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
Vorasidenib (Grade 2 astrocytoma or oligodendroglioma with an IDH1 R132 or IDH2 R172 mutation, following surgical intervention, ≥ 12 years ≥ 40 kg)

dated 7 May 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.

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 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 of 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, numbers 2 and 3 SGB V in conjunction with Chapter 5 Sections 5 et seqq. 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. In accordance with Section 35a, paragraph 1, sentence 12 SGB V, the pharmaceutical company shall provide evidence - within three months of being requested to do so by the G-BA - in accordance with Chapter 5 Section 5, paragraphs 1 to 6 VerfO, in particular regarding the additional medical benefit in relation to the appropriate comparator therapy specified by the G-BA in accordance with Chapter 5 Section 6 VerfO, and in this evidence, demonstrate the additional benefit over the appropriate comparator therapy.

In accordance with Section 35a, paragraph 2 SGB V, the G-BA decide 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 their session on 15 March 2012 to the effect that, for orphan drugs, the G-BA initially no longer independently determine 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 their 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 limit 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 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 relevant date for the start of the benefit assessment procedure was the first placing on the (German) market of the active ingredient vorasidenib on 15 November 2025 in accordance with Chapter 5 Section 8, paragraph 1, number 1, sentence 2 of the Rules of Procedure of the G-BA (VerfO). Pursuant to 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, No. 1 Rules of Procedure (VerfO), the pharmaceutical company submitted the final dossier to the G-BA on 10 November 2025.

Vorasidenib as monotherapy for the treatment of predominantly non-enhancing Grade 2 astrocytoma or oligodendroglioma with an IDH1 R132 or IDH2 R172 mutation in adult and adolescent patients aged 12 years and older and weighing at least 40 kg who only had surgical intervention and are not in immediate need of radiotherapy or 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 by the G-BA on the basis of the approval studies.

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 February 2026 together with the IQWiG assessment on the G-BA website (www.g-ba.de), thus initiating the written statement procedure. In addition, an oral hearing was held.

The G-BA adopted their 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 G25-32) 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 have assessed the studies relevant to the marketing authorisation on the basis of their therapeutic relevance (qualitative), in accordance with the criteria laid down in Chapter 5 Section 5, paragraph 7, sentence 1, numbers 1 to 4 VerfO. The methodology proposed by the IQWiG in accordance with the General Methods [1] was not used in the benefit assessment of vorasidenib.

[1] General Methods, version 8.0 from 19.12.2025. 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 Vorasidenib (Voranigo) in accordance with the product information

Voranigo as monotherapy is indicated for the treatment of predominantly non-enhancing Grade 2 astrocytoma or oligodendroglioma with an IDH1 R132 or IDH2 R172 mutation in adult and adolescent patients aged 12 years and older and weighing at least 40 kg who only had surgical intervention and are not in immediate need of radiotherapy or chemotherapy.

Therapeutic indication of the resolution (resolution of 7 May 2026):

See the approved therapeutic indication

2.1.2 Extent of the additional benefit and significance of the evidence

Adults and adolescents aged 12 years and older and weighing at least 40 kg with predominantly non-enhancing Grade 2 astrocytoma or oligodendroglioma with an IDH1 R132 or IDH2 R172 mutation who only had surgical intervention and are not in immediate need of radiotherapy or chemotherapy

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

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

Justification:

The pharmaceutical company submitted data from the INDIGO (AG881-C-004) approval study for the assessment of the extent of the additional benefit of vorasidenib in the therapeutic indication "treatment of predominantly non-enhancing Grade 2 astrocytoma or oligodendroglioma with an IDH1 R132 or IDH2 R172 mutation in adult and adolescent patients aged 12 years and older and weighing at least 40 kg who only had surgical intervention and are not in immediate need of radiotherapy or chemotherapy".

The INDIGO study is a multicentre, double-blind, randomised phase III study comparing vorasidenib with placebo. Adults and adolescents aged 12 years and older and weighing at least 40 kg who had Grade 2 astrocytoma or oligodendroglioma according to the 2016 WHO criteria, with an IDH1 R132 or IDH2 R172 mutation were eligible to participate in the study. In addition, patients had to have undergone at least one surgical intervention for a glioma, including biopsy, partial resection or complete resection, as their sole treatment, and, in the opinion of the principal investigator, they must not have had an instant need for immediate chemotherapy or radiotherapy, nor must have exhibited any high-risk characteristics. Study participants should have a non-enhancing tumour lesion that was measurable by MRI and had been confirmed by an independent review committee. A total of 331 patients were enrolled in the study, one of whom was below 18 years of age.

Randomised in a 1:1 ratio, 168 patients were assigned to the intervention arm and 163 patients to the control arm. The adolescent patient was assigned to the control arm.

The placebo arm of the ongoing INDIGO study included the option to switch treatment from placebo to vorasidenib. The prerequisites for this are radiological disease progression confirmed by an independent review committee, the principal investigator’s assessment that

no immediate chemotherapy, radiotherapy or other treatment is required and compliance with the basic inclusion and exclusion criteria - originally laid down for the start of study participation - at the final visit.

The study, which has been ongoing since 2020, is being conducted at 67 study sites across Europe, Israel and North America.

The primary endpoint of the study is progression-free survival, with radiological findings being assessed by an independent central review committee.

In the dossier, the pharmaceutical company presented data for the 3rd data cut-off from 7 March 2023 (data cut-off for unblinding; efficacy endpoints only) and the 4th data cut-off from 6 September 2023 (safety endpoints only). In their statement, the pharmaceutical company presented safety data for the 3rd data cut-off from 7 March 2023 relevant for the benefit assessment.

On the patient population and the transferability to the German healthcare context:

In accordance with the guidelines of the German Society for Haematology and Medical Oncology and the German Society of Neurology (S2k guideline), patients with IDH-mutated oligodendrogliomas and WHO Grade 2 diffuse astrocytomas may be treated with a "monitoring wait-and-see approach" following complete tumour resection (or in the presence of residual tumour in patients aged < 40 years) and in the absence of risk factors. If risk factors are present, radiotherapy followed by maintenance chemotherapy should be administered after the surgery. The guidelines identify the following risk factors: age ≥ 40 years, subtotal resection, neurological symptoms and uncontrolled epileptic seizures (at least three medications and at least one combination therapy).

The INDIGO study population has a good performance status and manageable epileptic seizures. As of the 2nd data cut-off, 74% of patients in the vorasidenib arm and 77% of patients in the placebo arm received an antiepileptic drug as concomitant medication. As of the 3rd data cut-off, no data are available. Half of the study participants were above 40 years of age, and a further 50% or so had undergone partial resection or biopsy of the tumour prior to enrolment in the study.

In their statement and during the oral hearing, the scientific-medical societies stated that an age ≥ 40 years, or the history of a partial resection in the therapeutic indication, is not considered an exclusion factor for a watch-and-wait strategy, and that the guidelines are currently being revised. The decision on the suitability of patients for a watch-and-wait strategy is sometimes based on individual criteria. The size and localisation of the tumours, as well as neurological symptoms and uncontrolled epilepsy, are key factors for making the treatment decision. The information on age in the guidelines to be updated was originally related to IDH wild-type tumours. Due to their diffuse growth, curative total resection of these tumours is not possible; the procedure always involves a macroscopic complete resection of the mutations visible on imaging.

The G-BA therefore consider the suitability of the INDIGO study population for a watch-and-wait strategy to be adequate.

Mortality

Overall survival was defined in the INDIGO study as the time between randomisation and death, regardless of the underlying cause of death.

Only one death was recorded in the vorasidenib arm, meaning that there is no relevant difference for the benefit assessment for this endpoint.

Morbidity

Progression-free survival (PFS)

Progression-free survival is operationalised in the study as the time between randomisation and radiologically confirmed disease progression or death (regardless of the underlying cause), based on the assessment by a blinded, independent review committee (BIRC) in accordance with the modified Response Assessment for Neuro-Oncology for Low-Grade Gliomas (RANO-LGG).

For the PFS endpoint, there was a statistically significant difference in favour of vorasidenib compared with placebo.

The present PFS endpoint is a composite endpoint consisting of endpoints from the "mortality" and "morbidity" categories. The endpoint component "mortality" is already assessed via the endpoint "overall survival" as an independent endpoint. The morbidity component was assessed using the modified RANO criteria, whilst disease progression in the PFS operationalisation by BIRC was assessed solely on the basis of radiological criteria.

Taking into account the aspects mentioned above, there are different opinions within the G-BA regarding the patient relevance of the PFS endpoint.

The overall statement on the extent of the additional benefit remains unaffected.

Symptomatology (PGI-S and PGI-F)

The Patient Global Impression of Severity (PGI-S) and Patient Global Impression of Frequency (PGI-F) questionnaires assess the perceived severity of symptoms (glioma symptoms, neurocognitive functions and epileptic seizures) and the perceived frequency of epileptic seizures, respectively. The change in disease symptomatology was operationalised as the "time to first deterioration" in the dossier.

The symptoms exactly reported by patients in the PGI-S questionnaire in relation to the severity of glioma symptomatology and neurocognitive function is unclear. The operationalisation of PGI-S and PGI-F in relation to epileptic seizures is considered adequate.

In the INDIGO study, the questionnaires were updated in line with the second protocol amendment (version 3.0; 17 December 2020) and were therefore not collected from all enrolled patients from the start of the study. At baseline, data are available for only 14% (vorasidenib arm) and 10% (control arm) of the study population. At the end of treatment, the return rates for the FAS population were 10% in the vorasidenib arm and 24% in the control arm. Consequently, the data from the PGI-S and PGI-F measurement tools are not assessable overall.

Health status (EQ-5D VAS)

The health status is assessed using the visual analogue scale (VAS) of the EQ-5D questionnaire.

In the dossier, the pharmaceutical company presented responder analyses, operationalised as the time to first deterioration by ≥ 15% (corresponding to ≥ 15 points).

There were no statistically significant differences between the treatment arms.

Epileptic seizures

For the "epileptic seizures" endpoint, the frequency and severity of epileptic seizures in the INDIGO study were collected in a patient diary. During each study visit, the entries in the patient diary were assessed by the principal investigators. In addition, seizure activity was assessed by tracking changes in the use of anti-epileptic medication (frequency of use; dosage).

The patient diary, including details of its standard use, not being submitted with the dossier was criticised in the benefit assessment. There was also a lack of information regarding the reliability and validity of patients' subjective assessment of the severity of their seizures and loss of consciousness, the validity of the retrospective assessments made by the medical study staff, and the completeness of the diary entries. Furthermore, it remained unclear to what extent the collection of epileptic seizures using the diary differed from the collection of epileptic seizures as part of the safety endpoints, as no criteria had been set out for this. The operationalisation of "persistent seizures" was also deemed unclear. With regard to the data basis, there was unclarity regarding the analyses of seizure activity at baseline and at visit 1, as different values had been reported. It was also unclear whether the statistical analysis method used in the negative binomial regression model presented was appropriate, given the extreme values recorded for individual subjects, and whether additional presentation of sensitivity analyses was considered necessary. To address the outliers, a graphical representation of the seizure frequency per visit and, if applicable, a further sensitivity analysis should be presented. Information on the total number of subject-years should also be included.

In their statement, the pharmaceutical company presented the patient diary, including details on the handling and training of patients and, according to the aforementioned points of criticism, information on the analyses of seizure activity regarding baseline data, the completeness of diary entries, "persistent epileptic seizures" and information on the classification of epileptic seizures as AEs or as part of the efficacy endpoint.

In response to the point of criticism regarding the lack of sensitivity analyses, the pharmaceutical company presented supplementary analyses as part of their statement, including the "rate ratio at the time of the median observation period", a "zero-inflated negative binomial regression model" and a graphical representation of the seizure frequency over time.

The G-BA consider the frequency and severity of epileptic seizures to be patient-relevant.

Patients report the number of epileptic seizures, their severity on a scale of 1 (not bad) to 10 (as bad as imaginable), and any loss of consciousness resulting from the seizures, in the patient diaries on the following day. At the start of each treatment cycle, the medical investigators review the patient diaries and record the findings in a separate study form. The seizure frequency, the number of seizures involving loss of consciousness, the severity of the most severe seizure (on the same scale as in the patient diary) and the number of days without a diary entry are collected. The use of a patient diary to record the frequency and severity of epileptic seizures is considered appropriate.

However, there is uncertainty regarding the validity of the baseline survey, specifically as to the extent to which the frequency of epileptic seizures can be retrospectively recorded over a 30-day period with sufficient validity.

With regard to return rates, data on the frequency of epileptic seizures were available for less than 70% of patients from visit 12 in the placebo arm and visit 16 in the vorasidenib arm (out of a maximum of 35 and 38 visits, respectively).

The graphical representation of the frequencies of epileptic seizures at baseline and during subsequent study visits shows that a small number of patients, predominantly in the placebo arm, experienced an extremely high seizure frequency (> 100 seizures in a 30-day treatment cycle). Furthermore, epileptic seizures occurred in only around one-third of study participants across both study arms of the INDIGO study.

It would have been desirable for the pharmaceutical company to have carried out further analyses, excluding the outliers, in order to take them into account. Whether a relatively small group of patients is responsible for the observed effect thus remains uncertain.

The pharmaceutical company presented data on the "rate of epileptic seizures per subject-year" in the dossier and subsequently submitted sensitivity analyses with consistent results in their statement. Overall, this means that the data on the "rate of epileptic seizures per subject-year" can be used for the benefit assessment in spite of methodological uncertainty.

In the endpoint of epileptic seizures, there was an advantage in the vorasidenib arm over the placebo arm; however, this advantage cannot be reliably quantified due to the mentioned uncertainties.

Tumour volume

In the INDIGO study, tumour volume is a component of the tumour growth endpoint and is operationalised as the percentage change in tumour volume (measured in cubic millimetres). The tumour volume, as measured by MRI, was determined based on the assessment of radiological findings by a blinded, independent review committee (BIRC) at baseline and, in line with the tumour assessment schedule for the "progression-free survival" endpoint, until disease progression was confirmed by the BIRC or until the start of a new anti-tumour therapy.

Given the increasingly high percentages of missing values during the study, the results of cycle 13 are considered, for which tumour volume measurements were available for at least 70% of patients from the FAS population in both study arms.

In the INDIGO study, cycle 13 showed a statistically significant smaller increase in tumour volume with vorasidenib compared with placebo, compared to baseline.

These results of change in tumour volume are not used for derivation of an additional benefit. As these are clinically relevant results, they are presented additionally.

Quality of life

Functional Assessment of Cancer Therapy – Brain (FACT-Br)

The health-related quality of life of patients in the INDIGO study is assessed using the FACT-Br questionnaire, which comprises the FACT-G[2] and a subscale for primary brain tumours (FACT-BrS[3]).

In the dossier, the pharmaceutical company presented responder analyses, operationalised as time to first deterioration by ≥ 15% of the scale range.

[2] The FACT-G is the generic core questionnaire of the "Functional Assessment of Chronic Illness Therapy" (FACIT) measurement

[3] FACT-BrS, subscale for primary brain tumours

There were no statistically significant differences between the treatment arms.

Side effects

In the dossier, results on side effects as of the 4th data cut-off from 6 September 2023 were presented. In their statement, the pharmaceutical company presented safety data for the 3rd data cut-off from 7 March 2023 relevant for the benefit assessment.

The results on adverse events without disease-related events are used for the benefit assessment. Uncertainty arises from the fact that the pharmaceutical company has not pre-specified the list of disease-related events and has not provided justification for the selection of disease-related events.

Adverse events (AEs) in total

In the INDIGO study, an AE occurred in almost all patients in the vorasidenib arm and in 95.1% of patients in the placebo arm. The results were only presented additionally.

Serious AEs (SAEs)

For the endpoint of SAEs, there was no statistically significant difference between the treatment arms.

Severe AEs (CTCAE grade ≥ 3)

For the endpoint of severe AEs, there was a statistically significant disadvantage.

Therapy discontinuation due to AEs

No data are available for the endpoint of therapy discontinuation due to AEs.

In the overall analysis of the endpoints on side effects, treatment with vorasidenib showed a disadvantage for severe AEs. No data are available for the endpoint of therapy discontinuation due to AEs.

Overall assessment

Results on mortality, morbidity, quality of life and side effects from the double-blind RCT INDIGO, which compared vorasidenib with placebo, are available for the benefit assessment of vorasidenib for the treatment of predominantly non-enhancing Grade 2 astrocytoma or oligodendroglioma with an IDH1 R132 or IDH2 R172 mutation in adult and adolescent patients aged 12 years and older and weighing at least 40 kg who only had surgical intervention and are not in immediate need of radiotherapy or chemotherapy.

For the endpoint of overall survival, there was no relevant difference for the benefit assessment.

Morbidity was assessed using the endpoints of epileptic seizures, symptomatology (PGI-S; PGI-F) and health status (EQ-5D VAS).

Vorasidenib showed an advantage in the endpoint of epileptic seizures.

No assessable data on symptomatology (using PGI-S and PGI-F) are available. With regard to the health status (EQ-5D VAS), there was no statistically significant difference between the treatment arms.

For the health-related quality of life, as assessed using the FACT-Br, there were no statistically significant differences between the treatment arms.

For the side effects, the overall rate of serious AEs (SAEs) showed no relevant difference between the treatment arms for the benefit assessment. For severe AEs, treatment with vorasidenib showed a disadvantage. No data are available for the endpoint of therapy discontinuation due to AEs.

The overall assessment showed an advantage for the endpoint of epileptic seizures in the morbidity endpoint category. Due to the uncertainties mentioned above, the extent of the improvement in epileptic seizures cannot be quantified with certainty. Furthermore, there was a disadvantage in terms of side effects for the overall rate of severe AEs; however, this does not cast a doubt on the additional benefit overall.

The G-BA therefore assess the extent of the additional benefit of vorasidenib for the treatment of predominantly non-enhancing Grade 2 astrocytoma or oligodendroglioma with an IDH1 R132 or IDH2 R172 mutation in adult and adolescent patients aged 12 years and older and weighing at least 40 kg who only had surgical intervention and are not in immediate need of radiotherapy or chemotherapy, as non-quantifiable, since the scientific data does not allow quantification.

Significance of the evidence

The double-blind RCT INDIGO forms the basis of the present benefit assessment.

Overall, the risk of bias at the study level is rated as low.

For the endpoint of overall survival, the risk of bias is not assessable.

The risk of bias for the "epileptic seizures" endpoint is estimated to be high. There is uncertainty regarding the validity of the baseline survey, the return rates and the fact that a small number of patients, predominantly in the placebo arm, experienced an extremely high seizure frequency. Furthermore, epileptic seizures occurred in only about one-third of the study participants across both study arms.

The endpoint-specific risk of bias for the results of the patient-reported endpoints on morbidity (EQ-5D-VAS) and health-related quality of life (FACT-Br) is rated as high in each case as the return rates of the questionnaires were < 70% early on.

There was a low risk of bias for the endpoint of side effects.

In summary, the G-BA derive a hint for the identified additional benefit with regard to the significance.

2.1.3 Summary of the assessment

The present assessment concerns the benefit assessment of the new medicinal product Voranigo with the active ingredient vorasidenib.

Vorasidenib was approved as an orphan drug for use as monotherapy for the treatment of predominantly non-enhancing Grade 2 astrocytoma or oligodendroglioma with an IDH1 R132 or IDH2 R172 mutation in adult and adolescent patients aged 12 years and older and weighing at least 40 kg who only had surgical intervention and are not in immediate need of radiotherapy or chemotherapy.

Results on mortality, morbidity, quality of life and side effects from the double-blind RCT INDIGO, which compared vorasidenib with placebo, are available for the benefit assessment.

For the endpoint of overall survival, there was no relevant difference for the benefit assessment.

Morbidity was assessed based on the endpoints of epileptic seizures, symptomatology (PGI-S; PGI-F) and health status (EQ-5D VAS).

Vorasidenib showed an advantage in the endpoint of epileptic seizures.

No assessable data on symptomatology (using PGI-S and PGI-F) are available. For the health status, there was no statistically significant difference between the treatment arms.

For the health-related quality of life, as assessed using the FACT-Br, there were no statistically significant differences between the treatment arms.

For the side effects without disease-related events, the overall rate of serious AEs (SAEs) showed no relevant difference between the treatment arms for the benefit assessment. For severe AEs, treatment with vorasidenib showed a disadvantage. No data are available for the endpoint of therapy discontinuation due to AEs.

The overall assessment showed an advantage for the endpoint of epileptic seizures in the morbidity endpoint category. However, this endpoint is subject to uncertainty regarding the validity of the baseline survey, the return rates and the fact that a small number of patients, predominantly in the placebo arm, experienced an extremely high seizure frequency. Furthermore, epileptic seizures occurred in only about one-third of the study participants across both study arms. Due to the uncertainties mentioned above, the extent of the improvement in epileptic seizures cannot be quantified with certainty. Furthermore, there was a disadvantage in terms of side effects for the overall rate of severe AEs; however, this does not cast a doubt on the additional benefit overall.

The G-BA therefore classify the extent of the additional benefit of vorasidenib as non-quantifiable since the scientific data does not allow quantification.

The reliability of data of the additional benefit identified is classified as a "hint".

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 pharmaceutical company’s derivation of the patient numbers in the dossier is subject to uncertainty overall.

This is especially due to possible discrepancies in the grading of astrocytomas and oligodendrogliomas resulting from the use of different WHO classification systems, the consideration of a reference period for prevalence that is too short, and a failure to take into account the most up-to-date data on population trends.

Given the uncertainty with regard to the data basis, overestimation as well as underestimation of patient numbers is possible.

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 Voranigo (active ingredient: vorasidenib) at the following publicly accessible link (last access: 29 April 2026):

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

Treatment with vorasidenib should only be initiated and monitored by specialists in internal medicine, haematology, and oncology, specialists in neurology, as well as specialists in neurosurgery or specialists in paediatrics and adolescent medicine with a specialisation in neuropaediatrics or paediatric haematology and oncology, all of whom are experienced in the treatment of patients with glioma, and other specialists from other specialist groups participating in the Oncology Agreement.

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: 1 March 2026). The calculation of treatment costs is generally based on the last revised LAUER-TAXE® version following the publication of the benefit assessment.

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

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 is different 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:				
Vorasidenib	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:					
Vorasidenib	40 mg	40 mg	1 x 40 mg	365	365 x 40 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:

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:					
Vorasidenib 40 mg	30 TAB	€ 22,440.73	€ 1.77	€ 1,281.00	€ 21,157.96
TAB = tablets					

LAUER-TAXE® last revised: 1 March 2026

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 additional SHI services required 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 designate 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 have 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 have 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 data from the product 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 requirements 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 have 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 statutory 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 and adolescents aged 12 years and older and weighing at least 40 kg with predominantly non-enhancing Grade 2 astrocytoma or oligodendroglioma with an IDH1 R132 or IDH2 R172 mutation who only had surgical intervention and are not in immediate need of radiotherapy or chemotherapy

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 approved in monotherapy.

References:
Product information for vorasidenib (Voranigo); SERVIER Voranigo film-coated tablets; last revised: September 2025

2.6 Percentage of study participants at study sites within the scope of SGB V in accordance with Section 35a, paragraph 3, sentence 5 SGB V

The medicinal product Voranigo is a medicinal product placed on the market from 1 January 2025. In accordance with Section 35a, paragraph 3, sentence 5 SGB V, the G-BA must determine whether a relevant percentage of the clinical studies on the medicinal product were conducted within the scope of SGB V. This is the case if the percentage of study participants who have participated in the clinical studies on the medicinal product to be assessed in the therapeutic indication to be assessed at study sites within the scope of SGB V is at least five per cent of the total number of study participants.

The calculation is based on all studies that were submitted as part of the benefit assessment dossier in the therapeutic indication to be assessed in accordance with Section 35a, paragraph 1, sentence 3 SGB V in conjunction with Section 4, paragraph 6 AM-NutzenV.

Approval studies include all studies submitted to the regulatory authority in section 2.7.3 (Summary of Clinical Efficacy) and 2.7.4 (Summary of Clinical Safety) of the authorisation dossier in the therapeutic indication for which marketing authorisation has been applied for. In addition, studies, which were conducted in whole or in part within the therapeutic indication described in this document, and in which the company was a sponsor or is otherwise financially involved, must also be indicated.

The percentage of study participants in the clinical studies of the medicinal product conducted or commissioned by the pharmaceutical company in the therapeutic indication to be assessed who participated at study sites within the scope of SGB V (German Social Security Code) is < 5 per cent (1.7%) of the total number of study participants according to the information provided by the pharmaceutical company.

The pharmaceutical company provide information on 4 studies (INDIGO [AG881-C-004], AG881-C-002, AG120-881-C-001, AG881-C-001) and state the percentage of study participants at study sites within the scope of SGB V as 1.7% across all relevant studies. In comparison with the Common Technical Document, further studies, which were submitted to the regulatory authority for the assessment of the clinical efficacy and safety of the medicinal product in the therapeutic indication to be assessed, were identified; however, these studies were conducted in other countries. It can therefore be assumed that the percentage of study participants at study sites within the scope of SGB V continue to remain below 5% of the total number of study participants.

The clinical studies of the medicinal product in the therapeutic indication to be assessed were therefore not conducted to a relevant percentage within the scope of SGB V.

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 10 November 2025, the pharmaceutical company submitted a dossier for the benefit assessment of vorasidenib 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 February 2026 together with the IQWiG assessment of treatment costs and patient numbers on the G-BA website (www.g-ba.de), thus initiating the written statement procedure. The deadline for submitting statements was 9 March 2026.

The oral hearing was held on 23 March 2026.

An amendment to the benefit assessment with a supplementary assessment of data submitted in the written statement procedure was submitted on 10 April 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 conclusively discussed at the Subcommittee's session on 28 April 2026, and the draft resolution was approved.

At their session on 7 May 2026, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee on Medicinal Products	10 February 2026	Information of the benefit assessment of the G-BA
Working group Section 35a	18 March 2026	Information on written statements received; preparation of the oral hearing
Subcommittee on Medicinal Products	23 March 2026	Conduct of the oral hearing
Working group Section 35a	1 April 2026 15 April 2026	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 on Medicinal Products	28 April 2026	Concluding discussion of the draft resolution
Plenum	7 May 2026	Adoption of the resolution on the amendment of the Pharmaceuticals Directive

Berlin, 7 May 2026

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

Prof. Hecken