

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, relapsed/refractory, ≥ 1
month to < 1 year, after ≥ 2 prior therapies or after allogeneic
stem cell transplantation)

of 21 August 2025

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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) 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, paragraphs 1–6 VerfO, in particular regarding the additional medical benefit in relation to the appropriate comparator therapy as defined by the G-BA according to Chapter 5 Section 6 VerfO and prove the additional benefit in comparison with the appropriate comparator therapy.

In accordance with Section 35a, paragraph 2 SGB V, the G-BA decides whether to carry out the benefit assessment itself or to commission the Institute for Quality and Efficiency in Health Care (IQWiG). 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 (Blinicyto) 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 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 for the treatment of paediatric patients aged 1 month or older with Philadelphia chromosome-negative CD19 positive B-cell precursor ALL which is refractory or in relapse after receiving at least two prior therapies or in relapse after receiving prior allogeneic haematopoietic stem cell transplantation."

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 2 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 G21-25) 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 approval 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 was not used in the benefit assessment of the active ingredient.

In the light of the above, and taking into account the statements received and the oral hearing, the G-BA have come to the following assessment:

2.1 Additional benefit of the medicinal product

2.1.1 Approved therapeutic indication of Blinatumomab (Blinicyto) in accordance with the product information

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

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

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

2.1.2 Extent of the additional benefit and significance of the evidence

Paediatric patients aged ≥ 1 month to < 1 year with Philadelphia chromosome-negative CD19 positive B-cell precursor ALL which is refractory or in relapse after receiving at least two prior therapies or in relapse after receiving prior allogeneic haematopoietic stem cell transplantation

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 quantification.

Justification:

Data basis

By means of evidence transfer, the pharmaceutical company refers to the benefit assessment procedures already conducted for children ≥ 1 year in the dossier for the determination of the extent of the additional benefit for infants (children aged ≥ 1 month to < 1 year) with high-risk first relapsed Ph-, CD19+ B-precursor ALL as part of the consolidation therapy and for infants (children aged ≥ 1 month to < 1 year) with refractory Ph-, CD19+ B-precursor ALL. The description of the additional benefit is presented here by the pharmaceutical company separately for infants (children aged ≥ 1 month to < 1 year) with high-risk first relapsed Ph-, CD19+ B-precursor ALL as part of the consolidation therapy and for infants (children aged ≥ 1 month to < 1 year) with refractory Ph-, CD19+ B-precursor ALL.

For transferability to refractory patients aged ≥ 1 month to < 1 year, the pharmaceutical company refers to the single-arm, multicentre phase I/II MT103-205 study from the benefit assessment procedure (resolution of 15 August 2019) of blinatumomab in paediatric patients aged ≥ 1 year to < 18 years, in which a non-quantifiable additional benefit was identified¹. The MT103-205 study investigated paediatric patients aged ≥ 28 days to < 18 years with B-ALL who were in relapse after receiving at least two prior therapies or after receiving prior allogeneic haematopoietic stem cell transplantation, or who were refractory to other treatments.

In the dossier, the pharmaceutical company assigns infants (≥ 1 month to < 1 year) with a relapse to high-risk first relapsed Ph-, CD19+ B-precursor ALL as part of the consolidation

¹ Blinatumomab for paediatric patients aged ≥ 1 year to < 18 years with r/r B-cell ALL – Resolution of 15 August 2019

therapy on the basis of the EMA's extension of the marketing authorisation. According to the statements made by the pharmaceutical company, all infants who suffer a relapse fall within the therapeutic indication of high-risk first relapsed Ph- CD19+ B-precursor ALL as part of the consolidation therapy due to the definition of any relapse within 18 months of initial diagnosis as a high-risk relapse. According to the assessment of the pharmaceutical company, this therapeutic indication described in dossier Module 4 corresponds to the therapeutic indication of an earlier benefit assessment procedure on blinatumomab (resolution of 20 January 2022)². The assessment basis for this procedure was the 2012/2015 study. This study is a multicentre, randomised, controlled, open-label, phase III study in paediatric patients with high-risk first relapsed Ph- CD19+ B-ALL for assessment of the efficacy and safety of blinatumomab as consolidation therapy versus high-risk consolidation therapy. Participation was possible from the age of 28 days, but only subjects aged ≥ 1 year to < 18 years were enrolled. As part of the benefit assessment procedure, a major additional benefit was identified on the basis of the data on overall survival, event-free survival and side effects.

The assessment report of the European Medicines Agency (EMA)³ describes the results of a systematic literature research on blinatumomab studies. Two studies sponsored by the pharmaceutical company investigated patients with r/r B-ALL aged < 1 year. According to the EPAR, 6 participants were enrolled in the single-arm, multicentre, expanded access RIALTO study and 3 participants aged ≥ 28 days to < 1 year were enrolled in the single-arm phase 2 MT103-205 study in the present therapeutic indication. Due to the small number of subjects aged < 1 year ($N=9$), the EMA does not consider assessment of the efficacy of blinatumomab possible, which is why the corresponding marketing authorisation for paediatric patients aged < 1 year is based on population pharmacokinetic (pop PK) or mechanistic physiology-based pharmacokinetic (M-PBPK) modelling of subjects aged ≥ 1 year in the same therapeutic indication. Based on this modelling, the EMA assumes comparable efficacy and safety of blinatumomab in infants and older paediatric patients.

The pharmaceutical company did not submit the specified clinical data of the 9 subjects aged < 1 year from the single-arm MT103-205 and RIALTO studies in the present benefit assessment procedure.

Assessment

Based on the information submitted by the pharmaceutical company, it is not possible to transfer the additional benefit from refractory patients aged > 1 year or from high-risk first relapsed patients aged > 1 year to the population in the present therapeutic indication due to the following points, which are justified below:

No clinical studies are available for infants with Philadelphia chromosome-negative CD19 positive B-cell precursor ALL which is refractory or in relapse after receiving at least two prior therapies or in relapse after receiving prior allogeneic haematopoietic stem cell transplantation. Only individual case reports are available. The clinical data of the 9 subjects aged < 1 year from the single-arm MT103-205 and RIALTO studies of the EMA literature research were not submitted for the benefit assessment.

² Blinatumomab for paediatric patients aged ≥ 1 year to < 18 years with high-risk first relapsed B-cell ALL – Resolution of 20 January 2022

³ **European Medicines Agency (EMA)**. Blincyto (blinatumomab): European public assessment report EMEA/H/C/003731/0000 [online]. 07.12.2015. Amsterdam (NED): EMA. [Accessed: 06.03.2025]. URL: https://www.ema.europa.eu/en/documents/assessment-report/blincyto-epar-public-assessment-report_en.pdf.

The clinical experts explained in the oral hearing that high-risk relapses are defined as relapses within the first 18 months of diagnosis, which means that all relapses in infancy (up to a maximum of 12 months) are by definition high-risk relapses. In this regard, the pharmaceutical company argues that a relapse in infancy is virtually impossible due to a treatment duration of several years. This reasoning can be followed, however, the present therapeutic indication defines the treatment setting of relapse after at least two prior therapies or after prior allogeneic haematopoietic stem cell transplantation. Thus, there is a relevant difference to the treatment setting of high-risk first relapsed Ph- CD19+ B-precursor ALL as part of the consolidation therapy. Consequently, the comparability of patient populations cannot be assumed with sufficient certainty overall.

With regard to refractory patients aged ≥ 1 month to < 1 year, the pharmaceutical company refers to the transfer of the additional benefit to refractory paediatric patients aged ≥ 1 year to < 18 years of the single-arm, multicentre study MT103-205 from the corresponding benefit assessment procedure by resolution of 15 August 2019. This procedure was based on results for the endpoint categories of mortality, morbidity and side effects, but a comparative assessment of the overall study results was not possible. Thus, a quantitative assessment of effects was not possible on the basis of the data presented. Consequently, there are no effects from this benefit assessment that could be transferred to refractory patients aged ≥ 1 month to < 1 year.

Conclusion

No comparator data from the clinical studies are available for the assessment of the extent of the additional benefit for infants with Philadelphia chromosome-negative CD19 positive B-cell precursor ALL which is refractory or in relapse after receiving at least two prior therapies or in relapse after receiving prior allogeneic haematopoietic stem cell transplantation. As the proof of the extent of the additional benefit, the pharmaceutical company takes the evidence transfer of the results of the clinical 20120215 and MT103-205 studies from older paediatric patients to infants as the basis. The evidence transfer from older paediatric patients to infants pursued by the pharmaceutical company is not followed here, especially because no comparator data, from which extrapolations could be made, were available for older paediatric patients in the present therapeutic indication.

As a result, the G-BA classified the extent of the additional benefit of blinatumomab in the treatment of paediatric patients aged ≥ 1 month to < 1 year with Philadelphia chromosome-negative CD19 positive B-cell precursor ALL which is refractory or in relapse after receiving at least two prior therapies or in relapse after receiving prior allogeneic haematopoietic stem cell transplantation as non-quantifiable. 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

Due to the limitations of the available evidence, a hint can be derived with regard to the reliability of data.

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 present therapeutic indication assessed is as follows: BLINCYTO is indicated as monotherapy for the treatment of paediatric patients aged ≥ 1 month to < 1 year with

Philadelphia chromosome-negative CD19 positive B-cell precursor ALL which is refractory or in relapse after receiving at least two prior therapies or in relapse after receiving prior allogeneic haematopoietic stem cell transplantation.

No data from the clinical studies are available for the assessment of the additional benefit for infants with Philadelphia chromosome-negative CD19 positive B-cell precursor ALL which is refractory or in relapse after receiving at least two prior therapies or in relapse after receiving prior allogeneic haematopoietic stem cell transplantation. The pharmaceutical company based the proof of additional benefit on an evidence transfer of the results of the MT103-205 and 20120215 clinical studies from older paediatric patients aged ≥ 1 year to < 18 years to infants aged ≥ 1 month to < 1 year.

The evidence transfer from older paediatric patients to infants pursued by the pharmaceutical company is not followed here, especially because no comparator data, from which extrapolations could be made, were available for older paediatric patients in the present therapeutic indication.

As a result, the G-BA classified the extent of the additional benefit of blinatumomab in the treatment of paediatric patients aged ≥ 1 month to < 1 year with Philadelphia chromosome-negative CD19 positive B-cell precursor ALL which is refractory or in relapse after receiving at least two prior therapies or in relapse after receiving prior allogeneic haematopoietic stem cell transplantation as non-quantifiable. 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.

Due to the limitations of the available evidence, the reliability of data is rated as a hint.

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

The pharmaceutical company estimates the number of patients in the SHI target population in several steps.

This pharmaceutical company's procedure for estimating the number of patients in the SHI target population is mathematically plausible.

Although the therapeutic indication according to the product information⁴ includes not only the refractory paediatric patients considered by the pharmaceutical company but also those who suffer a relapse after at least two prior therapies or after prior allogeneic hematopoietic stem cell transplantation, it is generally understandable that the pharmaceutical company does not consider these patients due to the age range of ≥ 1 month to < 1 year considered here and the duration of the required prior therapy.

Despite uncertainties, the number of patients in the SHI target population stated by the pharmaceutical company is in a plausible size.

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: 04 June 2025):

⁴ Amgen. Product information for BLINCYTO 38.5 microgram powder for concentrate and solution for the preparation of an infusion solution. Last revised: January 2025 [online]. 2025. URL: <https://www.fachinfo.de/>.

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 paediatrics and adolescent medicine with a focus on paediatric haematology and oncology who are 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 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: 1 August 2025).

According to the product information, the approved dosage (body surface area (BSA)-based dose) for subjects with a body weight < 45 kg is 5 µg/m²/day (must not exceed 9 µg/day) from day 1-7 and 15 µg/m²/day (must not exceed 28 µg/day) from day 8-28. A single treatment cycle comprises one continuous infusion over 28 days (4 weeks). The treatment cycles are separated by a 14-day (2-week) treatment-free interval. Subjects who have achieved a complete remission (CR) / complete remission with partial haematological recovery (CRh*) after 2 treatment cycles can receive up to 3 further cycles of blinatumomab as consolidation therapy at a BSA-based dose of 15 µg/m²/day (must not exceed 28 µg/day) on the basis of an individual risk-benefit assessment.

For paediatric patients < 45 kg, the consumption is based on body surface area. The calculations are based on the DuBois formula and the average body measurements for infants less than 1 year old according to the 2017 Microcensus data⁵. This results in a body surface area of 0.36 m².

The single blinatumomab preparation can be infused for up to 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	2 - 5	28	56 - 140

⁵ Statistisches Bundesamt (Federal Statistical Office). Body measurements by age group and sex 2021 [online]. 2023 [accessed: 02.09.2024]. URL: <https://www.destatis.de/DE/Themen/Gesellschaft-Umwelt/Gesundheit/Gesundheits-zustand-Relevantes-Verhalten/Tabellen/liste-koerpermasse.html>.

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					
Blinatumomab	1st cycle: 5 µg/m ² /day from day 1 – 7 15 µg/m ² /day From day 8 – 28 2nd to 5th cycle: 15 µg/m ² /day	1st cycle: 1.8 µg/day from day 1 – 7 5.4 µg/day From day 8 – 28 From 2nd cycle: 5.4 µg/day	2 * 38.5 µg 6 * 38.5 µg 7 * 38.5 µg	7 21 28 - 112	15 to 36 * 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:

Paediatric patients aged ≥ 1 month to < 1 year with Philadelphia chromosome-negative CD19 positive B-cell precursor ALL which is refractory or in relapse after receiving at least two prior therapies or in relapse after receiving prior allogeneic haematopoietic stem cell transplantation

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:

Paediatric patients aged ≥ 1 month to < 1 year with Philadelphia chromosome-negative CD19 positive B-cell precursor ALL which is refractory or in relapse after receiving at least two prior therapies or in relapse after receiving prior allogeneic haematopoietic stem cell transplantation

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.

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 June 2025	Information of the benefit assessment of the G-BA
Working group Section 35a	2 July 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	16.07.2025; 06.08.2025	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