/day on days 8 through 28 of the first cycle and days 1 through 28 of subsequent cycles. The average body weight of an adult is 77.0 kg according to the official representative statistics "Microcensus 2017 - Questions on health - Body measurements of the population".[2]

2 https://www.gbe-bund.de/gbe10/pkg_isgbe5.prc_isgbe?p_uid=gast&p_aid=0&p_sprache=D

A single blinatumomab preparation can be infused for up to 96 hours. Adult consumption is composed of 1 PIE[3] per 72 hours at a dosage of 9 µg/day and one PIE per day at a dosage of 28 µg/day, or 4 PIE in a preparation for 96 hours.

For the calculation of treatment costs, the infusion duration associated with the lowest blinatumomab consumption was used in each case.

Treatment duration:

Designation of the therapy	Treatment mode	Number of treatments/ patient/year	Treatment duration/ treatment (days)	Days of treatment/ patient/ year
Medicinal product to be assessed				
Blinatumomab	continuously on day 1 - 28 of an 42 day cycle	2 cycles of induction and up to 3 cycles of consolidation	28	56 - 140

Consumption:

Designation of the therapy	Dosage/ Application	Dosage/patient/days of treatment	Usage by potency/ day of treatment	Treatment days/ patient/ cycle	Average annual consumption by potency
Medicinal product to be assessed					
Blinatumomab	Induction				
	1st cycle: Day 1 - 7: 9 µg/d Day 8 – 28: 28 µg/d	 9 µg 28 µg	 9 µg 28 µg	 7 + 21	 3 PIE + 21 PIE à 38.5 µg
	2nd cycle: Day 1- 28: 28 µg/d	 28 µg	 28 µg	 28	 28 PIE à 38.5 µg
	Consolidation				
	3rd – 5th cycle: 28 µg/d	28 µg	28 µg/d	28	28 PIE à 38.5 µg

3 PIE: PIE = Powder for concentrate for solution for infusion

Costs:

Costs of the medicinal products:

Designation of the therapy	Packaging size	Costs (pharmacy sales price)	Rebate § 130 SGB V	Rebate Section 130a SGB V	Costs after deduction of statutory rebates
Medicinal product to be assessed					
Blinatumomab	1 PIE	€ 2,637.24	€ 1.77	€ 147.34	€ 2,488.13
Abbreviations: PIE = Powder for concentrate for solution for infusion					

LAUER-TAXE® last revised: 15 June 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 standard expenditure in the course of the treatment are not shown.

Because there are no regular differences in the necessary medical treatment or the prescription of other services when using the medicinal product to be assessed and the appropriate comparator therapy according to the product information, no costs for additionally required SHI services had to be taken into account.

Other SHI services:

The special agreement on contractual unit costs of retail pharmacist services (Hilfstaxe) (contract on price formation for substances and preparation of substances) from 1.10.2009 is not fully used to calculate costs. Alternatively, the pharmacy sales price publicly accessible in the directory services according to Section 131 paragraph 4 SGB V is a suitable basis for a standardised calculation.

According to the currently valid version of the special agreement on contractual unit costs of retail pharmacist services (Hilfstaxe), surcharges for the production of parenteral preparations containing cytostatic drugs a maximum amount of € 81 per ready-to-use preparation, and for the production of parenteral solutions c monoclonal antibodies, a maximum of € 71 per ready-to-use unit are to be payable. These additional costs are not added to the pharmacy retail price but rather follow the rules for calculating in the 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 sales 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 18 January 2021, 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 2 VerfO.

The benefit assessment of the G-BA was published on 03 May 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 25 May 2021.

The oral hearing was held on 7 June 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 the 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 July 2021, and the draft resolution was approved.

At its session on 15 July 2021, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee Medicinal products	27 April 2021	Information of the benefit assessment of the G-BA
Working group Section 35a	1 June 2021	Information on written statement procedures received; preparation of the oral hearing
Subcommittee Medicinal products	7 June 2021	Conduct of the oral hearing
Working group Section 35a	15 June 2021 29 June 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 products	6 July 2021	Concluding discussion of the draft resolution

Plenum	15 July 2021	Adoption of the resolution on the amendment of Annex XII AM-RL

Berlin, 15 July 2021

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

Prof. Hecken