Gemeinsamer Bundesausschuss

Justification

of the Resolution of the Federal Joint Committee (G-BA) on an Amendment of the Pharmaceuticals Directive (AM-RL):

Annex XII – Benefit Assessment of Medicinal Products with New Active Ingredients according to Section 35a SGB V
Selumetinib (neurofibromatosis (≥ 3 to < 18 years, type 1))

of 3 February 2022

Contents

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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 a rare disease (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), the additional medical benefit is considered to be proven through the grant of the marketing authorisation. 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 €50 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, subsection 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. Rather, the extent of the additional benefit is assessed exclusively on the basis of the marketing authorisation 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

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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 legal limit of €50 million and is therefore subject to an unrestricted benefit assessment (cf. Section 35a paragraph 1, sentence 12 SGB V). 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 forms part of the Pharmaceuticals Directive.

2. Key points of the resolution

The relevant date for the first placing on the (German) market of the active ingredient selumetinib in accordance with Chapter 5, Section 8, paragraph 1, number 1, sentence 2 of the Rules of Procedure of the G-BA (VerfO) is 15 August 2021. The pharmaceutical company submitted the final dossier to the G-BA in accordance with Section 4, paragraph 3, number 1 of the Ordinance on the Benefit Assessment of Pharmaceuticals (AM- NutzenV) in conjunction with Chapter 5, Section 8, paragraph 1, number 1 VerfO on 13 August 2021.

Selumetinib indicated for the treatment of inoperable plexiform neurofibromas in paediatric patients aged 3 years and -above 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 marketing authorisation 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 15 November 2021 together with the IQWiG assessment on the website of the G-BA (www.g-ba.de), thus initiating the written statement procedure. In addition, an oral hearing was held.

The G-BA made its resolution on the basis of the pharmaceutical company's dossier, the dossier assessment carried out by the G-BA, the IQWiG assessment of treatment costs and patient numbers (IQWiG G21-24) and the statements made in the written statement and oral hearing procedure, as well of the amendment drawn up by the G-BA on the benefit assessment.

In order to determine the extent of the additional benefit, the G-BA has evaluated the studies relevant for the marketing authorisation with regard to their therapeutic relevance (qualitative) in accordance with the criteria laid down in Chapter 5, Section 5, paragraph 7,

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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.

2.1 Additional benefit of the medicinal product

2.1.1 Approved therapeutic indication of Selumetinib (Koselugo) according to 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 3 February 2022):

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:

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

Justification:

The pharmaceutical company uses the results of the SPRINT study to demonstrate the extent of the additional benefit of selumetinib for the treatment of plexiform neurofibromas (PN) in paediatric patients aged 3 years and above with neurofibromatosis type 1. Since no data from studies for direct comparison are available, the pharmaceutical company also presents an indirect comparison with external control studies.

SPRINT study

The SPRINT study is an ongoing, open-label, single-arm, multicentre phase I/II study. For phase II, patients were enrolled in one of two strata, based on whether PN-related morbidity was already present at the time of their enrolment in the study (stratum 1) or whether there was no significant clinical morbidity but the potential for such (stratum 2). PN-related morbidity included pain, deformation or functional impairment caused by PN, such as vision loss, facial motor dysfunction, hearing loss, difficulty swallowing, speech impairment, airway obstruction,

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

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respiratory impairment, bladder dysfunction, bowel dysfunction, muscle weakness, limitation of range of movement or sensory disorders.

Stratum 1 of phase II of the SPRINT study is used for the benefit assessment. Stratum 2 of phase II includes asymptomatic subjects who are not considered for the therapeutic indication of selumetinib.

A total of 50 paediatric patients aged 3 years and above were enrolled in phase II for stratum 1. Treatment was given in cycles of 28 days with no breaks between cycles. Participants with disease progression within 1.5 years prior to enrolment in the study received the study medication as long as they had no severe side effects and the disease did not worsen. Treatment of study participants without disease progression in the 1.5 years prior to enrolment in the study and without response to treatment with selumetinib (reduction of tumour volume by ≥ 20%) should be stopped after 2 years. Patients should be followed up for a total of 7 years after start of treatment with selumetinib or 5 years after end of treatment with selumetinib in the SPRINT study, whichever is longer.

In the SPRINT study, the most clinically relevant inoperable PN that could be detected by volumetric 3D MRI measurement was defined as the target PN.

The study was conducted in 4 study sites across North America. The primary endpoint in phase II was defined as the objective response rate (ORR). Enrolment of patients in phase II began in August 2015.

A primary interim analysis was conducted on 29 June 2018. Results for all endpoints collected are available for this data cut-off. A further data cut-off dated 29 March 2019 was requested by the U. S. Food and Drug Administration (FDA). For this non-pre-specified data cut-off, results are available for the endpoint categories of mortality and side effects. Another data cut-off was commissioned by the European Medicines Agency (EMA) in connection with the conditional marketing authorisation of selumetinib (phase II: 31 March 2021). However, these data are not yet available to the pharmaceutical company.

Indirect comparisons

With external control studies, the pharmaceutical company presents in the dossier an indirect comparison of selumetinib versus best supportive care . For 4 studies (Fisher et al., 2008; Nguyen et al., 2012; Nguyen et al., 2013; Well et al., 2021), the comparison is based on published studies, some of which show large differences with regard to the enrolled study population and for which no sufficient comparability with the SPRINT study population can be demonstrated due to a lack of detailed information on baseline characteristics.

In addition, for the benefit assessment, the pharmaceutical company is conducting an indirect comparison with a prospective observational study (NCI-08-C-0079) on the natural course of NF1 disease and with the placebo arm of RCT 01-C-0222.

The study on the natural course of the disease acts as the framework protocol for the clinical studies programme of the National Cancer Institute - Pediatric Oncology Branch (NCI POB). The enrolled study population is more likely to include patients who are seeking treatment for their PN due to the severity of their disease and is therefore only mildly representative of the general NF1 population. There is a lack of information, for example, on the operationalisation

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of the endpoints assessed. Furthermore, there are differences in the inclusion and exclusion criteria (e.g. no need for PN-related morbidity; no criteria regarding liver, lung, kidney and heart function and infections; no exclusion of subjects with glioma or malignant peripheral nerve sheath tumour requiring treatment with chemotherapy or radiotherapy), so that the total patient population is broader than that of the SPRINT study.

The study population of the placebo arm of the 01-C-0222 study also differs substantially from the SPRINT study, as only subjects with progressive disease (≥ 20% increase in PN volume, or ≥ 13% increase in two-dimensional measurements, or ≥ 6% increase in one-dimensional measurements over the 2 most recent volumetric magnetic resonance imaging (MRI) scans or within one year prior to study enrolment) were enrolled in the 01-C-0222 study, with otherwise very similar inclusion criteria. In the SPRINT study, the percentage of subjects with progressive disease (≥ 20% increase in PN volume within 12 to 15 months before enrolment) was only 42%. Further differences between the study populations at baseline are shown with regard to demographic factors such as age (SPRINT study participants are about 2 years older than in control studies) and with regard to disease characteristics (tumour volume in the SPRINT study about 1.5 x larger than in external control studies). For the reasons mentioned above, the submitted external control studies are not used in the assessment for an indirect comparison with the SPRINT study.

About the results of the SPRINT study

Mortality

No deaths were observed in phase II of the SPRINT study up to the data cut-off of 29 March 2019. No statement can be made on the extent of the additional benefit due to the absence of a control group.

Morbidity

Progression-free survival (PFS)

PFS was assessed as a secondary endpoint in the SPRINT study and was defined as the time from the first cycle of study treatment to progression or death from any cause, regardless of whether study participants discontinued study treatment or received another PN treatment (after discontinuation of study treatment) before progression. Progression was defined as a minimum 20% increase in the volume of the target lesion according to REiNS criteria, as measured by volumetric MRI.

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

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

Change in tumour volume

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

In the present indication, there is the special case that the endpoint "change in tumour volume" is considered to be a patient-relevant endpoint due to the partial external visibility of the tumours, which partly manifest themselves as clearly visible deformations and can also be characterised by functional limitations irrespective of the visibility of the tumours, provided that it is shown by suitable operationalisation that the tumour size is relevantly reduced.

In the SPRINT study, a reduction of the target lesion (best achieved percentage volume reduction) of -25% was shown. Approximately 96% of patients experienced a volume reduction during the course of the study during treatment with selumetinib. Due to the absence of a control group, there is initially the fundamental question of the extent to which this is an effect of the treatment. However, with the present clinical picture and stage of the disease, it can be assumed with sufficient certainty that no spontaneous remissions occur in the natural course of the disease.

The following uncertainties come into play when interpreting the present results: Firstly, with regard to the operationalisation of the endpoint, the effect of selumetinib therapy on other plexiform neurofibromas present in the patients that were not classified as target lesions was not assessed for the majority of the study participants. Furthermore, the absence of a control group does not allow assessment of the extent to which the changes observed since study enrolment can be distinguished from naturally occurring fluctuations, e.g. due to the amount of fluid in the tumour caused by external factors.

Basically, however, a volume reduction of the tumours in this therapeutic indication is to be considered as a therapeutic goal, as such tumours represent the relevant manifestation of the disease and are causative for any existing symptomatology with functional limitations as well as deformation.

Against this background, despite remaining uncertainties, an improvement in the therapeutic benefit of treatment with selumetinib with regard to a relevant reduction in tumour volume can be found.

Objective response rate (ORR)

Objective response rate was assessed as the primary endpoint in the SPRINT study and defined as the percentage of patients in phase II who achieve a confirmed complete or partial (reduction in the volume of the target PN by 20% or more) response. The response is considered confirmed if it is observed again within 3 to 6 months.

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

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

In the SPRINT study, the following endpoints were assessed for the investigation of symptomatology, physical functions and/or functional limitations as well as health-related quality of life:

Global assessment of clinical change

Global assessment of clinical change was assessed using Global Impression of Change (GIC). The GIC is a 1-item scale to assess the clinical significance of changes in pain intensity or other symptoms. In the SPRINT study, an adapted version of the GIC with 3 items was used. The change in tumour pain, overall pain and PN-related morbidity compared to the time before taking the study medication was measured. A self-assessment was carried out for children aged 8 years and above while an external assessment was carried out by the parents/caregiver for children aged 5 years and above. Global assessment of clinical change using GIC is considered appropriate.

For the parent/carer version of the GIC, no separate evaluations for children aged 8 years and below were available in the dossier, but these were subsequently submitted by the pharmaceutical company as part of the written statement procedure.

The SPRINT study showed improvements over time compared to the time before the start of the 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 captures impairment caused by pain. The occurrence of pain and the influence of pain on everyday activities is patient-relevant. However, the validity of the version of the PII used in the SPRINT study is not sufficiently proven to be used for the benefit assessment.

Numerical Rating Scale (NRS-11)

The occurrence of pain and its intensity is considered patient-relevant. In the SPRINT study, children aged 8 years and above assessed the intensity of the pain they experienced using the NRS-11.

There are improvements over baseline over time in the endpoint "worst pain" for patients aged 8 years and above. The endpoint "pain" was not assessed in children aged 8 years and below.

Visual acuity

The 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 charts 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 striped pattern must be distinguished from a grey surface.

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Teller acuity cards

For the visual acuity measured by means of Teller acuity cards, the information on operationalisation is insufficient and the implementation and standardisation of the test is not comprehensible. Therefore, this endpoint is not used for the benefit assessment.

HOTV test

The measurement of visual acuity using the HOTV test is considered valid and is used for the benefit assessment.

In the analysis of visual acuity, a total of only 5 patients could be included for the PN-affected eye. No improvements were observed from baseline and a deterioration was observed for the PN-affected eye. However, the reliability and interpretability of the results are very limited due to the open-label study design without a control group and the small sample size, which is why no statements on the additional benefit of selumetinib can be derived.

Proptosis/ exophthalmos

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

Notwithstanding this, no statement on the additional benefit can be made on the basis of the results of the SPRINT study on the endpoint due to the absence of a control group. The endpoint of proptosis/ exophthalmos is presented additionally.

Assessment of the motor function by means of the Grooved Pegboard Test

The Grooved Pegboard Test was performed in paediatric patients aged 5 years and above 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. Here, the time until completion of the pegboard was recorded.

The restriction of motor function and 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.

With regard to the Grooved Pegboard Test, slight to moderate improvements are observed over time. However, the single-arm study design does not allow distinction of whether these improvements are due to treatment with selumetinib or, for example, exercise effects. For patients with unilateral PN, the improvements for the impaired hand are similar to those for the unimpaired hand, suggesting more of an influence of exercise effects.

For the reasons mentioned above, there are relevant uncertainties in the interpretation of the results for this endpoint, which is why they are not used in the present assessment 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 from all patients with PN that impaired motor function.

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The assessment of physical functioning using PROMIS is considered appropriate.

For the PROMIS scales "Mobility" and "Upper extremities", slight improvements from baseline are observed in patients aged 8 to 18 years at the study visit before cycle 13. For patients aged 8 years and below and for motor PN-related morbidity, there are no separate evaluations of the parent/carer version of the PROMIS questionnaire, but only evaluations of the parent/carer version for the total study population from 5 years of age, so that this population is not considered in the benefit assessment.

Symptomatology by means of a symptom checklist

With the help of the symptom checklist, the extent of 36 symptoms within the last 2 weeks is surveyed.

In the SPRINT study,improvement of symptoms was reported more frequently (≥ 10% difference at study visit before cycle 13) than deterioration from baseline for the symptoms "sleep disorders", "frequent waking at night", "headache", "choking", "snoring", "cough", "shortness of breath on exertion", "weakness", "muscle pain" and "tingling". Conversely, deterioration of symptoms was reported more frequently (≥ 10% difference) than improvement from baseline for the symptoms "swelling of the feet/hands" and "diarrhoea" at the time before cycle 13. At earlier survey time points, the symptoms "increased appetite", "abdominal pain", "nausea", "vomiting" and "dizziness" were also more frequently reported to have worsened than improved. Symptoms for which deterioration is recorded more frequently may reflect selumetinib tolerability rather than morbidity. However, the reliability and interpretability of the results is so limited due to the open-label study design without a control group that no statements on the additional benefit can be derived.

Quality of life

Paediatric Quality of Life Inventory (PedsQL)

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

The health-related quality of life is assessed directly for children aged 8 years and above by surveying them. For the parent/carer version of the PedsQL, no separate evaluations for children aged 8 years and below were available in the dossier, but these were subsequently submitted by the pharmaceutical company as part of the written statement procedure.

The results of phase II of the SPRINT study show an improvement in health-related quality of life over the course of the study compared to baseline for children aged 8 years and below as well as those aged 8 years and above.

Summary assessment of the above endpoints to examine symptomatology, physical functions and/or functional limitations as well as health-related quality of life:

The symptomatology and physical functions and/or functional limitations of patients with plexiform neurofibromas vary greatly from patient to patient. The G-BA expressly supports the assessment of these outcomes as well as health-related quality of life in clinical studies, such as the SPRINT study. Against the background of the special characteristics of the disease in the present therapeutic indication, correspondingly suitable endpoints have a high priority in the benefit assessment. Corresponding data could, among other things, enable the relevant

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assessment of how effects on tumour volume affect symptomatology, physical functioning and/or functional limitations as well as 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 uncertainties for individual endpoints, as outlined above. Overall, no statement on the additional benefit can be derived on the basis of these endpoints.

Side effects

Total adverse events (AEs)

One adverse event occurred in almost all patients enrolled in the study. The results are presented additionally (48 patients (98%)).

Serious adverse events (SAEs)

12 out of 50 of the patients (24%) had at least one serious adverse event (SAE). The most frequent SAEs are "infections and infestations" and "gastrointestinal disorders".

Severe adverse events (CTCAE grade ≥ 3)

31 out of 50 of the study participants (62%) had at least one severe AE with CTCAE grade ≥ 3. The most frequent AEs with a severity grade ≥ 3 were "gastrointestinal disorders", "examinations", "infections and infestations", "skin and subcutaneous tissue disorders", "respiratory, thoracic and mediastinal disorders", "general disorders and administration site conditions", "nervous system disorders", as well as "injury, poisoning and procedural complications".

Therapy discontinuation due to adverse events

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

AE of special interest

86% of the study participants experienced "muscle-related effects" as AE of special interest. Other adverse events of special interest include: "rash, non-acneiform", "rash, acneiform", "effects of oral mucositis", "diseases of the nail", "effects of leukopenia", "effects of erythropenia", "effects of heart failure", "retinal effects" and "effects of thrombocytopenia".

In the overall assessment of the results on side effects, no statements on the extent of additional benefit can be derived due to the absence of a control group.

Overall assessment

For the benefit assessment of selumetinib for the treatment of plexiform neurofibromas in paediatric patients aged 3 years and above with neurofibromatosis type 1, results from the uncontrolled SPRINT study on overall survival, morbidity, quality of life and side effects are available.

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In addition, the pharmaceutical company submits an indirect comparison with external control studies. The external control studies are not used for the benefit assessment due to a lack of information on baseline characteristics or a lack of comparability of the included study populations with the SPRINT study population.

Thus, no control group for a comparative assessment is available for the present assessment.

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

For the endpoint "change in tumour volume", there was a relevant reduction in tumour volume compared to the baseline at the start of study. In view of the special characteristics of the disease in the present therapeutic indication, which include externally visible tumours as well as tumour-related deformations and functional limitations independent of the visibility of the tumours, the reduction of the tumour volume is fundamentally an important therapeutic goal. Against this background, despite remaining uncertainties with regard to 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 found.

In the study, several endpoints were also recorded to examine the symptomatology and physical functions and/or functional limitations. Health-related quality of life was assessed with a measurement instrument suitable for the paediatric patient population. The assessment of these endpoints is basically supported and could enable the relevant assessment of how effects on tumour volume affect symptomatology, physical functioning and/or functional limitations as well as health-related quality of life. However, in the present assessment, no valid statements can be derived due to the absence of a control group.

With regard to the results for side effects, severe (CTCAE grade ≥ 3) and serious adverse events as well as therapy discontinuation due to adverse events occurred in part during treatment with selumetinib. Since there is no comparison with a control group, no valid statements can be derived.

In the overall assessment, a non-quantifiable additional benefit is determined for selumetinib for the treatment of symptomatic, inoperable, plexiform neurofibromas in paediatric patients aged 3 years and above with neurofibromatosis type 1, because 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.

This results in a hint for an additional benefit with regard to significance of the evidence.

2.1.3 Limitation of the period of validity of the resolution

The limitation of the period of validity of the resolution on the benefit assessment of selumetinib finds its legal basis in Section 35a paragraph 3 sentence 4 SGB V. Thereafter, the G-BA may limit the validity of the resolution on the benefit assessment of a medicinal product. In the present case, the limitation is justified by objective reasons consistent with the purpose of the benefit assessment according to Section 35a paragraph 1 SGB V.

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The results of a further data cut-off are expected for the SPRINT study on which this assessment is based. The European Medicines Agency (EMA) commissioned a data cut-off on 31 March 2021 in connection with the conditional marketing authorisation of selumetinib. However, the data from this data cut-off were not yet available to the pharmaceutical company for the present benefit assessment.

Since more clinical data are expected which are relevant for the benefit assessment of the medicinal product, it is justified to limit the validity of the resolution until further scientific knowledge is available for the assessment of the additional benefit of selumetinib. The time limit enables the inclusion of the expected results from another data cut-off of the SPRINT study in the benefit assessment of the medicinal product according to Section 35a SGB V. For this purpose, a time limit of the resolution until 1 July 2023 is considered appropriate.

Conditions for the limitation:

For the new benefit assessment after expiry of the deadline, the results on all patient-relevant endpoints used for the proof of an additional benefit on the basis of the data cut-off of 31 March 2021 from the SPRINT study are to be presented in the dossier.

A change in the limitation can generally be granted if it is justified and clearly demonstrated that the limitation is insufficient or too long.

In accordance with Section 3 paragraph 7 AM-NutzenV in conjunction with Chapter 5 Section 1, paragraph 2, number 7 VerfO, the procedure for the benefit assessment of selumetinib recommences when the deadline has expired. For this purpose, the pharmaceutical company must submit a dossier to the G-BA at the latest on the date of expiry to prove the extent of the additional benefit of selumetinib (Section 4, paragraph 3, number 5 AM-NutzenV in conjunction with Chapter 5 Section 8, number 5 VerfO).

The possibility that a benefit assessment for selumetinib can be carried out at an earlier point in time due to other reasons (cf. Chapter 5, Section 1 paragraph 2, Nos. 2 – 6 VerfO) remains unaffected hereof.

2.1.4 Summary of the assessment

The present assessment concerns the benefit assessment of the new medicinal product Koselugo with the active ingredient selumetinib.

Selumetinib has been approved as an orphan drug under special conditions for the treatment of inoperable, symptomatic, plexiform neurofibromas in paediatric patients aged 3 years and above with neurofibromatosis type 1.

The benefit assessment of selumetinib is based on the ongoing, single-arm, open-label, multicentre phase I/II SPRINT study.

In addition, the pharmaceutical company submits an indirect comparison with external control studies. The control studies are not used for the benefit assessment due to a lack of information on baseline characteristics or a lack of comparability of the included study populations with the SPRINT study population.

Thus, no control group for a comparative assessment is available for the present assessment.

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

For the endpoint "change in tumour volume", there was a relevant reduction in tumour volume compared to the baseline at the start of study. In view of the special characteristics of the disease in the present therapeutic indication, which include externally visible tumours as well as tumour-related deformations and functional limitations independent of the visibility of the tumours, the reduction of the tumour volume is fundamentally an important therapeutic goal. Against this background, despite remaining uncertainties with regard to 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 found.

In the study, several endpoints were also recorded to examine the symptomatology and physical functions and/or functional limitations. Health-related quality of life was assessed with a measurement instrument suitable for the paediatric patient population. The assessment of these endpoints is basically supported and could enable the relevant assessment of how effects on tumour volume affect symptomatology, physical functioning and/or functional limitations as well as health-related quality of life. However, in the present assessment, no valid statements can be derived due to the absence of a control group.

With regard to the results for side effects, severe (CTCAE grade ≥ 3) and serious adverse events as well as therapy discontinuation due to adverse events occurred in part during treatment with selumetinib. Since there is no comparison with a control group, no valid statements can be derived.

In the overall assessment, a non-quantifiable additional benefit is determined for selumetinib for the treatment of symptomatic, inoperable, plexiform neurofibromas in paediatric patients aged 3 years and above with neurofibromatosis type 1, because the scientific data basis does not allow quantification.

The significance of the evidence provides a hint for the additional benefit determined.

The period of validity of the resolution is limited until 1 July 2023 as results from a further data cut-off from the SPRINT study are expected.

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.

The information provided by the pharmaceutical company is an overestimation on the whole. For example, children who no longer have any symptoms after an operation and therefore, no longer fall within the therapeutic indication were not taken into account in the percentage calculation. In addition, there is a tendency to overestimate the percentage of patients with at least one plexiform neurofibroma.

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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: 23 December 2021):

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 was approved under "special conditions". 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 contents of the product information and the information listed in the LAUER-TAXE® (last revised: 15 January 2022).

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 is patient-individual 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

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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 height and -weight of children aged 3 years are 1.01 m and 16.2 kg respectively. 17-year-olds are on average 1.74 m 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 (calculated according to Du Bois 1916).

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

Designation of the therapy	Dosage/ application	Dosage/ 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	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 usage. 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.

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

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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 HC	€ 6,676.40	€ 1.77	€ 378.00	€ 6,296.63
Selumetinib 25 mg	60 HC	€ 16,604.57	€ 1.77	€ 945.00	€ 15,657.80
Abbreviation: HC: hard capsules					

LAUER-TAXE® last revised: 15 January 2022

Costs for additionally required SHI services:

Only costs directly related to the use of the medicinal product are taken into account.

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 costs for additionally required SHI services have to be taken into account since no regular medical treatment or other services have to be claimed when using the assessed medicinal product according to the product information.

3. Bureaucratic costs calculation

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

4. Process sequence

On 13 August 2021, 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, number 1, sentence 2 VerfO.

The benefit assessment of the G-BA was published on 15 November 2021 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 written statements was 6 December 2021.

The oral hearing was held on 21 December 2021.

An amendment to the benefit assessment with a supplementary assessment of data submitted in the written statement procedure was submitted on 11 January 2022.

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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 25 January 2022, and the proposed resolution was approved.

At its session on 3 February 2022, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee Medicinal product	9 November 2021	Information of the benefit assessment of the G-BA
Working group Section 35a	15 December 2021	Information on written statements received; preparation of the oral hearing
Subcommittee Medicinal product	21 December 2021	Conduct of the oral hearing
Working group Section 35a	5 January 2022 19 January 2022	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 product	25 January 2022	Concluding discussion of the draft resolution
Plenum	3 February 2022	Adoption of the resolution on the amendment of Annex XII AM-RL

Berlin, 3 February 2022

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

Prof. Hecken

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