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) Midostaurin (reassessment of an orphan drug after exceeding the 30 million euro limit: acute myeloid leukaemia (AML), FLT3 mutation)

of 2 May 2024

Contents

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1. Legal basis

According to Section 35a paragraph 1 German Social Code, Book Five (SGB V), the Federal Joint Committee (G-BA) 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 active ingredient midostaurin (Rydapt) was listed for the first time on 15 October 2017 in the "LAUER-TAXE®", the extensive German registry of available drugs and their prices. Rydapt® for the treatment of newly diagnosed acute myeloid leukaemia is approved as a medicinal product for the treatment of rare diseases under Regulation (EC) No. 141/2000 of the European Parliament and the Council of 16 December 1999.

At its session on 5 April 2018, the G-BA decided on the benefit assessment of midostaurin in the therapeutic indication "in combination with standard daunorubicin and cytarabine induction and high-dose cytarabine consolidation chemotherapy, and for patients in complete response followed by Rydapt single agent maintenance therapy, for adult patients with newly diagnosed acute myeloid leukaemia (AML) who are FLT3 mutation-positive" in accordance with Section 35a SGB V.

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If the sales of the orphan drug through the statutory health insurance at pharmacy sales prices and outside the scope of SHI-accredited medical care, including value-added tax, exceed an amount of € 30 million in the last twelve calendar months, the pharmaceutical company must submit evidence in accordance with Section 5, paragraphs 1 to 6 within three months of being requested to do so by the Federal Joint Committee, and in this evidence must demonstrate the additional benefit compared to the appropriate comparator therapy.

In a letter dated 1 December 2022, the pharmaceutical company was informed that the EUR 30 million turnover limit for midostaurin had been exceeded within the period from December 2021 to November 2022. By resolution of 2 February 2023 the procedure was suspended till 15 November 2023. By letter dated 2 February 2023, the pharmaceutical company was requested to submit a dossier for the benefit assessment according to Section 35a SGB V by 15 November 2023, due to exceeding the € 30 million turnover limit. The pharmaceutical company has 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 6 VerfO on 13 November 2023.

The G-BA commissioned the IQWiG to carry out the dossier assessment. The benefit assessment was published on 15 February 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 midostaurin 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, as well of the addendum drawn up by the IQWiG on the benefit assessment. 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 midostaurin.

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 Midostaurin (Rydapt) in accordance with the product information

Rydapt is indicated in combination with standard daunorubicin and cytarabine induction and high-dose cytarabine consolidation chemotherapy, and for patients in complete response followed by Rydapt single agent maintenance therapy, for adult patients with newly diagnosed acute myeloid leukaemia (AML) who are FLT3 mutation-positive.

Therapeutic indication of the resolution (resolution of 2 May 2024):

see the approved therapeutic indication

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

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2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

Adults with newly diagnosed acute myeloid leukaemia (AML) who are FLT3 mutation-positive

Appropriate comparator therapy for midostaurin in combination with standard chemotherapy with daunorubicin and cytarabine for induction followed by midostaurin in combination with high-dose chemotherapy with cytarabine for consolidation followed by midostaurin monotherapy for maintenance therapy in adults in complete remission:

- Induction chemotherapy:
  - cytarabine in combination with daunorubicin *or* idarubicin *or* mitoxantrone

  or

  - daunorubicin/ cytarabine (liposomal formulation) [only for subjects with therapy-related AML (t-AML) or AML with myelodysplastic changes (AML-MRC)]

- Followed by consolidation therapy:

  A patient-individual therapy under selection of chemotherapy (cytarabine or daunorubicin/ cytarabine (liposomal formulation)) and allogeneic stem cell transplantation, depending in particular on the subtype of AML, the patient's general condition and comorbidity.

- Followed by maintenance therapy:

  A patient-individual therapy under selection of:

  - azacitidine (only for subjects who are unsuitable for allogeneic stem cell transplantation)
  - sorafenib (only for subjects who are FLT3-ITD mutation-positive after allogeneic stem cell transplantation)
  - monitoring wait-and-see approach (only for subjects without FLT3-ITD mutation after allogeneic stem cell transplantation)

  taking into account the induction and consolidation therapy as well as the FLT3 mutational status.

Criteria according to Chapter 5 Section 6 of the Rules of Procedure of the G-BA and Section 6 para. 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:

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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.

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

on 1. In addition to midostaurin, the active ingredients azacitidine, cyclophosphamide, cytarabine, daunorubicin, daunorubicin/ cytarabine (liposomal formulation), decitabine, decitabine-cedazuridine, doxorubicin, etoposide, gemtuzumab ozogamicin, glasdegib, histamine dihydrochloride, idarubicin, ivosidenib, mitoxantrone, quizartinib, 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. Annex XII - Resolutions on the benefit assessment of medicinal products with new active ingredients according to Section 35a SGB V:

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- 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 June 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 care.

Since midostaurin 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.

For subjects with newly diagnosed AML, the treatment goal is curative. The therapy consists of induction therapy, followed by a consolidation and maintenance phase.

<u>Induction therapy</u>

Specifically, for subjects with activating FLT3 mutations, the active ingredient midostaurin is recommended as standard therapy in addition to a standard induction therapy consisting of cytarabine and daunorubicin according to the 7+3 regimen in the

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current guideline of the Alberta Health Services and in the written statements of the AkdÄ.[2]

Overall, it is clear from the present guideline recommendation and the statement of the scientific-medical society in the present benefit assessment procedure that induction 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 is accorded a correspondingly high priority in the treatment of patients with acute myeloid leukaemia and FLT3 mutation in the current medical treatment situation.

However, according to Section 6, paragraph 2, sentence 2 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. Effects on the medical treatment situation that only result from the addition of the new medicinal product must be disregarded.

Based on this, induction therapy with cytarabine in combination with an anthracycline represents a suitable comparator therapy. The active ingredients daunorubicin, idarubicin or mitoxantrone can be considered as anthracyclines, taking into account the evidence and the authorisation status. It cannot be deduced from the available evidence that one of these combination therapies should be preferred as a rule. Thus, all three combinations (cytarabine + daunorubicin, cytarabine + idarubicin or cytarabine + mitoxantrone) each represent a suitable comparator therapy.

The approved therapeutic indication of midostaurin is not limited to *de novo* AML. Accordingly, the present therapeutic indication also includes patients with therapy-related AML (t-AML) or AML with myelodysplastic changes (AML-MRC) in conjunction with an FLT3 mutation. During the oral hearing, the scientific-medical society explained that secondary AML is also treated genotype-specifically in the healthcare context, so that midostaurin would be used in the presence of an FLT3 mutation. In August 2018, the medicinal product Vyxeos®, which contains a liposomal formulation of the combination of active ingredients daunorubicin and cytarabine, was approved for the patient group with AML-MRC or t-AML. By resolution of the G-BA on 22 March 2019, the benefit assessment of orphan drugs for daunorubicin/ cytarabine (liposomal formulation) found a considerable additional benefit compared to the 7+3 regimen of daunorubicin and cytarabine. For subjects with FLT3-mutated t-AML and AML-MRC, daunorubicin/ cytarabine (liposomal formulation) in the induction phase is considered another suitable comparator therapy.

For patients aged 15 years of age and over with CD33-positive de novo AML, the active ingredient gemtuzumab ozogamicin is also approved. According to the available evidence, a meta-analysis showed a survival benefit from the addition of gemtuzumab

[2] Alberta Health Services (AHS). Acute myeloid leukaemia; version 6 [online]. 07.2019. Edmonton (CAN): AHS; 2019.

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ozogamicin to intensive induction therapy in patients with low cytogenetic risk, while no benefit was found in patients with high cytogenetic risk. Patients with an FLT3 mutation have an intermediate or adverse risk profile according to the ELN classification[3], taking into account cytogenetic and molecular aberrations. In the G-BA resolution of 21 February 2019, a non-quantifiable additional benefit was identified for gemtuzumab ozogamicin compared to daunorubicin and cytarabine. In the pivotal ALFA-0701 study, the addition of gemtuzumab ozogamicin to daunorubicin and cytarabine did not prolong overall survival. Taking the above aspects into account, gemtuzumab ozogamicin in combination with daunorubicin and cytarabine is not considered an appropriate comparator therapy for the present therapeutic indication of AML with FLT3 mutation.

Since the end of December 2023, quizartinib in combination with cytarabine and an anthracycline has been approved for the induction therapy of AML patients with an FLT3-ITD mutation. This is a new treatment option for which there are no therapy recommendations in the available evidence. According to the generally recognised state of medical knowledge, quizartinib in combination with cytarabine and an anthracycline is not considered an appropriate comparator therapy.

Consolidation therapy

For consolidation therapy, either chemotherapy or allogeneic stem cell transplantation is unanimously recommended in this guideline and in the written statement of the AkdÄ. The treatment decision should be made on the basis of patient-individual factors, in particular taking into account the subtype of AML, the patient's general condition and comorbidity.

According to the available evidence, the use of midostaurin in combination with high-dose cytarabine is specifically recommended as chemotherapy for patients with an FLT3 mutation. The present guideline recommendation and the statement of the scientific-medical society in the present benefit assessment procedure also show that combination therapy with midostaurin represents the therapy standard for patients with FLT3 mutation in the context of consolidation after midostaurin-containing induction therapy in the current medical treatment situation. As already explained above, midostaurin cannot be determined as an appropriate comparator therapy for the present benefit assessment, taking into account the requirements of Section 6, paragraph 2, sentence 2 AM-NutzenV.

Accordingly, high-dose therapy with cytarabine can be considered as chemotherapy, although a less intensive dose of cytarabine is also a treatment option for older subjects. For people with t-AML and AML-MRC, the use of daunorubicin/ cytarabine (liposomal formulation) is recommended, as described above. According to the product information for daunorubicin/ cytarabine (liposomal formulation), patients

[3] Döhner H. et al. Diagnosis and management of AML in adults: 2022 recommendations from an international expert panel on behalf of the ELN. Blood. 2022;140(12):1345-1377. doi:10.1182/blood.2022016867

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must have already been treated with daunorubicin/ cytarabine (liposomal formulation) as part of induction chemotherapy.

Chemotherapy is preferred to allogeneic stem cell transplantation in subjects with a favourable prognosis, as the benefit of allogeneic stem cell transplantation in this patient population does not outweigh the treatment-related mortality and morbidity risk. For people at intermediate risk, both chemotherapy and allogeneic stem cell transplantation are possible options. When deciding on treatment, the potentially increased probability of recurrence should be weighed against the increased treatment-associated mortality of allogeneic stem cell transplantation. Due to the high risk of relapse, allogeneic stem cell transplantation is the preferred therapy option for people with an unfavourable prognosis according to guideline recommendations.

Since the end of December 2023, quizartinib in combination with cytarabine has been approved as consolidation therapy for AML patients with an FLT3-ITD mutation. This is a new treatment option for which there are no therapy recommendations in the available evidence. According to the generally recognised state of medical knowledge, quizartinib in combination with cytarabine is not designated as an appropriate comparator therapy.

In the overall assessment, the G-BA determines a patient-individual therapy for the present resolution by selecting chemotherapy (cytarabine or daunorubicin/ cytarabine (liposomal formulation)) and allogeneic stem cell transplantation, depending on the subtype of AML, the patient's general condition and comorbidity, as an appropriate comparator therapy.

Maintenance therapy

On the basis of the comments of the scientific-medical society and the AkdÄ on the present benefit assessment procedure and the appropriate comparator therapy, the implementation of maintenance therapy following consolidation therapy is recommended for subjects with AML and FLT3 mutation who are in first remission. The active ingredient used in maintenance therapy should be selected, taking into account the induction and consolidation therapy as well as the FLT3 mutational status.

The active ingredients midostaurin and oral azacitidine are available for maintenance therapy after chemotherapy in accordance with their authorisation status. It cannot be inferred from the available evidence that one of these active ingredients is specifically recommended in the therapeutic indication of FLT3-mutated AML.

As already explained above, midostaurin cannot be determined as an appropriate comparator therapy for the present benefit assessment, taking into account the requirements of Section 6, paragraph 2, sentence 2 AM-NutzenV.

Oral azacitidine is approved as maintenance therapy for subjects who have achieved complete remission or complete remission with incomplete blood count recovery following induction therapy with or without consolidation therapy and who are

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unsuitable for haematopoietic stem cell transplantation, including those who have opted out. In the pivotal CC-486-AML-001 study, a survival benefit was shown for subjects at intermediate or high risk of recurrence. This advantage also existed for the subgroup of patients whose AML had an FLT3 mutation.

According to the available evidence, maintenance therapy following transplantation offers advantages in terms of overall survival and recurrence-free survival. No medicinal therapies are approved for the maintenance therapy 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 therapy of AML following stem cell transplantation.

In two randomised controlled studies of maintenance therapy in adults with acute myeloid leukaemia (AML) and FLT3-ITD mutation who are in first complete remission after stem cell transplantation, maintenance therapy with sorafenib significantly reduced the risk of relapse or death and prolonged overall survival compared to the monitoring wait-and-see approach. [4,5]

According to the available evidence, sorafenib may be considered for maintenance therapy in adults with acute myeloid leukaemia (AML) and FLT3-ITD mutation who are in first complete remission following stem cell transplantation. 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 therapy following allogeneic stem cell transplantation for the treatment of adults with AML and an FLT3-ITD mutation.

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 therapy is medically necessary.

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 therapy 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.

[4] Burchert A, Bug G, Fritz LV, Finke J, Stelljes M, Röllig C et al. Sorafenib Maintenance After Allogeneic Hematopoietic Stem Cell Transplantation for Acute Myeloid Leukemia With FLT3-Interal Tandem Duplication Mutation (SORMAIN). Journal of clinical oncology: official journal of the American Society of Clinical Oncology 2020; 38(26):2993-3002. Doi: 10.1200/JCO.19.03345.

[5] Xuan L, Wang Y, Huang F, Fan Z, Xu Y, Sun J et al. Sorafenib maintenance in patients with FLT3-ITD acute myeloid leukaemia undergoing allogenic haematopoietic stem-cell transplantation: an open-label, multicentre, randomised phase 3 trial. Lancet Oncol 2020; 21(9):1201-12. doi: 10.1016/S1470-2045(20)30455-1.

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None of the above recommendations apply to patients who have received allogeneic stem cell transplantation as part of consolidation therapy and who do not have an FLT3-ITD mutation. For patients without an FLT3-ITD mutation following allogeneic stem cell transplantation, the G-BA therefore considers monitoring wait-and-see approach to be an appropriate comparator therapy in the context of patient-individual maintenance therapy.

Since the end of December 2023, quizartinib has been approved as maintenance therapy for AML patients with an FLT3-ITD mutation. This is a new treatment option for which there are no therapy recommendations in the available evidence. According to the generally recognised state of medical knowledge, quizartinib is not determined to be an appropriate comparator therapy.

In summary, the G-BA determined an appropriate comparator therapy for maintenance therapy to be a patient-individual therapy under selection of azacitidine, sorafenib and monitoring wait-and-see approach, taking into account induction and consolidation therapy as well as FLT3 mutational status.

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 midostaurin is assessed as follows:

Adults with newly diagnosed acute myeloid leukaemia (AML) who are FLT3 mutation-positive

An additional benefit is not proven.

Justification:

For the benefit assessment of midostaurin for the treatment of adults with newly diagnosed acute myeloid leukaemia (AML) who are FLT3 mutation-positive, the pharmaceutical company presents data from the pivotal RATIFY study and the A2220 and AMLSG 16-10 studies.

RATIFY study

RATIFY is a completed, randomised, double-blind phase III study. The study enrolled adults between the ages of 18 and 60 years with newly diagnosed AML who are FLT3 mutation-positive. The study was conducted between 2008 and 2022 in 177 study sites in Europe, Australia and the USA. The pharmaceutical company has submitted the data cut-off from 26 March 2022. This is the pre-specified analysis of overall survival, which was planned 10 years after randomisation of the last patient or after 509 deaths.

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In the RATIFY study, midostaurin was compared with placebo, in each case in combination with daunorubicin and cytarabine as induction therapy, in combination with high-dose cytarabine as consolidation therapy and as monotherapy for maintenance therapy. A total of 717 patients were enrolled and randomised in a 1:1 ratio to the two study arms (midostaurin: N = 360; placebo: N = 357). Randomisation was stratified according to FLT3 mutational status (ITD with an allele ratio of < 0.7 vs ITD with an allele ratio of ≥ 0.7 vs TKD).

In the induction phase, midostaurin or placebo was compared in combination with cytarabine and daunorubicin in a 7+3 regimen. Midostaurin or placebo was given following chemotherapy. Patients who did not achieve a complete remission after the first cycle received another cycle of induction therapy.

Patients who achieved a complete remission with induction therapy received consolidation therapy with midostaurin or placebo in combination with high-dose cytarabine. Patients could also receive stem cell transplantation as consolidation therapy at the doctor's discretion. However, stem cell transplantation was not part of the study treatment. Following consolidation therapy, maintenance therapy was carried out with daily administration of midostaurin or placebo for 12 cycles of 28 days each.

Due to the potential presence of age-related, biologically unfavourable subentities of AML and possible comorbidities, older patients with AML have a significantly poorer prognosis compared to younger patients. Since the RATIFY study was only conducted with patients up to the age of 60 years, there are uncertainties regarding the transferability of the results of the study to older patients, especially since the dosage of high-dose cytarabine (3 g/m²) used in the study in consolidation therapy does not correspond to the recommendations for older, "fit" patients of 1.5 g/m². Updated recommendations also refer to a maximum dosage of 1.5 g/m² cytarabine for younger patients as part of consolidation therapy.

For the implementation of the appropriate comparator therapy in the consolidation phase

For consolidation therapy, a patient-individual therapy consisting of chemotherapy and allogeneic stem cell transplantation, taking into account the subtype of AML, general condition and comorbidity, represents the appropriate comparator therapy.

Stem cell transplantation, although not part of the study treatment, was documented for 60.8% of patients in the intervention arm and 55.5% of patients in the comparator arm during the course of the study. Here, 86.3% of stem cell transplantations in the intervention arm and 88.9% of stem cell transplantations in the comparator arm were labelled as "allogeneic" stem cell transplantation. In its written statement, the pharmaceutical company states that more than 75% of stem cell transplantations were performed prior to maintenance therapy. During the oral hearing in the present benefit assessment procedure, the German Society for Haematology and Medical Oncology explained that stem cell transplantation does not necessarily have to be carried out directly following induction therapy, but can also be carried out after bridging with one or a maximum of two consolidation cycles. The specific percentage of patients who received allogeneic stem cell transplantation after a maximum of two consolidation cycles is not clear from the pharmaceutical company's written statement.

As stem cell transplantation was not part of the study treatment, the decision criteria for performing allogeneic stem cell transplantation were not documented in the RATIFY study.

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Uncertainties therefore arise as to whether allogeneic stem cell transplantation was actually carried out for all patients for whom allogeneic stem cell transplantation was indicated based on the patient-individual decision criteria. During the oral hearing, the DGHO (German Society for Haematology and Medical Oncology) stated that the percentage of stem cell transplantation patients in the RATIFY study was sufficiently representative of the German healthcare context and that the decision criteria for performing allogeneic stem cell transplantation had not changed significantly between the study period of the RATIFY study and the current healthcare context. The comorbidity and general condition of the patients, which are also part of the patient-individual criteria for the treatment decision defined in the appropriate comparator therapy, were named as key decision factors in the healthcare context.

The implementation of the appropriate patient-individual therapy in the consolidation phase is therefore subject to uncertainties, but is considered sufficient overall for an assessment of the study data.

For the implementation of the appropriate comparator therapy in the maintenance phase

For maintenance therapy, a patient-individual therapy with the choice of azacitidine (only for subjects who are unsuitable for allogeneic stem cell transplantation), sorafenib (only for subjects with FLT3-ITD mutation after allogeneic stem cell transplantation) and monitoring wait-and-see approach (only for subjects without FLT3-ITD mutation after allogeneic stem cell transplantation), taking into account induction and consolidation therapy as well as the FLT3 mutational status, represents the appropriate comparator therapy.

In the RATIFY study, a placebo was used in the comparator arm for maintenance therapy. Taking into account the relevant aspects of the study implementation, it is considered a sufficient approximation to the monitoring wait-and-see approach. According to the appropriate comparator therapy, monitoring wait-and-see approach is only a suitable treatment option for patients with FLT3-TKD mutation after allogeneic stem cell transplantation, but in the RATIFY study the percentage of these patients was only 11.7% (84 of 717 patients enrolled). In addition, there was no patient-individual therapy with azacitidine, sorafenib and monitoring wait-and-see approach, which is why the appropriate comparator therapy for the maintenance phase was not implemented overall in the RATIFY study.

On the additional analyses presented

Three additional analyses were submitted by the pharmaceutical company as part of the written statement procedure.

In the additional analysis 1, the pharmaceutical company only considers patients who have received stem cell transplantation. The implementation of the appropriate comparator therapy in maintenance therapy for stem cell transplantation patients cannot be assessed from the data submitted. In addition, the therapeutic indication of midostaurin is not restricted with regard to stem cell transplantation. The additional analysis 1 is considered unsuitable for the benefit assessment and is not used.

In additional analysis 2, the pharmaceutical company only considered stem cell transplantation patients with an FLT3-TKD mutation. Patients with FLT3-TKD mutations represent only a small subgroup of the present therapeutic indication. Accordingly, the

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presented additional analysis 2 addresses only 11.7% of the study population of the RATIFY study. Therefore, the overall significance of this additional analysis is assessed as too low to derive sufficiently reliable conclusions for the assessment of the additional benefit of midostaurin.

In additional analysis 3, the pharmaceutical company censored the patients at the start of maintenance therapy and presented results on the endpoints of overall survival, event-free survival (EFS) and disease-free survival (DFS). Only the treatment phases of induction and consolidation therapy which cover an observation period of only 6 months are therefore considered in this additional analysis. Taking into account the 10-year follow-up in the RATIFY study, this period is considered insufficient to conduct an assessment of additional benefit on this basis. In addition, further events covered by the EFS endpoint occur to a relevant extent after 6 months. It cannot be concluded with sufficient certainty that the effect observed in this period will persist in the maintenance phase or in the follow-up phase if these treatment phases are considered alone. Irrespective of these aspects, the approved therapeutic indication of midostaurin also includes maintenance therapy as an integral component. The presented additional analysis 3 is therefore unsuitable for the assessment of the additional benefit for the entire approved therapeutic indication of midostaurin consisting of induction, consolidation and maintenance therapy. Therefore, the additional analysis 3 is not used for the benefit assessment.

Conclusion on the suitability of the data from the RATIFY study

Overall, it should be noted that the appropriate comparator therapy for maintenance therapy was not implemented in the RATIFY study. The additional analyses submitted with the written statement also do not represent a sufficiently suitable data basis for the assessment. The RATIFY study data therefore do not allow an assessment of the additional benefit compared to the present appropriate comparator therapy.

A2220 study

The study A2220 consists of two parts. The first part of the study is an open-label, single-arm study investigating the risk profile and tolerability of midostaurin in Japanese patients.

The second part of the study was randomised and double-blind and also enrolled patients outside Japan. A total of 62 patients were enrolled and randomised in a 1:1 ratio to the two study arms (midostaurin: N = 30; placebo: N = 32). Randomisation was stratified according to the chemotherapy regimen used and FLT3 mutational status (ITD with an allele ratio of < 0.7 vs ITD with an allele ratio of ≥ 0.7 vs TKD). The second part of this study was conducted analogue to the RATIFY study. However, the patients in Japan could also be treated with the JALSG regimen in induction and consolidation therapy. The JALSG regimen consists of the same active ingredients as in the RATIFY study, but differs in terms of dosage and dosing interval. Stem cell transplantation as consolidation therapy was not explicitly planned in this study either, but could be carried out at the doctor's discretion following induction therapy. The study medication was discontinued before stem cell transplantation and was not allowed to be resumed afterwards.

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Analogue to the RATIFY study, the appropriate comparator therapy was not implemented in the maintenance therapy of the A2220 study. The A2220 study is therefore unsuitable for the benefit assessment.

AMLSG 16-10 study

AMLSG is a single-arm study enrolled 440 patients aged 18 to 70 years with a FLT3-ITD mutation and diagnosed AML, AML-related myeloid precursor neoplasm or acute leukaemia of unclear lineage. The disease must not have been treated with chemotherapy.

The patients received induction therapy in accordance with the RATIFY study. Allogeneic stem cell transplantation should be performed as the primary consolidation therapy. If patients were unsuitable for stem cell transplantation, they were treated with 4 cycles of cytarabine as part of consolidation therapy. Following consolidation therapy, all patients received one year of maintenance therapy with midostaurin.

In the AMLSG 16-10 study, midostaurin was not used in accordance with its marketing authorisation as maintenance therapy after stem cell transplantation. Midostaurin is only approved as maintenance therapy after consolidation with high-dose chemotherapy.

The results of the AMLSG 16-10 study were compared with an external control cohort consisting of 415 patients from 5 studies between 1993 and 2009. The enrolled patients received induction therapy with 1 to 3 cycles of idarubicin, cytarabine and etoposide, followed by high-dose cytarabine-based consolidation therapy. The decision to carry out stem cell transplantation was at the doctor's discretion. Induction therapy consisting of idarubicin, cytarabine and etoposide is not an appropriate comparator therapy. In addition, maintenance therapy was largely not carried out.

The pharmaceutical company conducted and submitted a further comparison between the AMLSG 16-10 study and the control arm of the RATIFY study.

Due to the lack of implementation of the appropriate comparator therapy in the external control cohorts and the off-label use of midostaurin in the AMLSG 16-10 study, the study data and the indirect comparisons presented are unsuitable for the benefit assessment.

Overall assessment

For the present reassessment of midostaurin due to exceeding the 30 million euro limit of the orphan drug, the pharmaceutical company presents the results from the RATIFY, A2220 and AMLSG 16-10 studies for the demonstration of additional benefit in the treatment of newly diagnosed acute myeloid leukaemia (AML) with an FLT3 mutation. The A2220 and AMLSG 16-10 studies as well as the indirect comparisons presented with the AMLSG 16-10 study are unsuitable for the benefit assessment due to the lack of implementation of the appropriate comparator therapy or the off-label use of midostaurin.

The RATIFY study is a randomised, controlled study on the use of midostaurin in induction, consolidation and maintenance therapy. With regard to maintenance therapy, the present appropriate comparator therapy has not been implemented in the RATIFY study. The additional analyses submitted with the written statement also do not represent a sufficiently suitable data basis for the assessment. The RATIFY study data therefore do not allow an assessment of the additional benefit compared to the present appropriate comparator therapy.

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Overall, it is clear from the present guideline recommendation and the statement of the scientific-medical society in the present 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 is accorded a correspondingly high priority in the treatment of patients with acute myeloid leukaemia and FLT3 mutation in the current medical treatment situation. However, taking into account the requirements of Section 6 paragraph 2 sentence 2 AM-NutzenV, midostaurin cannot be determined as an appropriate comparator therapy for the present benefit assessment in this procedure. Depending on the induction and consolidation therapy, other medicinal products are recommended in addition to midostaurin for maintenance therapy.

Thus, an additional benefit of midostaurin in adults with newly diagnosed acute myeloid leukaemia (AML) who are FLT3 mutation-positive in combination with standard chemotherapy with daunorubicin and cytarabine for induction and with high-dose chemotherapy with cytarabine for consolidation and subsequently as monotherapy for maintenance therapy in patients in complete remission compared with the appropriate comparator therapy for the present resolution is not proven.

2.1.4 Summary of the assessment

The present assessment is a new benefit assessment of the medicinal product Rydapt with the active ingredient midostaurin due to the exceeding of the € 30 million turnover limit. Rydapt was approved as an orphan drug. The therapeutic indication assessed here is as follows:

"Rydapt is indicated in combination with standard daunorubicin and cytarabine induction and high-dose cytarabine consolidation chemotherapy, and for patients in complete response followed by Rydapt single agent maintenance therapy, for adult patients with newly diagnosed acute myeloid leukaemia (AML) who are FLT3 mutation-positive."

To demonstrate the additional benefit of midostaurin, the pharmaceutical company is presenting the study data from the RATIFY, A2220 and AMLSG 16-10 studies.

Induction chemotherapy followed by patient-individual consolidation therapy with a choice of chemotherapy and allogeneic stem cell transplantation and subsequent patient-individual maintenance therapy with a choice of azacitidine, sorafenib and monitoring wait-and-see approach was determined as the appropriate comparator therapy.

The A2220 and AMLSG 16-10 studies as well as the indirect comparisons presented with the AMLSG 16-10 study are unsuitable for the benefit assessment due to the lack of implementation of the appropriate comparator therapy or the off-label use of midostaurin.

With regard to maintenance therapy, the present appropriate comparator therapy has not been implemented in the RATIFY study. The RATIFY study data therefore do not allow an assessment of the additional benefit compared to the present appropriate comparator therapy.

No suitable data are available for a comparison with the appropriate comparator therapy defined for the present resolution.

An additional benefit of midostaurin 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).

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The resolution is based on the information from the dossier assessment of the IQWiG (mandate A23-110).

The G-BA considers the patient numbers specified by the pharmaceutical company in the dossier as the upper limit. The information provided by the pharmaceutical company is fraught with various uncertainties.

The pharmaceutical company uses a routine data analysis to determine the incidence. The extent to which the diagnosis codes used are suitable for data collection from only newly diagnosed patients is unclear. In addition, the pharmaceutical company does not submit a study report on the routine data analysis, so that the methodological procedure of the routine data analysis is not fully comprehensible.

Additional uncertainties exist with regard to the percentage value for an FLT3 mutation, which does not relate exclusively to newly diagnosed patients. The transferability of this percentage value to incidence sample sizes is subject to uncertainties. The percentage of patients suitable for intensive chemotherapy was determined independently of FLT3 mutational status. It is unclear whether these percentages can be transferred to an exclusively FLT3-mutated AML population. In addition, there are uncertainties as to whether the OPS codes taken into account represent the entirety of the intensive chemotherapy treatments carried out in this therapeutic indication. This leads to further uncertainties with regard to the determined percentage value for suitability for intensive chemotherapy.

The patient numbers from the first benefit assessment of midostaurin (resolution of 05.04.2017) is used as the lower limit. By using the lower limit from the initial resolution, the overall range of the patient numbers is increased and the uncertainties described are better taken into account.

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 Rydapt (active ingredient: midostaurin) at the following publicly accessible link (last access: 25 March 2024):

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

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

FLT3 detection

Before taking midostaurin, a FLT3 mutation (as internal tandem duplication [ITD] or in the tyrosine kinase domain [TKD]) must be confirmed with a validated test.

2.4 Treatment costs

The treatment costs are based on the requirements in the product information and the information listed in the LAUER-TAXE® (last revised: 15 April 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.

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

There is no marketing authorisation for sorafenib as maintenance therapy 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.[6]

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.

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				
Midostaurin	2x daily on 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
Consolidation therapy				
Midostaurin	Day 8 - 21: 28-day cycle	4	14	56
Cytarabine	2x daily on day 1, 3, 5: 28-day cycle	4	3	12
Maintenance therapy				

[6] 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.

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Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Midostaurin	2x daily on day 1-28: 28-day cycle	6.9 - 7.7	28	194 - 218
Appropriate comparator therapy				
Induction therapy				
Cytarabine + daunorubicin				
Cytarabine	Day 1 - 7: 28-day cycle	1 - 2	7	7 - 14
Daunorubicin	Day 1 - 3: 28-day cycle	1 - 2	3	3 - 6
Cytarabine + idarubicin				
Cytarabine	Day 1 - 7: 28-day cycle	1 - 2	7	7 - 14
Idarubicin	Day 1 - 3: 28-day cycle	1 - 2	3	3 - 6
Cytarabine + mitoxantrone				
Cytarabine	Day 1 - 7: 28-day cycle	1 - 2	7	7 - 14
Mitoxantrone	Day 1 - 3: 28-day cycle	1 - 2	3	3 - 6
Daunorubicin/ cytarabine (liposomal formulation)				
Daunorubicin/ cytarabine (liposomal formulation)	1st cycle: Day 1, 3, 5 2nd cycle: Day 1, 3 28-day cycle	1 - 2	1st cycle: 3 2nd cycle: 2	3 - 5
Consolidation therapy				
High-dose cytarabine				
Cytarabine	2x daily on day 1, 3, 5: 28-day cycle	4	3	12
Daunorubicin/ cytarabine (liposomal formulation)				
Daunorubicin/ cytarabine (liposomal formulation)	Day 1, 3: 28-day cycle	1 - 2	2	2 - 4
High-dose chemotherapy with allogeneic stem cell transplantation				

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Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Highly complex and intensive block chemotherapy	once	12.4 (average length of stay)	12.4	Highly complex and intensive block chemotherapy
Allogeneic stem cell transfusion	once	34.4 - 37.8 (average length of stay)	34.4 - 37.8	Allogeneic stem cell transfusion
Maintenance therapy				
Oral azacitidine	Day 1 - 14: 28-day cycle	7 - 10.8	14	98 - 151
Sorafenib[6]	Day 1 - 28: 28-day cycle	5.6 - 9.3	28	158-260

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)[7].

For the cost representation, only the dosages of the general case are considered. Patient-individual dose adjustments (e.g. because of side effects or comorbidities) 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					
Midostaurin	50 mg	100 mg	4 x 25 mg	14 - 28	56 - 112 x 25 mg
Cytarabine	200 mg/m²	382 mg	4 x 100 mg	7 - 14	28 - 56 x 100 mg
Daunorubicin	60 mg/m²	114.6 mg	6 x 20 mg	3 - 6	18 - 36 x 20 mg
Consolidation therapy					

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

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Designation of the therapy	Dosage/ application	Dose/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
Midostaurin	50 mg	100 mg	4 x 25 mg	56	224 x 25 mg
Cytarabine	3 g/m²	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 therapy					
Midostaurin	50 mg	100 mg	4 x 25 mg	201 - 225	776 - 872 x 25 mg
Appropriate comparator therapy					
Induction therapy					
Cytarabine + daunorubicin					
Cytarabine	100 - 200 mg/m²	191 - 382 mg	2 - 4 x 100 mg	7 - 14	14 - 56 x 100 mg
Daunorubicin	60 mg/m²	114.6 mg	6 x 20 mg	3 - 6	18 - 36 x 20 mg
Cytarabine + idarubicin					
Cytarabine	100 - 200 mg/m²	191 - 382 mg	2 - 4 x 100 mg	7 - 14	14 - 56 x 100 mg
Idarubicin	12 mg/m²	22.92 mg	1 x 20 mg 1 x 5 mg	3 - 6	3 - 6 x 20 mg 3 - 6 x 5 mg
Cytarabine + mitoxantrone					
Cytarabine	100 mg/m²	191 mg	2 x 100 mg	7 - 14	14 - 28 x 100 mg
Mitoxantrone	12 mg/m²	22.92 mg	1 x 25 mg	3 - 6	3 - 5 x 25 mg
Daunorubicin/ cytarabine (liposomal formulation)					
Daunorubicin/ cytarabine (liposomal formulation)	44 mg/m² / 100 mg/m²	84.0 mg/ 191.0 mg	2 x 44 mg/ 100 mg	3 - 5	6 - 10 x 44 mg /100 mg
Consolidation therapy					
High-dose cytarabine					
Cytarabine	3 g/m²	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
Daunorubicin/ cytarabine (liposomal formulation)					
Daunorubicin/ cytarabine (liposomal formulation)	29 mg/m² / 65 mg/m²	55.4 mg/ 124.2 mg	2 x 44 mg/ 100 mg	1 - 2	4 - 8 x 44 mg/ 100 mg

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Designation of the therapy	Dosage/ application	Dose/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
Maintenance therapy					
Oral azacitidine	300 mg	300 mg	1 x 300 mg	98 - 151	98 - 151 x 300 mg
Sorafenib[6]	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

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

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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					
Midostaurin 25 mg	4 x 28 SC	15,991.76	€ 2.00	€ 910.00	€ 15,079.76
Cytarabine 100 mg	10 SFI	€ 48.87	€ 2.00	€ 1.78	€ 45.09
Daunorubicin 20 mg	1 PII	€ 46.11	€ 2.00	€ 8.66	€ 35.45
Consolidation therapy					
Midostaurin 25 mg	4 x 28 SC	15,991.76	€ 2.00	€ 910.00	€ 15,079.76
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 therapy					
Midostaurin 25 mg	4 x 28 SC	15,991.76	€ 2.00	€ 910.00	€ 15,079.76
Appropriate comparator therapy					
Induction therapy					
Cytarabine + daunorubicin					
Cytarabine 100 mg	10 SFI	€ 48.87	€ 2.00	€ 1.78	€ 45.09
Daunorubicin 20 mg	1 PII	€ 46.11	€ 2.00	€ 8.66	€ 35.45
Cytarabine + idarubicin					
Cytarabine 100 mg	10 SFI	€ 48.87	€ 2.00	€ 1.78	€ 45.09
Idarubicin 5 mg	1 CIS	€ 181.53	€ 2.00	€ 8.08	€ 171.45
Idarubicin 20 mg	1 CIS	€ 678.36	€ 2.00	€ 31.66	€ 644.70
Cytarabine + mitoxantrone					
Cytarabine 100 mg	10 SFI	€ 48.87	€ 2.00	€ 1.78	€ 45.09
Mitoxantrone 25 mg	1 IFB	€ 366.28	€ 2.00	€ 19.65	€ 344.63
Daunorubicin/ cytarabine (liposomal formulation)					
Daunorubicin/ cytarabine (liposomal formulation) 44 mg/100 mg	1 PIC	€ 6,370.01	€ 2.00	€ 360.50	€ 6,007.51
Consolidation therapy					
High-dose cytarabine					
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
Daunorubicin/ cytarabine (liposomal formulation)					
Daunorubicin/ cytarabine (liposomal formulation) 44 mg/100 mg	1 PIC	€ 6,370.01	€ 2.00	€ 360.50	€ 6,007.51
Maintenance therapy					
Oral azacitidine 300 mg	14 FCT	€ 17,619.24	€ 2.00	€ 1,002.95	€ 16,614.29
Sorafenib 200 mg	112 FCT	€ 371.26	€ 2.00	€ 17.08	€ 352.18

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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
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 01.10.2009 is not fully used to calculate costs. Alternatively, the pharmacy sales price publicly accessible in the directory services according to Section 131 paragraph 4 SGB V is a suitable basis for a standardised calculation.

According to the currently valid version of the special agreement on contractual unit costs of retail pharmacist services (Hilfstaxe), surcharges for the production of parenteral preparations containing cytostatic drugs a maximum amount of € 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.

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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.

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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

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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.

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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) who are FLT3 mutation-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 midostaurin (Rydapt); product information for Rydapt® 25 mg soft capsules; last revised: June 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 20 December 2022, the Subcommittee on Medicinal Products determined the appropriate comparator therapy.

Against the background of the legal requirements introduced with the ALBVVG (Act to Combat Supply Shortages and Improve the Supply of Medicines) for the determination of the off-label use of medicinal products by way of exception, the appropriate comparator therapy was reviewed and newly implemented on 28 November 2023.

On 13 November 2023, the pharmaceutical company submitted a dossier for the benefit assessment of midostaurin to the G-BA in due time in accordance with Chapter 5 Section 8, paragraph 1, number 1, sentence 2 VerfO.

By letter dated 14 November 2023 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 midostaurin.

The dossier assessment by the IQWiG was submitted to the G-BA on 13 February 2024, and the written statement procedure was initiated with publication on the G-BA website on 15 February 2024. The deadline for submitting statements was 07 March 2024.

The oral hearing was held on 25 March 2024.

By letter dated 27 March 2024, the IQWiG was commissioned with a supplementary assessment. The addendum prepared by IQWiG was submitted to the G-BA on 12 April 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

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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 April 2024, and the proposed resolution was approved.

At its session on 2 May 2024, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee Medicinal products	20 December 2022	Implementation of the appropriate comparator therapy
Subcommittee Medicinal products	28 November 2023	New implementation of the appropriate comparator therapy
Working group Section 35a	20 March 2024	Information on written statements received, preparation of the oral hearing
Subcommittee Medicinal products	25 March 2024	Conduct of the oral hearing, if necessary: Commissioning of the IQWiG with the supplementary assessment of documents
Working group Section 35a	4 March 2024 17 April 2024	Consultation on the dossier evaluation by the IQWiG and evaluation of the written statement procedure
Subcommittee Medicinal products	23 April 2024	Concluding discussion of the draft resolution
Plenum	2 May 2024	Adoption of the resolution on the amendment of the Pharmaceuticals Directive

Berlin, 2 May 2024

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

Prof. Hecken

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