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
Selumetinib (new therapeutic indication: neurofibromatosis type 1 (≥ 18 years))

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. This includes in particular the assessment of the additional benefit and its therapeutic significance. The benefit assessment is carried out on the basis of evidence provided by the pharmaceutical company, which must be submitted to the G-BA electronically, including all clinical studies the pharmaceutical company have conducted or commissioned, at the latest at the time of the first placing on the market as well as the marketing authorisation of new therapeutic indications of the medicinal product, and which must contain the following information in particular:

1. approved therapeutic indications,
2. medical benefit,
3. additional medical benefit in relation to the appropriate comparator therapy,
4. number of patients and patient groups for whom there is a therapeutically significant additional benefit,
5. treatment costs for the statutory health insurance funds,
6. requirement for a quality-assured application,

The G-BA may commission the Institute for Quality and Efficiency in Health Care (IQWiG) to carry out the benefit assessment. According to Section 35a, paragraph 2 SGB V, the assessment must be completed within three months of the relevant date for submission of the evidence and published on the internet.

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

2. Key points of the resolution

The active ingredient selumetinib (Koselugo) was listed for the first time on 15 August 2021 in the “LAUER-TAXE®”, the extensive German registry of available drugs and their prices.

Selumetinib 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. Within the previously approved therapeutic indication, the sales volume of selumetinib with the statutory health insurance at pharmacy sales prices, including value-added tax exceeded € 30 million. Evidence must therefore be provided for selumetinib in accordance with Section 5, paragraph 1 through 6 VerfO, and the additional benefit compared with the appropriate comparator therapy must be demonstrated.

On 24 October 2025, selumetinib received marketing authorisation for a new therapeutic indication to be classified as a major type 2 variation as defined according to Annex 2, number

2, letter a to Regulation (EC) No. 1234/2008 of the Commission of 24 November 2008 concerning the examination of variations to the terms of marketing authorisations for medicinal products for human use and veterinary medicinal products (OJ L 334 from 12.12.2008, sentence 7).

On 14 November 2025, i.e. at the latest within four weeks of informing the pharmaceutical company about the approval for a new therapeutic indication, the pharmaceutical company submitted a dossier in due time in accordance with Section 4, paragraph 3, number 2 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with Chapter 5 Section 8, paragraph 1, number 2 of the Rules of Procedure (VerfO) of the G-BA on the active ingredient selumetinib with the new therapeutic indication

"Selumetinib is indicated for the treatment of symptomatic, inoperable plexiform neurofibromas (PN) in adult and paediatric patients with neurofibromatosis type 1 (NF1) aged 3 years and older" (the therapeutic indication to be reassessed covers adult patients)

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The G-BA commissioned the IQWiG to carry out the assessment of the dossier. The benefit assessment was published on 16 February 2026 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 came to a resolution on whether an additional benefit of selumetinib compared with the appropriate comparator therapy could be determined on the basis of the dossier of the pharmaceutical company, the dossier assessment prepared by the IQWiG, the statements submitted in the written statement and oral hearing procedure, and the addendum to the benefit assessment prepared by the IQWiG. In order to determine the extent of the additional benefit, the G-BA have evaluated the data justifying the finding of an additional benefit on the basis of their therapeutic relevance (qualitative), in accordance with the criteria laid down in Chapter 5 Section 5, paragraph 7 VerfO. The methodology proposed by the IQWiG in accordance with the General Methods[1] was not used in the benefit assessment of selumetinib.

In the light of the above, and taking into account the statements received and the oral hearing, the G-BA have made the following assessment:

[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 in relation to the appropriate comparator therapy

2.1.1 Approved therapeutic indication of Selumetinib (Koselugo) in accordance with the product information

Koselugo as monotherapy is indicated for the treatment of symptomatic, inoperable plexiform neurofibromas (PN) in adult and paediatric patients with neurofibromatosis type 1 (NF1) aged 3 years and older.

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

Koselugo as monotherapy is indicated for the treatment of symptomatic, inoperable plexiform neurofibromas (PN) in adults with neurofibromatosis type 1 (NF1).

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

Adults with symptomatic, inoperable plexiform neurofibromas (PN) in neurofibromatosis type 1 (NF1)

Appropriate comparator therapy for selumetinib as monotherapy:

- Best supportive care

Criteria according to Chapter 5 Section 6 of the Rules of Procedure of the G-BA and Section 6 paragraph 2 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV):

The appropriate comparator therapy must be an appropriate therapy in the therapeutic indication according to the generally recognised state of medical knowledge (Section 12 SGB V), preferably a therapy for which endpoint studies are available and which has proven its worth in practical application unless contradicted by the guidelines under Section 92, paragraph 1 SGB V or the principle of economic efficiency.

In determining the appropriate comparator therapy, the following criteria, in particular, must be taken into account as specified in Chapter 5 Section 6, paragraph 3 VerfO:

1. To be considered as a comparator therapy, the medicinal product must, principally, have a marketing authorisation for the therapeutic indication.
2. If a non-medicinal treatment is considered as a comparator therapy, this must be available within the framework of the SHI system.
3. As comparator therapy, medicinal products or non-medicinal treatments for which the patient-relevant benefit has already been determined by the G-BA shall be preferred.
4. According to the generally recognised state of medical knowledge, the comparator therapy should be part of the appropriate therapy in the therapeutic indication.

According to Section 6, paragraph 2, sentence 2 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV), the determination of the appropriate comparator therapy must be based on the actual medical treatment situation as it would be without the medicinal product to be assessed. According to Section 6, paragraph 2, sentence 3 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV), the G-BA may exceptionally determine the off-label use of medicinal products as an appropriate comparator therapy or as part of the appropriate comparator therapy if they determine by resolution on the benefit assessment according to Section 7, paragraph 4 that, according to the generally recognised state of medical knowledge, this is considered a therapy standard in the therapeutic indication to be assessed or as part of the therapy standard in the medical treatment situation to be taken into account according to sentence 2, and

1. for the first time, a medicinal product approved in the therapeutic indication is available with the medicinal product to be assessed,
2. according to the generally recognised state of medical knowledge, the off-label use is generally preferable to the medicinal products previously approved in the therapeutic indication, or
3. according to the generally recognised state of medical knowledge, the off-label use for relevant patient groups or indication areas is generally preferable to the medicinal products previously approved in the therapeutic indication.

An appropriate comparator therapy may also be non-medicinal therapy, the best possible add-on therapy including symptomatic or palliative treatment, or monitoring wait-and-see approach.

<u>Justification based on the criteria set out in Chapter 5 Section 6, paragraph 3 VerfO and Section 6, paragraph 2 AM-NutzenV:</u>

On 1. In addition to selumetinib, the active ingredient mirdametinib is approved in the present therapeutic indication.

On 2. Non-medicinal treatments as part of the appropriate comparator therapy are not considered in the present therapeutic indication.

On 3. Resolutions on the benefit assessment of medicinal products with new active ingredients according to Section 35a SGB V:

- Mirdametinib: resolution of 19.03.2026
- Selumetinib: resolution of 21.12.2023

On 4. The generally recognised state of medical knowledge was illustrated by a systematic search for guidelines as well as systematic reviews of clinical studies in the present indication and is presented in the "Research and synopsis of the evidence to determine the appropriate comparator therapy according to Section 35a SGB V". The scientific-medical societies and the Drugs Commission of the German Medical Association (AkdÄ) were also involved in writing on questions relating to the comparator therapy in the present therapeutic indication according to Section 35a paragraph 7 SGB V. There are no written statements.

The evidence in the present therapeutic indication is very limited. No methodologically sound reviews or guidelines could be identified during the systematic search. A total

of four guidelines subject to methodological limitations were presented additionally. These also include the S2k guideline issued by the German Society for Neurosurgery (DGNC) on the diagnosis and treatment of peripheral nerve tumours.

Surgical intervention for plexiform neurofibromas is not an option as they are classified as inoperable according to the therapeutic indication.

According to the guidelines, a therapy trial with an MEK inhibitor and/or an mTOR inhibitor should preferably be carried out as a non-surgical therapeutic concept within the clinical studies.

The two MEK inhibitors, selumetinib and mirdametinib, are approved for the therapeutic indication. As selumetinib is the medicinal product to be assessed, this therapy option is not considered as the appropriate comparator therapy.

By resolution of 19 March 2026, a hint for a non-quantifiable additional benefit of mirdametinib was identified in the benefit assessment thereof, since the scientific data did not allow quantification. The assessment was based on a single-arm study. The active ingredient mirdametinib is a new treatment option in the present therapeutic indication. The active ingredient was only recently approved (marketing authorisation on 17 July 2025). According to the generally recognised state of medical knowledge, the significance of this treatment option in the present treatment setting cannot yet be conclusively assessed; consequently, mirdametinib is not determined as the appropriate comparator therapy for the present resolution.

In the overall assessment, best supportive care (BSC) is determined as the appropriate comparator therapy for selumetinib in adults with symptomatic, inoperable plexiform neurofibromas in neurofibromatosis type 1 (NF1).

Best supportive care (BSC) is defined as the therapy that provides the best possible, patient-individually optimised, supportive treatment to alleviate symptoms and improve quality of life.

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

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

2.1.3 Extent and probability of the additional benefit

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

Adults with symptomatic, inoperable plexiform neurofibromas (PN) in neurofibromatosis type 1 (NF1)

Justification:

For the benefit assessment, the pharmaceutical company submitted the results of the COMET study:

The KOMET study is an ongoing, multicentre, randomised, double-blind phase III study comparing selumetinib (+ best supportive care, BSC) with placebo (+ BSC). Adult patients with neurofibromatosis type 1 and symptomatic, inoperable plexiform neurofibromas were enrolled in the study.

A total of 71 patients were randomly assigned to treatment with selumetinib and 74 patients to treatment with placebo. Randomisation was stratified according to the average score for chronic pain in the target lesion during the screening period (< 3 vs ≥ 3, on an 11-point Numerical Rating Scale [NRS] ranging from 0 [no pain] to 10 [maximum pain]) and geographical region (Europe vs China vs Japan vs rest of the world [Australia, Brazil, Canada and the USA]). The study has been conducted in 44 study sites since 2021.

Selumetinib was administered in accordance with the product information. The study comprised a randomised treatment phase lasting a total of 48 weeks (12 cycles of 28 days each) and an ongoing, open-label, single-arm study phase in which all patients were eligible to receive selumetinib.

The primary endpoint of the study is the objective response rate by the end of cycle 16, defined as the percentage of patients with a confirmed complete response of the target lesion or a confirmed partial response, based on an independent central review in accordance with the REiNS criteria. The target lesion was defined as the plexiform neurofibroma deemed most clinically relevant by the principal investigator and measurable by volumetric magnetic resonance imaging (MRI) (patients could have more than one clinically relevant plexiform neurofibroma). In addition, endpoints in the categories of morbidity and side effects were assessed.

In the KOMET study, a data cut-off was scheduled as a pre-specified primary analysis on 05.08.2024 when all patients had completed the 16th cycle. Another data cut-off was scheduled as a pre-specified final analysis on 17.03.2025 when all patients had completed the 24th cycle. The relevant results for this benefit assessment are based on data from the comparative, randomised 48-week treatment phase following 12 cycles (data cut-off from 05.08.2024).

Extent and probability of the additional benefit

Mortality

Overall mortality

No deaths were recorded in either treatment arm, meaning that there was no relevant difference for the benefit assessment for this endpoint.

Morbidity

Cross-endpoint analysis of the endpoints of chronic pain (NRS), pain peaks (NRS), impairment due to pain (PII-pNF), psychosocial morbidity (PlexiQoL), health status (EQ-5D VAS), Patient Global Impression of Severity [PGIS] and Patient Global Impression of Change 1 [PGIC-1]/ 2 [PGIC-2]

In the benefit assessment dossier, the pharmaceutical company presented analyses of the endpoints in the form of time-to-event analyses, both for the time to 1st improvement and the time to 1st deterioration by ≥ 15% of the scale range. In addition, analyses of the continuous data using mixed models for repeated measures (MMRM) were available for the endpoints of chronic pain (NRS), pain peaks (NRS), impairment due to pain (PII-pNF) and psychosocial morbidity (PlexiQoL).

As part of the written statement procedure, the pharmaceutical company also presented analyses of improvement by 15% of the scale range at week 48, as well as the time to permanent improvement.

Permanent improvement is defined as the time to improvement without any recurring subsequent deterioration. For the endpoints of chronic pain (NRS), pain peaks (NRS) and impairment due to pain (PII-pNF), data are available on the percentage of patients with a confirmed improvement (without subsequent deterioration), one-off improvement at the end of the study, and one-off improvement without a follow-up assessment. There is a lack of relevant information for the endpoints of psychosocial morbidity (PlexiQoL) and health status (EQ-5D VAS), which is why it is unclear whether the analysis of permanent improvement for the PlexiQoL and EQ-5D VAS endpoints also included patients who did not show permanent improvement but only one-off improvement (at the end of the study or without a follow-up assessment).

In view of the assessment of the patient-reported endpoints taking into account the comparable data basis, the analyses of permanent improvement are therefore not used overall.

This benefit assessment is based on the responder analyses of improvement at the end of the randomised study phase (week 48).

Chronic pain assessed using the Numerical Rating Scale [NRS], Patient Global Impression of Severity [PGIS] and Patient Global Impression of Change 1 [PGIC-1]/ 2 [PGIC-2]

The "chronic pain" endpoint assessed using the NRS was collected daily. This showed a statistically significant difference to the advantage of selumetinib compared with placebo.

The "chronic pain" endpoint was assessed using the PGIS, PGIC-1 and PGIC-2. The PGIC-1 and PGIS were each surveyed at visits at the end of cycles 1, 2, 4, 6, 8, 10 and 12, whilst the PGIC-2 at the end of cycle 12. Likewise, for the PGIS, PGIC-1 and PGIC-2, there was a statistically significant improvement of selumetinib compared with placebo in each case.

With regard to the available results of the PGIS, PGIC-1 and PGIC-2, there is a variation in the assessment of the "chronic pain" endpoint. Overall, the results of the PGIS, PGIC-1 and PGIC-2 are regarded as confirming the results of the NRS.

Pain peaks assessed using the Numerical Rating Scale [NRS], Patient Global Impression of Severity [PGIS] and Patient Global Impression of Change 1 [PGIC-1]/ 2 [PGIC-2]

The "pain peaks" endpoint assessed using the NRS was collected daily. There was a statistically significant difference to the advantage of selumetinib compared with placebo.

The "pain peaks" endpoint was assessed using the PGIS, PGIC-1 and PGIC-2. The PGIC-1 and PGIS were each surveyed at visits at the end of cycles 1, 2, 4, 6, 8, 10 and 12, whilst the PGIC-2 at the end of cycle 12. Likewise, for the PGIS, PGIC-1 and PGIC-2, there was a statistically significant improvement of selumetinib compared with placebo in each case.

With regard to the available results of the PGIS, PGIC-1 and PGIC-2, there is also a variation in the assessment of the "pain peaks" endpoint here – as is the case with the "chronic pain" endpoint. Overall, the results of the PGIS, PGIC-1 and PGIC-2 are regarded as confirming the results of the NRS.

Change in volume of the target lesion

For the endpoint of change in volume of the target lesion , the pharmaceutical company presented various analyses in their dossier (absolute/ percentage change in target lesion volume from baseline, maximum percentage change in target lesion volume achieved, and patients with a ≥ 20% reduction in target lesion volume from baseline). Operationalisation as the maximum percentage change in target lesion volume was assessed as a secondary endpoint in the KOMET study. The change in volume of the target lesion was measured using volumetric MRI.

The endpoint of change in volume of the target lesion is considered a patient-relevant endpoint as there is special case in the present therapeutic indication. Due to the partial external visibility of the tumours, which in some cases manifest themselves in clearly visible deformations, but can also be characterised by functional limitations independent of the visibility of the tumours, this endpoint is considered a patient-relevant endpoint, provided that significant reduction in the tumour size is shown by appropriate operationalisation. The operationalisation as the "maximum percentage change in volume of the target lesion achieved" from baseline is considered appropriate and is used for derivation of the additional benefit.

In the KOMET study, a reduction in target PN (maximum percentage volume reduction achieved) could be observed. This was -15.3% in the selumetinib arm and -4.18% in the placebo arm. This is interpreted as a relevant effect.

The results are subject to uncertainty: On the one hand, there were differences in the baseline characteristics of the patients. Accordingly, the median volume of the plexiform neurofibromas identified as target lesions by the principal investigator is significantly smaller in the selumetinib arm than in the control arm (92 ml vs 222 ml). Patients in the selumetinib arm were also less likely to develop another plexiform neurofibroma (25% vs 41%). On the other, due to the operationalisation of the endpoint, the effect of treatment with selumetinib on other existing plexiform neurofibromas that were not classified as target lesions was not assessed.

However, a reduction in tumour volume in this therapeutic indication should always be regarded as a therapeutic goal. The volume of PN represents the relevant manifestation of the disease and is the cause of any existing symptomatology with functional impairments and may also be accompanied by deformation.

Against this background, despite remaining uncertainties, an improvement in the therapeutic benefit of treatment with selumetinib in terms of a relevant reduction in tumour volume from baseline can be identified, thereby demonstrating an advantage of selumetinib in the endpoint of change in volume of the target lesion.

Impairment due to pain (PII-pNF)

The information in the pharmaceutical company's dossier indicated that, as early as the start of the study, more than 30% (34% vs 32%) of patients in both treatment arms had not submitted fully completed questionnaires, meaning that the validity of the data provided was unclear.

As part of the written statement procedure, the pharmaceutical company provided further information on the return rates for the individual items of the PII-pNF, including the item "challenging physical activities". This shows that a lower return rate was observed only for the item "challenging physical activities" due to the option "does not apply" being selected; for this reason, the PII-pNF analyses are used for the present assessment.

For the "impairment due to pain" endpoint assessed using the PII-pNF, there was no statistically significant difference between the treatment arms.

Psychosocial morbidity (Plexiform Neurofibroma Quality of Life Scale [PlexiQoL])

For the endpoint of psychosocial morbidity assessed using the PlexiQoL, there was no statistically significant difference between the treatment arms.

Physical functioning

In the KOMET study, physical functioning was assessed using 3 items from the Physical Function Short Form 8c (PF8c; v2.0) of the Patient-Reported Outcomes Measurement Information System (PROMIS). The full PROMIS-PF8c, by contrast, comprises 8 items. Consequently, no suitable data are available on the endpoint of physical functioning.

Health status (EQ-5D, visual analogue scale [VAS])

For the endpoint of health status assessed using EQ-5D VAS, there was no statistically significant difference between the treatment arms.

The overall analysis of the results in the endpoint category of morbidity showed advantages of selumetinib in the endpoints of change in volume of the target lesion, chronic pain (assessed using NRS, PGIS, PGIC-1 and PGIC-2) and pain peaks (assessed using NRS, PGIS, PGIC-1 and PGIC-2).

Quality of life

In their dossier, the pharmaceutical company presented PlexiQoL analyses and classified them under health-related quality of life. The PlexiQoL assesses exclusively social and psychological aspects in patients with plexiform neurofibromas associated with neurofibromatosis type 1. On the contrary, physical aspects are not included. The PlexiQoL results are therefore classified under the endpoint category of morbidity (psychosocial morbidity). Overall, no suitable data are therefore available on the endpoint category of quality of life.

Side effects

Adverse events (AEs) in total

In the KOMET study, an AE occurred in almost all patients in the selumetinib and placebo arms. The results were only presented additionally.

Serious AEs (SAEs) and discontinuation due to AEs

For the endpoints of SAEs and discontinuation due to AEs, there was no statistically significant difference between the treatment groups.

Severe AEs (CTCAE grade ≥ 3)

For the endpoint of severe AEs, there was a statistically significant difference to the disadvantage of selumetinib compared with placebo.

Specific AEs

Gastrointestinal disorders (SOC, AEs), skin and subcutaneous tissue disorders (SOC, AEs), peripheral oedema (PT, AEs), infections and infestations (SOC, severe AEs), investigations (SOC, severe AEs)

For the endpoints of gastrointestinal disorders (system organ class [SOC], AEs), skin and subcutaneous tissue disorders (SOC, AEs), peripheral oedema (PT [preferred term], AEs), infections and infestations (SOC, severe AEs), investigations (SOC, severe AEs), there was a statistically significant difference in each case to the disadvantage of selumetinib compared with placebo.

The overall assessment showed a disadvantage of selumetinib in terms of severe AEs, and, in detail, disadvantages in terms of specific AEs.

Overall assessment

The benefit assessment of selumetinib for the treatment of adults with symptomatic, inoperable PN in NF1 is based on the results of the KOMET study regarding the endpoint categories of mortality, morbidity and side effects compared with placebo.

There were no deaths in the KOMET study.

For the endpoint "change in volume of the target lesion" ("maximum percentage change in target lesion volume achieved' from baseline), a significant reduction in tumour volume was observed for selumetinib compared with placebo relative to the baseline value at the start of the study. The reduction in tumour volume is an important therapeutic goal in this setting due to the specific manifestations of the disease, which, in addition to externally visible tumours, can include tumour-related deformations and functional impairments, regardless of the visibility of the tumours. In light of this, despite remaining uncertainty, an improvement in the therapeutic benefit of treatment with selumetinib in terms of a relevant reduction in tumour volume from baseline can be identified.
Advantages in the endpoint category of morbidity are also evident for the endpoints "chronic pain" (assessed using the NRS, PGIS, PGIC-1 and PGIC-2) and "pain peaks" (assessed using the NRS, PGIS, PGIC-1 and PGIC-2).

No suitable data on the endpoint category of health-related quality of life were collected in the KOMET study.

In the endpoint category of side effects, there was a disadvantage of selumetinib in terms of severe AEs; there were no statistically significant differences in the endpoints of serious AEs and therapy discontinuation due to AEs.

The overall analysis showed advantages of selumetinib in the endpoints "chronic pain", "pain peaks" and "reduction in tumour volume", and a disadvantage in terms of severe AEs. Overall, even taking into account the lack of suitable data on health-related quality of life and physical functioning, a minor additional benefit of selumetinib + BSC compared with placebo + BSC for the treatment of adults with symptomatic, inoperable PN in NF1 was observed.

Reliability of data (probability of additional benefit)

The underlying KOMET study is an ongoing, multicentre, randomised, double-blind phase III study. The study compared the administration of selumetinib with placebo.

The risk of bias across endpoints for the KOMET study is rated as low at study level.

At the endpoint level, the risk of bias is also rated as low.

Overall, an indication is derived for the reliability of data of the additional benefit identified.

2.1.4 Summary of the assessment

The present assessment is the benefit assessment of a new therapeutic indication for the active ingredient selumetinib.

The therapeutic indication assessed here is as follows:

Treatment of adults with symptomatic, inoperable plexiform neurofibromas (PN) in neurofibromatosis type 1 (NF1).

Best Supportive Care (BSC) was determined as the appropriate comparator therapy.

The pharmaceutical company presented the ongoing, multicentre, randomised, double-blind phase III study, comparing selumetinib with placebo, for the benefit assessment. The study is suitable for the assessment of the additional benefit for patients in the therapeutic indication.

There were no deaths in the KOMET study.

For the endpoint "change in volume of the target lesion" ("maximum percentage change in target lesion volume achieved' from baseline), a significant reduction in tumour volume was observed for selumetinib compared with placebo relative to the baseline value at the start of the study. Further advantages are evident for the endpoints "chronic pain" and "pain peaks" in the endpoint category of morbidity.

No suitable data on the endpoint category of health-related quality of life were collected.

In the endpoint category of side effects, there was a disadvantage of selumetinib in terms of severe AEs.

The overall analysis showed advantages of selumetinib in the endpoints "chronic pain", "pain peaks" and "reduction in tumour volume", and a disadvantage in terms of severe AEs. Overall, even taking into account the lack of suitable data on health-related quality of life and physical functioning, a minor additional benefit of selumetinib + BSC compared with placebo + BSC for the treatment of adults with symptomatic, inoperable PN in NF1 was observed.

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

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

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

In order to ensure consistent determination of patient numbers in the present therapeutic indication, this resolution is based on the information from the resolution on the benefit assessment of mirdametinib (resolution of 19.03.2026).

The patient numbers presented by the pharmaceutical company in the present benefit assessment procedure are subject to uncertainty and have been overestimated. On the one hand, the use of prevalence rates based on a screening study of 6-year-olds is a key factor here. On the other, there is an over-represented percentage of patients with malignant peripheral nerve sheath tumours; this percentage was used to determine the percentage of those with at least one PN (this applies to the upper limit). Furthermore, the percentage of symptomatic and inoperable PN cases may be overestimated.

The patient numbers in the mirdametinib procedure was deemed to have been overestimated for the (broader) therapeutic indication to be assessed. For the target population to be assessed in the current procedure, the pharmaceutical company stated higher patient numbers, meaning that an even greater overestimation is to be expected for this population. Due to the absence of more suitable data, the information from the mirdametinib procedure – taking into account the uncertainties addressed in the assessment – should also be used for the present (narrower) therapeutic indication.

The resolution is therefore based on the information from the resolution on the benefit assessment of mirdametinib (resolution of 19.03.2026), which can be used despite the continuing uncertainties.

Additional uncertainties remain, as the number of patients in this therapeutic indication (NF1-PN; ≥ 18 years) is expected to be lower than in the mirdametinib procedure (NF1-PN; ≥ 2 years).

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 Koselugo (active ingredient: selumetinib) at the following publicly accessible link (last access: 28 April 2026):

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

Therapy with selumetinib should only be initiated and monitored by specialists in internal medicine, haematology and oncology experienced in the treatment of patients with NF1-related tumours and other doctors from other specialist groups participating in the Oncology Agreement.

This medicinal product received a conditional marketing authorisation. This means that further evidence of the benefit of the medicinal product is anticipated. The European

Medicines Agency (EMA) will assess new information on this medicinal product at least annually and update the product information where necessary.

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.

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.

The treatment costs for best supportive care are different for each individual patient. Because best supportive care has been determined as an appropriate comparator therapy, this is also reflected in the medicinal product to be assessed. The type and scope of best supportive care can vary depending on the medicinal product to be assessed and the comparator therapy.

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

Treatment period:

Adults with symptomatic, inoperable plexiform neurofibromas (PN) in neurofibromatosis type 1 (NF1)

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Medicinal product to be assessed:				
Selumetinib	Continuously, 2 x daily	365.0	1	365.0
Best supportive care	Different from patient to patient			
Appropriate comparator therapy				
Best supportive care	Different from patient to patient			

Consumption:

For dosages depending on body weight (BW) or body surface area (BSA), the average body measurements from the official representative statistics "Microcensus 2021 – body measurements of the population" were applied (average body height: 1.72 m; average body weight: 77.7 kg). This results in a body surface area of 1.91 m² (calculated according to Du Bois 1916).[2]

The doses per m² body surface area recommended in the product information were used as the calculation basis.

Adults with symptomatic, inoperable plexiform neurofibromas (PN) in neurofibromatosis type 1 (NF1)

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:					
Selumetinib	50 mg	100 mg	4 x 25 mg	365.0	1,460 x 25 mg
Best supportive care	Different from patient to patient				
Appropriate comparator therapy					
Best supportive care	Different from patient to patient				

[2] Federal Health Reporting. Average body measurements of the population (2021, both sexes, 15 years and older), www.gbe-bund.de

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.

Adults with symptomatic, inoperable plexiform neurofibromas (PN) in neurofibromatosis type 1 (NF1)

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:					
Selumetinib 25 mg	60 HC	€ 13,329.94	€ 1.77	€ 0.00	€ 13,328.17
Best supportive care	Different from patient to patient				
Appropriate comparator therapy					
Best supportive care	Different from patient to patient				
Abbreviations: HC = hard capsules					

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Costs for additionally required SHI services:

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

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

Because there are no regular differences in the necessary use of medical treatment or in the prescription of other services in the use of the medicinal product to be evaluated and the appropriate comparator therapy in accordance with the product information, no costs for additionally required SHI services had to be taken into account.

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 with symptomatic, inoperable plexiform neurofibromas (PN) in neurofibromatosis type 1 (NF1)

– 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.

3. Bureaucratic costs calculation

The proposed resolution does not create any new or amended information obligations for care providers within the meaning of Annex II to Chapter 1 VerfO and, accordingly, no bureaucratic costs.

4. Process sequence

At their session on 7 April 2021, the Subcommittee on Medicinal Products determined the appropriate comparator therapy.

A review of the appropriate comparator therapy took place. The Subcommittee on Medicinal Products newly determined the appropriate comparator therapy at their session on 9 December 2025.

On 14 November 2025, the pharmaceutical company submitted a dossier for the benefit assessment of selumetinib to the G-BA in due time in accordance with Chapter 5 Section 8, paragraph 1, No. 2 VerfO.

By letter dated 17 November 2025 in conjunction with the resolution of the G-BA of 1 August 2011 concerning the commissioning of the IQWiG to assess the benefit of medicinal products with new active ingredients in accordance with Section 35a SGB V, the G-BA commissioned the IQWiG to assess the dossier concerning the active ingredient selumetinib.

The dossier assessment by the IQWiG was submitted to the G-BA on 11 February 2026, and the written statement procedure was initiated with publication on the G-BA website on 16 February 2026. The deadline for submitting statements was 9 March 2026.

The oral hearing was held on 23 March 2026.

By letter dated 24 March 2026, the IQWiG was commissioned with a supplementary assessment of data submitted in the written statement procedure. The addendum prepared by IQWiG was submitted to the G-BA on 13 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	7 April 2021	Determination of the appropriate comparator therapy
Subcommittee on Medicinal Products	9 December 2025	New determination of the appropriate comparator therapy
Working group Section 35a	18 March 2026	Information on written statements received; preparation of the oral hearing
Subcommittee on Medicinal Products	23 March 2026 24 March 2026	Conduct of the oral hearing, commissioning of the IQWiG with the supplementary assessment of documents
Working group Section 35a	1 April 2026 15 April 2026	Consultation on the dossier assessment by the IQWiG and 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