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 and Annex XIIa – Combinations of Medicinal Products with New Active Ingredients according to Section 35a SGB V Dabrafenib (malignant glioma, BRAF V600E mutation, ≥ 1 year, low-grade (LGG)/ high-grade (HGG) after at least 1 prior therapy; combination with trametinib)

of 17 October 2024

Contents

1. Legal basis

According to Section 35a paragraph 6 SGB V, the G-BA can initiate a benefit assessment according to paragraph 1 for a medicinal product with an active ingredient that is not a new active ingredient according to Section 35a paragraph 1, if a new marketing authorisation with new dossier protection is granted for the medicinal product. According to Chapter 5 Section 16, paragraph 1, sentence 3 of the Rules of Procedure of the G-BA, a benefit assessment according to Section 35a paragraph 6 SGB V can be initiated in particular for medicinal products whose therapeutic indication differs from the therapeutic indication of medicinal products with the same known active ingredients. According to Chapter 5 Section 16, paragraph 1, sentence 4 of the Rules of Procedure of the G-BA, a deviation may result in particular from changes in a therapeutic indication that are attributable to a different therapeutic indication compared to the therapeutic indication of the medicinal product with the same known active ingredient, by the fact that:

– the therapeutic indication relates to a different group of patients or

– the therapeutic area (treatment, diagnosis or prevention) differs.

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 originally the first placing on the (German) market of the active ingredient dabrafenib on 1 May 2024 in accordance with Section 4, paragraph 3, number 1 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with Chapter 5 Section 8, paragraph 1, number 1, sentence 3 of the Rules of Procedure (VerfO) of the G-BA. At that time, the medicinal product Finlee with the active ingredient dabrafenib was still a medicinal product with a new active ingredient according to Section 2, paragraph 1, sentence 2 AM-NutzenV, as the first approved medicinal product Tafinlar with this active ingredient was still under dossier protection.

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 25 April 2024.

The dossier protection for the medicinal product Tafinlar expired on 26 August 2024.

For the medicinal product with the active ingredient dabrafenib, which was approved and placed on the market for the first time in Germany, there is therefore no longer any dossier protection at the time of adoption of the resolution. The active ingredient dabrafenib is therefore a known active ingredient.

As a new dossier protection is to be considered in the context of the marketing authorisation for the medicinal product Finlee with the active ingredient dabrafenib, the factual requirements of Chapter 5 Section 16, paragraph 1 VerfO are met and a benefit assessment according to Section 35a paragraph 6 SGB V in conjunction with Chapter 5 Section 16, paragraph 1 VerfO can be initiated. The therapeutic indication of the new medicinal product Finlee with the active ingredient dabrafenib differs from the therapeutic indication of the already approved medicinal products with the active ingredient dabrafenib, as a marketing authorisation was granted for the first time for this active ingredient in the therapeutic indication of low-grade and high-grade gliomas, which is aimed at the treatment of paediatric patients aged one year and older. The new medicinal product therefore relates to a group of patients other than the already approved medicinal products. The G-BA therefore came to the conclusion that a benefit assessment should be initiated for the medicinal product Finlee with

the active ingredient dabrafenib, which is based on Section 35a paragraph 6 SGB V at the time of adoption of the resolution.

Dabrafenib in combination with trametinib for the treatment of paediatric patients aged 1 year and older with low-grade glioma (LGG) with a BRAF V600E mutation who require systemic therapy and for the treatment of paediatric patients aged 1 year and older with high-grade glioma (HGG) with a BRAF V600E mutation who have received at least one prior radiation and/or chemotherapy treatment, is approved as a medicinal product for the treatment of rare diseases in accordance with Regulation (EC) No 141/2000 of the European Parliament and 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 1 August 2024 together with the IQWiG assessment on the website of the G-BA (www.g-ba.de), thus initiating the written statement procedure. In addition, an oral hearing was held.

The G-BA made its resolution on the basis of the pharmaceutical company's dossier, the dossier assessment carried out by the G-BA, the IQWiG assessment of treatment costs and patient numbers (IQWiG G24-07) and the statements made in the written statement and oral hearing procedure, as well of the amendment drawn up by the G-BA on the benefit assessment.

In order to determine the extent of the additional benefit, the G-BA has evaluated the studies relevant for the marketing authorisation 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 dabrafenib.

2.1 Additional benefit of the medicinal product

2.1.1 Approved therapeutic indication of Dabrafenib (Finlee) in accordance with the product information

Low-grade glioma

Finlee in combination with trametinib is indicated for the treatment of paediatric patients aged 1 year and older with low-grade glioma (LGG) with a BRAF V600E mutation who require systemic therapy.

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

High-grade glioma

Finlee in combination with trametinib is indicated for the treatment of paediatric patients aged 1 year and older with high-grade glioma (HGG) with a BRAF V600E mutation who have received at least one prior radiation and/or chemotherapy treatment.

Therapeutic indication of the resolution (resolution of 17 October 2024):

"see approved therapeutic indication"

2.1.2 Extent of the additional benefit and significance of the evidence

In summary, the additional benefit of dabrafenib in combination with trametinib is assessed as follows:

a) Paediatric patients aged 1 year and older with low-grade glioma (LGG) with a BRAF V600E mutation who require systemic therapy

a1) Patients without prior treatment of LGG

Hint for a considerable additional benefit.

Justification:

For the assessment of the extent of the additional benefit of dabrafenib in combination with trametinib in the therapeutic indication of non-pretreated low-grade glioma (LGG) with BRAF V600E mutation, the pharmaceutical company presented data from the pivotal phase II CDRB436G2201 (G2201) study.

G2201 study

The G2201 study is a multicentre, open-label phase II study with 2 cohorts started in December 2017 to investigate the efficacy and safety of dabrafenib combination with trametinib children and adolescents aged ≥ 12 months to < 18 years with low-grade glioma (LGG cohort) and high-grade glioma (HGG cohort) and BRAF V600E mutation. Only patients under the age of 18 years were enrolled in the G2201 study according to the product information.

The LGG cohort is the randomised controlled part of the study comparing dabrafenib in combination with trametinib against carboplatin in combination with vincristine in children and adolescents with progressive unresectable BRAF V600E-positive LGG who require initial systemic treatment due to the risk of neurological impairment with disease progression (after surgical resection and in unresectable cases). A total of 110 patients with a Karnofsky/Lansky Performance Status (K-/LPS) ≥ 50% were enrolled and randomised in a ratio of 2:1 to the study arms dabrafenib + trametinib (N = 73) and carboplatin + vincristine (N = 37).

The study was conducted in 58 study sites in particular in Australia, Europe as well as North and South America.

The primary endpoint of the study was the overall response rate (ORR), whereby the radiological findings were assessed by an independent central review committee. Other endpoints, among others, on overall survival, response, quality of life and adverse events were collected.

In the dossier for the benefit assessment, the pharmaceutical company submitted the final data cut-off from 28.04.2023, which is used for the benefit assessment.

Mortality

Overall survival was defined in the G2201 study as the time from the start of treatment until death from any cause.

For paediatric patients with non-pretreated LGG, there was no statistically significant difference based on the results of the G2201 study.

Morbidity

Overall response rate

The overall response rate (ORR) was the primary endpoint in the G2201 study. The response was assessed on the basis of the Response Assessment Neuro-Oncology (RANO) criteria by an independent central review committee and by the investigators.

The RANO criteria include imaging procedures, an assessment of the clinical condition and the use of corticosteroids.

The clinical condition was assessed by the principal investigator using the Karnofsky/Lansky Performance Status (K-/LPS), whereby the Lansky PS was collected for children under 16 years of age and the Karnofsky PS for children aged 16 and older.

The overall response rate was operationalised as follows:

- Percentage of subjects with a confirmed partial response (PR) or complete response (CR) as best response

Complete response was defined as follows:

- Disappearance of all measurable and non-measurable lesions for at least 4 weeks in the MRI scan and no new lesions
- No intake of steroids or only physiological replacement doses
- Stable or improved clinical condition

Partial response was defined as follows:

- 50% reduction in all measurable lesions compared to baseline for at least 4 weeks
- No progression of the non-measurable disease and no new lesions.
- Corticosteroid dose must not be higher than the dose at the time of the baseline scan
- Stable or improved clinical condition

If there is no confirmatory scan 4 weeks later in both cases (CR and PR), this is only assessed as stable disease. In addition, all the criteria listed had to be fulfilled for a CR and PR (AND operation).

The RANO criteria used in the study correspond to the clinical standard at the start of the study, which was also correspondingly implemented according to the statements of the clinical experts at the oral hearing.

When looking at the results of the overall response rate, 52.1% of patients in the intervention arm showed a PR and 2.7% a CR. In the control arm, a PR was observed in 13.5% and a CR in 2.7% of the patients. Overall, there was a statistically significant advantage in the overall response rate of dabrafenib in combination with trametinib compared to carboplatin and vincristine.

There are uncertainties regarding the assessment of the clinical condition by the medical investigators:

The study protocol only included criteria for deterioration, but not for improvement. Accordingly, a reduction in the K-/LPS by around 20 points indicated a deterioration in the health status. As it emerged from the oral hearing, however, the final judgement as to whether there was a deterioration lay with the medical investigators. The analyses presented show that the observed changes in the K-/LPS were predominantly 10 points, thus not corresponding to the 15% scale range as defined in the IQWIG methods paper for complex scales.

An improvement/ deterioration in the clinical condition was therefore based predominantly on the subjective judgement of the medical investigators. Furthermore, it cannot be ruled out that the assessment of the clinical condition was made with knowledge of the radiological findings.

The data presented also shows that the baseline value for over 80% of patients was 100 points (normal, no conditions, no indication of illness/ completely active, normal) or 90 points (able to carry out a normal activity, few signs of disease symptoms/ few restrictions on physically strenuous activities). An improvement by 20 points would not have been possible in these cases.

Furthermore, no systematic collection of the K/LPS by the medical investigators was ensured over the entire observation period, as the return rates at week 16 were approx. 93% in the intervention arm and only approx. 46% in the comparator arm.

Due to these relevant uncertainties, the G-BA is of the opinion that the available data on response cannot be assessed with sufficient certainty using the RANO criteria. Therefore, no advantage of dabrafenib in combination with trametinib relevant for the benefit assessment was derived. As this is the primary endpoint of the G2201 study, the data submitted are shown.

Irrespective of this, the response based on the RANO criteria is considered a relevant clinical parameter in this therapeutic indication.

Progression-free survival

Progression-free survival in the G2201 study was defined as the time from randomisation to first documented progression assessed using RANO criteria or death from any cause.

With dabrafenib in combination with trametinib, the PFS was statistically significantly prolonged by 17.7 months compared to carboplatin in combination with vincristine.

The present PFS endpoint is a composite endpoint consisting of endpoints from the categories "mortality" and "morbidity". The endpoint component "mortality" has already been assessed as an independent endpoint via the endpoint "overall survival". The collection of the morbidity component was on the basis of the RANO criteria, whereby at least one criterion had to be fulfilled for progression.

In addition to imaging procedures, the RANO criteria also take into account the clinical condition of the patients and their consumption of corticosteroids, whereby the clinical condition was collected and assessed by the medical investigators using the Karnofsky/Lansky Performance Status (K-/LPS).

The same uncertainties as described under the overall response rate apply to the assessment of the clinical condition. In addition, for PFS, the presence of a fulfilled criterion was sufficient to be counted as disease progression. It is unclear in how many patients there was a deterioration in the clinical condition and in how many a change in the imaging procedures was the decisive factor. In addition, there were no (assessable) results on disease-specific symptomatology and patient-reported endpoints from the categories of morbidity and health-related quality of life. These results were relevant in the present case because radiologically disease progression may be associated to effects on morbidity and/or quality of life.

It therefore remains unclear in particular to what extent the prolonged PFS with dabrafenib in combination with trametinib in the G2201 study was associated with an advantage in terms of disease-specific symptomatology.

In summary, it is not clear from the available data that the statistically significant prolongation in the time of progression-free survival under dabrafenib in combination with trametinib - measured using the RANO criteria - is associated with an improvement in morbidity and/or quality of life.

The results on the PFS endpoint are therefore not used.

Symptomatology (PROMIS PGH 7+2)

The symptomatology endpoint of the LGG cohort of the G2201 study was assessed using PROMIS PGH 7+2. However, the data cannot be analysed due to a return rate < 70% in one arm and large differences in the return rates between the study arms (> 15%).

Quality of life

Quality of life in the LGG cohort of the G2201 study was assessed using PROMIS PGH 7+2. However, the data cannot be analysed due to a return rate < 70% in one arm and large differences in the return rates between the study arms (> 15%).

Side effects

In the G2201 study, all adverse events that occurred from the day of study consent until 30 days after the last administration of the study medication were categorised as AEs.

In the dossier for the benefit assessment, no evaluations excluding AEs that are due to the underlying disease were presented. Only the progression of the tumour was not assessed as an AE. Therefore, it cannot be excluded that events of the underlying disease are included in the observed AEs.

AEs occurred in all patients with non-pretreated LGG in both the intervention and control arms.

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

For the endpoints of severe AEs and therapy discontinuation due to AEs, there were statistically significant differences to the advantage of dabrafenib in combination with trametinib, which are assessed as a significant improvement.

In detail, there were statistically significant differences to the advantage of dabrafenib in combination with trametinib in the specific AEs with regard to "Lymphatic system disorders", "Gastrointestinal disorders", "investigations", "Neutropenia", "Leukopenia" and, in detail, advantages and disadvantages in the AEs of special interest.

Overall, there was a significant advantage of dabrafenib in combination with trametinib over carboplatin and vincristine in the endpoint category of side effects in paediatric patients with non-pretreated LGG.

Overall assessment

Comparator data from the LGG cohort of the pivotal G2201 study on overall survival, morbidity, health-related quality of life and side effects compared to carboplatin and vincristine are available for the benefit assessment.

In the endpoint category of mortality, there was no statistically significant difference between the treatment arms.

In the endpoint category of morbidity, results are available on overall response and progression-free survival, which were collected using the RANO criteria. However, these results cannot be assessed with sufficient certainty due to relevant uncertainties regarding the data collected on the clinical condition.

The results on symptomatology, collected using PROMIS PGH, are not assessable.

For the endpoint category of morbidity, there were no relevant differences for the benefit assessment overall.

The results on health-related quality of life collected using PROMIS PGH are not assessable.

For the endpoint category of side effects, there were statistically significant advantages for severe AEs and therapy discontinuation due to AEs, which are assessed as a significant improvement. In detail, there were predominantly advantages for specific AEs.

In the overall assessment, the G-BA identified a considerable additional benefit of dabrafenib in combination with trametinib for paediatric patients with LGG without prior treatment due to the significant advantages in side effects.

Significance of the evidence

The present benefit assessment is especially based on the results of the randomised, open-label, multicentre controlled G2201 study.

As part of the written statement procedure, the clinical experts emphasised the relevance of the disease-specific symptomatology in this therapeutic indication. However, this was not collected in the G2201 study. With the RANO criteria, only the clinical condition was assessed using Karnofsky/Lansky-PS, which does not reflect the disease-specific symptomatology. Usable data on health-related quality of life were also not available.

In summary, the G-BA deduces a hint for the identified additional benefit with regard to the reliability of data (probability of additional benefit).

a) Paediatric patients aged 1 year and older with low-grade glioma (LGG) with a BRAF V600E mutation who require systemic therapy

a2) Patients with previous treatment of LGG

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

Justification:

For the assessment of the extent of the additional benefit of dabrafenib in combination with trametinib in the therapeutic indication of low-grade glioma (LGG) with BRAF V600E mutation after prior treatment, the pharmaceutical company submitted data from the single-arm CTMT212X2101 (X2101) study.

X2101 study

The X2101 study is an open-label, single-arm study conducted between January 2015 and December 2020 consisting of 4 parts to investigate dabrafenib in combination with trametinib in children and adolescents with recurrent or refractory solid tumours after at least one prior

therapy, whereby parts C and D are used for the benefit assessment, as only these mainly investigate a combination of dabrafenib and trametinib that is essentially in line with the product information. Only patients under the age of 18 years were enrolled in the X2101 study according to the product information.

A total of 36 patients with LGG (N = 34) and HGG (N = 2) from - part C on dose finding in children and adolescents with BRAF V600E-positive solid tumours and part D of the study on the evaluation of safety, tolerability and clinical activity of dabrafenib + trametinib in children and adolescents with BRAF V600E-positive tumours - are relevant for the benefit assessment (part C n = 16; part D n = 20). Of these 36 patients, 31 received a dosage that was essentially in line with the product information.

The study was conducted in 16 study sites in Australia, Europe and North America.

Overall survival and adverse events were collected as patient-relevant endpoints.

The primary endpoint of the study was the determination of the safe and tolerable dose of trametinib for the treatment of paediatric patients (including AE).

The final data cut-off from 29.12.2020 is used for the benefit assessment.

Mortality

Overall survival was defined in the X2101 study as the time from the start of treatment until death from any cause.

No comparator data are available for patients after previous treatment of LGG, so that no statement on the extent of the additional benefit can be made on the basis of the results of the X2101 study.

Morbidity

Overall response rate

The overall response rate (ORR) in the X2101 study was determined in the same way as in the G2201 study. The response was assessed on the basis of the Response Assessment Neuro-Oncology (RANO) criteria by an independent central review committee and by the investigators.

The RANO criteria include imaging procedures, an assessment of the clinical condition and the use of corticosteroids.

The clinical condition was assessed by the principal investigator using the Karnofsky/Lansky Performance Status (K-/LPS), whereby the Lansky PS was collected for children under 16 years of age and the Karnofsky PS for children aged 16 and older.

The overall response rate was operationalised analogously to the G2201 study (see above comments on "Tumour response" in patient group a1)).

The overall response rate was 8 (25.8%) patients.

Essentially, the uncertainties mentioned above (see comments on "Tumour response" for patient group a1)) exist with regard to the threshold values, the subjective assessment by the medical investigators and the return rates.

Regardless of this, the results of the X2101 study do not allow a statement to be made on the extent of the additional benefit due to the absence of a control group.

The overall response rate is only presented additionally.

Progression-free survival

Progression-free survival in the X2101 study was defined as the time from the date of the first dose of test preparation to the first documented progression as assessed by RANO criteria or death from any cause.

In addition to imaging procedures, the RANO criteria also take into account the clinical neurological status of the patients and their consumption of corticosteroids, whereby the clinical neurological status was collected and assessed by the principal investigator using the Karnofsky/Lansky Performance Status (K-/LPS).

The present PFS endpoint is a composite endpoint consisting of endpoints from the categories "mortality" and "morbidity". The endpoint component "mortality" has already been assessed as an independent endpoint via the endpoint "overall survival". The collection of the morbidity component was on the basis of the RANO criteria, whereby at least one criterion had to be fulfilled for progression.

In addition to imaging procedures, the RANO criteria also take into account the clinical condition of the patients and their consumption of corticosteroids, whereby the clinical condition was collected and assessed by the medical investigators using the K-/LPS.

Essentially, the above-mentioned uncertainties exist (see comments on "Progression-free survival" for patient group a1)).

Regardless of this, the results of the X2101 study do not allow a statement to be made on the extent of the additional benefit due to the absence of a control group.

Quality of life

No health-related quality of life data were collected in the X2101 study.

Side effects

In the X2101 study, AEs occurred in all patients with pretreated LGG, 22 (61.1%) had a severe AE and 15 (41.7%) had an SAE. A total of 8 (22.2%) patients discontinued study medication due to AEs.

Due to the absence of comparator data, no statement can be made on the extent of the additional benefit for paediatric patients with pretreated LGG on the basis of these results.

Overall assessment

For the benefit assessment, non-comparator data on overall survival, morbidity and side effects are available from the X2101 study in patients with LGG and BRAF V600E mutation after previous treatment.

However, these data do not allow for a comparative assessment due to the single-arm study design. In the overall assessment, the extent of the additional benefit is classified as non-quantifiable since the scientific data does not allow quantification.

Significance of the evidence

The benefit assessment is based on data from the single-arm X2101 study. Due to the single-arm design of this study, a comparative assessment is not possible. The reliability of data is therefore assessed as a hint.

b) Paediatric patients aged 1 year and older with high-grade glioma (HGG) with a BRAF V600E mutation who have received at least one prior radiation and/or chemotherapy treatment

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

Justification:

For the assessment of the extent of the additional benefit of dabrafenib in combination with trametinib in the therapeutic indication of high-grade glioma (LGG) with BRAF V600E mutation, the pharmaceutical company presented data from the pivotal phase II CDRB436G2201 (G2201) study.

G2201 study

As described above, the G2201 study is a multicentre, open-label phase II study with 2 cohorts started in December 2017 to investigate the efficacy and safety of dabrafenib combination with trametinib children and adolescents aged ≥ 12 months to < 18 years with low-grade glioma (LGG cohort) and high-grade glioma (HGG cohort) and BRAF V600E mutation. Only patients under the age of 18 years were enrolled in the G2201 study according to the product information.

The HGG cohort is the single-arm part of the study in which dabrafenib in combination with trametinib was investigated in children and adolescents with relapsed or refractory BRAF V600 mutation-positive HGG after at least one previous line of therapy. A total of 41 patients with a Karnofsky/Lansky performance score ≥ 50% were enrolled.

The primary endpoint of the study was the overall response rate (ORR) with an assessment of the radiological findings by an independent central review committee. Secondary endpoints were collected in particular on overall survival and adverse events.

In the dossier for the benefit assessment, the pharmaceutical company submitted the final data cut-off from 28.04.2023, which is used for the benefit assessment.

Mortality

Overall survival was defined in the G2201 study as the time from the start of treatment until death from any cause.

17 (41.5%) deaths occurred. Since no comparator data are available, no statement on the extent of the additional benefit can be made on the basis of these results.

Morbidity

Overall response rate

The overall response rate (ORR) was the primary endpoint in the G2201 study. The response was assessed on the basis of the Response Assessment Neuro-Oncology (RANO) criteria by an independent central review committee and by the investigators.

The RANO criteria include imaging procedures, an assessment of the clinical condition and the use of corticosteroids.

The clinical condition was assessed by the principal investigator using the Karnofsky/Lansky Performance Status (K-/LPS), whereby the Lansky PS was collected for children under 16 years of age and the Karnofsky PS for children above 16 years of age.

The overall response rate was the primary endpoint of the G2201 study and was operationalised as follows:

- Percentage of subjects with a confirmed partial response (PR) or complete response (CR) as best response.

Complete response was defined as follows:

- Complete disappearance of all enhanced measurable and non-measurable diseases/ lesions on contrast-enhanced MRI scans over a period of at least 4 weeks.
- No new lesions and stable or improved non-enhanced (T2/FLAIR) lesions.
- No intake of steroids or only physiological replacement doses.
- Stable or improved clinical condition

Partial response was defined as follows:

- 50% reduction in all measurable lesions compared to baseline for at least 4 weeks.
- No progression of the non-measurable disease.
- No new lesions and stable or improved non-enhanced (T2/FLAIR) lesions.
- Corticosteroid dose must not be higher than the dose at the time of the baseline scan.
- Stable or improved clinical condition.

If there is no confirmatory scan 4 weeks later in both cases (CR and PR), this response is only assessed as stable disease. In addition, all the criteria listed had to be fulfilled for a CR and PR (AND operation).

The overall response rate was 23 (56.1%) patients.

Essentially, the uncertainties mentioned above (see comments on "Tumour response" for patient group a1)) exist with regard to the threshold values, the subjective assessment by the medical investigators and the return rates.

Regardless of this, the results of the HGG cohort of the single-arm part of the G2201 study do not allow a statement to be made on the extent of the additional benefit due to the absence of a control group.

As this is the primary endpoint of the G2201 study, it is nevertheless presented additionally.

Progression-free survival

Progression-free survival in the G2201 study was defined as the time from randomisation to the first documented progression or death from any cause, assessed using RANO criteria.

In addition to imaging procedures, the RANO criteria also take into account the clinical neurological status of the patients and their consumption of corticosteroids, whereby the clinical neurological status was collected and assessed by the principal investigator using the Karnofsky/Lansky Performance Status (K-/LPS).

The present PFS endpoint is a composite endpoint consisting of endpoints from the categories "mortality" and "morbidity". The endpoint component "mortality" has already been assessed as an independent endpoint via the endpoint "overall survival". The collection of the morbidity component was on the basis of the RAPNO criteria, whereby at least one criterion had to be fulfilled for progression.
In addition to imaging procedures, the RANO criteria also take into account the clinical condition of the patients and their consumption of corticosteroids, whereby the clinical condition was collected and assessed by the principal investigator using the K-/LPS.

Essentially, the above-mentioned uncertainties exist (see comments on "Progression-free survival" for patient group a1)).

Regardless of this, the results of the HGG cohort of the single-arm part of the G2201 study do not allow a statement to be made on the extent of the additional benefit due to the absence of a control group.

Quality of life

No health-related quality of life data were collected in the HGG cohort of the G2201 study.

Side effects

In the G2201 study, all adverse events that occurred from the day of study consent until 30 days after the last administration of the study medication were categorised as AEs.

In the dossier for the benefit assessment, no evaluations excluding AEs that are due to the underlying disease were presented. Only the progression of the tumour was not assessed as an AE. Therefore, it cannot be excluded that events of the underlying disease are included in the observed AEs.

AEs occurred in all patients. Severe AEs occurred in 28 (68.3%) and SAEs in 30 (73.2%) patients. A total of 2 (4.9%) patients discontinued treatment with dabrafenib in combination with trametinib due to AEs.

Since no comparator data are available, no statement on the extent of the additional benefit can be made on the basis of these results.

Overall assessment

Non-comparator data on overall survival, morbidity and side effects are available from the HGG cohort of the pivotal G2201 study for the benefit assessment.

However, these data do not allow for a comparative assessment due to the single-arm study design. In the overall assessment, the extent of the additional benefit is classified as non-quantifiable since the scientific data does not allow quantification.

Significance of the evidence

The benefit assessment is based on single-arm data from the HGG cohort of the G2201 study. Due to the single-arm design of this study, a comparative assessment is not possible. The reliability of data is therefore assessed as a hint.

2.1.3 Summary of the assessment

The present benefit assessment concerns the benefit assessment of the new medicinal product Finlee with the active ingredient dabrafenib.

Dabrafenib was approved in combination with trametinib as orphan drug for the treatment of paediatric patients aged 1 year and older with low-grade glioma (LGG) with a BRAF V600E mutation who require systemic therapy and for the treatment of paediatric patients aged 1 year and older with high-grade glioma (HGG) with a BRAF V600E mutation who have received at least one prior radiation and/or chemotherapy treatment.

Data from the partly comparator, pivotal, phase II G2201 study comparing dabrafenib + trametinib versus carboplatin + vincristine (only in patients with LGG) and the single-arm X2101 study are available for the benefit assessment.

From the data presented, the following patient groups, which differ in terms of tumour entity and the line of therapy to be considered, can be defined for the benefit assessment:

a) Paediatric patients aged 1 year and older with low-grade glioma (LGG) with a BRAF V600E mutation who require systemic therapy

a1) Patients without prior treatment of LGG

a2) Patients with previous treatment of LGG

b) Paediatric patients aged 1 year and older with high-grade glioma (HGG) with a BRAF V600E mutation who have received at least one prior radiation and/or chemotherapy treatment

On a1)

For the benefit assessment, the pharmaceutical company submitted the data from the comparator cohort of the phase II G2201 study. In this open-label, randomised, controlled study, patients with non-pretreated LGG were randomised in a 2:1 ratio into the treatment arm (dabrafenib + trametinib) and the control arm (carboplatin + vincristine).

In the endpoint category of mortality, there was no statistically significant difference between the treatment arms.

In the endpoint category of morbidity, results are available on overall response and progression-free survival, which were collected using the RANO criteria. However, these results cannot be assessed with sufficient certainty due to relevant uncertainties regarding the data collected on the clinical condition.

The data presented on symptomatology using PROMIS PGH are not assessable. Despite the relevance of the disease-specific symptomatology in the therapeutic indication, this was not collected in the present study.

For the endpoint category of morbidity, there were no relevant differences for the benefit assessment overall.

No assessable data were available in the endpoint category of health-related quality of life.

In the endpoint category of side effects, there were statistically significant advantages in severe AEs and therapy discontinuation due to AEs in favour of dabrafenib + trametinib, which were assessed as a significant improvement. In detail, there were predominantly advantages for specific AEs.

As a result, the G-BA identified a considerable additional benefit of dabrafenib in combination with trametinib.

The reliability of data for the additional benefit identified is classified in the "hint" category.

On a2)

For the benefit assessment, the pharmaceutical company submitted data from the non-comparator X2101 study.

Since no comparator data are available, no statement on the extent of the additional benefit can be made on the basis of these results.

In the overall assessment, a hint for a non-quantifiable additional benefit of dabrafenib in combination with trametinib is identified since the scientific data does not allow quantification.

On b)

For the benefit assessment, the pharmaceutical company submitted the data from the non-comparator HGG cohort of the phase II G2201 study.

Since no comparator data are available, no statement on the extent of the additional benefit can be made on the basis of these results.

In the overall assessment, a hint for a non-quantifiable additional benefit of dabrafenib in combination with trametinib is identified since the scientific data does not allow quantification.

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 information provided by the pharmaceutical company. These are however subject to uncertainties.

With regard to patient group a), patients who require renewed systemic therapy are not included in the lower limit. On the one hand, the upper limit does not exclude patients who have deceased or been cured; on the other, patients who were diagnosed more than 10 years ago are not included.

With regard to patient group b), literature sources for the traceability of the percentage values are missing. Secondly, the information on the 1-year mortality rate used by the pharmaceutical company only refers to certain histological subtypes and therefore does not refer to all patients with HGG. Furthermore, the pharmaceutical company's implicit equation of prior radiation and/or chemotherapy with disease progression within 12 months is not justified by the pharmaceutical company and is therefore not comprehensible.

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 Finlee (active ingredient: dabrafenib) agreed upon in the context of the marketing authorisation at the following publicly accessible link (last access: 2 October 2024):

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

Treatment with dabrafenib should only be initiated and monitored by specialists in paediatrics and adolescent medicine with a focus on neuropaediatrics or paediatric haematology and oncology who are experienced in the treatment of patients with gliomas.

Before taking dabrafenib in combination with trametinib, the BRAF V600E mutation must have been detected in patients by a validated test.

2.4 Treatment costs

The treatment costs are based on the requirements in the product information and the information listed in the LAUER-TAXE® (last revised: 15 September 2024).

For the cost representation, one year is assumed for all medicinal products.

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

The dosage of dabrafenib and trametinib depends on body weight.

Dosage recommendations for patients with a body weight between 8 kg and ≥ 51 kg are listed in the product information for Finlee and Spexotras (each last revised October 2024).

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				
Dabrafenib	Continuously 2x daily	365	1	365
Trametinib	Continuously 1x daily	365	1	365

Consumption:

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					
Dabrafenib	20 – 150 mg	40 – 300 mg	4 x 10 mg – 30 x 10 mg	365	1,460 x 10 mg – 10,950 x 10 mg
Trametinib	0.3 – 2 mg	0.3 – 2 mg	1 x 0.3 mg – 1 x 2 mg	365	365 x 0.3 mg – 365 x 2 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:

a) Paediatric patients aged 1 year and older with low-grade glioma (LGG) with a BRAF V600E mutation who require systemic therapy

and

b) Paediatric patients aged 1 year and older with high-grade glioma (HGG) with a BRAF V600E mutation who have received at least one prior radiation and/or chemotherapy treatment

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					
Dabrafenib	210 TOS	€ 2,078.67	€ 2.00	€ 0	€ 2,076.67
Trametinib	1 POS	€ 568.51	€ 2.00	€ 0	€ 566.51
Abbreviations: POS = powder for preparation of an oral solution; TOS = tablet for oral suspension					

LAUER-TAXE® last revised: 15 September 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 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 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:

a) Paediatric patients aged 1 year and older with low-grade glioma (LGG) with a BRAF V600E mutation who require systemic therapy

   a1) Patients without prior treatment of LGG

   The following medicinal products with new active ingredients that can be used in a combination therapy with the assessed medicinal product in the therapeutic indication of the present resolution on the basis of the marketing authorisation under Medicinal Products Act are excluded from the designation, as the G-BA has identified at least

considerable additional benefit for the combination with the assessed medicinal product in the present resolution:

Trametinib (Spexotras)

a2) Patients with previous treatment of LGG

Each of the designated medicinal products is an active ingredient that is specifically named as a concomitant active ingredient in the product information for the assessed medicinal product. Corresponding text extract from the product information for the assessed medicinal product:

"Finlee in combination with trametinib is indicated for the treatment of paediatric patients aged 1 year and older with low-grade glioma (LGG) with a BRAF V600E mutation who require systemic therapy."

"Finlee in combination with trametinib is indicated for the treatment of paediatric patients aged 1 year and older with high-grade glioma (HGG) with a BRAF V600E mutation who have received at least one prior radiation and/or chemotherapy treatment."

For the designated medicinal products, the requirements of Section 35a, paragraph 3, sentence 4 SGB V are also fulfilled.

References:
Product information for dabrafenib (Finlee); Finlee 10 mg tablets for oral suspension; last revised: 2 October 2024

b) Paediatric patients aged 1 year and older with high-grade glioma (HGG) with a BRAF V600E mutation who have received at least one prior radiation and/or chemotherapy treatment

Each of the designated medicinal products is an active ingredient that is specifically named as a concomitant active ingredient in the product information for the assessed medicinal product. Corresponding text extract from the product information for the assessed medicinal product:

"Finlee in combination with trametinib is indicated for the treatment of paediatric patients aged 1 year and older with low-grade glioma (LGG) with a BRAF V600E mutation who require systemic therapy."

"Finlee in combination with trametinib is indicated for the treatment of paediatric patients aged 1 year and older with high-grade glioma (HGG) with a BRAF V600E mutation who have received at least one prior radiation and/or chemotherapy treatment."

For the designated medicinal products, the requirements of Section 35a, paragraph 3, sentence 4 SGB V are also fulfilled.

References:
Product information for Dabrafenib (Finlee); Finlee 10 mg tablets for oral suspension; last revised: 2 October 2024

Supplement to Annex XIIa of the Pharmaceuticals Directive

Since the resolution under I.5 mentions medicinal products with new active ingredients according to Section 35a, paragraph 3, sentence 4 SGB V, which can be used in a combination

therapy with the assessed active ingredient in the therapeutic indication of the resolution, the information on this designation is to be added to Annex XIIa of the Pharmaceuticals Directive and provided with patient-group-related information on the period of validity of the designation.

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 25 April 2024, the pharmaceutical company submitted a dossier for the benefit assessment of dabrafenib 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 1 August 2024 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 22 August 2024.

The oral hearing was held on 9 September 2024.

An amendment to the benefit assessment with a supplementary assessment was submitted on 26 September 2024.

In order to prepare a recommendation for a resolution, the Subcommittee on Medicinal Products commissioned a working group (Section 35a) consisting of the members nominated by the leading organisations of the care providers, the members nominated by the SHI 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 8 October 2024, and the draft resolution was approved.

At its session on 17 October 2024, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee Medicinal products	23 July 2024	Information of the benefit assessment of the G-BA
Working group Section 35a	3 September 2024	Information on written statements received; preparation of the oral hearing
Subcommittee Medicinal products	9 September 2024	Conduct of the oral hearing

Working group Section 35a	17 September 2024 30 September 2024	Consultation on the dossier assessment by the G-BA, the assessment of treatment costs and patient numbers by the IQWiG, and the evaluation of the written statement procedure
Subcommittee Medicinal products	8 October 2024	Concluding discussion of the draft resolution
Plenum	17 October 2024	Adoption of the resolution on the amendment of the Pharmaceuticals Directive

Berlin, 17 October 2024

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

Prof. Hecken