Gemeinsamer Bundesausschuss

Justification

of 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) Decitabine/ cedazuridine (acute myeloid leukaemia, first-line)

of 15 August 2024

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 all reimbursable medicinal products with new active ingredients. This includes in particular the assessment of the additional benefit and its therapeutic significance. The benefit assessment is carried out on the basis of evidence provided by the pharmaceutical company, which must be submitted to the G-BA electronically, including all clinical trials the pharmaceutical company has conducted or commissioned, at the latest at the time of the first placing on the market as well as the marketing authorisation of new therapeutic indications of the medicinal product, and which must contain the following information in particular:

1. approved therapeutic indications,
2. medical benefit,
3. additional medical benefit in relation to the appropriate comparator therapy,
4. number of patients and patient groups for whom there is a therapeutically significant additional benefit,
5. treatment costs for the statutory health insurance funds,
6. requirements for a quality-assured application.

The G-BA may commission the Institute for Quality and Efficiency in Health Care (IQWiG) to carry out the benefit assessment. According to Section 35a, paragraph 2 SGB V, the assessment 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 relevant date for the start of the benefit assessment procedure was the first placing on the (German) market of the active ingredient decitabine/ cedazuridine on 1 March 2024 in accordance with Chapter 5 Section 8, paragraph 1, number 1, sentence 2 of the Rules of Procedure (VerfO) of the G-BA. The pharmaceutical company submitted the final dossier to the G-BA in accordance with Section 4, paragraph 3, number 1 of the Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with Chapter 5 Section 8, paragraph 1, number 1 VerfO on 28 February 2024.

The G-BA commissioned the IQWiG to carry out the assessment of the dossier. The benefit assessment was published on 3 June 2024 on the G-BA website (www.g-ba.de), thus initiating the written statement procedure. In addition, an oral hearing was held.

The G-BA came to a resolution on whether an additional benefit of decitabine/ cedazuridine compared with the appropriate comparator therapy could be determined on the basis of the

dossier of the pharmaceutical company, the dossier assessment 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 has evaluated the data justifying the finding of an additional benefit on the basis of their therapeutic relevance (qualitative), in accordance with the criteria laid down in Chapter 5 Section 5, paragraph 7 VerfO. The methodology proposed by the IQWiG in accordance with the General Methods [1] was not used in the benefit assessment of decitabine/ cedazuridine.

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

2.1 Additional benefit of the medicinal product in relation to the appropriate comparator therapy

2.1.1 Approved therapeutic indication of Decitabine/ cedazuridine (Inaqovi) in accordance with the product information

Inaqovi is indicated as monotherapy for the treatment of adult patients with newly diagnosed acute myeloid leukaemia (AML) who are ineligible for standard induction chemotherapy

Therapeutic indication of the resolution (resolution of 15 August 2024):

see the approved therapeutic indication

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

Adult patients with newly diagnosed acute myeloid leukaemia (AML) who are ineligible for standard induction chemotherapy

Appropriate comparator therapy for decitabine/ cedazuridine as monotherapy*:*

- azacitidine

  or

- decitabine

  or

- glasdegib in combination with low-dose cytarabine

  or

- venetoclax in combination with azacitidine

  or

- venetoclax in combination with decitabine

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

Criteria according to Chapter 5 Section 6 of the Rules of Procedure of the G-BA and Section 6 paragraph 2 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV):

The appropriate comparator therapy must be an appropriate therapy in the therapeutic indication in accordance with the generally recognised state of medical knowledge (Section 12 SGB V), preferably a therapy for which endpoint studies are available and which has proven its worth in practical application unless contradicted by the guidelines under Section 92, paragraph 1 SGB V or the principle of economic efficiency.

In determining the appropriate comparator therapy, the following criteria, in particular, must be taken into account as specified in Chapter 5 Section 6, paragraph 3 VerfO:

1. To be considered as a comparator therapy, the medicinal product must, principally, have a marketing authorisation for the therapeutic indication.
2. If a non-medicinal treatment is considered as a comparator therapy, this must be available within the framework of the SHI system.
3. As comparator therapy, medicinal products or non-medicinal treatments for which the patient-relevant benefit has already been determined by the G-BA shall be preferred.
4. According to the generally recognised state of medical knowledge, the comparator therapy should be part of the appropriate therapy in the therapeutic indication.

According to Section 6, paragraph 2, sentence 2 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV), the determination of the appropriate comparator therapy must be based on the actual medical treatment situation as it would be without the medicinal product to be assessed. According to Section 6, paragraph 2, sentence 3 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV), the G-BA may exceptionally determine the off-label use of medicinal products as an appropriate comparator therapy or as part of the appropriate comparator therapy if it determines by resolution on the benefit assessment according to Section 7, paragraph 4 that, according to the generally recognised state of medical knowledge, this is considered a therapy standard in the therapeutic indication to be assessed or as part of the therapy standard in the medical treatment situation to be taken into account according to sentence 2, and

1. for the first time, a medicinal product approved in the therapeutic indication is available with the medicinal product to be assessed,
2. according to the generally recognised state of medical knowledge, the off-label use is generally preferable to the medicinal products previously approved in the therapeutic indication, or
3. according to the generally recognised state of medical knowledge, the off-label use for relevant patient groups or indication areas is generally preferable to the medicinal products previously approved in the therapeutic indication.

An appropriate comparator therapy may also be non-medicinal therapy, the best possible add-on therapy including symptomatic or palliative treatment, or monitoring wait-and-see approach.

Justification based on the criteria set out in Chapter 5 Section 6, paragraph 3 VerfO and Section 6, paragraph 2 AM-NutzenV:

on 1. Medicinal products with the following active ingredients are approved for the present therapeutic indication: azacitidine, cytarabine, daunorubicin, decitabine, doxorubicin, etoposide, glasdegib, histamine dihydrochloride, ivosidenib, idarubicin, mitoxantrone,

tioguanine and venetoclax. In addition, hydroxycarbamide is prescribable for off-label use.

on 2. No non-medicinal treatment options can be considered for patients with AML who are ineligible for intensive induction chemotherapy.

on 3. Annex XII - Resolutions on the benefit assessment of medicinal products with new active ingredients according to Section 35a SGB V:

- ivosidenib (resolution of 18 January 2024)
- venetoclax (resolution of 2 December 2021)
- glasdegib (resolution of 18 February 2021)
- decitabine (resolution of 2 May 2013)

Annex VI to Section K of the Pharmaceuticals Directive (last revised: 8 November 2022) – medicinal products that are prescribable for unapproved therapeutic indications (off-label use):

- hydroxycarbamide in chronic myelomonocytic leukaemia (CMML) or in CMML after transition to acute myeloid leukaemia.

on 4. The generally recognised state of medical knowledge was illustrated by a systematic search for guidelines as well as systematic reviews of clinical studies in the present indication and is presented in the "Research and synopsis of the evidence to determine the appropriate comparator therapy according to Section 35a SGB V".

The scientific-medical societies and the Drugs Commission of the German Medical Association (AkdÄ) were also involved in writing on questions relating to the comparator therapy in the present therapeutic indication according to Section 35a, paragraph 7 SGB V. (see "Information on the appropriate comparator therapy"). A written statement from the German Society for Haematology and Medical Oncology (DGHO) is available.

Among the approved active ingredients listed under 1.), only certain active ingredients named below will be included in the appropriate comparator therapy, taking into account the evidence on therapeutic benefit, the guideline recommendations and the reality of health care provision.

In determining the appropriate comparator therapy, it is taken into account that patients with acute promyelocytic leukaemia are not included in the therapeutic indication. This patient population differs in aetiology and therapeutic approach.

In patients with AML, who are ineligible for standard induction chemotherapy, the therapeutic goal is to prolong overall survival with the highest possible quality of life.

The NCCN guideline recommends venetoclax in combination with azacitidine and venetoclax in combination with decitabine for the treatment of patients with AML who are ineligible for standard induction chemotherapy. The NCCN guideline also mentions the active ingredients azacitidine, decitabine, cytarabine and gemtuzumab ozogamicin, each as monotherapy, as well as the combination therapies venetoclax in combination with low-dose cytarabine and glasdegib in combination with low-dose cytarabine (LDAC) as well as best supportive care. The ASH guideline also recommends monotherapies with azacitidine, decitabine and cytarabine.

According to the written statement of the German Society for Haematology and Medical Oncology (DGHO), the combination of venetoclax with a hypomethylating

agent (HMA) in conjunction with optimal supportive therapy represents a new therapy standard for patients who are not eligible for intensive standard induction chemotherapy. For the combination of venetoclax with an HMA (azacitidine or decitabine) approved on 19 May 2021, a hint for a considerable additional benefit was identified by resolution of 2 December 2021 based on the comparison between the combination of venetoclax with azacitidine versus azacitidine. No data regarding the combination therapy of venetoclax specifically with decitabine were available. In the context of the marketing authorisation, the effect of venetoclax in combination with azacitidine was extrapolated to venetoclax in combination with decitabine on the basis of the comparable mode of action. Uncertainties remained in the benefit assessment regarding the extent to which the results - on which the assessment was based - from the Viale-A study on patient-relevant therapeutic effects can be transferred to the combination venetoclax + decitabine, particularly with regard to the quantification of the extent of the additional benefit. Taking this uncertainty into account, the G-BA nevertheless considered it appropriate to assess the extent and probability of additional benefit beyond venetoclax in combination with azacitidine, i.e. in combination with an HMA, on the basis of the Viale-A study. Therefore, both venetoclax in combination with azacitidine and venetoclax in combination with decitabine are determined to be equally appropriate comparator therapies.

For glasdegib in combination with low-dose cytarabine, a hint of a considerable additional benefit over low-dose cytarabine was identified in the benefit assessment by resolution of 18 February 2021. This treatment option is determined to be another appropriate comparator therapy.

For decitabine, there is a resolution of the G-BA of 2 May 2013 on the benefit assessment, in which a minor additional benefit was identified compared to the therapy of choice of best supportive care or cytarabine. Overall, the available evidence does not show that one of the two HMA active ingredients (decitabine or azacitidine) is superior to the other in the treatment of patients with AML who are not eligible for intensive chemotherapy. Against the background of corresponding therapy recommendations, monotherapy with azacitidine or decitabine continues to assume appropriate significance even after the introduction of combination therapy with venetoclax. Therefore, monotherapy with azacitidine as well as with decitabine is considered to be another equally appropriate comparator therapy.

With regard to the significance of monotherapy with cytarabine, the statements on glasdegib in combination with low-dose cytarabine and decitabine are taken into account. Based on the respective approval studies, both decitabine and glasdegib in combination with low-dose cytarabine show an advantage over low-dose cytarabine which was also determined in the respective resolution on the benefit assessment. In addition, cytarabine is also mentioned by the DGHO (German Society for Haematology and Medical Oncology)as being of lower priority than HMA or glasdegib in combination with low-dose cytarabine. Therefore, monotherapy with cytarabine is not determined as an appropriate comparator therapy.

The combination of venetoclax with low-dose cytarabine is not approved in Europe, which is why this combination is not an appropriate comparator therapy.

According to the marketing authorisation, gemtuzumab ozogamicin should only be used in patients who are eligible for intensive induction chemotherapy, which is why gemtuzumab ozogamicin is not considered in the present therapeutic indication.

For the determination of the appropriate comparator therapy, it is assumed that best supportive care alone is not an option for all patients in the therapeutic indication at the time of therapy with decitabine/ cedazuridine, and therefore, does not represent an appropriate comparator therapy. The possible implementation of accompanying supportive measures to alleviate symptoms and improve the quality of life remains unaffected.

The active ingredient ivosidenib is a new treatment option for patients with an isocitrate dehydrogenase 1 (IDH1) R132 mutation in the present therapeutic indication. For ivosidenib in combination with azacitidine, an indication of a major additional benefit compared with azacitidine was identified in the benefit assessment by resolution of 18 January 2024.

The active ingredient was only recently approved (marketing authorisation on 04.05.2023). Based on the generally accepted state of medical knowledge, ivosidenib is not determined to be an appropriate comparator therapy for the present resolution.

In the overall assessment, for patients with AML who are ineligible for intensive induction chemotherapy, the combination therapies venetoclax + azacitidine, venetoclax + decitabine and glasdegib + low-dose cytarabine as well as the monotherapies with azacitidine or decitabine are considered equally appropriate comparator therapies on the basis of the available evidence.

The findings in Annex XII do not restrict the scope of treatment required to fulfil the medical treatment mandate.

A change in the appropriate comparator therapy requires a resolution by the G-BA linked to the prior review of the criteria according to Chapter 5 Section 6, paragraph 3 Rules of Procedure.

2.1.3 Extent and probability of the additional benefit

In summary, the additional benefit of decitabine/ cedazuridine is assessed as follows:

<u>Adult patients with newly diagnosed acute myeloid leukaemia (AML) who are ineligible for standard induction chemotherapy</u>

An additional benefit is not proven.

Justification:

For the benefit assessment of decitabine/ cedazuridine for the treatment of adults with newly diagnosed acute myeloid leukaemia (AML) who are ineligible for standard induction chemotherapy, the pharmaceutical company presented data from the pivotal ASTX727-02 study.

ASTX727-02 is a completed phase III study divided into an open-label, active-controlled phase and a single-arm phase. The study aims at investigating bioequivalence using a cross-over design. The primary endpoint of the study was the 5-day total exposure to decitabine as measured by area under the curve.

The study investigated patients with myelodysplastic syndrome, chronic myelomonocytic leukaemia and AML. A total of 89 patients with AML were enrolled in the active controlled phase. The patients were randomised in a 1:1 ratio to the two study arms. In this study phase, orally administered decitabine/ cedazuridine was compared with intravenously (IV) administered decitabine over a cycle of 28 days, followed by a cross-over to the other therapy.

In the subsequent single-arm extension phase of the study, all patients received decitabine/ cedazuridine until disease progression or unacceptable toxicity.

The ASTX727-02 study is unsuitable for the assessment of the additional benefit of decitabine/ cedazuridine. According to the product information for decitabine/ cedazuridine, treatment must be given for at least 4 cycles. This is also recommended in the product information for decitabine. Consequently, the treatment duration for both decitabine/ cedazuridine and the comparator therapy decitabine in the controlled phase of the study, which would allow a comparison of decitabine/ cedazuridine with the appropriate comparator therapy, is too short at 1 treatment cycle each and does not comply with the requirements in the respective product information.

Conclusion

The results of the approval study ASTX727-02 are available for the assessment of the additional benefit of decitabine/ cedazuridine. Due to the fact that the treatment duration was too short for both decitabine/ cedazuridine and the comparator therapy decitabine in the controlled phase of the study, there is no adequate comparison with the appropriate comparator therapy.

In summary, there are no suitable data available to allow an assessment of the additional benefit, which is why an additional benefit of decitabine/ cedazuridine for the treatment of adults with newly diagnosed AML who are ineligible for standard induction chemotherapy is not proven.

2.1.4 Summary of the assessment

The present assessment concerns the benefit assessment of the new medicinal product "Inaqovi" with the active ingredient decitabine/ cedazuridine.

The active ingredient decitabine/ cedazuridine is approved for the treatment of adults with newly diagnosed acute myeloid leukaemia (AML) who are ineligible for standard induction chemotherapy.

Treatment with azacitidine or decitabine or glasdegib in combination with low-dose cytarabine or venetoclax in combination with azacitidine or venetoclax in combination with decitabine was determined by the G-BA as the appropriate comparator therapy.

For the benefit assessment, the pharmaceutical company presented data from the pivotal ASTX727-02 study. In the active-controlled phase of the study, decitabine/ cedazuridine was compared with IV decitabine over a cycle of 28 days, followed by a cross-over to the other therapy. According to the product information for decitabine/ cedazuridine, treatment must be given for at least 4 cycles. This is also recommended in the product information for decitabine. Due to the fact that the treatment duration was too short for both decitabine/ cedazuridine and the comparator therapy decitabine in the controlled phase of the study, there is no adequate comparison with the appropriate comparator therapy.

In summary, no suitable data are available to allow an assessment of the additional benefit, which is why an additional benefit of decitabine/ cedazuridine is not proven.

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 derivation of the patient numbers in the dossier is mathematically comprehensible. The information is however subject to a potential underestimate.

The underestimation results in particular from the potentially higher incidence of AML and the potentially higher percentage of patients who are unsuitable for standard induction chemotherapy. Older patients are underrepresented in the underlying publication from which the percentage values originate. Since older patients in particular are unsuitable for standard induction chemotherapy, the percentage is likely to be higher than assumed in the publication.

In order to ensure a consistent determination of the patient numbers in the present therapeutic indication, the G-BA refers to the derivation of the target population used as a basis in the resolution on the benefit assessment of venetoclax (resolution of 02.12.2021).

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 Inaqovi (active ingredient: decitabine/ cedazuridine) agreed upon in the context of the marketing authorisation at the following publicly accessible link (last access: 24 July 2024):

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

Treatment with decitabine/ cedazuridine should only be initiated and monitored by specialists in internal medicine, haematology and oncology experienced in the treatment of patients with acute myeloid leukaemia.

2.4 Treatment costs

The treatment costs are based on the contents of the product information and the information listed in the LAUER-TAXE® (last revised: 15 July 2024).

For the cost representation, one year is assumed for all medicinal products. The (daily) doses recommended in the product information were used as the calculation basis.

The annual treatment costs shown refer to the first year of treatment.

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				
Induction therapy				
Decitabine - cedazuridine	Day 1 - 5: 28-day cycle	13.0	5	65.0
Appropriate comparator therapy				
Azacitidine	Day 1 - 7: 28-day cycle	13.0	7	91.0
Decitabine	Day 1 - 5: 28-day cycle	13.0	5	65.0
Glasdegib in combination with low-dose cytarabine				
Glasdegib	Continuously 1 x daily	365.0	1	365.0
Cytarabine	2 x daily Day 1 - 10: 28-day cycle	13.0	10	130.0
Venetoclax in combination with azacitidine				
Venetoclax	Continuously 1 x daily	365.0	1	365.0
Azacitidine	Day 1 - 7: 28-day cycle	13.0	7	91.0
Venetoclax in combination with decitabine				
Venetoclax	Continuously 1 x daily	365.0	1	365.0
Decitabine	Day 1 - 5: 28-day cycle	13.0	5	65.0

Consumption:

For dosages depending on body weight (BW) or body surface area (BSA), the average body measurements from 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). This results in a body surface area of 1.91 m² (calculated according to Du Bois 1916)[2].

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

For the cost representation, only the dosages of the general case are considered. Patient-individual dose adjustments (e.g. because of side effects or co-morbidities) are not taken into account when calculating the annual treatment costs.

Designation of the therapy	Dosage/ application	Dose/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Annual average consumption by potency
Medicinal product to be assessed					
Induction therapy					
Decitabine - cedazuridine	35 mg/100 mg	35 mg/100 mg	35 mg/100 mg	65.0	65 x 35 mg/100 mg
Appropriate comparator therapy					
Azacitidine	75 mg/m² = 143.3 mg	143.3 mg	1 x 150 mg	91.0	91 x 150 mg
Decitabine	20 mg/m² = 38.2 mg	38.2 mg	1 x 50 mg	65.0	65 x 50 mg
Glasdegib in combination with low-dose cytarabine					
Glasdegib	100 mg	100 mg	1 x 100 mg	365.0	365 x 100 mg
Cytarabine	20 mg	40 mg	1 x 40 mg	130.0	130 x 40 mg
Venetoclax in combination with azacitidine					
Venetoclax	Day 1: 100 mg Day 2: 200 mg Afterwards: 400 mg	Day 1: 100 mg Day 2: 200 mg Afterwards: 400 mg	Day 1: 1 x 100 mg Day 2: 2 x 100 mg Afterwards: 4 x 100 mg	365.0	1,455 x 100 mg
Azacitidine	75 mg/m² = 143.3 mg	143.3 mg	1 x 150 mg	91.0	91 x 150 mg
Venetoclax in combination with decitabine					
Venetoclax	Day 1: 100 mg Day 2: 200 mg Afterwards: 400 mg	Day 1: 100 mg Day 2: 200 mg Afterwards: 400 mg	Day 1: 1 x 100 mg Day 2: 2 x 100 mg Afterwards: 4 x 100 mg	365.0	1,455 x 100 mg
Decitabine	20 mg/m² = 38.2 mg	38.2 mg	1 x 50 mg	65.0	65 x 50 mg

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:

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					
Decitabine - cedazuridine 35 mg/100 mg	5 FCT	€ 7,224.43	€ 2.00	€ 409.30	€ 6,813.13
Appropriate comparator therapy					
Azacitidine 150 mg	1 VIA	€ 525.69	€ 2.00	€ 24.41	€ 499.28
Cytarabine 40 mg	10 PCI	€ 35.34	€ 2.00	€ 1.14	€ 32.20
Decitabine 50 mg	1 SFI	€ 1,242.38	€ 2.00	€ 0.00	€ 1,240.38
Glasdegib 100 mg	30 FCT	€ 9,282.13	€ 2.00	€ 526.81	€ 8,753.32
Venetoclax 100 mg	112 FCT	€ 5,926.31	€ 2.00	€ 0.00	€ 5,924.31
Abbreviations: VIA = vial; FCT = film-coated tablets; SFI = solution for injection; PCI = powder for a concentrate for the preparation of an infusion solution					

LAUER-TAXE® last revised: 15 July 2024

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.

Because there are no 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, no costs for additionally required SHI services need to be taken into account.

Prophylactic premedication

Antiemetic premedication, which must be considered in accordance with the product information for decitabine - cedazuridine , is not shown with specific dosage recommendations and therefore cannot be quantified in terms of costs.

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 1.10.2009 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 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 do not add to the pharmacy sales price but follow the rules for calculation in the special agreement on contractual unit costs of retail pharmacist services (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 designates 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 has 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 has 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 information 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 has 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:

Adult patients with newly diagnosed acute myeloid leukaemia (AML) who are ineligible for standard induction chemotherapy

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

At its session on 10 January 2023, the Subcommittee on Medicinal Products determined the appropriate comparator therapy.

On 28 February 2024, the pharmaceutical company submitted a dossier for the benefit assessment of decitabine/ cedazuridine to the G-BA in due time in accordance with Chapter 5 Section 8, paragraph 1, number 1, sentence 2 VerfO.

By letter dated 4 March 2024 in conjunction with the resolution of the G-BA of 1 August 2011 concerning the commissioning of the IQWiG to assess the benefit of medicinal products with new active ingredients in accordance with Section 35a SGB V, the G-BA commissioned the IQWiG to assess the dossier concerning the active ingredient decitabine/ cedazuridine.

The dossier assessment by the IQWiG was submitted to the G-BA on 29 May 2024, and the written statement procedure was initiated with publication on the G-BA website on 3 June 2024. The deadline for submitting statements was 24 June 2024.

The oral hearing was held on 8 July 2024.

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 6 August 2024, and the proposed draft resolution was approved.

At its session on 15 August 2024, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee Medicinal products	10 January 2023	Determination of the appropriate comparator therapy
Working group Section 35a	3 July 2024	Information on written statements received; preparation of the oral hearing
Subcommittee Medicinal products	8 July 2024	Conduct of the oral hearing
Working group Section 35a	16.07.2024; 30.07.2024	Consultation on the dossier evaluation by the IQWiG and evaluation of the written statement procedure
Subcommittee Medicinal products	6 August 2024	Concluding discussion of the draft resolution
Plenum	15 August 2024	Adoption of the resolution on the amendment of the Pharmaceuticals Directive

Berlin, 15 August 2024

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

Prof. Hecken