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 Ivosidenib (acute myeloid leukaemia with IDH1 R132 mutation, first-line, combination with azacitidine)

of 18 January 2024

Contents

1. Legal basis

According to Section 35a paragraph 1 German Social Code, Book Five (SGB V), the Federal Joint Committee (G-BA) assesses the benefit of reimbursable medicinal products with new active ingredients.

For medicinal products for the treatment of rare diseases (orphan drugs) that are approved according to Regulation (EC) No. 141/2000 of the European Parliament and the Council of 16 December 1999, the additional medical benefit is considered to be proven through the grant of the marketing authorisation according to Section 35a, paragraph 1, sentence 11, 1st half of the sentence German Social Code, Book Five (SGB V). Evidence of the medical benefit and the additional medical benefit in relation to the appropriate comparator therapy do not have to be submitted (Section 35a, paragraph 1, sentence 11, 2nd half of the sentence SGB V). Section 35a, paragraph 1, sentence 11, 1st half of the sentence SGB V thus guarantees an additional benefit for an approved orphan drug, although an assessment of the orphan drug in accordance with the principles laid down in Section 35a, paragraph 1, sentence 3, No. 2 and 3 SGB V in conjunction with Chapter 5 Sections 5 et seq. of the Rules of Procedure (VerfO) of the G-BA has not been carried out. In accordance with Section 5, paragraph 8 AM-NutzenV, only the extent of the additional benefit is to be quantified indicating the significance of the evidence.

However, the restrictions on the benefit assessment of orphan drugs resulting from the statutory obligation to the marketing authorisation do not apply if the turnover of the medicinal product with the SHI at pharmacy sales prices and outside the scope of SHI-accredited medical care, including VAT exceeds € 30 million in the last 12 calendar months. According to Section 35a, paragraph 1, sentence 12 SGB V, the pharmaceutical company must then, within three months of being requested to do so by the G-BA, submit evidence according to Chapter 5, Section 5, paragraphs 1–6 VerfO, in particular regarding the additional medical benefit in relation to the appropriate comparator therapy as defined by the G-BA according to Chapter 5, Section 6 VerfO and prove the additional benefit in comparison with the appropriate comparator therapy.

In accordance with Section 35a, paragraph 2 SGB V, the G-BA decides whether to carry out the benefit assessment itself or to commission the Institute for Quality and Efficiency in Health Care (IQWiG). Based on the legal requirement in Section 35a, paragraph 1, sentence 11 SGB V that the additional benefit of an orphan drug is considered to be proven through the grant of the marketing authorisation the G-BA modified the procedure for the benefit assessment of orphan drugs at its session on 15 March 2012 to the effect that, for orphan drugs, the G-BA initially no longer independently determines an appropriate comparator therapy as the basis for the solely legally permissible assessment of the extent of an additional benefit to be assumed by law. Rather, the extent of the additional benefit is assessed exclusively on the basis of the approval studies by the G-BA indicating the significance of the evidence.

Accordingly, at its session on 15 March 2012, the G-BA amended the mandate issued to the IQWiG by the resolution of 1 August 2011 for the benefit assessment of medicinal products with new active ingredients in accordance with Section 35a, paragraph 2 SGB V to that effect that, in the case of orphan drugs, the IQWiG is only commissioned to carry out a benefit assessment in the case of a previously defined comparator therapy when the sales volume of the medicinal product concerned has exceeded the turnover threshold according to Section 35a, paragraph 1, sentence 12 SGB V and is therefore subject to an unrestricted benefit assessment. According to Section 35a, paragraph 2 SGB V, the assessment by the G-BA must be completed within three months of the relevant date for submission of the evidence and published on the internet.

According to Section 35a paragraph 3 SGB V, the G-BA decides on the benefit assessment within three months of its publication. The resolution is to be published on the internet and is part of the Pharmaceuticals Directive.

2. Key points of the resolution

The relevant date for the start of the benefit assessment procedure was the first placing on the (German) market of the active ingredient ivosidenib on 15 July 2023 in accordance with Chapter 5 Section 8, paragraph 1, number 1, sentence 2 of the Rules of Procedure (VerfO) of the G-BA. The pharmaceutical company submitted the final dossier to the G-BA in accordance with Section 4, paragraph 3, number 1 of the Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with Chapter 5 Section 8, paragraph 1, number 1 VerfO on 13 July 2023.

Ivosidenib in combination with azacitidine for the treatment of adults with newly diagnosed acute myeloid leukaemia (AML) with an isocitrate dehydrogenase 1 (IDH1) R132 mutation who are ineligible for standard induction chemotherapy is approved as a medicinal product for the treatment of rare diseases under Regulation (EC) No. 141/2000 of the European Parliament and of the Council of 16 December 1999.

In accordance with Section 35a, paragraph 1, sentence 11, 1st half of the sentence SGB V, the additional benefit is considered to be proven through the grant of the marketing authorisation. The extent of the additional benefit and the significance of the evidence are assessed on the basis of the approval studies by the G-BA.

The G-BA carried out the benefit assessment and commissioned the IQWiG to evaluate the information provided by the pharmaceutical company in Module 3 of the dossier on treatment costs and patient numbers. The benefit assessment was published on 16 October 2023 together with the IQWiG assessment on the website of the G-BA (www.g-ba.de), thus initiating the written statement procedure. In addition, an oral hearing was held.

The G-BA made its resolution on the basis of the pharmaceutical company's dossier, the dossier assessment carried out by the G-BA, the IQWiG assessment of treatment costs and patient numbers (IQWiG G23-16) and the statements made in the written statement and oral hearing procedure, as well of the amendment drawn up by the G-BA on the benefit assessment.

In order to determine the extent of the additional benefit, the G-BA has evaluated the studies relevant for the approval with regard to their therapeutic relevance (qualitative) in accordance with the criteria laid down in Chapter 5 Section 5, paragraph 7, sentence 1, numbers 1 – 4 VerfO. The methodology proposed by the IQWiG in accordance with the General Methods [1] was not used in the benefit assessment of ivosidenib.

1 General Methods, version 6.1 from 24.01.2022. Institute for Quality and Efficiency in Health Care (IQWiG), Cologne.

2.1 Additional benefit of the medicinal product

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 18 January 2024):

see the approved therapeutic indication

2.1.2 Extent of the additional benefit and significance of the evidence

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

Indication of a major additional benefit

Justification:

The AGILE study is a randomised, multicentre, controlled phase III study ongoing since March 2018 which compared 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 ineligible for standard induction chemotherapy.

The study is being conducted in 199 study sites across Australia, Asia, Europe, Asia, and North and South America.

Randomisation was stratified by "de novo status" (de novo AML; secondary AML) and "geographic region" (USA and Canada; Western Europe; Israel and Australia; Japan; rest of the world) in a 1:1 ratio (ivosidenib arm N = 73; control arm N = 75).

Patients should undergo treatment with ivosidenib + azacitidine or placebo + azacitidine for at least 6 cycles of 4 weeks each. Treatment was continued until relapse, disease progression, development of unacceptable toxicity, pregnancy, withdrawal of consent form, protocol violation or end of study. The primary endpoint was changed from "overall survival" to "event-free survival" during the course of the study. This change led to a reduction in the sample size from 392 to 200 subjects.

Recruitment was terminated early following a recommendation by the IDMC, which was supported by the FDA (data cut-off: 18.03.2021). The investigators and patients were unblinded. This allowed subjects in the control arm to switch to the ivosidenib arm (cross-over; n = 5).

As part of the marketing authorisation procedure, in addition to the 1st data cut-off, results of the 90-day follow-up data cut-off (01.10.2021) and a long-term observation (data cut-off: 30.06.2022) were also evaluated. For the long-term data cut-off, results are available for the endpoints "overall survival", "transfusion independence" and "adverse events".

The data cut-offs from 30.06.2022 (mortality, side effects) and 18.03.2021 (morbidity, quality of life) are used for the benefit assessment.

Mortality

Treatment with ivosidenib + azacitidine results in a statistically significant benefit in overall survival compared to placebo + azacitidine.

The extent of this advantage is also assessed as a major improvement in overall survival against the background of the known poor prognosis for patients in the therapeutic indication.

Morbidity

Event-free survival (EFS)

The EFS endpoint is the primary endpoint of the AGILE study and is defined as the time between randomisation and the first occurrence of one of the following events: Treatment failure (failure to achieve CR by week 24), confirmed relapse after remission or death from any cause.

The tumour response was assessed using the IWG response criteria and ELN guidelines.

The failure of a curative therapeutic approach is fundamentally patient-relevant. However, based on the therapy options used to date, a palliative treatment setting rather than a potentially curative therapeutic intention can be assumed in this therapeutic indication.

The extent to which ivosidenib represents a potentially curative therapeutic approach cannot be currently assessed based on the available information.

Against this background, the EFS endpoint is not used for the benefit assessment.

Transfusion independence

Patients in the present therapeutic indication require frequent and lifelong transfusions. A long-term or sustainable avoidance of transfusions (transfusion independence) while maintaining a defined minimum value of haemoglobin represents a relevant therapeutic goal in the present therapeutic indication, with which a control of anaemia and anaemia-related symptoms is achieved, while avoiding transfusions.

Transfusion independence was defined in the dossier of the pharmaceutical company as the percentage of subjects who have not received any transfusions (with platelets or erythrocytes) for at least 24 weeks. The time from the start of study medication to the last administration of study medication + 28 days, disease progression, death or data cut-off (whichever occurs first) was considered.

In its statement, the pharmaceutical company also submitted information on the number of subjects who had an evaluation period of at least 24 weeks. This evaluation is considered relevant for the benefit assessment. However, the percentage of subjects with an evaluation period of at least 24 weeks was significantly higher in the ivosidenib arm (62%) than in the placebo arm (33%).

Uncertainties also remain regarding the validity of the endpoint.

No information was available in the dossier of the pharmaceutical company on the criteria governing the administration of transfusions in the study. The pharmaceutical company did not provide any information in this regard during the written statement procedure either.

According to the statements of the clinical experts during the written statement procedure, the patient-individual procedure for the administration of transfusions corresponds to the reality of care.

According to this, the need for transfusion in patients is not only based on laboratory-chemical parameters (e.g. Hb value), but is very much oriented towards patient-individual factors such as the patients' symptoms, age and concomitant diseases. However, information on reasons for transfusion administration was not presented by the pharmaceutical company. The lack of information results in uncertainty about the extent to which transfusions were administered under comparable conditions in different study sites and whether this corresponds to the German health care context.

The results for the endpoint of transfusion independence are only presented additionally, taking into account the uncertainties mentioned. There were no statistically significant differences in the relative risk of receiving a transfusion among subjects with an evaluation period of at least 24 weeks.

Symptomatology (EORTC QLQ-C30)

Disease symptomatology was assessed in the AGILE study using the cancer-specific questionnaire EORTC QLQ-C30. In the dossier, the pharmaceutical company submitted responder analyses for the percentage of patients with a change of ≥ 10 points for the time to 1st deterioration. The "death" event was also categorised as an event.

In its statement, the pharmaceutical company presented further responder analyses without the "death" event. These responder analyses are used for the benefit assessment.

The time-to-event analyses showed a statistically significant difference in favour of ivosidenib in the endpoint of constipation.

For each of the other endpoints, there is no statistically significant difference between the treatment groups.

Overall, no relevant differences for the benefit assessment were derived for ivosidenib in combination with azacitidine with regard to symptomatology.

Health status (EQ-5D VAS)

The health status is assessed in the AGILE study using the EQ-5D visual analogue scale (VAS). In the dossier, the pharmaceutical company submitted responder analysis, operationalised as time to 1st deterioration with a change of ≥ 15 points. The "death" event was also categorised as an event.

In its statement, the pharmaceutical company presented further responder analyses without the "death" event. These responder analyses are used for the benefit assessment.

With regard to the health status, there were no statistically significant differences between the treatment arms.

Conclusion on morbidity

In the overall analysis of the results on symptomatology as well as the health status, no relevant difference for the benefit assessment between the treatment groups was found.

Quality of life

Quality of life is assessed in the AGILE study using the cancer-specific questionnaire EORTC QLQ-C30. In the dossier, the pharmaceutical company submitted responder analyses for the percentage of patients with a change of ≥ 10 points for the time to 1st deterioration. The "death" event was also categorised as an event.

In its statement, the pharmaceutical company presented further responder analyses without the "death" event. These responder analyses are used for the benefit assessment.

The time-to-event analyses showed a statistically significant difference to the advantage of ivosidenib on the emotional functioning scale.

However, this advantage is not reflected in any other subscale of the EORTC QLQ-C30. In the overall assessment, no relevant difference for the benefit assessment was derived in the quality of life endpoint category.

Side effects

The evaluations of side effects refer to adverse events (AEs) that occurred from the administration of the study medication until 4 weeks after the last dose. Serious AEs (SAEs) caused by an intervention provided by the protocol during the screening period, and SAEs occurring 28 days after the end of treatment and related to study treatment were also included. AEs due to disease progression as well as anticipated SAEs associated with the underlying disease were not categorised as AEs.

Adverse events (AEs) in total

AEs occurred in almost all study participants. The results were only presented additionally.

Serious AEs (SAEs), severe AEs (CTCAE grade ≥ 3) and therapy discontinuations due to AE

There were no statistically significant differences between treatment arms for SAEs, severe AEs (CTCAE grade ≥ 3), and therapy discontinuations due to AE.

Specific AEs

In detail, the results on SAEs and severe AEs (CTCAE grade ≥ 3) at system organ class level, which occurred with an incidence > 5% of patients in at least one study arm, show statistically significant effects in favour of ivosidenib in combination with azacitidine for "infections and infestations" (SAEs) and "metabolism and nutrition disorders" (severe AEs), including PT "loss of appetite". In addition, the PTs "asthenia" and "hypotension" (severe AEs) showed statistically significant effects in favour of ivosidenib in combination with azacitidine.

The results on AEs by system organ class (SOC) and preferred term (PT), which occurred with an incidence of > 10%, show statistically significant effects in favour of ivosidenib in combination with azacitidine (infections and infestationns, general disorders and administration site conditions (incl. PT asthenia and PT peripheral oedema), metabolism and nutrition disorders (incl. PT loss of appetite and PT hypokalaemia), renal and urinary tract disorders, as well as PT constipation and PT cough. Only the PT "electrocardiogram QT-prolonged" and haematomas show statistically significant effects to the disadvantage of ivosidenib in combination with azacitidine. In the overall assessment of the results on adverse events, no relevant advantage or disadvantage for the benefit assessment can be derived from this.

Conclusion on side effects

In the overall analysis, there were no relevant differences for the benefit assessment with regard to the endpoint category of side effects for ivosidenib in combination with azacitidine. In detail, there are predominantly advantages in some specific AEs.

Overall assessment

For the assessment of the additional benefit of ivosidenib in combination with azacitidine, results from the double-blind, randomised, controlled study AGILE are available for the endpoint categories of mortality, morbidity, quality of life, and side effects. The ongoing study compares ivosidenib in combination with azacitidine to placebo in combination with azacitidine.

For the endpoint of overall survival, there was a statistically significant difference to the advantage of ivosidenib in combination with azacitidine. The extent of this advantage is also assessed as a major improvement in overall survival against the background of the known poor prognosis for patients in the therapeutic indication.

With regard to symptomatology (assessed using the EORTC QLQ-C30) and health status (assessed using the EQ5D-VAS), no relevant difference for the benefit assessment was found between the treatment groups.

Overall, no relevant difference for the benefit assessment was derived for the endpoint category of quality of life.

Based on the results on side effects, there were neither positive nor negative effects for ivosidenib in combination with azacitidine in the endpoints of SAEs, severe AEs (CTCAE grade ≥ 3) and therapy discontinuations due to AEs. In detail, there are predominantly advantages for some specific adverse events.

In the overall assessment, a major additional benefit was identified for ivosidenib in combination with azacitidine for the treatment of adults with newly diagnosed acute myeloid leukaemia (AML) with an isocitrate dehydrogenase 1 (IDH1) R132 mutation who are ineligible for standard induction chemotherapy.

Significance of the evidence

This assessment is based on the results of the randomised, controlled, double-blind phase III AGILE study comparing ivosidenib in combination with azacitidine and placebo in combination with azacitidine.

The risk of bias is assessed as low at endpoint level.

At the study level, an imbalance between the study arms with regard to comorbidities is noticeable. At the start of study, patients in the control arm had various concomitant diseases more frequently than patients in the ivosidenib arm, according to patient characteristics.
Recruitment for the study was terminated early following a recommendation by the IDMC (Independent Data Monitoring Committee). This was followed by early unblinding, as a result of which patients were able to switch from the control arm to the ivosidenib arm (cross-over). In the overall assessment against the background of the extent of the advantage for mortality, the reliability of data of the study is not reduced.

Overall, the significance of the evidence is categorised in the "indication" category.

2.1.3 Summary of the assessment

The present assessment concerns the benefit assessment of the new medicinal product Tibsovo with the active ingredient ivosidenib.

Ivosidenib in combination with azacitidine was approved as an orphan drug for the treatment of adults with newly diagnosed acute myeloid leukaemia (AML) with an isocitrate dehydrogenase 1 (IDH1) R132 mutation who are ineligible for standard induction chemotherapy.

The benefit assessment of ivosidenib is based on the ongoing, randomised, controlled, double-blind phase III AGILE study, in which ivosidenib in combination with azacitidine and placebo in combination with azacitidine are being compared.

For the endpoint of overall survival, there was a statistically significant difference to the advantage of ivosidenib in combination with azacitidine. The extent of this advantage is also assessed as a major improvement in overall survival against the background of the known poor prognosis for patients in the therapeutic indication.

With regard to symptomatology (assessed using the EORTC QLQ-C30) and health status (assessed using the EQ5D-VAS), no relevant difference for the benefit assessment was found between the treatment groups.

Overall, no relevant difference for the benefit assessment was derived for the endpoint category of quality of life.

Based on the results on side effects, there were neither positive nor negative effects for ivosidenib in combination with azacitidine in the endpoints of SAEs, severe AEs (CTCAE grade ≥ 3) and therapy discontinuations due to AEs. In detail, there are predominantly advantages for some specific adverse events.

In the overall assessment, a major additional benefit was identified for ivosidenib in combination with azacitidine for the treatment of adults with newly diagnosed acute myeloid leukaemia (AML) with an isocitrate dehydrogenase 1 (IDH1) R132 mutation who are ineligible for standard induction chemotherapy.

The significance of the evidence is categorised in the "indication" category.

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 resolution is based on the information from the dossier of the pharmaceutical company regarding the number of patients.

The information provided by the pharmaceutical company is subject to uncertainty, but overall tends to be underestimated. The main reasons for this are the indicated percentages of adults with AML and patients for whom standard induction chemotherapy is unsuitable.

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: 30 November 2023):

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 requirements in the product information and the information listed in the LAUER-TAXE® (last revised: 1 January 2024).

The (daily) doses recommended in the product information or in the labelled publications were used as the basis for calculation.

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

Treatment period:

If no maximum treatment duration is specified in the product information, the treatment duration is assumed to be one year (365 days), even if the actual treatment duration varies from patient to patient and/or is shorter on average. The time unit "days" is used to calculate the "number of treatments/ patient/ year", time intervals between individual treatments and for the maximum treatment duration, if specified in the product information.

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	Continuously, 1 x daily	365	1	365.0
Azacitidine	1 x daily on day 1-7 of a 28-day cycle	13	7	91.0

Consumption:

For dosages depending on body weight (BW) or body surface area (BSA), the average body measurements of the official representative statistics "Microcensus 2017 – body measurements of the population" were applied (average body height: 1.72 m; average body weight: 77 kg). This results in a body surface area of 1.90 m² (calculated according to Du Bois 1916)[2].

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	500 mg	500 mg	2 x 250 mg	365.0	730.0 x 250 mg
Azacitidine	75 mg/m² = 142.5 mg	142.5 mg	1 x 150 mg	91.0	91.0 x 150 mg

[2] Federal Statistical Office, Wiesbaden 2018: http://www.gbe-bund.de/

Costs:

Costs of the medicinal products:

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 fixed reimbursement rates shown in the cost representation may not represent the cheapest available alternative.

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	€ 18,395.92	€ 2.00	€ 1050.00	€ 17,343.92
Azacitidine 150 mg	1 CIS	€ 525.69	€ 2.00	€ 24.41	€ 499.28
Abbreviations: FCT = film-coated tablets; CIS = concentrate for the preparation of an infusion solution					

LAUER-TAXE® last revised: 1 January 2024

Costs for additionally required SHI services:

Only costs directly related to the use of the medicinal product are taken into account. If there are regular differences in the necessary use of medical treatment or in the prescription of other services in the use of the medicinal product to be evaluated and the appropriate comparator therapy in accordance with the product information, the costs incurred for this must be taken into account as costs for additionally required SHI services.

Medical treatment costs, medical fee services, and costs incurred for routine examinations (e.g. regular laboratory services such as blood count tests) that do not exceed the standard expenditure in the course of the treatment are not shown.

No additionally required SHI services are taken into account for the cost representation.

Other SHI services:

The special agreement on contractual unit costs of retail pharmacist services (Hilfstaxe) (Sections 4 and 5 of the Pharmaceutical Price Ordinance) from 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 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 special agreement on contractual unit costs of retail pharmacist services (Hilfstaxe).

2.5 Designation of medicinal products with new active ingredients according to Section 35a, paragraph 3, sentence 4 SGB V that can be used in a combination therapy with the assessed medicinal product

According to Section 35a, paragraph 3, sentence 4, the G-BA designates all medicinal products with new active ingredients that can be used in a combination therapy with the assessed medicinal product for the therapeutic indication to be assessed on the basis of the marketing authorisation under Medicinal Products Act.

Basic principles of the assessed medicinal product

A designation in accordance with Section 35a, paragraph 3, sentence 4 SGB V requires that it is examined based on the product information for the assessed medicinal product whether it can be used in a combination therapy with other medicinal products in the assessed therapeutic indication. In the first step, the examination is carried out on the basis of all sections of the currently valid product information for the assessed medicinal product.

If the assessed medicinal product contains an active ingredient or a fixed combination of active ingredients in the therapeutic indication of the resolution (assessed therapeutic indication) and is approved exclusively for use in monotherapy, a combination therapy is not considered due to the marketing authorisation under Medicinal Products Act, which is why no designation is made.

A designation is also not considered if the G-BA has decided on an exemption as a reserve antibiotic for the assessed medicinal product in accordance with Section 35a, paragraph 1c, sentence 1 SGB V. The additional benefit is deemed to be proven if the G-BA has decided on an exemption for a reserve antibiotic in accordance with Section 35a, paragraph 1c, sentence 1 SGB V; the extent of the additional benefit and its therapeutic significance are not to be assessed by the G-BA. Due to the lack of an assessment mandate by the G-BA following the resolution on an exemption according to Section 35a, paragraph 1c, sentence 1 SGB V with regard to the extent of the additional benefit and the therapeutic significance of the reserve antibiotic to be assessed, there is a limitation due to the procedural privileging of the pharmaceutical companies to the effect that neither the proof of an existing nor an expected at least considerable additional benefit is possible for exempted reserve antibiotics in the procedures according to Section 35a paragraph 1 or 6 SGB V and Section 35a paragraph 1d SGB V. The procedural privileging of the reserve antibiotics exempted according to Section 35a, paragraph 1c, sentence 1 SGB V must therefore also be taken into account at the level of designation according to Section 35a, paragraph 3, sentence 4 SGB V in order to avoid valuation contradictions.

With regard to the further examination steps, a differentiation is made between a "determined" or "undetermined" combination, which may also be the basis for a designation.

A "determined combination" exists if one or more individual active ingredients which can be used in combination with the assessed medicinal product in the assessed therapeutic indication are specifically named.

An "undetermined combination" exists if there is information on a combination therapy, but no specific active ingredients are named. An undetermined combination may be present if the information on a combination therapy:

- names a product class or group from which some active ingredients not specified in detail can be used in combination therapy with the assessed medicinal product, or
- does not name any active ingredients, product classes or groups, but the assessed medicinal product is used in addition to a therapeutic indication described in more detail in the relevant product information, which, however, does not include information on active ingredients within the scope of this therapeutic indication.

Concomitant active ingredient:

The concomitant active ingredient is a medicinal product with new active ingredients that can be used in combination therapy with the assessed medicinal product for the therapeutic indication to be assessed.

For a medicinal product to be considered as a concomitant active ingredient, it must be classified as a medicinal product with new active ingredients according to Section 2 paragraph 1 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with the corresponding regulations in Chapter 5 of the Rules of Procedure of the G-BA as of the date of the present resolution. In addition, the medicinal product must be approved in the assessed therapeutic indication, whereby a marketing authorisation is sufficient only for a sub-area of the assessed therapeutic indication.

Based on an "undetermined combination", the concomitant active ingredient must be attributable to the information on the product class or group or the therapeutic indication according to the product information of the assessed medicinal product in the assessed therapeutic indication, whereby the definition of a product class or group is based on the corresponding information in the product information of the assessed medicinal product.

In addition, there must be no reasons for exclusion of the concomitant active ingredient from a combination therapy with the assessed medicinal product, in particular no exclusive marketing authorisation as monotherapy.

In addition, all sections of the currently valid product information of the eligible concomitant active ingredient are checked to see whether there is any information that excludes its use in combination therapy with the assessed medicinal product in the assessed therapeutic indication under marketing authorisation regulations. Corresponding information can be, for example, dosage information or warnings. In the event that the medicinal product is used as part of a determined or undetermined combination which does not include the assessed medicinal product, a combination with the assessed medicinal product shall be excluded.

Furthermore, the product information of the assessed medicinal product must not contain any specific information that excludes its use in combination therapy with the eligible concomitant active ingredient in the assessed therapeutic indication under marketing authorisation regulations.

Medicinal products with new active ingredients for which the G-BA has decided on an exemption as a reserve antibiotic in accordance with Section 35a, paragraph 1c, sentence 1 SGB V are ineligible as concomitant active ingredients. The procedural privileging of the reserve antibiotics exempted according to Section 35a, paragraph 1c, sentence 1 SGB V also applies accordingly to the medicinal product eligible as a concomitant active ingredient.

Designation

The medicinal products which have been determined as concomitant active ingredients in accordance with the above points of examination are named by indicating the relevant active ingredient and the invented name. The designation may include several active ingredients, provided that several medicinal products with new active ingredients may be used in the same combination therapy with the assessed medicinal product or different combinations with different medicinal products with new active ingredients form the basis of the designation.

If the present resolution on the assessed medicinal product in the assessed therapeutic indication contains several patient groups, the designation of concomitant active ingredients shall be made separately for each of the patient groups.

Exception to the designation

The designation excludes combination therapies for which - patient group-related - a considerable or major additional benefit has been determined by resolution according to Section 35a, paragraph 3, sentence 1 SGB V or it has been determined according to Section 35a, paragraph 1d, sentence 1 SGB V that at least considerable additional benefit of the combination can be expected. In this context, the combination therapy that is excluded from the designation must, as a rule, be identical to the combination therapy on which the preceding findings were based.

In the case of designations based on undetermined combinations, only those concomitant active ingredients - based on a resolution according to Section 35a, paragraph 3, sentence 1 SGB V on the assessed medicinal product in which a considerable or major additional benefit had been determined - which were approved at the time of this resolution are excluded from the designation.

Legal effects of the designation

The designation of combinations is carried out in accordance with the legal requirements according to Section 35a, paragraph 3, sentence 4 and is used exclusively to implement the combination discount according to Section 130e SGB V between health insurance funds and pharmaceutical companies. The designation is not associated with a statement as to the extent to which a therapy with the assessed medicinal products in combination with the designated medicinal products corresponds to the generally recognised state of medical knowledge. The examination was carried out exclusively on the basis of the possibility under Medicinal Products Act to use the medicinal products in combination therapy in the assessed

therapeutic indication based on the product information; the generally recognised state of medical knowledge or the use of the medicinal products in the reality of care were not the subject of the examination due to the lack of an assessment mandate of the G-BA within the framework of Section 35a, paragraph 3, sentence 4 SGB V.

The findings made neither restrict the scope of treatment required to fulfil the medical treatment mandate, nor do they make statements about expediency or economic feasibility.

Justification for the findings on designation in the present resolution:

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

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 ivosidenib (Tibsovo); Tibsovo 250 mg film-coated tablets; last revised: July 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

On 13 July 2023, 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 1, sentence 2 VerfO.

The benefit assessment of the G-BA was published on 16 October 2023 together with the IQWiG assessment of treatment costs and patient numbers on the website of the G-BA (www.g-ba.de), thus initiating the written statement procedure. The deadline for submitting statements was 6 November 2023.

The oral hearing was held on 27 November 2023.

An amendment to the benefit assessment with a supplementary assessment was submitted on 20 December 2023.

In order to prepare a recommendation for a resolution, the Subcommittee on Medicinal Products commissioned a working group (Section 35a) consisting of the members nominated by the leading organisations of the care providers, the members nominated by the SHI umbrella organisation, and representatives of the patient organisations. Representatives of the IQWiG also participate in the sessions.

The evaluation of the written statements received and the oral hearing was discussed at the session of the subcommittee on 9 January 2024, and the proposed resolution was approved.

At its session on 18 January 2024, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee Medicinal products	10 October 2023	Information of the benefit assessment of the G-BA
Working group Section 35a	14 November 2023	Information on written statements received, preparation of the oral hearing
Subcommittee Medicinal products	27 November 2023	Conduct of the oral hearing
Working group Section 35a	6 December 2023 4 January 2024	Consultation on the dossier assessment by the G-BA, the assessment of treatment costs and patient numbers by the IQWiG, and the evaluation of the written statement procedure
Subcommittee Medicinal products	9 January 2024	Concluding discussion of the draft resolution
Plenum	18 January 2024	Adoption of the resolution on the amendment of the Pharmaceuticals Directive

Berlin, 18 January 2024

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

Prof. Hecken