Gemeinsamer Bundesausschuss

# Justification

for 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
Ivosidenib (reassessment of an orphan drug after exceeding the EUR 30 million limit: acute myeloid leukaemia with IDH1 R132 mutation, first-line, in combination with azacitidine)

From 20 August 2026

**Contents**

## 1. Legal basis

According to Section 35a paragraph 1 German Social Code, Book Five (SGB V), the Federal Joint Committee (G-BA) assess the benefit of all reimbursable medicinal products with new active ingredients. 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 studies the pharmaceutical company have 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 decide 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 ivosidenib (Tibsovo) was listed for the first time on 15 July 2023 in the "LAUER-TAXE®", the extensive German registry of available drugs and their prices. Tibsovo® for the treatment of 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 their session on 18 January 2024, the G-BA decided on the benefit assessment of ivosidenib for the therapeutic indication "in combination with azacitidine is indicated for the treatment of adult patients with newly diagnosed acute myeloid leukaemia (AML) with an isocitrate dehydrogenase-1 (IDH1) R132 mutation who are not eligible to receive standard induction chemotherapy" according to Section 35a SGB V.

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 Chapter 5 Section 5, paragraphs 1 to 6 Rules of Procedure (VerfO) 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.

By letter dated 24 November 2025, the pharmaceutical company was requested to submit a dossier for the benefit assessment according to Section 35a SGB V by 1 March 2026, due to exceeding the EUR 30 million turnover limit within the period from January 2024 to December 2024. Pursuant to Section 4, paragraph 3, number 4 of the Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with Chapter 5 Section 8, paragraph 1, number 6 of the Rules of Procedure (VerfO), the pharmaceutical company submitted the final dossier to the G-BA on 27 February 2026.

The G-BA commissioned the IQWiG to carry out the assessment of the dossier. The benefit assessment was published on 1 June 2026 on the G-BA website at (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 ivosidenib 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, the statements submitted in the written statement and oral hearing procedure, and the addendum to the benefit assessment prepared by IQWiG. In order to determine the extent of the additional benefit, the G-BA have 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 ivosidenib.

In the light of the above, and taking into account the statements received and the oral hearing, the G-BA have made 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 ivosidenib (Tibsovo) in accordance with the product information

Tibsovo in combination with azacitidine is indicated for the treatment of adult patients with newly diagnosed acute myeloid leukaemia (AML) with an isocitrate dehydrogenase-1 (IDH1) R132 mutation who are not eligible to receive standard induction chemotherapy.

**Therapeutic indication of the resolution (resolution of 20 August 2026):**

See the approved therapeutic indication

[1] General Methods, version 8.0 from 19.12.2025. Institute for Quality and Efficiency in Health Care (IQWiG), Cologne.

### 2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

Adults with newly diagnosed acute myeloid leukaemia (AML) with an isocitrate dehydrogenase-1 (IDH1) R132 mutation who are not eligible to receive standard induction chemotherapy

**Appropriate comparator therapy**:

- venetoclax in combination with azacitidine

*or*

- venetoclax in combination with decitabine

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 according to 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 they determine 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 for 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 for 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 ivosidenib, medicinal products with the following active ingredients are approved for the present therapeutic indication: Azacitidine, cytarabine, daunorubicin, decitabine, decitabine/ cedazuridine, doxorubicin, etoposide, glasdegib, histamine dihydrochloride, idarubicin, mitoxantrone, tioguanine and venetoclax.

On 2. No non-medicinal treatment options are considered for patients with newly diagnosed AML with an IDH1 R132 mutation who are not eligible to receive standard induction chemotherapy.

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

- Decitabine/ cedazuridine (resolution of 15 August 2024)
- Ivosidenib (resolution of 18 January 2024)
- Venetoclax (resolution of 2 December 2021)
- Glasdegib (resolution of 18 February 2021)
- Decitabine (resolution of 2 May 2013)

Annex VI to Section K of the Pharmaceuticals Directive (last revised: 10 August 2024) – Medicinal products that are prescribable for unapproved therapeutic indications (off-label use):

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

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

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

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

When determining the appropriate comparator therapy, it is assumed that, within the therapeutic indication, none of the patients are eligible for best supportive care alone at the time of treatment. Furthermore, the fact that patients with acute promyelocytic leukaemia differ in terms of aetiology and therapeutic approach is taken into account. It is assumed that treatment with ivosidenib in combination with azacitidine is not indicated for this patient population.

These guidelines designate ivosidenib in combination with azacitidine and venetoclax in combination with a hypomethylating agent (HMA; azacitidine or decitabine) as first-line therapy options for patients with newly diagnosed AML with an IDH1 R132 mutation who are not eligible to receive standard induction chemotherapy. As alternatives, venetoclax in combination with LDAC (low-dose cytarabine) and the monotherapies azacitidine and decitabine are designated.

Ivosidenib is specifically approved for patients with an IDH1 R132 mutation. According to Section 6, paragraph 2, sentence 2 of the 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. Accordingly, ivosidenib in combination with azacitidine is not considered an appropriate comparator therapy.

Regardless of the mutational status, the present guidelines recommend venetoclax-based HMA combination therapies as the preferred option over monotherapies for patients with newly diagnosed AML who are not eligible to receive standard induction chemotherapy. The present systematic reviews indicate an advantage of venetoclax-based combination therapies over chemotherapy alone in terms of overall survival in patients with AML.

Venetoclax in combination with a hypomethylating agent is approved for the treatment of adults with newly diagnosed AML who are not eligible to receive intensive chemotherapy. In the benefit assessment, the combination of venetoclax with an HMA (azacitidine or decitabine) was found to provide a hint of a considerable additional benefit compared with azacitidine (G-BA resolution of 2 December 2021). No data on the combination therapy of venetoclax and decitabine were submitted for the benefit assessment. In the context of the marketing authorisation, the effect of venetoclax in combination with azacitidine was extrapolated to venetoclax in combination with decitabine on the basis of the comparable mode of action. Uncertainties remained in the benefit assessment regarding the extent to which the results - on which the assessment was based - from the Viale-A study on patient-relevant therapeutic effects can be transferred to the combination venetoclax + decitabine, particularly with regard to the quantification of the extent of the additional benefit. Taking this uncertainty into account, the G-BA nevertheless considered it appropriate to assess the extent and probability of additional benefit beyond venetoclax in combination with the HMA azacitidine on the basis of the Viale-A study. Therefore, venetoclax in combination with azacitidine and venetoclax in combination with decitabine are determined as appropriate comparator therapies.

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

Glasdegib in combination with LDAC is also approved for this therapeutic indication, regardless of mutational status. A hint of a considerable additional benefit of glasdegib in combination with low-dose cytarabine over low-dose cytarabine was identified in the benefit assessment by the resolution of 18 February 2021. The NCCN guideline does not designate glasdegib in combination with LDAC as a recommended therapy option

for patients with an IDH-1 mutation. Furthermore, the present guidelines recommend glasdegib in combination with LDAC over venetoclax-based combination therapies as a second-line therapy option for patients with AML whose mutational status has not been specified. Glasdegib in combination with LDAC is therefore not included in the appropriate comparator therapy for patients with an IDH-1 mutation.

Decitabine/ cedazuridine as monotherapy is approved as an additional therapy option. No additional benefit over the appropriate comparator therapy could be established in the benefit assessment by the resolution of 15 August 2024, as no assessable data were available. Decitabine/ cedazuridine as an oral HMA formulation is not explicitly mentioned in these guidelines. In line with the preference for venetoclax-based combination therapies, decitabine/ cedazuridine as monotherapy is not included in the appropriate comparator therapy.

The combination of active ingredients decitabine/ cedazuridine plus venetoclax also offers a new treatment option in this therapeutic indication. The combination of active ingredients was only recently approved (marketing authorisation on 19.06.2026). Based on the generally recognised state of medical knowledge, decitabine/ cedazuridine in combination with venetoclax is not determined as an appropriate comparator therapy for the present resolution.

The DGHO's written statement recommends venetoclax in combination with an HMA and ivosidenib in combination with azacitidine as equivalent therapy options for patients with newly diagnosed AML and an IDH1 R132 mutation who are not eligible to receive standard induction chemotherapy.

Also, during the written statement procedure and the oral hearing, the clinical experts confirmed the significance of ivosidenib in combination with azacitidine and venetoclax in combination with HMA as the therapy standard in this therapeutic indication. According to the clinical assessment experts, HMA monotherapies are only used when combination therapy is not feasible.

In the overall assessment, the G-BA determined both venetoclax in combination with azacitidine and venetoclax in combination with decitabine as equally appropriate comparator therapies for adults with newly diagnosed acute myeloid leukaemia (AML) with an isocitrate dehydrogenase-1 (IDH1) R132 mutation who are not eligible to receive standard induction chemotherapy.

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

Any change to the appropriate comparator therapy requires a decision by the G-BA based on a prior review of the criteria set out in Chapter 5 Section 6, paragraph 3 VerfO.

### 2.1.3 Extent and probability of the additional benefit

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

An additional benefit is not proven.

Justification:

The pharmaceutical company submitted the data from the AGILE study for the benefit assessment of ivosidenib in combination with azacitidine for the treatment of adults with newly diagnosed acute myeloid leukaemia (AML) with an IDH1 R132 mutation who are not eligible to receive standard induction chemotherapy. This is a comparison between ivosidenib

in combination with azacitidine and placebo in combination with azacitidine. The appropriate comparator therapy was not implemented in the AGILE study. The comparator data from the AGILE study therefore do not allow an assessment of the additional benefit compared to the present appropriate comparator therapy.

As part of the written statement procedure, the pharmaceutical company submitted indirect comparisons of ivosidenib in combination with azacitidine versus the appropriate comparator therapy, venetoclax in combination with azacitidine, as supportive evidence.

The subsequently submitted comparisons are indirect comparisons according to Bucher with or without inverse variance (IV) weighting of ivosidenib in combination with azacitidine versus venetoclax in combination with azacitidine, using azacitidine plus placebo as the bridge comparator. To this end, the AGILE study was included on the intervention side and the VIALE-A study on the comparator side. The presented indirect comparisons according to Bucher are based, on the one hand, on the total population or the G-BA population and, on the other, on a post-hoc IDH1 sub-population from the VIALE-A study (according to Bucher with inverse variance (IV) weighting).

About the AGILE study

The AGILE study is a randomised, multicentre, controlled phase III study, ongoing since March 2018, comparing ivosidenib in combination with azacitidine versus placebo in combination with azacitidine in adult patients with newly diagnosed AML with an IDH1 R132 mutation who are not eligible to receive standard induction chemotherapy. The patients were aged ≥ 75 years, had an ECOG performance status (PS) of 2 and were not permitted to have any severe heart or lung conditions.

The study is being conducted in 199 study sites across Australia, Europe, Asia, and North and South America. Patients were randomised in a 1:1 ratio (ivosidenib arm N = 72; control arm N = 74). Patients were on average 76 years old, about 63% had intermediate risk and 25% poor risk.

The primary endpoint was changed from "overall survival" to "event-free survival" during the course of the study.

For the indirect comparisons, the pharmaceutical company considered the data cut-offs from 18 March 2021 and 30 June 2022 on the intervention side.

About the VIALE-A study

The Viale-A study is a double-blind, randomised, controlled, multicentre phase III study comparing the combination therapy of venetoclax and azacitidine with placebo plus azacitidine. The study ongoing since 2017 enrolled adults with previously untreated AML (according to WHO criteria[2]) who are not eligible to receive standard induction therapy with cytarabine and an anthracycline. Here, patients ≥ 75 years of age had an ECOG-PS of 0-2 while those ≥ 18 to 74 years of age had an ECOG-PS of 0-3. In addition, only patients with intermediate or poor cytogenetic risk (according to the National Comprehensive Cancer Network [NCCN] classification, 2017) were enrolled, and not patients with low risk.

A total of 134 study sites across Europe (including Germany), North and South America, Asia and the rest of the world were involved. Of a total of 433 patients, 287 were assigned to the

[2] Arber DA et al. The 2016 revision to the World Health Organisation classification of myeloid neoplasms and acute leukaemia. Blood 2016; 127(20): 2391-2405.

intervention arm (venetoclax + azacitidine) and 146 to the control arm (placebo + azacitidine). Patients were on average 78 years old, about 65% had intermediate risk and 35% poor risk. Patients were enrolled in the VIALE-A study regardless of whether they had an IDH1 mutation. In total, 10% of the study population enrolled had such a mutation (23 vs 21 patients in the intervention and comparator arms, respectively).

For the VIALE-A study, analyses of the total population as well as analyses of a sub-population (G-BA population; N = 210 vs N = 103) used in the benefit assessment of venetoclax (resolution of 2 December 2021) are available. The criteria for unsuitability for intensive standard induction therapy were defined more narrowly for this sub-population: Patients ≥ 75 years of age with at least one other pre-existing disease, patients < 75 years of age with ECOG-PS 2 and at least one other pre-existing disease, and patients < 75 years of age with ECOG-PS 3, regardless of other pre-existing diseases. These more stringent criteria make the VIALE-A study population more similar to the AGILE study population in terms of the inclusion criteria.

For the comparator side of the indirect comparisons, the pharmaceutical company considered the data cut-offs from 4 January 2020 and 1 December 2021 for the VIALE-A total study population and the data cut-off from 4 July 2020 for the G-BA population.

Assessment of the indirect comparisons

A core requirement for the consideration of studies in the indirect comparison via a bridge comparator is the similarity between the studies. The AGILE and VIALE-A studies are randomised, double-blind, multicentre studies which began in March 2018 and February 2017, respectively, and are still ongoing. Their study durations are therefore comparable. Even in terms of inclusion criteria, the AGILE study is broadly comparable with the G-BA population of the VIALE-A study, particularly given their similar criteria for determining the unsuitability for standard induction therapy.

However, there are significant differences between the two studies with regard to the characteristics of the patients enrolled. The AGILE study enrolled only patients with an IDH1 R132 mutation, whereas only 10% of patients in the VIALE-A study had this mutation. Although the pharmaceutical company defines a sub-population of IDH1 patients in the VIALE-A study, the lack of patient characteristics of this population leaves it unclear to what extent the IDH1 mutation acts as a potential effect modifier during treatment with venetoclax in combination with azacitidine. This uncertainty is supported by analyses of the IDH1 sub-population of the VIALE-A study, which showed a significantly shorter median overall survival (2.2 months) in the VIALE-A study than that observed in the azacitidine arm of the AGILE study (7.9 months)[3].

Also, during the written statement procedure, the clinical experts pointed out that the two studies include highly heterogeneous patient populations and that a comparison is methodologically difficult, particularly given the small number of patients with an IDH1 mutation in the VIALE-A study.

There are also relevant differences between the patient populations in the two studies in terms of age, ECOG-PS and cytogenetic risk profile. Although the median age of 76 to 78 years appears to be comparable between the two study populations, there are differences in the age distributions within the populations of the respective studies. As a consequence, the percentage of patients aged 75 years and over in the VIALE-A study (G-BA population) is more

[3] DiNardo CD, Jonas BA, Pullarkat V et al. Azacitidine and Venetoclax in Previously Untreated Acute Myeloid Leukaemia. N Engl J Med 2020; 383(7): 617-629. https://doi.org/10.1056/NEJMoa2012971.

than 80%, significantly higher than the 56% in the AGILE study. A similar picture emerges with regard to health status, as assessed by the ECOG-PS, as the VIALE-A study, unlike the AGILE study, included a significant percentage of patients with an ECOG-PS of 3. The percentage of patients with a poor cytogenetic risk profile is also higher in the VIALE-A study than in the AGILE study.

It also remains unclear to what extent the alternative therapy regimen permitted in the AGILE study was used for the bridge comparator azacitidine, and whether the operationalisation of the endpoints for the indirect comparison is sufficiently comparable, as this was not investigated by the pharmaceutical company.

Overall, there is no similarity between the study populations of the AGILE and VIALE-A studies, either for the total population or for the G-BA population. It is therefore inappropriate to carry out an indirect comparison on the basis of these studies.

The indirect comparison between the AGILE study and the IDH sub-population of the VIALE-A study is assessed as inadequate due to the unverifiable patient characteristics as well as the methodological shortcomings.

As a result, the indirect comparisons presented are assessed as unsuitable overall for drawing conclusions on the additional benefit.

Conclusion

The pharmaceutical company presented the results from the AGILE study for this new assessment because the orphan drug ivosidenib for the treatment of newly diagnosed acute myeloid leukaemia (AML) with an IDH1 R132 mutation exceeded the EUR 30 million turnover limit. Furthermore, as part of the written statement procedure, the pharmaceutical company presented various indirect comparisons (according to Bucher) of ivosidenib in combination with azacitidine versus venetoclax in combination with azacitidine, using azacitidine plus placebo as the bridge comparator. To this end, the AGILE study was included on the intervention side and the VIALE-A study on the comparator side.

The AGILE study does not allow for a direct comparison with the appropriate comparator therapy and is therefore unsuitable for the assessment of the additional benefit.

The indirect comparisons presented are assessed as unsuitable overall for drawing conclusions on the additional benefit.

No adequate data are therefore available to allow an assessment of the additional benefit. Therefore, an additional benefit of ivosidenib in combination with azacitidine over the specified appropriate comparator therapy for this resolution is not proven for the treatment of adults with newly diagnosed acute myeloid leukaemia (AML) with an IDH1 R132 mutation who are not eligible to receive standard induction chemotherapy.

### 2.1.4 Summary of the assessment

The present assessment is the new benefit assessment of the active ingredient ivosidenib due to the EUR 30 million turnover limit being exceeded. Ivosidenib in combination with azacitidine was approved as an orphan drug. The therapeutic indication assessed here is as follows:

"Tibsovo in combination with azacitidine is indicated for the treatment of adult patients with newly diagnosed acute myeloid leukaemia (AML) with an isocitrate dehydrogenase-1 (IDH1) R132 mutation who are not eligible to receive standard induction chemotherapy."

Venetoclax in combination with azacitidine or venetoclax in combination with decitabine was determined as the appropriate comparator therapy.

The pharmaceutical company presented the results of the AGILE study. Furthermore, as part of the written statement procedure, the pharmaceutical company presented various indirect comparisons (according to Bucher) of ivosidenib in combination with azacitidine versus venetoclax in combination with azacitidine, using azacitidine plus placebo as the bridge comparator. To this end, the AGILE study was included on the intervention side and the VIALE-A study on the comparator side.

The AGILE study does not allow for a direct comparison with the appropriate comparator therapy and is therefore unsuitable for the assessment of the additional benefit.

The indirect comparisons presented are assessed as unsuitable overall for drawing conclusions on the additional benefit.

No adequate data are therefore available to allow an assessment of the additional benefit. Therefore, an additional benefit of ivosidenib in combination with azacitidine over the specified appropriate comparator therapy for this resolution is not proven for the treatment of adults with newly diagnosed acute myeloid leukaemia (AML) with an IDH1 R132 mutation who are not eligible to receive standard induction chemotherapy.

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

Adults with newly diagnosed acute myeloid leukaemia (AML) with an isocitrate dehydrogenase-1 (IDH1) R132 mutation who are not eligible to receive standard induction chemotherapy

The information on the number of patients is based on the target population in statutory health insurance (SHI).

The G-BA base their resolution on the patient numbers indicated by the pharmaceutical company in the dossier, which are higher compared to the initial assessment of ivosidenib. In particular, the data basis used to calculate incidence rates is more up to date and comprehensive, and the percentage of patients who are not eligible to receive intensive therapy is drawn from a more representative source. The pharmaceutical company's approach to determining patient numbers is largely plausible in mathematical and methodological terms. Although individual steps in the calculation are subject to uncertainty, it is generally assumed that the number of patients in the SHI target population is likely to fall within the specified range.

## 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 Tibsovo (active ingredient: ivosidenib) at the following publicly accessible link (last access: 21 May 2026):

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

Treatment with ivosidenib 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 (incl. patient identification card).

The training material contains, in particular, information and warnings about differentiation syndrome.

An electrocardiogram (ECG) must be performed before start of treatment and at least once a week during the first 3 weeks of therapy.

## 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 2026).

The calculation of treatment costs is generally based on the last revised LAUER-TAXE® version following the publication of the benefit assessment.

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

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

Treatment period:

Adults with newly diagnosed acute myeloid leukaemia (AML) with an isocitrate dehydrogenase-1 (IDH1) R132 mutation who are not eligible to receive standard induction chemotherapy

| Designation of the therapy | Treatment mode | Number of treatments/ patient/ year | Treatment duration/ treatment (days) | Treatment days/ patient/ year |
|---|---|---|---|---|
| Medicinal product to be assessed | | | | |
| Ivosidenib in combination with azacitidine | | | | |
| Ivosidenib | Continuously 1 x daily | 365.0 | 1 | 365.0 |
| Azacitidine | Day 1 - 7: 28-day cycle | 13.0 | 7 | 91.0 |
| Appropriate comparator therapy | | | | |
| Venetoclax in combination with azacitidine | | | | |
| Venetoclax | Continuously 1 x daily | 365.0 | 1 | 365.0 |
| Azacitidine | Day 1 - 7: 28-day cycle | 13.0 | 7 | 91.0 |
| Venetoclax in combination with decitabine | | | | |

| Designation of the therapy | Treatment mode | Number of treatments/ patient/ year | Treatment duration/ treatment (days) | Treatment days/ patient/ year |
|---|---|---|---|---|
| Venetoclax | Continuously 1 x daily | 365.0 | 1 | 365.0 |
| Decitabine | Day 1 - 5: 28-day cycle | 13.0 | 5 | 65.0 |

Consumption:

For dosages depending on body weight (BW) or body surface area (BSA), the average body measurements from the official representative statistics "2025 Microcensus – body measurements of the population" were applied (average body height: 1.73 m; average body weight: 78.3 kg). This results in a body surface area of 1.92 m² (calculated according to Du Bois 1916)[4].

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.

Adults with newly diagnosed acute myeloid leukaemia (AML) with an isocitrate dehydrogenase-1 (IDH1) R132 mutation who are not eligible to receive standard induction chemotherapy

| 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 | | | | | |
| Ivosidenib in combination with azacitidine | | | | | |
| Ivosidenib | 500 mg | 500 mg | 2 x 250 mg | 365.0 | 730.0 x 250 mg |
| Azacitidine | 75 mg/m² = 144 mg | 144 mg | 2 x 100 mg | 91.0 | 182.0 x 100 mg |
| Appropriate comparator therapy | | | | | |
| Venetoclax in combination with azacitidine | | | | | |
| Venetoclax | Day 1: 100 mg Day 2: 200 mg | Day 1: 100 mg Day 2: 200 mg | Day 1: 1 x 100 mg Day 2: 2 x 100 mg | 365.0 | 1,455 x 100 mg |

[4]Federal Health Reporting. Average body measurements of the population (2025, both sexes), 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 |
|---|---|---|---|---|---|
| | Afterwards: 400 mg | Afterwards: 400 mg | Afterwards: 4 x 100 mg | | |
| Azacitidine | 75 mg/m² = 144 mg | 144 mg | 2 x 100 mg | 91.0 | 182.0 x 100 mg |
| Venetoclax in combination with decitabine | | | | | |
| Venetoclax | Day 1: 100 mg<br>Day 2: 200 mg<br>Afterwards: 400 mg | Day 1: 100 mg<br>Day 2: 200 mg<br>Afterwards: 400 mg | Day 1: 1 x 100 mg<br>Day 2: 2 x 100 mg<br>Afterwards: 4 x 100 mg | 365.0 | 1,455 x 100 mg |
| Decitabine | 20 mg/m² = 38.4 mg | 38.4 mg | 1 x 50 mg | 65.0 | 65 x 50 mg |

Costs:

In order to improve comparability, the costs of the medicinal products were approximated both on the basis of the pharmacy sales price level and also deducting the statutory rebates in accordance with Section 130 and Section 130a SGB V. To calculate the annual treatment costs, the required number of packs of a particular potency was first determined on the basis of consumption. Having determined the number of packs of a particular potency, the costs of the medicinal products were then calculated on the basis of the costs per pack after deduction of the statutory rebates. Any reference prices shown in the cost representation may not represent the cheapest available alternative.

**Costs of the medicinal products:**

Adults with newly diagnosed acute myeloid leukaemia (AML) with an isocitrate dehydrogenase-1 (IDH1) R132 mutation who are not eligible to receive standard induction chemotherapy

| 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 | | | | | | |
| Ivosidenib 250 mg | 60 | FCT | € 13,036.43 | € 1.77 | € 0.00 | € 13,034.66 |
| Azacitidine 100 mg | 1 | VIA | € 199.69 | € 1.77 | € 8.94 | € 188.98 |
| Appropriate comparator therapy | | | | | | |
| Venetoclax 100 mg | 112 | FCT | € 5,926.31 | € 1.77 | € 0.00 | € 5,924.54 |
| Azacitidine 100 mg | 1 | VIA | € 199.69 | € 1.77 | € 8.94 | € 188.98 |

| 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 |
|---|---|---|---|---|---|---|
| Decitabine 50 mg | 1 | PCI | € 1,242.38 | € 1.77 | € 68.16 | € 1,172.45 |
| Abbreviations: VIA = vials; FCT = film-coated tablets; PCI = powder for a concentrate for the preparation of an infusion solution | | | | | | |

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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 had 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 October 2009 is not fully used to calculate costs. Alternatively, the pharmacy sales price publicly accessible in the directory services according to Section 131 paragraph 4 SGB V is a suitable basis for a standardised calculation.

According to the currently valid version of the special agreement on contractual unit costs of retail pharmacist services (Hilfstaxe), surcharges for the production of parenteral preparations containing cytostatic agents a maximum amount of € 100 per ready-to-use preparation, and for the production of parenteral solutions containing monoclonal antibodies a maximum of € 100 per ready-to-apply unit are to be payable. These additional other costs are not added to the pharmacy sales price but rather follow the rules for calculating in the Hilfstaxe. The cost representation is based on the pharmacy retail price and the maximum surcharge for the preparation and is only an approximation of the treatment costs. This presentation does not take into account, for example, the rebates on the pharmacy purchase price of the active ingredient, the invoicing of discards, the calculation of application containers, and carrier solutions in accordance with the regulations in Annex 3 of the Hilfstaxe.

## 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 their session on 27 January 2026, the Subcommittee on Medicinal Products determined the appropriate comparator therapy.

On 27 February 2026, the pharmaceutical company submitted a dossier for the benefit assessment of ivosidenib to the G-BA in due time in accordance with Chapter 5 Section 8, paragraph 1, number 6 VerfO.

By letter dated 2 March 2026 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 ivosidenib.

The dossier assessment by the IQWiG was submitted to the G-BA on 27 February 2026, and the written statement procedure was initiated with publication on the G-BA website on 1 June 2026. The deadline for submitting written statements was 22 June 2026.

The oral hearing was held on 6 July 2026.

By letter dated 7 July 2026, the IQWiG was commissioned with a supplementary assessment of data submitted in the written statement procedure. The addendum prepared by the IQWiG was submitted to the G-BA on 31 July 2026.

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 were discussed at the Subcommittee's session on 11 August 2026, and deliberation of the draft resolution was concluded.

At their session on 20 August 2026, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

**Chronological course of consultation**

| Session | Date | Subject of consultation |
|---|---|---|
| Subcommittee on Medicinal Products | 27 January 2026 | Determination of the appropriate comparator therapy |
| Working group Section 35a | 30 June 2026 | Information on written statements received; preparation of the oral hearing |
| Subcommittee on Medicinal Products | 6 July 2026 | Conduct of the oral hearing, commissioning of the IQWiG with the supplementary assessment of documents |
| Working group Section 35a | 14 July 2026<br>4 August 2026 | Consultation on the dossier assessment by the IQWiG and evaluation of the written statement procedure |
| Subcommittee on Medicinal Products | 11 August 2026 | Concluding discussion of the draft resolution |
| Plenum | 20 August 2026 | Adoption of the resolution on the amendment of the Pharmaceuticals Directive |

Berlin, 20 August 2026

Federal Joint Committee
in accordance with Section 91 SGB V
The Chair

Dr Optendrenk