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) Quizartinib (acute myeloid leukaemia, FLT3-ITD-positive)

of 1 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 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 quizartinib on 1 February 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 30 January 2024.

The G-BA commissioned the IQWiG to carry out the assessment of the dossier. The benefit assessment was published on 2 May 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 quizartinib 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 quizartinib.

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 Quizartinib (Vanflyta) in accordance with the product information

VANFLYTA is indicated in combination with standard cytarabine and anthracycline induction and standard cytarabine consolidation chemotherapy, followed by VANFLYTA single-agent maintenance therapy for adult patients with newly diagnosed acute myeloid leukaemia (AML) that is FLT3-ITD positive.

Therapeutic indication of the resolution (resolution of 01.08.2024):

see the approved therapeutic indication

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

Adults with newly diagnosed acute myeloid leukaemia (AML) that is FLT3-ITD positive

Appropriate comparator therapy for quizartinib in combination with standard cytarabine and anthracycline induction and standard cytarabine consolidation chemotherapy, followed by quizartinib monotherapy for maintenance treatment of adults:

- An induction chemotherapy:

  Cytarabine in combination with daunorubicin and midostaurin

- Followed by consolidation therapy:

  A patient-individual therapy under selection of chemotherapy (cytarabine in combination with midostaurin) and allogeneic stem cell transplantation, depending in particular on the subtype of AML, the general condition and comorbidity of the patients.

- Followed by maintenance treatment:

  A patient-individual therapy under selection of:

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

- azacitidine (only for subjects who are unsuitable for allogeneic stem cell transplantation)
- midostaurin (only for subjects who are unsuitable for allogeneic stem cell transplantation)
- sorafenib (only for subjects after allogeneic stem cell transplantation)

taking into account induction and consolidation therapy

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. In addition to quizartinib, the active ingredients azacitidine, cyclophosphamide, cytarabine, daunorubicin, daunorubicin/ cytarabine (liposomal formulation), decitabine, decitabine-cedazuridine, doxorubicin, etoposide, gemtuzumab ozogamicin, glasdegib, histamine dihydrochloride, idarubicin, ivosidenib, midostaurin, mitoxantrone, tioguanine and venetoclax are approved in the present therapeutic indication.

on 2. Allogeneic stem cell transplantation is basically considered as a non-medicinal therapy in the present therapeutic indication.

on 3. The following resolutions on the benefit assessment of medicinal products with new active ingredients according to Section 35a SGB V are available:

- midostaurin (resolution of 02.05.2024)
- ivosidinib (resolution of 18.01.2024)
- venetoclax (resolution of 2 December 2021)
- glasdegib (resolution of 18 February 2021)
- daunorubucin/ cytarabine (resolution of 22 March 2019)
- gemtuzumab ozogamicin (resolution of 21 February 2019)
- decitabine (resolution of 2 May 2013)

Annex VI to Section K of the Pharmaceuticals Directive (last revised: 24.06.2023):

medicinal products that are prescribable for unapproved therapeutic indications (off-label use)

- XIV. Hydroxycarbamide in chronic myelomonocytic leukaemia (CMML).

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. A written statement has been issued by the Drugs Commission of the German Medical Association (AkdÄ).

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

Since quizartinib is used in combination with intensive chemotherapy, it is assumed for the present determination of the appropriate comparator therapy that the patients are generally suitable for intensive therapy. Medicinal products that are approved exclusively for patients for whom intensive therapy is not an option are therefore not considered as appropriate comparator therapy.

The therapeutic goal for patients with newly diagnosed AML is curative. The therapy consists of an induction phase followed by a consolidation and maintenance phase.

Induction therapy

Specifically, the active ingredient midostaurin is available for patients with newly diagnosed acute myeloid leukaemia that is FLT3-ITD positive. In the current guideline recommendations of the American Society of Hematology (ASH) from 2020 and Alberta Health Services from 2019, the use of midostaurin is recommended for patients with activating FLT3 mutations in addition to standard induction therapy consisting of cytarabine and daunorubicin according to the 7 + 3 regimen. Midostaurin is accordingly approved for induction therapy in combination with cytarabine and daunorubicin.

In a new benefit assessment of midostaurin due to exceeding the EUR 30 million turnover limit, it was determined that an additional benefit of midostaurin was not proven, as no suitable data were available for a comparison with the appropriate comparator therapy (resolution of 2 May 2024).

Overall, however, it is clear from the present guideline recommendation and the available statements of the scientific-medical society in the present and conducted benefit assessment procedure that induction and consolidation therapy with a midostaurin combination therapy represents the current therapy standard in the present indication in the presence of an FLT3 mutation and that midostaurin assumes a correspondingly high priority in the treatment of patients with acute myeloid leukaemia and FLT3 mutation in the current medical treatment situation.

Therefore, the combination therapy of cytarabine, daunorubicin and midostaurin is the only appropriate comparator therapy for patients with newly diagnosed acute myeloid leukaemia that is FLT3-ITD positive.

Consolidation therapy

For consolidation therapy, the present guidelines unanimously recommend either chemotherapy or allogeneic stem cell transplantation. For patients with activating FLT3 mutations, the available evidence recommends midostaurin combination therapy for chemotherapy. Taking into account the above explanations, the combination therapy of midostaurin and cytarabine alone is considered appropriate for the chemotherapy component of consolidation therapy since the combination therapy of midostaurin with cytarabine and daunorubicin was determined to be the only appropriate comparator therapy for induction therapy.

The treatment decision in favour of chemotherapy or allogeneic stem cell transplantation should be made on a patient-individual basis, taking into account the subtype of AML, the general condition and comorbidity of the patients.

Maintenance treatment

With regard to maintenance treatment, according to the available evidence, a distinction must first be made as to whether patients have received allogeneic stem cell transplantation or chemotherapy in the preceding consolidation therapy.

The two approved treatment options midostaurin and azacitidine are available for the maintenance treatment of patients who are ineligible for allogeneic stem cell transplantation. There is also a written statement from the AkdÄ stating that the treatment options midostaurin and azacitidine can be considered as maintenance treatment for patients for whom no allogeneic stem cell transplantation is planned. Both therapy options are recommended here, regardless of the use of midostaurin in the previous treatment phases. The background to this is a randomised comparator study of azacitidine in which a survival benefit was also found for the subgroup of patients with FLT3-positive AML.

No medicinal therapies are approved for the maintenance treatment of adults with acute myeloid leukaemia (AML) and FLT3-ITD mutation who are in first complete remission after stem cell transplantation. The active ingredients mentioned in the therapy recommendations are also not explicitly approved for the maintenance treatment of AML following stem cell transplantation.

In two phase III studies of maintenance treatment in adults with acute myeloid leukaemia (AML) and FLT3-ITD mutation who are in first complete remission after stem cell transplantation, maintenance treatment with sorafenib significantly reduced the risk of relapse or death and prolonged overall survival compared to the monitoring wait-and-see approach.

From the point of view of the scientific-medical societies in accordance with Section 35a, paragraph 7, sentence 4 SGB V, sorafenib is also eligible with reference to the mentioned studies for maintenance treatment in adults with acute myeloid leukaemia (AML) and FLT3-ITD mutation who are in first complete remission after stem cell transplantation.

In the definable group of patients with FLT3-ITD mutation after allogeneic stem cell transplantation in consolidation, the use of sorafenib as an unapproved therapy option in maintenance treatment is medically necessary.

At its session on 18 August 2022, the G-BA decided to commission the Expert Group on Off-Label Use in accordance with Section 35c, paragraph 1 SGB V (off-label expert group) to assess the state of scientific knowledge on sorafenib in maintenance treatment following allogeneic stem cell transplantation for the treatment of adults with AML and an FLT3-ITD mutation.

In accordance with the generally recognised state of medical knowledge, the overall assessment is that the off-label use of sorafenib in the absence of other approved medicinal products for maintenance treatment following allogeneic stem cell

transplantation in the context of patient-individual therapy, taking into account induction and consolidation therapy for relevant patient groups or indication areas, is generally preferable to the medicinal products previously approved in the therapeutic indication; Section 6, paragraph 2, sentence 3, number 3 AM-NutzenV.

As a result, with regard to maintenance treatment, the G-BA determines a patient-individual therapy, taking into account induction and consolidation therapy as the appropriate comparator therapy, whereby azacitidine, midostaurin and sorafenib are considered to be components of the appropriate comparator therapy, taking into account the addition information in brackets.

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 quizartinib is assessed as follows:

Adults with newly diagnosed acute myeloid leukaemia (AML) that is FLT3-ITD positive

An additional benefit is not proven.

Justification:

For the benefit assessment, the pharmaceutical company submitted results of the QuANTUM-First study. In the completed double-blind phase III QuANTUM-First study, quizartinib is compared with placebo in the 3 phases of induction, consolidation and maintenance treatment. The study was conducted between September 2016 and June 2023 in 193 study sites in America, Australia, Asia and Europe.

Adults up to the age of 75 years with AML diagnosed according to the 2008 World Health Organisation (WHO) classification and a documented FLT3-ITD mutation were enrolled in the study.

A total of 539 patients were enrolled, randomised into the intervention arm (N = 268) or the comparator arm (N = 271). Randomisation was stratified by region, age and leukocyte count at the time of AML diagnosis.

The study treatment was divided into the induction, consolidation and maintenance phases. As induction therapy, patients received 1 to 2 cycles of treatment with quizartinib or placebo in combination with cytarabine and daunorubicin or idarubicin. Patients with a complete remission after the induction phase could receive quizartinib or placebo in combination with high-dose cytarabine and/or an allogeneic stem cell transplantation in the consolidation phase. The consolidation chemotherapy consisted of up to 4 cycles. Patients with a complete remission after completion of consolidation therapy received maintenance treatment with quizartinib or placebo for up to 36 cycles of 28 days each, regardless of the type of consolidation therapy.

Treatment with quizartinib in the intervention arm was carried out according to the requirements in the product information. The dosage regimens of the chemotherapeutic components corresponded to the requirements in the product information and the guidelines with minor deviations without consequences for the benefit assessment.

The primary endpoint of the study was overall survival. Secondary endpoints were collected in the categories of morbidity, health-related quality of life and adverse events (AEs).

Assessment

In the QuANTUM-First study, the appropriate comparator therapy was not implemented in all 3 therapy phases; in particular, there was no comparison with the therapy standard of midostaurin. The QuANTUM-First study is therefore unsuitable for the assessment of an additional benefit of quizartinib compared with the appropriate comparator therapy.

As part of the written statement procedure, the pharmaceutical company submitted an indirect comparison of quizartinib versus midostaurin. For this purpose, the study population of the QuANTUM-First study was compared with the population of non-pretreated AML patients aged < 60 years with an FLT3-ITD mutation from the RATIFY study. The results of the

indirect comparison could not be used for the benefit assessment due to a lack of data for an assessment of the similarity assumption, the procurement of information, the similarity of the operationalisation and a lack of information on the characteristics of the patient populations.

No data are therefore available to allow an assessment of the additional benefit.

An additional benefit of quizartinib compared with the appropriate comparator therapy is therefore not proven.

2.1.4 Summary of the assessment

The present assessment concerns the benefit assessment of the new medicinal product Vanflyta with the active ingredient quizartinib.

The active ingredient quizartinib is approved in combination with standard cytarabine and anthracycline induction and standard cytarabine consolidation chemotherapy, followed by quizartinib single-agent maintenance therapy for adult patients with newly diagnosed acute myeloid leukaemia (AML) that is FLT3-ITD positive.

For the benefit assessment of quizartinib, the pharmaceutical company submitted results of the QuANTUM-First study.

The data presented are unsuitable for comparison with the appropriate comparator therapy.

An additional benefit of quizartinib in combination with standard cytarabine and anthracycline induction and standard cytarabine consolidation chemotherapy, followed by VANFLYTA single-agent maintenance therapy for adult patients with newly diagnosed acute myeloid leukaemia (AML) that is FLT3-ITD positive is therefore 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).

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 midostaurin (resolution of 2 May 2024).

In addition, with regard to existing uncertainties for the lower limit of the target population as well as for the range for the percentage of patients who are eligible for intensive chemotherapy, the derivation of the patient numbers in the procedure for midostaurin appears more suitable.

Since treatment with quizartinib is limited to patients with FLT3-ITD mutation, a narrowing of the target population using the range of 18.9 % to 23.3 % specified in the dossier for quizartinib is estimated. It should be noted that this range is also subject to uncertainties with regard to the upper and lower limits.

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 Vanflyta (active ingredient: quizartinib) agreed upon in the context of the marketing authorisation at the following publicly accessible link (last access: 23 July 2024):

https://www.ema.europa.eu/en/documents/overview/vanflyta-epar-medicine-overview_en.pdf

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

In accordance with the European Medicines Agency (EMA) requirements regarding additional risk minimisation measures, the pharmaceutical company must provide training material that contains information for medical professionals and patients.

The training material contains, in particular, information and warnings on prolongation of the QTc interval.

FLT3 detection

Before taking quizartinib, AML patients must have confirmation of FLT3-ITD positive AML using a CE-marked in vitro diagnostic (IVD) medical device with the corresponding intended purpose. If a CE-marked IVD is not available, confirmation of FLT3-ITD positive AML should be assessed by an alternate validated test.

2.4 Treatment costs

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

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

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.

There is no marketing authorisation for sorafenib as maintenance treatment in patients with FLT3-ITD mutation after stem cell transplantation in this therapeutic indication. The G-BA uses the treatment regimen of the NCCN guideline as the basis for cost calculation in the context of the off-label use of this therapy.[2]

Inpatient treatments

Some treatment options of the appropriate comparator therapy are carried out on an inpatient basis. The inpatient costs are calculated on the basis of the case flat fee revenues, which result from the valuation ratios of the respective DRG (Diagnosis Related Group) multiplied by the federal base rate value of 2024 (€ 4,210.59). Furthermore, the nursing revenue is included in the inpatient costs. This is calculated from the average length of stay of the concerned DRG multiplied by the nursing fee according to Section 15 para. 2a KHEntgG (Act on Fees for Full and Semi-inpatient Hospital Services) (since 28 March 2024: € 250) and the treatment-specific nursing revenue valuation ratio.

Adults with newly diagnosed acute myeloid leukaemia (AML) that is FLT3-ITD positive:

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				
Quizartinib	Day 8 - 21: 28-day cycle	1 - 2	14	14 - 28
Cytarabine	Day 1 - 7: 28-day cycle	1 - 2	7	7 - 14
Daunorubicin	Day 1 - 3: 28-day cycle	1 - 2	3	3 - 6
Idarubicin	Day 1 - 3: 28-day cycle	1 - 2	3	3 - 6
Consolidation therapy				

[2] National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines). Acute myeloid leukaemia. Version 4.2023 [online]. 2023. URL: https://www.nccn.org/professionals/physician_gls/pdf/aml.pdf.

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Quizartinib	Day 6 - 19: 28-day cycle	1 - 4	14	14 - 56
Cytarabine	2 x daily on day 1, 3, 5: 28-day cycle	1 - 4	3	3 - 12
Maintenance treatment				
Quizartinib	Day 1 - 28: 28-day cycle	7 - 11	28	197 - 309
Appropriate comparator therapy				
Induction therapy				
Cytarabine + daunorubicin + midostaurin				
Cytarabine	Day 1 - 7: 28-day cycle	1 - 2	7	7 - 14
Daunorubicin	Day 1 - 3: 28-day cycle	1 - 2	3	3 - 6
Midostaurin	2x daily on day 8 - 21: 28-day cycle	1 - 2	14	14 - 28
Consolidation therapy				
Cytarabine + midostaurin				
Midostaurin	Day 8 - 21: 28-day cycle	4	14	56
Cytarabine	2x daily on day 1, 3, 5: 28-day cycle	4	3	12
High-dose chemotherapy with allogeneic stem cell transplantation				
Highly complex and intensive block chemotherapy	once	12.4 (average length of stay)	12.4	Highly complex and intensive block chemotherapy
Allogeneic stem cell transplantation	once	34.4 - 37.8 (average length of stay)	34.4 - 37.8	Allogeneic stem cell transplantation
Maintenance treatment				
Oral azacitidine	Day 1 - 14: 28-day cycle	7.2 – 8.0	14	100 - 112
Sorafenib[2]	Day 1 - 28:	5.8 - 9.3	28	158 - 260

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
	28-day cycle			
Midostaurin	2 x daily on day 1-28: 28-day cycle	6.9 – 7.7	28	194 - 218

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)[3].

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	Average annual consumption by potency
Medicinal product to be assessed					
Induction therapy					
Quizartinib	17.7 mg	35.4 mg	2 x 17.7 mg	14 - 28	28 – 56 x 17.7 mg
Cytarabine	100 – 200 mg/m² = 191 – 382 mg	191 mg – 382 mg	2 - 4 x 100 mg	7 - 14	14 – 56 x 100 mg
Daunorubicin	45 mg/m² = 86 mg	86 mg	5 x 20 mg	3 - 6	15 – 30 x 20 mg
Idarubicin	12 mg/m² = 22.9 mg	22.9 mg	2 x 10 mg + 1 x 5 mg	3 - 6	6 x 10 mg + 3 x 5 mg – 12 x 10 mg + 6 x 5 mg
Consolidation therapy					
Quizartinib	17.7 mg = 35.4 mg	35.4 mg	2 x 17.7 mg	14 - 56	28 – 112 x 17.4 mg

[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
Cytarabine	3 g/m² = 5.73 g	2 x 5.73 g	2 x 5,000 mg + 1 x 2,000 mg	3 - 12	6 x 5,000 mg + 3 x 2,000 mg – 24 x 5,000 mg + 12 x 2,000 mg
Maintenance treatment					
Quizartinib	Day 1 – 14 cycle 1: 26.5 mg From day 15 cycle 1: 53 mg	26.5 mg - 53 mg	1 - 2 x 26.5 mg	197 - 309	380 - 604 x 26.5 mg
Appropriate comparator therapy					
Induction therapy					
Midostaurin + cytarabine + daunorubicin					
Midostaurin	50 mg	100 mg	4 x 25 mg	14 - 28	56 - 112 x 25 mg
Cytarabine	200 mg/m² = 382 mg	382 mg	4 x 100 mg	7 - 14	28 - 56 x 100 mg
Daunorubicin	60 mg/m² = 114.6 mg	114.6 mg	6 x 20 mg	3 - 6	18 - 36 x 20 mg
Consolidation therapy					
Midostaurin	50 mg	100 mg	4 x 25 mg	56	224 x 25 mg
Cytarabine	3 g/m² = 5.73 g	2 x 5.73 g	2 x 5,000 mg + 1 x 2,000 mg	12	24 x 5,000 mg + 12 x 2,000 mg
Maintenance treatment					
Oral azacitidine	300 mg	300 mg	1 x 300 mg	100 - 112	100 - 112 x 300 mg
Sorafenib[2]	Cycle 1 - 3: 200 mg From cycle 4 onwards: 400 mg	400 - 800 mg	2 - 4 x 200 mg	158 - 260	464 - 872 x 200 mg
Midostaurin	50 mg	100 mg	4 x 25 mg	194 - 218	776 - 872 x 25 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.

Inpatient treatments:

Calculation year	DRG	Average length of stay [d]	DRG valuation ratio (main department)	Federal base case value	Nursing revenue valuation ratio	Nursing fee	Case flat fee revenue	Nursing revenue	Total case flat fee revenue and nursing revenue
Appropriate comparator therapy									
High-dose chemotherapy with allogeneic stem cell transplantation									
2024	R60D	12.4	1.835	€ 4,210.59	1.0441	€ 250	€ 7,726.43	3236.71	€ 10,963.14
2024	A04D	37.8	10.265	€ 4,210.59	1.7827	€ 250	€ 43,221.71	16,846.52	€ 60,068.22
2024	A04E	34.4	8.985	€ 4,210.59	1.9317	€ 250	€ 37,832.15	16,612.62	€ 54,444.77

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					
Induction therapy					
Quizartinib 17.7 mg	28 FCT	€ 9,219.76	€ 2.00	€ 523.25	€ 8,694.51
Cytarabine 100 mg	10 SFI	€ 48.87	€ 2.00	€ 1.78	€ 45.09
Daunorubicin 20 mg	1 PII	€ 48.16	€ 2.00	€ 9.16	€ 37.00
Idarubicin 5 mg	1 HC	€ 94.31	€ 2.00	€ 11.85	€ 80.46
Idarubicin 10 mg	1 HC	€ 171.85	€ 2.00	€ 24.45	€ 145.40
Consolidation therapy					
Quizartinib 17.7 mg	28 FCT	€ 9,219.76	€ 2.00	€ 523.25	€ 8,694.51
Cytarabine 5000 mg	1 IIS	€ 194.65	€ 2.00	€ 8.70	€ 183.95
Cytarabine 2000 mg	1 IIS	€ 77.06	€ 2.00	€ 3.12	€ 71.94
Maintenance treatment					
Quizartinib 26.5 mg	56 FCT	€ 18,381.87	€ 2.00	€ 1,046.50	€ 17,333.37
Appropriate comparator therapy					
Induction 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
Cytarabine + daunorubicin + midostaurin					
Cytarabine 100 mg	10 SFI	€ 48.87	€ 2.00	€ 1.78	€ 45.09
Daunorubicin 20 mg	1 PII	€ 48.16	€ 2.00	€ 9.16	€ 37.00
Midostaurin 25 mg	4 x 28 SC	€ 15,991.76	€ 2.00	€ 910.00	€ 15,079.76
Consolidation therapy					
High-dose cytarabine + midostaurin					
Cytarabine 5000 mg	1 IIS	€ 194.65	€ 2.00	€ 8.70	€ 183.95
Cytarabine 2000 mg	1 IIS	€ 77.06	€ 2.00	€ 3.12	€ 71.94
Midostaurin 25 mg	4 x 28 SC	€ 15,991.76	€ 2.00	€ 910.00	€ 15,079.76
Maintenance treatment					
Oral azacitidine 300 mg	14 FCT	€ 18,655.37	€ 2.00	€ 1,062.12	€ 17,591.25
Sorafenib 200 mg	112 FCT	€ 371.26	€ 2.00	€ 17.08	€ 352.18
Midostaurin 25 mg	4 x 28 SC	€ 15,991.76	€ 2.00	€ 910.00	€ 15,079.76
Abbreviations: FCT = film-coated tablets; CIS = concentrate for the preparation of an infusion solution; IFB = infusion bottles; IIS = injection/infusion solution; SFI = solution for injection; PII = powder for the preparation of an injection or infusion; PIC = powder for the preparation of an infusion solution concentrate; SC = soft capsules					

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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.

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:

Adults with newly diagnosed acute myeloid leukaemia (AML) that is FLT3-ITD positive

- No medicinal product with new active ingredients that can be used in a combination therapy and fulfils the requirements of Section 35a, paragraph 3, sentence 4 SGB V.

References:
Product information for quizartinib (Vanflyta); product information for VANFLYTA film-coated tablets; last revised: November 2023

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 28 November 2023, the Subcommittee on Medicinal Products determined the appropriate comparator therapy.

On 30 January 2024, the pharmaceutical company submitted a dossier for the benefit assessment of quizartinib to the G-BA in due time in accordance with Chapter 5 Section 8, paragraph 1, number 1, sentence 2 VerfO.

By letter dated 1 February 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 quizartinib.

The dossier assessment by the IQWiG was submitted to the G-BA on 25 April 2024, and the written statement procedure was initiated with publication on the G-BA website on 2 May 2024. The deadline for submitting statements was 23 May 2024.

The oral hearing was held on 10 June 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 23 July 2024, and the proposed draft resolution was approved.

At its session on 1 August 2024, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee Medicinal products	28 November 2023	Determination of the appropriate comparator therapy
Working group Section 35a	5 June 2024	Information on written statements received; preparation of the oral hearing
Subcommittee Medicinal products	10 June 2024	Conduct of the oral hearing
Working group Section 35a	19.06.2024; 16.07.2024	Consultation on the dossier evaluation by the IQWiG and evaluation of the written statement procedure
Subcommittee Medicinal products	23 July 2024	Concluding discussion of the draft resolution
Plenum	1 August 2024	Adoption of the resolution on the amendment of the Pharmaceuticals Directive

Berlin, 1 August 2024

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

Prof. Hecken