Gemeinsamer Bundesausschuss

Justification

to the Resolution of the Federal Joint Committee (G-BA) on an Amendment of the Pharmaceuticals Directive:
Annex XII – Benefit Assessment of Medicinal Products with New Active Ingredients according to Section 35a (SGB V)
Blinatumomab

(new therapeutic indication: acute lymphoblastic B-cell leukaemia, Ph-, CD19+, newly diagnosed)

of 21 August 2025

Contents

1. Legal basis

According to Section 35a paragraph 1 German Social Code, Book Five (SGB V), the Federal Joint Committee (G-BA) assess the benefit of all reimbursable medicinal products with new active ingredients.

For medicinal products for the treatment of rare diseases (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 SGB V, the additional medical benefit is considered to be proven through the grant of the marketing authorisation. Evidence of the medical benefit and the additional medical benefit in relation to the appropriate comparator therapy do not have to be submitted (Section 35a, paragraph 1, sentence 11, 2nd half of the sentence SGB V). Section 35a, paragraph 1, sentence 11, 1st half of the sentence SGB V thus guarantees an additional benefit for an approved orphan drug, although an assessment of the orphan drug in accordance with the principles laid down in Section 35a, paragraph 1, sentence 3, No. 2 and 3 SGB V in conjunction with Chapter 5 Sections 5 et seq. of the Rules of Procedure (VerfO) of the G-BA has not been carried out. In accordance with Section 5, paragraph 8 AM-NutzenV, only the extent of the additional benefit is to be quantified indicating the significance of the evidence.

However, the restrictions on the benefit assessment of orphan drugs resulting from the statutory obligation to the marketing authorisation do not apply if the turnover of the medicinal product with the SHI at pharmacy sales prices and outside the scope of SHI-accredited medical care, including VAT exceeds € 30 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 their 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 their 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 turnover threshold according to Section 35a, paragraph 1, sentence 12 SGB V and is therefore subject to an unrestricted benefit assessment. 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 is 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 23 January 2025, 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, 12.12.2008, sentence 7).

Blinatumomab for the treatment of newly diagnosed acute lymphoblastic B-cell leukaemia is approved as a medicinal product for the treatment of rare diseases under Regulation (EC) No. 141/2000 of the European Parliament and the Council of 16 December 1999.

In accordance with Section 35a, paragraph 1, sentence 11, 1st half of the sentence SGB V, the additional benefit is considered to be proven through the grant of the marketing authorisation. The extent of the additional benefit and the significance of the evidence are assessed on the basis of the approval studies by the G-BA.

On 18 February 2025, i.e. at the latest within four weeks after informing the pharmaceutical company about the approval for a new therapeutic indication, the pharmaceutical company have submitted a dossier in due time 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

"BLINCYTO is indicated as monotherapy as part of consolidation therapy for the treatment of adult patients with newly diagnosed Philadelphia chromosome negative CD19 positive B-cell precursor ALL".

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 02 June 2025 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 have adopted their resolution on the basis of the dossier of the pharmaceutical company, the dossier assessment carried out by the G-BA, the assessment of treatment costs and patient numbers (IQWiG G12-01) prepared by the IQWiG, and the statements submitted in the written statement and oral hearing procedure.

In order to determine the extent of the additional benefit, the G-BA have 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.

[1] General Methods, version 7.0 from 19.09.2023. Institute for Quality and Efficiency in Health Care (IQWiG), Cologne.

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 as part of consolidation therapy for the treatment of adult patients with newly diagnosed Philadelphia chromosome negative CD19 positive B-cell precursor ALL.

Therapeutic indication of the resolution (resolution of 21 August 2025):

see the approved therapeutic indication

2.1.2 Extent of the additional benefit and significance of the evidence

Adults with newly diagnosed Philadelphia chromosome negative CD19 positive B-cell precursor ALL; consolidation therapy

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

Hint for a considerable additional benefit

Justification:

For the benefit assessment, the pharmaceutical company submits results of the phase III E1910 study. The E1910 study is an ongoing, randomised, controlled, open-label study to investigate the efficacy and safety of blinatumomab monotherapy alternating with chemotherapy (4+4=8 cycles) versus chemotherapy alone (4 cycles) in adult patients with newly diagnosed BCR/ABL-negative B-cell precursor ALL as part of a consolidation therapy. The study is being conducted in 77 study sites in the USA, Canada and Israel.

The study comprised several study phases. Registration phase (step 0), induction phase (step 1), intensification phase (step 2), consolidation phase (step 3) and maintenance phase (step 4). Blinatumomab is used exclusively in step 3 according to the study protocol. Prior to randomisation, patients were able to consent to allogeneic haematopoietic stem cell transplantation (alloHSCT).

In step 3, a total of 286 subjects were enrolled and randomised in a 1:1 ratio into the intervention arm (N = 152; blinatumomab and chemotherapy) or control arm (N = 134; chemotherapy) - stratified according to the criteria "age" (< 55 years; ≥ 55 years), "MRD status after intensification chemotherapy" (positive; negative), "CD20 status" (positive; negative), "rituximab use" (yes; no), "intention to receive alloHSCT" (planned; not planned).

By amendment 14 (23.05.2018), after FDA marketing authorisation for MRD-positive subjects (defined as MRD status ≥ 0.01% or ≥ 10-4), these subjects could be enrolled in the intervention arm without randomisation. Although the percentage in relation to the step 3 Analysis Set (N = 286) is low at 6.3%, the percentage of subjects in the intervention arm (N = 152) is 11.8%; in relation to the total number of MRD-positive subjects (N = 62), 29.0% of participants were enrolled in the intervention arm without randomisation.

The primary endpoint of the study is overall survival. Other endpoints include endpoints in the categories of morbidity and side effects.

For the benefit assessment, the results of the interim data cut-off from 23.06.2023 are used.

About the alternating chemotherapy:

The chemotherapy regimens used alternately with blinatumomab monotherapy as part of the consolidation therapy correspond to the German healthcare context according to the assessment of the scientific-medical societies in the written statement procedure.

Mortality

The overall survival is defined as the time period from the time of randomisation to death from any cause.

For the overall survival endpoint, there was a statistically significant difference in favour of blinatumomab alternating with chemotherapy compared to chemotherapy alone.

At this data cut-off, 30 subjects (19.7%) in the blinatumomab arm and 53 subjects (39.6%) in the chemotherapy arm had died. The median survival time has not yet been reached in either treatment arm.

The extent of the prolongation achieved in overall survival is assessed as significant improvement.

Morbidity

Recurrence-free survival

The endpoint of recurrence-free survival (RFS) is defined as the time from randomisation/ inclusion in step 3 to the time of recurrence or death from any cause.

Recurrence after achieving complete remission (CR) or complete remission with incomplete haematological recovery (CRi) was defined as follows:

- Recurrence or persistence of blasts in the peripheral blood or
- > 5% blasts in the bone marrow that could not be explained otherwise (e.g. regeneration of the bone marrow) or
- isolated recurrence in the central nervous system (CNS).

CR was defined as follows:

- Neutrophil count ≥ 1.0 x 10^9/l (≥ 1,000/mm^3) and
- platelet count ≥ 100 x 10^9/l (≥ 100,000/mm^3) and
- no blasts in the peripheral blood and
- sufficient cellularity with haematopoiesis of all three lines in the bone marrow and
- ≤ 5% leukaemic blasts in the bone marrow and
- extramedullary leukaemia, such as CNS or soft tissue involvement, must not be present.

The definition of a CRi corresponded to that of a CR, with the exception that incomplete regeneration

- of platelets (> 75 and < 100 x 10^9/l (> 75,000 and < 100,000 mm^3) independent of platelet infusions) or
- of neutrophil count (> 0.75 but < 1 x 10^9/l (> 750 but < 1,000/mm^3)

could be present.

The cytogenetic analyses of the bone marrow samples were carried out centrally by laboratories of the committee "Eastern Cooperative Oncology Group – American College of Radiology Imaging Network (ECOG-ACRIN) Leukemia Translational Research Laboratory".

For the endpoint of recurrence-free survival, there was a statistically significant difference in favour of blinatumomab alternating with chemotherapy compared to chemotherapy alone. The median time to event was not reached.

The extent of the prolongation achieved in recurrence-free survival is assessed as significant improvement.

However, there is uncertainty as to the extent to which the curative therapeutic goal can be considered achieved soon after the intensification therapy and before receipt of the consolidation phase.

Quality of life

No data on quality of life were assessed.

Side effects

In the E1910 study, complete data collection was only planned for severe adverse events (AEs) with CTCAE grade ≥ 3, with the exception of "Blood and lymphatic system disorders" and "Metabolism and nutrition disorders", where only AEs of CTCAE grade 4 and 5 were collected, as well as for AEs of special interest. Thus, no data is available for the total number of AEs and for serious AEs (SAEs).

Only a selective collection of individual AEs regardless of severity grade and SAEs was planned. "Expedited AEs" were classified according to CTCAE version 5.0. However, these are AEs, some of which were defined and collected selectively for one treatment group only. In addition, collection of AEs with a possible, probable or proven connection to the study medication was described. This is considered invalid.

Information on the median duration of observation for AEs was not provided. According to the information provided by the pharmaceutical company, a treatment duration of 296 days is described for the intervention arm and 133 days for the control arm during the consolidation phase (step 3), based on the study protocol (without taking into account any further allogeneic stem cell transplantation). The treatment duration in the intervention arm is therefore 163 days (approx. 5.5 months) longer. The actual treatment duration for step 3 and the subsequent study phase or until the end of the data cut-off is not available. As part of the written statement procedure, the pharmaceutical company submitted exposure data showing a median number of cycles prolonged by 3 cycles.

The pharmaceutical company submitted post hoc analyses of the relative risk (RR) for step 3.

Due to the alternating application of the chemotherapy, which is prone to side effects, there is uncertainty as to whether a time-to-event analysis would be less biased than the RR in this case.

A time-to-event analysis may in principle be more suitable than the relative risk analysis carried out due to the longer treatment duration in the intervention arm than in the comparator arm (alternating application of chemotherapy with blinatumomab). However, it can be assumed that the advantages of the evaluation methodology of a time-to-event analysis fade into the background in view of the fact that almost all patients in both arms had

severe adverse events and chemotherapy-related AEs in the intervention arm only occurred with a time delay due to the alternating administration.

Severe AEs (CTCAE grade ≥ 3)

There was no significant difference for the endpoint of severe AEs.

Discontinuation due to AEs

No information on the complete collection of AEs that led to discontinuation of the study medication could be identified. It is unclear to what extent AEs that led to therapy discontinuation were collected in full. However, therapy discontinuation due to an AE described in some cases for AEs of CTCAE grade ≥ 3. It is also unclear whether AEs attributable to the underlying disease were considered. The data are considered non-assessable overall.

Specific AE

The E1910 study showed a significant difference to the disadvantage of blinatumomab for the endpoint "Nervous system disorders" (severe AE) and "Neurological events" (AE of special interest).

For the endpoint "Leukopenia" (severe AE), there was a significant difference to the advantage of blinatumomab.

In the overall assessment of the results on side effects, no data are available for SAEs and no suitable data for therapy discontinuation due to AEs. For the severe AEs, there was no statistically significant difference between the treatment arms. In detail, there were predominantly disadvantages in the specific AEs.

<u>Overall assessment</u>

For the benefit assessment, results on mortality, morbidity and side effects from the ongoing, randomised, controlled, open-label E1910 study comparing blinatumomab monotherapy alternating with chemotherapy versus chemotherapy alone are available.

For the endpoint of overall survival, there was a significant advantage in favour of blinatumomab. The extent of the prolongation achieved in overall survival is assessed as significant improvement.

For the endpoint of recurrence-free survival, there was a statistically significant difference in favour of blinatumomab. The extent of the prolongation achieved in recurrence-free survival is assessed as significant improvement.

No data are available for the endpoint category of quality of life.

For the endpoint category of side effects, data are only available for severe AEs (CTCAE grade ≥ 3), AEs of CTCAE grade 4 and 5 (SOC "Blood and lymphatic system disorders" and "Metabolism and nutrition disorders") as well as for AEs of special interest. For the severe AEs, there was no statistically significant difference between the treatment arms. In detail, there were predominantly disadvantages in the specific AEs.

In the overall assessment, the G-BA identified a considerable additional benefit of blinatumomab for patients with newly diagnosed Philadelphia chromosome negative CD19

positive B-cell precursor ALL as part of the consolidation therapy due to significant advantages in overall survival and recurrence-free survival.

Significance of the evidence

The present benefit assessment is based on the results of the open-label, randomised, controlled phase III E1910 study.

The risk of bias for the presented E1910 study is classified as high at study level due to the open-label study design.

Limitations arise from the fact that no data on health-related quality of life are available.

Further uncertainties arise due to the enrolment of MRD-positive subjects in the intervention arm without randomisation. In addition, owing to the participation of patients aged ≥ 30 and ≤ 70 years in the E1910 study, it only represents this age group and not the age group < 30 years and > 70 years, which is also approved in the therapeutic indication. Uncertainties arise regarding the transferability of the results to the entire therapeutic indication.

With regard to the assessment of the results on side effects, there are relevant uncertainties in that no data are available for SAEs and no suitable data are available for therapy discontinuation due to AEs.

Overall, the G-BA derives a hint for the identified additional benefit with regard to the 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 medicinal product Blincyto with the active ingredient blinatumomab.

Blincyto was approved as an orphan drug.

The therapeutic indication assessed here is as follows: BLINCYTO is indicated as monotherapy as part of consolidation therapy for the treatment of adult patients with newly diagnosed Philadelphia chromosome negative CD19 positive B-cell precursor ALL.

For the benefit assessment, the pharmaceutical company presented results on mortality, morbidity and side effects from the ongoing, randomised, controlled, open-label E1910 study comparing blinatumomab monotherapy alternating with chemotherapy versus chemotherapy alone.

For the endpoints of overall survival and recurrence-free survival, there was a statistically significant difference to the advantage of blinatumomab, the extent of which was assessed as a significant improvement in each case.

No data are available on health-related quality of life.

The data on side effects are limited, as only certain categories of adverse events (AEs) were collected in the E1910 study. This is why there are no data on serious AEs and no suitable data on therapy discontinuation due to AEs. For the severe AEs, there was no statistically significant difference between the treatment arms. In detail, there were predominantly disadvantages in the specific AEs.

Overall, a considerable additional benefit of blinatumomab was identified.

The significance of the evidence for the additional benefit identified is classified in the "hint" category overall.

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 pharmaceutical company's data on the number of patients in the SHI target population are uncertain overall.

In accordance with the newly approved therapeutic indication, blinatumomab is used in adult patients with newly diagnosed Ph-negative, CD19 positive B-precursor ALL as part of the consolidation therapy. Deviating from this, the pharmaceutical company limits the patients in the target population in this step to those without MRD, as those with MRD have already been determined in a previous procedure for blinatumomab[2]. The therapeutic indication at that time also covered adult patients with Ph-negative and CD19 positive B-precursor ALL, but was additionally limited to patients in first or second complete remission with an MRD of at least 0.1%.

The total target population in the current procedure, i.e. including those subjects with MRD, can be calculated as follows, based on the information provided by the pharmaceutical company:

Patients with Ph-negative, CD19 positive B-precursor ALL: 176 to 305 patients.

Of which in SHI (88.2% SHI percentage): 155 to 269 patients.

Uncertainties remain with regard to the assumed percentages, as it is not clear from the underlying literature sources how the percentages were determined in detail.

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: 30 May 2025):

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

Treatment with blinatumomab should only be initiated and monitored by specialists in internal medicine, haematology and oncology experienced in the treatment 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] D-429 blinatumomab, resolution from 15.08.2019 - https://www.g-ba.de/Blinatumomab_D-429

2.4 Treatment costs

The treatment costs are based on the contents of the product information and the information listed in the LAUER-TAXE® (last revised: 1 August 2025).

Adult patients with newly diagnosed Philadelphia chromosome negative CD19 positive B-cell precursor ALL can receive up to 4 cycles of BLINCYTO therapy as part of the consolidation therapy. There is a 14-day treatment-free interval between individual cycles.

A single treatment cycle comprises one continuous infusion over 28 days. Patients with a body weight of 45 kg or more receive 28 µg/day, patients with a lower body weight receive 15 µg/m^2/day (maximum 28 µg/day).

For dosages depending on body weight (BW) or body surface area (BSA), the average body measurements of the official representative statistics "Microcensus 2021 – body measurements of the population" were applied (average body height: 1.72 m; average body weight: 77.7 kg)[3].

A single blinatumomab preparation can be infused for up to 96 hours. At a dosage of 28 µg/day, adult consumption results in one PCI per day in a preparation for 24 hours or 4 PCI 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 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	on day 1 - 28 of a 28-day cycle	1 - 4	28	28 - 112

Consumption:

Designation of the therapy	Dosage/ application	Dose/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
Medicinal product to be assessed					

[3] Federal Health Reporting. Average body measurements of the population (2021, both sexes, 15 years and older), www.gbe-bund.de

Designation of the therapy	Dosage/ application	Dose/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
Blinatumomab	28 µg	28 µg	1 x 38.5 µg every 24 hours	28 - 112	28 x 38.5 µg - 112 x 38.5 µg

Costs:

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

Costs of the medicinal products:

Adults with newly diagnosed Philadelphia chromosome negative CD19 positive B-cell precursor ALL; consolidation therapy

Designation of the therapy	Packaging size	Costs (pharmacy sales price)	Rebate Section 130 SGB V	Rebate Section 130a SGB V	Costs after deduction of statutory rebates
Medicinal product to be assessed					
Blinatumomab	1 PCI	€ 2,615.04	€ 1.77	€ 148.75	€ 2,464.52
Abbreviations: PCI = powder for a concentrate for the preparation of an infusion solution					

LAUER-TAXE® last revised: 1 August 2025

Costs for additionally required SHI services:

Only costs directly related to the use of the medicinal product are taken into account. If there are regular differences in the necessary use of medical treatment or in the prescription of other services in the use of the medicinal product to be evaluated and the appropriate comparator therapy in accordance with the product information, the costs incurred for this must be taken into account as costs for additionally required SHI services.

Medical treatment costs, medical fee services, and costs incurred for routine examinations (e.g. regular laboratory services such as blood count tests) that do not exceed the standard expenditure in the course of the treatment are not shown.

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) (Sections 4 and 5 of the Pharmaceutical Price Ordinance) from 1 October 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 agents a maximum amount of € 100 per ready-to-use preparation, and for the production of parenteral solutions containing monoclonal antibodies a maximum of € 100 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 retail price and the maximum surcharge for the preparation and is only an approximation of the treatment costs. This presentation does not take into account, for example, the rebates on the pharmacy purchase price of the active ingredient, the invoicing of discards, the calculation of application containers, and carrier solutions in accordance with the regulations in Annex 3 of the Hilfstaxe.

2.5 Designation of medicinal products with new active ingredients according to Section 35a, paragraph 3, sentence 4 SGB V that can be used in a combination therapy with the assessed medicinal product

According to Section 35a, paragraph 3, sentence 4, the G-BA designate all medicinal products with new active ingredients that can be used in a combination therapy with the assessed medicinal product for the therapeutic indication to be assessed on the basis of the marketing authorisation under Medicinal Products Act.

Basic principles of the assessed medicinal product

A designation in accordance with Section 35a, paragraph 3, sentence 4 SGB V requires that it is examined based on the product information for the assessed medicinal product whether it can be used in a combination therapy with other medicinal products in the assessed therapeutic indication. In the first step, the examination is carried out on the basis of all sections of the currently valid product information for the assessed medicinal product.

If the assessed medicinal product contains an active ingredient or a fixed combination of active ingredients in the therapeutic indication of the resolution (assessed therapeutic indication) and is approved exclusively for use in monotherapy, a combination therapy is not considered due to the marketing authorisation under Medicinal Products Act, which is why no designation is made.

A designation is also not considered if the G-BA have decided on an exemption as a reserve antibiotic for the assessed medicinal product in accordance with Section 35a, paragraph 1c, sentence 1 SGB V. The additional benefit is deemed to be proven if the G-BA have decided on an exemption for a reserve antibiotic in accordance with Section 35a, paragraph 1c, sentence 1 SGB V; the extent of the additional benefit and its therapeutic significance are not to be assessed by the G-BA. Due to the lack of an assessment mandate by the G-BA following the resolution on an exemption according to Section 35a, paragraph 1c, sentence 1 SGB V with regard to the extent of the additional benefit and the therapeutic significance of the reserve antibiotic to be assessed, there is a limitation due to the procedural privileging of the pharmaceutical companies to the effect that neither the proof of an existing nor an expected at least considerable additional benefit is possible for exempted reserve antibiotics in the

procedures according to Section 35a paragraph 1 or 6 SGB V and Section 35a paragraph 1d SGB V. The procedural privileging of the reserve antibiotics exempted according to Section 35a, paragraph 1c, sentence 1 SGB V must therefore also be taken into account at the level of designation according to Section 35a, paragraph 3, sentence 4 SGB V in order to avoid valuation contradictions.

With regard to the further examination steps, a differentiation is made between a "determined" or "undetermined" combination, which may also be the basis for a designation.

A "determined combination" exists if one or more individual active ingredients which can be used in combination with the assessed medicinal product in the assessed therapeutic indication are specifically named.

An "undetermined combination" exists if there is information on a combination therapy, but no specific active ingredients are named. An undetermined combination may be present if the information on a combination therapy:

- names a product class or group from which some active ingredients not specified in detail can be used in combination therapy with the assessed medicinal product, or
- does not name any active ingredients, product classes or groups, but the assessed medicinal product is used in addition to a therapeutic indication described in more detail in the relevant product information, which, however, does not include information on active ingredients within the scope of this therapeutic indication.

Concomitant active ingredient

The concomitant active ingredient is a medicinal product with new active ingredients that can be used in combination therapy with the assessed medicinal product for the therapeutic indication to be assessed.

For a medicinal product to be considered as a concomitant active ingredient, it must be classified as a medicinal product with new active ingredients according to Section 2 paragraph 1 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with the corresponding regulations in Chapter 5 of the Rules of Procedure of the G-BA as of the date of the present resolution. In addition, the medicinal product must be approved in the assessed therapeutic indication, whereby a marketing authorisation is sufficient only for a sub-area of the assessed therapeutic indication.

Based on an "undetermined combination", the concomitant active ingredient must be attributable to the information on the product class or group or the therapeutic indication according to the product information of the assessed medicinal product in the assessed therapeutic indication, whereby the definition of a product class or group is based on the corresponding requirements in the product information of the assessed medicinal product.

In addition, there must be no reasons for exclusion of the concomitant active ingredient from a combination therapy with the assessed medicinal product, in particular no exclusive marketing authorisation as monotherapy.

In addition, all sections of the currently valid product information of the eligible concomitant active ingredient are checked to see whether there is any information that excludes its use in combination therapy with the assessed medicinal product in the assessed therapeutic

indication under marketing authorisation regulations. Corresponding information can be, for example, dosage information or warnings. In the event that the medicinal product is used as part of a determined or undetermined combination which does not include the assessed medicinal product, a combination with the assessed medicinal product shall be excluded.

Furthermore, the product information of the assessed medicinal product must not contain any specific information that excludes its use in combination therapy with the eligible concomitant active ingredient in the assessed therapeutic indication under marketing authorisation regulations.

Medicinal products with new active ingredients for which the G-BA have decided on an exemption as a reserve antibiotic in accordance with Section 35a, paragraph 1c, sentence 1 SGB V are ineligible as concomitant active ingredients. The procedural privileging of the reserve antibiotics exempted according to Section 35a, paragraph 1c, sentence 1 SGB V also applies accordingly to the medicinal product eligible as a concomitant active ingredient.

Designation

The medicinal products which have been determined as concomitant active ingredients in accordance with the above points of examination are named by indicating the relevant active ingredient and the invented name. The designation may include several active ingredients, provided that several medicinal products with new active ingredients may be used in the same combination therapy with the assessed medicinal product or different combinations with different medicinal products with new active ingredients form the basis of the designation.

If the present resolution on the assessed medicinal product in the assessed therapeutic indication contains several patient groups, the designation of concomitant active ingredients shall be made separately for each of the patient groups.

Exception to the designation

The designation excludes combination therapies for which - patient group-related - a considerable or major additional benefit has been determined by resolution according to Section 35a, paragraph 3, sentence 1 SGB V or it has been determined according to Section 35a, paragraph 1d, sentence 1 SGB V that at least considerable additional benefit of the combination can be expected. In this context, the combination therapy that is excluded from the designation must, as a rule, be identical to the combination therapy on which the preceding findings were based.

In the case of designations based on undetermined combinations, only those concomitant active ingredients - based on a resolution according to Section 35a, paragraph 3, sentence 1 SGB V on the assessed medicinal product in which a considerable or major additional benefit had been determined - which were approved at the time of this resolution are excluded from the designation.

Legal effects of the designation

The designation of combinations is carried out in accordance with the legal requirements according to Section 35a, paragraph 3, sentence 4 and is used exclusively to implement the combination discount according to Section 130e SGB V between health insurance funds and pharmaceutical companies. The designation is not associated with a statement as to the extent to which a therapy with the assessed medicinal products in combination with the designated medicinal products corresponds to the generally recognised state of medical knowledge. The examination was carried out exclusively on the basis of the possibility under Medicinal Products Act to use the medicinal products in combination therapy in the assessed therapeutic indication based on the product information; the generally recognised state of medical knowledge or the use of the medicinal products in the reality of care were not the subject of the examination due to the lack of an assessment mandate of the G-BA within the framework of Section 35a, paragraph 3, sentence 4 SGB V.

The findings made neither restrict the scope of treatment required to fulfil the medical treatment mandate, nor do they make statements about expediency or economic feasibility.

Justification for the findings on designation in the present resolution:

Adults with newly diagnosed Philadelphia chromosome negative CD19 positive B-cell precursor ALL; consolidation therapy

No designation of medicinal products with new active ingredients that can be used in combination therapy pursuant to Section 35a, paragraph 3, sentence 4 SGB V, as the active ingredient to be assessed is an active ingredient authorised in monotherapy.

References:
Product information for blinatumomab (Blincyto); BLINCYTO® 38.5 microgram powder for the preparation of a concentrate and solution for the preparation of an infusion solution; last revised: March 2025

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 February 2025 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, paragraph 1, number 2 VerfO.

The benefit assessment of the G-BA was published on 2 June 2025 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 statements was 23 June 2025.

The oral hearing was held on 7 July 2025.

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

The evaluation of the written statements received and the oral hearing was discussed at the session of the subcommittee on 12 August 2025, and the draft resolution was approved.

At their session on 21 August 2025, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee on Medicinal Products	27 May 2025	Information of the benefit assessment of the G-BA
Working group Section 35a	17 June 2025	Information on written statements received; preparation of the oral hearing
Subcommittee on Medicinal Products	7 July 2025	Conduct of the oral hearing
Working group Section 35a	16 July 2025 6 August 2025	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	12 August 2025	Concluding discussion of the draft resolution
Plenum	21 August 2025	Adoption of the resolution on the amendment of the Pharmaceuticals Directive

Berlin, 21 August 2025

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

Prof. Hecken