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 Selumetinib (reassessment after the deadline: neurofibromatosis (≥ 3 to < 18 years, type 1))

of 21 December 2023

Contents

1. Legal basis

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

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

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

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

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

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

2. Key points of the resolution

The pharmaceutical company submitted a dossier for the early benefit assessment of the active ingredient selumetinib (Koselugo) on 13 August 2021. For the resolution of 3 February 2022 made by the G-BA in this procedure, a limitation up to 1 July 2023 was pronounced.

In accordance with Section 4, paragraph 3, No. 5 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with Chapter 5 Section 1, paragraph 2, number 7 VerfO, the procedure for the benefit assessment of the medicinal product Koselugo recommences when the deadline has expired.

The pharmaceutical company submitted the dossier for the benefit assessment to the G-BA in due time on 30 June 2023 (Section 4, paragraph 3, number 5 AM-NutzenV in conjunction with Chapter 5 Section 8, paragraph 1, number 5 VerfO).

Selumetinib for the treatment of neurofibromatosis (≥ 3 to < 18 years, type 1) is approved as a medicinal product for the treatment of rare diseases under 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 2 October 2023 together with the IQWiG assessment on the website of the G-BA (www.g-ba.de), thus initiating the written statement procedure. In addition, an oral hearing was held.

The G-BA has adopted its resolution on the basis of the dossier of the pharmaceutical company, the dossier assessment carried out by the G-BA, the assessment of treatment costs and patient numbers (IQWiG G23-14) prepared by the IQWiG, and the statements submitted in the written statement and oral hearing procedure.

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

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

2.1 Additional benefit of the medicinal product

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

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

Therapeutic indication of the resolution (resolution of 21 December 2023):

see the approved therapeutic indication

2.1.2 Extent of the additional benefit and significance of the evidence

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

Paediatric patients aged 3 years and above with symptomatic, inoperable plexiform neurofibromas (PN) in neurofibromatosis type 1 (NF1)

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

Justification:

For the re-assessment of the extent of additional benefit after the deadline, the pharmaceutical company submitted the results of the SPRINT, D1346C00013 and D1346C00011 studies for selumetinib. For the present benefit assessment, the D1346C00013 and D1346C00011 studies were not included due to the shorter observation duration compared to the SPRINT study, the small number of study participants and the uncertainty regarding transferability to the German healthcare context.

The SPRINT study is an ongoing, multicentre, open-label, single-arm phase I/II study. The study has been conducted in 4 study sites in the USA since August 2011.

For the phase II, study participants with type 1 neurofibromatosis with at least one inoperable PN were enrolled in one of two strata based on whether PN-related morbidity was already present at the time of enrolment (stratum 1) or whether there was no significant clinical morbidity but the potential for such morbidity (stratum 2). PN-related morbidity included PN-induced pain, deformation or functional impairment such as vision loss, facial motor impairment, hearing loss, swallowing problems, speech impairment, airway obstruction, respiratory impairment, bladder dysfunction, bowel dysfunction, muscle weakness, restricted range of motion or sensory impairment.

Stratum 1 of phase II is used for the present benefit assessment. Recruitment of patients for phase II began in August 2015. Stratum 2 of phase II comprises asymptomatic subjects who are not included in the therapeutic indication of selumetinib. A total of 50 children 3 years and older and adolescents were enrolled in stratum 1 of phase II.

Only patients under the age of 18 were enrolled in the SPRINT study. The pharmaceutical company does not provide data for adults. According to the requirements in the product information, only limited data are available in patients older than 18 years, so continuation of treatment in adulthood should be based on the benefits and risks for the individual patient based on medical assessment.

In the SPRINT study, the most clinically relevant, inoperable PN that could be detected using volumetric 3D MRI measurement was defined as the target PN. The primary study endpoint of phase II is the objective response rate (ORR). In addition, data on mortality, morbidity, quality of life and side effects are collected.

In the dossier, the pharmaceutical company presents the results of the data cut-off from 31 March 2021, which was required by the European Medicines Agency (EMA) in connection with the conditional marketing authorisation of selumetinib. Further data cut-offs were carried out on 29 June 2018 (primary interim analysis) and 29 March 2019.

The submission of the results on all patient-relevant outcomes based on the data cut-off from 31 March 2021 from the SPRINT study was part of the time limit requirements that were imposed in the previous benefit assessment procedure for the active ingredient selumetinib by resolution of 2 February 2022.

On the results of the SPRINT study:

Mortality

No deaths were observed in phase II of the SPRINT study up to the data cut-off from 31 March 2021. No statement can be made on the extent of the additional benefit as there is no control group.

Morbidity

Progression-free survival (PFS)

In the SPRINT study, PFS was collected as a secondary endpoint. PFS was defined as the time from the 1st cycle of study treatment to the MRI assessment in which progression was detected or to death from any cause, regardless of whether patients discontinued study treatment or received another PN treatment (after discontinuation of study treatment) prior to progression. Progression was defined as at least a 20% increase in the volume of the target lesion according to REiNS criteria, measured using volumetric MRI images.

The PFS endpoint is a composite endpoint composed of endpoints of the mortality and morbidity categories. The "mortality" endpoint component was assessed as an independent endpoint in the present study via the "overall survival" endpoint. The morbidity component was not assessed on the basis of symptoms according to the operationalisation, but exclusively using imaging procedures.

Taking into account the aspects mentioned above, there are different opinions within the G-BA regarding the patient-relevance of the endpoint PFS. The overall statement on the extent of the additional benefit remains unaffected.

Regardless of this, the results of the SPRINT study for the PFS endpoint do not allow a statement to be made on the extent of the additional benefit due to the absence of a control group. The PFS endpoint is presented additionally.

Change in tumour volume

The endpoint of change in tumour volume was collected as a secondary endpoint in the SPRINT study. The endpoint was operationalised as the change in volume of the PN defined as the target lesion, measured by volumetric 3D MRI.

The endpoint "change in tumour volume" is considered a patient-relevant endpoint as this indication is a special case. 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 it is shown by suitable operationalisation that the tumour size is reduced to a relevant extent.

In the SPRINT study, a reduction in the target lesion (best percentage volume reduction achieved) of -27% was demonstrated. A volume reduction was observed in 96% of patients. Due to the lack of a control group, the first fundamental question is to what extent this is an effect of the treatment. According to the clinical experts at the oral hearing, however, it can be assumed that no spontaneous remissions occur in the natural course of the disease in the present clinical picture and stage.

The following uncertainties must be taken into account when interpreting the present results: Firstly, with regard 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 for the majority of study participants. Furthermore, due to the lack of a control group, it is not possible to distinguish naturally occurring fluctuations (e.g. due to the fluid content in the tumour caused by external factors) from changes observed since the enrolment in the study.

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 can be identified.

Objective response rate (ORR)

The objective response rate was collected as the primary endpoint in the SPRINT study.

ORR was defined as the percentage of patients in stratum 1 of phase II who achieved a confirmed complete or partial response (reduction in the volume of the target PN by 20% or more). The response is considered confirmed if it is observed again within 3 to 6 months.

The objective response rate endpoint was not determined on the basis of symptoms, but by means of imaging procedures. The objective response rate is therefore assessed as being not directly patient-relevant in the present operationalisation.

The endpoint is not used for the benefit assessment as the change in tumour volume was already considered as an endpoint. The endpoint is however presented additionally.

Endpoints to analyse symptomatology, physical functions or functional impairments and health-related quality of life

Global assessment of the clinical change

The global assessment of clinical change was recorded using the Global Impression of Change (GIC), a 1-item scale to assess the clinical significance of changes in pain intensity or other symptoms. An adapted version of the GIC with 3 items was used in the SPRINT study. The change in tumour pain, overall pain and PN-related morbidity compared to the time before taking the study medication was measured. For children 8 years and older, a self-assessment was carried out; for children aged 5 to 7, an external assessment was carried out by the parents/ caregivers. The collection of the global assessment of clinical change using GIC is considered suitable.

The corresponding evaluations for children from the age of 8 up to the study visit before cycle 13 and for children between the ages of 5 and 7 up to the study visit before cycle 25 are included, as the respective return rates were over 70% up to these survey time points.

In the SPRINT study, improvements were observed over time compared to the time before the start of treatment in the global assessment of clinical change reported by GIC for patients aged 3 to 18 years.

Pain

Pain Interference Index (PII)

The PII assesses a pain-induced impairment. The occurrence of pain and the influence of pain on everyday activities is relevant to patients. The validity of the version of the PII used in the SPRINT study is not adequately proven, which is why it was not considered for the present benefit assessment.

Numerical Rating Scale (NRS-11)

The occurrence of pain and its intensity is considered patient-relevant. In the SPRINT study, children 8 years and older assessed the intensity of the pain they experienced using the NRS-11. The endpoint "pain" was not assessed in children under 8 years of age.

The corresponding evaluations at the study visit before cycle 13 are included, since up to this survey time point the return rate remained above 70%. For patients aged 8 years and older, improvements compared to baseline were observed over time in the endpoint "worst pain".

Visual acuity

Visual acuity or the preservation thereof is assessed as patient-relevant. Distance visual acuity was determined for all patients in the SPRINT study with orbital PN using HOTV or Teller acuity cards. In the HOTV test, the letters H, O, T and V must be recognised in decreasing size. In younger children, visual acuity was measured using Teller acuity cards. A stripe pattern must be distinguished from a grey surface.

Teller acuity cards

This endpoint is not used for the benefit assessment because the information on the operationalisation of this endpoint is insufficient and the conduct and standardisation of the test are incomprehensible.

HOTV test

The measurement of visual acuity using HOTV is considered valid and taken into account in the present benefit assessment.

Only 5 patients in total could be included in the analysis of visual acuity for the eye affected by PN. The eye affected by PN shows no improvement and a deterioration compared to baseline. Due to the open-label study design without a control group and the small sample size, the reliability and interpretability of the results are very limited, so no conclusions can be drawn about the additional benefit of selumetinib.

Proptosis/ exophthalmos

With regard to the endpoint of proptosis/ exophthalmos, it is unclear what relevance possible deformations associated with proptosis have in the therapeutic indication. Against this background, this endpoint is not used for the present assessment.

Nevertheless, no statement on the additional benefit can be made on the basis of the data on this endpoint, as there is no control group. The endpoint of proptosis/ exophthalmos is presented additionally.

Assessment of motor function using the grooved pegboard test

The grooved pegboard test was performed in children aged 5 years and older with PN in the upper extremities or with known compression of the cervical or upper thoracic spinal cord.

In this test, 25 key-like pegs must be inserted into holes with randomly arranged slots on the pegboard. The time until the pegboard was completed was recorded.

The impairment of motor function and the associated impairment of manual dexterity and eye-hand coordination is seen as a relevant symptom in plexiform neurofibromas. Therefore, the endpoint is considered patient-relevant.

The evaluations at the study visit before cycle 13 are included, since up to this survey time point the return rate remained above 70%. With regard to the grooved pegboard test, slight to moderate improvements were observed over time. However, due to the single-arm study design, it is not possible to differentiate whether these improvements are due to treatment with selumetinib or, for example, effects of rehearsal. For children and adolescents with unilateral PN, the improvements for the impaired hand are similarly pronounced as for the unimpaired hand, which rather indicates an influence of the effects of rehearsal.

Thus, there are relevant uncertainties in the interpretation of the results for this endpoint, which is why this is not used to quantify the extent of additional benefit. The endpoint is presented additionally.

Patient-Reported Outcomes Measurement Information System (PROMIS)

The PROMIS for physical functioning was assessed in all patients with PN that impaired motor function.

The assessment of physical functioning using PROMIS is considered suitable.

The results at the study visit before cycle 13 are included, since up to this survey time point the return rate remained above 70%. For the PROMIS scales "Mobility" and "Upper extremities", slight improvements compared to baseline were observed in patients aged 8 to 18 years at the study visit before cycle 13. Descriptive evaluations are available for children under 8 years of age and motor-PN-related morbidity, which indicate only a slight change in the T-score compared to baseline.

Symptomatology by means of a symptom checklist

The symptom checklist is used to determine the extent of 36 symptoms within the last 2 weeks.

In the SPRINT study, an improvement in symptoms was reported more frequently (≥ 10% difference at the study visit before cycle 25) than deterioration compared to the baseline for the symptoms "Tiredness/ fatigue", Sleep disorders", "Loss of appetite", "Difficulty swallowing", "Snoring", "Frequent waking at night", "Cough", "Weakness" and "Muscle pain". Conversely, for the symptom "Nausea", deterioration of the symptom was reported as an

improvement compared to the baseline at the time before cycle 25. At earlier collection time points, deterioration was also reported more frequently than improvement for the symptoms "Swelling of the feet/ hands", "Diarrhoea", "Increased appetite", "Abdominal pain", "Nausea", "Vomiting" and "Dizziness". Symptoms for which deterioration is collected more frequently could reflect the tolerability of selumetinib rather than morbidity. The certainty of the results and their interpretability are however so limited due to the open-label study design without a control group that no statements can be derived on the additional benefit. Only the symptoms with a ≥ 10% difference at the study visit before cycle 25 are presented additionally.

Quality of life

Paediatric Quality of Life Inventory (PedsQL)

The assessment of quality of life using PedsQL is considered suitable.

The health-related quality of life for children aged 8 years and older is assessed directly via the survey of the children and is limited to the period up to the study visit before cycle 13 due to the return rate. For the patient population aged 5 - 7 years, the results of the parent-reported version up to the study visit before cycle 25 were used, as the return rate was less than 70% thereafter.

For health-related quality of life, the results of the SPRINT study show an improvement over the course of the study compared to the baseline for patients under 8 years of age and those 8 years and older.

Summarised assessment of the aforementioned endpoints to investigate symptomatology, physical functions or functional impairments and health-related quality of life

Patients with plexiform neurofibromas show patient-individual differences in terms of symptomatology and physical functions or functional impairments. The G-BA expressly welcomes the collection of these target variables and health-related quality of life in clinical studies as in the SPRINT study. In view of the specific manifestations of the disease, appropriate endpoints are of great significance in the benefit assessment. Among other things, this data could allow an assessment of how changes in tumour volume also influence symptomatology, physical functioning or functional impairments and health-related quality of life.

However, in the present assessment, no valid interpretation and assessment of the results on the present endpoints can be made due to the missing control group. In addition, there are further relevant uncertaintiesfor individual endpoints as outlined above. No statement on the additional benefit can therefore be derived on the basis of these endpoints.

Side effects

Total adverse events (AEs)

An adverse event occurred in almost all children and adolescents (49 patients (99%)). These are only presented additionally.

Serious adverse events (SAEs)

13 out of 50 patients (30%) had at least one serious adverse event. The most frequent SAEs observed were "Infections and infestations", "Gastrointestinal disorders" and "Injury, poisoning and procedural complications".

Severe adverse events (CTCAE grade ≥ 3)

At least one severe AE with CTCAE grade ≥ 3 occurred in 34 of 50 study participants (68%). The most common AEs with a severity grade ≥ 3 are "Gastrointestinal disorders", "Investigations", "Infections and infestations", "Skin and subcutaneous tissue disorders", "Respiratory, thoracic and mediastinal disorders", "General disorders and administration site conditions" and "Nervous system disorders".

Therapy discontinuation due to adverse events

In 6 patients (12%), an adverse event occurred that led to the discontinuation of the study medication.

AEs of special interest

In 88% of the study participants, "muscle-related effects" occurred as AEs of special interest. Other adverse events of special interest were "Rash, non-acneiform", "Rash, acneiform", "Effects of oral mucositis", "Nail disorders", "Effects of leucopenia", "Effects of erythropenia", "Effects of heart failure", "Ocular toxicities" and "Effects of thrombocytopenia".

In summary, no conclusions can be drawn on the extent of the additional benefit for the side effects category due to the absence of a control group.

Overall assessment

For the benefit assessment of selumetinib for the treatment of plexiform neurofibromas in children aged 3 years and older and adolescents with type 1 neurofibromatosis after the expiry of the deadline, results from the uncontrolled SPRINT study are available. Due to the single-arm study design, no comparative assessment is possible for the endpoints of mortality, morbidity, quality of life and side effects.

The pharmaceutical company also submits the two studies D1346C00013 and D1346C00011. These studies were not used due to the shorter duration of observation compared to the SPRINT study and the uncertainty regarding transferability to the German healthcare context.

No deaths were observed in the SPRINT study up to the data cut-off from 31 March 2021.

For the endpoint "change in tumour volume", there was a relevant reduction in tumour volume compared to the baseline at the start of study. Due to the specific manifestations of the disease, which can include tumour-related deformations and functional impairments regardless of the visibility of the tumours, in addition to externally visible tumours, the reduction of the tumour volume is an important therapeutic goal in this setting. In view of this, despite remaining uncertainties in the operationalisation of the endpoint and an overall limited interpretability of the results, an improvement in the therapeutic benefit of treatment with selumetinib with regard to a relevant reduction in tumour volume can be determined.

The study also included several endpoints to analyse symptomatology and physical functions or functional impairments. Health-related quality of life was assessed with a measurement instrument suitable for the paediatric patient population. The collection of these endpoints is generally favoured and could enable a relevant assessment of the effects of tumour volume on symptomatology, physical functioning or functional impairments and health-related quality of life. However, due to the absence of a control group, no valid conclusions can be drawn.

With regard to side effects, severe (CTCAE grade ≥ 3) and serious adverse events as well as therapy discontinuations due to adverse events occurred in part during treatment with

selumetinib. No valid statements can be derived since there is no comparison with a control group.

In the overall assessment, a non-quantifiable additional benefit was identified for selumetinib for the treatment of symptomatic, inoperable, plexiform neurofibromas in children aged 3 years and older and adolescents with type 1 neurofibromatosis since the scientific data basis does not allow quantification.

Significance of the evidence

The SPRINT study is a single-arm study so that a comparative assessment is not possible.

Against this background, the reliability of data is classified under the "hint" category.

2.1.3 Summary of the assessment

The present assessment is a new benefit assessment of the active ingredient selumetinib due to the expiry of the limitation of the resolution of 3 February 2022.

Koselugo received a conditional marketing authorisation as an orphan drug for the treatment of children aged 3 years and older and adolescents with symptomatic, inoperable plexiform neurofibromas in type 1 neurofibromatosis.

The benefit assessment of selumetinib is based on the ongoing, single-arm, open-label, multicentre phase I/II SPRINT study. Data on mortality, morbidity, quality of life and side effects are available.

No deaths were observed in the SPRINT study up to the data cut-off from 29 March 2019.

For the endpoint "change in tumour volume", there is a relevant reduction in tumour volume compared to the baseline. Due to the specific manifestations of the disease, which can include tumour-related deformations and functional impairments regardless of the visibility of the tumours, in addition to externally visible tumours, the reduction of the tumour volume is an important therapeutic goal in this setting. In view of this, despite remaining uncertainties in the operationalisation of the endpoint and an overall limited interpretability of the results, an improvement in the therapeutic benefit of treatment with selumetinib with regard to a relevant reduction in tumour volume can be determined.

Endpoints on symptomatology and physical functions or functional impairments were also collected. Health-related quality of life was assessed with a measurement instrument suitable for the paediatric patient population. The collection of these endpoints is generally supported and could enable the relevant assessment of how tumour volume changes affect symptomatology, physical functioning or functional impairments and health-related quality of life. Due to the absence of a control group, no valid conclusions can be drawn.

With regard to side effects, severe (CTCAE grade ≥ 3) and serious adverse events as well as therapy discontinuations due to adverse events occurred in part with selumetinib. No valid statements can be derived due to the absence of a control group.

In the overall assessment, a non-quantifiable additional benefit is identified for selumetinib since the scientific data basis does not allow quantification.

The reliability of data is classified in the category "hint".

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

The information on the number of patients is based on the target population in statutory health insurance (SHI). The resolution is based on the information from the dossier of the pharmaceutical company regarding the number of patients.

Overall, the information provided by the pharmaceutical company represents an overestimation. For example, children who no longer show any symptoms after an operation and therefore no longer fall within the therapeutic indication were not included in the determination of the percentage of patients. In addition, there is a tendency to overestimate the percentage of patients with at least one plexiform neurofibroma.

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: 21 August 2023):

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

Treatment 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, or specialists in paediatrics and adolescent medicine specialising in neuropaediatrics, paediatric haematology and oncology.

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 will evaluate new information on this medicinal product at a minimum once per year and update the product information where necessary.

2.4 Treatment costs

The treatment costs are based on the requirements in the product information and the information listed in the LAUER-TAXE® (last revised: 1 December 2023.

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.

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

Treatment period:

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Medicinal product to be assessed				
Selumetinib	2 x daily	365	1	365

Consumption:

For dosages depending on body surface area, the average body measurements from the official representative statistics "Microcensus 2017 – body measurements of the population" were applied.[2] Average body height and -weight for children aged 3 years are 1.01 m and 16.2 kg respectively. 17-year-olds are on average 1.74 metres tall and weigh 67 kg. This results in body surface areas (BSA) of 0.67 m² for 3-year-olds and 1.81 m² for 17-year-olds (calculation according to Du Bois 1916).

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

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					
3 years	25 mg/m² BSA = 20 mg + 10 mg[3]	30 mg	3 x 10 mg	365	1095 x 10 mg
17 years	25 mg/m² BSA = 45 mg + 45 mg[3]	90 mg	(1 x 25 mg + 2 x 10 mg) + (1 x 25 mg + 2 x 10 mg)	365	(365 x 25 mg + 730 x 10 mg) + (365 x 25 mg + 730 x 10 mg)

Costs:

In order to improve comparability, the costs of the medicinal products were approximated both on the basis of the pharmacy sales price level and also deducting the statutory rebates in accordance with Section 130 and Section 130a SGB V. To calculate the annual treatment costs, the required number of packs of a particular potency was first determined on the basis of consumption. Having determined the number of packs of a particular potency, the costs of the medicinal products were then calculated on the basis of the costs per pack after deduction of the statutory rebates. Any fixed reimbursement rates shown in the cost representation may not represent the cheapest available alternative.

2 Federal Statistical Office, Wiesbaden 2018: http://www.gbe-bund.de/
3 Dosage according to the regimen in the product information for selumetinib

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 10 mg	60	€ 5,489.30	€ 2.00	€ 223.50	€ 5,263.80
Selumetinib 25 mg	60	€ 13,707.62	€ 2.00	€ 558.75	€ 13,146.87
Abbreviation: HC: hard capsules					

LAUER-TAXE® last revised: 1 December 2023

Costs for additionally required SHI services:

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

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

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

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

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

Basic principles of the assessed medicinal product

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

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

A designation is also not considered if the G-BA has decided on an exemption as a reserve antibiotic for the assessed medicinal product in accordance with Section 35a, paragraph 1c, sentence 1 SGB V. The additional benefit is deemed to be proven if the G-BA has decided on an exemption for a reserve antibiotic in accordance with Section 35a, paragraph 1c, sentence 1 SGB V; the extent of the additional benefit and its therapeutic significance are not to be

assessed by the G-BA. Due to the lack of an assessment mandate by the G-BA following the resolution on an exemption according to Section 35a, paragraph 1c, sentence 1 SGB V with regard to the extent of the additional benefit and the therapeutic significance of the reserve antibiotic to be assessed, there is a limitation due to the procedural privileging of the pharmaceutical companies to the effect that neither the proof of an existing nor an expected at least considerable additional benefit is possible for exempted reserve antibiotics in the procedures according to Section 35a paragraph 1 or 6 SGB V and Section 35a paragraph 1d SGB V. The procedural privileging of the reserve antibiotics exempted according to Section 35a, paragraph 1c, sentence 1 SGB V must therefore also be taken into account at the level of designation according to Section 35a, paragraph 3, sentence 4 SGB V in order to avoid valuation contradictions.

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

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

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

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

Concomitant active ingredient:

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

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

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

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

In addition, all sections of the currently valid product information of the eligible concomitant active ingredient are checked to see whether there is any information that excludes its use in

combination therapy with the assessed medicinal product in the assessed therapeutic indication under marketing authorisation regulations. Corresponding information can be, for example, dosage information or warnings. In the event that the medicinal product is used as part of a determined or undetermined combination which does not include the assessed medicinal product, a combination with the assessed medicinal product shall be excluded.

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

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

Designation

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

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

Exception to the designation

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

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

Legal effects of the designation

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

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

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

Justification for the findings on designation in the present resolution:

Paediatric patients aged 3 years and above 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 authorised 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

On 30 June 2023, 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, number 5 VerfO.

The benefit assessment of the G-BA was published on 2 October 2023 together with the IQWiG assessment of treatment costs and patient numbers on the website of the G-BA (www.g-ba.de), thus initiating the written statement procedure. The deadline for submitting statements was 23 October 2023.

The oral hearing was held on 6 November 2023.

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

The evaluation of the written statements received and the oral hearing was discussed at the session of the subcommittee on 12 December 2023, and the proposed resolution was approved.

At its session on 21 December 2023, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee Medicinal products	26 September 2023	Information of the benefit assessment of the G-BA
Working group Section 35a	1 November 2023	Information on written statements received, preparation of the oral hearing
Subcommittee Medicinal products	6 November 2023	Conduct of the oral hearing
Working group Section 35a	15 November 2023 6 December 2023	Consultation on the dossier assessment by the G-BA, the assessment of treatment costs and patient numbers by the IQWiG, and the evaluation of the written statement procedure
Subcommittee Medicinal products	12 December 2023	Concluding discussion of the draft resolution
Plenum	21 December 2023	Adoption of the resolution on the amendment of Annex XII AM-RL

Berlin, 21 December 2023

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

Prof. Hecken