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 (cholangiocarcinoma with IDH1 R132 mutation, after at least 1 prior therapy)

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 for the treatment of locally advanced or metastatic cholangiocarcinoma with IDH1 R132 mutation, after at least one prior line of systemic therapy 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 has adopted its resolution on the basis of the dossier of the pharmaceutical company, the dossier assessment carried out by the G-BA, the assessment of treatment costs

and patient numbers (IQWiG G23-15) prepared by the IQWiG, and the statements submitted in the written statement and oral hearing procedure.

In order to determine the extent of the additional benefit, the G-BA has evaluated the 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.

2.1 Additional benefit of the medicinal product

2.1.1 Approved therapeutic indication of Ivosidenib (Tibsovo) in accordance with the product information

Tibsovo monotherapy is indicated for the treatment of adult patients with locally advanced or metastatic cholangiocarcinoma with an IDH1 R132 mutation who were previously treated by at least one prior line of systemic therapy.

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:

Hint for a non-quantifiable additional benefit since the scientific data does not allow quantification.

Justification:

The pharmaceutical company has submitted data from the pivotal, randomised, double-blind, placebo-controlled phase III ClarIDHy study for benefit assessment. In this study, ivosidenib was compared with placebo, whereby additional supportive measures as part of best supportive care (BSC) were permitted in both study arms.

Adult patients with unresectable or metastatic cholangiocarcinoma with an IDH1 R132 mutation and proven disease progression after at least one but no more than two prior lines of systemic therapy for advanced cholangiocarcinoma were enrolled in the study. Randomisation was in a ratio of 2:1 to the study arms ivosidenib + BSC (intervention arm, N = 124) and placebo + BSC (control arm, N = 61), stratified according to the number of prior lines

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

of systemic therapy (1 vs 2). After the first data cut-off, 2 more subjects were enrolled in the study and randomised into the intervention arm.

Treatment in the study arms was initially double-blind. After confirmed disease progression, the blinding could be cancelled at the principal investigator's request and participants from the control arm could switch to treatment with ivosidenib (crossover).

The patients were recruited between 2017 and 2019 from study sites in the USA, South Korea and Europe. The primary endpoint of the study that ended in 2021 was progression-free survival (PFS), additional endpoints were collected on mortality, symptomatology, health-related quality of life and adverse events.

The pharmaceutical company reported a total of three data cut-offs for the ClarIDHy study in the dossier (from 31 January 2019, 31 May 2020 and 21 June 2021). The first two data cut-offs were performed according to pre-specified number of events (131 PFS and 150 death events). The data cut-off from 21 June 2021, on the contrary, is not considered to be pre-specified. It is not clear why the study was continued after the second data cut-off, which according to the study protocol was supposed to be the end of the study. In this context, it is also unclear whether the follow-up was continued after the second data cut-off in accordance with the study protocol. For this assessment, the data cut-off date of 31 May 2020 is used accordingly for all endpoints with the exception of PFS. The results for the PFS endpoint are based on the data cut-off from 31 January 2019 (final analysis of PFS after 131 events).

Mortality

The overall survival is defined in the ClarIDHy study as the time between randomisation and death from any cause.

For the endpoint of overall survival, no statistically significant difference was detected between the treatment arms.

The overall survival analyses are based on the ITT population, which means that patients from the control arm, who switched to the intervention arm after disease progression, are also enrolled. At the time of the data cut-off from 31 May 2020, 43 (70.5%) of patients had switched from the control arm to treatment with ivosidenib.

In the dossier, the pharmaceutical company presents an analysis of the adjustment for treatment switching using the Rank Preserving Structural Failure Time Model (RPSFTM). Although the European Medicines Agency (EMA) listed the results on overall survival using the RPSFT model in the European Assessment Report,[2] it also pointed out the questionable relevance of a hypothetical treatment effect determined in this way and the risk of bias in the analysis conducted. The analysis was categorised as exploratory by the EMA and was not included in the assessment of the clinical efficacy of ivosidenib.

[2] Assessment Report -Tibsovo, 23 February 2023, EMA/173654/2023

Analytical methods for adjusting effect estimators for treatment switching pose a high risk of bias. There is no validated statistical method that allows the assessment of a therapy with sufficient certainty with regard to the endpoint of overall survival in studies with treatment switching.

The RPSFT model used here assumes a "common treatment effect", according to which the effect of the therapy is independent of the time point in the course of the disease at which the treatment takes place. This assumption is implausible for the present disease of pretreated locally advanced or metastatic cholangiocarcinoma. It can be assumed that the characteristics of the disease in relation to the effect of the therapy at the time of disease progression are no longer the same as at the time of randomisation in the ClarIDHy study. This assessment was also presented by the scientific-medical society in the oral hearing of the present benefit assessment procedure. In the G-BA's view, the assumption required to apply the RPSFT model is therefore not fulfilled.

In the overall evaluation, the analysis of overall survival with the RPSFT model is not considered in the present benefit assessment.

With regard to the analysis of overall survival based on the ITT population, there is an effect modification for the ECOG status characteristic at the start of the study. For patients with ECOG status 0, there is a statistically significant effect in favour of ivosidenib. For patients with ECOG status ≥ 1, there is no statistically significant difference between the study arms. As this effect modification is not shown for further endpoints of the ClarIDHy study, the significance of the available subgroup result for the overall assessment of the additional benefit is considered inadequate and is not used.

Morbidity

Progression-free survival (PFS)

The PFS was the primary endpoint of the ClarIDHy study and was operationalised as the time between randomisation and first evidence of disease progression (according to RECIST criteria version 1.1) or death from any cause, whichever occurred first.

The PFS was statistically significantly longer with ivosidenib + BSC compared to placebo + BSC.

The PFS endpoint is a composite endpoint composed of endpoints of the categories "mortality" and "morbidity". The endpoint component "mortality" has already been assessed as an independent endpoint via the endpoint "overall survival". The morbidity component of “disease progression” is assessed according to RECIST-V1.1 criteria and thus not symptom-related, but by means of imaging procedures. Taking into account the aspects mentioned above, there are different opinions within the G-BA regarding the patient-relevance of the endpoint PFS.

Data on morbidity and health-related quality of life are potentially relevant for the interpretation of the PFS results, especially when, as in the present case, a radiologically determined disease progression is associated with effects on morbidity and/or quality of life.

However, no suitable data on morbidity and health-related quality of life are available from the ClarIDHy study. Accordingly, it cannot be assessed to what extent the advantage in PFS determined in the ClarIDHy study using imaging procedures is associated with an advantage in terms of morbidity and/or health-related quality of life. The results on the PFS endpoint are therefore not used in the present assessment.

Symptomatology (EORTC QLQ-C30 and EORTC QLQ-BIL21)

Data on patient-reported symptomatology was assessed in the ClarIDHy study using EORTC QLQ-C30 and EORTC QLQ-BIL21 measurement tools.

However, the return rates fall below 70%, so that the significance of the results is to be considered unreliable. The data are therefore not usable and do not allow any conclusions to be drawn about the extent of the additional benefit.

Health status

The patient-reported health status was assessed using the EQ-5D visual analogue scale (VAS). However, the return rates here are also below 70%, meaning that the data are considered unusable and do not allow any conclusions to be drawn about the extent of the additional benefit.

Quality of life

Functional scales (EORTC QLQ-C30 and EORTC QLQ-BIL21)

In line with the above comments on symptomatology (EORTC QLQ-C30 and EORTC QLQ-BIL21), there are also no usable data on health-related quality of life due to return rates below 70% that would allow statements to be made on the extent of the additional benefit.

Side effects

Adverse events (AEs) in total

AEs occurred in almost all patients in the ClarIDHy study. The results were only presented additionally.

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

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

Specific AEs

In detail, there are no statistically significant differences in the results for SAEs and severe AEs (CTCAE grade ≥ 3) at the system organ class (SOC) level, which occurred with an incidence > 5% or ≥ 10 events and ≥ 1% of patients in at least one study arm. The results for AEs at the SOC and preferred term (PT) level, which occurred with an incidence of ≥ 10% in the placebo arm or ≥ 10 events and ≥ 1% in the ivosidenib arm, show statistically significant effects in

favour of ivosidenib for PTs dyspnoea and hypercalcaemia. 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 are no relevant differences for the benefit assessment with regard to the endpoint category of side effects for ivosidenib + BSC. In detail, there are advantages in some specific AEs.

Overall assessment

The results of the ClarIDHy study are available for the benefit assessment of ivosidenib as monotherapy for the treatment of adults with locally advanced or metastatic cholangiocarcinoma with an IDH1 R132 mutation who were previously treated by at least one prior line of systemic therapy. The study, completed in 2021, compared ivosidenib + BSC versus placebo + BSC.

However, there were no statistically significant differences between the treatment arms for the overall survival.

In the endpoint category of morbidity, no usable data are available for patient-reported symptomatology and health status that would allow conclusions to be drawn about the extent of the additional benefit due to a lack of sufficient return rates.

Due to the lack of return rates, there is also no usable data on health-related quality of life that would allow statements to be made on the extent of the additional benefit.

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

In the overall assessment, the G-BA classifies the extent of the additional benefit of ivosidenib as monotherapy for the treatment of patients with locally advanced or metastatic cholangiocarcinoma with an IDH1 R132 mutation who were previously treated by at least one prior line of systemic therapy as non-quantifiable because the scientific data basis does not allow quantification.

Significance of the evidence

The present benefit assessment is based on the results of the randomised, double-blind, placebo-controlled phase III ClarIDHy study.

At study level, a high risk of bias is assumed, particularly due to the high percentage of patients from the control arm who switched to treatment with ivosidenib in the event of disease progression.

At endpoint level, the risk of bias in overall survival is also rated as high due to this fact.

It should also be noted that the ClarIDHy study did not provide any usable data on patient-reported morbidity and health-related quality of life.

In the overall assessment, this results in the classification of the significance of the evidence in the “hint" 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. Tibsovo was approved as an orphan drug in the following therapeutic indication:

"Tibsovo monotherapy is indicated for the treatment of adult patients with locally advanced or metastatic cholangiocarcinoma with an IDH1 R132 mutation who were previously treated by at least one prior line of systemic therapy."

For the benefit assessment, the pharmaceutical company submitted data from the randomised, double-blind, placebo-controlled phase III ClarIDHy study, in which ivosidenib + best supportive care (BSC) was compared with placebo + BSC.

However, there were no statistically significant differences between the treatment arms for the overall survival.

In the endpoint category of morbidity, no usable data that would allow conclusions to be drawn on the extent of the additional benefit are available for patient-reported symptomatology and health status or in the endpoint category of health-related quality of life due to a lack of sufficient return rates.

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

In the overall assessment, the G-BA classifies the extent of the additional benefit of ivosidenib as monotherapy as non-quantifiable because the scientific data basis does not allow quantification.

A high risk of bias is assumed especially due to the high percentage of patients from the control arm who switched to treatment with ivosidenib after disease progression (approx. 70%). The significance of the evidence is classified in the "hint" category.

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

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

The G-BA bases its resolution on the patient numbers from the dossier submitted by the pharmaceutical company. The procedure of the pharmaceutical company for deriving the patient numbers is mathematically comprehensible, but different calculation steps are subject

to both overestimates and underestimates. For example, in the pharmaceutical company's derivation, the neglect of patients who are eligible for lines of therapy higher than second-line in the year under review leads to an underestimation and the assumption that all patients with locally advanced or metastatic cancer receive first-line chemotherapy leads to an overestimation. There are also uncertainties regarding the calculated incidences for extrahepatic cholangiocarcinomas and the assumed percentages for unresectable or metastatic disease at initial diagnosis and for recurrence following resection of the tumour during prior therapy.

Overall, the patient numbers are therefore subject to uncertainty and the number of patients may be higher or lower.

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: 5 October 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, internal medicine and gastroenterology, and specialists participating in the Oncology Agreement experienced in the treatment of adults with cholangiocarcinoma.

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).

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.

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				
Ivosidenib	Continuously, 1 x daily	365	1	365

Consumption:

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					
Ivosidenib	500 mg	500 mg	2 x 250 mg	365	730 x 250 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 fixed reimbursement rates shown in the cost representation may not represent the cheapest available alternative.

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					
Ivosidenib	60 FCT	€ 18,395.92	€ 2.00	€ 1,050.00	€ 17,343.92
Abbreviations: FCT = film-coated tablets					

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.

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 locally advanced or metastatic cholangiocarcinoma with an IDH1 R132 mutation who were previously treated by at least one prior line of systemic therapy

No designation of medicinal products with new active ingredients that can be used in combination therapy pursuant to Section 35a, paragraph 3, sentence 4 SGB V, as the active ingredient to be assessed is an active ingredient authorised in monotherapy.

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.

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	9 October 2023	Information of the benefit assessment of the G-BA
Working group Section 35a	15 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 20 December 2023	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